ASYMMETRIC STRATEGIES FOR THE SYNTHESIS OF BIOLOGICALLY RELEVANT MOLECULES

By

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DECLARATION

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DEDICATED TO.....

MA, BABA and DADA

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CONTENTS

SYNOPSIS

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Extensive research on natural products chemistry especially with an eye to drug development has led to the isolation of myriads of bioactive compounds and also identification of suitable pharmacophore for their potential medicinal values. These compounds often bear a complex structure and possess chirality. Hence, even at the height of maturity, synthetic organic chemistry is facing the challenge to design and develop efficient syntheses for such functionally enriched complex biologically active compounds. This warrants facile, atom economic, high yielding and selective organic reactions. Given the importance of stereochemistry in bio-recognition, the issue of asymmetric synthesis has become overwhelming in modern organic synthesis. In view of these, the present work is focused on the development of operationally simple and practically viable asymmetric strategies that include some metal-catalyzed asymmetric routes and non-conventional protocols, and their possible application to the enantiomeric syntheses of a few chosen bio-active molecules. Accordingly the content of the thesis is presented in four chapters as detailed below.

Chapter I: Introduction to Asymmetric Synthesis

This chapter deals with broad reviews on asymmetric synthesis,[1] the major focus of the present investigation. The salient features of the deliberation include the genesis and importance of chirality, and different methods of enantiomeric synthesis with special emphasis on asymmetric transformations. The aspect of using chiral compounds as building blocks for the synthesis of enantiomerically pure compounds is discussed subsequently. The influences of substrate, reagent, catalyst and auxiliary to direct the asymmetric transformation have also been elaborately explained. Finally, the theoretical

models (*e. g*. Cram's model, Felkin-Anh model and Zimmerman-Traxler model) to explain the diastereoselectivities as well as the energy profile for an asymmetric transformation explaining kinetic and thermodynamic controls have been elaborated.

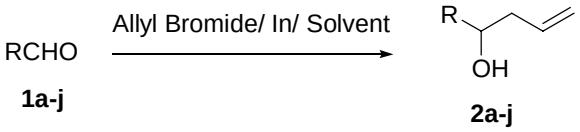
Chapter II: [bmim][Br] : a Green and Efficient Media for Allylation of Aldehydes

Chiral carbinols are one of the most versatile synthons for synthesis of various target molecules with structural diversity.[2] Hence, various methods for diastereoselective synthesis of chiral carbinols[3] has been presented at the beginning of this chapter. In this pursuit, special attention has been paid to the allylation reactions of aldehydes, since the alkene formed may easily be functionalized in many ways. Accordingly various protocols for allylation have been developed both in organic and aqueous media, and also in room temperature ionic liquids (RTILs). To this end, the Barbier type allylation protocol with metals (Zn, Sn, In etc.) is conveniently used.[4] However, still alternative methods are warranted especially for better acyclic stereocontrol that has been a pressing concern in modern organic chemistry.[5] In this chapter, the results of our studies in the In and Ga-mediated allylation of carbonyl compounds in [bmim][Br], an inexpensive and relatively unexplored RTIL has been presented. The outcome of the reaction has been subsequently mechanistically rationalized. Besides the usual advantages of the RTILs,[6] the choice of [bmim][Br] as the reaction medium was dictated by its excellent hydrophilicity that assists the Barbier type reactions.

Initially, to optimize the protocol, the In-mediated allylation of benzaldehyde (**1a**) was carried out in H_2O, THF and three different RTILs, establishing [bmim][Br] as the best solvent. The reaction was much faster in [bmim][Br], did not require any metal activator, and could be carried out with stoichiometric amounts of the organic reactants.

The reaction could also be accomplished even with 20 mol% In, although it became slower under this condition. The protocol was equally effective with both aromatic and aliphatic aldehydes **1a-1j** (**Scheme 1**, **Table 1**) furnishing the products in good yields, and proceeded with complete chemoselectivity furnishing the 1,2-addition product (*e. g*., **2g**) only with the conjugated aldehyde **1g**.

The ^{1}H NMR spectroscopic studies of the reaction between In and allyl bromide revealed formations of CH_2=$CHCH_2$-In (**I**) in H_2O and CH_2=$CHCH_2$-$InBr_2$ (**II**) in THF / [bmim][Br], as the active allylating agents. However, the species **I** got easily hydrolyzed, explaining the requirement of a large excess of the reagents in the aqueous phase allylation. In contrast, the species **II** remained stable up to 6 h in [bmim][Br], when the reaction was complete. The activation of the In metal surface was caused by polarization of the In electrons to [bmim][Br], as revealed from the upfield shift of imidazole protons (4.2 Hz) as well as carbons (10 Hz) in NMR spectra when In metal was incubated in [bmim][Br].



1a-j **2a-j**

Scheme 1

Table 1. Reaction course of In-mediated allylation of aldehydes in [bmim][Br][a]

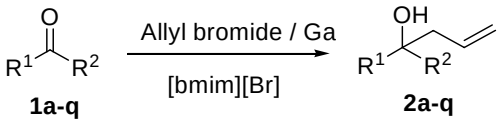
Entry	Substrate	R	Aldehyde : Allyl bromide : Metal (equiv.)	Time (h)	Product (%)
1	**1a**	C_6H_5	1 : 1.5 : 0.2	22	**2a** (84)
2	**1b**	4-Bromo-C_6H_4	1 : 1.5 : 0.2	20	**2b** (81)
3	**1c**	3-Methoxy-C_6H_4	1 : 1.5 : 0.2	22	**2c** (88)

4	**1d**	4-$(CH_3)_2CH$-C_6H_4	1 : 1.5 : 0.2	22	**2d** (91)
5	**1e**	4-C_6H_5- C_6H_4	1 : 1.5 : 0.2	20	**2e** (86)
6	**1f**	C_6F_5	1 : 1.5 : 0.2	18	**2f** (88)
7	**1g**	C_6H_5CH=CH	1 : 1.5 : 0.2	22	**2g** (86)
8	**1h**	$(CH_3)_2CH$	1 : 1.5 : 0.2	48	**2h** (68)
9	**1i**	$CH_3(CH_2)_5$	1 : 1.5 : 0.2	22	**2i** (87)
10	**1j**	$CH_3(CH_2)_8$	1 : 1.5 : 0.2	22	**2j** (91)

[a]The reactions were carried out at 2 mmol scale using 20 mol% In. The yields refer to those of isolated pure products.

Regarding the catalytic role of In metal in the reaction, its oxidation by [bmim][Br] generated $InBr_3$, which eventually produced In^{+1} (InBr) at the acidic pH (5.78) of [bmim][Br] following the equilibrium 2 In (s) + In^{+3} = 3 In^{+1}. The species **II** was produced by the reaction of allyl bromide with InBr, as well as the activated In metal. Finally reaction of **II** with the aldehyde followed by hydrolysis of the intermediate with the trace amount of H_2O (present in [bmim][Br]) furnished the allyl alcohol. The $InBr_3$, generated in the process got reduced by the [bmim] radicals to form [$InBr_2$] radical or its dimer, which finally disproportionated to give InBr, thus maintaining the cycle without further addition of In metal.

The Ga-mediated allylation of the aldehydes **1a-k**, and even ketones **1l-q** (**Scheme 2**) also followed a similar course to furnish the respective homoallylic alcohols (**Table 2**). The protocol proceeded with complete regio- (mono allylated product with the diketone **1n**), chemo- (1,2-addition with the conjugated carbonyls **1g** and **1o**, and diastereo-selectivities (exclusive formation of *trans*-product with **1q**).



1a-q **2a-q**

Scheme 2

In this case also, [bmim][Br] activated Ga metal surface via electron polarization, but produced $(CH_2CH{=}CH_2)_2GaBr$ (**III**) as active allyl-Ga species, possibly due to the smaller size of Ga. In view of this, the reaction could be accomplished with 50 mol% of Ga.

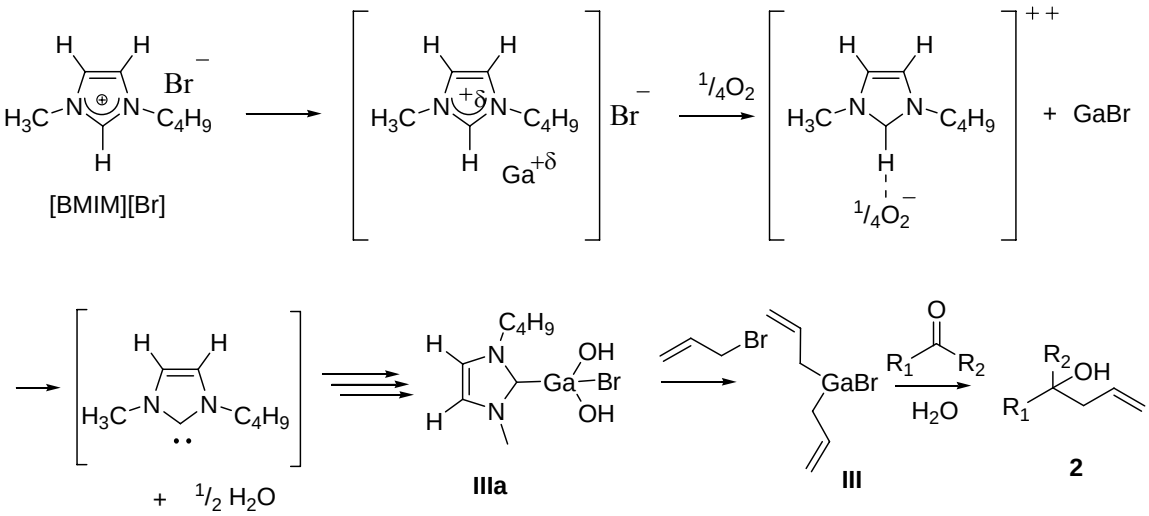
Table 2. Reaction course of Ga-mediated allylation of carbonyls in [bmim][Br][a]

Entry	Substrate	R_1	R_2	Product	Time (h)	Yield (%)
1	**1a**	C_6H_5	H	**2a**	4	84
2.	**1b**	4-Br-C_6H_4	H	**2b**	6	77
3.	**1c**	3-0Me-C_6H_4	H	**2c**	5	84
4.	**1d**	4-$(CH_3)_2CH$ - C_6H_4	H	**2d**	5	87
5.	**1e**	4-C_6H_5-C_6H_4	H	**2e**	6	83
6.	**1f**	C_6F_5	H	**2f**	5	83
7.	**1g**	$C_6H_5CH{=}CH$	H	**2g**	12	79
8.	**1h**	$(CH_3)_2CH$	H	**2h**	8	67
9.	**1i**	$CH_3(CH_2)_5$	H	**2i**	6	84
10.	**1j**	$CH_3(CH_2)_8$	H	**2j**	5	95
11.	**1k**	3-indolyl	H	**2k**	5	72
12.	**1l**	C_6H_5	CH_3	**2l**	10	71
13.	**1m**	C_6H_5	C_6H_5	**2m**	16	67

14.	**1n**	C_6H_5CO	C_6H_5	**2n**	8	77
15.	**1o**	$C_6H_5CH=CH$	Ph	**2o**	8	81
16.	**1p**	Cyclohexanone		**2p**	7	78
17.	**1q**	2-Methylcyclohexanone		**2q**	7	77

[a]The reactions were carried out at 2 mmol scale using 50 mol% In. The yields refer to those of isolated pure products.

However, formation of **III** followed an absolutely novel mechanism. Initially, reaction between [bmim][Br] and Ga produced a Ga-N-heterocyclic carbene complex [NHC-GaBr(OH)$_2$] (**IIIa**) that required presence of O_2. Evidently, the initially formed charge transfer-



Scheme 3

like transient Ga-[bmim][Br] transferred electron to O_2 to form $O_2^{-\cdot}$, which got stabilized by the C-8 acidic proton of the imidazole moiety. Subsequent decomposition of the intermediate generated the NHC diradical, which on reaction with Ga furnished **IIIa**. The species was fully characterized by spectral (IR, NMR, MS) data, as well as

thermogavimetric and elemental analyses. The intermediate **IIIa** subsequently reacted with allyl bromide to furnish the active allylating species **III** (characterized by ^{1}H NMR spectrum and synthesizing it separately), and generating active Ga-metal surface for sustaining the reaction. The entire mechanistic pathway is presented in **Scheme 3**.

Chapter III: Diastereoselective synthesis of chiral carbinols

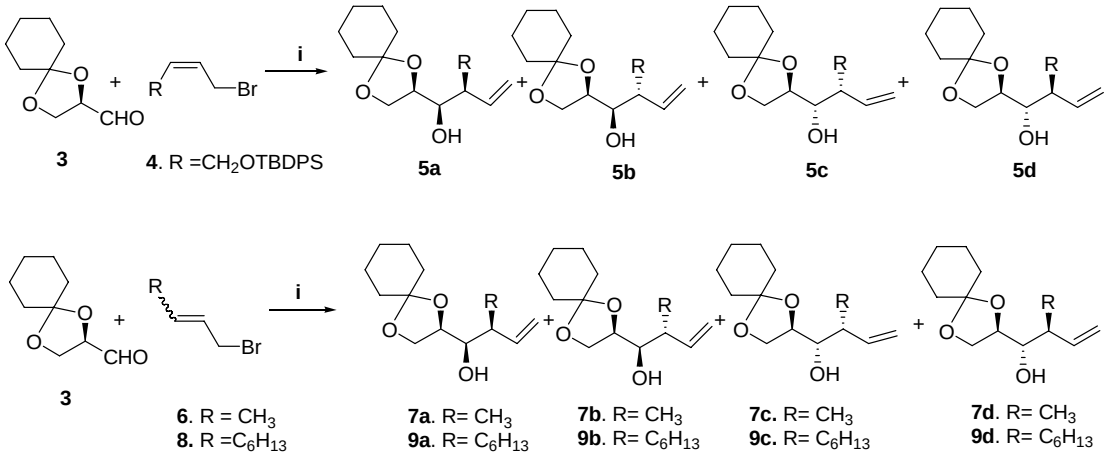
Given that the major interest of the study was the development of some asymmetric protocol for allylation, two substrate-controlled approaches were explored for this purpose, using (*R*)-cyclohexylideneglyceraldehyde **3**[7] as the chiral template. In one of these, a bimetallic redox strategy was employed for allylation and even for benzylation. In the other approach, different metal-solvent combinations were used to tune the diastereoselectivity of the Barbier type allylation. For both these, unsubstituted and γ-alkylated allyl bromides were used. The results of the studies are presented below.

The bimetallic redox strategy involves spontaneous reduction of a metal salt (**M_1X**) in aqueous environment with another metal (**M_2**) that have higher oxidation potential, to produce the activated metal (**M_1**). This, in turn, reacts with allylic bromides to give the active allyl-metal species, which eventually reacts with the aldehyde **3**. Based on its higher oxidation potential compared to Fe, Co, Cu and Sn, Zn was chosen as the reducing metal in separate combinations with the commercially available salts *viz*. Zn/$CuCl_2.2H_2O$, Zn/$CoCl_2.6H_2O$, Zn/$FeCl_3$ and Zn/$SnCl_2$.

Different allylic bromides *viz.* 1-bromo-4-hydroxy-*cis*-2-butene (**4**), 1-bromo-2-butene (**6**) and 1-bromo-2-nonene (**8**) were reacted with **3** in the presence of the above

bimetallic systems**.** In all the cases, however, exclusive γ-addition products with trace quantities of the respective *syn-anti* compounds were obtained.

In the reaction of **4** with **3** (**Scheme 4, Table 3,** entries 1-4), the Fe-mediated reaction was very fast and gave a significantly better yield of the products, albeit with poor diastereoselectivity. Interestingly, while the Cu-mediated reaction produced predominantly the *anti-anti* isomer, the *anti-syn* isomer was the major product in the Co-mediated reaction.



i) . $Zn/CuCl_2.2H_2O$, $Zn/CoCl_2.6H_2O$, $Zn/FeCl_3$ or $Zn/SnCl_2$, moist THF, 25 ^oC.

Scheme 4

Table 3. Reaction course of allylation of **3** using bimetallic redox strategy[a]

Entry	R	Metal/ salt	**3** : metal : salt	Time (h)	Yield (%)	Product	Product ratio (**b** : **c** : **d**)
1	$CH_2OTBDPS$	Zn/aq NH_4Cl	1 : 3.5 : -	5	73	**5**	3.5:52.3:44.2
2	$CH_2OTBDPS$	$Zn/FeCl_3$	1 : 3: 3	0.5	83	**5**	2.4:50.5:47.1
3	$CH_2OTBDPS$	$Zn/CuCl_2.2H_2O$	1: 3.5 : 3.5	20	70	**5**	2.6:33.4:64.0
4	$CH_2OTBDPS$	$Zn/CoCl_2.8H_2O$	1: 3.5 : 3.5	20	72	**5**	2.1:69.8:28.1

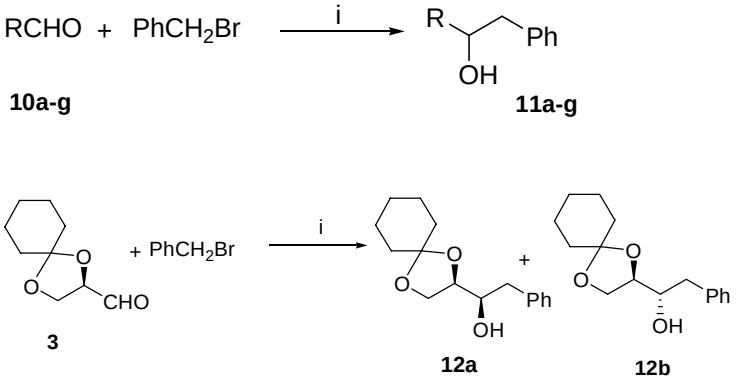
5	CH_3	Zn/aq NH_4Cl	1 : 3.5 : -	5	74	**7**	2.4:32.5:65.1
6	CH_3	Zn/$FeCl_3$	1: 2.0 : 2.0	0.2	86.9	**7**	1.5: 48.4: 50.1
7	CH_3	Zn/$CuCl_2.2H_2O$	1: 2.5 : 2.0	15	78.7	**7**	4.2: 29.5:66.3
8	CH_3	Zn/$CoCl_2.8H_2O$	1: 2.5 : 2.0	24	77.8	**7**	3.8: 47.5:48.7
9	CH_3	Zn/$SnCl_2$	1: 2.0 : 2.0	0.75	80.4	**7**	7.1: 78.2:14.7
10	*cis*-C_6H_{13}	Zn/aq NH_4Cl	1 : 3.5 : -	4	77.5	**9**	2.7:51.9:45.4
11	*cis*-C_6H_{13}	Zn/$FeCl_3$	1 : 3: 3	3	84	**9**	3.1:28.4:68.5
12	*cis*-C_6H_{13}	Zn/$CuCl_2.2H_2O$	1: 3.5 : 3.5	4	77	**9**	1.0:48.0:51.0
13	*cis*-C_6H_{13}	Zn/$CoCl_2.8H_2O$	1 : 4.5 : 4	15	NR	--	--
14	*trans*-C_6H_{13}	Zn/aq NH_4Cl	1 : 3.5 : -	4	77.9	**9**	4.5:55.5:40.0
15	*trans*-C_6H_{13}	Zn/$FeCl_3$	1 : 4.5 : 4	15	NR	--	--
16	*trans*-C_6H_{13}	Zn/$CuCl_2.2H_2O$	1 : 3: 3	3.5	83	**9**	15.1:40.9:44.0
17	*trans*-C_6H_{13}	Zn/$CoCl_2.8H_2O$	1: 3.5 : 3.5	4	78.7	**9**	7.0:62.0:31.0

[a]The reactions were carried out at 2 mmol scale. The yields refer to those of isolated pure isomers. The isomeric ratios were determined from the isolated yields. NR: no reaction.

While the reaction of **6** with **3** (**Scheme 4, Table 3,** entries 5-9) using low valent Cu yielded **7d** as the major product, the Co and Fe mediated reactions produced **7c** and **7d** in comparable proportions. In contrast, low valent Sn mediated reaction yielded **7c** as the major product. The effect of the olefin geometry on the stereoselectivity of the above allylation reactions was examined using the individual *cis* and *trans* isomers of the bromide **8.** The combination of Zn/$FeCl_3$ provided the best results. For a given bimetallic combination, both 3,4-*syn* **9c** and 3,4-*anti* **9d** were produced in almost similar proportions in all the reactions, irrespective of the olefin geometry in **8**. The preponderance of the 4,5-*anti* products in these reactions suggested that the addition followed the Felkin Anh model.

For the benzylation reaction, the combinations of $Zn/CuCl_2.2H_2O$ and $Zn/FeCl_3$ were unsuccessful. To our delight, the reaction between benzyl bromide and different aldehydes **10a-g** took place successfully with the $Mg/CuCl_2.2H_2O$ combination affording the homobenzylic alcohols **11a-g** in acceptable yields that varied from ~58-74% (**Scheme 5**, **Table 4)**. The protocol was effective for both aliphatic and aromatic aldehydes, although it was slightly slower with aliphatic substrates.

Interestingly, benzylation of **3** produced **12** in better yield (68.4%) and much improved *syn* selectivity [*syn*-**12a**: *anti*-**12b::** 80 : 20] compared to Grignard addition (56% yield and ~1:1 isomeric ratio). The predominant formation of *syn*-**12a** suggested the intermediacy of an α-chelate cyclic transition state that would be possible via the involvement of a nucleophilic attack by the organocopper reagent to **3**.



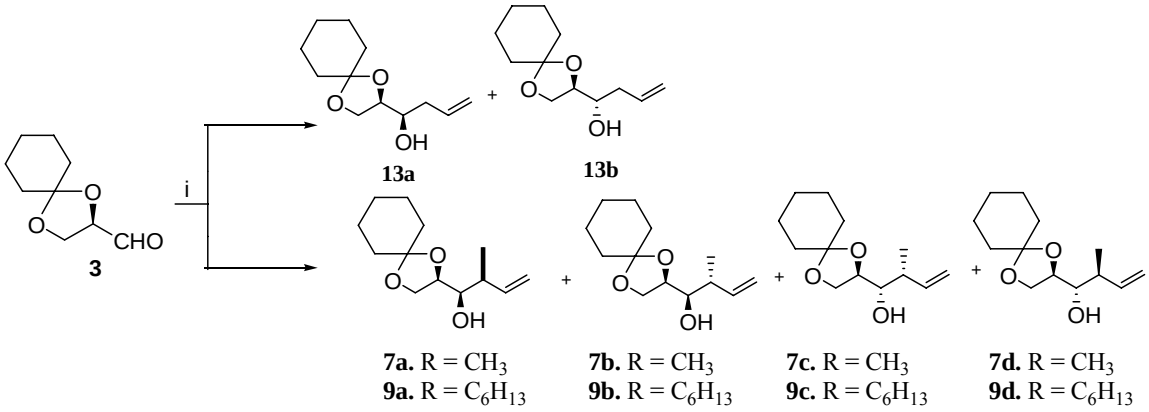
Scheme 5

Table 4. Reaction course of $Mg/CuCl_2.2H_2O$-mediated benzylation of aldehydes[a]

Entry	R	Time (h)	product	Yield (%)
1	*n*-C_6H_{13} (**10a**)	18	**11a**	61.8
2	*n*-C_9H_{19} (**10b**)	16	**11b**	64.4
2	*n*-$C_{13}H_{27}$ (**10c**)	16	**11c**	57.8
4	C_6H_5 (**10d**)	9	**11d**	71.7
5	3-$MeOC_6H_5$ (**10e**)	8	**11e**	73.8
6	4-Et-C_6H_5 (**10f**)	7	**11f**	70.7
7	4-Cl-C_6H_5 (**10g**)	11	**11g**	68.9
8	(*R*)-2,3-Cyclohexylideneglyceral (**3**)[b]	20	**12a + 12b**	68.4

[a]The reactions were carried out at 2 mmol scale. The yields refer to those of isolated pure products. [b]In this case the isomers **12a** and **12b** were isolated in 80:20 ratio.

The diastereoselectivity of the substrate-controlled asymmetric allylation is known to be governed by the nature of the metal and reaction medium.[8] In view of this, in an alternate approach, this aspect was investigated by carrying out the allylation of **3** with different allylic bromides using different metal-solvent combinations. For this, both Grignard and Barbier-type protocols were explored using different metals (Mg, Sb, In, Ga and Bi) and solvents (H_2O, THF, and [bmim][Br]) (**Scheme 6**), and the results are summarized in **Tables 5-7**.



i) Allyl bromide/g-alkylated allyl bromide, metal (Mg/Sb/In/Ga/Bi), solvent (H_2O/THF/[bmim][Br])

Scheme 6

The In-mediated allylation (**Scheme 6**, **Table 5**) produced best yield (78%) of the allylated products (**13a/b**) in [bmim][Br], while excellent *syn*:*anti* diastereoselectivity (2:98) was achieved in THF. Surprisingly, Ga was ineffective in THF and proceeded with modest yield and diastereoselectivity` in H_2O.

Table 5. Reaction course of allylation of **3** using different metals in different solvents[a]

Entry	Allyl bromide (equiv.)	Metal (equiv.)	Solvent	Additive	Time (h)	Yield (%)	**13a:13b**[c]
1	4	In (2.5)	H_2O	--	5	58	24.2 : 75.8
2	3.5	In (2.5)	THF	KI + LiCl	7	69	2.0 : 98.0
3	1.2	In (1.0)	[bmim][Br]	--	3	78	29.8 : 70.2
4	4	Ga (2.5)	H_2O	--	6	48	21.9 : 78.1
5	3.5	Ga (2.5)	THF	KI + LiCl	16	NR	--
6	1.2	Ga (1.0)	[Bmim][Br]	--	4	73	5.0 : 95.0

7	4	Bi (2.5)	H_2O	--	8	62	23.2 : 76.8
8	3.5	Bi (2.5)	THF	KI + LiCl	16	NR	--
9	1.2	Bi (1.0)	[bmim][Br]	--	4	75	31.6 : 68.4

[a]The reactions were carried out at 2 mmol scale. The yields refer to those of isolated pure isomers. The isomeric ratios were determined from the isolated yields. NR: no reaction.

Gratifyingly, the allylation reaction proceeded very well in [bmim][Br] to furnish excellent *anti* selectivity. Bi mediated allylation of **3** in H_2O produced predominantly the *anti* product (**13a**:**13b** = 23.2:76.8) with 62% yield; however the same reaction in [bmim][Br] proceeded with 75% yield of the products.

Table 6. Reaction course of crotylation of 3 using different metals in different solvents[a]

Entry	Crotyl bromide (equiv.)	Metal (equiv.)	Solvent	Additive	Time (h)	Yield (%)	**7b:7c:7d**
1	3.0	Mg (5.0)	Et_2O	--	8	74	38.1:33.2:28.7
2	3.0	Mg (5.0)	THF	--	8	35	29.0:26.1:44.9
3	2.5	Sb (5.0)	H_2O-THF (1:1)	KF (2M)	12	37	30.6:40.8:28.6
4	2.5	Sb (5.0)	H_2O	KF (2M)	14	48	40 :47.7: 12.2
5	3.0	In (5.0)	H_2O	--	14	75	4.0: 52.2:43.8
6	1.2	In (2.0)	H_2O	LiCl+ KI	14	72	3.7: 52.3:44.0
7	3.0	In (5.0)	H_2O	LiCl+ KI	14	72	3.7: 52.3:44.0
8	3.0	In (5.0)	THF	--	12	NR	--
9	4	Ga (2.5)	H_2O	--	20	NR	--

10	3.5	Ga (2.5)	THF	KI+LiCl	10	55	5.0: 35.0: 60.0
11	1.2	In (2.0)	[bmim][Br]	--	4	81	9.3:13.4:77.3
12	1.2	Ga (1.0)	[bmim][Br]	--	5	82	3.0 :5.0 :92.0
13	4.0	Bi (2.5)	H_2O	--	12	67	7.0: 31.0: 62.0
14	3.5	Bi (2.5)	THF	KI+LiCl	20	NR	--
15	1.2	Bi (1.0)	[bmim][Br]	--	3	73	11.4:82.6 :4.0

[a]The reactions were carried out at 2 mmol scale. The yields refer to those of isolated pure isomers. The isomeric ratios were determined from the isolated yields. NR: no reaction.

In-mediated crotylation of **3** (**Scheme 6**, **Table 6**) in H_2O yielded compounds **7c** and **7d** in a ~1:1 ratio. With Mg in ethereal solvents, practically no selectivity was obtained. The use of Sb in aqueous THF or H_2O gave a similar diastereoselectivity, but poor yields. On the other hand, the Ga-mediated reaction in THF produced the products in poor yields even under metal activation and resulted in a modest **7c**/**7d** selectivity. The In-mediated crotylation in [bmim][Br] proceeded with an improved diastereoselectivity for **7d**. Most importantly, while the Ga-mediated crotylation of **3** produced excellent selectivity for **7d**, Bi-mediated crotylation of **3** in [bmim][Br] proceeded with an improved diastereoselectivity for **7c.**

Table 7. Reaction course of **8** with **3** using different metals in different solvents[a]

Entry	1-Bromo-2-nonene(**8**) (equiv.)	Metal (equiv.)	Solvent	Additive	Time (h)	Yield (%)	**9b:9c:9d**
1	4	In (2.5)	H_2O	--	5	58	3.1:35.0:61.9
2	3.5	In (2.5)	THF	KI + LiCl	16	NR	--

3	1.2	In (1.0)	[bmim][Br]	--	6	78	11.0:42.0: 37.0
4.	4	Ga (2.5)	H_2O	KI + LiCl, sonication	16	NR	--
5	3.5	Ga (2.5)	THF	KI + LiCl, sonication	16	NR	--
6	1.2	Ga (1.0)	[bmim][Br]	--	7	79	3.4:44.5:52.1
7.	3.5	Bi (2.5)	H_2O	KI + LiCl	20	65	7.2:31.8:61.0
8	3.0	Bi (2.0)	THF	KI + LiCl	12	43	12.0:22.0:66.0
9	1.5	Bi (1.2)	[Bmim][Br]	--	--	72	5.0:35.4:59.6

[a]The reactions were carried out at 2 mmol scale. The yields refer to those of isolated pure isomers. The isomeric ratios were determined from the isolated yields. NR: no reaction.

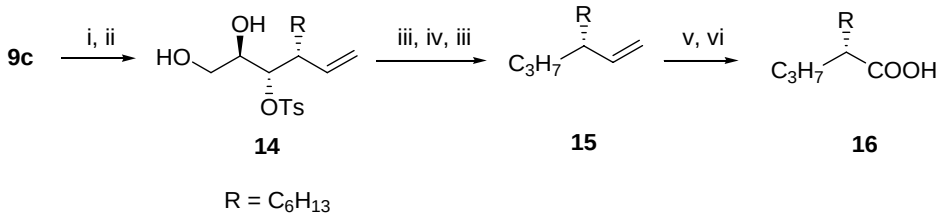
The reaction of **8** with **3** (**Scheme 6**, **Table 7**) using Bi in H_2O, THF and [bmim][Br]proceeded with modest diastereoselectivity, with the generation of *anti-anti* isomer **9d** as the major diastereoisomer in all the cases. All these reactions could be accomplished much faster in [bmim][Br] with almost stoichiometric amounts of the reagents. In other solvents, the results were significantly inferior, even with a large excess of the reagents and prolonged reaction time.

Chapter IV: Asymmetric synthesis of some bio-active organic compounds

In this chapter, the syntheses of i) (*R*)-arundic acid (**16**), a novel neuroprotective agent against Alzheimer disease;[9] ii) the octadienamide unit of the cryptophycins (**22**), potent, tumor-selective tubulin binding antimitotic agents with excellent activity against

multidrug-resistant (MDR) cancer cells;[10] iii) 3'-C-branched nucleoside analogue (**25**), the building block for the 3'-C-modified oligonucleotides with better enzymatic stability and membrane permeability;[11] iv) 2(*S*)-[1(*S*)-azido-2-phenyl]oxirane (**27**), a versatile synthon of potent and selective inhibitors of HIV-1 protease;[12] and v) *trans*-oak lactone (**32**), a 4,5-disubstituted γ-lactone, produced during fermentation and storage of alcoholic beverages in oak barrels[13] are described.

For the synthesis of **16** (**Scheme 7**), the alcohol **9c** was converted to **14** via tosylation followed by hydrolysis of its acetal function. Its reductive detosylation followed by dimesylation of both the hydroxyl groups and subsequent treatment with $LiAlH_4$ produced the alkene **15**. Oxidative ozonolysis of **15**, alkaline hydrolysis of the resultant ester and acidification furnished the title compound **16** in good yield.

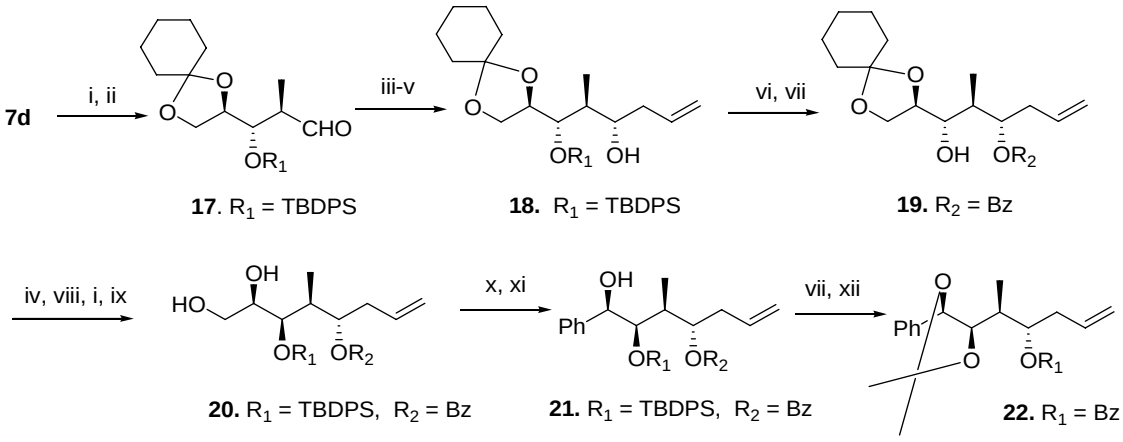


i) p-TsCl, pyridine, 25 ^oC ; ii) Aqueous CF_3CO_2H, H_2O, 0 ^oC; iii) $LiAlH_4$, △ ,THF ; iv) MsCl, Et_3N, CH_2Cl_2, 25 ^oC; v) O_3, MeOH, NaOH, -15 ^oC; vi) a) NaOH, MeOH; b) aqueous 2 N HCl, 25 ^oC.

Scheme 7

For the synthesis of **22** (**Scheme 8**), a more efficient approach involving prior introduction of the chiral diol unit for generating the required epoxide pharmacophore was followed, instead of a late-stage non-selective epoxidation. Thus, the alcohol **7d**, obtained from the Ga mediated crotylation of **3** in [bmim][Br], was converted to the aldehyde **17** via silylation and reductive ozonolysis. Its Zn-mediated allylation furnished a non-separable diastereomeric mixture of the homoallylic alcohol **18**, which on PCC oxidation

and $NaBH_4$ reduction afforded the stereochemically pure 1,3-*syn* isomer of **18.** The bulky protecting group on the hydroxyl moeity was instrumental in controlling the 1,3-asymmetric induction. Benzoylation of the carbinol function of **18**, followed by desilylation furnished **19**. This was converted to the 1,3-anti diol **19** following a oxidation-reduction protocol (using PCC as the oxidant and K-selectride® as the reductant). Acid catalyzed deketalization of **19** furnished the diol **20**. Cleavage of its α-glycol unit with $NaIO_4$ followed by reaction of the resultant aldehyde with PhMgBr furnished the required alcohol **21** with excellent enantioselectivity (ee 95%). Its desilylation, conversion into acetonide and debenzoylation gave the target synthon **22.**

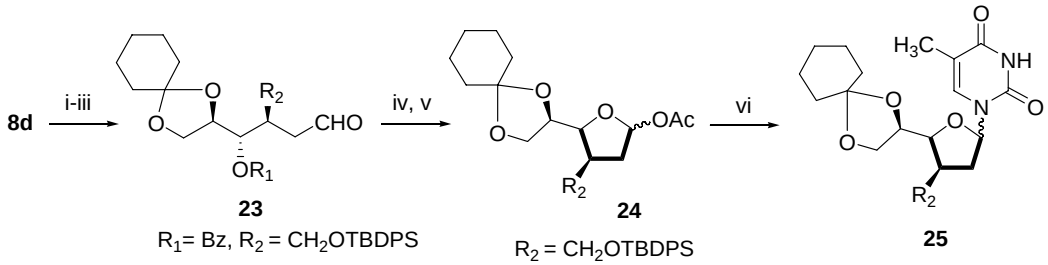


i) TBDPSCl, Imidazole, CH_2Cl_2,25 ^oC; ii) O_3, CH_2Cl_2, -78 ^0C; PPh_3; iii) Allyl bromide, Zn, THF, Satd aqueous NH_4Cl; iv) PCC, CH_2Cl_2, 25 ^0C; v) $NaBH_4$, MeOH, O^0C; vi) BzCN, Et_3N, 0^0C; vii) $^nBu_4N^+F^-$, THF, 0^0C; viii) K-Selectride$^{(R)}$, THF, -78^0C; ix) Aqueous CF_3CO_2H, CH_2Cl_2, O^0C; x) $NaIO_4$, 25 ^0C; xi) C_6H_5MgBr, THF, -20^0C; xii) 2,2'-dimethoxypropane, PPTS, rt.

Scheme 8

For the synthesis of **25** (**Scheme 9**), compound **8d** was benzoylated, subjected to hydroboration-oxidation of its terminal olefin moiety, and the resultant alcohol oxidized with PCC to yield the aldehyde **23**. This on debenzoylation under alkaline conditions

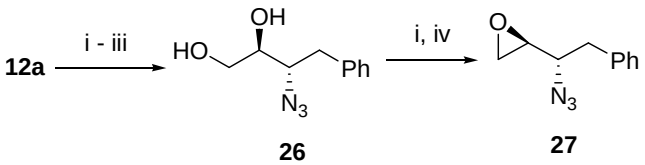
directly afforded the furanose, which was acetylated to produce the acetate derivative **24**. Finally, coupling of **24** with silylated thymine gave the 3'-C branched nucleoside **25**.



i) BzCl, pyridine, 0 ^{o}C; ii) Me_2S-BH_3, hexane, H_2O_2-NaOH; iii) PCC, CH_2Cl_2; iv) K_2CO_3, MeOH; v) Ac_2O, pyridine; vi) Thymine, HMDS, $(NH4)_2SO_4$, TMSOTf, CH_2Cl_2.

Scheme 9

The synthesis of **27** (**Scheme 10**) was accomplished starting from *syn*-**12a**, which on tosylation, acid-catalyzed deketalization and subsequent reaction with NaN_3 gave the azidodiol **26**. Regio-selective monotosyalation of its primary hydroxyl function and base treatment of the resultant tosylate furnished the target azido epoxide **27**.

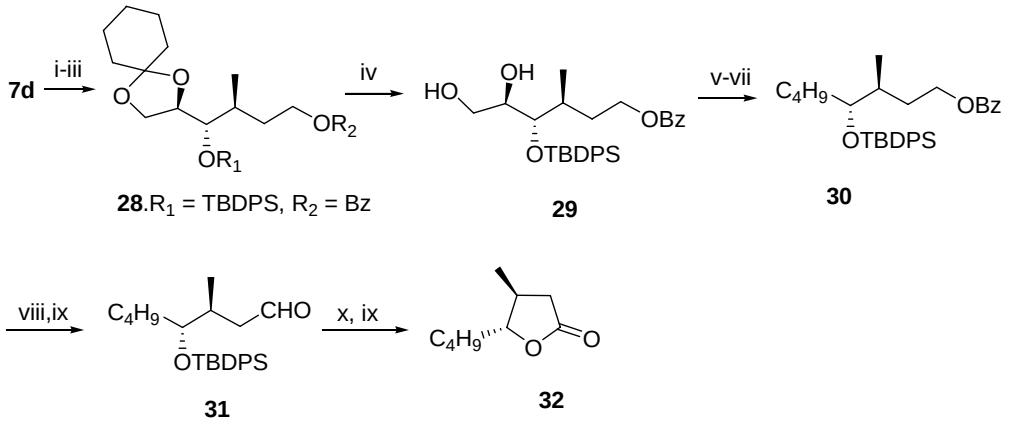


i) p-TsCl, pyridine, 0 ^{o}C; ii) NaN_3, DMF, $\triangle$; iii) Aqueous CF_3CO_2H, CH_2Cl_2, 0 ^{o}C; iv) K_2CO_3, MeOH, 25 ^{o}C.

Scheme 10

For the synthesis of **32** (**Scheme 11**), **7d** was silylated, subjected to borane-mediated hydroxylation at the olefin moiety, and subsequently benzoylated to afford **28**. This was further deketalised in acidic condition to afford diol **29**. $NaIO_4$ cleavage of **29**, Wittig olefination of the resulting aldehyde, and catalytic hydrogenation yielded **30**. Alkaline hydrolysis of the benzoate **30** and PCC oxidation of the product alcohol yielded

the aldehyde **31**. Finally, desilylation of **31** afforded the lactol which on oxidation produced our desired *trans*-oak lactone (**32)**.



28.R_1 = TBDPS, R_2 = Bz

29

30

31

32

i) TBDPSCl, Imidazole, CH_2Cl_2, 25 ^oC; ii)$Me_2S.\ BH_3$, hexane, NaOH-H_2O_2; iii) BzCN, pyridine, CH_2Cl_2, 0 ^oC; iv) aqueous CF_3CO_2H, CH_2Cl_2, 0 ^oC; v) $NaIO_4$, 25 ^oC; vi) n-$C_3H_7PPh_3^+Br^-$, n-BuLi, THF, -60 ^oC; vii) 10% Pd-C, H_2 ,EtOH, 0 ^oC; viii) K_2CO_3, MeOH, 25 ^oC; ix) PCC, CH_2Cl_2, 25 ^oC; x) $^nBuN^+F^-$, THF.

Scheme 11

References

1. Stephenson, G. R. *Advanced Asymmetric Synthesis*. Chapman and Hall, 1996.
2. (a) Miller, S.J.; Blackwell, H.E.; Grubbs, R.H. *J. Am. Chem. Soc.* **1996**, *118*, 9606-9614. (b) Loh. T.P.; Hu. Q.Y.; Ma. L.T. *J. Am. Chem. Soc.* **2001**, *123*, 2450-2451. (c) Adam. W.; Saha-Moller, C.R.; Schmidt, K.S. *J. Org. Chem*. **2001**, *66*, 7365-7371.
3. Lin, G.Q.; Li, Y-M.; Chan, A.S.C. *Principles and Applications of Asymmetric Synthesis*, 1st ed.; Wiley, John & Sons, 2001.
4. (a) Sui, M.; Panek, J.S. *Org. Lett*. **2001**, *3*, 2439-2442. (b) Hirashita, T.; Kamei, T.; Satake, M.; Horie, T.; Shimizu, H.; Araki, S. *Org. Biomol. Chem*. **2003**, *1*, 3799-3803. (c) Chemler, S.R..; Roush, W.R. *J. Org. Chem*. **2003**, *68*, 1319-1333.
5. (a) Yamamoto, Y.; Asao, N. *Chem Rev*. **1993**, *93*, 2207-2293. (b) McCluskey, A. *Green Chem*. **1999**, 167-168. (c) Fukama, T.; Lock, S.; Miyoshi, N.; Wada, M. *Chem. Lett.* **2002**, 376-377.
6. (a) Welton. T. *Chem. Rev*. **1999**, *99*, 2071-2083. (b) Wasserscheid, P.; Kiem, W. *Angew. Chem. Int. Ed*. **2000**, *39*, 3772-3789.
7. (a) Chattopadhyay, A.; Mamdapur, V. R. *J Org. Chem*. **1995**, *60*, 585-587. (b) Chattopadhyay, A. *J Org. Chem*. **1996**, *61*, 6104-6107.
8. (a) Klemeyer, H. J.; Paquette, L. A. *J Org. Chem*. **1994**, *59*, 7924-7927. (b) Lindsay, H. A.; Salisbury, C. L.; Cordes, W.; McIntosh, M. C. *Org. Lett*. **2001**, *3*, 4007-4010.
9. (a) Sorbera, l. A.; Castaner, J.; Castaner, R. M. *Drugs Future* 2004, *29*, 441-448. (b) Pelotier, B.; holmes, T.; Piva, O. *Tetrahedron Asymmetry* 2005, *16*, 1513-1520.
10. (a) Barrow, R.; Hemscheidt, T.; Paik, S.;Liang, J.; Moore, R.E.; Tius, M.A. *J. Am. Chem. Soc*. **1995**, *117*, 2479-2490. (b) Shih, C.; Teicher, B.A. *Curr. Pharm. Des*.

2001, *7*, 1259-1276. (c) Eissler, S.; Nahrwold, M.; Neumann, B.; Stammler, H-G.; Sewald, N. *Org. Lett*. **2007,** *9*, 817-819.

11. (a) Heinemann, U.; Rudolph, L. N.; Alings, C.; Morr, M.; Heikens, W.; Frank, R.; Blocker, H. *Nucleic Acids Res.* **1991**, *19*, 427-433. (b) Hossain, N.; Plavec, J.; Chattopadhyay, J. *Tetrahedron* **1994**, *50*, 4167-4178. (c) Robins, M. J.; Doboszewski, B.; Timoshchuk, V.A.; Peterson, M. A. *J. Org. Chem*. **2000**, *65*, 2939-2945.
12. (a) S. Park, S. Lee, H-J. Kang, *Bull Korean Chem. Soc*. **2008**, *29*, 1073-1079. (b) A. K. Ghosh, S. P. McKee, H. Y. Lee, W. J. Thompson, *J. Chem. Soc. Chem. Commun*. **1992**, 273-274. (c) B. M. Kim, S. J. Bae, S. M. So, H. T. Yoo, S. K. Chang, J. H. Lee, J. Kang, *Org. Lett.* **2001**, *3*, 2349-2351.
13. (a) Ghosh, M.; Bose, S.; Ghosh, S. *Tetrahedron Letters* **2008**, *49*, 5424-5426, and references cited therein. (b) Suzuki, K.; Shoji, M.; Kobayashi, E.; Inomata, K. *Tetrahedron Asymm.* **2001**, *12*, 2789-2792. (c) Schlapbach, A.; Hoffman, R. W.; *Eur. J. Org. Chem.* **2001**, 323-328.

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CHAPTER I

INTRODUCTION

I.1 PREAMBLE

Demand for speciality chemicals that are not only target and purpose-specific, but also bear extremely complex structure, has increased due to the recent advances in biological and material sciences. Organic synthesis plays a pivotal role in this respect. Apart from synthesizing the target compounds in sufficient amounts, it also assists in developing tailored and functional entities, with improved molecular properties. Although synthetic chemistry has advanced a long way since its inception, it is still facing challenge towards developing an ideal atom-economic route for a particular synthesis, while generating minimum or no waste.

An ideal (the ultimate practical) synthesis is generally regarded as one in which the target molecule (natural or designed) is prepared from readily available, inexpensive starting materials in one simple, safe, environmentally acceptable, and resource-effective operation that proceeds quickly and in quantitative yield. Because most syntheses proceed from simple starting materials to complex targets, there are two general ways of approaching this ideal synthesis (i.e., achieving maximum relevant complexity increase while minimizing step count): the use of strategy-level reactions (e.g., the Diels−Alder reaction) that allow in one step for a great increase in target-relevant complexity or the use of multistep processes (e.g., polydirectional synthesis, tandem, serial, cascade, domino, and homo- and heterogenerative sequences) that produce similar or greater complexity changes in one operation. The design and development of new reactions and reaction sequences that allow for a great increase in target-relevant complexity are clearly essential for progress toward the next level of sophistication in organic synthesis.[1]

A given synthetic protocol becomes reliable only when it can be employed to achieve a given organic transformation efficiently and cleanly with no undesired

conversions occurring under the chosen conditions. Even if this condition is met, the problems associated with this are far from being fully solved. Frequently a substrate may have multiple functional groups that react with the reagents used. Hence, the development of efficient catalytic system for selective organic transformation is currently one of the challenging tasks in synthetic organic chemistry.[2] This is generally achieved using metal complexes and/ or biocatalysts that ensures higher degree of selectivity, better efficacy, and thus, fulfills the criteria of ideal organic synthesis.

Of late, there is a paradigm shift of the perspectives of organic synthesis. For example, the stereoisomers of a compound are now considered as separate molecular entities with specific properties. Hence there is a great demand for developing highly stereoselective asymmetric routes for the synthesis of the target compounds. Thus, selectivity has become the keyword of modern organic synthesis as it provides solutions to the above problems, besides furnishing the so-called "tailored molecules" in the most efficient way.

Given the importance of stereoselectivity in organic synthesis, a brief account of stereoselective asymmetric synthesis is provided in this chapter. The present work was mainly focused on the development of operationally simple and practically viable asymmetric strategies that include some metal-mediated routes and non-conventional protocols, and their possible application to the homologation of (*D*)-mannitol derived (*R*) -2,3-cyclohexylideneglyceraldehyde (**1**). [3]

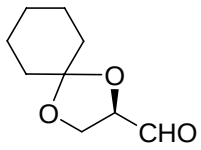


Fig. I.1.1. Structure of (*R*) -2,3-cyclohexylideneglyceraldehyde (1)

I.2 INTRODUCTION TO CHIRALITY AND ASYMMETRIC SYNTHESIS

The demand for chiral compounds, often as single enantiomers, has escalated sharply in recent years, driven particularly not only by the demands of the pharmaceutical industry, but also by other applications, including agricultural chemicals, flavors, fragrances, and materials, especially in chiral polymers and liquid crystals. Two-thirds of prescription drugs are chiral, with the majority of new chiral drugs being single enantiomers. This widespread demand for enantiomerically pure chiral compounds has stimulated intensive research to develop improved methods for synthesizing such compounds. In addition to this, enantiomerically pure compounds are of most importance because of the fact that two enantiomers are considered different when screened for pharmacological activity,[4] and in some cases, it could mean between life and death if the manufactured drug is not enantiomerically pure. There are many examples of pharmaceutical drugs,[5] agrochemicals[6] and other chemicals, where the desired biological property is very much related to the absolute configuration. Some representative examples are shown in **Fig. I.2.1**.

The recognition events in biology and the action of drugs that intervene in these events almost always involve the molecular recognition of a biologically active molecule by a chiral non-racemic receptor structure. The two enantiomers of a drug molecule cannot be expected to bind equally well to the receptor and so should cause different biological responses. Thus, only one enantiomer of the drugs is often endowed with the desired biological activity, while the other enantiomer is inactive or possesses a different activity and may cause toxic side effects. For example, in the series of eight possible stereoisomers of dibromovinyl-2,2-dimethylcyclopropane carboxylic esters (pyrethroid insecticides) the

(*R,R,S)*-isomer of deltametrine (**2**) is the most powerful insecticide, while its (*S*)-enantiomer is inactive.[7] In food additives, (*S,S)*-aspartame (**3**) is an artificial sweetener, whereas its antipode tastes bitter. In the case of propanolol (**4**), the (*S*) enantiomer is a β-blocker, whilst the (*R*) form possesses contraceptive activity.

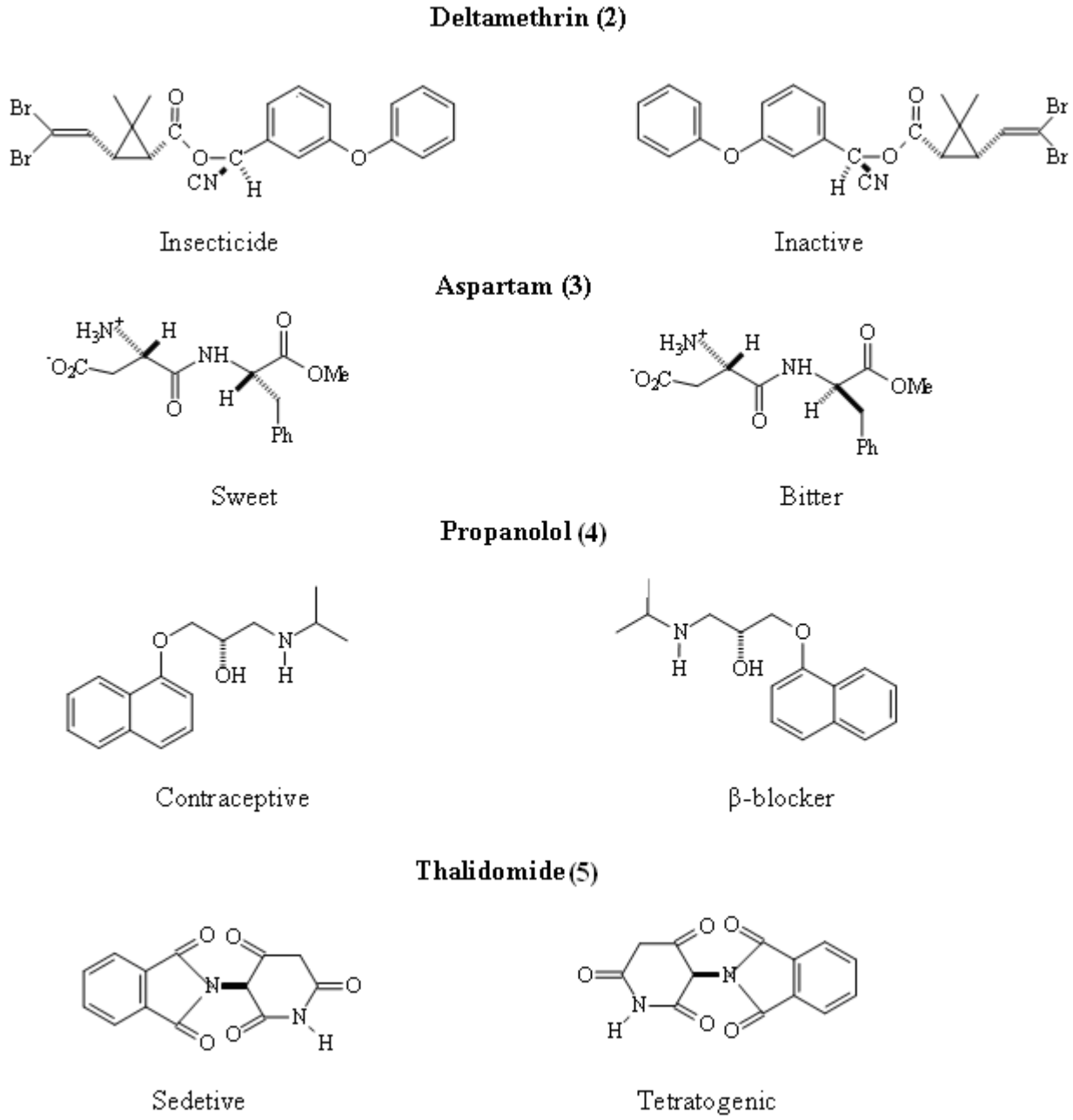


Fig. I.2.1. Chiral compounds having different biological activities

The most dramatic example in this aspect is the well known case of thalidomide (**5**). Its (*R*)-enantiomer is sedative and was used for morning sickness of pregnant women. However, the (*S*)-enantiomer was later found to be teratogenic causing wide spread birth defects. This tragedy really emphasized the importance of synthesis of enantiomerically pure compounds. From the viewpoint of drug delivery, the potency of the active enantiomer compared with racemic active and inactive enantiomers is such that the dose is reduced by half. Also the production of inert isomer represents a waste of starting materials and resources, and hence prepataion of a pure enantiomer is advantageous from economic point of view. Moreover, the problems that arise with optically impure pharmaceuticals, even when employed at high enantiomeric excess (ee), are no less significant. Enantiomers may also be competitive antagonists. This is the case for (+)- and (-)-isopropylnoradrenaline acting on the α_1-adrenergic receptors in rats.[8] A further possibility is that the non-beneficial enantiomer may preferentially participate in biotoxication. An example is deprenyl, an antidepressant and anti-Parkinson's disease drug, for which the less active (*S*) isomer is converted into (*S*)-(+)-amphetamine, which causes undesired CNS stimulation.[9]

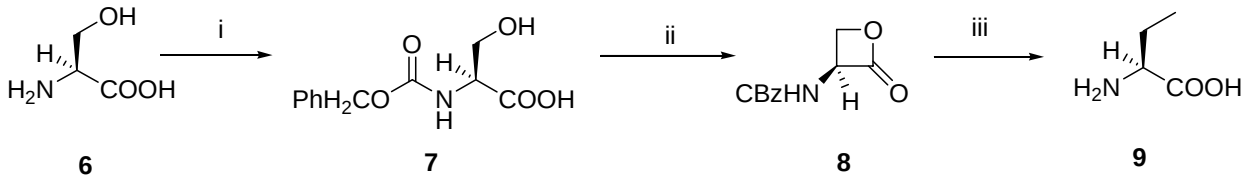
From the foregoing the importance of chirality especially on drugs, agrochemicals, perfumeries and food-additives are obvious. In view of this, development of enantiomeric synthesis has assumed great significance. This is especially most important for the pharmaceutical industries, since the enantiomers of chiral drugs are considered as two different compounds. Enantiomeric synthesis of target compounds can be accomplished using different strategies, which are briefly presented below.

I.3. STRATEGIES OF ENANTIOMERIC SYNTHESIS

Before considering in detail the different approaches to asymmetric synthesis, it is worth looking briefly at all the methods available to obtain chiral compounds in a non-racemic form.

a) Use of naturally occurring chiral compounds as building blocks.[10]

This method actually does not involve any formation of new stereogenic centres, instead the stereogenic centres are derived from the starting chiral material. Nature provides a large repertoire of optically active compounds, the so called chiral pool materials. The most commonly used natural compounds are the amino acids, monoterpenes and sugars, the latter being most versatile. However, the steroids, alkaloids and triterpenoids, omnipresent in various plants are hardly of use in such chiral pool synthesis. This strategy is especially helpful if the desired molecule bears a great resemblance to cheap enantiopure natural products. Otherwise, a long, tortuous synthesis involving many steps with attendant losses in yield may be required. At times, it may be difficult to find a suitable enantiopure starting material; other techniques may prove more fruitful. Also, utmost care needs to be taken so that there is no chance of racemisation during the reaction sequence. A well known example[11] of such a synthetic approach is the synthesis of unnatural amino acids from (*S*)-serine (**6**), which is converted to its N-protected analogue **7**. Under Mitsonobu conditions, the primary hydroxyl is displaced giving compound **8.** This strained β-lactone undergoes S_N2 ring-opening when treated with a methyl Grignard reagent in the presence of Cu(I) salts. To complete the synthesis the CBz group is removed to give the enantiomerically pure product **9** (**Scheme I.3.1**).



6 **7** **8** **9**

(i) $PhCH_2OCOCl$, 2 N NaOH, THF, 5 ^oC; (ii) (a) PPh_3, $EtO_2CN{=}NCO_2Et$, MeCN/ THF (9:1), -55 ^oC ; (b) $PhCH_2OCOCl$, Na_2CO_3, H_2O, 0 ^oC.; (iii) (a) $Me_2Cu(CN)Li_2$, THF, -78 ^oC to -23 ^oC; (b) H_2, Pd-C.

Scheme I.3.1

b) Resolution.

This is the classical method[12] in which the racemic compound is derivatised by reaction with a naturally occurring enantiomerically pure compound, so that the resulting diastreomeric compounds may be separated most commonly by crystallization, chromatography or using other physical properties; and then separately treated to liberate the two enantiomers. The resolving agent is recovered unchanged after this procedure and can be reused repeatedly. For example, many organic acids were resolved using bases such as quinine, brucine etc. Resolution of enantiomers may also be performed by the covalent attachment of an enantiomerically pure compound, more commonly used as a chiral auxiliary e.g. (+)-(*R*,*R*)-2,3-butanediol, followed by separation of the diastereomers.[13] Reliable resolution methods have been developed for many other types of compounds and these have provided most cost-effective way to obtain enantiomerically pure compounds on a large scale.

c) Kinetic resolution with biochemical and chemical protocols.

Another important strategy in the preparation of enantiomerically pure compounds is the kinetic resolution of racemic substrates by enzymatic or chemical protocols. This strategy is based on the fact that the enantiomeric compounds often show different reaction rates under a given condition. Thus, by proper choice of the reagents/ conditions, a very effective means of separating the enantiomers can, in principle, be obtained. Especially enzymes are nowadays accepted as useful tools in organic synthesis as they catalyze many reactions under very mild conditions, and show high reaction and enantio-selectivity as well as substrate specificity. Because many important enzymes are readily available - for example, esterases ($CO_2R \rightarrow CO_2H$), amidases ($CONHR \rightarrow CO_2H$), hydrogenases ($C{=}O \rightarrow CHOH$) and aldolases ($RCHO \rightarrow RCH(OH)CH_2COR'$), biocatalysis plays a significant role in the development of asymmetric synthesis.[14a] It is also possible to rationalize the specificity of an enzyme-catalyzed reaction, when the enzyme's active site structure is known. In these cases, it is usually found that the enzyme binds the substrate *via* hydrogen bonding, electrostatic or polarization forces or Van der Waals interactions. The enzymatic reactions can be carried out in aqueous and organic media.

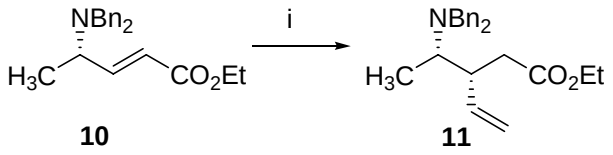
An offshoot in the age-old method for the preparation of enantiomerically pure compounds is fermentation which is defined as the transformation mediated by growing microorganisms under anaerobic conditions. Various speciality chemicals like the β-lactam antibiotics, vitamins and other pharmaceutical compounds are mostly prepared by this route. A major drawback of enzymatic and fermentation processes is that only one of the two possible enantiomers can be prepared by these. Several reviews and books on the application of biocatalysts in organic synthesis have appeared.[14a,b]

Methods of Asymmetric Synthesis:[15] In 1894, Emil Fischer laid the foundation of modern asymmetric synthesis by homologation of sugars via cyanohydrins reaction.[16] An asymmetric reaction is defined as a reaction in which a prochiral unit in an substrate molecule is converted to a chiral unit such that the possible stereoisomers are produced in unequal amounts. The reactants may be chiral reagents, solvents, catalysts or physical forces such as circularly polarized light. The stereoselectivity is primarily influenced by the chiral catalyst, reagent, or auxiliary, despite any stereogenic elements that may be present in the substrate. The efficacy and success of an asymmetric reaction is denoted by enantiomeric excess (ee) of the desired enantiomer, which is defined as the absolute difference between the mole fractions of each enantiomer and is expressed in percentage. A common strategy to achieve efficient asymmetric synthesis is to use a chiral auxiliary in proximity to the location where the new stereogenic center is to be introduced. When the reaction proceeds, the configuration of the new stereogenic centers being formed are influenced by the chirality of the chiral reactant; the chiral reactant "induces" chirality at the newly formed stereogenic centers. In some cases, a chiral solvent or a chiral catalyst is used to induce chirality. In all cases, the existing chiral entity in the reaction (reactant or solvent or catalyst) is involved in the transition state, resulting in diastereomeric transition states of which the lower-energy one is favored. The known methods can be conveniently divided into four major classes, depending on how this influence is exerted. The classes are as follows.

a) Substrate-Controlled methods.

In this method, a chiral substrate is reacted with an achiral reagent so that the reaction is directed intramolecularly by a stereogenic unit already present in the substrate.

The new stereogenic centre formed at a diastereotopic site is controlled by the nearby stereogenic unit. A good example is provided by the conjugate addition of enoate **10** in presence of vinylmagnesium bromide and CuI, leading to adduct **11** in moderate yield (**Scheme I.3.2**).[17]



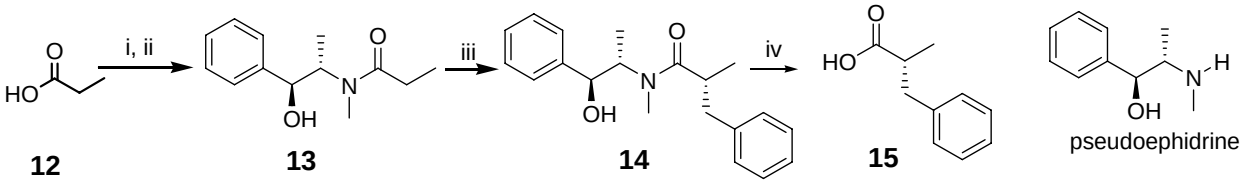
i) vinylmagnesium bromide, CuI, TMSCl, HMPA, THF, -78 ^{o}C.

Scheme I.3.2

A disadvantage of this method is based on the fact that this method deals with mere addition of an additional stereogenic unit to an already enentiomerically pure substrate, and hence an enantiomerically pure substrate is necessary.

b) Auxilliary controlled methods.

In this method, the 'chiral auxiliary' is deliberately attached to an achiral substrate in order to direct the reaction of an incoming group and can be removed once it has served its purpose. This approach leads to the formation of a mixture of diastereomers because of the presence of an additional stereogenic centre of the auxiliary. After removing the auxiliary, the final product is obtained in very high enantiomeric excess. An example is the diastereoselective alkylation of propionic acid (**12**) via its amide formation with ([1*S*, 2*S*]-(+))-Pseudoephedrine to give **15** in >97% ee (**Scheme I.3.3**). [18]

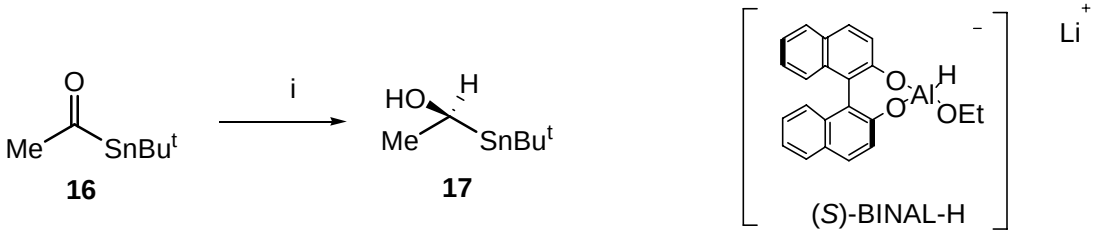


(i) $SOCl_2$, pyridine; (ii) pseudoephidrine, reflux; (iii) $PhCH_2Br$, LDA, LiCl, THF, 0 ^oC; (iv) H_2SO_4, dioxane.

Scheme I.3.3

c) Reagent controlled methods.

This method involves a direct conversion of an achiral substrate to the chiral product by use of a chiral reagent in which the control of the reaction is intermolecular. However, the range of reactions for which effective chiral reagents exist is somewhat limited. An example is provided by the asymmetric reduction of **16** in presence of (*S*)-BINAL-H to prepare enantiomerically enriched **17** in 94% ee (**Scheme I.3.4**).[19]



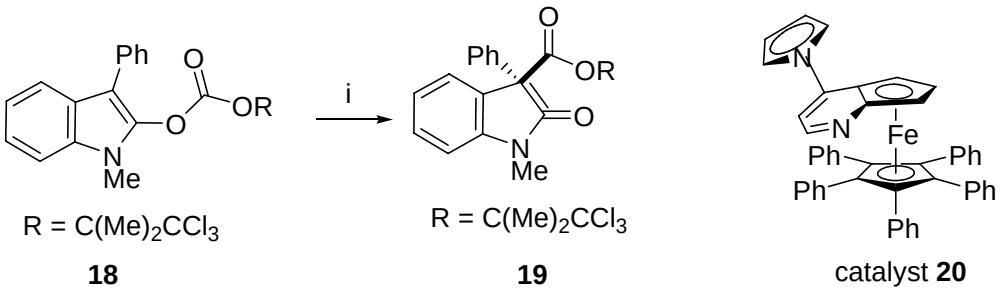
(i) (*S*)-BINAL-H, THF, -78 ^oC

Scheme I.3.4

d) Catalyst controlled methods.

Asymmetric catalysis, in which each molecule of chiral catalyst, by virtue of being continually regenerated, can yield many molecules of chiral product, and so has significant potential advantages over other procedures. Indeed, enantiomerically pure compounds are produced in nature by such chirality transfer from enzymic catalysts. However, it was only

relatively recently that such asymmetric catalysis, with enantiomeric excesses approaching 100%, was achieved with synthetic catalysts. This method involves the conversion of an achiral substrate to a chiral product with an chiral catalyst. The control of the reaction is also intermolecular. For example, oxindole **19** was formed in high enantiopurity from 2-acyloxindole precursor **18** (**Scheme I.3.5**) by using planar chiral 4-aminopyridine catalyst **20**.[20]



R = $C(Me)_2CCl_3$ **18**

R = $C(Me)_2CCl_3$ **19**

catalyst **20**

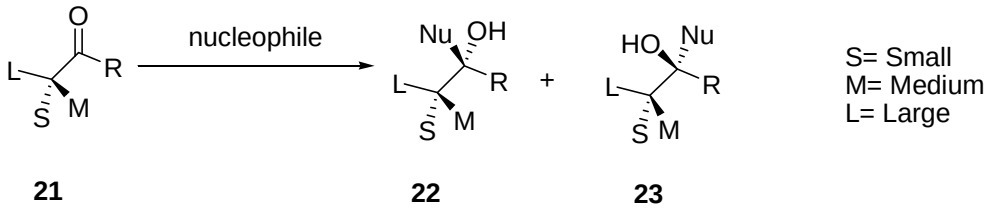
(i) 5 mol% catalyst **20**, CH_2Cl_2, 35 ^oC.

Scheme I.3.5

Chemical catalysts have some advantages over bio-catalysts. First of all, chemical catalysts can promote reactions that are not known to occur in nature. Secondly, the chirality of a chemical catalyst can be changed relatively easily by using the antipode as the starting material in its preparation. In most cases, essential chiral intermediates are taken from the 'chiral pool' and often both enantiomers are available. Thirdly, the substrates that are not accepted in enzymatic reactions may be transformed using chemical catalysts. In many cases, high substrate concentrations can be used and separation and recovery of the products are easy, compared to biocatalytic reactions. Finally, most of these catalysts have a greater stability than enzymes, which are often very sensitive to heat and pH of the medium.

Models for Asymmetric Synthesis.[21] In asymmetric synthesis, when a new chiral centre is created in a molecule already containing one or more stereocentres, two diastereomers are formed in unequal amounts. The existing chiral centre (or centres) is said to bring about asymmetric induction. Such an influence of a chiral centre on a prochiral reaction centre within the same molecule is one of the fundamental stereochemical issues addressed in organic synthesis. Ever since D.J.Cram[22] outlined almost 60 years ago an edifice to explain the steereoselectivity in the addition of nucleophiles to α-chiral carbonyl compounds, which became known as the Cram's rule, a fabric was created which proved to be most fruitful in understanding, predicting, and controlling diastereoselectivity induced by a remote stereocenter. Since it can be expected that a chiral center being in close proximity to a prochiral reaction center will exhibit the strongest influence, there is an overwhelming number of examples for 1,2-induction. Consequently, several models have been proposed to explain such a diastereoselectivity. The fundamental models such as Cram's model and Felkin-Anh model can be found today in almost every organic chemistry textbook. Nevertheless, the underlying concepts still form the basis for further modifications and extensions are applied to the current research problems.

The addition of nucleophiles to α-chiral carbonyl compounds **21** can lead to two diastereomeric products **22** and **23**.

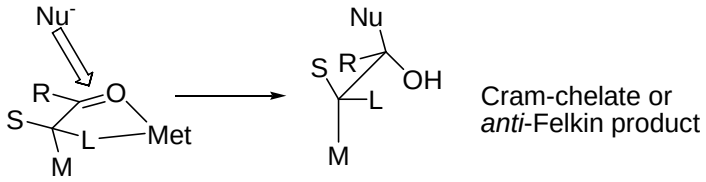


21 **22** **23**

Scheme I.3.6

Cram rule actually allows the analysis of the stereochemical outcome of such a reaction. On the basis of the nature of the substituents at the chiral centre, two different conformations of the substrate **21** were proposed together with the favored trajectory of the attacking nucleophile to explain the preferential formation of **22** and **23**, respectively (**Scheme I.3.6**).

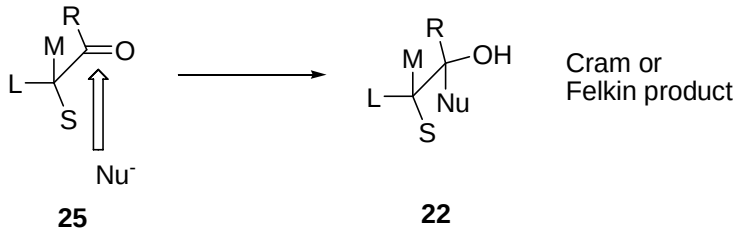
a) Cram-chelate rule :[23] If chelation between the carbonyl group and one of the substituents of the α-stereocentre facilitated by a metal cation can occur, the transition state is locked into the conformation **24**, leading to **23** as the major product (**Scheme I.3.7**).



24 **23**

Scheme I.3.7

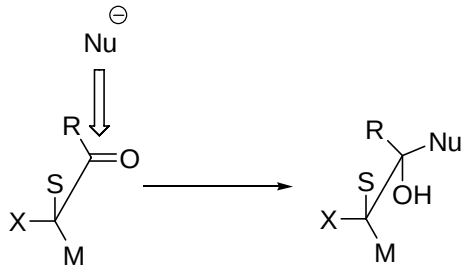
***b) Cram rule*:**[22b] If chelation can not occur, **25** was proposed to be the preferred reactive conformation based on steric reasons. Consequently, L is oriented *anti* to the carbonyl group. A nucleophile will now preferably attack from side of S, leading to **22** as the major product (**Scheme I.3.8**).



25 **22**

Scheme I.3.8

If a strongly electronegative group, *e. g*., a halogen atom is present α to the C=O group, a *dipolar* model is suggested to predict the stereochemical outcome of the reaction. The dipoles of the carbonyl bond and the C-X bond oppose each other and so they are placed *anti* as in the model **26** so as to minimize the dipolar repulsion. The nucleophile adds from the side of S giving the major product as shown in **Scheme I.3.9**.



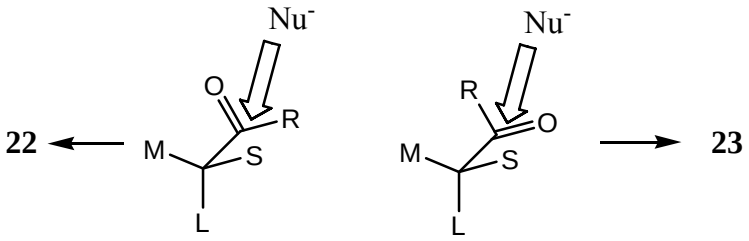
26 **27**

Scheme I.3.9

Desptite correctly predicting the stereochemical course of the reactions, the Cram's models often fails to give a quantitative assessment of the asymmetric induction in terms of steric interactions. A few alternative models have been proposed to predict the stereochemical outcome of the designated reactions in more quantitative terms. Of these the Felkin-Anh model, discussed below has gained consensus.

In Felkin-Anh model,[24] In this model, two reactive conformations **28** and **29** (**Scheme I.3.10**) have been considered in which either the largest (L) or the most electron withdrawing group (which provides the greatest σ*-π* overlap with the carbonyl π* orbital, allowing delocalization of the electron density by hyperconjugation from the reaction centre towards L) at C_α is placed at right angle to the C=O double bond. Between the two, the first with M opposing C=O and S gauche to R is usually preferred. The non-bonded interactions which involve R and S (rather than R and M as in **29**) are thus minimized. The model predicts the same stereochemistry as Cram's, but provides a more

quantitative assessment of the 1,2-asymmetric induction. . Moreover the reaction pathway is advantageous compared to the one starting from the Cram configuration since it directly leads to a staggered conformation in the product.

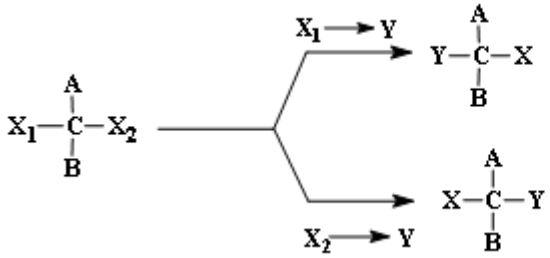


Scheme I.3.10

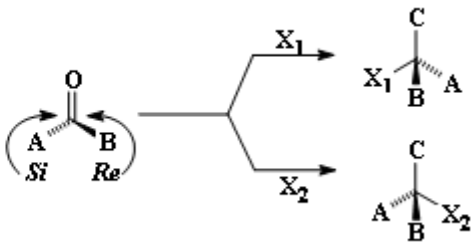
Many addition recations to carbonyl compounds proceed via cyclic six-membered transition states. The course of such reactions can be understood by the Zimmerman-Traxler model,[25] which requires the arrangement of the reaction partners in a chair like transition state, placing the large substituents equatorially, if possible. This model is usually strictly followed in ene, allylation, and aldol reactions.

Energy considerations in asymmetric synthesis. Asymmetric synthesis can involve i) the selective displacement of an enantiotopic ligand (**Scheme I.3.11a**) or (ii) the selective addition of a reagent to the *Re*/*Si*-face of a π-bond (**Scheme I.3.11b**).[26a] The energy profile of such reactions suggests favourable formation of racemates as the transition states $R^{\#}$ and $S^{\#}$ are enantiomeric and therefore, are isoenergic. As a consequence, the rate of formation of the *R*-isomer is equal to that of the *S*-isomer, and the reaction affords a racemic mixture. Thus, for the development of an asymmetric synthesis, the transition state must be diastereomeric so that potential energies are different. This would ensure that the

enantiomeric products are formed at different rates because of the involvement of different activation energies in their generation.

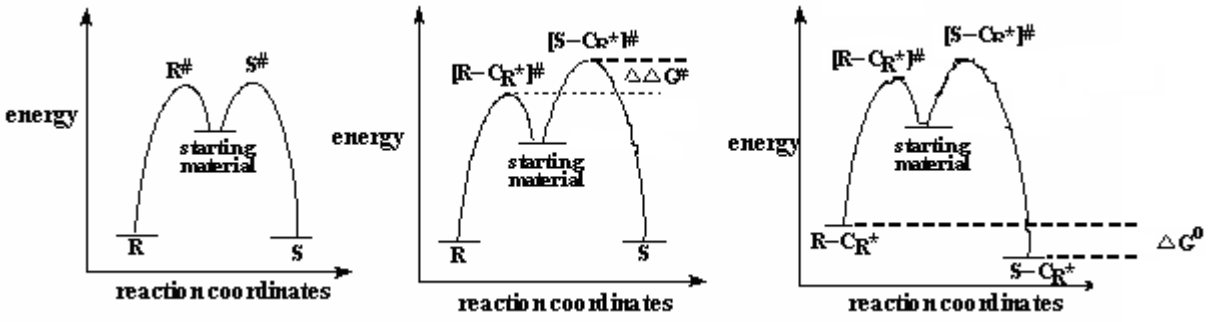


Scheme I.3.11a



Scheme I.3.11b

The selectivity achieved in the reactions will depend on the energy differences of activation, $\Delta\Delta G^{\#}$ (**Fig. I.3.1**), since they take place under kinetic control. This implies that the most abundant product is that originating *via* the lowest activation energy. When the products in the asymmetric synthesis are diastereomeric, the selectivity can be dictated also by the difference in kinetic energies (kinetic control), but when the reaction is reversible, the selectivity will depend (at equilibrium), on the difference between the free energies of the products, $\Delta G°$ (thermodynamic control).



a **b** **c**

Fig. I.3.1. Energy profiles for different types of reactions

Fig. I.3.1b. describes a unique situation in which, initially, the kinetically-controlled product with *R*-configuration predominates. By contrast, the thermodynamic

control leads to the predominant formation of the most stable product (S-C_R*). The ratios of the products depend directly on the magnitude of $\Delta\Delta G^{\#}$ (for kinetic control) or $\Delta G°$ (for thermodynamic control). This would require a $\Delta G°$ or $\Delta\Delta G^{\#} \geq 1.0$ kcal/mol for achieving an enantioselectivity of 70% and such an energy difference is usually provided by simple electrostatic interactions.

Many examples of kinetic/thermodynamic control of enantioselectivity are available in the literature. It becomes clear from various observations that the design of an asymmetric reaction must aim at maximization of $\Delta\Delta G^{\#}$ or $\Delta G°$, depending on whether product formation is kinetically or thermodynamically controlled.

In spite of all these attributes, and even after handling hundreds of asymmetric reactions, very little is known concerning the nature of the transition states of a particular reaction. But, it has become clear that more rigid and organized transition states magnify the effect of the strike interactions, hydrogen bonds, selective solvation *etc*. Considering that the rigidity of the transition state is more pronounced at lower temperatures, asymmetric induction is usually best achieved by carrying out the reactions at lower temperatures. Eliel[26b] has summarized conditions for an efficient asymmetric process as follows:

i) It has to be highly selective.

ii) The new centre of chirality must be cleanly separated from the rest of the molecule.

iii) The chiral auxiliary centre must be recovered without any racemization.

iv) The chiral auxiliary reagent must be easily and inexpensively available.

v) The reaction must proceed in good chemical yield.

vi) The balance between chiral auxiliary/reagent and product with the new chiral centre

of chirality is also important. Thus, best chiral auxiliary is an efficient chiral catalyst.

CHAPTER II

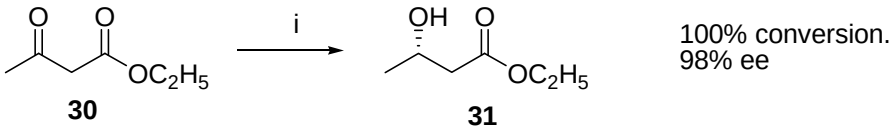
[bmim][Br]: A GREEN AND EFFICIENT MEDIA FOR ALLYLATION OF CARBONYLS

II.1 INTRODUCTION TO CHIRAL CARBINOLS

Majority of the natural and non-natural chiral organic molecules owe their chirality to the presence of an alkyl (primarily methyl) branching and/or oxygenated functionality. Hence, in the context of asymmetric synthesis, development of synthetic protocols for (i) the formation of carbon-carbon bond, and (ii) the reduction of prochiral ketones remain two most fundamental and important goals. The most commonly adopted method for the former is by addition of a nucleophile, usually an organometallic species, to a carbonyl function (aldehyde/ketone). Enveloped within this class of reactions is the conjugate addition of various organometallic reagents to the enals/enones, that leads to specific introduction of a hydrocarbon unit to the position β to a carbonyl function.[27] On the other hand, with a simple carbonyl compound, a secondary or tertiary alcohol is obtained. Alternatively, addition of a hydride as the nucleophile to the ubiquitous ketones provides chiral alcohols that are often useful target bioactive compounds or their precursors.[28] Notably, the secondary carbinols are often functionalized further to the required target compounds like lactones, deoxysugars, sugar modified nucleosides, macrolides, spiroketals, allenes, amines and even heterocycles.[3,29] Yet another alternative for the synthesis of the carbinols is the asymmetric dihydroxylation (ADH) of alkenes, for which the inventor, Prof. K. B. Sharpless got the Nobel Prize in chemistry. In a nutshell, the important reagent- and/or substrate-controlled asymmetric strategies for the formation of chiral carbinols have been (a) ketone reduction, (b) ADH route, and (c) addition of organometallic species to carbonyls. These strategies have been briefly presented in this section.

***Asymmetric reduction of ketones*:**

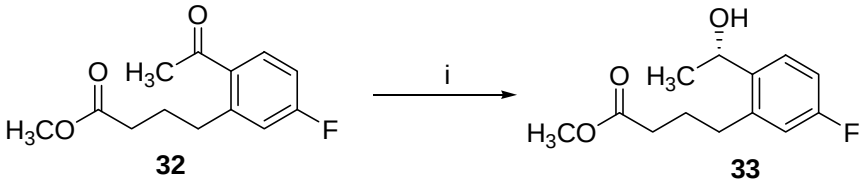
This reaction can be performed in a number of ways. Asymmetric chemocatalysis,[30a] and the often complementary biocatalysis offer solutions to the stereoselective reduction of C=O groups. These two techniques have found wide industrial applications.[30b] From the perspective of green chemistry, asymmetric biocatalytic reduction has attracted a lot of attention,[31] and many new biocatalytic systems using both whole cells and isolated enzymes have been developed.[32] For example, the Baker's yiest mediated reduction of ethyl acetoacetate to the alcohol **31** (**Scheme II.1.1**) is extensively used in organic synthesis.[33a]



(i) Baker's yeast, sucrose, H_2O, 40 ^oC, 24 h.

Scheme II.1.1

Regarding the use of pure enzymes, the reductase from *Pichia Methanolica* SC 13825 was cloned and expressed in *E. Coli* and the recombinant culture has been used for preparative scale reduction of methyl 4-(2'-acetyl-5'-fluorophenyl) (**32**) with excellent yield (98%) and ee (99%) (**Scheme II.1.2**).[33b]

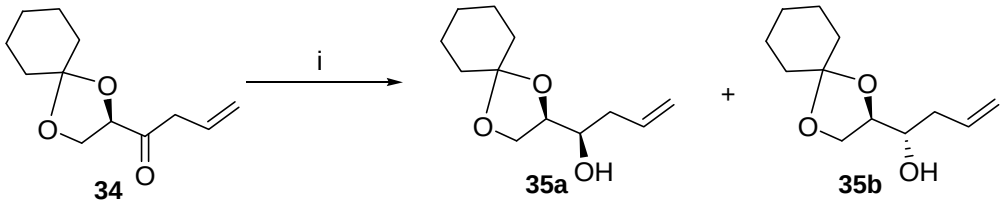


(i) Alcohol dehydrogenase from *Pichia Methanolica* (overexpressed in *E. Coli*), glucose, glucose dehydrogenase.

Scheme II.1.2

However, availability of ketoreductases with anti-Prelog enantioselectivity, broader substrate specificity, larger active site for bulky substrates, higher thermostability and tolerance of organic solvents remains a challenge in the biocatalytic reductive protocols.

Regarding chemocatalysis, a variety of reagents, prepared using various aluminum or boron hydrides and enantiomers of diols or amino alcohols have been formulated.[34a] Due to the empirical character and the often uncertain nature of the reducing species and their mode of action, the results with most of these proved disappointing.[34b] Among the borohydride reagents, those obtained through modification of mild and inexpensive sodium borohydride ($NaBH_4$) are of particular interest.[35a,b] Particularly, lithium and potassium tri-*s*-butylborohydrides (L and K-Selectride®), and lithium triethyl borohydride were found useful. A good example can be the substrate-controlled reduction of (*R*) -2,3-cyclohexylideneglyceraldehyde-derived ketone **34** by K-Selectride® developed by our group that provided the *syn*-alcohol **35a** with >99% ee (**Scheme II.1.3**).[35c]

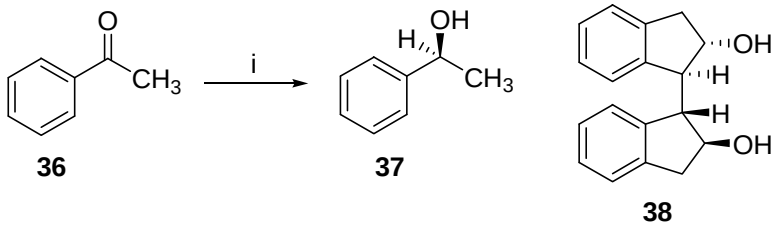


(i) K-Selectride®, dry THF, -78 ^{o}C.

Scheme II.1.3

Several researchers found that both reaction rate and chiral induction improved when Lewis acids, such as salts of zinc or zirconium, were included in the reaction mixture.[36a,b] In this category, the Corey-Bakshi-Shibata (CBS) catalyst,[36c] Mukaiyama's alcohol-modified $NaBH_4$ with catalytic amount of a chiral Co(II) complex[36d] and a tartaric

acid-derived boronate ester, with lithium borohydride ($LiBH_4$) or $NaBH_4$[36e] are known to reduce ketones and sometimes imines with high enantioselectivity. Amongst the $LiAlH_4$–based reagents those modified with BINAL-H,[37a] ephedrine,[37b] Darvon-alcohol (CHIRALD®)[37c] or TADDOL[37d] are very popular and find widespread use in asymmetric synthesis. Recently, chiral diols were also used as a chiral modifier in the $LiAlH_4$ reduction of achiral ketones. For example, $LiAlH_4$ reduction of acetophenone (**36**) in presence of an α-amino alcohol and **38** as the chiral modifier gave secondary alcohol **37** (**Scheme II.1.4**) (>98% ee).[37e]



36 **37** **38**

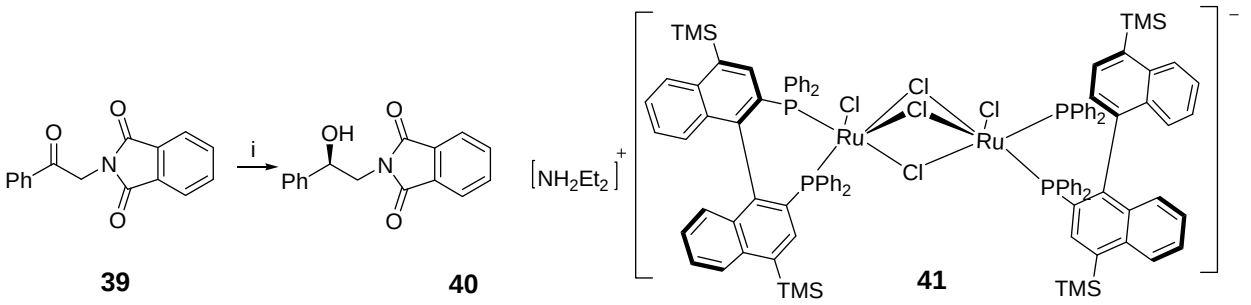
(i) $LiAlH_4$, $(Me)_2NC_2H_4OH$, **38**, THF, -78 °C.

Scheme II.1.4

In addition a few B-based reagents, non-borohydrides such as Alpine Hydride®, NB-Enantride™, diisopinocampheyl boron chloride etc. also work efficiently especially with conjugated or α-alkyne ketones.[37f] The mechanism of reduction by these reagents is postulated to involve the formation of a complex between the reagent (Lewis acid) and the carbonyl compound, followed by transfer of a β-hydrogen. The hydrogen transfer is usually depicted as proceeding through a six-membered cyclic 'boat-like' transition state. The asymmetric induction is ascribed to an unfavourable steric interaction between the larger of the two groups on the carbonyl and the alkyl groups in the reagents.

Finally, the importance of the ruthenium-based dihydrogenation or transfer hydrogenation for asymmetric reduction of prochiral ketones needs special mention.[38]

Prof. R. Noyori received the Nobel Prize for his stupendous contributions in this area. This type of clean asymmetric hydrogenation of ketones is particularly important in the pharmaceutical industries. These are based on a ruthenium metal centre bearing a chiral diphosphine and/or a chiral diamine ligand, wherein the catalyst acts as a 'bifunctional' scaffold for anchoring the substrate and transferring the hydride without the direct coordination of the substrate to the metal centre. Hydrogenation is accomplished within the external coordination sphere of the catalyst. For example, 4,4'-bisubstituted BINAPs were effectively utilized as a chiral ligand in diastereoselective asymmetric hydrogenation of protected amino ketones (**Scheme II.1.5**).[39]



(i) catalyst **41**, EtOH, H_2, 25 ^oC.

Scheme II.1.5

Asymmetric dihydroxylation of alkenes:

Amongst the powerful asymmetric methodologies, the dihydroxylation of alkenes occupies a prominent place in terms of research and industrial applications. The asymmetric dihydroxylation (ADH) reaction is much less limited in the choice of substrate, since it does not need any directing functional group to be present, and crucially depends on the ligand acceleration effect (LAE),[40] which ensures that the reaction is funneled through a pathway involving the chiral catalyst. The method is based on the classical

reaction of OsO_4 with olefins which was shown to be accelerated by pyridine.[41a] The cost considerations, however, make the stoichiometric osmylation uneconomical. Not surprisingly, catalytic variants of the reaction, which employ relatively inexpensive reagents for the reoxidation of the osmium (VI) glycolate products, greatly enhance its synthetic utility.[41b] Introduction of inorganic cooxidants, such as $KClO_4$ or $NaClO_4$ or H_2O_2 led to diminished yields due to over-oxidation. Better results were obtained with alkaline *tert*-BuOOH,[41c] or *N*-methylmorpholine *N*-oxide (NMO),[41d] or even better with $K_3Fe(CN)_6$-K_2CO_3.[41e] Initial efforts to induce enantioselectivity in the osmylation with chiral pyridine derivatives failed due to the low affinity of these ligands for OsO_4.[42] Consequently, quinuclidine derivatives like the acetates of cinchona alkaloids (**Fig. II.1.1**) were used more efficiently due to their intrinsically higher affinity for OsO_4.[43]

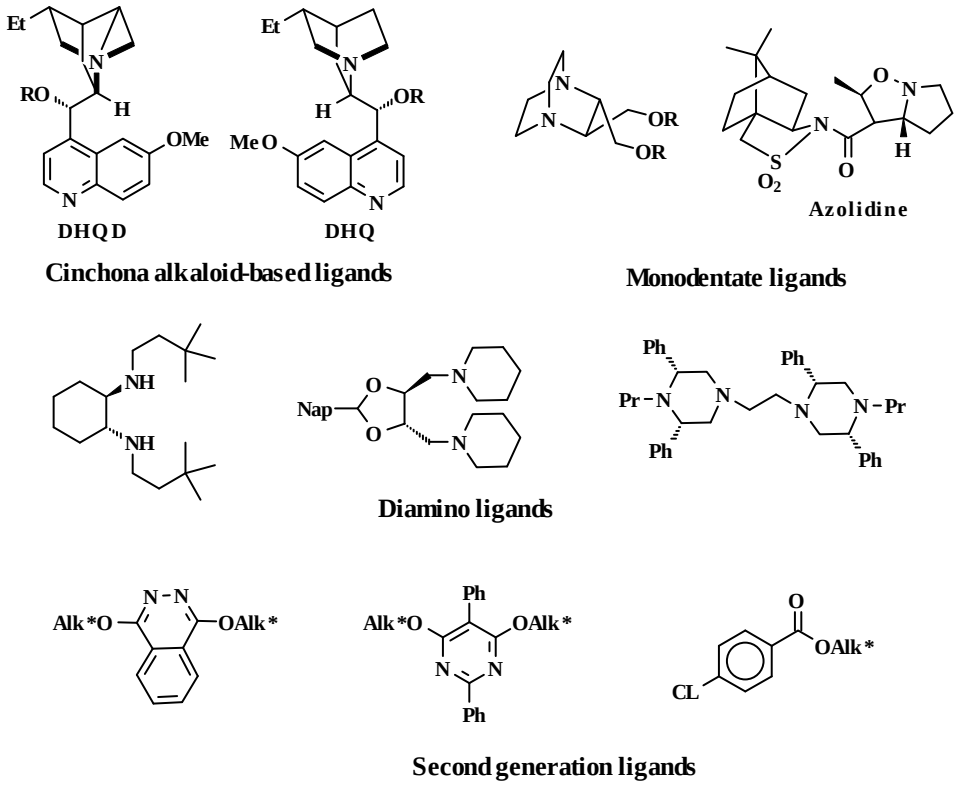
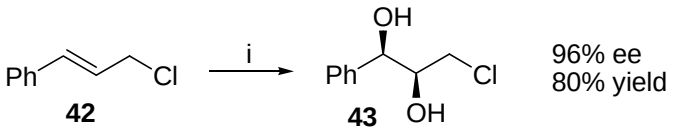


Fig. II.1.1. Chiral ligands used in ADH

Apart from the cinchona alkaloids, few other ligands such as a monodentate 1,4-diazabicyclo[2.2.2]octane,[44a] chiral oxazolidines,[44b] etc. have also been used to effect the transformation with modest 41-73% ees. Some simple chiral diaminocyclohexyl ligands produced better enantioselection, but a serious drawback results from their bidentate nature.[45] They form very stable chelates with the osmium (VI) glycolate products which lead to inhibition of hydrolysis, and as a consequence prevent *in situ* recycling of the osmium and the ligand. Thus, all the reactions involving bidentate ligands are stoichiometric in both OsO_4 and the chiral ligand.

ADH with derivatives of cinchona alkaloids was made catalytic using NMO as the cooxidant, albeit with less enantioselectivity than the stoichiometric version.[46a] A second catalytic cycle,[46b] which exhibited only low or no enantioselectivity accounted for this discrepancy. Two key discoveries led to a dramatic growth in the ADH reaction. First, the second catalytic cycle could be eliminated by carrying out the reaction in a biphasic condition with $K_3Fe(CN)_6$ as the stoichiometric cooxidant.[46c] Under this condition, OsO_4 is the only oxidant in the organic phase where the ADH reaction takes place. Hydrolysis of the osmate ester provides only OsO_4 in the aqueous phase, where it gets reoxidized. Thus, the combination of $K_2Os_2(OH)_4$, as a non-volatile osmium source, and the cooxidant, $K_3Fe(CN)_6$ was developed for carrying out the reaction conveniently. The reagent, AD-mix is now commercially available. Further, the discovery of second generation ligands with two independent cinchona alkaloid units attached to a heterocyclic spacer, has led to a considerable increase in both enantioselectivity and scope of the reaction.[46d-f] One representative example of this strategy is the conversion of cinnamyl chloride (**42**) to the diol **43.** in high ee *via* the ADH reaction (**Scheme II.1.6**).[46g]



(i) AD-mix β, $NaHCO_3$, $CH_3SO_2NH_2$, t-BuOH-H_2O, 0 ^oC.

Scheme II.1.6

***Asymmetric addition of organometallics to ketones*:**

Addition of a carbon-nucleophile to a carbonyl compound is one of the most widely used synthetic protocols for the synthesis of carbinols through homologation. This is generally done using organometallic reagents prepared from various metals *viz*. Li, Mg, Zn, Sn etc. Amongst these, the Zn-mediated routes offer better opportunity of stereocontrol. However, because most of the dialkyl zinc reagents are not commercially available, the Zn-mediated reactions are primarily restricted to either allylation/propargylation by Barbier type methods or with the commercially available Et_2Zn. Indeed, addition of Et_2Zn to aldehydes in the presence of a chiral ligand is often used to test its efficacy as a chiral auxiliary. The works carried out till 1992 on this reaction has been reviewed.[47] The origin of the enantioselectivity of the reaction has also been discussed, which provides references of the most successful developments in this field.[48] Although the R_2Zn reagents react extremely sluggishly with carbonyl compounds, effective catalysis has been achieved by coordinating these with organic ligands. The ligand-induced activation of the R_2Zn reagents can be explained on the basis of the changes in geometry and bond energy of the reagents, caused by the coordination of Zn.[49a-b] For example, dimethyl zinc has a linear structure with a Zn-C bond length of 1.95 Å (**Fig. II.1.2**) and is not reactive towards aldehydes or ketones. However, on coordination with a

ligand, it assumes a tetrahedral configuration at the Zn atom. This results in an elongated Zn-C bond (1.98 Å) leading to its enhanced reactivity.[49c]

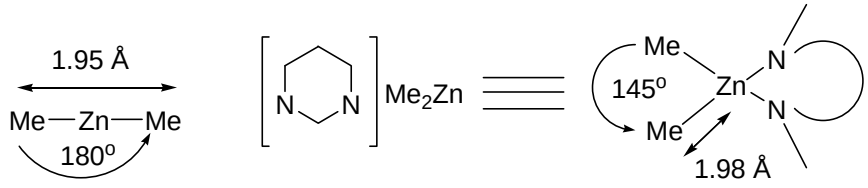
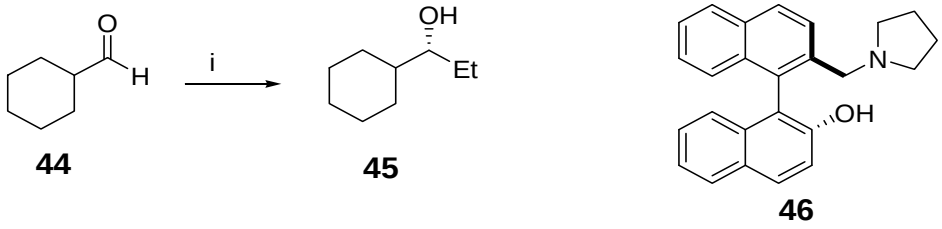


Fig. II.1.2. Tetrahedral configuration of Et_2Zn

Using this strategy, both 1,2- and 1,4-addition of R_2Zn to various carbonyl substrates have been carried out.[47] In one such example, aldehyde **44** was converted to enantiomerically enriched alcohol **45** with 98% eeusing dialkylzinc in presence of binapthyl derivative **46** (**Scheme II.1.7**).[50]



44 **45** **46**

(i) 3 mol% **46**, Et_2Zn, toluene, 25 °C.

Scheme II.1.7

Various homogeneous chiral catalysts and ligands which have been utilized for the reaction include amino alcohols, piperazines, transition metal salts with diols, quaternary ammonium salts, secondary and tertiary amino alcohols, bipyridyl diol, amino alcohols, and oxazaborolidines. Some of these combinations can effectively catalyze the addition of Et_2Zn as well as other alkyl/alkynyl zinc reagents to aldehydes with high ees. In addition, heterogeneous chiral catalysts comprising of polymer-, alumina-, and silica gel-supported chiral amino alcohols have also been utilized for these transformations. The polymer supported catalysts are most efficient in this class. Addition of dialkylzincs to racemic

aldehydes in the presence of chiral catalysts affords optically active alcohols, resulting from the enantioselective, but not diastereoselective addition. Also, the selectivity of the addition to chiral aldehydes is mostly dictated by the configuration of the chiral catalyst than that of the substrate, resulting in kinetic resolution of the starting aldehyde, when used in excess. Interestingly, some chiral amino alcohols show a nonlinear effect in the relationship between the ee of the chiral catalysts and the ee of the products. In these cases, the ee of the products are higher than those of the catalysts. With keto-aldehydes, as well as conjugated aldehydes, the reaction is also reported to proceed chemoselectively at the aldehyde function. Some of the chiral ligands used to carry out addition of R_2Zn to various carbonyl substrates include chiral bi-pyridines[51a] *e. g.* **I**, amino alcohols **II-VI**,[51b] arene-chromium amino alcohols *e. g.* **VII**,[51c] proline amides *e. g.* **VIII**,[51d] diamines *e. g.* **IX**,[51e] and is shown in **Fig. II.1.3**.

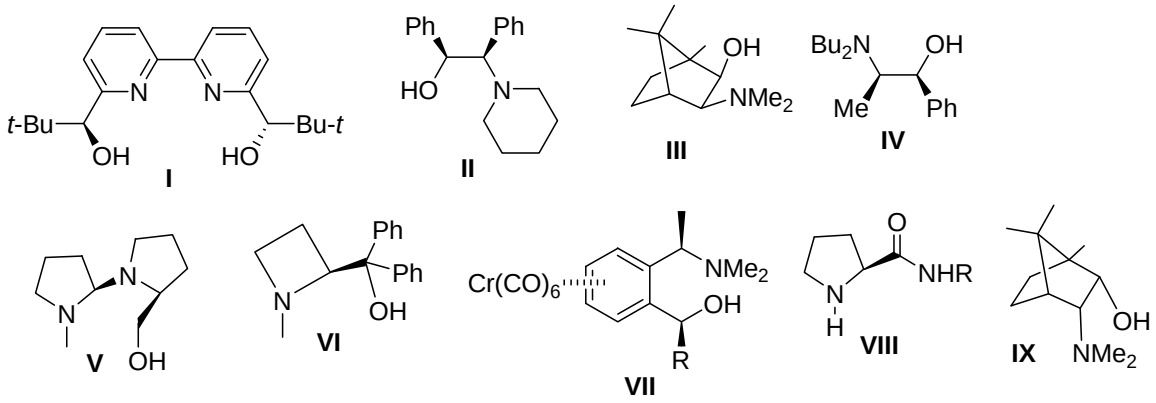
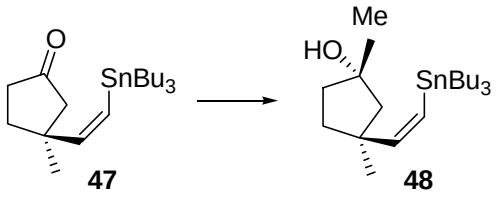


Fig. II.1.3. Chiral ligands used in asymmetric addition of R_2Zn to carbonyls

Thomas[52a-f] and Nishigaichi[52j,k] showed the potential of the allyltin moiety in the construction of multichiral centers, wherein, even, remote asymmetric induction could be realized using allylstannanes and carbonyl derivatives. An important area of asymmetric synthesis involving reactions of chiral allylstannanes was thoroughly reviewed by

Marshall.[53] More recently, Barbero *et al*. demonstrated the addition of various organometallic reagents (RLi, RMgX etc.) to (Z)-β-vinylstannylated ketones with high enentio- or diaseteroselectivity. The presence of the stannylvinyl group in the ketone **47** ensures a remarkable stereocontrol in the organometallic addition at the carbonyl centre (**Scheme II.1.8**).[54]



47 **48**

(i) CH_3Li, THF, -78 ^oC

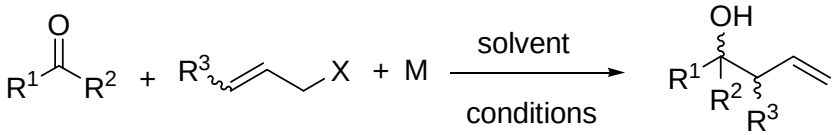
Scheme II.1.8

Besides these, allylation of carbonyls has also emerged as an important method to obtain chiral homoallylic alcohols. Several protocols have been developed towards this endeavour, which are briefly discussed in the following section**.**

II.2 INTRODUCTION TO HOMOALLYLIC ALCOHOLS: ALLYLATION OF CARBONYLS

Homoallylic alcohols are important building blocks in organic syntheses, since the alkene functionality can be readily transformed into a wide variety of functional groups such as aldehydes (via ozonolysis), δ-lactones, epoxides, and other olefinic compounds (via cross-metathesis).[55] Furthermore, they are widely distributed in many biological active molecules such as macrolides, polyhydroxylated natural products, polyether antibiotics and alkaloids.[56] Various methods *e.g.* Alder-ene reaction,[57a] Hosomi-Sakurai Reaction,[57b] Nozaki-Hiyama coupling reaction[57c] etc. have been developed for the diastereoselective synthesis of homoallylic alcohols. However, the metal-mediated allylation of aldehydes is the most popular for its efficiency and ease of operation.

The reaction generates a stereogenic carbinol centre with unsubstituted allyl halides. More importantly, reactions with the γ-substituted allyl halides (R-CH=CHCH$_2$X, R = Aryl, alkyl; X = Cl, Br) generates two stereogenic centres due to the involvement of allylic rearrangement in the allylic-metal reagents (**Scheme II.2.1**). The reaction is highly efficient in terms of atom economy, as all the carbons form the scaffold of the desired molecules.



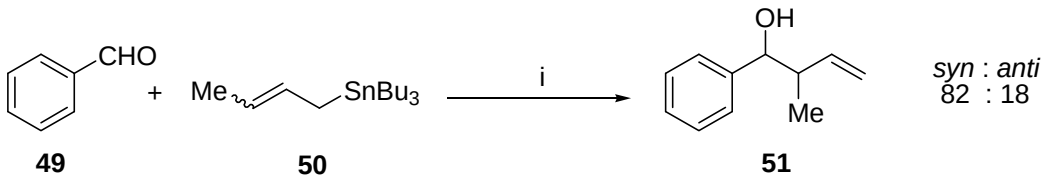
R^1/R^2 = H/alkyl, R^3 = H (allyl halide), Me (crotyl halide), Ph (cinnamyl halide)
M = metal (Zn, Sn, In, Ga etc.)

Scheme II.2.1

Various protocols have been developed for allylation of carbonyls.[58] Amongst these, the Barbier type protocol is convenient since the reactions can be carried out without the need to isolate the active allyl-metal species responsible for allylation.[59a] Currently, considerable attention is given to perform the reaction in "green solvents" *viz*. H_2O[59b-d] and room temperature ionic liquids (RTILs)[59e] from environmental concerns.

Reported methods of metal mediated allylation

Ever since Luche *et al.* used Zn metal in moist THF with aqueous saturated NH_4Cl for allylation,[60] other metals such as Mn, Sn, In, Ga, etc. have also been explored for this purpose. Li *et al*. studied the Mn mediated allylation of aromatic aldehydes in presence of catalytic amount of Cu metal.[61a] Sn has also been used as a metal of choice for carrying out allylation reactions in THF, H_2O and RTILs.[61b-h] Likewise, preformed allyltin[62a,b] and crotyltin[62c] reagents have also been successfully employed for this reaction. For example, the crotyl stannane **50** was used for diastereoselective crotylation of benzaldehyde in the presence of $BF_3.Et_2O$ (**Scheme II.2.2**).[62d]

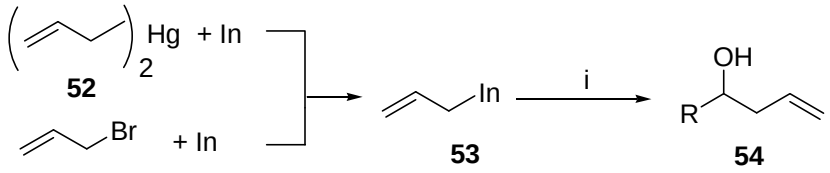


(i) $BF_3.Et_2O$, CH_2Cl_2.

Scheme II.2.2

Other metals *viz*. Cd,[63a] Bi with KF as metal activator[63b] and Sb[63c] have also been utilized for the allyaltion of carbonyls. Of late, In metal, belonging to group 13 is being used extensively for this reaction.[64] The pioneering work of Araki *et al.* showed[65a] that even α,β-unsaturated aldehydes could be chemoselectively allylated in a 1,2-fashion using

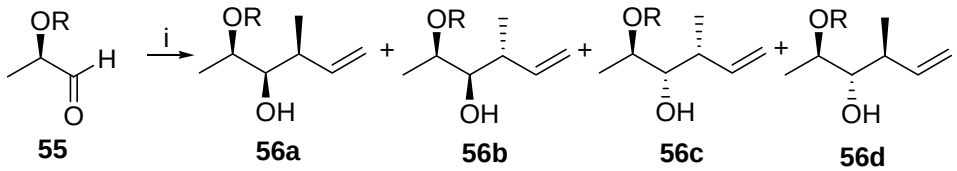
In metal in DMF. In another important approach, Chan *et al.* used Me_2Hg in the presence of In or InI_3 (**Scheme II.2.3**) to generate the allylindium intermediate which could carry out allylation of aldehydes and ketones even in water.[65b]



(i) RCHO, H_2O.

Scheme II.2.3

Several RTILs *viz*. [bmim][BF_4], [bmim][PF_6] and [bmim][Tf_2N] have also been used for the allylation of aromatic and aliphatic aldehydes in moderate to good yields. [65c] In the In-mediated crotylation, the diastereoselectivities of crotylation of aromatic aldehydes were largely dependent on the ligands attached to the allylic indium reagents,[65d] as well as on the substrate chirality and reaction media. Crotylation of the α-oxygenated aldehyde **55** proceeded with moderate *syn*-selectivity in H_2O, but a mixture of diastereomers were obtained in water-THF or THF (**Scheme II.2.4**).[65e,f]



(i) Crotyl bromide, In, solvent.

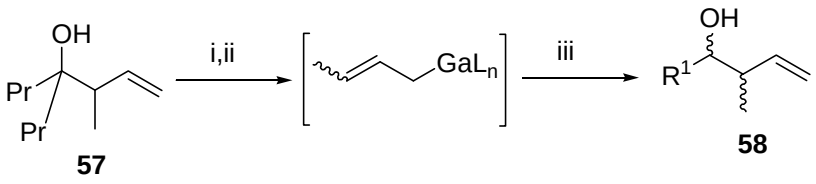
Scheme II.2.4

In the absence of a sterically-bulky substituent at the carbonyl or allyl bromide, the allylation of an aldehyde with a γ-substituted allylic indium reagent occurs regioselectively at the γ-position to afford the γ-homoallylic alcohol. Loh *et al*., however, have succeeded in carrying out the In-mediated allylation via α-addition without the use of a sterically-hindered substituent.[65g] Interestingly, the solvent plays an important role in determining the regioselectivity in these reactions. While water (10 M) and water/dichloromethane (10 M/10 M) exhibited excellent α-selectivity, the reactions in DMF, ethanol, THF and water (0.5 M) followed exclusive γ-attack.

Compared to In, reports on the Ga-mediated allylation are limited. Till so far, the Ga-mediated Barbier type reactions have been conducted in water and/ or organic solvents using both metallic Ga/allyl halide[66] as well as preformed allyl-Ga dihalides. The Ga-mediated allylation of aldehydes and ketones with allyl iodide in THF under ultrasonication afforded the homoallylic alcohols.[66a] Aldehydes were more reactive than ketones, the reaction being more facile with allyl iodide. A similar reaction under heating conditions is also reported in water.[66b] Chemical additives, such as KI, LiCl (in THF)[66c] or HCl, NH_4Cl (in H_2O)[66b] are required when the reaction is carried out with allyl bromide. The reaction proceeded with excellent chemoselectivity with α,β-conjugated aldehydes/ ketones (exclusive 1,2-addition), and with esters, cyanides and acyl chlorides to furnish the corresponding products. Regarding regioselectivity, only mono addition product was formed with benzyl halides, while the γ-adducts were predominantly produced with the γ-substituted allyl halides. Alternatively, the reaction could also be carried out under solvent-free conditions, but needed metal activation by ultrasound.[66d]

Given that the Ga-mediated Barbier-type allylation reactions require metal activation, other methods for the generation of allylgallium species via transmetallation of (i) allylmagnesium bromide with $GaCl_3$, and (ii) allylindium sesquihalides with Ga metal have been developed. The allylic-Ga reagents, prepared from the first route, could execute allylation of carbonyl compounds in excellent yields in aqueous as well as organic media.[66e] Some related reactions like propargylation of aldehydes,[66f,g] allylation of epoxides,[66h] aromatic hydrazones and *N*-oxides,[66i] as well as addition of propargyl bromide to terminal alkynes[66j] and alkylation of haloesters[66k] have also been accomplished using metallic Ga.

In an innovative approach, Ga has been used for the allyl transfer from a bulky substrate to an aldehyde to get the homoallylic alcohols.[67a-c] In these approaches, treatment of the bulky homoallylic alcohols such as **57** with a Grignard reagent and $GaCl_3$ led to retro-allylation furnishing the σ-allylgallium reagents, which on reaction with a suitable aldehyde/ketone furnished the new homoallylic alcohols **58**. Notably, depending on the stereochemistry (*threo* or *erythro*) of **57**, the retro-allylation reaction selectively generated the *E*- or *Z*-allylgallium reagents from the γ-substituted allyl halides. This is advantageous for better diastereocontrol with these allyl halides (**Scheme II.2.5**).



57 **58**

(i) MeMgI, dioxane; (ii) $GaCl_3$; (iii) RCHO.

Scheme II.2.5

II.3. PRESENT WORK

It is well known that the stereoselectivity of a metal mediated allylation depends on the electronic configuration and physical state of the metal, and also on the reaction medium. From this perspective, use of different solvents *viz*. THF, DMF, THF- H_2O, H_2O and RTILs have attracted considerable attention. Amongst these, RTILs have been more popular because of certain environmental advantages.Many studies have revealed that the metal-mediated allylation in RTILs proceed smoothly with improved diastereoselectivity and yield. However, the exact mechanisms of the reactions as well as full characterization of the active allylmetal species formed in the reactions remain unclear. Hence it is still a challenge to look into the mechanistic aspects of a reaction in RTIL. The present study is focused on the allylation of aldehydes in RTILs and their mechanistic interpretation.

II.3.1 Introduction to Ionic Liquids

Although any liquid consisting of ions can be considered as ionic liquid, but only those which are liquid at room temperature and have relatively low viscosity are more useful as solvents in organic transformations.[59e,68] Some interesting physical properties which make these RTILs potentially useful solvents are: (a) These can dissolve both organic and inorganic reagents, and hence these two unusual combination of reagents can be made monophasic; (b) They often provide noncoordinating polar systems; (c) The hydrophobic RTILs can be used as immiscible polar phases with water; (d) These are nonvolatile, and hence can be used in high vacuum systems. Availability of RTILs, which are stable to air, moisture and heat has boosted their use as solvents in a number of organic reactions *viz.* Diels-Alder reactions,[69a,b] Beckmann rearrangement,[69c] Friedel-Crafts acylation,[69d] Heck reactions,[69e,f] Henry reaction[69g] and allylation reaction.[69h-j] Although,

earlier, the halogenoaluminate(III) and the closely related alkylhalogenoaluminate(III) ionic liquids have mostly been used, those based on dialkylimidazolium salts have recently attracted particular attention[69e] as they possess wide liquid range, and are easy to prepare and handle. The emerging use of these ionic liquids has opened up a wide field for investigations into this new class of solvents.

RTILs are either organic salts or mixtures consisting of at least one organic component. The most common salts in use are those with *N*-alkylpyridinium, alkylammonium, alkylphosphonium, and *N*, *N'*-dialkylimidazolium cations (**Fig. II.3.1**).

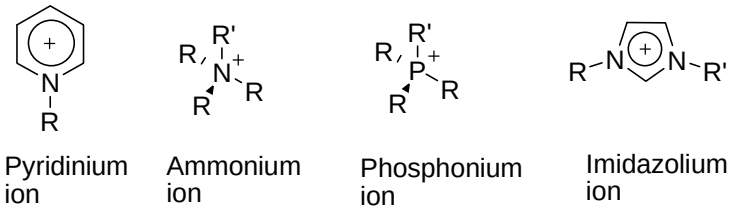
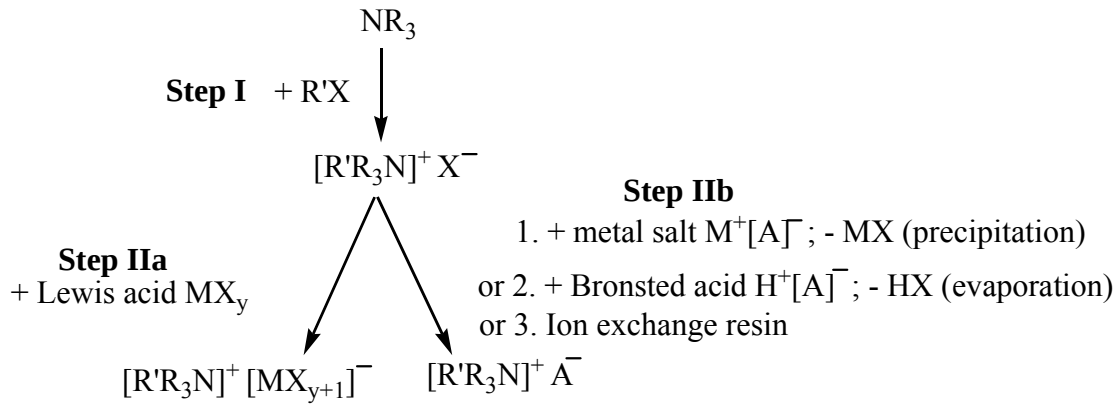


Fig. II.3.1. Cations used in RTILs

The initial step in the synthesis of ionic liquids is the quaternisation of an amine or phosphine for example, to form the cation.[70a,b] Preparation of the pyridinium and imidazolium halides can be achieved similarly.[70c] In this approach, the anionic components of the RTILs are derived from that of the alkylating agents. Interestingly, ionic liquids with melting points <100ºC can be obtained by changing the combinations of cation/anion in this way.

In cases where it is not possible to form the desired anion directly by the quarternisation reaction (step I in **Scheme II.3.1**), a further step (IIa or IIb) is required. Either $[R'R_3N]^+X^-$ can be treated with a Lewis acid MX_y leading to $[R'R_3N]^+[MX_{y+1}]$, or can be treated with an acid or salt to exchange the halide ion by the desired anion. Different ionic liquids *viz*. [pyridinium][$AlCl_4$], [imidazolium][$AlEtCl_3$],

[pyridinium][Sn_2Cl_5] etc. can be prepared by the reaction of a halide with a Lewis acid (step IIa). In 1992, metathesis (step IIb) was first used to synthesize [emim][BF_4]. The preparation of [emim][PF_6] shortly followed; and since then, thiocyanate, trifluoroacetate and heptafluorobutonate salts have all been prepared by metathesis reactions.



Scheme II.3.1

The physical and chemical properties of ionic liquids can be specifically varied over a wide range by the selection of suitable cations and anions.[71] In general,[58e,72] the ionic liquids can be considered to be polar phases with the solvent properties largely determined by the ability of the salt to act a hydrogen-bond donor and/or acceptor and the degree of localization of the charge on the anions. Furthermore the increasing chain length of alkyl substituents on both the cations and anions leads to greater lipophilicity of ionic liquids. Such ionic liquids which show a miscibility gap with water have also been used as a substitute of volatile organic solvents in extractive separation processes.

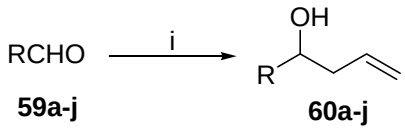
More recently, ionic liquids have been referred as promising solvents for “clean processes” and “green chemistry”. These reflect the current efforts to reduce drastically the amounts of side products and also the solvent and catalyst consumption in chemical

processes. Although the aspects of their toxicity and disposal have not been fully explored yet, the use of ionic liquids can definitely make a contribution in this area, particularly with regard to solvent and catalyst usage.

II.3.2 *Indium mediated allylation in [bmim][Br]*

Indium mediated allylation of carbonyl compounds to give the corresponding homoallylic alcohol has been extensively studied in the past two decades,[65a,73] especially with the discovery that the reaction can be carried out in aqueous media.[64b,65b,74] As opposed to other metals, In is less air- and moisture-sensitive, significantly less toxic, and able to tolerate numerous functionalities offering advantages for the allylation reactions.[64,75]

In this investigation, we used In as the metal mediator and [bmim][Br] as the solvent to develop an efficient method for allylation of aldehydes. In general, only the hydrophobic RTILs are used for the Barbier type reactions. The simplest RTIL, [bmim][Br] has so far been used for bromination of arylamines and α,β-unsaturated carboxylic acids, synthesis of cyclic urethane and pyrimidinediones,[76a,b] dealkylation of aryl alkyl ethers,[76c] and most interestingly for Heck reaction.[69e] However, due to its excellent hydrophilicity, it was expected to mimic aqueous medium and appeared best suited for the Barbier type reactions. This study also provided new mechanistic insights in the allyl-In chemistry in [bmim][Br], eventually leading to a protocol with catalytic quantity of In.



(i) Allyl bromide, In, solvent.

Scheme II.3.2

Initially, the In-mediated allylation of benzaldehyde (**59a**) was carried out in H_2O, THF and three different RTILs, including [bmim][Br], and the results (**Scheme II.3.2**, **Table II.3.1**) established the efficacy of [bmim][Br] as the best solvent.

Table II.3.1. Reaction profile of the In-mediated allylation of different aldehydes in various solvents[a]

entry	substrate	R	allyl bromide (equiv.)	metal (equiv.)	solvent	time (h)	product	yield (%)[b]
1	**59a**	C_6H_5	3	5	H_2O	18	**60a**	59
2	**59a**	C_6H_5	3	5	THF	18	**60a**	65
3	**59a**	C_6H_5	1.5	1.2	[bmim][Br]	4	**60a**	89
4	**59a**	C_6H_5	1.5	1.2	[bmim][BF_4]	20	**60a**	64
5	**59a**	C_6H_5	1.5	1.2	[bmim][PF_6]	20	**60a**	62
6	**59b**	4-BrC_6H_4	1.5	1.2	[bmim][Br]	4	**60b**	88
7	**59h**	$(CH_3)_2CH$	1.5	1.2	[bmim][Br]	5	**60h**	68
8	**59i**	$CH_3(CH_2)_5$	1.5	1.2	[bmim][Br]	5	**60i**	81

[a]The reactions were carried out at 2 mmol scale. [b]Isolated yields of the products.

Allylation of **59a** in H_2O and THF were slow affording **60a** in 59% and 65% yields respectively after 18 h (**Table II.3.1**, entries 1, 2). In these solvents, a large excess of the metal (5 equiv.) and allyl bromide (3 equiv.) were used. Reducing their amounts led to poorer results. In contrast, the reaction could be accomplished much faster in [bmim][Br], and with only 1.5 equiv. of the bromide and 1.2 equiv. of In to obtain **60a** in 89% yield (**Table II.3.1**, entry 3) within 4 h. For comparison, the allylation of **59a** was also carried out separately in two other RTILs, [bmim][BF_4], and [bmim][PF_6]. As reported earlier, the reactions in these RTILs took a much longer time.[65c,77] However, in the cases, the yields of **60a** were less than that reported (**Table II.3.1**, entries 4,5). Earlier, this kind of variation in yields of allylation with different batches of the same RTIL was reported.[77a]

The scope of the protocol was studied using a number of aromatic and aliphatic aldehydes. The results with two aromatic (**59a**,**b**) and two aliphatic aldehydes (**59h**,**i**) are shown in **Table II.3.1** (entries 3, 6-8). The reactions were very fast, and the starting materials were completely consumed. The homoallylic alcohols **60a**, **60b**, and **60i** were obtained in good yields, while the lower yield of **60h** might be due to its volatility. Formation of the homoallylic alcohols was confirmed from the hydroxyl band at ~3500 cm^{-1} along with the terminal olefinic band at 910-930 cm^{-1} in place of the CHO band in the respective IR spectrum. Furthermore, all the products showed ^{1}H NMR resonances at δ 5.0-5.2 (2H) and δ 5.7-5.9 (1H), and ^{13}C NMR resonances at δ ~114 and δ ~134 ppm due to terminal olefins. As a representative example, the ^{1}H NMR and ^{13}C NMR of **60b** are shown in **Fig. II.3.2** and **Fig. II.3.3**.

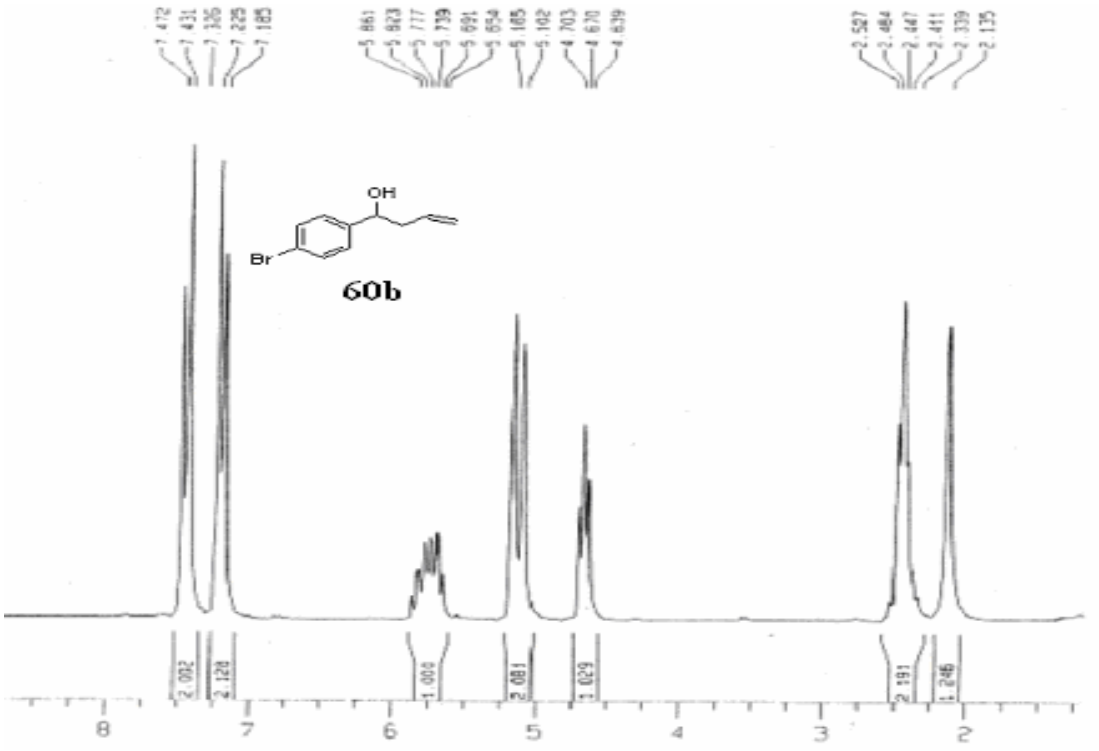


Fig. II.3.2. ^{1}H NMR spectrum of 60b

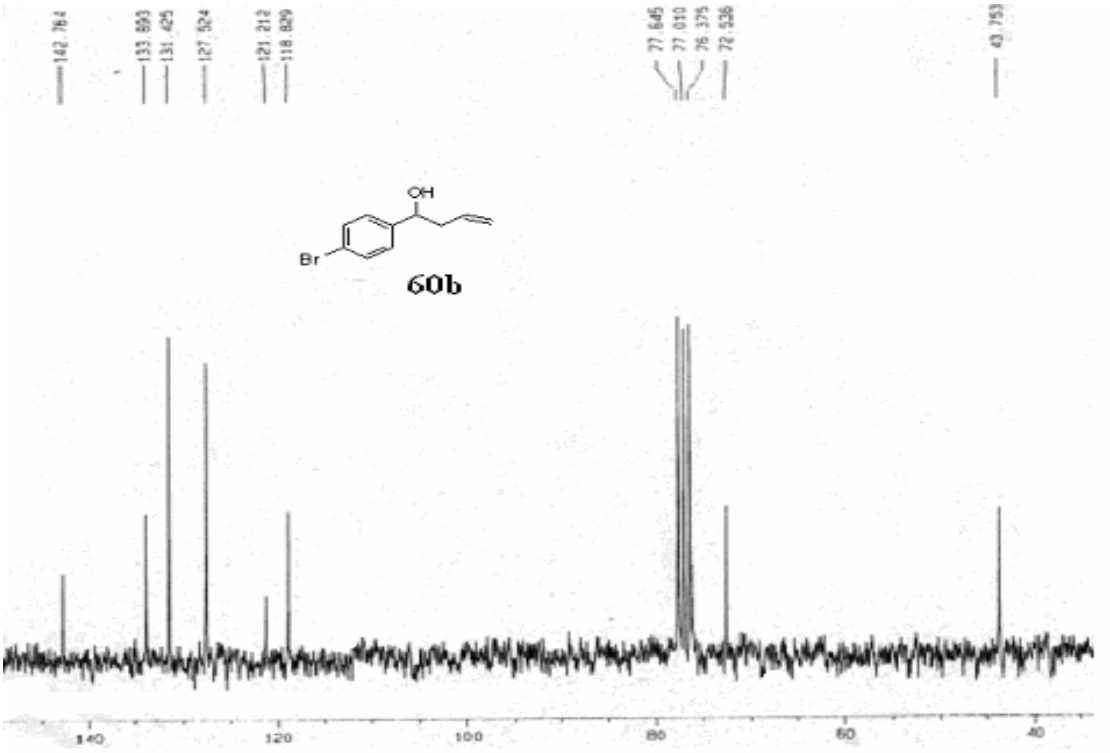


Fig. II.3.3. ^{13}C NMR spectrum of 60b

Table II.3.2. Reaction profile of allylation in [bmim][Br] using sub-stoichiometric In[a]

Entry	substrate	R	metal (equiv.)	time (h)	product (%)[b]
1	**59a**	C_6H_5	In (0.6)	12	**60a** (89)
2	**59a**	C_6H_5	In (0.5)	16	**60a** (86)
3	**59a**	C_6H_5	In (0.2)	22	**60a** (84)
4	**59b**	4-Br-C_6H_4	In (0.2)	20	**60b** (81)
5	**59c**	3-OMe-C_6H_4	In (0.2)	22	**60c** (88)
6	**59d**	4-$(CH_3)_2CH$-C_6H_4	In (0.2)	22	**60d** (91)
7	**59e**	4-C_6H_5- C_6H_4	In (0.2)	20	**60e** (86)
8	**59f**	C_6F_5	In (0.2)	18	**60f** (88)
9	**59g**	C_6H_5CH=CH	In (0.2)	22	**60g** (86)
10	**59h**	$(CH_3)_2CH$	In (0.2)	48	**60h** (68)
11	**59i**	$CH_3(CH_2)_5$	In (0.2)	22	**60i** (87)
12	**59j**	$CH_3(CH_2)_8$	In (0.2)	22	**60j** (91)

[a]The reactions were carried out using 1.5 equiv. of allyl bromide at 2 mmol scale. [b]Isolated yields of the products.

Next, the allylation of **59a** using sub-stoichiometric amounts (0.2-0.7 equiv.) of In, was attempted and the results are shown in **Table II.3.2**, entries 1-3. Although the reaction became progressively slower with the reduced amount of In, **60a** was obtained in appreciable yields. Interestingly, the reaction could be accomplished even with 0.2 equiv. of In, when **60a** was obtained in 84% yield in 22 h (**Table II.3.2**, entry 3). The results were significant considering that very poor yield was reported earlier[77b] in the allylation of **59a**

in [bmim][BF_4] using sub-stoichiometric amount of Sn. Such a protocol with In metal in RTIL is unprecedented.

Subsequently, the catalytic protocol (0.2 equiv. of In) was extended to the other aromatic and aliphatic aldehydes **59b-j** (**Table II.3.2**, entries 4-12). The protocol was equally effective with both aromatic and aliphatic aldehydes, furnishing the products **60b-j** in good yields. The nature of the substituents in the aromatic ring or alkyl chain length did not have any appreciable effect on the course of the reaction. The slow reaction of **59h** was surprising. With the conjugated aldehyde **59g**, the reaction proceeded with complete chemoselectivity furnishing the 1,2-addition product **60g** only. The products, obtained from the allylation reaction in [bmim][Br] could be conveniently isolated by extracting the reaction mixture with Et_2O followed by concentration. The reactions were clean without any side products and/ or starting materials. The RTIL was reused three times after discarding the metallic products, settled at the bottom of the flask.

Overall, the above results clearly established [bmim][Br] as the best RTIL among those chosen for the In-mediated allylation. Under stoichiomteric conditions, the reactions proceeded much faster in [bmim][Br] without needing any metal activator, and furnished the products in excellent yields in only 4-5 h. Most importantly, the reaction could be carried out using only 0.2 equiv. of the metal. In contrast, even with stoichiometric amounts of In, it required overnight stirring in the other RTILs, while a large excess of the reagents and extended time were essential for the reaction in H_2O and THF. The marked metal activation provided by [bmim][Br] as well as the requirement of only catalytic amount of In were of interest for further studies.

Mechanistic studies: For the mechanistic insight of the activating role of [bmim][Br] and the recycling of the metal, the nature of the organometallic species responsible for the reaction was probed. For this, the reactions between In (1 mmol) and allyl bromide (1 mmol) in D_2O / THF / [bmim][Br] (3 mL) were followed by recording the ^1H NMR spectra of the aliquots of the reaction mixture over a time period of 8 h. The intensity of the NMR peak due to the allyl-indium species was quantified by comparing with that of the CH_2Br signal.

The ^1H NMR spectra of the reaction carried out in D_2O showed the appearance of a new doublet at δ 1.63 (J = 8.4 Hz) after 10 min, at the expense of the $–CH_2Br$ signal at δ 3.9. However, no new olefinic resonances were observed. The intensity of the peak (δ 1.63) reached maximum (33.6%) in 25 min, and thereafter declined gradually to vanish in 2 h. **Fig II.3.4** shows the ^1H NMR spectrum of the reaction between In and allyl bromide in D_2O, recorded after 25 min of stirring. The ^1H NMR spectrum was attributed to $CH_2{=}CHCH_2{-}In$ (**I**).[65b] The NMR investigations clearly revealed that the active In-species **I** produced in H_2O is unstable and gets hydrolyzed. This was evident from the fact that the depletion of its ^1H NMR resonances (δ 1.63) was associated with an increase in the intensity of the resonances at ~ δ 3.8. This suggested the formation of allyl alcohol, which was detected earlier.[77a] Thus, during allylation of an aldehyde in H_2O, the species **I** reacts via two competitive routes *viz*. with H_2O (leading to its decomposition) and the aldehyde. The former process prevails due to its higher rate (revealed from the ^1H NMR experiments) and the high concentration of H_2O. This accounts for the need of the large excess the reagents (In and allyl bromide) in the allylation of aldehydes in H_2O.

The reaction in THF was also followed as above. However, due to the overlapping resonances of the solvent in the region of interest (δ 1-2.5), the allylic methylene signals of the allyl-In species could not be seen. Nevertheless, the appearance of the new olefinic multiplets at δ 4.67 and at δ 4.80 after 4 h confirmed formation of CH_2=$CHCH_2$─$InBr_2$ (**II**).[77a,65a] In this case, although the allyl-In species remained stable up to 6.5 h (revealed by the NMR spectra), its formation required a long induction time. This might possibly account for the need to use the reagents in large excesses.

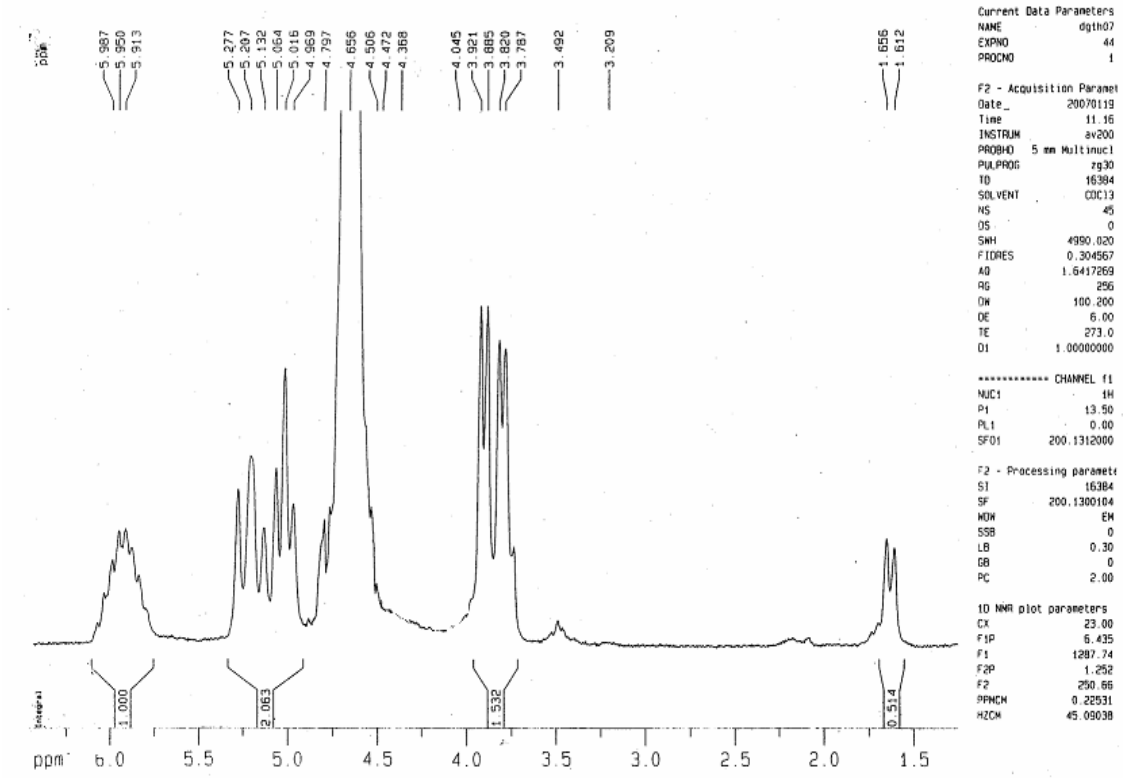


Figure II.3.4. ^{1}H NMR spectrum of the reaction mixture of In and allyl bromide in D_2O.

The ^{1}H NMR spectra of the reaction mixtures obtained in [bmim][Br] showed a new doublet at δ 2.01 as well as new olefinic multiplets at δ 4.59 and at δ 4.78, with

simultaneous reduction of the signal at δ 3.9. **Fig. II.3.5** shows the ^{1}H NMR spectrum of the reaction between In and allyl bromide in [bmim][Br], recorded in $CDCl_3$ after 2.5 h of stirring. Based on the previous report (^{1}H NMR signal at ~δ 2.01),[77] the allyl-In species generated in [bmim][Br] was also assigned structure **II**. In this solvent also, due to the overlapping NMR peaks at δ 1-2 from [bmim][Br], it was difficult to identify the species **I**, if any. However, the intensity of the ^{1}H NMR resonances in this region remained almost constant throughout the period of the study. This suggested that, possibly, **II** was the only species formed in the reaction mixture. It is worth mentioning that besides allenylindium, formation of allenylindium dibromide was also reported in the reaction between propargyl bromide and In.[78]

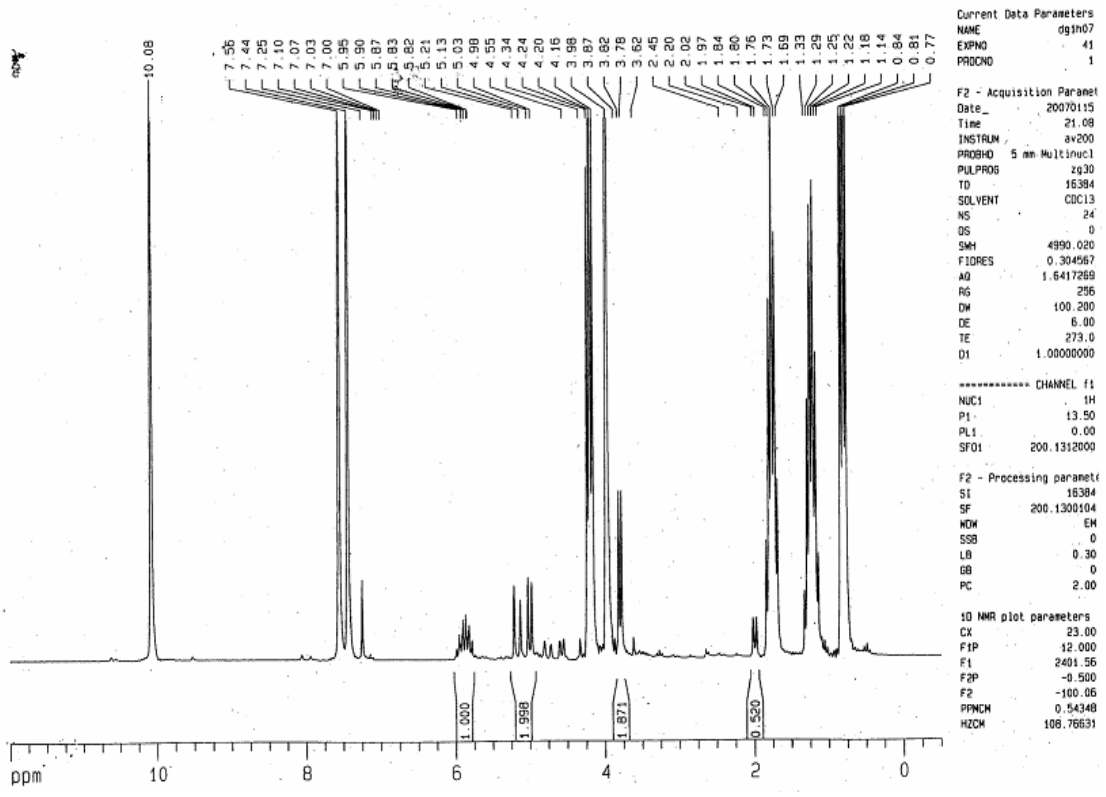
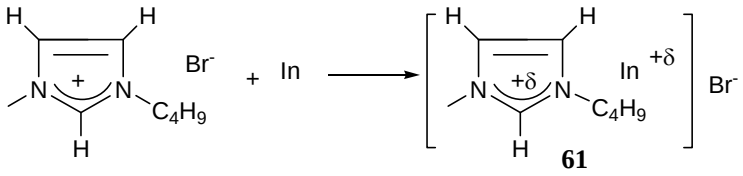


Figure II.3.5. ^{1}H NMR spectrum of the reaction mixture of In and allyl bromide in RTIL.

The integration of the signal at δ 2.01 reached a maximum (52.3%) in ~ 2.75 h, and remained steady up to 3 h. In spite of a very marginal decline in its intensity thereafter, a significant amount of the allyl-In species remained up to 5 h. Since the allylation was over in ~4 h, the reaction could be carried out without using excess of the reagents. Interestingly, the maximum concentration of the active species **II** formed in [bmim][Br] was significantly higher than that of **I** in H_2O. During the reaction with **59a**, complete depletion of the doublet (δ 2.01) confirmed **II** as the active organometallic species, as reported previously.[77b]

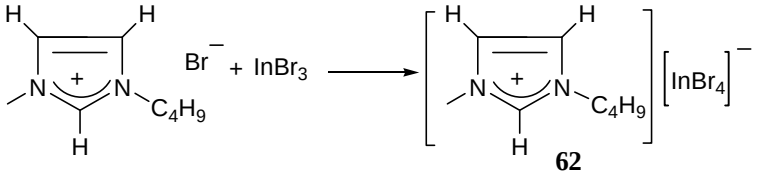
Recently Law et al. reported[77a] generation of both **I** and **II** in the reaction between In and allyl bromide in [bpy][BF_4]. They also suggested the possibility of the transformation of **I** to **II**, which, however, is slowed down when the RTIL contains a higher amount (>8.5 mol%) of its precursor, [bpy][Br]. Our results of the exclusive formation of **II** in [bmim][Br] (resembling [bpy][Br]) was most striking, and revealed a different operative mechanism in this medium. To confirm this, we also followed the reaction between In (1.5 mmol) and allyl bromide (1.5 mmol) separately in neat [bmim][BF_4], and [bmim][PF_6], as well as in the presence of [bmim][Br] (10 and 20%), using ^{1}H NMR experiments. Amongst the various combinations, only the combination of [bmim][BF_4] + [bmim][Br] (20%) produced the more downfield doublet (δ 2.01, J = 8.2 Hz) after 3 h, although appreciable signal was not detected up to 2 h. The maximum intensity of the signal (50.4%) was similar to that observed in [bmim][Br] alone. No such ^{1}H NMR resonances were, however, visible in [bmim][PF_6] even in the presence of [bmim][Br]. These results confirmed that unlike the previous observations,[77a] the RTIL, [bmim][Br] is essential for generating the species **II**.

The acceleration of the reaction in [bmim][Br] suggested activation of In metal by the RTIL so that its subsequent conversion to the species **II** is triggered. For investigating this aspect, the ^{1}H NMR spectrum of the RTIL (5 mL) was recorded after incubating with In (1.0 mmol) for 0.5 h. This led to upfield shifts of its imidazole protons. The shift followed the expected trend, and was maximum (4.2 Hz) for H-2, and less (3.8 Hz) for H-4 and H-5. The same trend could also been seen for the imidazole carbons, where an upfield shift of 10 Hz for C-2 and 6 Hz for both C-4 and C-5 were noticed. Addition of allyl bromide to the above mixture restored the ^{1}H and ^{13}C NMR resonances of the imidazole moiety of the RTIL. The upfield shifts of the ^{1}H and ^{13}C NMR resonances suggested electron transfer from In to [bmim][Br], activating the In-metal surface. Earlier surface reaction with In metal has been reported.[79] The metal-mediated Barbier reaction is proposed to be mediated through radicals on metal surface[80a,b] as well as metal surface activation especially in aqueous acidic media.[80c] The occurrence of charge transfer (CT) in RTILs is not also unprecedented.[79b,c] Although, The possibility of having free cations in ILs is quite remote,[81a] the imidazolium-based ILs have remarkable ability to promote electron transfer reactions.[79b,81b-c] However, the direct involvement of a metal in this process is unprecedented. Possibly the combination of In and [bmim][Br] forms ion pairs or more complex ion-aggregates such as **61** with a partially charged activated In as shown in **Scheme II.3.3**.



Scheme II.3.3

The standard reduction potential of [bmim][Br], measured using cyclic voltammetry (std. Calomel electrode as reference) was found to be 0.641 V. This also supported the possibility of CT between In and the RTIL. Regeneration of the RTIL on addition of allyl bromide also confirmed that the CT generated an activated In transient species. This facilitates its subsequent reaction with allyl bromide to furnish the active allylating species **II**. Although the allyl-In species **I** has been reported to be more reactive than the species **II**, our results revealed otherwise. This might be due to the polar nature of [bmim][Br]. The reduction potential of [bmim][Br] also suggested that In metal may got oxidized by [bmim][Br] to generate $InBr_3$, which would for **62** by reaction with [bmim][Br] (**Scheme II.3.4**). This was isolated and characterized by comparing the ^1H and ^{13}C NMR spectra with those reported[82] for the analogous chloride compound, as well as from the elemental analysis data. Addition of demineralized water to the above mixture produced $In(OH)_3$, which also indicated the presence of In(III) in the mixture.



62

Scheme II.3.4

The formation of the species **II** and the catalytic role of In could be partially rationalized considering the reactions shown in **Scheme II.3.5**. In the 1st path, the reaction of allyl bromide with the ([bmim][Br]—In) species directly produced the active species **II** along with propene or its precursor (eq. 1). Formation of the alkene was confirmed by trapping it with Br_2/CCl_4 to produce 1,2-dibromopropane that was characterized by ^1H NMR spectrum. The RTIL subsequently reacts with the evolved propene or most likely its

precursor to partially replenish the lost allyl bromide (**Scheme II.3.5**, eq. 2). The amount of alkene trapped by Br_2 was very less since very little amount of 1,2-dibromopropane was isolated. This suggested that most of propene or its precursor gets converted to allyl bromide. It is most likely that [bmim][Br] would react with propene precursor (allyl radical), producing less amount of propene.

Our ^{1}H NMR studies also suggested the operation of eq. 2, since there was a built-up of the peak at δ 3.8 at ~1.5-2 h. This was confirmed by a time-dependent GLC analysis (**Fig. II.3.6**) of the reaction mixture that showed a sharp decline (60-110 min), followed by a gradual rise of the concentration of allyl bromide, which finally became steady. Evidently, at the initial stage, formation of **II** was very fast due to the high concentration of allyl bromide, and the growth of the latter could only be seen at a latter stage. A steady concentration of **II** at ~3 h (NMR results) was also in consonance with these results.

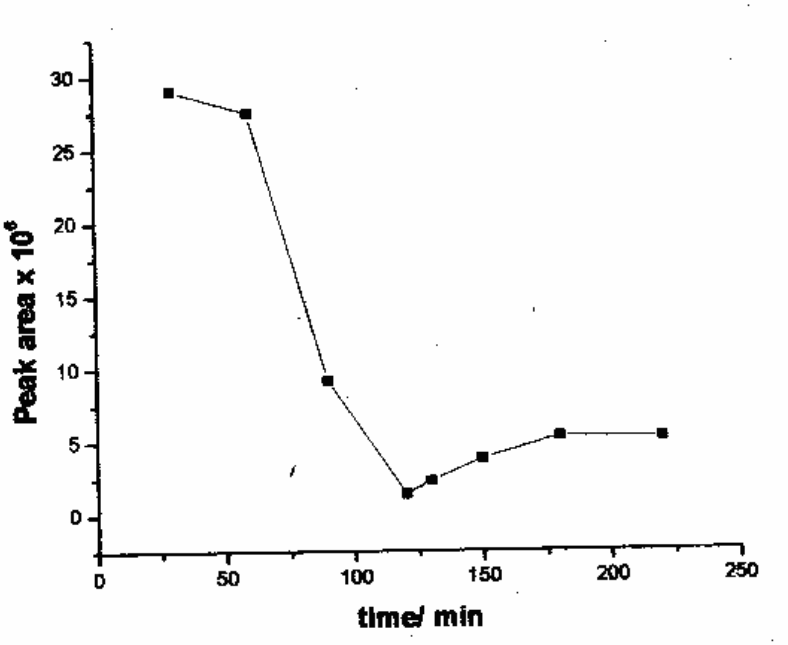
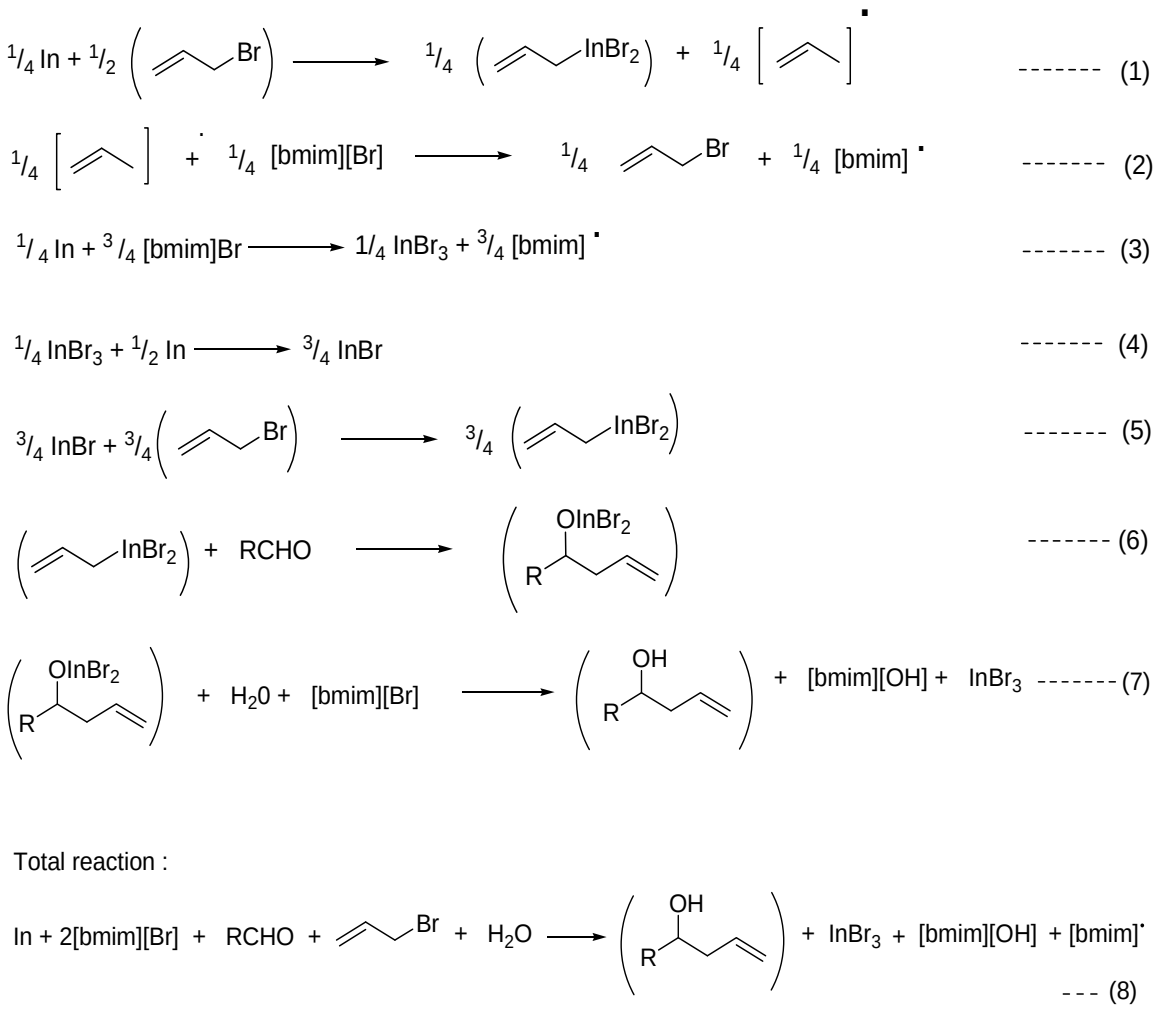


Fig. II.3.6. GLC analysis of the time dependent concentration variation of allyl bromide

It has also been reported,[83a,b] that in acidic conditions, there is equilibrium such as 2In (s) + 2 In^{+3} = 3 In^{+1}. Given that [bmim][Br] is acidic (pH = 5.78), such an equilibrium exists in the acidic protic ionic liquid. Therefore, InBr was formed in the reaction mixture. The resultant InBr would then react with allyl bromide to furnish the active species **II** (eq. 5). Hence, there are two competitive pathways for the formation of **II,** viz. (i) formation of **II** from activated In metal (**Scheme II.3.5**, eq. 1), and (ii) formation of **II** via oxidation of In metal and subsequent reaction with allyl bromide (**Scheme II.3.5**, eq. 3-5).



Scheme II.3.5

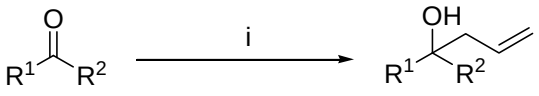
Once produced, the species **II** reacts with the aldehyde to produce the homoallyloxy-In species (eq. 6). Its hydrolysis by H_2O (measured as 230 ppm by Karl-Fischer titrimeter) present in the RTIL, gave the homoallylic alcohol product and $InBr_3$ (eq. 7). Though we could not isolate [bmim][OH] from the reaction mixture, the increase of pH from 5.78 to 8.23 indicated its formation. Also, it has been observed that a slight excess (1.2 eqv.) of allyl bromide is required for the completion of the reaction. This may be because of slow conversion of allyl bromide to allyl alcohol by [bmim][OH]. Only trace amount of allyl alcohol could be detected in the reaction mixture, and it indicated its slow formation.

During the process, the reaction medium becomes alkaline (pH 8.23) due to the formation of [bmim][OH], which is known to generate the NHC-carbene diradical from imidazolium ionic liquids.[84] This, eventually, forms a bisimidazolidene moiety which is reported to be a super electron donor, and is used as a reducing agent in some reactions.[85] We also speculated that such moiety may have been formed in the reaction mixture, and this moiety, along with the radical [bmim]$^{\cdot}$**,** is responsible for the reduction of In^{+3} to metallic In. Thus the catalytic cycle is maintained without further addition of In metal.

Thus, a catalytic protocol for allylation of aldehydes, involving use of indium metal and allyl bromide in [bmim][Br] has been developed. Besides acting as a solvent, the chosen RTIL also participates chemically to activate the In-metal and helps in regeneration of In from In(III), produced during the allylation reaction. This makes the process catalytic with regard to the In-metal. The stability of the active allylmetal species **II** in the RTIL during the reaction also ensures the use of stochiometric amount of allyl bromide.

II.3.3 *Gallium mediated allylation in [bmim][Br]*

Despite several advantages of Ga-metal such as low first ionization potential (5.99 eV), non-toxicity, ease of handling (as a liquid at room temperature), and least reactivity with air and moisture, studies on Ga-mediated allylation protocols are limited. The earlier reports with Ga-mediated Barbier type reactions were primarily restricted to reactions in water and/ or organic solvents, but not in RTIL. Based on our above studies on the In-mediated allylation, [bmim][Br] appeared best suited for such a transformation. It was envisaged, that, like in the case of indium, the stronger oxidizing power of [bmim][Br] might facilitate a dipolar interaction between Ga-metal and the imidazolium moiety of [bmim][Br], leading to the required metal activation. The standard reduction potential of [bmim][Br] (0.641 V) was also suggestive of such an interaction. Thus, it was envisaged that a combination of Ga and [bmim][Br] might trigger the allylation reaction without the need of any metal activation by chemical additives and/ or energy sources (thermal/ultrasonic). Based on this rationale, a novel method for metallic gallium activation was explored using [bmim][Br] as the solvent as well as a reacting partner. This also led to an efficient method for a green and energy-efficient route to the Barbier-type allylation of aldehydes and ketones.



59a-q **60a-q**

(i) Allyl bromide, Ga, solvent.

Scheme II.3.6

Initial studies (**Scheme II.3.6**, **Table II.3.3**) were carried out with benzaldehyde (**59a**) as the substrate in various media and under different conditions (stoichiometry,

presence or absence of additives etc.) revealed [bmim][Br] as the most efficient medium for the Ga-mediated allylation. The reaction carried out in H_2O or THF even in the presence of activators proceeded slowly giving the product **60a** in 63% and ~49% yields respectively (**Table II.3.3**, entries 1-3) , while even under sonication in THF, **60a** was obtained in 71-73% yield (**Table II.3.3**, entries 4,5) in 16 h. A large excess of Ga (5 equiv.) and allyl bromide (3 equiv.), as well as extended reaction time were required for the reactions in H_2O or THF, while reducing the amounts of the reagents and/ or the reaction time led to significantly poorer results. The commonly used RTILs, [bmim][BF_4], and [bmim][PF_6], even in the presence of [bmim][Br] (20 mol%) as the activator furnished **60a** in 62-64% yields after 20 h (**Table II.3.3**, entries 6-8). However, allylation of **59a** in [bmim][Br] was very fast (4 h) furnishing **60a** in 82-84% yield, without requiring any metal activator (**Table II.3.3**, entries 9,10). Instead, the reactions in [bmim][Br] could be accomplished with only 1.2 equiv. of the bromide and 1 equiv. of Ga. Subsequently we accomplished the allylation of **59a** using only 0.5 equiv. of Ga to obtain **60a** in a similar yield (**Table II.3.3**, entry 11). So far, similar attempt with Ga has not been reported in any RTIL.

Table II.3.3. Reaction profile of Ga-mediated allylation of **59a** in various solvents[a]

entry	Allyl bromide (equiv.)	metal (equiv.)	Solvent	additive	time (h)	yield (%) of **60a**[b]
1	3.0	5.0	H_2O	LiCl+KI[c]	16	63
2	3.0	5.0	H_2O	--	24	47
3	3.0	5.0	THF	LiCl+KI[c]	24	49
4	3.0	5.0	THF	--	16[d]	73

5	3.0	5.0	THF	LiCl+KI[c]	14[d]	71
6	1.2	2.0	[bmim][BF_4]		20	64
7	1.2	2.0	[bmim][PF_6]		20	62
8	1.2	2.0	[bmim][BF_4]	[bmim]Br][c]	20	64
9	1.2	2.0	[bmim][Br]	--	4	82
10	1.2	1.0	[bmim][Br]	--	4	84
11	1.2	0.5	[bmim][Br]	--	4	84

[a]The reactions were carried out at 2 mmol scale. [b]Yield of isolated product. [c]The reaction was carried out in the presence 1.0 equiv. of LiCl+KI or 20 mol% [bmim][Br]. [d]The reaction was carried out under ultrasonic irradiation.

The scope of the sub-stoichiometric protocol (0.5 equiv. Ga) was further explored with several aromatic and aliphatic aldehydes **59b-k** as well as ketones **59l-q** (**Scheme II.3.6**, **Table II.3.4**). The protocol was equally effective with both aromatic and aliphatic aldehydes. With the aromatic aldehydes, the products **60b-g** were produced in moderate to good (67-87%, **Table II.3.4**, entries 1-6) yields, irrespective of the presence of any electron withdrawing or donating group, or a heteroatom in the aromatic ring. However, no reaction was observed with 2-hydroxy-4-ethoxybenzaldehyde, containing a free phenolic group. This is consistent with a previous report where alkyl gallium compounds are reported to react preferably with the acidic phenolic moiety.[86] Likewise, the aliphatic aldehydes also furnished the corresponding allylated products **60h-60j** in high yields (**Table II.3.4**, entries 7-9). The lower yield of **60h** might be due to its volatility. The protocol was also useful with both aromatic and aliphatic ketones **59l-q** furnishing the products **60l-q** in 67-81% yields (**Table II.3.4**, entries 11-16) without any significant role of the steric and/ or electronic factors. Earlier, the Zn, Bi, and In-mediated allylation of

acetophenone (**59l**) under a solvent-free condition was largely unsuccessful,[87a] although the In-mediated allylation of **59l** and **59q** was reported in water.[65b] So far, Ga-mediated allylation of only one ketone, **59l** has been reported.[87b] Thus, this protocol was more versatile and could be used even for the bulky and electronically demanding substrates such as **59m-59p**. As in earlier cases with In mediated allylations, the formation of homoallylic alcohols was confirmed from the hydroxyl band at ~3500 cm^{-1} along with the terminal olefinic band at 910-930 cm^{-1} in the respective IR spectrum. Furthermore, all the products showed ^{1}H NMR resonances at δ 5.0-5.2 (2H) and δ 5.7-5.9 (1H), and ^{13}C NMR resonances at δ ~114 and δ ~134 due to terminal olefins. As representative examples, the ^{1}H NMR and ^{13}C NMR of **60g** are shown in **Fig. II.3.7** and **Fig. II.3.8**.

Chemo- and stereoselective allylation of multifunctional compounds is one of the most fundamental goals in constructing complex molecules. The new protocol of allylation proceeded with complete chemoselectivity with the conjugated carbonyls, **59g** and **59o**, furnishing the respective 1,2-addition products **60g** and **60o** only, while only the mono allylated product **60n** was obtained with the diketone **59n**. Interestingly, allylation of 2-methylcyclohexanone (**59q**) under the above conditions exclusively furnished *E*-**60q** in excellent yield (**Table II.3.4**, entry 16).

Table II.3.4. Reaction profile of Ga-mediated allylation of various aldehydes in [bmim][Br][a]

Entry	Substrate	R_1	R_2	Product	Time (h)	Yield (%)[b]
1	**59b**	4-Br-C_6H_4	H	**60b**	6	77
2	**59c**	3-OMe-C_6H_4	H	**60c**	5	84

3	**59d**	4-$(CH_3)_2CH$-C_6H_4	H	**60d**	5	87
4	**59e**	4-C_6H_5- C_6H_4	H	**60e**	6	83
5	**59f**	C_6F_5	H	**60f**	5	83
6	**59g**	C_6H_5CH=CH	H	**60g**	12	79
7	**59h**	$(CH_3)_2CH$	H	**60h**	8	67
8	**59i**	$CH_3(CH_2)_5$	H	**60i**	6	84
9	**59j**	$CH_3(CH_2)_8$	H	**60j**	5	95
10	**59k**	3-Indolyl	H	**60k**	5	72
11	**59l**	C_6H_5	CH_3	**60l**	10	71
12	**59m**	C_6H_5	C_6H_5	**60m**	16	67
13	**59n**	C_6H_5CO	C_6H_5	**60n**	8	77
14	**59o**	C_6H_5CH=CH	Ph	**60o**	8	81
15	**59p**	Cyclohexanone		**60p**	7	78
16	**59q**	2-Methylcyclohexanone		**60q**	7	77[c]

[a]The reactions have been carried out at 2 mmol scale. [b]Yields of the isolated products. [c]Exclusively *E*-product was obtained.

The reactions proceeded smoothly without any side reactions such as reduction and coupling, and furnished the products devoid of side products and/ or starting materials. Only with the ketone **59m**, the reaction was incomplete allowing the recovery of 18% of the substrate. In general, the reaction yields were more than those reported in other solvents.

The above results clearly established [bmim][Br] as the best RTIL among those chosen for the Ga-mediated allylation also. The reactions were much faster in [bmim][Br],

even without any metal activator, and could be executed with only a sub-stoichiometric quantity of Ga, providing economic and environmental advantages. Excess reagents and toxic metal activators such as acid or fluoride, were required in H_2O. Finally, unlike in H_2O or THF, the reaction in [bmim][Br] took place at an ambient temperature, which was conducive while using more volatile reagents such as allyl bromide.

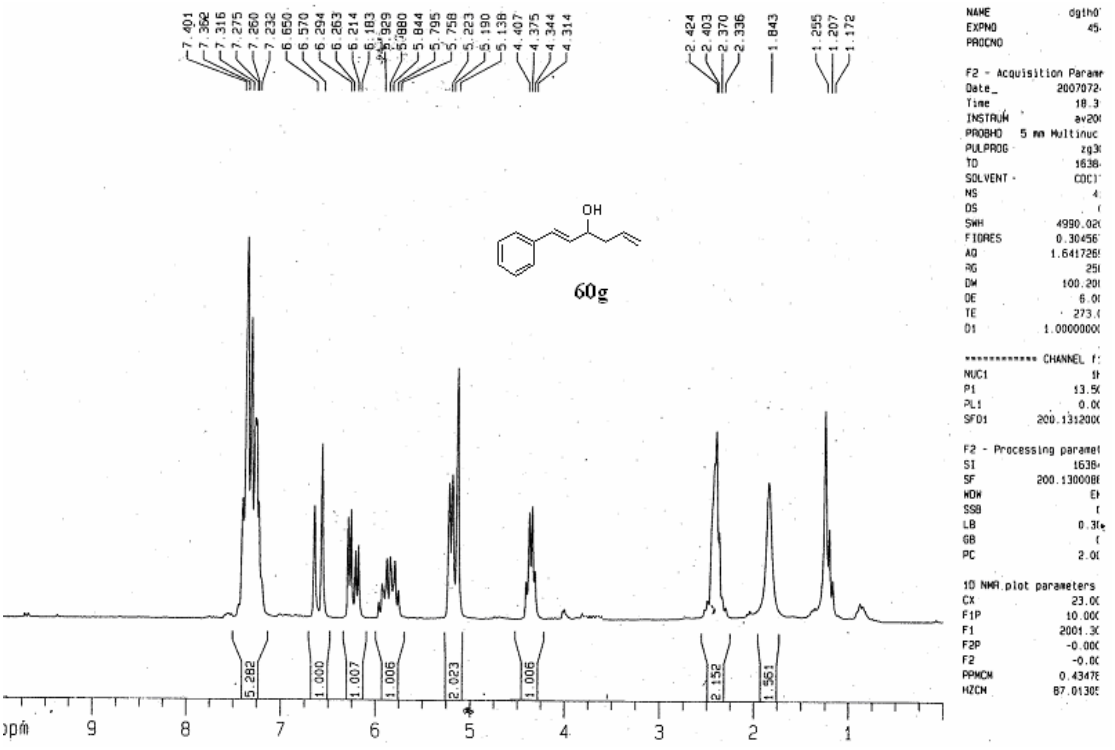


Fig. II.3.7. ^{1}H NMR spectrum of 60g

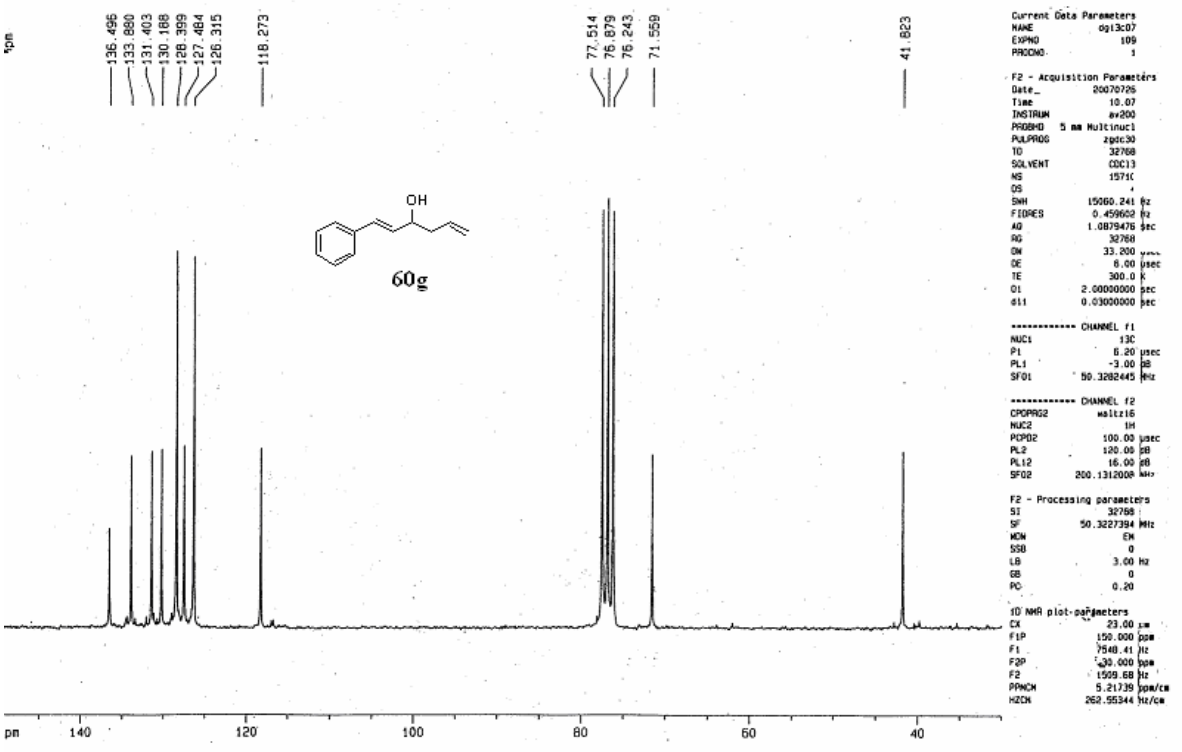


Fig. II.3.8. ^{13}C NMR spectrum of 60g

Mechanistic studies: For the mechanistic insight of the activating role of [bmim][Br], the nature of the organometallic species, responsible for allylation was probed. For this, the course of the reaction between Ga (1 mmol) and allyl bromide (1 mmol) in [bmim][Br] (2 mL) was followed over a time period (up to 8 h), by ^{1}H NMR spectra. The intensity of the NMR peak due to the CH_2-Ga protons in the allyl-gallium species was quantified by comparing with that of the CH_2Br signal of allyl bromide. The ^{1}H NMR spectra of the reaction mixtures obtained in [bmim][Br] showed a new doublet at δ 1.63 (J = 6.4 Hz) with simultaneous reduction of the signal at δ 3.9. In addition, new olefinic multiplets at δ 4.59 at the expense of that at δ 4.78 also emerged, and these resonances together accounted for two protons over the entire period of studies. The ^{1}H NMR doublets for the CH_2-Ga protons suggested[66a] $(CH_2CH{=}CH_2)_2GaBr$ (**III**) as the active allyl-Ga species, which was confirmed by its isolation (distillation at 45 ^{o}C), followed by spectral (^{1}H and ^{13}C NMR),

and chemical analysis. ^{1}H NMR spectra (**Fig. II.3.9**) of **III** showed olefinic signals at δ 4.91-5.06 and at δ 5.71-5.91 ppm, whereas the allylic protons gave a doublet at δ 1.69 ppm. Its ^{13}C NMR spectrum (**Fig. II.3.10**) showed the peak due to allylic carbon at δ 33.1 ppm. An analogous compound, $(CH_2CH{=}CH_2)_2GaCl$, synthesized following a reported procedure,[88] also provided a similar ^{1}H NMR spectrum. The sesquibromide, $(CH_2CH{=}CH_2)_3GaBr_3$, produced[66b] in THF, was not formed in [bmim][Br]. The integration of the NMR signals for **III** reached a maximum (~48%) in ~ 3.5 h, and remained steady even up to 8 h. Addition of **59a** to the reaction mixture led to complete depletion of the signal, confirming **III** as the active organometallic species.

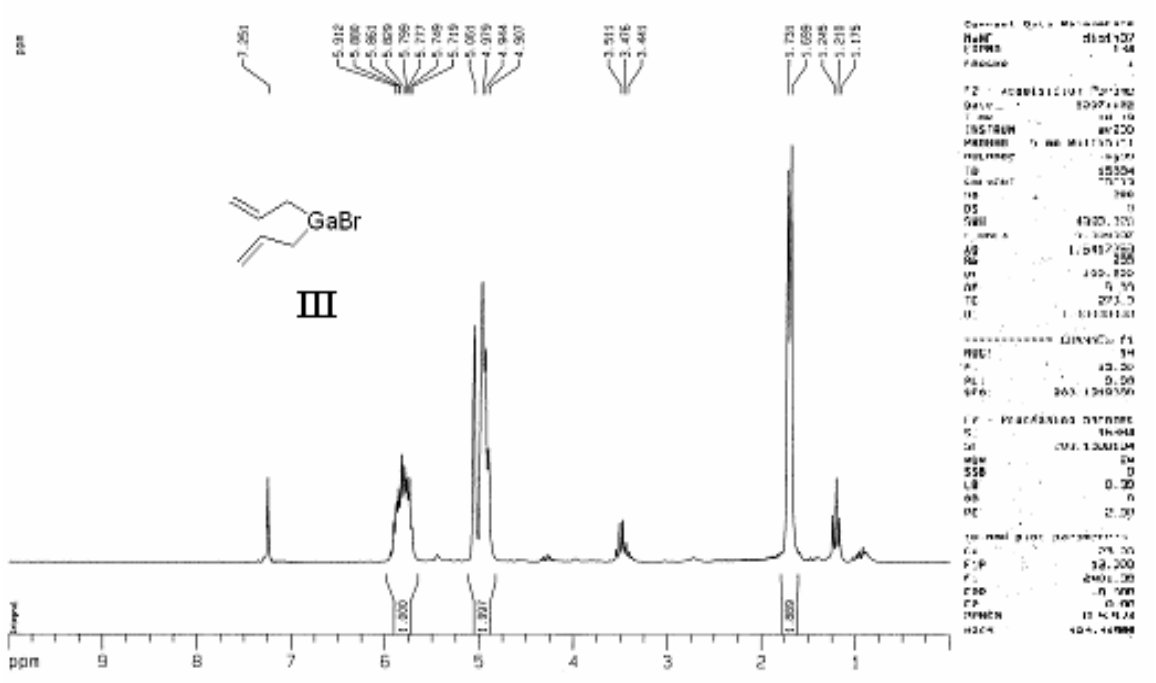


Fig. II.3.9. ^{1}H NMR spectrum of III

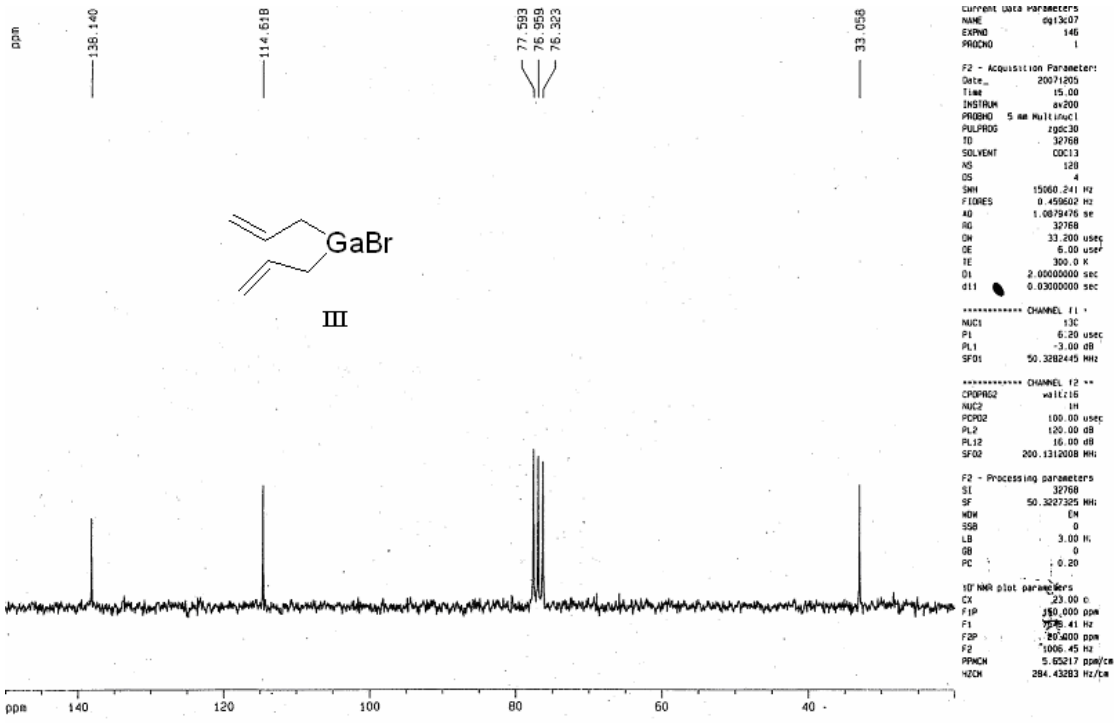
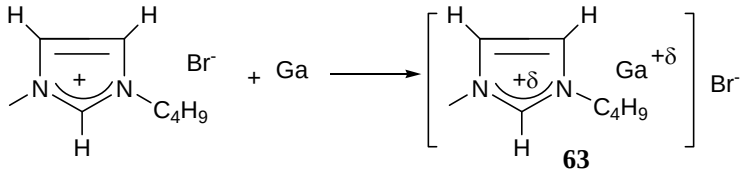


Fig. II.3.10. ^{13}C NMR spectrum of III

With regard to the activation of Ga metal, a dipole induced dipole interaction with [bmim][Br] was envisaged. The ^{1}H NMR spectrum of the reaction mixture after incubating [bmim][Br] (5 mL) with Ga (1.0 mmol) for 0.5 h, showed upfield shifts for the imidazole H-2 (3.8 Hz), and H-4 and H-5 (each 3.4 Hz) protons. The shift followed the expected trend, considering maximum positive charge density at C-2 of the imidazole ring. The same trend could also been seen for the imidazole carbons , where an upfield shift of 10 Hz for C-2 and 6 Hz for both C-4 and C-5 were noticed. These results suggested that polarization of Ga metal took place in presence of [bmim][Br] which would activate the Ga-metal surface. The NMR shifts of similar magnitudes are generally attributed to the charge transfer phenomenon. Possibly the combination of Ga and [bmim][Br] initially forms ion pairs or more complex ion-aggregates with an activated Ga (**Scheme II.3.7**). The

standard reduction potential (0.641 V) of [bmim][Br] also supported the possibility of CT between Ga and the RTIL.

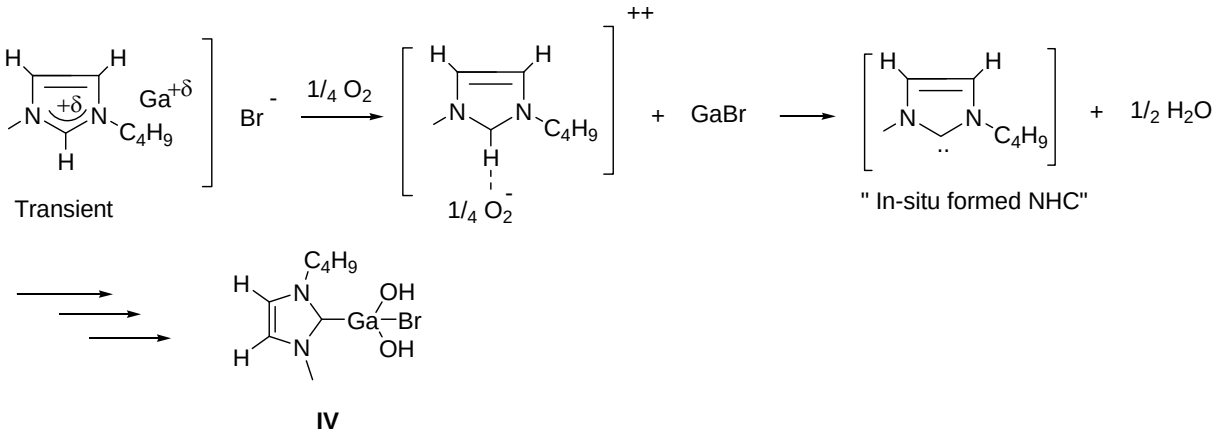


63

Scheme II.3.7

On continued stirring for 1-1.5 h, the mixture of [bmim][Br] and Ga (1.0 mmol) eventually produced a gray solid. The thermal stability of the solid was studied using differential scanning calorimetry (DSC). This showed a gradual mass loss starting at ~120^{o}C accompanied by a large endothermic thermal transition at ~162 ^{o}C producing Ga metal (**Fig. II.3.11**). The residue after first heating was cooled and again heated; this time it clearly indicated the presence of Ga metal. Sucessive experiments produced Ga metal in pure form, leaving the carbine residue, which was confirmed by recording the ^{1}H NMR spectrum of the organic residue left after the DSC experiment. This indicated the generation of a *N*-heterocyclic carbene (NHC), suggesting it to be an organometallic compound containing a NHC moiety. Its IR spectrum (thin film) displayed a strong –O-H stretching band (3545 cm^{-1}), while a ^{1}H NMR singlet at δ 7.21 (2H) (**Fig. II.3.12**) and ^{13}C NMR (**Fig. II.3.13**) resonances at δ 121.7 and 123.3 (olefin) along with δ 175.9 (carbene) revealed the presence of a *N*-heterocyclic carbene (NHC) moiety. The Raman spectrum confirmed the Ga-C (697 cm^{-1}) and Ga-O (330 and 662cm^{-1}) bonds, while excluding any Ga-Ga and Ga-O-Ga bonds.[89] The electron impact mass spectrum showed a [M^{+}-57] ion peak at m/z 264 (17 %), a [M^{+}-Br] ion peak at m/z 241 (11%), and a major fragmentation peak at m/z 184 (18%) ($GaBr(OH)_2$) in the correct isotopic pattern. In addition, a major

fragmentation peak at m/z 138 (19%) accounted for the NHC moiety. Also the moiety was heated under Ar atmosphere, and the evolved gases were characterized. It was found that the moiety produced Br_2 and H_2O, which clearly established that the moiety contained –OH and Br. Based on these, the intermediate was assigned the structure [NHC-GaBr$(OH)_2$] (**IV**). The NMR data was also clean without showing presence of any isomers, consistent with the proposed monocarbene structure of the complex. Possibly, the dipole induced dipolar interaction between Ga and RTIL helped in a transfer of one electron to the oxygen dissolved in the RTIL.[90] This furnisheed the superoxide radical anion, which was stabilized by the acidic C-2 hydrogen of [bmim][Br], facilitating the process.[91] This eventually produced the proposed NHC, which, in view of its good σ-donating ability stabilized the Ga (I) species. Further, the poor stability of the sterically less hindered cyclic carbine:Ga(I) eventually produced the species **IV** by oxidation (**Scheme II.3.8**). This type of reaction is well established in M-NHC chemistry, but the mechanism remains unclear.[92]



Scheme II.3.8

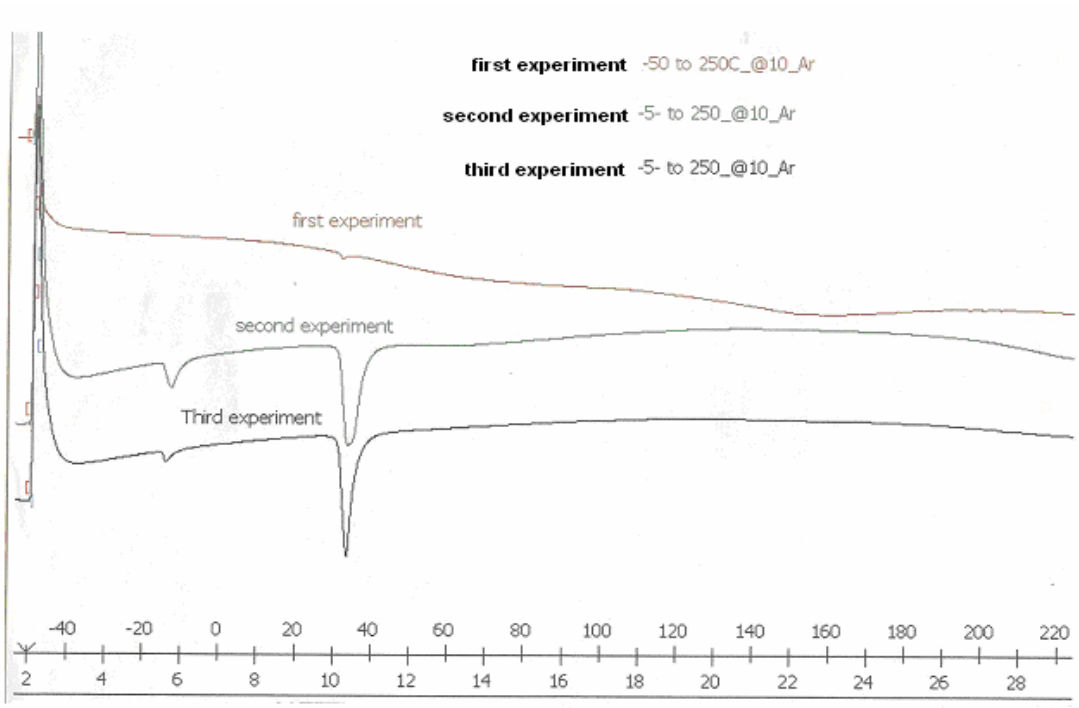


Fig. II.3.11. DSC results of compound IV

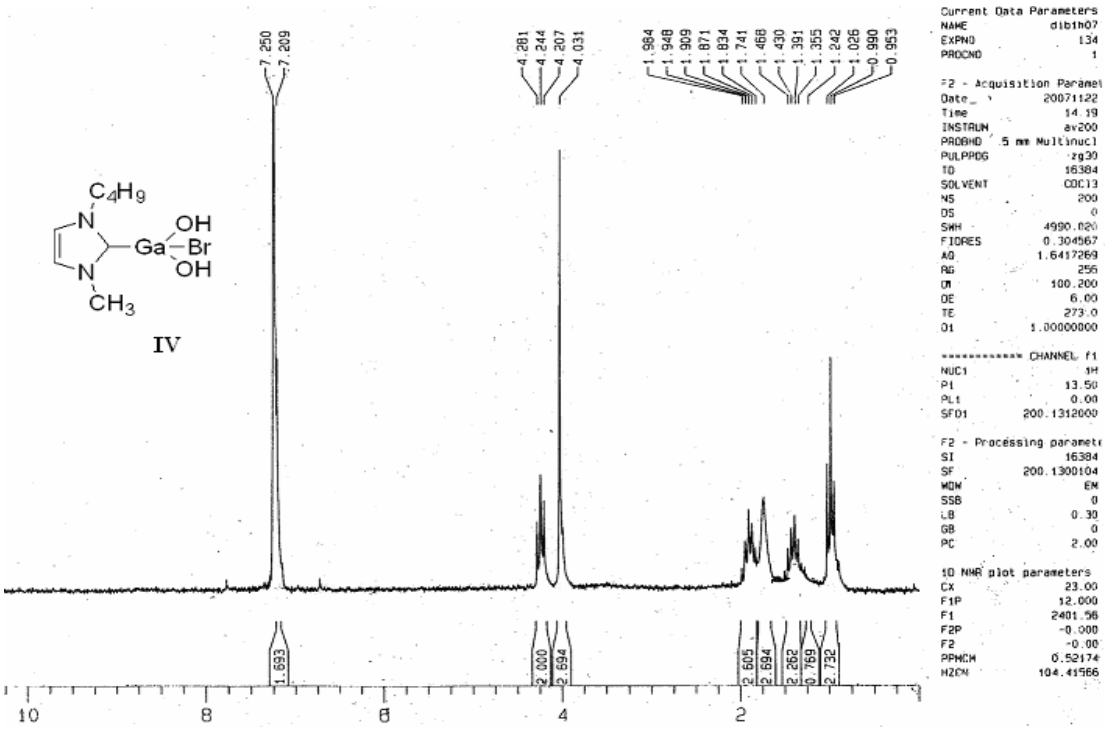


Fig. II.3.12. ^{1}H NMR spectrum of IV

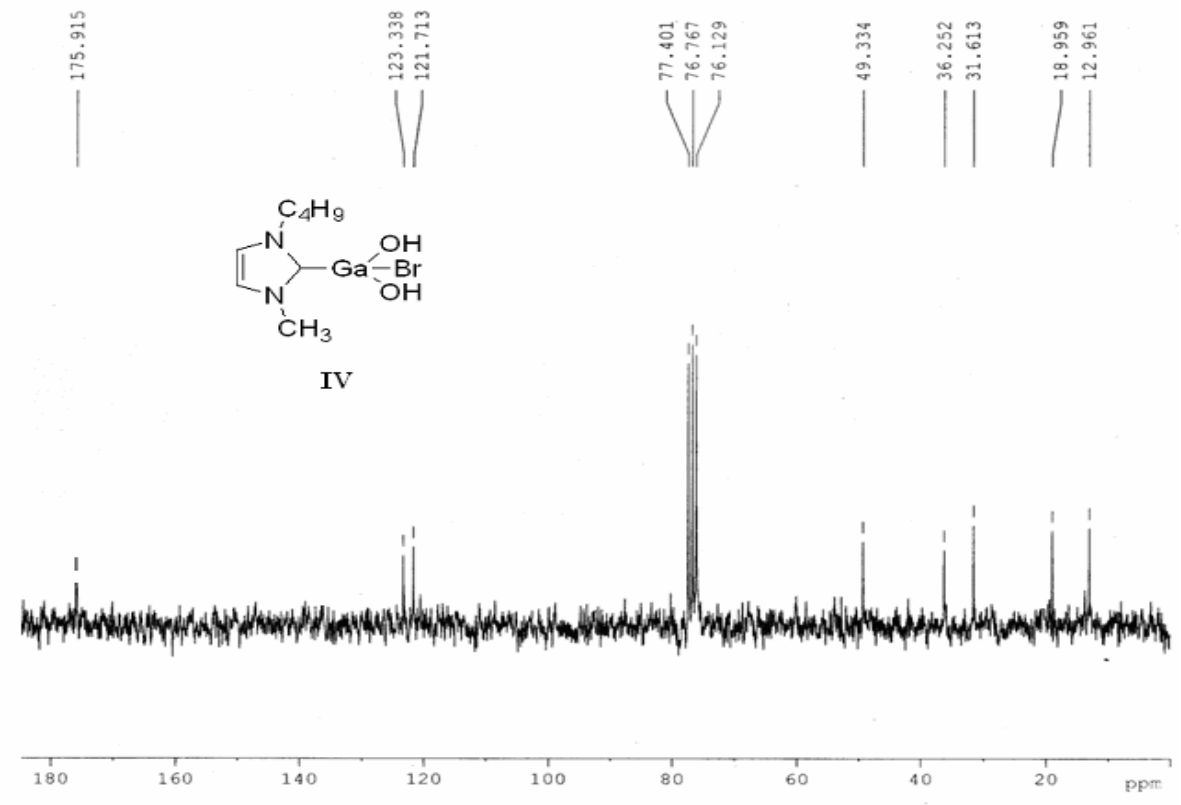


Fig. II.3.13. ^{13}C NMR spectrum of IV

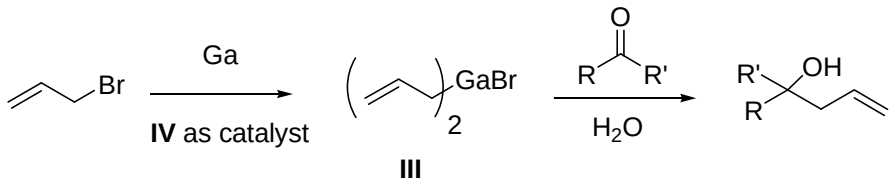
To support the hypothesis, the reaction between Ga and allyl bromide was carried out in deaerated [bmim][Br], where the formation of **IV** was not noticed. Expectedly, purging the same reaction mixture with O_2 produced the same Ga-intermediate, establishing the proposed mechanism. The compound **IV** was volatile and could be purified by sublimation in high vacuum. However, despite intensive efforts, we failed to isolate it in crystalline form, restricting the complete identification of its structure. The XRD analysis was inconclusive except for showing its amorphous nature.

Several authors have suggested a link for the fast chemical conversion of imidazolium ion to the NHC on the surface of a nanoparticle.[93] Our hypothesis of direct adduct formation of a NHC with Ga metal was consistent with this. Our hypothesis was also in tune with the theoretical DFT calculation wherein a similar oxidative addition of

the imidazolium salts to Pt(o) has been shown to be exothermic.[94] Since their description by Wanzlic[95a-c] and Arduengo,[95d-f] stable NHCs have been a significant area of study and several crystalline and well-characterized NHC complexes with main group and especially transition metals have been synthesized.[96] The NHCs can stabilize thermally labile or low oxidation state metal fragments, and the complexes can be used for various organic transformation. The use of NHCs as good σ-donor molecules to stabilize trivalent group 13 compounds is well established.[96a,97] Over the past few years there has been a rapidly increasing interest in the chemistry of metastable gallium complexes. The propensity of alkyl gallium reagents to interact with Lewis bases has become a cornerstone in organometallic chemistry. To this end, a large number of NHC-complexes with metal (Al, In, and Ga) hydrides and halides have since been synthesized.[95e,98] However, formation of Ga-NHC directly from the metal is novel and opens various new possibilities in organic synthesis as well as material developments. Sterically non-hindered NHCs are often sensitive to air and moisture, making their isolation and use difficult.[95d,99] However, in this case its formation was achieved in a hygroscopic RTIL, also required O_2.

Earlier, the Pd-carbene complexes have been shown to be efficient catalysts for the Heck and related C–C bond forming reactions.[69e] It was also found that the Ga-carbene complex **IV** acts as a catalyst in the formation of **III**. A catalytic amout of **IV** was added to the mixture of Ga metal and [bmim][Br] prior to the addition of allyl bromide, and it was observed that the formation of **III** was catalysed and subsequently the reaction (**Scheme II.3.9**) was also faster. The exact mechanism of the catalysis is at present, far from clear. It may in fact turn out to follow a much more complex pathway. The Ga-NHC complex might be the precursor, which would generate a zero-valent Ga-NHC species as the likely

active catalyst, as suggested for the Pd-catalyzed heck reaction in [bmim][Br]. The probable reaction sequence involved in the process of Ga-activation and the allylation reaction is shown in **Scheme II.3.9**.



Scheme II.3.9

Actually the Ga-NHC **(IV)** forms a coating over the Ga-metal surface. Consumption of **IV** for the the formation of the active allylgallium species **III** leads to the exposure of new metal surface, which, inturn, gets activated and takes part in the reaction. The carbine complex is catalytically active for allylation reaction.

In summary, a novel method for Ga metal mediated allylation reaction of carbonyls in [bmim][Br] could be accomplished. This type of Ga mediated allylation of carbonyls in any RTIL was not previously known. The imidazolium cation is usually considered as a simple inert component of a solvent system, and its possible involvement in a catalytic cycle, especially with a free a metal is rarely an issue. The present study established that [bmim][Br] reacts with Ga to give the Ga-NHC complex (**IV**). This also provided a method of base-free generation of NHCs through aerobic oxidation of a free metal, although a similar protocol was reported with transition metal complexes.[81b,c] This is very interesting since strong bases can cause various side reactions. It is also expected that the present results will open up many applications towards synthesizing stable NHCs in RTILs and applying those as versatile heterogeneous catalysts in many organic reactions.

II.4 EXPERIMENTAL SECTION

Typical procedure for the In-and Ga-mediated allylation reaction in ionic liquids. A mixture of In/Ga and allyl bromide in the RTIL (3 mL/mmol) was stirred at room temperature for 0.5 h, followed by addition of the aldehyde. The reaction mixture was stirred at room temperature till the completion of the reaction (*cf*. TLC). The mixture was thoroughly extracted with Et_2O (10 mL), the combined ether extracts evaporated in vacuo and the residue purified by column chromatography (silica gel, EtOAc/hexane) to give the respective products. Quantities of allyl bromide and the reaction times are specified in the respective tables.

Following a similar method, allylation of **59a** was also carried out in H_2O and THF using the amounts of the reagents as specified in the respective tables.

NMR experiments. A mixture of the In or Ga (1.0 mmol) and allyl bromide (1.0 mmol) in the respective solvent (3 mL) was magnetically stirred at room temperature. Aliquots (35 μL) of reaction mixture were taken at different time intervals, and the ^{1}H NMR spectra were recorded in $CDCl_3$ or D_2O.

GLC experiments. A mixture of In (1.0 mmol) and allyl bromide (1.0 mmol) in [bmim][Br] (3 mL) was magnetically stirred at room temperature. Aliquots (66 and 132 μL) of reaction mixture were drawn at different time intervals, extracted with Et_2O (1 mL) and the ether extract (1 μL) was analyzed by GLC (3% OV-17, 45 ^{o}C, isothermal).

1-Phenyl-but-3-en-1-ol 59a. Colourless liquid; IR: 3468, 922 cm^{-1}; ^{1}H NMR: δ 1.94 (broad s, 1H), 2.45-2.56 (m, 2H), 4.74 (t, *J* = 6.8 Hz, 1H), 5.10-5.25 (m, 2H), 5.65-5.93 (m, 1H), 7.26-7.40 (m, 5H); ^{13}C NMR: δ 43.8, 73.2, 118.4, 125.8, 127.5, 128.4, 134.4, 143.8. Anal. Calcd. for $C_{10}H_{12}O$: C, 81.06; H, 8.16%. Found: C, 81.26; H, 7.89%.

1-(4-Bromophenyl)-but-3-en-1-ol 59b. Colourless liquid; IR: 3389, 910 cm^{-1}; ^{1}H NMR: δ 2.14 (broad s, 1H), 2.34-2.53 (m, 2H), 4.67 (t, *J* = 6.6 Hz, 1H), 5.10-5.17 (m, 2H), 5.65-5.86 (m, 1H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR: δ 43.8, 72.5, 118.8, 121.2, 127.5, 131.4, 133.9, 142.8. Anal. Calcd. for $C_{10}H_{11}BrO$: C, 52.89; H, 4.88%. Found: C, 52.66; H, 4.72%.

1-(3-Methoxyphenyl)-but-3-en-1-ol 59c. Colourless liquid; IR: 3418, 916 cm^{-1}; ^{1}H NMR: δ 2.18 (broad s, 1H), 2.49-2.53 (m, 2H), 3.80 (s, 3H), 4.69 (t, *J* = 6.2 Hz, 1H), 5.10-5.19 (m, 2H), 5.70-5.91 (m, 1H), 6.79-6.91 (m, 3H), 7.21-7.29 (m, 1H); ^{13}C NMR: δ 43.7, 55.2, 73.2, 111.3, 112.9, 118.1, 118.3, 129.4, 134.4, 145.6, 159.7. Anal. Calcd. for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92%. Found: C, 73.86; H, 7.68%.

1-(4-Isopropylphenyl)-but-3-en-1-ol 59d. Colourless liquid; IR: 3388, 915 cm^{-1}; ^{1}H NMR: δ 1.26 (d, *J* = 6.8 Hz, 6H), 2.08 (broad s, 1H), 2.51 (t, *J* = 6.6 Hz, 2H), 2.88-2.94 (m, 1H), 4.70 (t, *J* = 6.6 Hz, 1H), 5.12-5.21 (m, 2H), 5.76-5.84 (m, 1H), 7.26 (q, *J* = 8.0 Hz, 4H); ^{13}C NMR: δ 24.0, 33.8, 43.7, 73.2, 112.0, 118.1, 125.8, 126.4, 134.7, 141.3, 148.2. Anal. Calcd. for $C_{13}H_{18}O$: C, 82.06; H, 9.53%. Found: C, 82.16; H, 9.74%.

1-(4-Phenylphenyl)-but-3-en-1-ol 59e. Colourless liquid; IR: 3583, 911 cm^{-1}; ^{1}H NMR: δ 2.18 (broad s, 1H), 2.53-2.59 (m, 2H), 4.78 (t, *J* = 6.6 Hz, 1H), 5.15-5.24 (m, 2H), 5.75-5.95 (m, 1H), 7.24-7.41 (m, 5H), 7.45-7.61 (m, 4H); ^{13}C NMR: δ 43.8, 73.0, 118.5, 126.3, 127.0, 127.1, 127.3, 128.8, 134.4, 140.4, 140.8, 142.9. Anal. Calcd. for $C_{16}H_{16}O$: C, 85.68; H, 7.19%. Found: C, 85.56; H, 7.02%.

1-Pentafluorophenyl-but-3-en-1-ol 59f. Colourless liquid; IR: 3408, 926 cm^{-1}; ^{1}H NMR: δ 2.50-2.82 (m, 3H), 5.05-5.17 (m, 3H), 5.62-5.79 (m, 1H); ^{13}C NMR: δ 41.1, 65.6, 116.3

(t, $^{2}J_{F}$ = 13.5 Hz), 119.4, 132.4, 137.5 (m), 140.5 (m), 144.7 (m). Anal. Calcd. for $C_{10}H_7F_5O$: C, 50.43; H, 2.96%. Found: C, 50.24; H, 3.14%.

(*E*)-1-Phenylhexa-1,5-dien-3-ol 59g. Colourless liquid; IR: 3425, 916 cm^{-1}; ^{1}H NMR: δ 1.84 (broad s, 1H), 2.33-2.42 (m, 2H), 4.31-4.41 (m, 1H), 5.13-5.22 (m, 2 H), 5.75-5.93 (m, 1H), 6.18-6.29 (dd, *J* = 6.2 Hz and 16.0 Hz, 1H), 6.61 (d, *J* = 16.0 Hz, 1H), 7.23-7.40 (m, 5H); ^{13}C NMR: δ 41.8, 71.6, 118.3, 126.3, 127.5, 128.4, 130.2, 131.4, 133.9, 136.5. Anal. Calcd. for $C_{12}H_{14}O$: C, 82.72; H, 8.10%. Found: C 82.56; H 7.94%.

2-Methylhex-5-en-3-ol 59h. Colourless liquid; IR: 3419, 908 cm^{-1}; ^{1}H NMR: δ 0.90 (d, *J* = 5.4 Hz, 5H), 1.61-1.67 (m, 1H), 2.01-2.16 (m, 2H), 2.22 (broad s, 1H), 3.31-3.38 (m, 1H), 5.06-5.14 (m, 2H), 5.71-5.92 (m, 1H); ^{13}C NMR: δ 17.5, 18.7, 33.0, 38.8, 75.3, 117.7, 135.4. Anal. Calcd. for $C_7H_{14}O$: C, 73.63; H, 12.36%. Found: C, 73.42; H, 12.15%.

1-Decen-4-ol 59i. Colourless liquid; IR: 3408, 912 cm^{-1}; ^{1}H NMR: δ 0.85 (t, *J* = 6.4 Hz, 3H), 1.22-1.60 (m, 10H), 1.92 (broad s, 1H), 2.02-2.29 (m, 2H), 3.52-3.65 (m, 1H), 4.98-5.17 (m, 2H), 5.65-5.93 (m, 1H); ^{13}C NMR: δ 14.0, 22.6, 25.6, 29.3, 31.8, 36.8, 41.9, 70.6, 117.8, 134.9. Anal. Calcd. for $C_{10}H_{20}O$: C, 76.86; H, 12.90%. Found: C 76.61; H 13.05%.

1-Tridecen-4-ol 59j. Colourless liquid; IR: 3462, 908 cm^{-1}; ^{1}H NMR: δ 0.91 (t, *J* = 6.4 Hz, 3H), 1.29-1.47 (m, 16H), 1.75 (broad s, 1H), 2.08-2.37 (m, 2H), 3.59-3.68 (m, 1H), 5.12-5.18 (m, 2H), 5.76-5.93 (m, 1H); ^{13}C NMR: δ 14.0, 22.6, 25.6, 29.3, 29.6, 31.8, 36.7, 41.8, 70.6, 117.7, 134.9. Anal. Calcd. for $C_{13}H_{26}O$: C, 78.72; H, 13.21%. Found: C, 78.57; H, 13.15%.

1-(3-Indolyl) -but-3-en-1-ol 59k. Colourless liquid, IR: 3458, 910 cm^{-1}; ^{1}H NMR: δ 2.04 (broad s, 1H), 2.42-2.53 (m, 1H), 2.82-2.90 (m, 1H), 4.07-4.18 (m, 1H), 4.97-5.13 (m, 2H), 5.84-5.96 (m, 1H), 6.95-7.01 (m, 1H), 7.07-7.26 (m, 1H), 7.34-7.37 (m, 1H), 7.59-7.69 (m,

1H), 7.90-7.93 (m, 1H); ^{13}C NMR: δ 41.3, 60.3, 110.9, 114.5, 116.2, 118.8, 119.0, 121.0, 121.8, 138.7. Anal. Calcd. for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N 7.48%. Found: C, 76.81; H, 6.92; N, 7.34%.

2-Phenylpent-4-en-2-ol 59l. Colourless liquid, IR: 3499, 925 cm^{-1}; ^{1}H NMR: δ 1.54 (s, 3H), 1.98 (broad s, 1H), 2.44-2.74 (m, 2H), 5.08-5.18 (m, 2H), 5.56-5.64 (m, 1H), 7.23-7.46 (m, 5H); ^{13}C NMR: δ 29.8, 48.4, 73.6, 119.4, 124.7, 126.5, 128.1, 128.5, 133.6, 147.6. Anal. Calcd. for $C_{11}H_{14}O$: C, 81.44; H, 8.70%. Found: C, 81.51; H, 8.45%.

1,1-Diphenylbut-3-en-1-ol 59m. Colourless liquid, IR: 3434, 929 cm^{-1}; ^{1}H NMR: δ 2.04 (broad s, 1H), 3.08 (d, *J* = 8 Hz, 2H), 5.15-5.28 (m, 2H), 5.56-5.73 (m, 1H), 7.21-7.35 (m, 7H), 7.43-7.47 (m, 3H); ^{13}C NMR: δ 46.5, 77.2, 120.3, 125.8, 126.7, 128.0, 133.2, 146.3. Anal. Calcd. for $C_{16}H_{16}O$: C, 85.68; H, 7.19%. Found: C, 85.82; H, 7.05%.

2-Hydroxy-1,2-diphenylpent-4-en-1-one 59n. Colourless liquid, IR: 3478, 917 cm^{-1}; ^{1}H NMR: δ 2.16 (broad s, 1H), 2.91-3.19 (m, 2H), 4.96-5.13 (m, 2H), 5.63-5.80 (m, 1H), 7.24-7.52 (m, 8H), 7.71-7.75 (m, 2H); ^{13}C NMR: δ 43.7, 81.2, 111.9, 120.2, 125.4, 127.9, 128.7, 129.9, 132.1, 132.6, 134.3, 141.5, 200.6. Anal. Calcd. for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39%. Found: C, 81.21; H, 6.15%.

(*E*)-1,3-Diphenylhexa-1,5-dien-3-ol 59o. Colourless liquid; IR: 3431, 911 cm^{-1}; ^{1}H NMR: δ 2.17 (broad s, 1H), 2.82 (d, *J* = 6.8 Hz, 2H), 5.18-5.27 (m, 2H), 5.64-5.85 (m, 1H), 6.50-6.72 (m, 2H),7.23-7.42 (m, 8H),7.52-7.56(m, 2H); ^{13}C NMR: δ 47.1, 75.7, 120.1, 125.0, 125.5, 126.4, 127.0, 127.4, 127.8, 128.2, 128.3, 132.5, 135.2, 137.4, 145.3. Anal. Calcd. for $C_{18}H_{18}O$: C, 86.36; H, 7.25%. Found: C, 86.60; H, 7.01%.

1-Allylcyclohexanol 59p. Colourless liquid; IR: 3451, 913 cm^{-1}; ^{1}H NMR: δ 1.23 (broad s, 1H), 1.45-1.61 (m, 10H), 2.20 (d, *J* = 7.4 Hz, 2H), 5.04-5.14 (m, 2H), 5.77-5.98 (m, 1H); ^{13}C NMR: δ 21.5, 25.5, 30.3, 36.3, 37.9, 45.2, 72.5, 117.6, 134.0. Anal. Calcd. for $C_9H_{16}O$: C, 77.09; H, 11.50%. Found: C, 76.81; H, 11.29%.

1-Allyl-2-methylcyclohexanol 59q. Colourless liquid; IR: 3454, 908 cm^{-1}; ^{1}H NMR: δ 0.79 (d, *J* = 2.4 Hz, 3H), 1.16-1.50 (m, 9H), 1.70 (broad s, 1H), 2.14 (d, *J* = 7.4 Hz, 2H), 4.93-4.99 (m,1H), 5.65-5.82 (m, 1H); ^{13}C NMR: δ 14.6, 21.4, 25.4, 30.2, 35.8, 37.8, 45.1, 72.3, 117.5, 133.9. Anal. Calcd. for $C_{10}H_{18}O$: C, 77.87; H, 11.76%. Found: C, 77.51; H, 11.64%.

n-Butylmethylimidazolium tetrabromoindate(III) ([bmim][$InBr_4$]) 61. ^{1}H NMR: δ 0.98 (t, *J* = 7.2 Hz, 3H), 1.31-1.49 (m, 2H), 1.82-1.97 (m, 2H), 4.04 (s, 3H), 4.27 (t, *J* =7.4 Hz, 2H), 7.32-7.35 (m, 2H), 8.95 (s, 1H); ^{13}C NMR: δ 13.6, 19.9, 32.4, 37.6, 50.7, 122.7, 124.1, 136.1. Anal. Calcd. for $C_8H_{15}Br_4InN_2$: C, 16.75; H, 2.64; N, 4.88%. Found: C, 16.47; H, 2.82; N, 5.01%.

Diallylgallium bromide III. Colourless liquid; ^{1}H NMR: δ 1.69 (d, *J* = 6.4 Hz, 4H), 4.91-5.06 (m, 4H), 5.71-5.91 (m, 2H); ^{13}C NMR: δ 33.1, 114.6, 138.1. EIMS: *m*/*z*(%) 152 [{M − Br}$^{+}$, 11].

N-butyl-N-methyl-imidazolinylidine-galliumdihydroxybromide [Ga(bmiy)Br($OH)_2$] IV: Grey amorphous solid; IR: 3545, 3466, 3229, 2853, 1616, 1187, 924, 637, 538, 479 cm^{-1}; ^{1}H NMR: δ 0.99 (t, *J* = 7.4 Hz, 3H), 1.21-1.28 (m, 2H), 1.74 (broad s, 2H), 1.87-1.92 (m, 2H), 4.03 (s, 3H), 4.24 (t, *J* = 7.4 Hz, 2H), 7.21 (s, 2H); ^{13}C NMR: δ 12.9, 18.9, 31.6, 36.2, 49.3, 121.7, 123.3, 175.9. EIMS: *m*/z(%) 264 [{M − C_4H_9}$^{+}$, 17], 241 [{M − Br}$^{+}$, 11], 184 [{Ga($OH)_2$Br}$^{+}$, 18], 138 [{$C_8H_{14}N_2$}$^{+}$, 19] . Raman: 697, 330,

662, 980, 1079, 1332, 1374 cm^{-1}. Anal. Calcd. for $C_8H_{16}BrGaN_2O_2$: C, 29.85; H, 5.01; N, 8.70%. Found: C, 29.64; H, 5.18; N, 8.61%.

CHAPTER III

DIASTEREOSELECTIVE SYNTHESIS OF CHIRAL CARBINOLS

III.1 DIASTEREOSELECTIVE SYNTHESIS OF CHIRAL CARBINOLS *VIA* BI-METALLIC REDOX STRATEGIES

III.1.1 Introduction

Metal-mediated transformations are among the most powerful tools in synthetic organic chemistry.[100] In particular, addition of organometallic compounds to aldehydes and ketones have been extensively studied. Amongst various methods of organometallic addition to carbonyls, the Barbier type reactions[101] are operationally simple as they allow *in-situ* formation of the active organometallic species. The effectiveness of metals as the mediator for such a reaction is closely related to the location of the metals in the periodic table and can be tentatively rationalized via inner-sphere and outer-sphere single-electron transfer processes. Directly or indirectly, their utility depends on their propensity to undergo electron transfer and/or to form coordination compounds with appropriate reactivity and geometry.[102] However, in spite of the many applications, the mechanism of the metal mediated Barbier reactions is not well-understood.[103] Involvement of a radical pathway, or a discrete allylmetal species have been speculated in the literature.[104] Recent computational and NMR studies indicate that Barbier reactions with indium, tin and antimony metals proceed directly through nucleophilic addition, whereas that with magnesium proceeds via a single electron transfer process. Nevertheless, issues regarding the nature of the organometallic species and the involvement of single electron-transfer processes, remain unanswered.

From this perspective, there is a scope for exploring the potential of different metals in varied physical states to participate in the Barbier type allylation of carbonyls. However, preparation of the activated metal to form the required active organometallic

species is a prerequisite for any metal mediated addition of organic halides to carbonyls, both under anhydrous and aqueous conditions. Hence, the metal activation, either as a whole or at its surface that enables the metal to insert into the C-halogen bond of the organic halides, has become an important technique for preparative organic chemistry. For surface activation of the metals, several techniques *viz*. addition of I_2 or CH_2I_2 to Mg for the preparation of the Grignard reagent, sonication of metals (Mg, Zn, Sn, Cu etc),[60d] treatment of Zn with aqueous NH_4Cl for allylation[3,60] and BF_3-ethereate for Reformatsky reactions,[105] cementation[106] to form a surface alloy etc. are employed. Rieke *et al*.[107] have introduced a general approach for the preparation of several active metals employing the reduction of the corresponding metal halides with K, Li etc. The simultaneous co-reduction of two metal salts by complex hydrides[108] (*e. g*. $NaBEt_3H$), potassium graphaite,[109] or electrolysis[110] have also been utilized for the generation of highly active bimetallic systems such as bimetallic colloids, alloys, and intimate conglomerates of very fine metal particles. However, most of these strategies operate strictly under anhydrous conditions.

III.1.2 Present Work

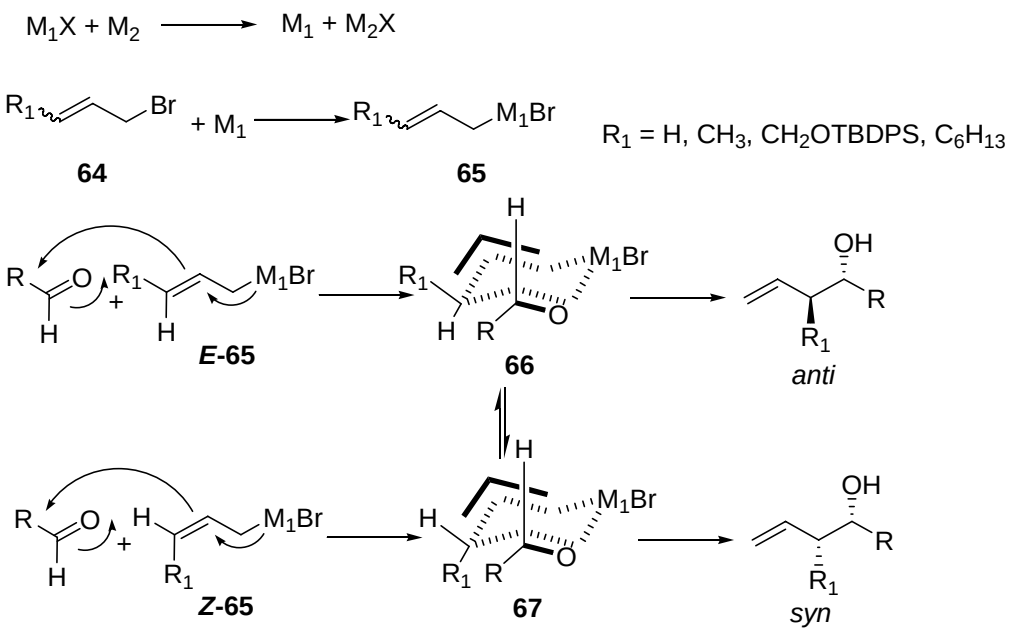
The lack of metal activation procedures in aqueous medium led us to formulate a bimetallic redeox strategy in which a metal salt is used in combination with a reducing metal. The metal salt, after reduction, produces the highly active metal. This, in turn, reacts with the allylic/benzylic halides to form the active organometallic species. This strategy works well even in moist condition. For, this, several combinations of metal halides *viz*. $CuCl_2.2H_2O$, $CoCl_2.6H_2O$, $FeCl_3$ and $SnCl_2.2H_2O$ and reducing metals such as Zn and Mg were used to generate the active metals. The chiral aldehyde (*R*)-2,3-

cyclohexylideneglyceraldehyde (**1**)[3] **(Chapter I.1)** was chosen as the substrate, since it serves as an extremely versatile, easily available, and inexpensive chiral template for various stereoselective transformations. Many of these have also been used by our group for the syntheses of a diverse array of bioactive compounds.[3,29c-h] Its cyclohexylidene moiety provides considerable steric bias in the organometallic addition to its aldehyde function, and also ensures easy separation of the resultant epimeric carbinols by normal column chromatography. The reactions were performed using different allylic and γ-substituted allylic bromides. In addition, benzylation of aldehyde **1** with benzyl bromide was also accomplished using the same strategy. The results are discussed in the following section.

(A) ***Allylation of aldehydes***

The primary aim of the study was to develop a simple procedure for allylation of aldehydes under environmentally benign moist reaction conditions. The strategy (**Scheme III.1.1**) involves spontaneous reduction of a metal salt $\mathbf{M_1X}$ in aqueous environment with another metal $\mathbf{M_2}$ having higher oxidation potential, to produce the metal $\mathbf{M_1}$ in its active form. The freshly generated and highly reactive metal $\mathbf{M_1}$ can easily react with allylic bromides **64** to produce the respective allylic-M_1 species **65** in ***Z*** or ***E*** geometries. The γ-substituted allylic metal species can follow a γ-addition pathway with an aldehyde/ketone, while reaction with simple allylmetal would proceed *via* α or γ (equivalent) attack. The species ***E*-65** would add to the carbonyl substrate *via* a Zimmerman and Traxler transition state **66** even in wet reaction conditions to produce the *anti*-product. Alternatively, **66** can

undergo *in situ* isomerization to the other transition state **67**, which can also be generated from the corresponding *Z*- bromide ***Z*-65**. This would result in the *syn*-product.



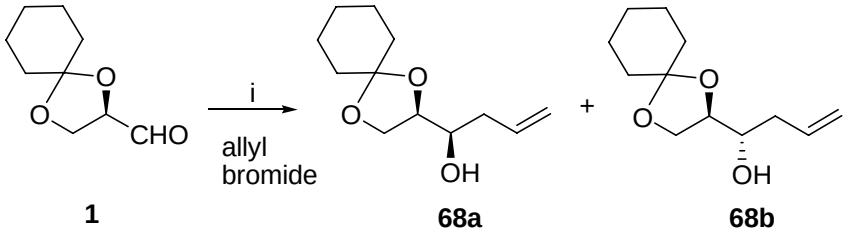
Scheme.III.1.1

To explore the viability of this approach, Zn was chosen as the reducing metal in separate combinations with four commercially available salts *viz*. $CuCl_2.2H_2O$, $CoCl_2.6H_2O$, $FeCl_3$ and $SnCl_2.2H_2O$. These were chosen in consideration of the redox potentials of the following couples: $E^0_{Zn= Zn^{2+} + 2e}$ (+0.761 V), $E^0_{Co= Co^{2+} + 2e}$ (+ 0.280 V), $E^0_{Cu= Cu^{2+} + 2e}$ (-0.337 V), $E^0_{Fe= Fe^{2+} + 2e}$ (+ 0.441 V), $E^0_{Fe^{2+} = Fe^{3+} + e}$ (- 0.771 V) and $E^0_{Sn= Sn^{2+} + 2e}$ (+0.140 V). This implied that the reduction of Co(II), Cu(II), Fe(III) and Sn(II) salts can be effected on treatment with metallic Zn to produce Co, Cu, Fe and Sn respectively in their active states. Due to higher surface area, use of Zn powder is advantageous for the reduction. For the studies, the α-oxygenated chiral aliphatic aldehyde **1** was chosen in order to compare the stereochemical course of the new protocol with that observed earlier by our group using Mg[29d] and Zn[3] as the metal mediators. Thus, in the synthetic protocol, a

mixture of Zn dust, allyl or γ-substituted allyllic bromide, the aldehyde **1** and the respective metal salts was stirred in THF for definite time periods, as specified in the respective tables. Importantly, for the accomplishment of the reactions, anhydrous THF was not required. The results are as follows.

(i) *Reaction of aldehyde 1 with allyl bromide*

Initially, allylation of **1** was performed (**Scheme III.1.2**). To our delight, in all the cases the reactions furnished the expected products, albeit in varying yields as shown in **Table III.1.1**. Compared to the Luche method,[3b] the Fe-mediated reaction was faster (entry 4, **Table III.1.1**). Both Co- and Cu-mediated allylation took place smoothly furnishing predominantly the *anti*-product **68b** (entries 2,3, **Table III.1.1**) in good yields.



1 **68a** **68b**

(i) Zn, aqueous saturated NH_4Cl, THF, 25 ^oC.; or $CuCl_2$, $2H_2O$, Zn, THF, 0 ^oC-25 ^oC; or $FeCl_3$, Zn, THF, 10 ^oC-25 ^oC; or $CoCl_2$, $8H_2O$, Zn, THF, 10 ^oC-25 ^oC.

Scheme III.1.2

Compound **68b** was characterized by the presence of a sharp IR hydroxyl band at 3453 cm^{-1} and terminal olefinic signals *viz*. ^1H NMR multiplets at δ 5.13-5.16 (2H) and δ 5.75-5.88 (1H) and ^{13}C NMR peaks at δ 118.6 and δ 134.4 ppm. The minor isomer **68a** showed terminal olefinic signals at δ 5.06-5.16 (2H) and δ 5.77-5.91 (1H) in the ^1H NMR spectrum and at δ 117.4 and δ 133.8 in the ^{13}C NMR spectrum. The ^1H NMR and ^{13}C

NMR of **68a** and **68b** are shown in **Fig. III.1.1**, **Fig. III.1.2, Fig. III.1.3** and **Fig. II.1.4**. The spectral data were commensurate with those reported earlier.[3]

Table III.1.1 Course of allylation of **1** using the bi-metallic strategy[a]

Entry	Reagents	**1**: bromide: metal : metal salt	Time	Yield[b] (%)	Product ratio[c] **68a : 68b**
1	Zn/ Aq. saturated NH_4Cl	1 : 3.0 : 3.5 : ---	4 h	73.0	3.5 : 96.5
2	$CoCl_2$. $6H_2O$, Zn	1 : 3.5 : 3.0 : 3.5	19 h	77.5	6.2 : 93.8
3	$CuCl_2.2H_2O$, Zn	1 : 3.5 : 3.5 : 3.0	14 h	75.4	5.9 : 94.1
4	$FeCl_3$, Zn	1 : 3.0 : 3.0 : 3.5	15 min	53.7	7.2 : 92.8

[a]The reactions were carried out at 5 mmol scale. [b]Combined yields of isolated pure products. [c]Based on isolated yields.

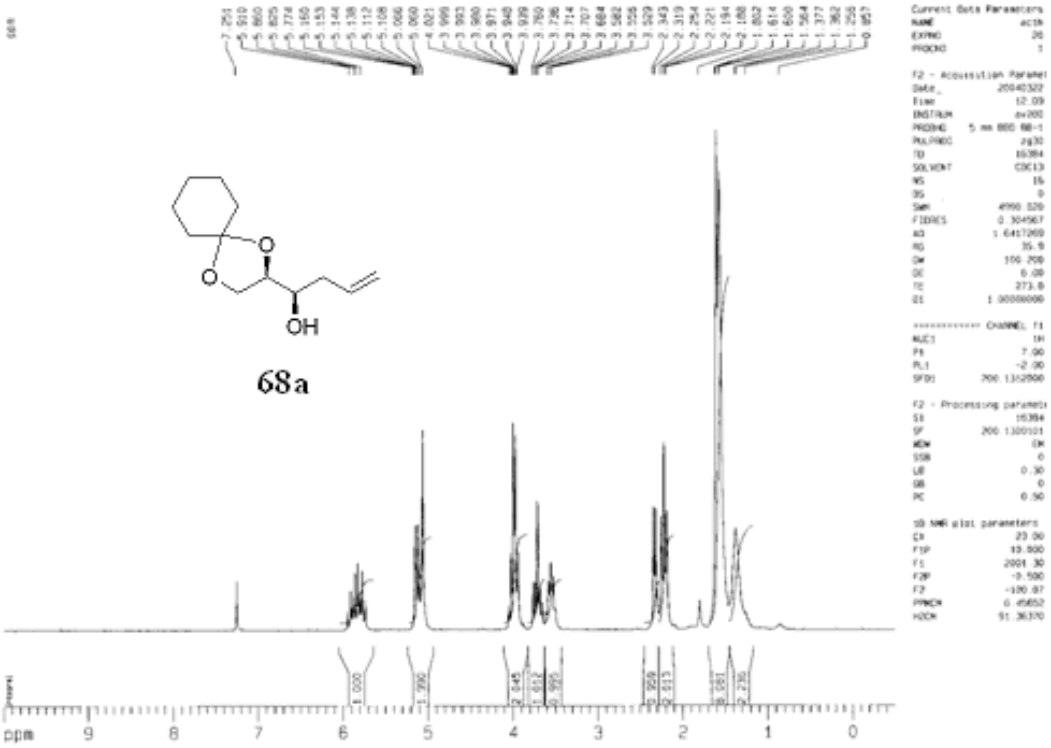


Fig. III.1.1. ^{1}H NMR spectrum of 68a

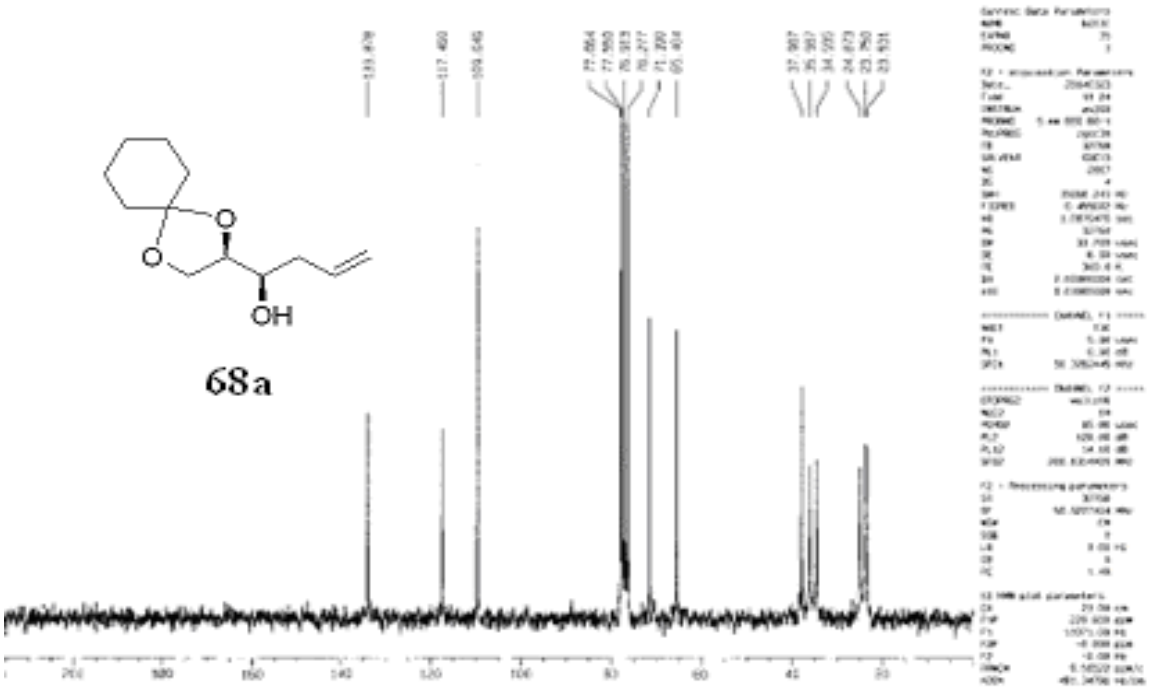


Fig. III.1.2. ^{13}C NMR spectrum of 68a

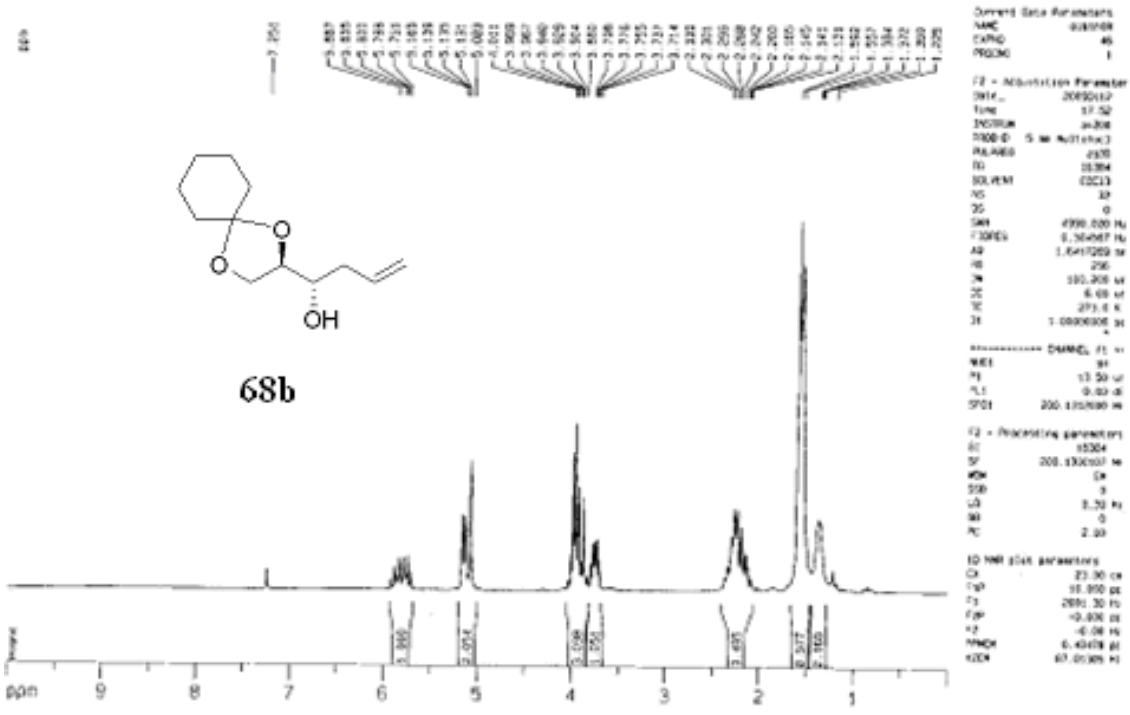


Fig. III.1.3. ^{1}H NMR spectrum of 68b

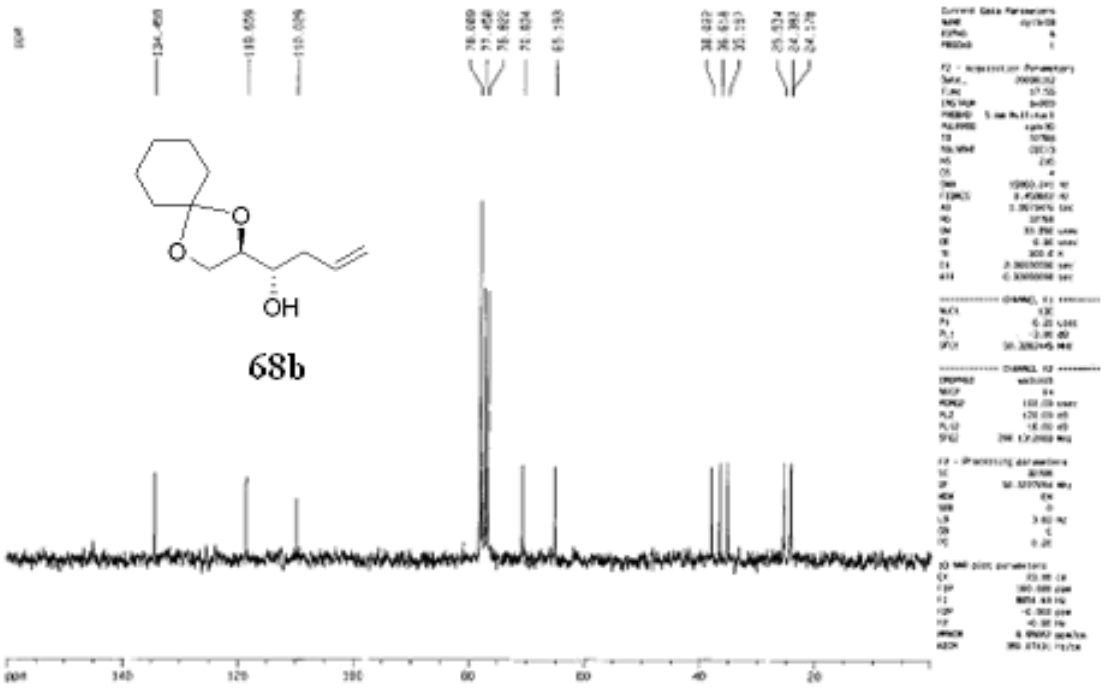


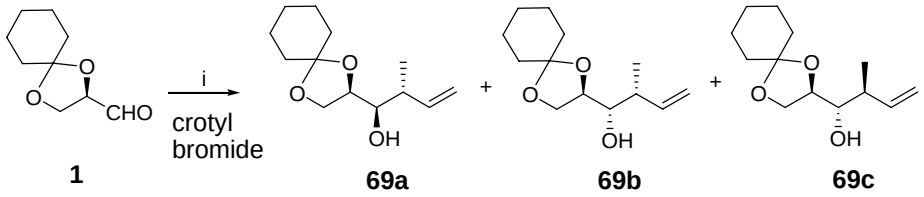
Fig. III.1.4. ^{13}C NMR spectrum of 68b

Due to large values of $\Delta E^0_{Zn\text{-}Cu}$ (1.098 V), reduction of Cu(II) by Zn was highly exothermic, requiring the reaction mixture to be cooled (0 ^oC) during the addition of Zn dust. In comparison, the reduction of Co(II) was slow. In general, the Co-mediated reactions required longer time to obtain good yield. Interestingly, the Fe-mediated reaction was complete within few minutes. In view of the heterogeneity of the reaction mixtures, the metal salts and Zn dust were used in excess. To compensate for the evaporative loss of the volatile allyl bromide, it was also used in excess.

(ii) *Reaction of aldehyde 1 with γ-Substituted allylic bromide*

Different allylic bromides with varied γ-substitutions (*viz*. CH_3, C_6H_{13} and $CH_2OTBDPS$) have been reacted with **1**, and these are discussed in the following section.

Reaction with crotyl bromide: In case of crotylation of **1 (Scheme III.1.3)**, all these four low valent metals (Cu, Co, Fe and Sn) were found to be successful mediators.[111] Of them, Fe- and Sn-mediated reactions took place faster compared to Luche's procedure[3b] (entries 1, 3 and 5, **Table III.1.2**); whereas the reactions with Cu and Co metals were sluggish (entries 2 and 4, **Table III.1.2**). All the reactions yielded two diastereomers (**69b** and **69c**) as the major products that were chromatographically isolable in homochiral forms. The other diastereisomer **69a** was produced in minor amounts, whereas the *syn*, *syn*-isomer was not formed at all. As usual, the ratio of **69a**, **69b** and **69c** in each reaction was determined by their actual isolation by column chromatography.



1 **69a** **69b** **69c**

(i) Zn, aqueous satd. NH_4Cl, THF, 25 ^oC; or $CuCl_2$, $2H_2O$, Zn, THF, 0 ^oC-25 ^oC; or $FeCl_3$, Zn, THF, 10 ^oC-25 ^oC; or $CoCl_2$, $8H_2O$, Zn, THF, 10 ^oC-25 ^oC; or Zn, $SnCl_2.2H_2O$, THF, 10 ^oC-25 ^oC.

Scheme III.1.3

Table III.1.2: Course of crotylation of **1** using the bi-metallic strategy[a]

Entry	Reagents	**1** : bromide : metal : metal salt	Time	Yield[b] (%)	Products ratio[c] (**69a : 69b: 69c**)
1	Zn/ Aq. Satd. NH_4Cl	1 : 3.0 : 3.5 : ---	5 h	74	2.4 : 32.5 : 65.1
2	Zn/ $CoCl_2$, $6H_2O$	1 : 3.5 : 2.5 : 2.0	24 h	77.8	3.8 : 47.5 : 48.7
3	Zn/ $FeCl_3$	1 : 3.0 : 2.0 : 2.0	10 min	86.9	1.5 : 48.4 : 50.1

4	Zn/ $CuCl_2$, $2H_2O$	1 : 3.0 : 2.5 : 2.0	15 h	78.7	4.2 : 29.5 : 66.3
5	Zn/ $SnCl_2$, $2H_2O$	1 : 3.0 : 2.0 : 2.0	45 min	80.4	11 : 78.2 : 10.8

[a]The reactions were carried out at 5 mmol scale. [b]Combined yields of isolated pure products. [c]Based on isolated yields.

The spectral data and optical data resonances of the crotylated products **69a-c** corroborated with those reported.[3b] For example, the ^{1}H NMR resonances of the $-CH_2O$ protons of **69a** appeared as three multiplets in the ratio of 1:1:2 protons at δ ~3.3-4.2, those for the compound **69b** (more polar) were seen as multiplets (1:2:1) at δ 3.6-4.1 and for compound **69c** it appeared as two multiplets (1:3) at δ ~3.5-4.1. They also showed typical hydroxyl bands at ~3400 cm^{-1} in their IR spectra, and also the presence of olefinic resonances in their ^{1}H NMR and ^{13}C NMR spectra. The ^{1}H NMR and ^{13}C NMR spectra of **69b** and **69c** are shown in **Fig. III.1.5** and **Fig III.1.6** (for **69b**)**, Fig III.1.7** and **Fig. III.1.8** (for **69c**). The stereochemical assignments of these diastereomers are separately presented.

It is worth noting that the reactions with low valent Co and Fe gave **69b** and **69c** in ~1:1 ratio, whereas the reaction with Cu gave preponderance of **69c** (entries 2-4, **Table III.1.2**). In contrast, the low valent Sn mediated reactions yielded **69b** as the major product. (entry 5, **Table III.1.2**) with a good diastereoselectivity. These results are very important from preparative point of view, since both the diastereomers **69b** and **69c** could be obtained individually as the major diastereomers using different metal salts.

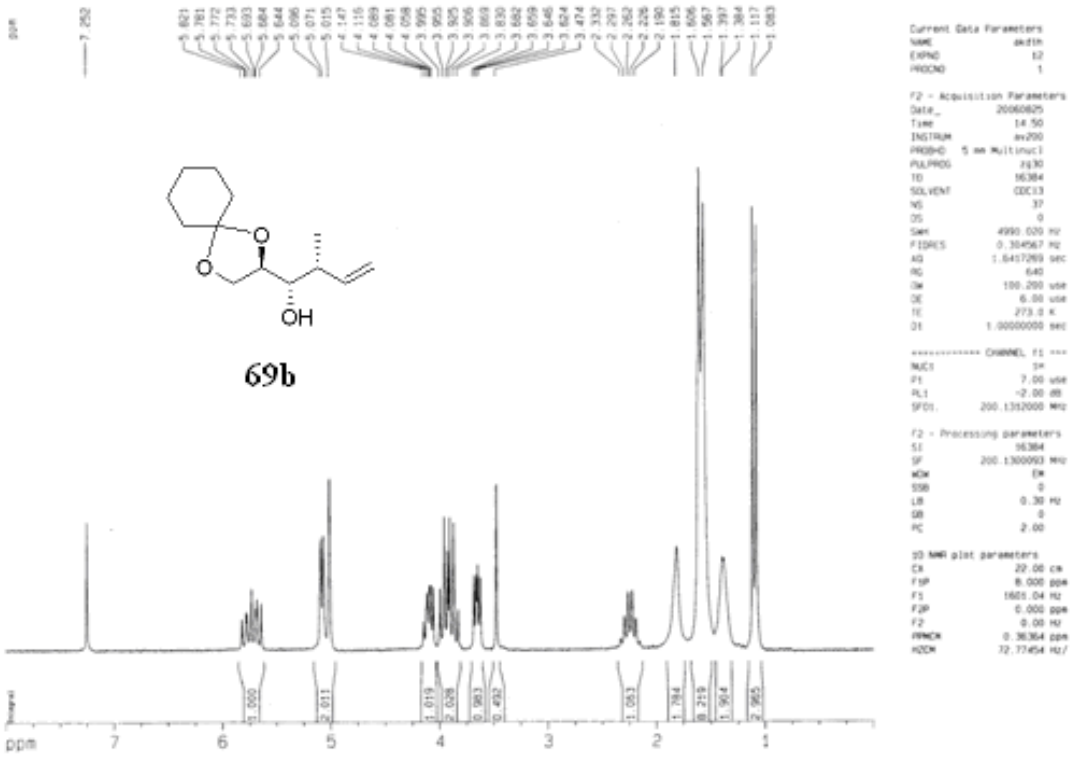


Fig. III.1.5. ^{1}H NMR spectrum of 69b

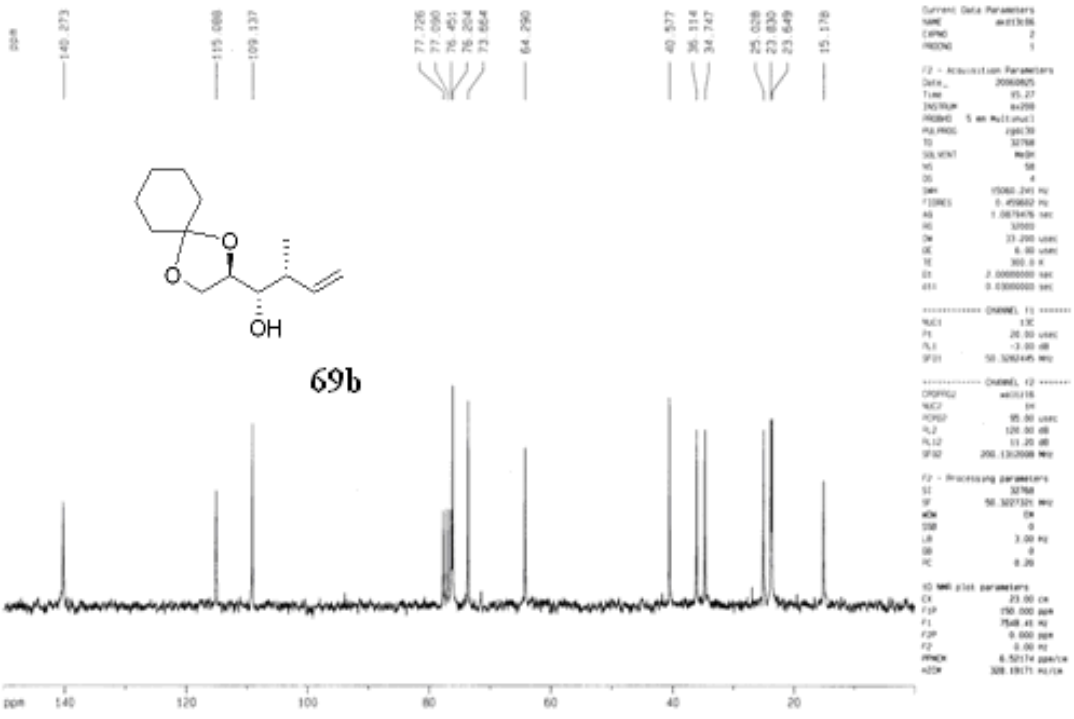


Fig. III.1.6. ^{13}C NMR spectrum of 69b

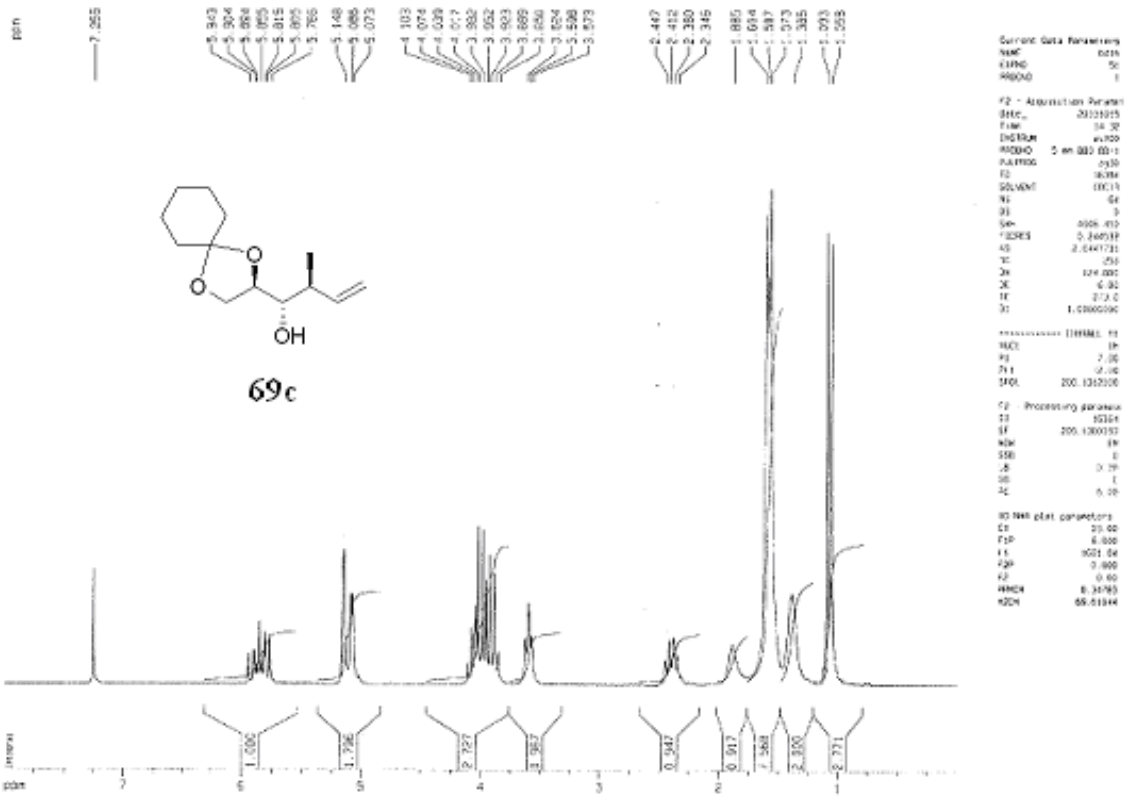


Fig. III.1.7. ^{1}H NMR spectrum of 69c

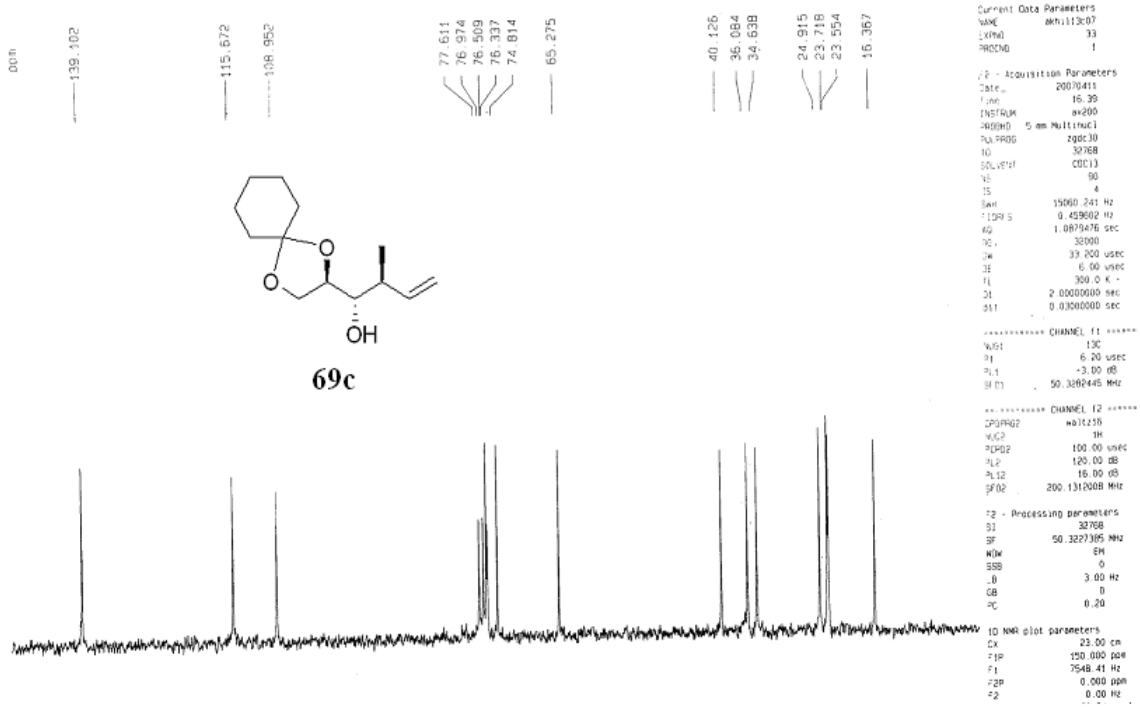


Fig. III.1.8. ^{13}C NMR spectrum of 69c

The formation of the 2,3-*anti* addition products, **69b** and **69c** in major amounts suggested that the reactions took place following Felkin-Anh model (**Fig. III.1.9**).[24b,112] However, the presence of 3,4-*syn* and 3,4-*anti* stereochemistry in the two major products **69b** and **69c** respectively could be explained through Zimmerman-Traxler model.[25a,113] This model suggested an inter conversion between the (*E*)-crotylmetal and (*Z*)-crotylmetal species (**Scheme III.1.1**), prior to C-C bond formation between crotylmetal and the aldehyde.

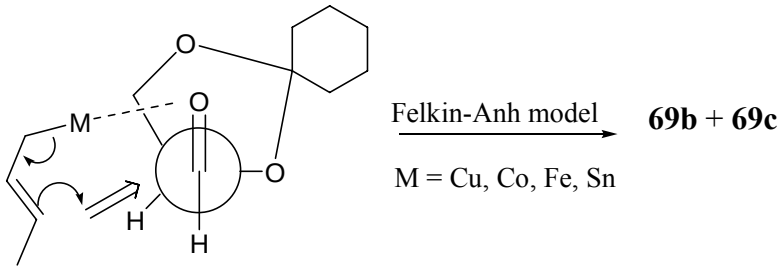
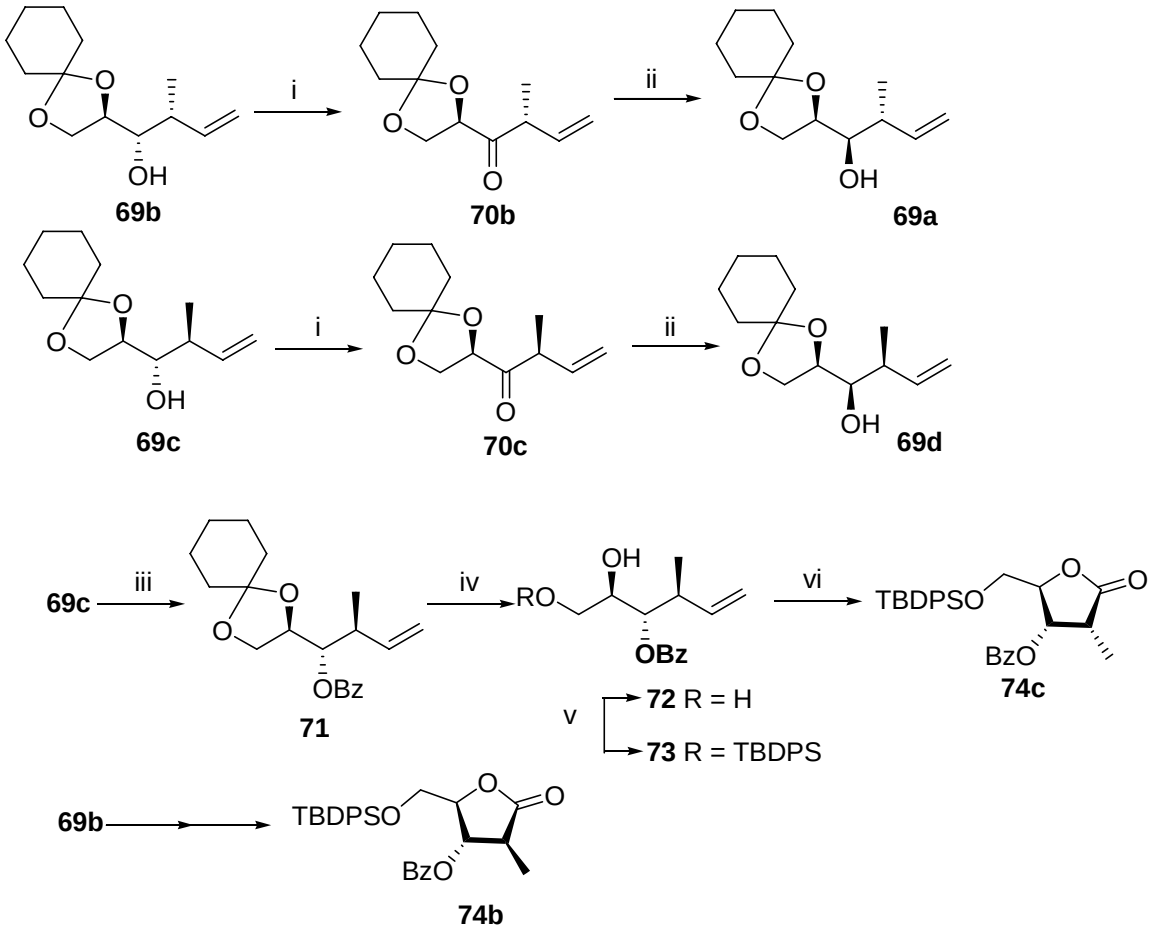


Fig. III.1.9. Felkin-Anh model for crotylation of 1

The stereochemistry of each of the diastereomers (**69a-c**) was empirically assigned by comparing the pattern of the signals in the region of δ 3.3-4.2 of their ^{1}H NMR spectra with those reported.[3b,114] For further confirmation (**Scheme III.1.4**), **69b** and **69c** were separately oxidized with pyridinium chlorochromate (PCC)[115] to get the respective ketones **70b** and **70c** (appearance of the CO stretching band at ~1740 cm^{-1} in lieu of hydroxyl band in the IR spectrum). Following our own method,[35c] the ketone **70b** was reduced with K-selectride® to furnish the corresponding alcohol, which showed identical NMR spectra as that of **69a**. This confirmed that compounds **69a** and **69b** were the C-2 epimers. However, reduction of the ketone **70c** with K-selectride® furnished the other diastereomer **69d**, as

revealed by its ^{1}H NMR spectral pattern in the region δ 3.2-4.2 ppm. The ^{13}C NMR spectrum showed peaks due to the olefinic carbons at δ 115.2 and 140.4 ppm. Since the K-selectride® reduction is known to produce the 2,3-s*yn* carbinols almost exclusively, the alcohol **69d** will have 2*R*,3*R*-configuration, and hence the 2,3-sterochemistry of its progenitor **69c** would be 2*R*,3*S*.



(i) PCC, NaOAc, CH_2Cl_2, 25 ^{o}C; (ii) K-selectride®, THF, -78 ^{o}C; (iii) BzCN, Et_3N, CH_2Cl_2, 0 ^{o}C; (iv) Aqueous CF_3CO_2H, CH_2Cl_2, 0 ^{o}C; (v) TBDPSCl, imidazole, CH_2Cl_2, 25 ^{o}C; (vi) O_3, NaOH in MeOH, -15 ^{o}C.

Scheme III.1.4

To establish the C-4 configuration of **69c**, it was converted to the corresponding benzoate derivative **71** by treating with BzCN in the presence of Et_3N. The product showed a carbonyl band at 1722 cm^{-1}, and ^1H NMR resonances at δ 5.26 ppm (dd, *J* = 4.0 and 6.6 Hz,1H), δ 7.38-7.54 (m, 3H) and δ 7.99-8.04 (m, 2H) for the –CH(OBz) group. Deacetalization of **71** with aqueous trifluroacetic acid (TFA) in CH_2Cl_2 afforded the diol **72,** which showed a strong hydroxyl band at 3411 cm^{-1}. The ^1H and ^{13}C NMR spectra of **72** are shown in **Fig III.1.10** and **Fig III.1.11** respectively. Treatment of **72** with *tert*-butyldiphenylsilyl chloride (TBDPSCl) in the presence of Et_3N in CH_2Cl_2 furnished the monosilylated compound **73**. Its ozonolysis under an alkaline condition[116] directly produced the γ-lactone **74c** (**Scheme III.1.4**), which showed a strong IR band at 1742 cm^{-1}. The ^1H NMR resonance of the –CH(OBz) proton appeared at δ 5.96 (dd, *J* = 13.7, 2.4 Hz). The coupling constant values established the *syn* and *anti* relationships of H-4 (containing the OBz group) with its two neighboring protons, H-3 and H-5. This revealed the absolute stereochemistry of **74c** as 3*S*,4*S*,5*R*, and hence that of **69c** as 2*R*,3*S*,4*S*. The 2*R*,3*S*,4*R* configuration of **69b** was also ascertained in a similar manner. Hence, compound **69a** must possess 2*R*,3*R*,4*R* configuration as it was the C-3 epimer of **69b**[117].

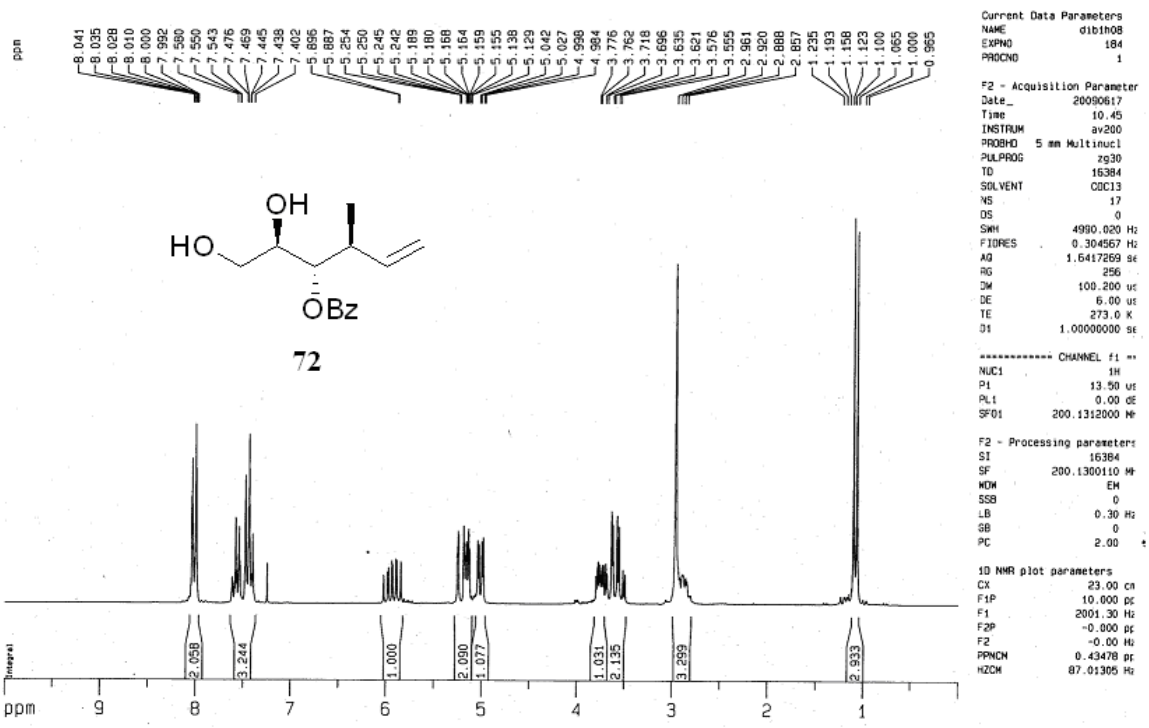


Fig. III.1.10. ^{1}H NMR Spectrum of 72

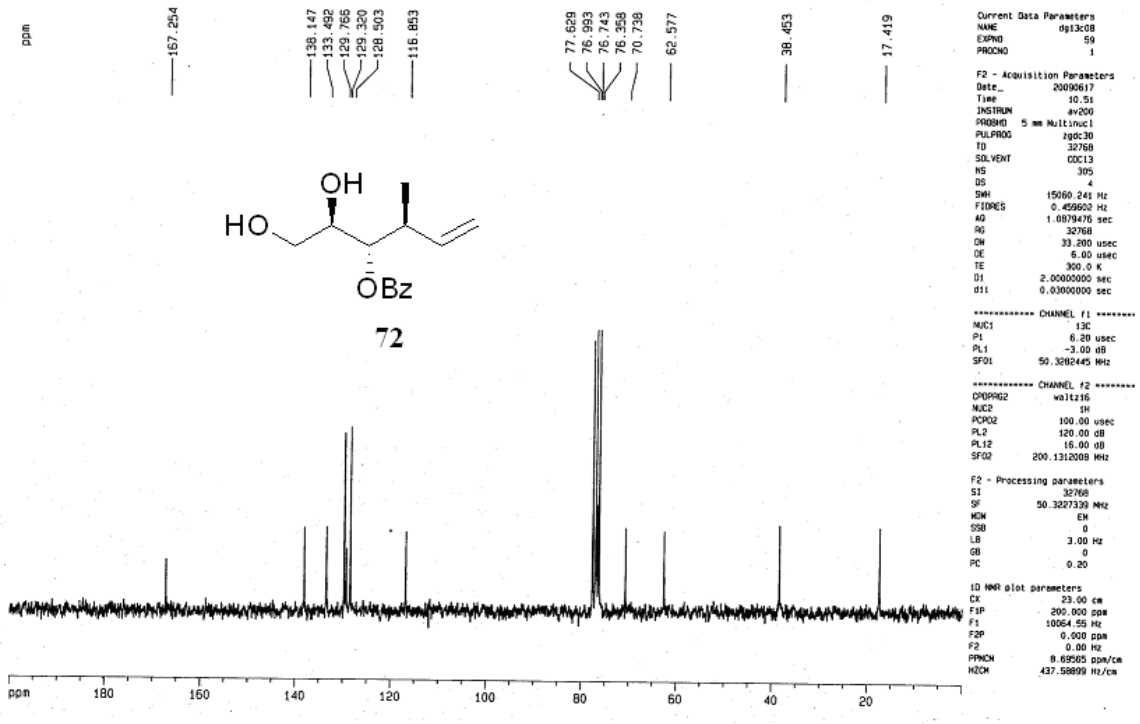
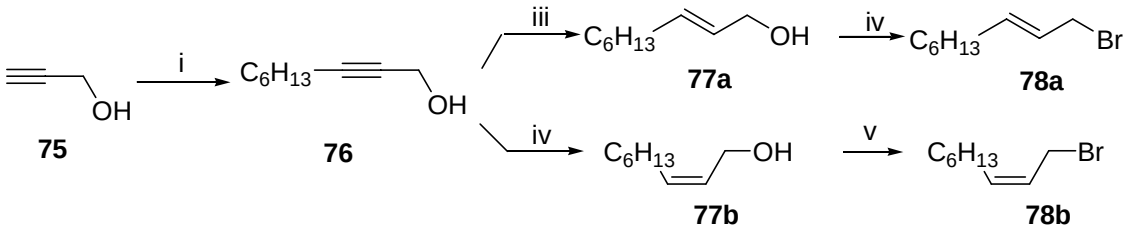


Fig. III.2.11. ^{13}C NMR Spectrum of 72

Allylation with (E) and (Z)-1-bromo-2-nonene* (78a/78b):** Next we explored the efficacy of the bi-metallic strategy for the allylation of **1** with another γ-substituted allylic bromide 7**8**, using all the three designated metals.[118] The reaction was also performed following Luche's procedure. Further the ***E- and ***Z***- isomers of the allylic bromide **78a**/**78b** were prepared and used separately for the reaction to examine the role of olefin geometry of the bromide in dictating the steric course of the reaction.

The bromides **78a** and **78b** were prepared (**Scheme III.1.5**) from commercially available propargyl alcohol **75** in good overall yields *via* a) C-alkylation with bromohexane in the presence of $LiNH_2$ to furnish the propargylic alcohol **76**, b) *E*-reduction[119] of **76** with $LiAlH_4$ for **77a,** and partial hydrogenation of **76** in the presence of P-2 Ni catalyst[120] for **77b** and c) bromination of the resultant *E*- and *Z*-allylic alcohols (**77a** and **77b** respectively) in two steps *via* mesylation and subsequent reaction with NaBr.

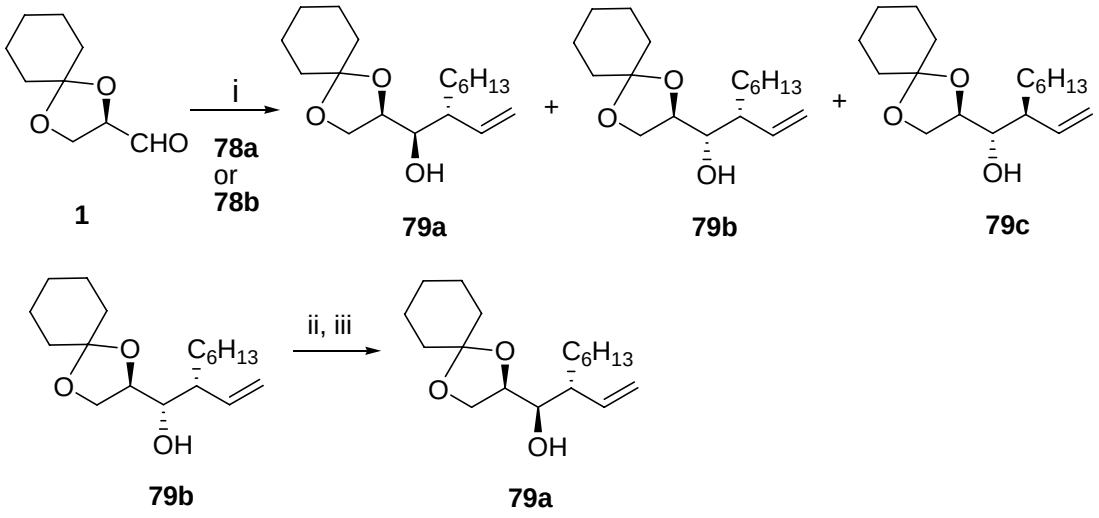


i) $LiNH_2$, 1-bromohexane, liquid NH_3, -33 ^oC; ii) $LiAlH_4$, THF, Δ; iii) P-2 Ni, H_2, EtOH, 25 ^oC; iv) MsCl, Et_3N, CH_2Cl_2, 0 ^oC; v) NaBr, acetone, 25 ^oC.

Scheme III.1.5

Compound **78a** was characterized by IR peak at 964 cm^{-1}, olefinic resonances at δ 5.52-5.84 ppm in ^1H NMR spectra and at δ 125.9 and 135.9 ppm in ^{13}C NMR spectra. The other isomer, **78b** was likewise characterized by NMR spectroscopy [^1H NMR at δ 5.59-5.73 and ^{13}C NMR peaks at δ 125.1 and 135.5 ppm].

For the allylation, compound **1** was treated separately with **78a** and **78b** following Luche's procedure as well as our own protocol (**Scheme III.1.6**). The results of these studies are summarised in **Table III.1.3**. The Co- and Fe-mediated reactions with both **78a** and **78b** took place very efficiently with similar rates as that in Luche's procedure (**Table III.1.3**). Unfortunately, the Co-mediated reactions proved abortive (entries 4 and 8, **Table III.1.3**) even after stirring the mixture up to 15 h. It was interesting to note that compared to the earlier case, the reactivity of Cu was considerably higher with the bromides **78a** and **78b**. Interestingly, in all the successful cases three of the four possible diastereoisomers **79a-c** were produced with good overall yields. The *syn*,*syn*-isomer was not formed with either of the reagents. Moreover, all the successful additions took place with a similar type of diastereoselectivity yielding **79b** and **79c** as the major products and a very minor amount of **79a**. Of these, both Zn- and Cu-mediated additions afforded better 3,4-*syn* selectivity with **78b** with slight preponderance of **79b** (entries 5 and 6, **Table III.1.3**).



(i) Zn, aqueous satd. NH_4Cl, THF, 25 ^oC; or $CuCl_2$, $2H_2O$, Zn, THF, 0 ^oC-25 ^oC; or $FeCl_3$, Zn, THF, 10 ^oC-25 ^oC; or $CoCl_2$, $8H_2O$, Zn, THF, 10 ^oC-25 ^oC; (ii) PCC, NaOAc, CH_2Cl_2, 25 ^oC; (iii) K-selectride®, THF, -78 ^oC;

Scheme III.1.6

The individual diastereoisomeric carbinols **79a-c** were easily separable by normal column chromatography to obtain each of them in homochiral form. The stereochemistry of **79b** and **79c** were confirmed from their ^1H NMR spectra. The pattern of the resonances due to their oxygenated C-Hs in the region of δ 3.0-4.5 ppm were well comparable with that of the corresponding diastereoisomers of the crotylated products **69a-c**.[3b]

Further, the stereochemistry of **79a** was characterized following an oxidation-reduction protocol (**Scheme III.1.6**). Oxidation of **79b** with PCC[115], followed by K-selectride® reduction[35c] of the resultant ketone yielded **79a** with absolute stereosectivity. Since it is known that K-selectride® reduction proceeds with absolute *syn*-selectivity, it was established that compound **79a** possesses 3,4-*anti*, 4,5-*syn*-stereochemistry.

Table III.1.3: Reaction course of addition of **78a/78b** to **1**[a]

Entry	Metal/ salt	Bromide	**1** : bromide : metal : metal salt	Time (h)	Yield[b] (%)	Product ratio[c] **79a**:**79b**:**79c**
1	Zn/ Aq NH_4Cl	**78a**	1 : 3.0 : 3.5 : --	4	77.5	2 : 52 : 46
2	Zn/$CuCl_2.2H_2$	**78a**	1 :3.0 :3.0 : 3.0	4	77	1 : 48 : 51
3	Zn/ $FeCl_3$	**78a**	1 :3.0 : 4.5 : 4.0	3	84	3 : 28 : 69

4	$Zn/CoCl_2.8H_2O$	**78a**	1 : 3.0 :3.5 : 3.5	15	NR[d]	
5	Zn/ aq NH_4Cl	**78b**	1 : 3.0: 3.5 : --	4	77.9	4 : 56 : 40
6	$Zn/CuCl_2.2H_2O$	**78b**	1 :3.0 : 3.5 : 3.5	4	78.7	7 : 62 : 31
7	Zn/ $FeCl_3$	**78b**	1 : 3.0: 3.0 : 3.0	3.5	83	15 : 40 : 45
8	$Zn/CoCl_2.8H_2O$	**78b**	1 : 3.0: 4.5 : 4.0	15	NR[d]	

[a]The reactions were carried out at 5 mmol scale. [b]Combined yields of isolated pure products. [c]Based on isolated yields. [d]no reaction.

Formation of 2,3-*anti* **79b** and 2,3-*anti* **79c** in major amounts in all these reactions suggested that the addition of the organometallic species followed the Felkin-Anh model[112]. Moreover, the formation of both 3,4-*syn* **79b** and 3,4-*anti* **79c** in almost similar proportion revealed that the olefin geometry of the allylic halide does not have any bearing on the 3,4-diastereoselectivities of the reactions. Possibly, equilibrium of allylic-metal species took place, as suggested by the Zimmerman-Traxler model.[25a,113] The ^1H and ^{13}C NMR spectra of **79b** and **79c** are shown in **Figs. III.1.12-Fig. III.1.15**.

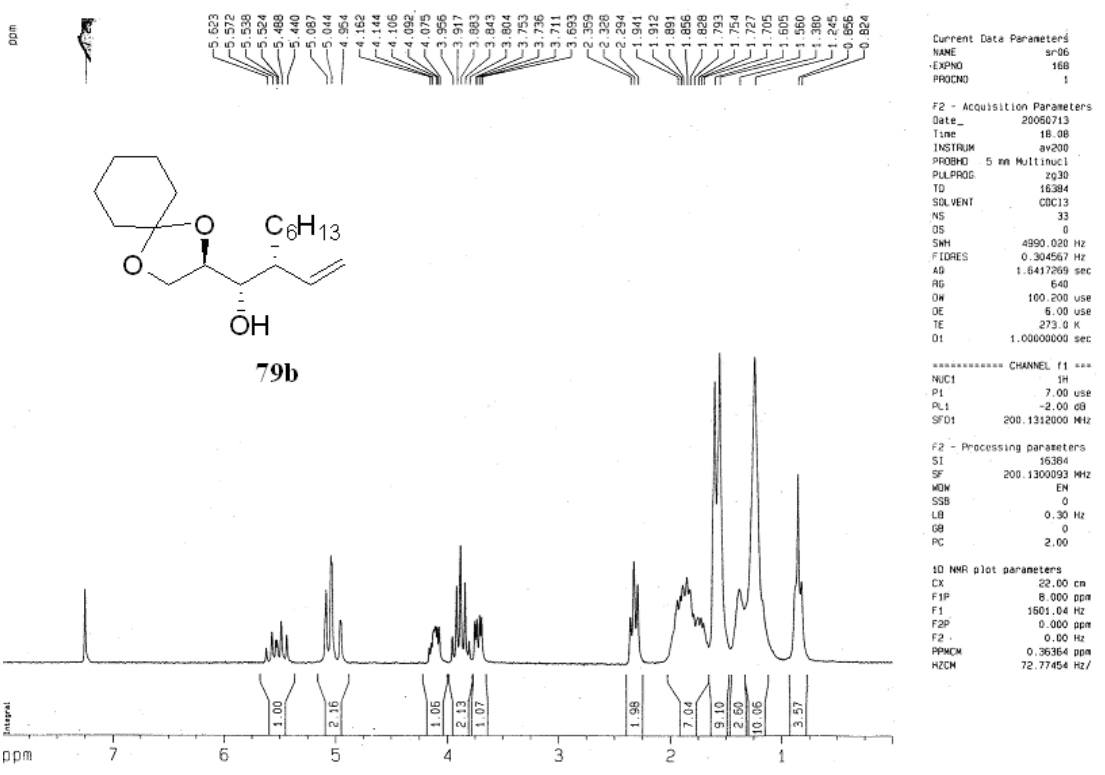


Fig. III.1.12. ^{1}H NMR spectrum of 79b

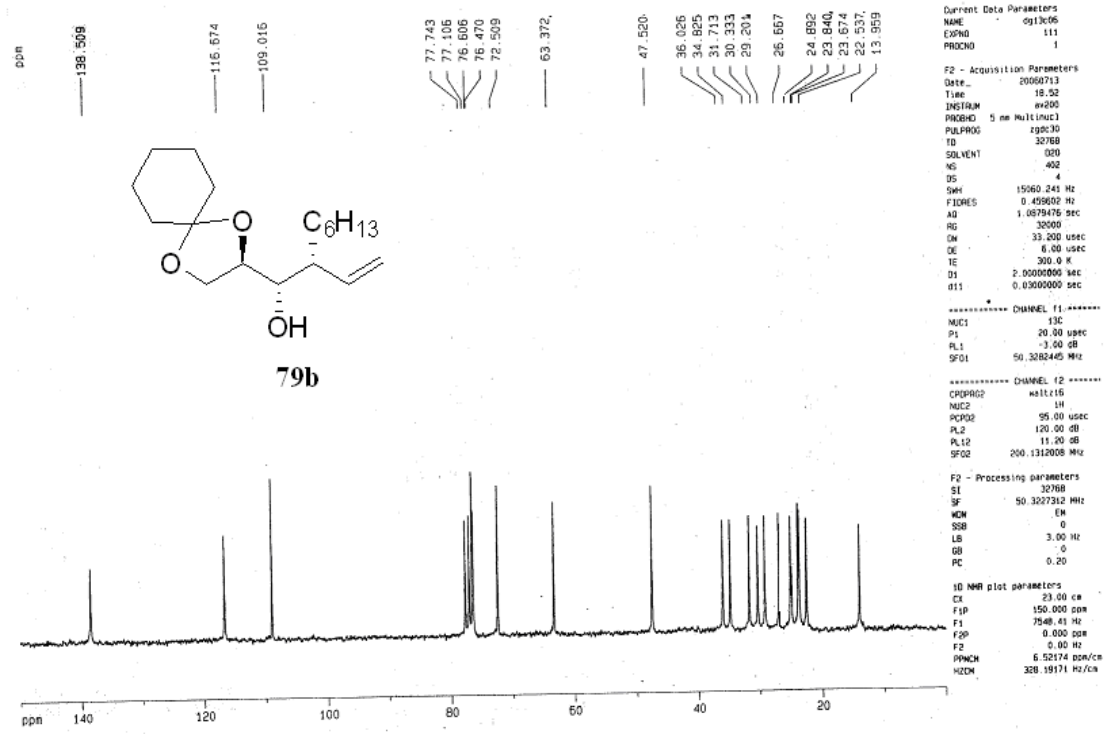


Fig. III.1.13. ^{13}C NMR spectrum of 79b

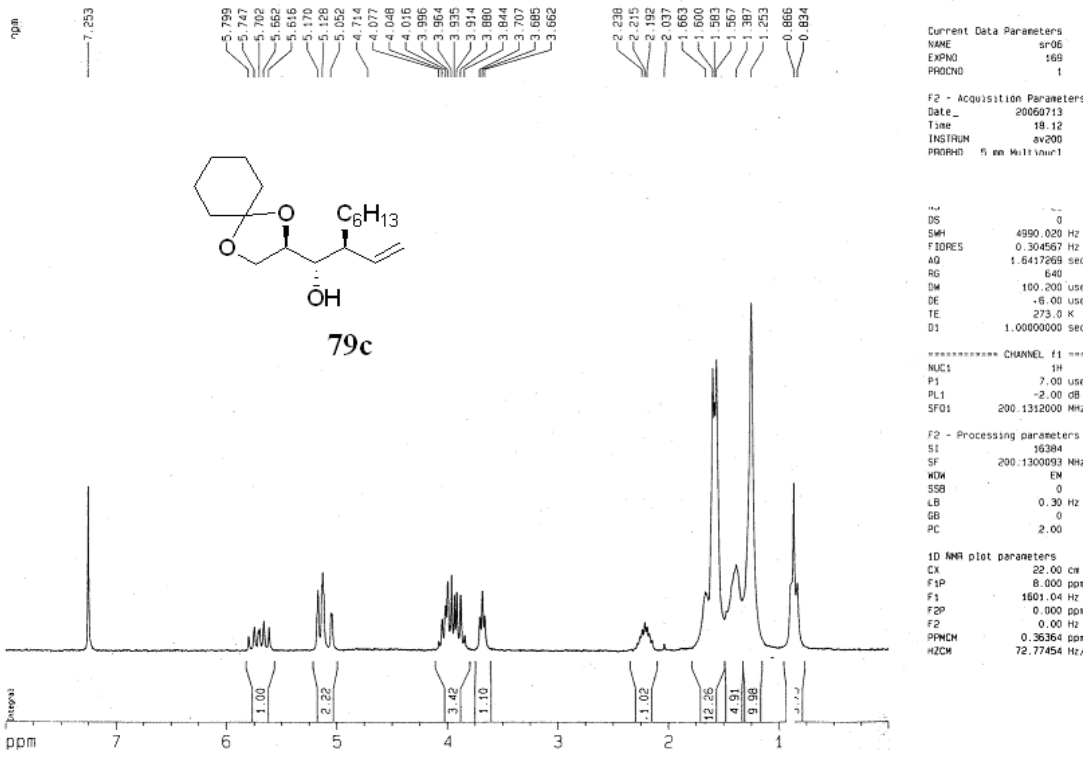


Fig. III.1.14. ^{1}H NMR spectrum of 79c

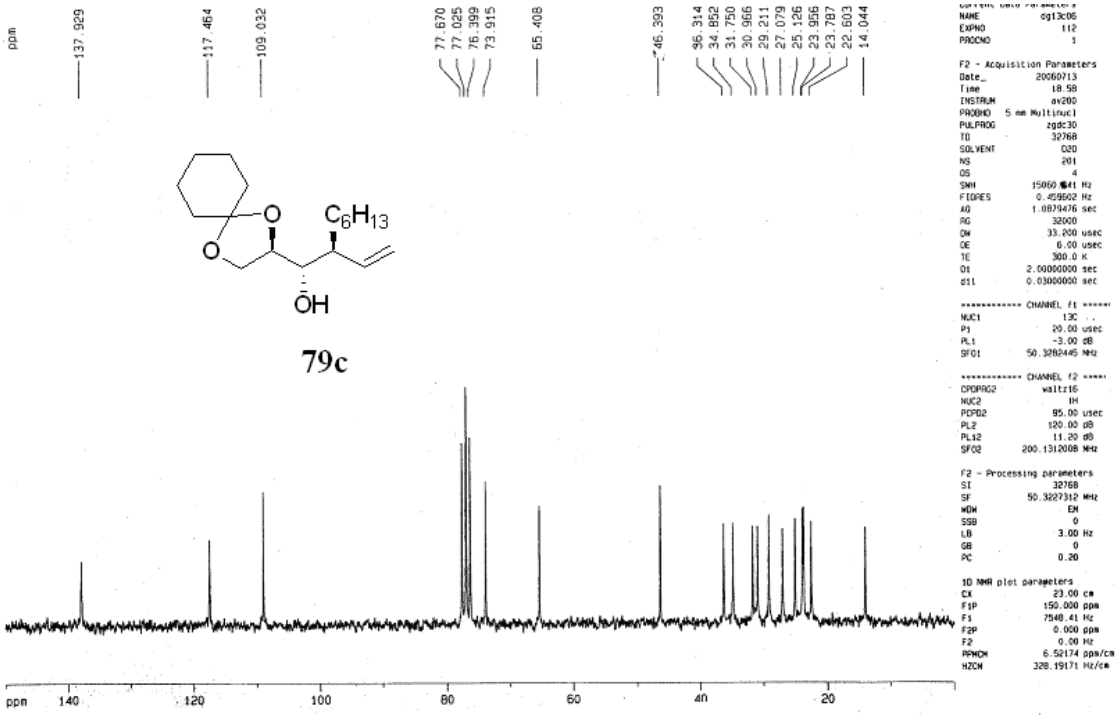
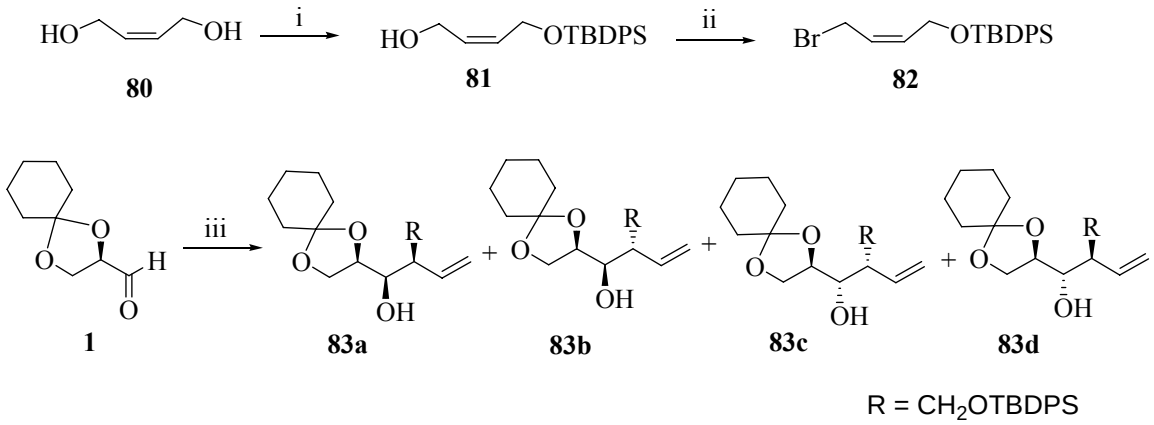


Fig. III.1.15. ^{1}H NMR Spectrum of 79c

***Allylation with 1-Bromo-4-(tert)-butyldiphenylsilyloxy-2Z-butene* (82):** In another reaction, the γ-substituted allylic bromide **82** was chosen for coupling with **1** (**Scheme III.1.7**). Compound **82** was derived from commercially available (*Z*)-but-2-en-1,4-diol (**80**) via (i) monosilylation of its carbinol function with TBDPSCl in the presence of imidazole as the base to afford **81**, (ii) subsequent bromination of **81** to **82** in 71% overall yield *via* mesylation and reaction with NaBr. Compound **82** was characterized from the absence of IR hydroxyl band and the ^{1}H NMR resonances for the TBDPS group. As earlier, the Barbier type addition of **82** to **1** was carried out using the bi-metallic strategy (**Scheme III.1.7**) as well as following Luche's procedure[3] to obtain a mixture of all possible diastereomers **83a-d** of the γ-addition product. The results of the study are summarized in **Table III.2.4.**[121]

In all the cases, the diastereoisomers, with 2,3-*anti*, 3,4-s*yn* **83c** and 2,3-*anti*, 3,4-*anti* **83d** stereochemistry, were produced predominantly. Fortunately the stereomers **83c** and **83d** were separable by column chromatography. Formation of these isomers were confirmed by the IR band at ~3500 cm^{-1} and also from the terminal olefinic signals at δ 5.00-5.23 (2H) and δ 5.80-6.00 (1H) for **83c**, and at δ 5.11-5.23 (2H) and δ 5.70-6.02 (1H) for **83d** in their respective ^{1}H NMR spectra. Compounds **83a** and **83b** were produced only in very small quantities and could not be separated from each other by column chromatography.



i) TBDPSCl, imidazole, CH_2Cl_2, 25 ^oC; (ii) MsCl, Et_3N, CH_2Cl_2, 0 ^oC; NaBr, acetone, 25 ^oC.; iii) Zn, aqueous satd. NH_4Cl, THF, 25 ^oC; or $CuCl_2$, $2H_2O$, Zn, THF, 0 ^oC-25 ^oC; or $FeCl_3$, Zn, THF, 10 ^oC-25 ^oC; or $CoCl_2$, $8H_2O$, Zn, THF, 10 ^oC-25 ^oC.

Scheme III.1.7

Table III.1.4. Reaction course of addition of **82** to **1**[a]

Entry	Metal/ salt	**1** : bromide : metal : metal salt	time	Product ratio[b] **83a/b**: **83c** : **83d**	Yield[c] (%)
1	Zn/ aq NH_4Cl	1: 3.0 : 3.5 : -	5 h	3 : 52 : 45	73.0
2	Zn / $CoCl_2.8H_2O$	1:3.0: 3.5:3.5	20 h	2 : 70 : 28	72.1
3	Zn/ $CuCl_2.2H_2O$	1:3.0: 3.5:3.5	20 h	2 : 33 : 65	70.0
4	Zn/ $FeCl_3$	1:3.0: 3.0:3.0	30 min	2 : 50 : 48	83.0

[a]The reactions were carried out at 5 mmol scale. [b]Combined yields of isolated pure products. [c]Based on isolated yields.

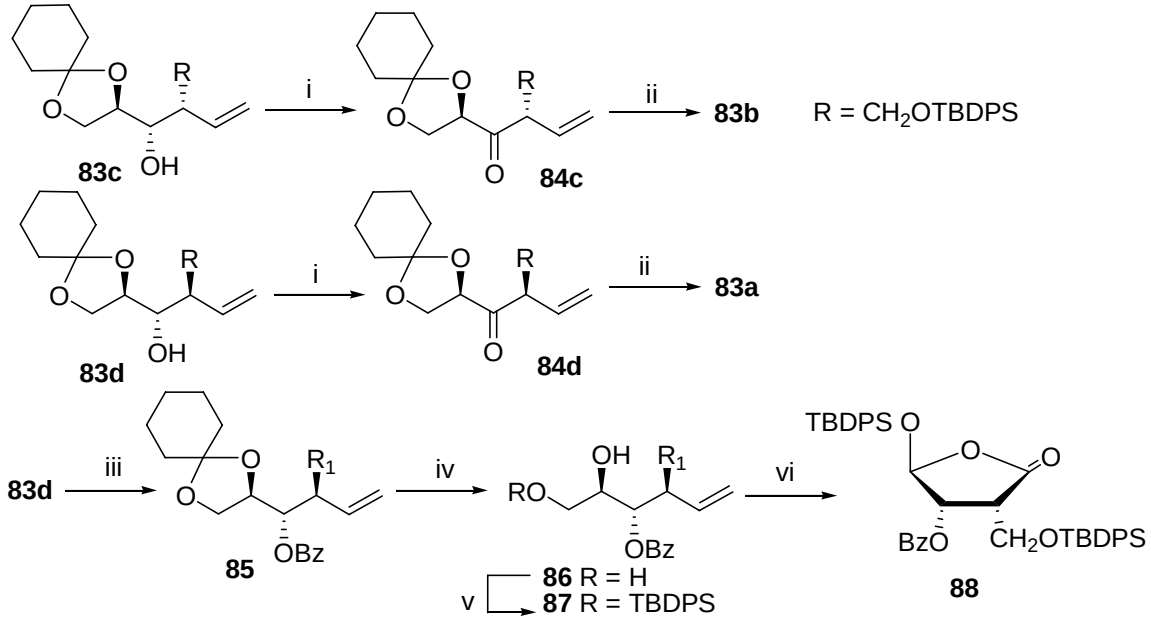
The overall yields of the products from the Co-, Cu- and Zn-mediated additions were comparable (entries 1-3, **Table III.1.4**), but the reactions were sluggish requiring extended stirring. The **83c**/**83d** ratio for the Cu- and Co-mediated reactions were reverse. (entries 2-3, **Table III.1.4**). The Fe-mediated reaction (entry 4, **Table III.1.4**) was very

fast and gave a significantly better yield (83%) of the products. Both Zn- and Fe-mediated reactions produced the alcohols, **83c** and **83d** in almost 1:1 ratio.

In this case also, the observed excellent 2,3-*anti* selectivity suggested that the reactions followed the Felkin Anh model,[24b,112] irrespective of the metal chosen. Apparently the α-chelate attack was not favored due to hydration of metals in the moist reaction environment. Interestingly, of the four cases, the Cu-mediated addition produced a higher amount of the 3,4-*anti* product. The formation of significant amounts of both 3,4-*syn*- and 3,4-*anti*-products gave ample evidence of a considerable amount of *E*,*Z* equilibration of the allylic intermediate during carbon-carbon bond formation.

As evident from the above, none of the above protocols were suitable for the preparation of **83a** and **83b**, which are also useful chiral intermediates, and may be required for the synthesis of suitable target compounds. Since both these compounds possess a β-hydroxy function, in principle, the previously described oxidation-reduction strategy might be suitable for their synthesis. Hence, for their preparation (**Scheme III.1.8**), compounds **83c** and **83d** were separately oxidized with PCC to afford the respective ketones **84c** and **84d** in good yields. Formations of these compounds were confirmed from the appearance of sharp carbonyl IR board band at ~1715 cm^{-1} in place of the hydroxyl band. Reduction of these ketones with K-selectride® furnished the desired 2,3-*syn* products **83b** and **83a** in good yields, almost exclusively. As expected, the IR spectra of these compounds showed broad bands at ~3500 cm^{-1} and absence of the CO peak. The mechanistic rationalization of the steric course of the reduction established the 2,3-*syn* stereochemistry of **83a** and **83b**, confirming the 2,3-*anti* relationship in their progenitors, **83c** and **83d**. Thus, the studies provided efficient routes to prepare all the four

possible diastereomers **83a-d** in substantial amounts, using two operationally simple protocols.



(i) PCC, NaOAc, CH_2Cl_2, 25 ^oC; (ii) K-selectride®, THF, -78 ^oC; (iii) BzCl, pyridine, CH_2Cl_2, 0 ^oC; (iv) Aqueous CF_3CO_2H, CH_2Cl_2, 0 ^oC; (v) TBDPSCl, imidazole, CH_2Cl_2, 25 ^oC; (vi) O_3, NaOH in MeOH, -15 ^oC.

Scheme III.1.8

Next, using the alcohol **83d** as the model substrate, the relative 3,4-stereochemistry was determined. For this, it was converted to the corresponding benzoate derivative **85** in 95% yield, by treating with BzCN in the presence of pyridine. The absence of any IR hydroxyl band, and presence of ^1H NMR multiplets at δ 5.66-5.71 (1H) (**Fig. III.1.16**) and ^{13}C NMR peak at δ 165.5 (**Fig. III.1.17**) confirmed its formation. Compound **85** was subjected to deketalization with aqueous TFA in CH_2Cl_2 to afford the diol **86** in 86% yield. The broad IR band at 3411 cm^{-1} was indicative of the diol function. This was confirmed from the absence of ^1H NMR and ^{13}C NMR resonances (**Fig. III.1.18** and **Fig. III.1.19**

respectively) due to the cyclohexylidene moiety. Treatment of **86** with TBDPSCl and imidazole furnished the monosilylated compound **87** in 80% yield. As expected, its ^{1}H NMR spectrum showed a singlet at δ 1.1 for the *tert*-Bu protons of the TBDPS group. Ozonolysis of compound **87**, following a reported procedure[116] directly produced the γ-lactone **88** in 72% yield. The presence of the γ-lactone function in it was confirmed from the strong IR band at 1742 cm^{-1} and the ^{1}H NMR resonance at δ 5.96 (dd, J = 13.7 and 2.4 Hz). The coupling values, 2.4 Hz and 13.7 Hz of H-3 established its *syn* and *anti* relationships of H-3 with the two neighboring protons, H-2 and H-4. This, in turn proved the *anti-anti* relationship of H-4 in **83d** (**Scheme III.1.8**). Accordingly, the stereochemistry of all other diastereomers **83a-c** was ascertained.

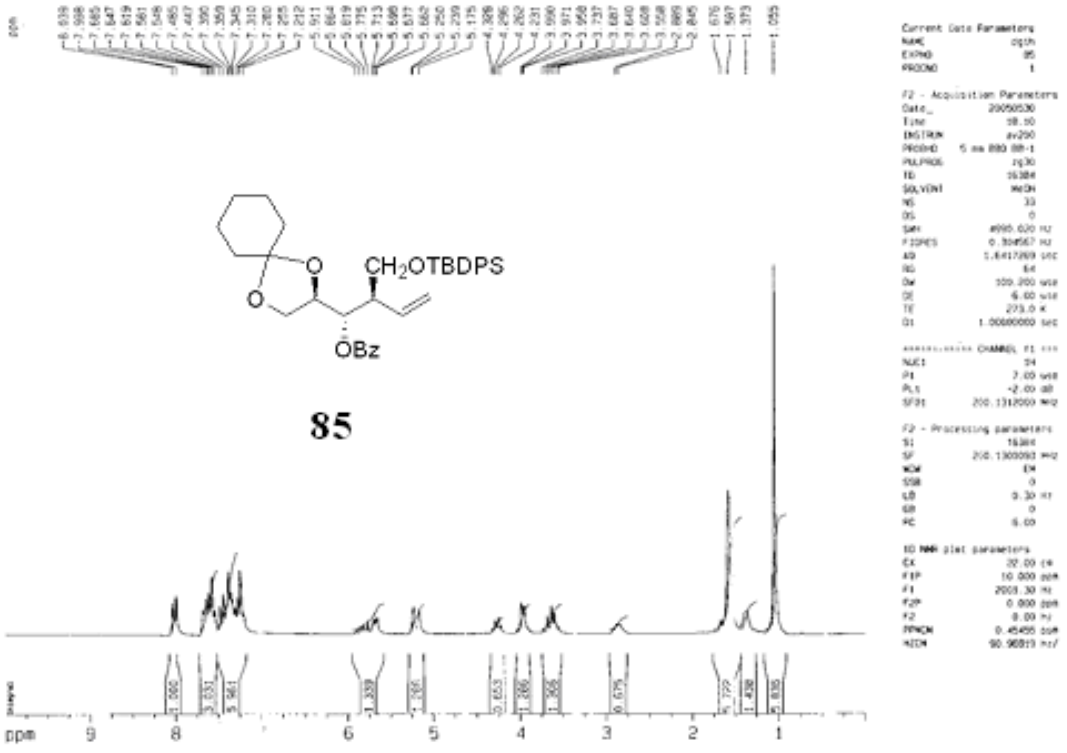


Fig. III.1.16. ^{1}H NMR spectrum of 85

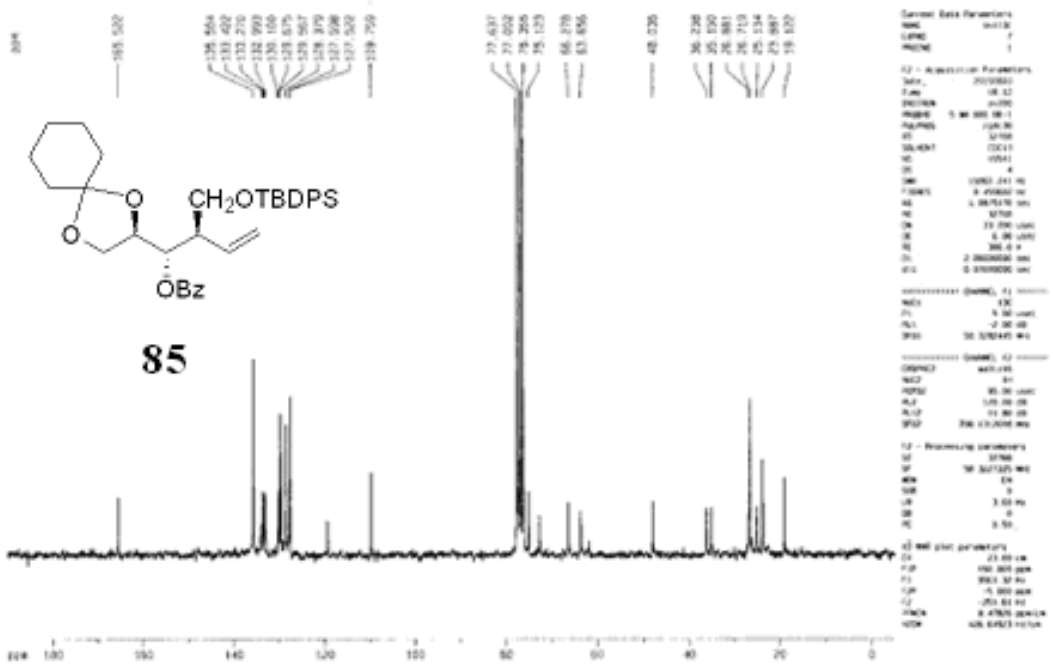


Fig. III.1.17. ^{13}C NMR spectrum of 85

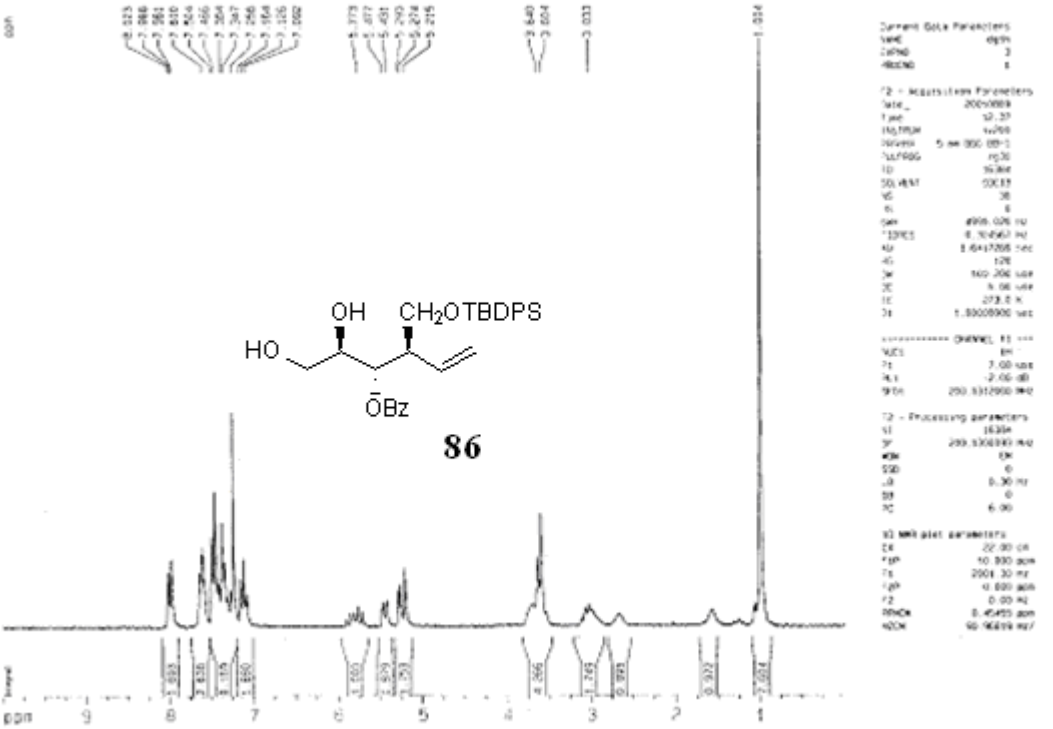


Fig. III.1.18. ^{1}H NMR spectrum of 86

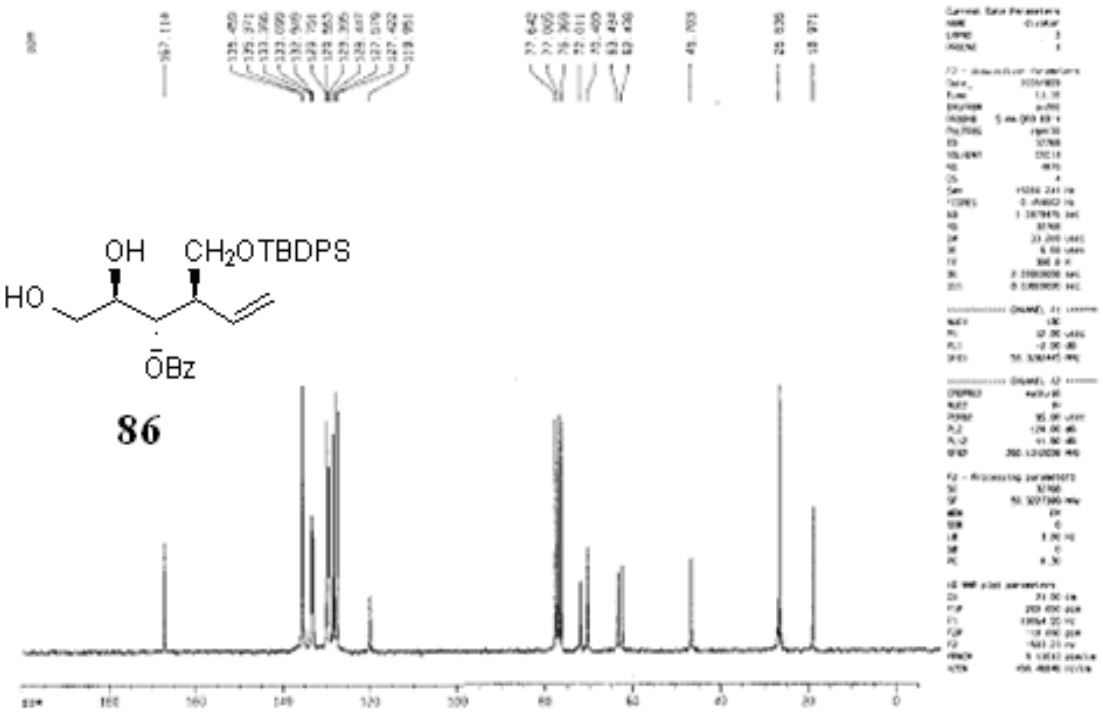


Fig. III.1.19. ^{13}C NMR spectrum of 86

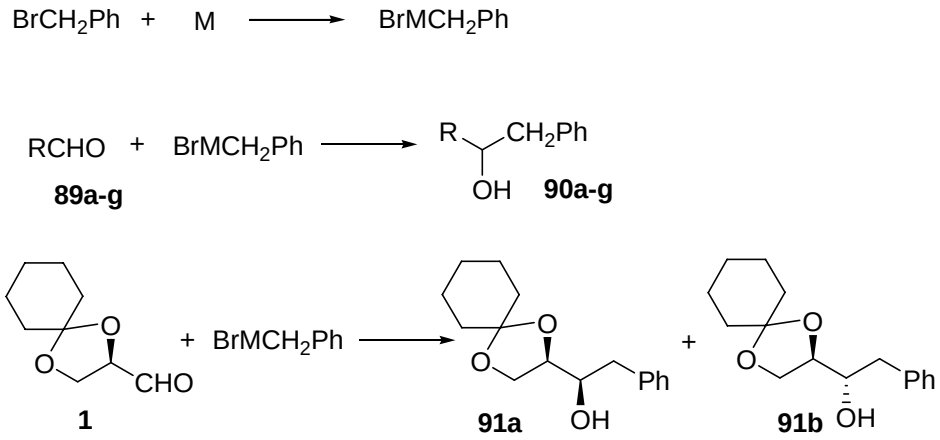
Overall, a practically viable bimetallic protocol for allylation of a versatile chiral template **1** was developed with various unsubstituted and γ-substituted allyl bromides. This new procedure could be of considerable significance in organic synthesis. The stability of cyclohexylidene moiety in **1** allowed all these metal- mediated allylations to be performed easily by stirring under moist conditions in the presence of metal-metal salts combinations. Moreover, the bulky ketal moiety was responsible for the stereoselective interconversion of the carbinol stereochemistry *via* an oxidation-reduction protocol. In hindsight, all possible diastereomers could be synthesized starting from the same combination of substrates.

(B) ***Benzylation of aldehydes***

Addition of benzyl moiety to aldehydes is an important carbon-carbon bond forming reactions in organic synthesis. Due to their functional richness, the resultant homobenzylic alcohols are amenable for different applications in organic synthesis.[119] The most common procedure to prepare homobenzylic alcohols involves addition of benzylmagnesium bromide to carbonyls, that requires anhydrous conditions. Besides this, some other strategies have also been reported to prepare the homobenzylic alcohols. These include hydroboration of 1-aryl alkenes,[122] solvolyses of sulfonates obtained from bridged hydrocarbons[123] and regio-selective hydrogenation of aromatic epoxides.[124] In view of current interest on performing many organic reactions in environmentally friendly aqueous media,[125] considerable attention has been focused on performing Barbier type additions of benzyl bromide to aldehydes. This has resulted in several reports where metals such as Cd, obtained from a tri-metal system,[126a,b] Zn in presence of catalytic Ag[126c] etc. In a recently reported approach, silver catalyzed Mn mediated Barbier type benzylation has also been performed in anhydrous THF.[127]

The present work describes a very mild and inexpensive procedure in moist medium for the metal mediated Barbier type benzylation of aldehydes as an application of the previously described bimetallic redox strategy.[128] First, we investigated the efficacy of the present reaction using all four possible combinations between two reducible salts $FeCl_3$ and $CuCl_2$-$2H_2O$ and two reducing metals, Zn dust and Mg turning. Three classes of aldehyde substrates viz aliphatic, aromatic and a chiral were chosen, with a view to understanding the generality of this strategy. In all these heterogeneous reactions, aldehyde

was treated with excess amount of benzyl bromide, metal salts ($CuCl_2$, $2H_2O$ or $FeCl_3$) and metal to ensure the progress of the successful ones at faster rate.



Scheme III.1.9

The combination of Zn and metal salts were ineffective for the benzylation of all the aldehydes **89a-g**. Likewise, the combination of $FeCl_3$/Mg system also did not give the desired products with any of these aldehydes. However, using a combination of Mg and $CuCl_2.2H_2O$, the benzylation of the aldehydes **89a-g** proceeded smoothly to furnish the corresponding homobenzylic alcohols **90a-g** in modest to good yields (58-74%) (**Table III.1.5**). The reaction was comparatively faster (7-9h) with the aromatic aldehydes, while the aliphatic substrates reacted sluggishly (16-18h). The homobenzyl alcohols were characterized from their IR peak at ~3400 cm^{-1} (-OH group), the ^1H NMR peaks at δ 3.0-3.3 ppm [-CH(OH)] and multiplet at δ 7.2-8.0 ppm (-Ph) and as well as the ^{13}C NMR peaks at δ ~45 ppm (benzylic carbon). As a representative example, ^1H and ^{13}C NMR spectra of **90e** are shown in **Fig. III.1.20** and **Fig. III.1.21** respectively.

Table III.1.5 Reaction course of Cu-mediated Benzylation of aldehydes[a]

Entry	R of aldehyde	Aldehyde: Mg:$CuCl_2$, $2H_2O$: $PhCH_2Br$	Time (h)	product	yield[b] (%)
1	*n*-C_6H_{13} **89a**	1.0: 4.0:4.0:1.5	18	**90a**	61.8
2	*n*-C_9H_{19} **89b**	1.0: 4.0:4.0:1.5	16	**90b**	64.4
3	*n*-$C_{13}H_{27}$ **89c**	1.0: 4.0:4.0:1.5	16	**90c**	57.8
4	C_6H_5 **89d**	1.0: 3.0:3.0:1.5	9	**90d**	71.7
5	3-$MeOC_6H_5$ **89e**	1.0: 3.0:3.5:1.5	8	**90e**	73.8
6	4-Et-C_6H_5 **89f**	1.0: 3.0:3.5:1.5	7	**90f**	70.7
7	4-Cl-C_6H_5 **89g**	1.0: 4.0:4.0:1.5	11	**90g**	68.9
8	(*R*)-2,3-cyclohexylidene glyceraldehyde **1**	1.0: 7.0:7.0:2.5	20	**91a** + **91b**	68.4[c]

[a]The reactions were carried out at 5 mmol scale. [b]Combined yields of isolated pure products. [c]The product was obtained as 80:20 mixture of **91a** and **91b** as determined from ^{13}C NMR spectrum.

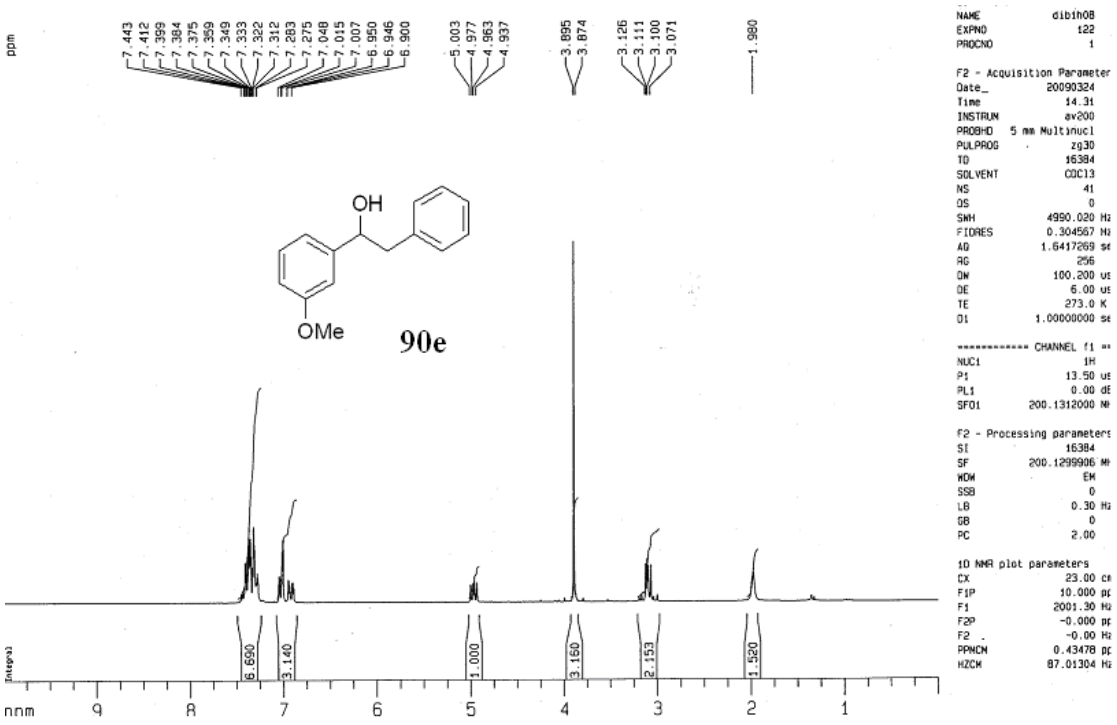


Fig. III.1.20. ^{1}H NMR spectrum of 90e

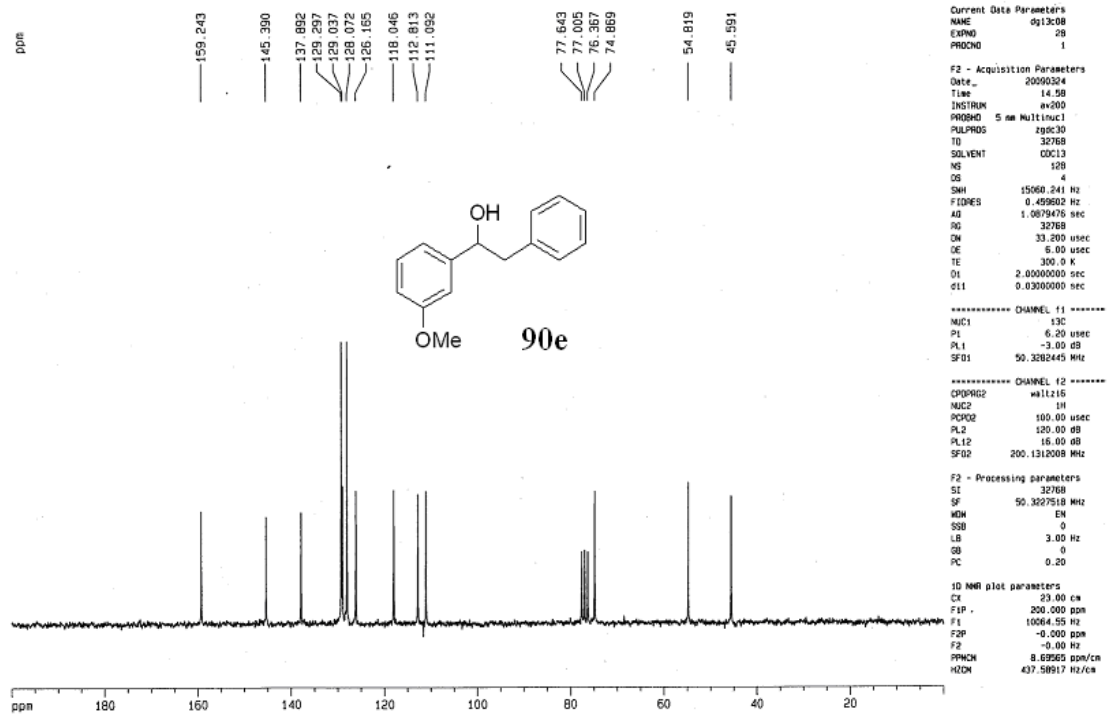


Fig. III.1.21. ^{13}C NMR Spectrum of 90e

In general, aromatic aldehydes reacted comparatively at faster rates (entries 4-7, **Table III.1.5**) than the aliphatic substrates. Benzylation of the chiral aldehyde **1** (entry 8, **Table III.1.5**) also proceeded efficiently to produce the homobenzylic alcohol as a mixture of *syn* (**91a**) and *anti*-isomers (**91b**) in good yield and *syn* selectivity [*syn* : *anti* ~ 80 : 20]. Owing to the inseparability of the diastereomers (**91a**/**91b**) by column chromatography, their ratio could be assayed from ^{13}C NMR spectrum (**Fig III.1.22**) of this mixture. In general, all the ^{13}C NMR peaks of **91a** consistently appeared at more downfield compared to the corresponding signals of *anti*-isomer **91b**. This could be evident from the fact that following oxidation of this isomeric mixture and *syn*-selective K-selectride® reduction of the diastereomeric mixture **91a** and **91b**, the downfield signals of *syn*-**91a** enhanced very much. This will be further discussed in **Chapter IV**. This enabled us to determine the proportion (**91a**:**91b**) in the diasterisomeric mixture of the benzylation product of **1**.

According to literature precedence,[129] the predominant formation of *syn*-**91a** suggested that the addition of the active organocopper reagent **(Scheme III.1.9**) proceeds through α-chelate cyclic model. It is worth noting that addition of $PhCH_2MgBr$ was found to produce a mixture of **91a** and **91b** in much lower yield (43.8%) and diastereoselectivity (*syn*/*anti* = 35:65). Thus, the present protocol was much superior. Also, the Grignard reaction was more *anti*-selective. This also supports our proposed stereochemical model; as compared to PhCH2MgBr, the benzyl-Cu intermediate would follow a chelate-controlled path.

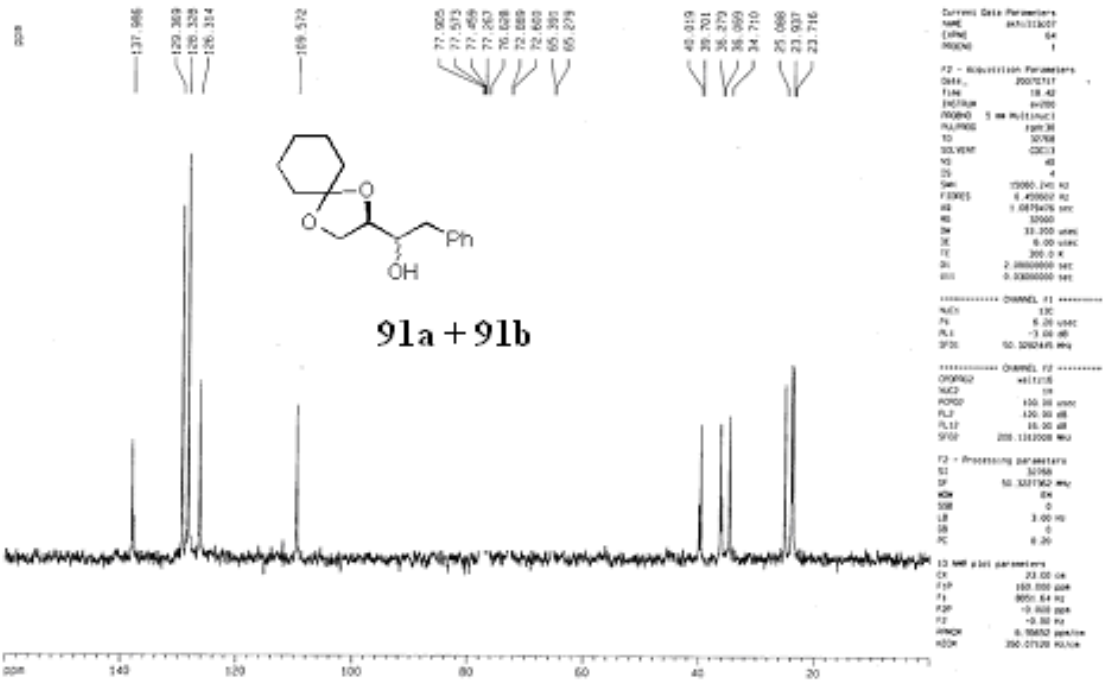


Fig. III.1.22. ^{13}C NMR spectrum of 91a+91b

Overall, a very mild procedure for benzylation of aldehydes was developed using $Mg/CuCl_2.2H_2O$ as the active metal mediators. Its novelty was due to exploitation of the spontaneous bimetal redox reaction in an environmentally benign wet medium. In addition, its inexpensiveness, practical viability and good success with different kinds of aldehyde substrates contributed significantly together to its overall efficacy. In this context, it is worth mentioning that some of the reported procedures for benzylation of aldehydes have a few limitations due to varied reasons *viz* use of toxic $CdCl_2$, expensive Ag catalyst, anhydrous conditions etc. Hence this method proved out to be more efficient and environmentally benign compared to other procedures.

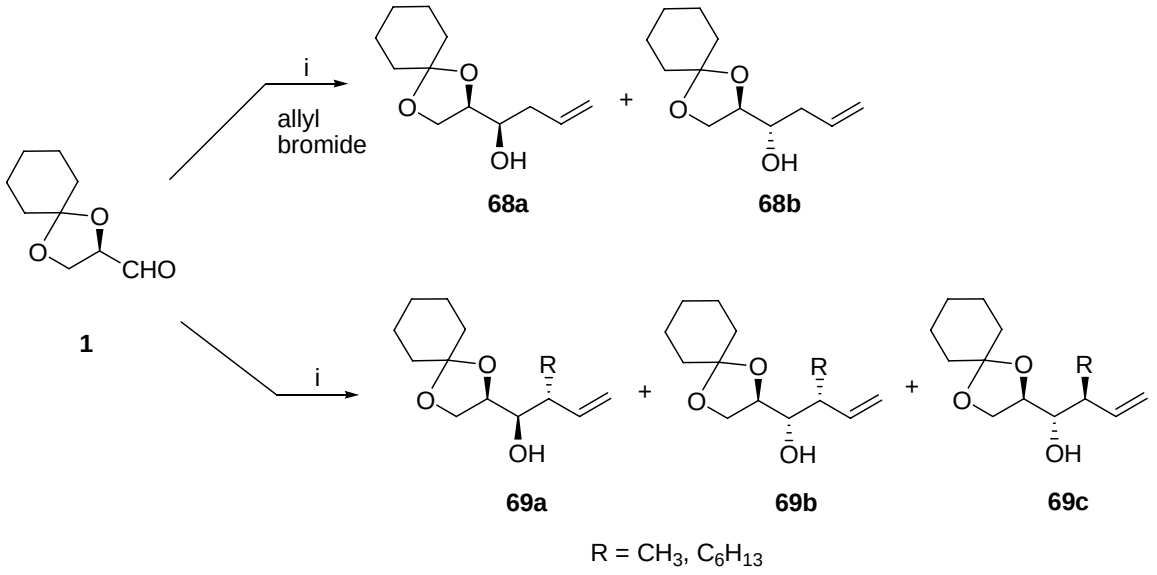
III.2 METAL DEPENDENT MODULATION OF DIASTEREOSELECTIVITY IN THE BARBIER TYPE ALLYLATION/CROTYLATION

For the past decade, our group has established the aldehyde **1** as a versatile chiral template for carrying out different asymmetric transformations. The homoallyl alcohol diastereomers **68** and **69** contain several stereogenic centres and are highly functionalized for subsequent chemo- and enantio-selective reactions. In particular, the alkene functions in these are amenable to (i) oxidative degradation to aldehyde/acids,[111,130] (ii) stereoselective epoxidation, (iii) different types of metathesis reactions etc. Many of these methodologies have been used in this investigation for the synthesis of a large number of bioactive compounds and some of them have been published. The detailed synthetic procedures will be discussed in **chapter IV**. The previous deliberation on allylation of **1** revealed moderate to good diastereoselectivity, which is of significance when the different diastereomers are required for the syntheses of the target compounds. Nevertheless, improvement of the diastereoselectivity of such a reaction is highly desirable. The influence of the substrate and its substituents as well as the influence of the solvent on the course of the metal mediated Barbier reaction was previously reported.[55a] However, the dependence of the stereochemical outcome of such a Barbier reaction on the metal as well as on the halide used has been rarely studied.[131] This prompted us to look into the metal dependent modulation of stereoselectivity in Barbier type reactions.

III.2.1 Present Work

The initial motivation for the present work stems from our own results with the bimetallic system and the previous observation by Rübsam *et. al.*[131] that the

stereochemistry of allylation of β-hydroxy-α-aminoaldehydes could be tuned by changing the metals. Hence for the present work, we surveyed a range of pure metals *viz*. In, Ga and Bi for the allylation of **1** (**Scheme III.2.1**) was performed with different in different media *e.g*. THF, H_2O and a room temperature ionic liquid (RTIL), and the results are presented in **Table III.2.1**.



(i) Metal, Solvent, 25 ^{o}C.

Scheme III.2.1

The choice of group 13 elements, In and Ga, was mainly based on their stability towards air/moisture and also their non-toxicity[66a,132] (discussed previously in **Chapter II**). Bismuth is also attractive as a reagent for the reductive allylation of carbonyl compounds, since it is also non-toxic and low-priced.[133] Earlier, Bi mediated allylation has been performed in DMF,[134] and also in H_2O.[135] In this study, we have used Bi metal for allylation of aldehyde **1** in different solvents *viz*. THF, H_2O and a room temperature ionic liquid (RTIL). Amongst different RTILs, [bmim][Br] was of our choice, since, due to its excellent hydrophilicity, it was expected to mimic aqueous medium and appeared best

suited for the Barbier type reactions. Also the metal mediated allylation reactions of achiral aldehydes and ketones were most efficient in [bmim][Br] (**Chapter II**), and hence this was choosen as RTIL for carrying out allylation reactions with the chiral aldehyde **1**.

Table III.2.1. Reaction course of allylation of **1**[a]

Entry	Allyl bromide (equiv.)	Metal (equiv.)	Solvent	Additive	Time (h)	Yield[b] (%)	Product ratio[c] **68a:68b**
1	4	In (2.5)	H_2O	--	5	58	24.2 : 75.8
2	3.5	In (2.5)	THF	KI+ LiCl	7	69	2.0 : 98.0
3	1.2	In (1.0)	[bmim][Br]	--	3	78	29.8 : 70.2
4	4	Ga (2.5)	H_2O	--	6	48	21.9 : 78.1
5	3.5	Ga (2.5)	THF	KI+ LiCl	16	NR[d]	--
6	1.2	Ga (1.0)	[Bmim][Br]	--	4	73	5.0 : 95.0
7	4	Bi (2.5)	H_2O	--	8	62	23.2 : 76.8
8	3.5	Bi (2.5)	THF	KI+ LiCl	16	NR[d]	--
9	1.2	Bi (1.0)	[bmim][Br]	--	4	75	31.6 : 68.4

[a]The reactions were carried out at 2 mmol scale. [b]The yields refer to those of isolated pure isomers. [c]The isomeric ratios were determined from the isolated yields. [d]NR: no reaction.

The stereochemical outcome of the metal mediated allylation of **1** was found to be highly dependent on the metal, as well as on the reaction media. In general, for all the metals, reactions could be accomplished in [bmim][Br] with stoichiometric amount of the metal and allyl bromide in a much lesser time with appreciably higher yields of the products (entries 3, 6 and 9, **Table III.2.1**). In H_2O, even after using activators, the yields

of the products were modest (48-62%). More importantly, a large excess of metal and allyl bromide was required for the completion of the reaction. All the reactions in H_2O proceeded with a modest diastereoselectivity for the *anti*-isomer **68b** (entries 1, 4 and 7, **Table III.2.1**). Surprisingly, the Ga- and Bi-mediated allylations in THF did not take place at room temperature (entries 5 and 8, **Table III.2.1**). However, the In-mediated allylation in THF proceeded with excellent *anti*-selectivity (entry 2, **Table III.2.1**). Although the In- and Bi-mediated allylation in [bmim][Br] proceeded with modest *anti*-selectivity, use of Ga for the allylation in [bmim][Br] yielded the *anti*-isomer **68b** with 90% diastereoselective excess (entry 6, **Table III.2.1**). In all the cases, the predominant formation of the *anti*-isomer indicated that all the reaction took place *via* the Felkin-Anh model.[24b,112]

In case of crotylation (**Scheme III.2.1**), we also used two additional metals, Mg and Sb. In this case also the diastereoselectivity could be tuned by changing the metals, and solvents.[117] The results are summarized in **Table III.2.2**. With Mg in ethereal solvents, practically no selectivity was obtained, and the diastereomers **69a-c** were produced in almost equal amounts (entries 1, 2, **Table III.2.2**). Use of Sb in aqueous THF or H_2O gave a similar diastereoselectivity, but poor yields, and required an additional metal activator (KF) (entries 3, 4, **Table III.2.2**). The In-mediated reaction proceeded well in H_2O, but not in THF (entries 5-8, **Table III.2.2**), resulting in preferential formation of **69b** and **69c** in ~1:1 ratio, as the major products. On the other hand, the Ga-mediated reaction in THF produced the products in poor yields even under metal activation and resulted in modest **69b**/**69c** selectivity (entry 10, **Table III.2.2**). A similar stereoselectivity was earlier observed using Zn metal (**Table III.1.2**, **Chapter III.1.2**). The inability of Ga to carry out

the reaction in H_2O (entry 9, **Table III.2.2**) is consistent with the fact that Ga requires thermal or ultrasonic activation, while we carried out the reactions at room temperature.

Next, we carried out the In and Ga-mediated reaction in [bmim][Br] as the RTIL. The In-mediated crotylation in [bmim][Br] proceeded with an improved diastereoselectivity *viz*. **69a**:**69b**:**69c** ~ 9.3:13.4:77.3 (entry 11, **Table III.2.2**). Gratifyingly, the selectivity of **69a**:**69b**:**69c** could be improved further to 3:5:92 by carrying out the reaction with Ga-metal (entry 12, **Table III.2.2**). The yields of the reactions were also very good with both In and Ga, and the reaction could be accomplished much faster with almost stoichiometric amounts of the reagents. In other solvents, the results were significantly inferior, even with a large excess of the reagents and prolonged reaction time. Surprisingly, the Zn-mediated crotylation of **1** did not take place in [bmim][Br]. The compounds **69a-c** could be separated by column chromatography and characterized as mentioned earlier.

Table III.2.2. Reaction course of crotylation of **1**[a]

Entry	bromide (equiv.)	Metal (equiv.)	Solvent	Additive	Time (h)	Yield[b] (%)	Product ratio[c] **69a:69b:69c**
1	3.0	Mg (5.0)	Et_2O	--	8	74	38.1:33.2:28.7
2	3.0	Mg (5.0)	THF	--	8	35	29.0:26.1:44.9
3	2.5	Sb (5.0)	H_2O-THF (1:1)	KF (2M)	12	37	30.6:40.8:28.6
4	2.5	Sb (5.0)	H_2O	KF (2M)	14	48	40 :47.7: 12.2
5	3.0	In (5.0)	H_2O	--	14	75	4.0: 52.2:43.8

6	1.2	In (2.0)	H_2O	LiCl+ KI	14	72	3.7: 52.3:44.0
7	3.0	In (5.0)	H_2O	LiCl+ KI	14	72	3.7: 52.3:44.0
8	3.0	In (5.0)	THF	--	12	NR[d]	--
9	4	Ga (2.5)	H_2O	--	20	NR[d]	--
10	3.5	Ga (2.5)	THF	KI+LiCl	10	55	5.0: 35.0: 60.0
11	1.2	In (2.0)	[bmim][Br]	--	4	81	9.3:13.4:77.3
12	1.2	Ga (1.0)	[bmim][Br]	--	5	82	3.0 :5.0 :92.0
13	4.0	Bi (2.5)	H_2O	--	12	67	7.0: 31.0: 62.0
14	3.5	Bi (2.5)	THF	KI+LiCl	20	NR	--
15	1.2	Bi (1.0)	[bmim][Br]	--	3	73	11.4:82.6 :4.0

[a]The reactions were carried out at 2 mmol scale. [b]The yields refer to those of isolated pure isomers. [c]The isomeric ratios were determined from the isolated yields. [d]NR: no reaction.

We then attempted crotylation of carbonyls in these three solvents using Bi metal. When Bi was used for crotylation of **1** in H_2O, the reaction proceeded with moderate yield and diastereoselectivity even with high excess of the reagents (entry 13, **Table III.2.2**). No reaction was observed in THF even after metal activation with KF (entry 14, **Table III.2.2**). However, to our delight, the reaction in [bmim][Br] was very fast, and could be carried out with stoichiometric amounts of the reagents (entry 15, **Table III.2.2**). Strikingly, this yielded **69b** as the major diastereomer, for which this reaction became important from preparative point of view.

The reactions of **78a** with **1** using different metals in different solvents were also studied. In this case also, the reactions were faster in [bmim][Br], without the need of a metal activator and using stoichiometric amount of the reagents. Also the yields were

higher in [bmim][Br]. The results are tabulated in **Table III.2.3**. In almost all the cases the *anti*,*anti* isomer **79c** was formed as the major diastereomer.

Table III.2.3. Reaction course of **78a** with **1**[a]

Entry	**78a** (equiv.)	Metal (equiv.)	Solvent	Additive	Time (h)	Yield (%)[b]	Product ratio[c] **79a:79b:79c**
1	4	In (2.5)	H_2O	--	5	58	3.1:35.0:61.9
2	3.5	In (2.5)	THF	KI+LiCl	16	NR[e]	--
3	1.2	In (1.0)	[bmim][Br]	--	6	78	11.0:42.0:37.0
4.	4	Ga (2.5)	H_2O	KI+LiCl[d]	16	NR[e]	--
5	3.5	Ga (2.5)	THF	KI+LiCl[d]	16	NR[e]	--
6	1.2	Ga (1.0)	[bmim][Br]	--	7	79	3.4:44.5:52.1
7.	3.5	Bi (2.5)	H_2O	KI+LiCl	20	65	7.2:31.8:61.0
8	3.0	Bi (2.0)	THF	KI+LiCl	12	43	12.0:22.0:66.0
9	1.5	Bi (1.2)	[bmim][Br]	--	--	72	5.0:35.4:59.6

[a]The reactions were carried out at 2 mmol scale. [b]The yields refer to those of isolated pure isomers. [c]The isomeric ratios were determined from the isolated yields. [d]The reactions were carried out under ultrasonication. [e]NR: no reaction.

Mechanism of the reaction. Although an α- or a β-oxygenation in carbonyl compounds is reported to be most effective for chelation to the metals,[136] the aldehyde **1** gave predominantly 4,5-*anti*-diols with both In and Ga. This indicated that due to the bulky cyclohexanedioxy group in **1** precluded any chelation control in the reaction. The results

are consistent with our previous results with the bimetallic protocols and can be rationalized by the Felkin-Anh model.

The 3,4-diastereoselectivity of the reaction involving γ-substituted (Me or C_6H_{13}) allylic metal reagents and aldehydes may, in principle, involve a series of cyclic transition states, wherein the allylmetal reagent coordinates intramolecularly to the oxygen atom of the carbonyl group (**Fig. III.2.1**). Formation of TS**1** and/or TS**2** leads to the *syn*-adduct, while the *anti*-product is obtained from TS**3** and/or TS**4**. Given that no other intramolecular chelation operates for this reaction, the transition state TS**3** leading to the 3,4-*anti*-adduct is most favourable from the steric point of view, because both R and R' (cyclohexylidene) groups adopt equatorial positions in it, and the allylic-metal exists as the *E*-form, irrespective of the geometry of the starting bromide.[137] The stereoselectivity is considered to be the outcome of the orientation of R group. These explain the preferential formation of **69c** in the Ga-mediated crotylation of **1**. On the other hand, the preferential formation of 3,4-*syn* product **69b** in the Bi-mediated crotylation reaction suggested an extensive conversion of the initially formed *E*-allylbismuth species to the corresponding *Z*-isomer. However, the effect of the metal and solvent on the diastereoselectivity of the reactivity is unclear. A large number of other factors such as nature of the metal,[138] counterion-dependence, aggregation state of the nucleophiles[139] may be involved in dictating this diastereoselectivity and any more detailed rationalization would be, at best, speculative.

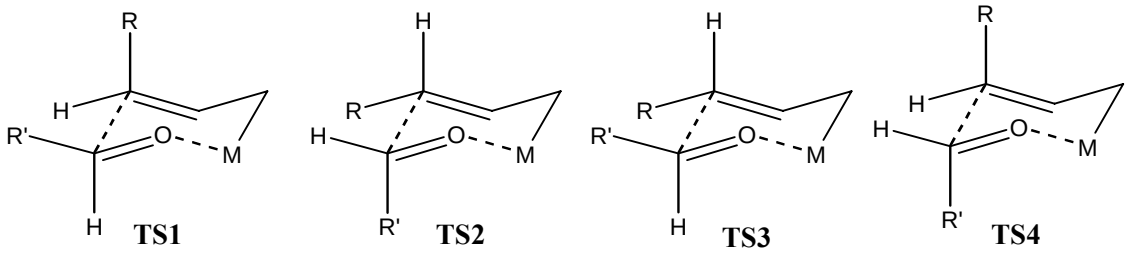


Fig. III.2.1. Cyclic transition states for metal mediated crotylation of 1.

It is worth mentioning that earlier, better stereocontrol in crotylation was accomplished with reagents such as crotyltrifluorosilane,[140] and crotyltrifluoroborates[141] that need to be synthesized. In that light, the present approach, using inexpensive and commercially available reagents such as crotyl bromide, [bmim][Br] and Ga, and the widely used chiral template, **1** provides a simple and convenient strategy for asymmetric crotylation. Incidentally, this is the first application of a hydrophilic RTIL in the Barbier type allylation. Amongst the imidazole-based RTILs, [bmim][Br] is least expensive and possess negligible vapour pressure, providing additional advantages for the process. In addition, the present study also demonstrated that by judicious choice of the mediating metals *viz*. Ga and Bi, the reaction can be directed to produce **69c** and **69b** with excellent diastereoselectivity.

Overall, we disclosed that by careful choice of metal and solvent, the stereochemical profile of the Barbier type crotylation of the aldehyde **1** can be tuned. Of particular interest was the combination of Ga/[bmim][Br] and Bi/[bmim][Br], which ensured a very fast reaction with stoichiometric amounts of the reagents, without any additional metal activation (chemical, thermal or ultrasonic). The reaction provided functionalized chiral homoallylic alcohols with high yield and diastereoselectivity. Also, this provided an example of the Barbier type allylation in a hydrophilic RTIL.

III.3 EXPERIMENTAL SECTION:

General procedure for allylation of aldehydes *via* bi-metallic redox strategy. To a well stirred and cooled (10 ^{o}C for $CoCl_2$, and $FeCl_3$, 0 ^{o}C for $CuCl_2$) suspension of aldehyde (10 mmol), allylic bromide (amounts as specified in tables) and the respective metal salt (amounts specified in tables) in THF (100 mL) was added Zn dust (amount specified in tables) in portions over a period of 10 min. After stirring for 30 min, it was gradually brought to room temperature and stirred for the time specified in the tables. The mixture was treated successively with water (50 mL) and EtOAc (100 mL), stirred for 10 min, and filtered through a sintered funnel. The filtrate was acidified with 2% aqueous HCl, the organic layer was separated and the aqueous layer extracted with EtOAc (50mL). The combined organic extracts were washed with water and brine, and dried. Solvent removal in vacuo followed by normal column chromatography of the residue (silica gel, 0-15% EtOAc/hexane) afforded the respective products.

General procedure of benzylation reaction. To a well stirred mixture of aldehyde (0.01 mol), BnBr (amounts specified in **Table III.1.5**) and $CuCl_2$,$2H_2O$ (amounts specified in **Table III.1.5**) in THF (100 mL) was added Mg turnings (amount specified in **Table III.1.5**) in one lot. The mixture was stirred at ambient temperature for the period, shown in **Table III.1.5**. The reaction mixture was treated successively with water (50 mL) and EtOAc (100 mL), stirred for 10 min and filtered. The filtrate was acidified with 2% aqueous HCl, the organic layer was separated and the aqueous layer extracted with EtOAc (50mL). The combined organic extracts were washed with water and brine, and dried. Solvent removal and column chromatography of the residue (silica gel, 0-20 % EtOAc/hexane) afforded the desired benzylation products in pure form.

General procedure for Barbier type allylation/crotylation of 1 in H_2O or THF. Finely divided metal powder (In, Sb, Ga or Bi) was added to a mixture of **1** (5.0 g, 0.029 mol) and allyl /crotyl bromide (equivalents specified in **Table III.2.1** and **Table III.2.2**) in H_2O (30 mL) or THF (30 mL). After stirring the mixture for the time specified in **Table III.2.1** and **Table III.2.2**, it was filtered and worked-up as above to isolate the pure products. For the reaction with Sb, an aqueous solution of KF (5-6 mL, 2M) was also added in the reaction mixture. The In-mediated reaction was also carried out in the presence of LiCl and KI (1.0 equiv. each).

Procedure for allylation/crotylation in [bmim][Br]. A mixture of the metal (In, Ga or Bi) and allyl/crotyl bromide (quantities specified in **Table III.2.1** and **Table III.2.2**) in [bmim][Br] (3 mL/mmol) was stirred at room temperature for 0.5 h, followed by addition of the aldehyde **1**. The reaction mixture was stirred at room temperature for 4-5 h. After completion of the reaction (*cf*. TLC), the mixture was extracted with Et_2O (30 mL), the ether extract evaporated in vacuo and the residue purified by column chromatography (silica gel, 0-15% EtOAc/hexane) to give the respective products as colourless oils.

Crotylation of 1 via the Grignard route. To a stirred solution of **1** (1.70 g, 0.01 mol) in THF (25 mL) was slowly injected the Grignard reagent [prepared from crotyl bromide (4.10 g, 0.03 mol) and Mg-turnings (1.20 g, 0.05 mol)] in Et_2O or THF (40 mL). After stirring for 12 h, the reaction was quenched with aqueous saturated NH_4Cl (2 mL). The organic layer was separated and the aqueous portion extracted with Et_2O (30 mL). The combined organic extracts were washed with brine (5 mL), and dried. Solvent removal in vacuo and column chromatography of the residue afforded the pure homoallylic alcohols **69a-c**.

(2*R*,3*R*)-1,2-Cyclohexylidenedioxy-5-hexene-3-ol 68a. colourless oil; R_f = 0.80 (20% EtOAc/hexane); $[\alpha]_D^{24}$ +5.3 (*c* 1.24, $CHCl_3$); IR: 3451, 1640, 1098, 1042 cm^{-1}; ^1H NMR: δ 1.25-1.37 (m, 2H), 1.56-1.61 (m, 8H), 2.22 (t, *J* = 6.5 Hz, 2H), 2.31(d, *J* = 4.8 Hz, D_2O exchangeable, 1H), 3.52-3.58 (m, 1H), 3.68-3.76 (m, 1H), 3.93-4.02 (m, 2H), 5.06-5.16 (m, 2H), 5.77-5.91 (m, 1H); ^{13}C NMR: δ 23.5, 23.7, 24.8, 34.5, 35.9, 37.9, 65.4, 71.3, 77.8, 109.6, 117.4, 133.8.

(2*R*,3S)-1,2-Cyclohexylidenedioxy-5-hexene-3-ol 68b. colourless oil; R_f = 0.73 (20% EtOAc/hexane; $[\alpha]_D^{24}$ +10.2 (*c* 1.38, $CHCl_3$); IR: 3453, 1642, 1101, 1044 cm^{-1}; ^1H NMR: δ 1.36-1.38 (m, 2H), 1.55-1.59 (m, 8H), 2.13-2.33 (m overlapped with broad s, 3H), 3.71-3.79 (m, 1H), 3.88-4.01 (m, 3H), 5.13-5.16 (m, 2H), 5.75-5.88 (m,1H); ^{13}C NMR: δ 24.1, 24.3, 25.5, 35.2, 36.6, 38.0, 65.2, 71.0, 78.0, 110.0, 118.6, 134.4.

(2*R*,3*R*,4*R*)-1,2-Cyclohexylidenedioxy-4-methyl-5-hexen-3-ol 69a. colourless oil; R_f = 0.83 (20% EtOAc/hexane); $[\alpha]_D^{24}$ +47.1 (*c* 1.41, $CHCl_3$); IR: 3408, 1648, 990 cm^{-1}; ^1H NMR: δ 1.09 (d, *J* = 6.8 Hz, 3H), 1.33-1.58 (m, 10H), 2.22-2.30 (m, 1H), 2.68 (broad s, 1H), 3.31-3.39 (m, 1H), 3.71-3.76 (m, 1H), 3.93-4.15 (m, 2H), 4.98-5.08 (m, 2H), 5.68-5.84 (m, 1H); ^{13}C NMR: δ 12.4, 16.9, 23.9, 25.1, 35.0, 36.2, 41.3, 65.7, 74.6, 75.4, 109.6, 112.8, 139.6.

(2*R*,3*S*,4*R*)-1,2-Cyclohexylidenedioxy-4-methyl-5-hexen-3-ol 69b. colourless oil; R_f = 0.75 (20% EtOAc/hexane); $[\alpha]_D^{24}$ +29.7 (*c* 1.45, $CHCl_3$); IR: 3400, 1651, 995 cm^{-1}; ^1H NMR: δ 1.09 (d, *J* = 6.8 Hz, 3H), 1.39-1.61 (m, 10H), 1.81 (broad s, 1H), 2.19-2.29 (m, 1H), 3.63-3.69 (m, 1H), 3.83-3.99 (m, 2H), 4.06-4.15 (m, 1H), 5.02-5.09 (m, 2H), 5.65-5.82 (m, 1H); ^{13}C NMR: δ 12.5, 17.4, 24.1, 25.4, 35.3, 35.8, 41.2, 65.4, 74.7, 75.6, 109.2, 114.1, 138.8.

(2*R*,3*S*,4*S*)-1,2-Cyclohexylidinedioxy-4-methyl-5-hexen-3-ol 69c. colourless oil; R_f = 0.66 (20% EtOAc/hexane); $[\alpha]_D^{24}$ +2.4 (*c* 1.21, $CHCl_3$); IR: 3408, 1657, 997 cm^{-1}; ^1H NMR: δ 1.03 (d, *J* = 6.6 Hz, 3H), 1.22-1.57 (m, 10H), 1.97 (broad s, 1H), 2.32-2.42 (m, 1H), 3.56-3.59 (m, 1H), 3.82-4.07 (m, 3H), 5.05-5.12 (m, 2H), 5.74-5.91 (m, 1H); ^{13}C NMR: δ 12.7, 16.4, 23.9, 25.1, 34.8, 36.2, 40.7, 65.1, 71.7, 74.8, 109.1, 115.9, 139.8.

(2*R*,4*R*)- and **(2*R*,4*S*)-1,2-Cyclohexylidenedioxy-4-methyl-5-hexen-3-one 70b and 70c.** To a cooled (0 ^oC) and stirred suspension of PCC (1.6 g, 5.84 mmol) and NaOAc (0.3 g) in CH_2Cl_2 (10 mL) was added **69b** and **69c** (1.0 g, 4.42 mmol) in CH_2Cl_2 (10 mL). After stirring the reaction mixture for 3 h, it was diluted with dry Et_2O (80 mL), and the supernatant filtered through a pad of silica gel. The eluate was concentrated in vacuo and the residue subjected to column chromatography (silica gel, 0-15% EtOAc/hexane) to give **70b** and **70c**.

70b: Yield 0.74 g (75%); colourless thick oil; IR: 1741 cm^{-1}; $[\alpha]_D^{24}$ +10.2 (c 1.56, $CHCl_3$); ^1H NMR: δ 1.04 (d, *J* = 7.6 Hz, 3H), 1.41-1.63 (m, 10H), 3.62-3.75 (m, 1H), 3.85-4.05 (m, 2H), 4.43 (dd, *J* = 5.8 and 7.4 Hz, 1H), 4.82-5.07 (m, 2H), 5.64-5.84 (m, 1H); ^{13}C NMR: δ 14.7, 23.4, 23.6, 24.7, 34.2, 35.3, 46.0, 65.5, 78.4, 110.9, 116.8, 136.2, 209.7.

70c: Yield 0.78 g (79%); colourless thick oil; $[\alpha]_D^{24}$ +5.9 (*c* 1.08, $CHCl_3$); IR: 1740 cm^{-1}; ^1H NMR: δ 1.01 (d, *J* = 7.0 Hz, 3H), 1.32-1.54 (m, 10H), 3.41-3.62 (m, 1H), 3.78-3.91 (m, 1H), 3.97-4.21 (m, 1H), 4.35-4.48 (m, 1H), 4.85-5.05 (m, 2H), 5.72-5.96 (m, 1H); ^{13}C NMR: δ 13.9, 22.8, 23.1, 25.0, 34.6, 35.8, 46.2, 63.3, 76.5, 110.7, 116.9, 135.8, 205.4.

(2*R*,3*R*,4*R*/4*S*)-1,2-Cyclohexylidenedioxy-4-methyl-5-hexen-3-ol 69a or **69d.** To a well stirred and cooled (-78 ^oC) solution of the ketone **70b** or **70c** (0.6 g, 2.68 mmol) in THF (50 mL) was injected K-selectride (3.0 mL, 1M in THF). The mixture was stirred at -78 ^oC

for an additional 2 h, gradually brought to room temperature and treated successively with water and EtOAc. The organic layer was separated and the aqueous layer extracted with EtOAc. The combined organic extracts were washed with water and brine, and dried. Removal of solvent in vacuo followed by column chromatography of the residue (silica gel, 0-15% EtOAc/hexane) afforded of **69a** or **69d**.

69d : Yield: 0.56 g (93%); colourless thick oil; $[\alpha]_D^{23}$ -12.3 (*c* 2.4, $CHCl_3$); IR: 3410, 1646, 979 cm^{-1}; ^1H NMR: δ 1.1 (d, *J* = 6.8 Hz, 3H), 1.4-1.6 (m, 10H), 2.02 (m, 1H), 2.28-2.32 (m, 1H), 3.29 (dd, *J* = 4.6, 6.8 Hz, 1H), 3.70-3.77 (m, 1H), 3.98 (dd, *J* = 6.4, 8.0 Hz, 1H), 4.10-4.15 (m, 1H), 5.01-5.07 (m, 2H), 5.6-5.8 (m, 1H); ^{13}C NMR: δ 15.7, 23.7, 23.9, 25.0, 34.8, 36.0, 42.2, 66.1, 74.5, 76.2, 109.5, 115.2, 140.4. Anal. Calcd. for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80%. Found: C, 69.23; H, 9.56%.

(3*S*,4*R*,5*R*)-4-Benzoyloxy-5,6-cyclohexylidenedioxy-3-methyl-1-hexene 71. To a well stirred and cooled (0 ^oC) solution of **69c** (1.1 g, 4.86 mmol) and Et_3N (0.74 g, 7.3 mmol) in CH_2Cl_2 (25 mL) was added a solution BzCN (0.76 g, 5.83 mmol) in CH_2Cl_2 (10 mL) in 40 min. After the completion of the reaction (*cf*. TLC, 2 h) the reaction mixture was poured into water, the organic layer separated and the aqueous layer extracted with $CHCl_3$ (30 mL). The combined organic extracts were washed with water (30 mL) and brine (5 mL), and dried. Solvent removal in vacuo followed by column chromatography (silica gel, 5-15% EtOAc/hexane) of the residue gave **71**. Yield: 1.52 g (95%); colourless oil; $[\alpha]_D^{24}$ +14.2 (*c* 1.47, $CHCl_3$); IR: 1722, 995, 920 cm^{-1}; ^1H NMR: δ 1.07 (d, *J* = 7.0 Hz, 3H), 1.31-1.43 (m, 8H), 1.58-1.67 (m, 2H), 2.65-2.75 (m, 1H) 3.83-3.90 (m, 1H), 3.95-4.03 (m, 1H), 4.20-4.26 (m, 1H), 5.06-5.18 (m, 2H), 5.26 (dd, *J* = 4.0 and 6.6 Hz, 1H), 5.77-5.87 (m, 1H), 7.38-7.54 (m, 3H), 7.99-8.04 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 16.9, 23.8, 25.0, 34.9,

36.1, 39.8, 65.9, 74.9, 76.7, 109.6, 116.3, 128.3, 129.6, 129.9, 132.9, 138.4, 165.8. Anal. Calcd. for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93%. Found: C, 72.72; H, 8.12%.

(*2R,3S,4S*)-3-Benzoyloxy-4-methyl-5-hexene-1,2-diol 72. To a cooled (0 ^oC) and stirred solution of **71** (1.4 g, 4.24 mmol) in CH_2Cl_2 (25 mL) was added aqueous TFA (10 mL) in portions. When the reaction was complete (after ~2.5 h, *cf*. TLC), the mixture was treated with $NaHCO_3$, and water, and the mixture extracted with $CHCl_3$ (20 mL). The combined organic extracts were washed with water (20 mL) and brine (5 mL), and dried. Removal of solvent in vacuo followed by column chromatography (silica gel, 5% $CHCl_3$/MeOH) of the residue afforded **72**. Yield: 0.92 g (86%); colourless thick oil; $[\alpha]_D^{24}$ +7.5 (*c* 1.04, $CHCl_3$); IR: 3411, 1724, 995, 920 cm^{-1}; ^1H NMR: δ 0.98 (d, *J* = 7.0 Hz, 3H), 2.86-2.96 (m, 3H), 3.56-3.71 (m, 2H), 3.76-3.84 (m, 1H), 5.01 (dd, *J* = 2.8 and 8.6 Hz, 1H), 5.13-5.25 (m, 2H), 5.77-5.88 (m, 1H), 7.40-7.58 (m, 3H), 7.99-8.04 (m, 2H); ^{13}C NMR: δ 17.4, 38.5, 62.6, 70.7, 76.7, 116.8, 128.5, 129.3, 129.8, 133.5, 138.1, 167.2. Anal. Calcd. for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25%. Found: C, 67.32; H, 7.09%.

(3*S*,4*R*,5*R*)-4-Benzoyloxy-6-*(tert)*-butyldiphenylsilyloxy-3-methyl-1-hexene 73. A cooled (0 ^oC) solution of **72** (0.8 g, 3.2 mmol), TBDPSCl (0.89 g, 3.2 mmol) and imidazole (0.26 g, 3.82 mmol) in CH_2Cl_2 (20 mL) was stirred for 4 h. Water was added to the mixture, which was extracted with $CHCl_3$ (20 mL). The combined organic extracts were washed with water (20 mL) and brine (5 mL), dried and concentrated in vacuo. The residue was subjected to column chromatography (silica gel, 5-15% EtOAc/hexane) to afford **73**. Yield: 1.25 g (80%); colourless oil; $[\alpha]_D^{24}$ +7.9 (*c* 0.971, $CHCl_3$); IR: 3450, 1726, 997, 924 cm^{-1}; ^1H NMR: δ 1.01 (d, *J* = 6.8 Hz, 3H), 1.09 (s, 9H), 1.12 (broad s, 1H), 2.66-2.70 (m, 1H), 3.00-3.35 (m, 2H), 3.81-4.12 (m, 1H), 5.03 (dd, *J* = 2.4 and 7.8 Hz, 1H), 5.21-5.29

(m, 2H), 5.82-5.98 (m, 1H), 7.25-7.38 (m, 4H), 7.46-7.84 (m, 9H), 7.98-8.02 (m, 2H); ^{13}C NMR: δ 17.4, 19.1, 37.7, 63.5, 72.1, 75.9, 116.6, 127.2, 127.5, 128.5, 129.3, 130.4, 133.5, 138.3, 171.2. Anal. Calcd. for $C_{30}H_{36}O_4Si$: C, 73.73; H, 7.43%. Found: C, 73.61; H, 7.59%.

(3*S*,4*S*,5*R*)-(4-Benzoyloxy-3-methyl-5-(*tert*)-butyldiphenylsilyloxymethyl) dihydro-2(3*H*)-furanone 74c. Ozone was bubbled for 20 min through a solution of **73** (1 g, 2.03 mmol) and methanolic NaOH (1.5 mL, 2.5 M) in CH_2Cl_2 (20 mL) at -78 ^oC. After stirring the mixture for 3 h, it was diluted with $CHCl_3$ and water, and brought to room temperature. The organic layer was separated and the aqueous layer extracted with $CHCl_3$. The combined organic extracts were washed with water and brine, and dried. Removal of solvent in vacuo followed by chromatographic purification (silica gel, 5-15% $CHCl_3$/MeOH) afforded **74c**. Yield: 0.72 g (72%); colourless oil; $[\alpha]_D^{22}$ +16.3 (c 0.884, $CHCl_3$); IR: 1742, 1695 cm^{-1}; ^{1}H NMR: δ 0.91 (d, *J* = 6.8 Hz, 3H), 1.14 (s, 9H), 3.40-3.50 (m, 1H), 3.90-4.20 (m, 2H), 4.63-4.70 (m, 1H), 5.96 (dd, *J* = 13.7 and 2.4 Hz, 1H), 7.27-7.37 (m, 4H), 7.44-7.81 (m, 9H), 7.97-8.01 (m, 2H). Anal. Calcd. for $C_{29}H_{32}O_5Si$: C, 71.28; H, 6.60%. Found, C, 71.37; H, 6.81%.

(3*R*,4*S*,5*R*)-(4-Benzoyloxy-3-methyl-5-(*tert*)-butyldiphenylsilyloxymethyl) dihydro-2(3*H*)-furanone 74b. colourless oil; $[\alpha]_D^{22}$ +21.1 (c 0.721, $CHCl_3$); IR: 1739, 1692 cm^{-1}; ^{1}H NMR: δ 0.93 (d, *J* = 6.4 Hz, 3H), 1.17 (s, 9H), 2.92-2.98 (m, 1H), 3.78-3.88 (m, 2H), 4.61-4.67 (m, 1H), 5.84 (dd, *J* = 12.2 and 9.7 Hz, 1H), 7.29-7.37 (m, 4H), 7.48-7.75 (m, 9H), 7.95-8.02 (m, 2H). Anal. Calcd. for $C_{29}H_{32}O_5Si$: C, 71.28; H, 6.60%. Found, C, 71.15; H, 6.62%.

Non-2-yn-1-ol 76. To a stirred solution of Fe $(NO_3)_2$ (0.4g) in liquid ammonia (700 mL) Li-metal (3.9g, 0.561 mol) in small pieces in 30 min. Freshly distilled propargyl alcohol **75** (15.0 g, 0.27 mol) was added to the suspension dropwise over 1 h. After stirring for 30 min, 1-bromohexane (53.1 g, 0.32 mol) was added very slowly into it and stirring was continued for additional 6 h. The mixture was slowly brought to room temperature, allowing the ammonia to evaporate. The mixture was treated with aqueous saturated NH_4Cl (200 mL) and extracted with ethyl acetate (300 mL). The combined organic extracts were dried, concentrated in vacuo, and the residue chromatographed (silica gel, 5-15% EtOAc/hexane) to afford the compound **76.** Yield: 23.0 g (61%); colourless oil; IR: 3347, 2225, 1013 cm^{-1}; ^1H NMR: δ 0.77 (t, *J* = 6.8 Hz, 3H), 1.10-1.38 (m, 8H), 2.04-2.12 (m, 2H), 3.37 (broad s, 1H), 4.01-4.13 (m, 2H); ^{13}C NMR: δ 13.9, 18.6, 22.4, 28.4, 28.5, 31.3, 50.7, 78.3, 85.8. Anal. Calcd. for $C_9H_{16}O$: C, 77.09; H, 11.5%. Found, C, 77.25; H, 11.62%.

(*E*)-Non-2-en-1-ol 77a : To a suspension of $LiAlH_4$ (5.32 g, 0.14 mol) in dry THF (200 mL) was added a solution of **76** (10.16 g, 72.5 mmol) in dry THF (150 mL). The reaction mixture was stirred at 45 °C for 30 mins and gradually brought to 0 °C. The excess hydride was decomposed with aqueous saturated Na_2SO_4 solution, extracted with Et_2O (300 mL). The combined ethereal extracts were dried, concentrated under reduced pressure, and the residue was purified by flash chromatography (20% EtOAc/hexane) to give the *trans*-allylic alcohol **77a.** Yield: 7.82 g (76%); colourless oil; IR: 3340, 1203 cm^{-1}; ^1H NMR: δ 0.80 (t, *J* = 6.6 Hz, 3H), 1.17-1.23 (m, 8H), 1.50 (broad s, 1H), 1.94-1.99 (m, 1H), 2.12-2.23 (m, 1H), 4.00-4.12 (m, 2H), 5.48-5.71 (m, 2H); ^{13}C NMR: δ 13.9, 22.5, 28.8, 29.0,

31.6, 32.2, 63.4, 128.8, 133.0. Anal. Calcd. for $C_9H_{18}O$: C, 76.00; H, 12.76%. Found, C, 75.78; H, 12.53%.

(*Z*)-Non-2-en-1-ol 77b: To a suspension of $Ni(OAc)_2 \cdot 4H_2O$ (64.35 g, 72.5 mmol) in anhydrous EtOH (200 mL) at 0 °C was added $NaBH_4$ (13.7 g, 0.37 mol) under Ar. The reaction mixture was stirred for 20 min, ethylenediamine (50 ml) and **76** (10.16 g, 72.5 mmol) added and stirred at room temperature under a positive pressure of H_2 for an additional 4 h. The mixture was filtrated through a Celite pad, the filtrate concentrated in vacuo, and the residue purified by flash column chromatography on silica gel (20% EtOAc/hexane) to give **77b**. Yield: 9.06g (88%); colourless oil; IR: 3343, 969 cm^{-1}; ^1H NMR: δ 0.85 (t, *J* = 6.4 Hz, 3H), 1.24-1.39 (m, 8H), 1.98-2.04 (merged m with broad s, 3H), 4.03-4.21 (m, 2H), 5.42-5.62 (m, 2H); ^{13}C NMR: δ 13.9, 22.5, 27.3, 28.8, 29.5, 31.6, 58.3, 128.3, 132.7. Anal. Calcd. for $C_9H_{18}O$: C, 76.00; H, 12.76%. Found, C, 76.15; H, 12.61%.

(*E*) and (*Z*)-1-bromo-2-nonene 78a and 78b : To a cooled (0 ^oC) and stirred solution of **77a** or **77b** (7.0 g, 49.3 mmol) in Et_3N (20 mL) was added mesyl chloride (6.20 g, 54.23 mmol) and the solution was stirred for 3 h. After completion of reaction (*cf*. TLC), water and EtOAc was added to the mixture, the organic layer separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with water, brine and dried. Removal of solvent in vacuo afforded the crude product in good yield.

A mixture of the above crude product and NaBr (5.75g, 64.09 mmol) in acetone (150 mL) was stirred for 4 h. To this reaction mixture water was added. The organic layer separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with water, brine and dried. Removal of solvent in vacuo followed by

chromatography (silica gel, 5-10% EtOAc/hexane) afforded pure **78a** (Yield 9.14g, 90%) or **78b** (Yield 9.34g, 92%).

78a: light yellow oil; IR: 2956, 2856, 1665, 1249, 964 cm^{-1}; ^1H NMR: δ 0.87 (t, *J* = 6.8 Hz, 3H), 1.22-1.41 (m, 8H), 1.97-2.07 (m, 2H), 3.92-4.04 (dd, *J* = 6.2 and 6.6 Hz, 2H), 5.52-5.84 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 13.9, 22.6, 28.7, 31.6, 32.0, 45.2, 125.9, 135.9. Anal. Calcd. for $C_9H_{17}Br$: C, 52.70; H, 8.35. Found, C, 52.79; H, 8.12.

78b : light yellow oil; IR: 2958, 2929, 2252, 1465, 1251, 903, 733 cm^{-1}; ^1H NMR: δ 0.88 (t, *J* = 6.4 Hz, 3H), 1.21-1.47 (m, 8H), 1.99-2.06 (m, 2H), 3.92-4.15 (m, 2H), 5.59-5.73 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 14.0, 22.6, 27.0, 29.1, 31.6, 39.5, 125.1, 135.5. Anal. Calcd. for $C_9H_{17}Br$: C, 52.70; H, 8.35%. Found, C, 52.82; H, 8.47%.

1,2-Cyclohexylidenedioxy-4-vinyl-decan-3-ol 79 : As described before, the reactions between **1** and **78a** or **78b** were carried out using bi-metal system or Zn dust. For the Zn-mediated reaction, aqueous saturated NH_4Cl was used for the activation of Zn. After the work up, the crude product, in each case was subjected to column chromatography (silica gel, 0-20 % EtOAc/Hexane) to isolate pure **79a**, **79b** and **79c** sequentially.

(2*R*,3*R*,4*R*)-1,2-Cyclohexylidenedioxy-4-vinyldecan-3-ol 79a : Colourless oil; $[\alpha]_D^{23}$ -0.29 (*c* 1.4, $CHCl_3$); IR: 3464, 2931, 2856, 1637, 1103 cm^{-1}; ^1H NMR: δ 0.84 (broad t, 3H), 1.23 (m, 10H), 1.37 (m, 2H), 1.46-1.60 (m, 8H), 1.91 (broad s, 1H), 2.13 (m, 1H), 3.44 (dd, *J* = 6.6, 3.2 Hz, 1H), 3.62 (t, *J* = 6.6 Hz, 1H), 3.9-4.1 (m, 2H), 5.0-5.2 (m, 2H), 5.4-5.8 (m, 1H); ^{13}C NMR: δ 14.06, 22.61, 23.78, 23.99, 25.09, 27.13, 29,21, 31.30, 31.75, 35.01, 36.39, 47.20, 65.63, 74.88, 76.37, 109.84, 116.70, 138.08. Anal. calcd. for $C_{18}H_{32}O_3$: C, 72.93; H, 10.88%. Found, C, 72.65; H, 10.78%.

(2*R*,3*S*,4*R*)-1,2-Cyclohexylidenedioxy-4-vinyldecan-3-ol 79b : Colourless oil; $[\alpha]_D^{23}$ 12.04 (*c* 4.6, $CHCl_3$); IR: 3476, 2931, 2857, 1639, 1103 cm^{-1}; ^1H NMR: δ 0.82 (broad t, 3H), 1.24 (m, 10H), 1.38 (m, 2H), 1.5-1.7 (m, 8H), 1.95 (broad s, 1H), 2.32 (m, 1H), 3.72 (dd, *J* = 8.8, 3.4 Hz, 1H), 3.80-3.95 (m, 2H), 4.07-4.16 (m, 1H), 5.0-5.2 (m, 2H), 5.5-5.7 (m, 1H). ^{13}C NMR: δ 13.95, 22.53, 23.67, 23.84, 24.89, 26.66, 29,20, 30.33, 31.71, 34.82, 36.02, 47.52, 63.37, 72.50, 76.47, 109.01, 116.67, 138.50. Anal. calcd. for $C_{18}H_{32}O_3$: C, 72.93; H, 10.88%. Found, C, 72.95; H, 10.67%.

(2*R*,3*R*,4*S*)-1,2-Cyclohexylidenedioxy-4-vinyldecan-3-ol 79c : Colourless oil; $[\alpha]_D^{23}$ +17.71 (*c* 2.6, $CHCl_3$); IR: 3465, 2931, 2856, 1101, 913 cm^{-1}; ^1H NMR: δ 0.84 (broad t, 3H), 1.25 (m, 10H), 1.38 (m, 2H), 1.56-1.66 (m, 8H), 2.19-2.38 (m, 1H), 3.68 (t, *J* = 4.5 Hz, 1H), 3.8-4.0 (m, 3H), 4.71 (broad s, 1H), 5.0-5.2 (m, 2H), 5.6-5.8 (m, 1H); ^{13}C NMR: δ 14.0, 22.6, 23.8, 24.0, 25.1, 27.1, 29,2, 31.0, 31.7, 34.8, 36.3, 46.40, 65.4, 73.9, 76.4, 109.0, 117.5, 137.9. Anal. calcd. for $C_{18}H_{32}O_3$: C, 72.93; H, 10.88%. Found, C, 73.05; H, 10.80%.

4-(*tert*)-Butyldiphenylsilyloxy-*2Z*-buten-1-ol 81. To a cooled (0 ^oC) and stirred solution of **80** (5.0 g, 56.81 mmol) and imidazole (4.25 g, 62.5 mmol) in CH_2Cl_2 (75 mL) was added TBDPSCl (17.12 g, 62.5 mmol) in CH_2Cl_2 (25 mL). After stirring for 2.5 h (*cf*. TLC), the mixture was poured into water, the organic layer separated and the aqueous layer extracted with $CHCl_3$. The combined organic extracts were washed with water and brine, and dried. Solvent removal in vacuo and column chromatography (silica gel, 2-10% EtOAc/hexane) of the residue afforded pure **81**. Yield 14.22 g (77%); colourless oil; IR: 3450, 3397, 3063, 3028 cm^{-1}; ^1H NMR: δ 1.1 (s, 9H), 1.93 (broad s, D_2O exchangeable,

1H), 3.72-4.00 (m, 4H), 5.22-5.53 (m, 2H), 7.22-7.54 (m, 10H). Anal. Calcd. for $C_{20}H_{26}O_2Si$: C, 73.59; H, 8.02%. Found, C, 73.65; H, 8.08%.

1-Bromo-4-(*tert*)-butyldiphenylsilyloxy-*2Z*-butene 82. To a cooled (0 ^oC) and stirred solution of compound **81** (10.0 g, 30.67 mmol) in Et_3N (20 mL) was added MsCl (4.21 g, 36.80 mmol) and the solution was stirred for 3 h (*cf*. TLC). Water and EtOAc was added to the mixture, the organic layer separated and the aqueous layer extracted with EtOAc. The combined organic extracts were washed with water and brine, and dried. Removal of solvent in vacuo afforded the crude product.

A mixture of the above crude product and NaBr (4.0 g, 44.55 mmol) in acetone (50 mL) was stirred for 4 h. The reaction mixture was diluted with water, the organic layer separated and the aqueous layer extracted with EtOAc. The combined organic extracts were washed with water and brine, and dried. Removal of solvent in vacuo followed by chromatography (silica gel, 5-10% EtOAc/hexane) afforded pure **82.** Yield: 10.73 g (90%); Light yellow oil; IR: 3063, 3030 cm^{-1}; ^1H NMR: δ 1.04 (s, 9H), 3.80-3.92 (m, 2H), 4.11-4.32 (m, 2H), 5.32-5.50 (m, 2H), 7.21-7.53 (m, 10H). Anal. Calcd. for $C_{20}H_{25}BrOSi$: C, 61.69; H, 6.47%. Found, C, 61.73; H, 6.52%.

1,2-Cyclohexylidenedioxy-4-C-(*tert*)-butyldiphenylsilyloxy-5-hexene-3-ol 83a-d. As described before, the reaction between **1** (3.50 g, 20.56 mmol) and **82** (8.0 g, 20.56 mmol) was carried out using bi-metal system or Zn dust. For the Zn-mediated reaction, aqueous saturated NH_4Cl was used for the activation of Zn. After the work up, the crude product, in each case was subjected to column chromatography (silica gel, 0-20% EtOAc/hexane) to isolate the mixture of **83a** and **83b**, pure **83c** and **83d**. The R_f (20% EtOAc/hexane) values of **83a**/**83b**, **83c** and **83d** were 0.60, 0.57, 0.51 and 0.45 respectively.

(2*R*,3*S*,4*S*)-1,2-Cyclohexylidenedioxy-4-C-(*tert*)-butyldiphenylsilyloxy-5-hexene-3-ol

83c. colourless oil; $[\alpha]_D^{25}$ +20.75 (*c* 1.6, $CHCl_3$); IR: 3420, 997, 922 cm^{-1}; ^1H NMR: δ 1.07 (s, 9H), 1.41 (m, 2H), 1.56-1.62 (m, 8H), 2.26 (m, 1H), 3.02 (broad s, D_2O exchangeable, 1H), 3.81 (dd, *J* = 10.0, 4.1 Hz, 1H), 3.88-4.01 (m, 5H), 5.00-5.23 (m, 2H), 5.80-6.00 (m, 1H), 7.41 (m, 6H), 7.68 (m, 4H); ^{13}C NMR: δ 19.2, 23.8, 23.9, 25.2, 26.9, 34.9, 36.2, 48.5, 64.5, 65.1, 71.5, 76.8, 109.4, 117.3, 127.7, 129.8, 133.1, 133.2, 135.6, 136.6. Anal. Calcd. for $C_{29}H_{40}O_4Si$: C, 72.47 H, 8.38%. Found, C, 72.40; H, 8.40%.

(2*R*,3*S*,4*R*)-1,2-Cyclohexylidenedioxy-4-C-(*tert*)-butyldiphenylsilyloxy-5-hexene-3-ol

83d. colourless oil; $[\alpha]_D^{25}$ -4.68 (*c* 1.8, $CHCl_3$); IR: 3434, 920 cm^{-1}; ^1H NMR: δ 1.05 (s, 9H), 1.4 (m, 2H), 1.55-1.68 (m, 8H), 2.53 (m, 1H), 2.84 (broad s, D_2O exchangeable, 1H), 3.84 (m, 2H), 3.92-4.01 (m, 4H), 5.11-5.23 (m, 2H), 5.70-6.02 (m, 1H), 7.41 (m, 6H), 7.66 (m, 4H); ^{13}C NMR: δ 19.0, 23.7, 23.9, 25.1, 26.7, 34.8, 36.4, 47.4, 66.4, 76.0, 109.2, 117.4, 127.6, 129.7, 132.7, 132.8, 135.4, 135.5. Anal. Calcd. for $C_{29}H_{40}O_4Si$: C, 72.47; H, 8.38%. Found, C, 72.50; H, 8.42%.

(2*R*,4*R/S*)-1,2-Cyclohexylidenedioxy-4-C-(*tert*)-butyldiphenylsilyloxy-3-one-5-hexene

84c or 84d. To a cooled (0 ^oC) and stirred suspension of PCC (0.534 g, 2.5 mmol) and NaOAc (0.3 g) in CH_2Cl_2 (40 mL) was added **83c** or **83d** (1.0 g, 2.08 mmol) in CH_2Cl_2 (40 mL). After stirring for 3 h (*cf*. TLC), dry Et_2O (80 mL) was added. The supernatant was filtered through a pad of silica gel, which was subsequently eluted with Et_2O. The eluate was concentrated in vacuo to afford a crude residue, which on column chromatography (silica gel, 0-15% EtOAc/hexane) gave **84c** or **84d**.

(2*R*,4*S*)-1,2-Cyclohexylidenedioxy-4-C-(*tert*)-butyldiphenylsilyloxy-3-one-5-hexene

84c. Colourless oil**;** Yield: 0.708 g (71.5%); $[\alpha]_D^{25}$ +20.75 (*c* 1.60, $CHCl_3$); IR: 1715 cm^{-1};

^{1}H NMR: δ 1.03 (s, 9H),1.40-1.62 (m, 10H), 2.66 (m, 1H), 3.63-3.77 (m, 2H), 3.80-4.12 (m, 3H), 5.00-5.22 (m, 2H), 5.82-6.01 (m, 1H), 7.21-7.52 (m, 10H).

(2*R*,4*R*)-1,2-Cyclohexylidenedioxy-4-C-(*tert*)-butyldiphenylsilyloxy-3-one-5-hexene 84d. Colourless oil; Yield: 0.702g (70.0%); $[\alpha]_D^{25}$ -4.68 (*c* 1.80, $CHCl_3$); IR: 1717 cm^{-1}; ^{1}H NMR: δ 1.05 (s, 9H),1.38-1.61 (m, 10H), 2.65 (m, 1H), 3.64-3.80 (m, 2H), 3.82-4.13 (m, 3H), 5.04-5.24 (m, 2H), 5.83-6.03 (m, 1H), 7.22-7.55 (m, 10H).

(2*R*,3*R*,4*R*/4*S*)-1,2-Cyclohexylidenedioxy-4-C-(*tert*)-butyldiphenylsilyloxy-5-hexene-3-ol 83a or **83b.** To a cooled (-78 ^oC) and stirred solution of the ketone **84c** or **84d** (0.5 g, 1.04 mmol) in THF (50 mL) was injected K-selectride (1.0 mL, 1M in THF). The mixture was stirred at -78 ^oC for an additional 2 h, gradually brought to room temperature, and water and EtOAc were added. The organic layer was separated and the aqueous layer extracted with EtOAc. The combined organic extracts were washed with water and brine, and dried. Removal of solvent in vacuo followed by column chromatography of the residue (silica gel, 0-15% EtOAc/hexane) afforded of **83a** or **83b**.

(2*R*,3*R*,4*R*)-1,2-Cyclohexylidenedioxy-4-C-(*tert*)-butyldiphenylsilyloxy-5-hexene-3-ol 83a. Colourless oil; Yield: 0.465 (93%); $[\alpha]_D^{25}$ -2.0 (*c* 0.9, CHCl3); IR: 3400, 920 cm^{-1}; ^{1}H NMR: δ 1.04 (s, 9H), 1.41 (m, 2H), 1.55-1.62 (m, 8H), 2.25-2.50 (m, 1H), 2.88 (broad s, 1H), 3.60-3.71 (m, 1H), 3.75-4.02 (m, 4H), 4.11-4.23 (m, 1H), 5.00-5.22 (m, 2H), 5.70-6.00 (m, 1H), 7.40 (m, 6H), 7.65 (m, 4H); Anal. Calcd. for $C_{29}H_{40}O_4Si$: C, 72.47 H, 8.38%. Found, C, 72.42; H, 8.44%.

(2*R*,3*R*,4*S*)-1,2-Cyclohexylidenedioxy-4-C-(*tert*)-butyldiphenylsilyloxy-5-hexene-3-ol 83b. Colourless oil; Yield: 0.456 g (91.5%); $[\alpha]_D^{25}$ -7.2 (*c* 1.0, CHCl3); IR: 3400, 922 cm^{-1}; ^{1}H NMR: δ 1.03 (s, 9H), 1.42 (m, 2H), 1.56-1.62 (m, 8H), 1.90 (broad s, 1H), 2.23-2.44

(m, 1H), 3.50-4.02 (m, 5H), 4.10-4.22 (m, 1H), 5.00-5.22 (m, 2H), 5.80-6.00 (m, 1H), 7.39 (m, 6H), 7.64 (m, 4H); Anal. Calcd. for $C_{29}H_{40}O_4Si$: C, 72.47 H, 8.38%. Found, C, 72.39; H, 8.42%.

(2*R*,3*S*,4*S*)-1,2-Cyclohexylidenedioxy-3-Benzoyloxy-4-C-(*tert*)-butyldiphenylsilyloxy-5-hexene 85. To a cooled (0 ^oC) and stirred solution of **83d** (1.80 g, 3.75 mmol) and Et_3N (0.454 g, 4.5 mmol) in CH_2Cl_2 (25 mL) was added BzCN (0.589 g, 4.5 mmol) in CH_2Cl_2 (10 mL) over a period of 40 min. After the completion of the reaction (*cf*. TLC) it was poured into water. The organic layer was separated and the aqueous layer extracted with $CHCl_3$. The combined organic extracts were washed with water and brine, and dried. Solvent removal in vacuo followed by column chromatography (silica gel, 5-15% EtOAc/hexane) gave **85**. Colourless oil; Yield 2.08 g (95%); IR: 1722,1650 cm^{-1}; ^1H NMR: δ 1.05 (s, 9H), 1.31-1.43 (m, 8H), 1.58-1.67 (m, 2H), 2.58-2.64 (m, 1H) 3.82-3.86 (m, 2H), 3.95-4.10 (m, 2H), 4.23-4.38 (m, 1H), 5.12-5.25 (m, 2H), 5.66-5.71 (m, 1H), 5.77-5.91 (m, 1H), 7.21-7.39 (m, 10H), 7.48-7.68 (m, 3H), 7.99-78.03 (m, 2H); ^{13}C NMR: δ 19.1, 23.9, 25.1, 26.7, 26.9, 35.1, 36.2, 48.0, 63.6, 66.3, 69.8, 75.1, 109.7, 118.0, 127.5, 127.6, 128.4, 129.6, 129.7, 130.1, 133.0, 133.3, 133.4, 135.6, 165.5. Anal. Calcd. for $C_{36}H_{44}O_5Si$: C, 73.94 H, 7.58%. Found, C, 73.89; H, 7.52%.

(*2R,3S,4S*)-3-Benzoyloxy-4-C-(*tert*)-butyldiphenylsilyloxy-5-hexene-1,2-diol 86. To a cooled (0 ^oC) and stirred solution of **85** (1.50 g, 2.56 mmol) in CH_2Cl_2 (25 mL) was added 80% aqueous TFA (10 mL) in portions. After stirring the mixture for 2.5 h, when the reaction was completed (*cf*. TLC), $NaHCO_3$ was added to decompose excess TFA, followed by water, and the mixture was extracted with $CHCl_3$. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$. The combined organic extracts

were washed with water and brine, and dried. Removal of solvent in vacuo followed by chromatography of the residue (silica gel, 5% $CHCl_3$/MeOH) afforded **86**. Colourless thick oil; Yield: 1.12 g (86%); IR: 3411, 3074, 1724 cm^{-1}; ^1H NMR: δ 1.00 (s, 9H), 1.50 (broad s, D_2O exchangeable, 2H), 2.66 (m, 1H), 3.0-3.35 (m, 2H), 3.8-4.1 (m, 3H), 5.21-5.29 (m, 2H), 5.43-5.47 (m, 1H), 5.77-5.88 (m, 1H), 7.09-7.16 (m, 2H), 7.25-7.38(m, 8H), 7.46-7.61 (m, 3H), 7.98-8.02 (m, 2H); ^{13}C NMR: δ 19.0, 26.6, 46.7, 62.4, 63.4, 70.4, 72.0, 120.0, 127.4, 127.6, 128.4, 129.4, 129.6, 129.8, 132.9, 133.1, 133.4, 135.4, 137.5, 167.5. Anal. Calcd. for $C_{30}H_{36}O_5Si$: C, 71.39 H, 7.19%. Found, C, 71.23; H, 7.12%.

(2*R*,3*S*,4*S*)-1-*(tert*)-Butyldiphenylsilyloxy-3-Benzoyloxy-4-C-(*tert*)-butyldiphenylsilyl oxy-5-hexene 87. Silylation of **86** (1.0 g, 1.98 mmol) with TBDPSCl (0.60 g, 2.18 mmol) and imidazole (0.15 g, 2.18 mmol) in CH_2Cl_2 (40 mL) followed by work up and column chromatography (silica gel, 5-15% EtOAc/hexane) afforded **87**. Colourless oil; Yield: 1.12 g (80%); IR: 3450, 3074, 1726 cm^{-1}; ^1H NMR: δ 1.10 (s, 18H), 1.12 (broad s, D_2O exchangeable, 1H), 2.66-2.70 (m, 1H), 3.00-3.35 (m, 2H), 3.81-4.12 (m, 3H), 5.21-5.29 (m, 2H), 5.43-5.47 (m, 1H), 5.77-5.88 (m, 1H), 7.09-7.16 (m, 4H), 7.25-7.38 (m, 16H), 7.46-7.61 (m, 3H), 7.98-8.02 (m, 2H). Anal. Calcd. for $C_{46}H_{54}O_5Si_2$: C, 74.35 H, 7.32%. Found, C, 74.49; H, 7.36%.

5-(*tert*)-butyldiphenylsilyloxy-3-benzoyloxy-2-C-(*tert*)-butyldiphenylsilyloxy-2-deoxy-1-ribofuranose 88. Ozone was bubbled for 20 min through a solution of **87** (0.50 g, 0.67 mmol) and methanolic NaOH (1.5 mL, 2.5 M) in CH_2Cl_2 (20 mL) at -78 ^oC. After stirring the mixture for 3 h at the same temperature, it was diluted with $CHCl_3$ and water, and brought to room temperature. The organic layer was separated and the aqueous layer extracted with $CHCl_3$. The combined organic extracts were washed with water and brine,

and dried. Removal of solvent in vacuo followed by chromatography (silica gel, 5-25% $CHCl_3$/MeOH) afforded **88**. Colourless oil; Yield: 0.35 g (72%); $[\alpha]_D^{25}$ +2.3 (*c* 1.4, $CHCl_3$); IR: 1742 cm^{-1}; ^1H NMR: δ 0.97 (s, 9H), 1.1 (s, 9H), 3.40-.3.50 (m, 1H, H-2), 3.90-4.20 (m, 4H), 4.63-4.70 (m, 1H, H-4), 5.96 (dd, *J* = 13.7 and 2.4 Hz, 1H, H-3), 7.10-7.90 (m, 25H); Anal. Calcd. for $C_{45}H_{50}O_6Si_2$: C, 72.74; H, 6.78%. Found: C, 72.96; H, 7.01%.

Benzylation of aldehydes : Benzylation of aldehydes were accomplished according to the procedure described above. The products **90a-g** were isolated in pure form. In case of benzylation of **1**, the products **91a** and **91b** were isolated as a non-separable mixture.

1-Phenyl-octan-2-ol 90a. ^1H NMR: δ 1.00 (t, *J* = 6.2 Hz, 3H), 1.38-1.69 (m, 10H), 1.70 (broad s, 1H), 2.70-2.81 (m, 1H), 2.91-3.00 (m, 1H), 3.79-3.93 (m, 1H), 7.32-7.49 (m, 5H); ^{13}C NMR: δ 14.1, 22.6, 25.7, 29.3, 31.8, 36.8, 44.0, 72.7, 126.4, 128.5, 129.4, 138.6. Anal. Calcd. for $C_{14}H_{22}O$: C, 81.50; H, 10.75%. Found: C, 81.34; H, 10.49%.

1-Phenyl-undecan-2-ol 90b. ^1H NMR: δ 1.04 (t, *J* = 6.6 Hz, 3H), 1.42-1.62 (m, 16H), 1.91 (broad s, 1H), 2.71-2.82 (m, 1H), 2.91-3.00 (m, 1H), 3.89-3.94 (m, 1H), 7.33-7.49 (m, 5H); ^{13}C NMR: δ 14.1, 22.7, 25.8, 29.4, 29.7, 31.9, 36.8, 44.0, 72.7, 126.4, 128.5, 129.4, 138.7. Anal. Calcd. for $C_{17}H_{28}O$: C, 82.20; H, 11.36%. Found: C, 82.31; H, 11.24%.

1-Phenyl-pentadecan-2-ol 90c. ^1H NMR: δ 0.97 (broad t, 3H), 1.2-1.6 (m, 24H), 1.7 (bs, 1H), 2.73 (dd, j = 13.4 & 8.4 Hz, 1H), 2.93 (dd, j = 13.6 & 4.4 Hz, 1H), 3.8-3.9 (m, 1H), 7.2-7.5 (m, 5H); ^{13}C NMR: δ 14.1, 22.6, 25.7, 29.3, 29.6, 31.9, 36.8, 44.0, 72.6, 126.4, 128.5, 129.4, 138.6. Anal. Calcd. for $C_{21}H_{36}O$: C, 82.83; H, 11.91%. Found: C, 82.64; H, 12.14%.

1-(phenyl)-2-phenylethanol 90d. ^{1}H NMR: δ 2.16 (broad s, 1H), 2.99-3.04 (m, 2H), 4.89 (dd, *J* = 7.8 and 5.4 Hz, 1H), 7.17-7.37 (m, 10H). ^{13}C NMR: δ 45.8, 75.2, 125.8, 126.4, 127.4, 128.2, 128.3, 129.4, 137.9, 143.7. Anal. Calcd. for $C_{14}H_{14}O$: C, 84.81; H, 7.12%. Found: C, 84.88; H, 7.05%.

1-(3-Methoxyphenyl)-2-phenylethanol 90e. ^{1}H NMR: δ 1.98 (broad s, 1H), 3.10 (m, 2H), 3.8 (s, 3H), 4.97 (dd, *J*= 8.0, 5.2 Hz, 1H), 6.9-7.2 (m, 3H), 7.3-7.4 (m, 6H); ^{13}C NMR: δ 45.5, 54.8, 74.8, 111.0, 112.8, 118.0, 126.1, 128.0, 129.0, 129.2, 137.8, 145.3, 159.2. Anal. Calcd. for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06%. Found: C, 78.98; H, 6.80%.

1-(4-Ethylphenyl)-2-phenylethanol 90f. ^{1}H NMR: δ 1.43 (t, *J* = 7.6 Hz, 3H), 2.26 (broad s, 1H), 2.84 (q, *J*= 7.8 Hz, 2H), 3.16 (m, 2H), 5.0 (m, 1H), 7.3-7.5 (m, 9H); ^{13}C NMR: δ 15.5, 28.4, 45.8, 75.0, 125.8, 126.4, 127.7, 128.3, 129.4, 138.2, 141.0, 143.5. Anal. Calcd. for $C_{16}H_{18}O$: C, 84.91; H, 8.01%. Found: C, 84.77; H, 8.16%.

1-(4-Chlorophenyl)-2-phenylethanol 90g. ^{1}H NMR: δ 2.13 (broad s, 1H), 3.04-3.08 (m, 2H), 4.95 (dd, *J*= 7.6 and 5.8 Hz, 1H), 7.23-7.44 (m, 9H); ^{13}C NMR: δ 45.9, 74.5, 126.6, 127.2, 128.3, 128.4, 129.4, 133.0, 137.4, 142.1. Anal. Calcd. for $C_{14}H_{13}ClO$: C, 72.26; H, 5.63%. Found: C, 72.08; H, 5.72%.

Addition of $PhCH_2MgBr$ to 1: The Grignard reagent was prepared by drop wise addition of $PhCH_2Br$ (3.42 g, 0.02 mole) in THF (50 mL) to a stirred suspension of Mg (0.60 g, 0.025 mol) in THF (50 mL). After stirring for 3 h at room temperature, it was cooled to -40 ^{o}C. To it, a solution of **1** (1.70 g, 0.01 mol) in THF (50 mL) was added over a period of 1 h. The mixture was further stirred for 2h at -40 ^{o}C, brought to room temperature and stirred for additional 3 h. Aqueous saturated NH_4Cl (10 mL) was added to it, the mixture extracted with EtOAc and the combined organic extracts were washed with water and

brine, and dried. Solvent removal under reduced pressure and column chromatography of the residue (silica gel, 0-20 % EtOAc/hexane) afforded the mixture of **91a** and **91b**.

91a + **91b** : Colourless oil; Yield: 1.15 g (43.8%); ^{1}H NMR: δ 1.2-1.6 (m, 10H), 2.40 (broad s, 1H), 2.72-2.82 (m, 2H), 3.64-3.75 (m, 2H), 3.87-4.10 (m, 2H), 7.18-7.34 (m, 5H); ^{13}C NMR: δ 23.7, 23.9, 25.0, 34.6, 36.1, 36.2, 39.5, 40.2, 64.9, 65.5, 72.4, 72.9, 77.3, 109.6, 109.7, 126.4, 128.4, 128.6, 129.3, 137.6.

CHAPTER IV

ASYMMETRIC SYNTHESIS OF SOME BIO-ACTIVE ORGANIC COMPOUNDS

IV.1 SYNTHESIS OF ENANTIOPURE (*R*)-ARUNDIC ACID

IV.1.1: Introduction

In recent years, neurodegenerative diseases such as Alzheimer's disease are recognized as one of the biggest threats to human life, especially for the upcoming aging society. Hence, development of new therapeutic agents against these is strongly demanded. Alzheimer's disease is characterized by a progressive loss of memory and cognition, emotional disturbance and personality changes. This is the major cause of dementia among the elderly population, and is associated with a deficiency in the cholinergic neurotransmission. Pharmacological studies have suggested that this is triggered by excessive response of reactive astrocytosis.[142] Based on this hypothesis, (*R*)-arundic acid (**V**) was found to act as a novel neuroprotective agent, because it modulates astrocyte activation by inhibiting the enhanced astrocytic synthesis of S-1000β, responsible for inducing neuronal death.[143] Currently the compound is under phase II clinical trial for the treatment of Alzheimer's disease, as well as for acute ischemic stroke.[2] This emphasized the need for developing an efficient synthesis of **V**.

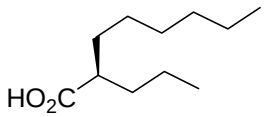
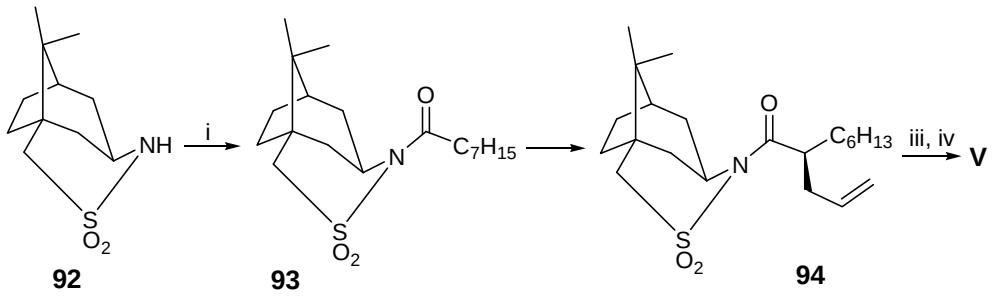


Fig. IV.1.1. Structure of (*R*)-(-)-Arundic acid (V)

IV.1.2: Previous syntheses

Given its biological importance, (*R*)-arundic acid has become an important target for the organic chemists, and a large number of enantioselective syntheses are reported in literature.[144] Some of the interesting approaches are briefly discussed in the following.

The first procedure, using the optical resolution of racemic 2-hexyl-4-pentynoic acid,[144a] gave poor yields (27%) due to the need of five recrystallization cycles to get a final enantiomeric purity of 90% ee.[144b] Next published methods were based on the asymmetric alkylation of chiral enolates. When *L*-prolinol was chosen as chiral auxiliary, arundic acid was prepared in 20% overall yield after a single recrystallization (96% ee).[144c] Hasegawa *et al*.,[144d,e] using Oppolzer's camphorsultam, obtained the acid **1** with >99% ee after two recrystallizations (59% overall yield), but the expensive chiral auxiliary could not be recycled. In such an approach,[144d] the amide **93** of Oppolzer's camphorsultam was subjected to α-allylation to produce **94**, which was converted to the target compound **V** via hydrolysis and hydrogenation (**Scheme IV.1.1**).

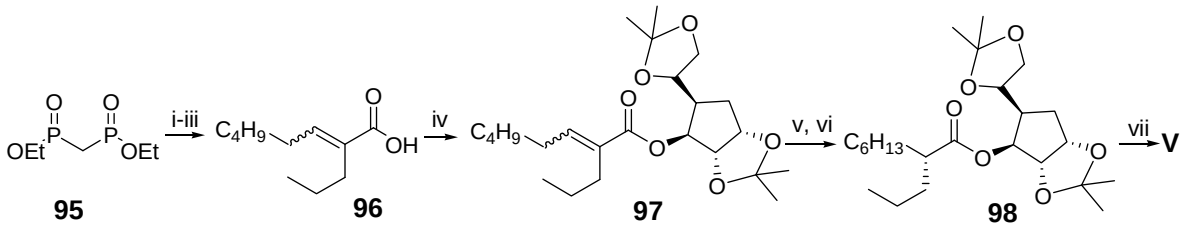


(i) $C_7H_{13}COCl$, Et_3N, DMAP, THF, 0 ^oC; (ii) LDA, THF, CH_2=$CHCH_2Br$, LiI/DMI, -78 ^oC; (iii) Aqueous Bu_4NOH, H_2O_2, 2-methyl-2-butene, DME, -10 ^oC; (iv) H_2, Pt-C, *i*-PrOH, 25 ^oC.

Scheme IV.1.1

The same group also developed a new chiral auxiliary[144f] derived from (*S*)-(−)-1-phenylethylamine to obtain crystalline intermediates with moderate diastereoselectivity, 50–69% de, which could be increased to 99% de after two recrystallizations (10% overall yield).

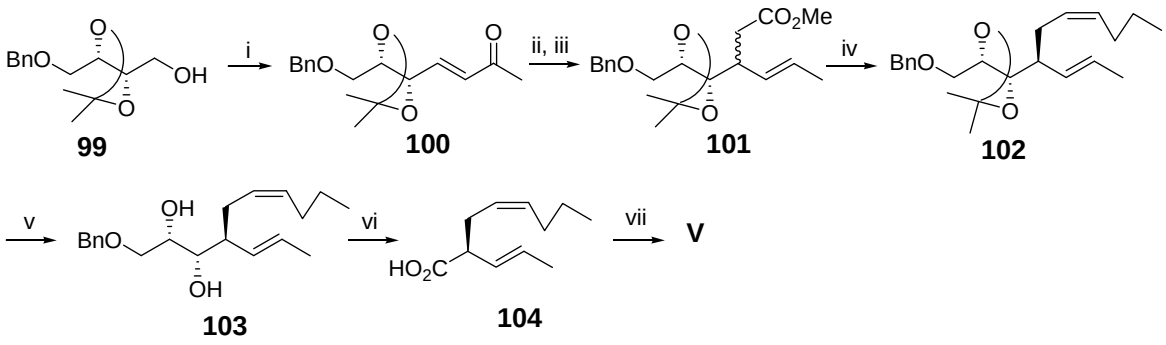
Pelotier *et al.*[144g] reported the synthesis of **V** via diasetereoselective photodeconjugation of diacetone-D-glucosyl α,β unsaturated ester **97** bearing a propyl chain at the α-position. For this, the required acid **96** was synthesized by alkylation of ethylphosphonoacetate **95**, Wittig-Horner reaction and saponification. Diastereoselective photoisomerisation of **97** proceeded with 72:28 enantiomeric ratio of *E*- and *Z*- isomers. Quantitative hydrogenation followed by removal of auxiliary gave **V** in 88% ee (**Scheme IV.1.2**).



i) *t*-BuOK, C_3H_7Br, NaI, DMSO, 65 ^oC; (ii) NaH, hexanal, THF, 0 ^oC-25 ^oC; (iii) KOH, H_2O/EtOH, 80 ^oC; (iv) diacetone-D-glucose, DCC, DMAP, CH_2Cl_2, 0 ^oC-25 ^oC; (v) hν (254 nm), *N*,*N*-dimethylaminoalcohol, CH_2Cl_2, -40 ^oC; (vi) H_2, PtO_2, Et_2O, 25 ^oC; (vii) $LiOH.H_2O$, H_2O_2, 25 ^oC.

Scheme IV.1.2

In a more recent report,[144j] the alcohol **99**, derived from (*R*,*R*)-diethyl tartrate, was oxidized and the product subjected to a Wittig olefination to get the α,β-unsaturated methyl ketone **100**. Reduction of ketone **100** to the corresponding allyl alcohol followed by Claisen ortho-ester rearrangement provided **101** as a diastereomeric mixture. Reduction of the ester followed by Wittig olefination and column chromatography provided **102**. Deprotection of the acetonide functionality, oxidative cleavage of the diol **103** and a further oxidation with $NaClO_2$ furnished the acid **104** which on catalytic hydrogenation provided compound **V** (**Scheme IV.1.3**).



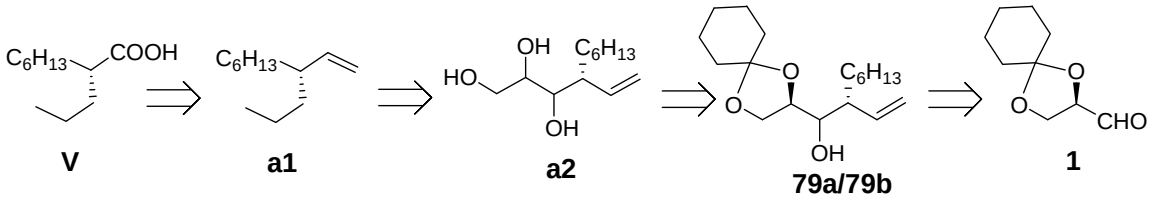
(i) (a) $(COCl)_2$, DMSO, -78 ^oC, then Et_3N, -60 ^oC-25 ^oC; (b) $Ph_3P{=}CHCOCH_3$, THF, 25 ^oC; (ii) DIBAL-H, CH_2Cl_2, 0 ^oC; (iii) $MeC(OMe)_3$, $EtCO_2H$, tolune, reflux; (iv) (a) DIBAL-H, CH_2Cl_2, -80 ^oC; (b) $Ph_3CH_2CH_2CH_2CH_3Br$, *n*-BuLi, THF, -80 ^oC; (v) 3 N HCl, MeOH, 25 ^oC; (vi) (a) $NaIO_4$, $NaHCO_3$, CH_2Cl_2, 25 ^oC; (b) $NaClO_2$, $NaH_2PO_4.H_2O$, cyclohexene, *t*-BuOH, 25 ^oC; (vii) H_2, Pd-C, MeOH, 25 ^oC.

Scheme IV.1.3

IV.1.3: Present work

Although several syntheses of compound **V** exist, most of these need multiple steps and expensive reagents. This prompted us to formulate an efficient and operationally simple synthesis.

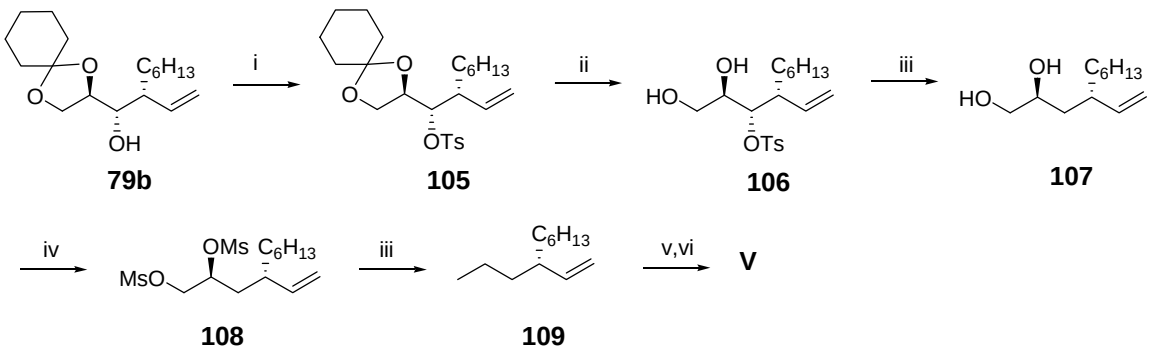
From retrosynthetic analysis (**Scheme IV.1.4**), we envisaged that easily accessible (*R*)-2,3-cyclohexylideneglyceraldehyde **1** could be used as a suitable chiral template for the construction of its C-2-alkylated stereogenic moiety *via* allylation with the allylic bromide **78** described in **Chapter III.1.2**. Based on the synthetic plan, the diastereomers **79a** and **79b** possesses the stereochemistry at the alkyl branched centre as is present in the target compound. The protected triol moiety of **79a**/**79b** can be converted to the propyl group as in **a1**. Oxidative cleavage of the alkene functionality in **a1** would furnish the required carboxylic acid group.



Scheme IV.1.4

Earlier (**Chapter III.1.2**), using bimetallic redox strategy, the diastereomers (**79a-c**) were synthesized by allylation of **1** with the bromide **78**. Using the bimetallic redox strategy involving a combination of $CuCl_2.2H_2O$ and Zn, the reaction of **1** with (*Z*)-**78b** yielded **79b** as the major diastereomer (shown in previous chapter). This was used for the present synthesis. For the required deoxygenationof its 1,2,3-triol unit to the C_3H_7-moietycompound **79b** was tosylated to afford **105**. This was characterized from the

appeaence of a sharp peak for the –Ots group at 1177 cm^{-1} in place of hydroxyl peak in the IR spectrum. The ^{1}H NMR peak at δ 2.42 (3H) and at δ 4.66 (dd, J = 7.4 Hz and 2.2 Hz) [–CH(OTs)] confirmed its formation. Subsequent hydrolysis of compound **105** with aqueous TFA afforded the diol **106** (IR hydroxyl band at 3417 cm^{-1} and the absence of resonances due to cyclohexylidene moiety in ^{1}H (**Fig IV.1.2**) and ^{13}C NMR (**Fig. IV.1.3**) spectra). Next, copmpund **106** was dimesylated and the resultant trisulphonate was subjected to $LiAlH_4$ reduction to produce the required C_3H_7 unit directly. Unfortunately, this gave a very poor yield of the desired product. Hence, an alternative strategy was employed. The diol **106** was subjected to reductive detosylation with excess $LiAlH_4$ to give **107**. The formation of **107** was confirmed from the disappearance of the characteristic resonances due to tosyl group in ^{1}H and ^{13}C NMR spectra. Dimesylation of hydroxyl groups of **107**, followed by $LiAlH_4$ reduction produced the alkene **109**. Its ^{1}H NMR spectrum (**Fig. IV.1.4**) showed a 6H triplet at δ 0.88 ppm for the two methyl groups. The ^{13}C NMR spectrum (**Fig IV.1.5**) was also devoid of the peaks at δ ~60-70 ppm due to the oxygenated carbons. Oxidative ozonolysis[116] of **109** under alkaline conditions, followed by base catalysed hydrolysis of the resultant ester and subsequent acidification furnished the title compound **V** in ~10% overall yield. The spectral and optical data of compound **V** were in well conformity with the reported values.[143g]



(i) p-TsCl, pyridine, 25 ^{o}C, ; (ii) Aqueous TFA, CH_2Cl_2, 0 ^{o}C; (iii) $LiAlH_4$, THF, Δ; (iv) MsCl, Et_3N, CH_2Cl_2, 25 ^{o}C; (v) O_3, MeOH, NaOH, -15 ^{o}C; (vi) (a) NaOH, MeOH, (b) Aqueous 20% HCl, 25 ^{o}C.

Scheme IV.1.5

Overall, the allylation of **1** with **78b** was utilized for a simple synthesis of (*R*)-arundic acid. The efficacy of this route was in its operational simplicity using inexpensive reagents in all the steps. The use of **1** as starting material was always advantageous compared to the corresponding isopropylidene derivative[145], because of its easy accessibility and high stability. The present one was developed starting from enantiomerically pure **79b**. Hence a late-stage separation of diastereomers, as used in the earlier syntheses was not required. Understandably, the other major allylated product **79c** can be converted to (*S*)-arundic acid following the same strategy.

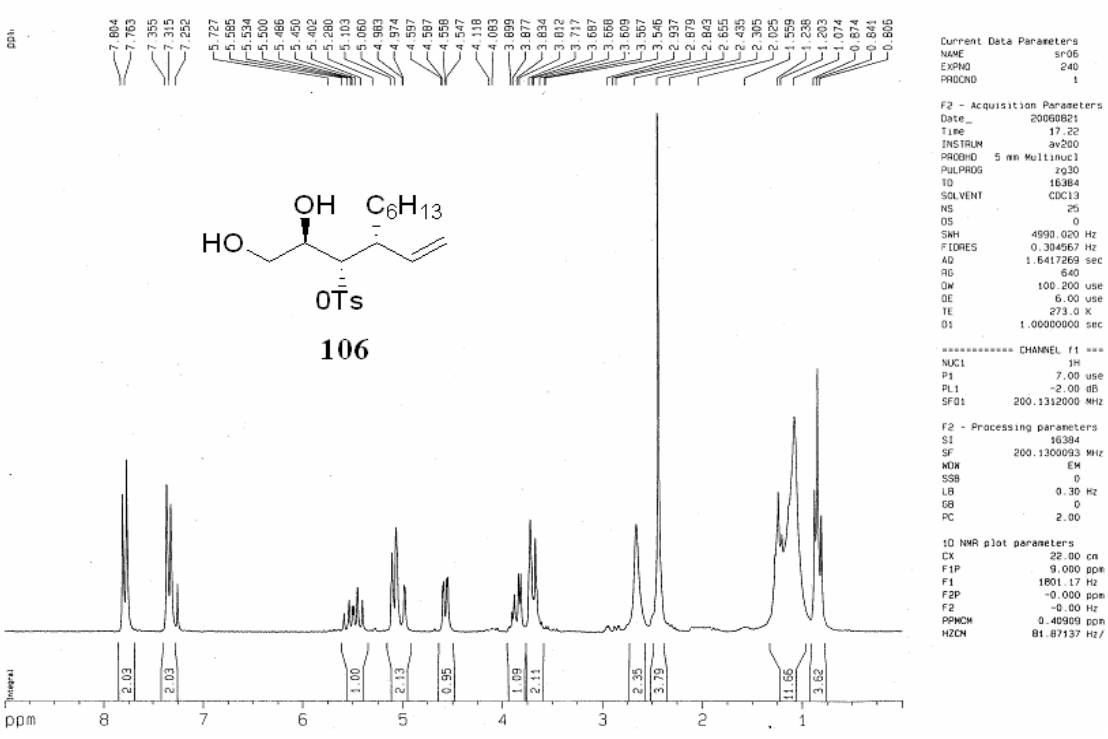


Fig. IV.1.2. ^{1}H NMR spectrum of 106

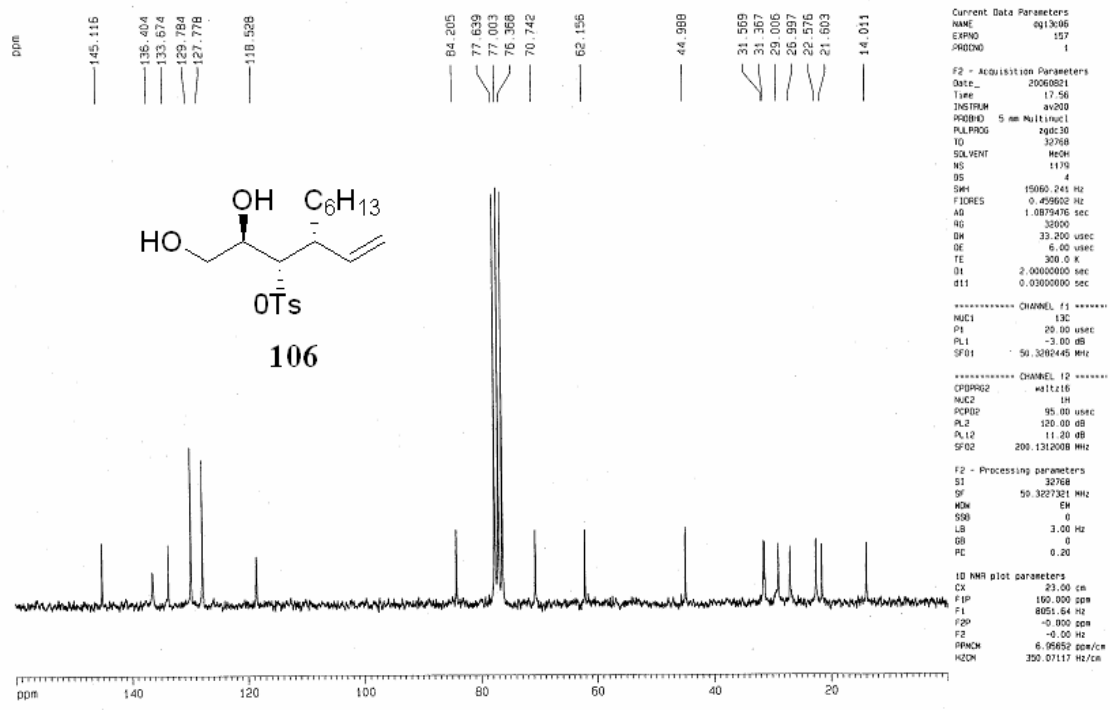


Fig. IV.1.3. ^{13}C NMR spectrum of 106

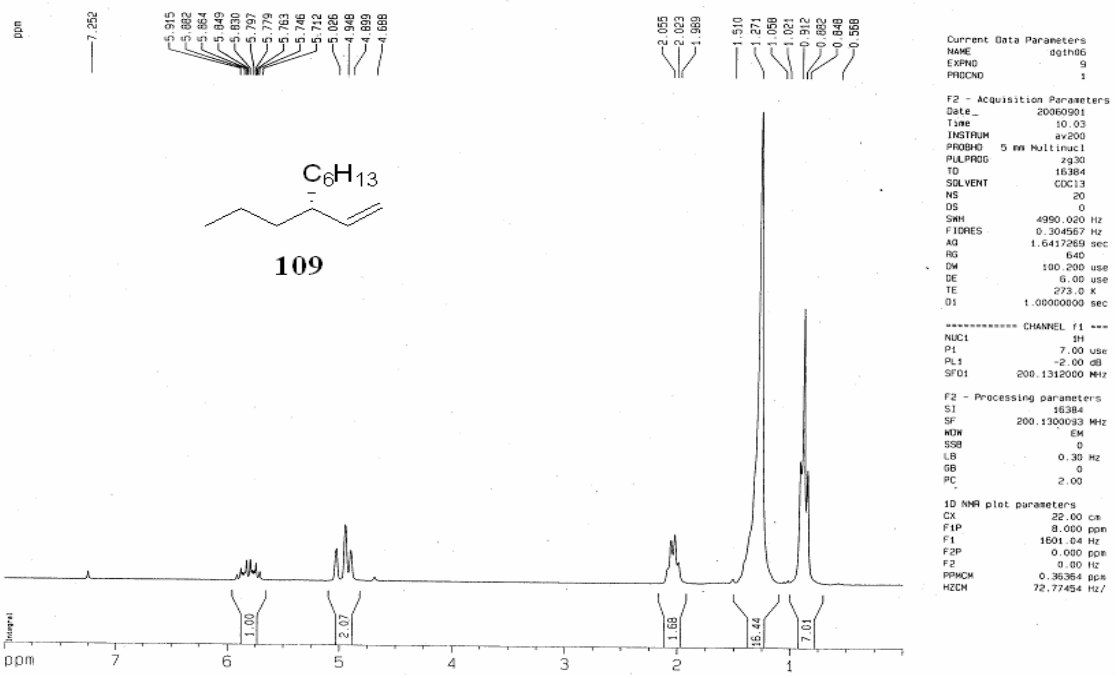


Fig. IV.1.4. ^{1}H NMR spectrum of 109

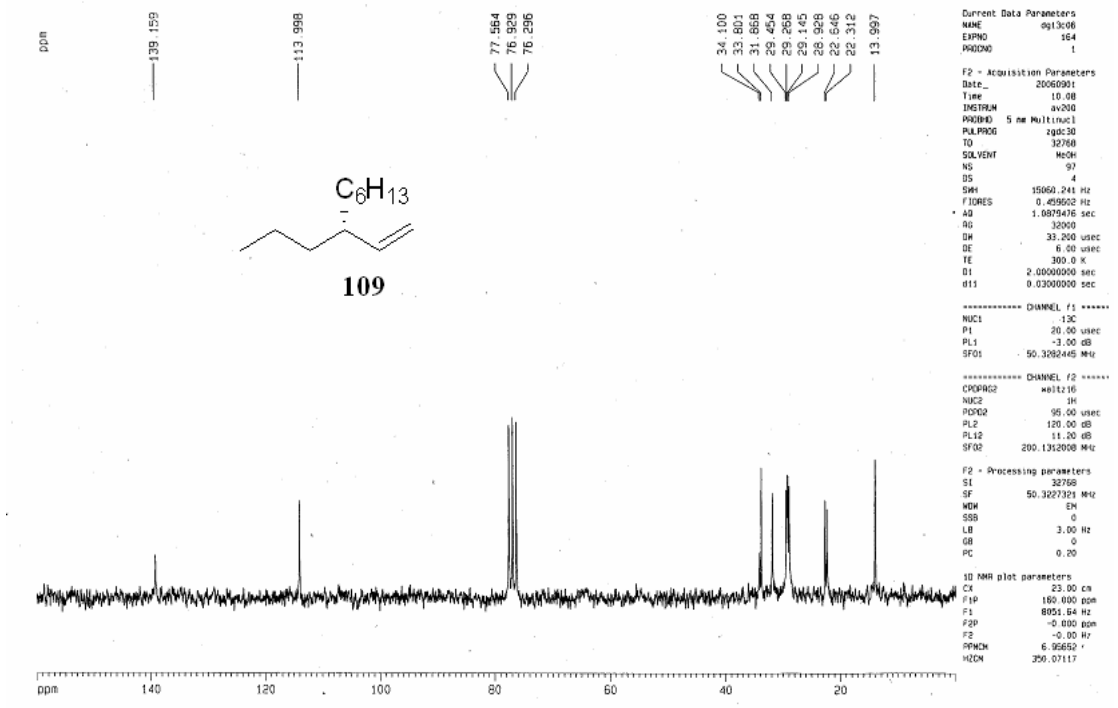


Fig. IV.1.5. ^{13}C NMR spectrum of 109

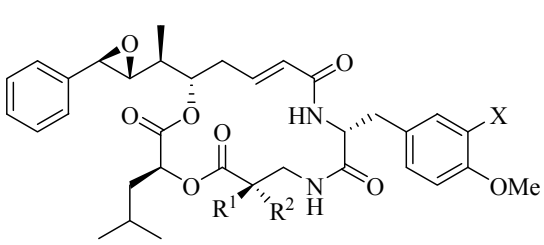
IV.2: SYNTHESIS OF OCTADIENOIC ACID UNIT OF CRYPTOPHYCINS

IV.2.1: Introduction

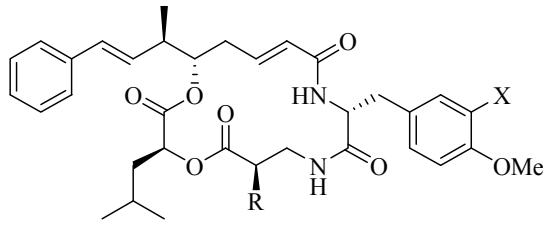
Cryptophycins (**Figure IV.2.1**) are potent, tumor-selective tubulin binding antimitotic agents[146] with excellent activity against multidrug-resistant (MDR) cancer cells.[147a-g] Cryptophycin-A (**110**), initially isolated from the blue green algae *Nostoc* sp. ATCC 53789[148a,b] and later from GSV 224,[148c] is an effective inhibitor of tubulin polymerization at substoichiometric concentrations,[149a] and inhibits vinblastine binding to tubulin.[149] A structurally related compound, arenastatin A (cryptophycin-24, **111**), isolated from the Okinawan marine sponge *Dysidea arenaria*[150a,b] and *Nostoc* sp. GSV 224[150c] is a potent inhibitor of tubulin polymerization[150d] and also shows excellent cytotoxicity against KB cells in vitro,[150a,b] but has a very short half-life. The metabolically stable synthetic analogue, cryptophycin-52 (**112**) shows exceptional in vivo potency and tumor-selective cytotoxicity, and is effective against drug-sensitive and drug-resistant tumor cells.[151]

Structural variation within the subset of macrocyclic cryptophycins is centered on three sites: (a) the styryl residue as in **114**-**116** that is epoxidized in **110**-**113**, (b) the β-alanine or α-methylated β-alanine residue as in **111** and **116**, and **110**, **112**-**115** respectively, and (c) the (*R*)-*O*-methyltyrosinyl residue of **111** and **113** that bears an *m*-chloro substituent in **110**, **112**, and **114**-**116**. Essentially, the structure of the cryptophycins can be assembled in a convergent manner (**Figure IV.2.1**) from the protected octadienoic acid (unit-**A**), D-tyrosine ester (unit-**B**), the protected β-amino acid derivative (unit-**C**) and the hydroxy acid (unit-**D**). Amongst these, the presence of the epoxide moiety in the unit-**A**, the methoxy and chloro substituents in the unit-**B**, and certain substitution patterns in

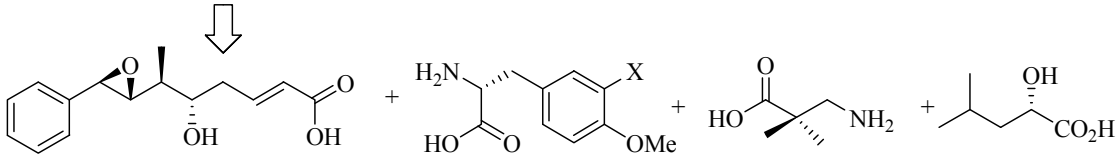
the unit-**C** contribute positively to their cytotoxic action.[151] In view of their potent bioactivity, a large number of formal[152a-f] and total[147a,153] syntheses of the cryptophycins have been reported. Given the units **B**-**D** are easily available, particular attention was focused to the synthesis of the octadienamide fragment (unit-**A** equivalent) of desoxycryptophycins, leading to a number of interesting methodologies.[153a,154,155] A strategical theme, common to majority of the syntheses of the epoxide-containing cryptophycins had been the introduction of the epoxide pharmacophore in a single late-stage operation through the use of *m*-CPBA or dimethyl dioxirane. The reported epoxidation methods proceeded with a diastereoselectivity of ~2-3:1, necessitating a chromatographic separation of the desired (major) β-isomer. In contrast, the more efficient protocols were based on prior introduction of the chiral diol unit at those centres. To this end, we developed a novel asymmetric synthesis of unit-**A** equivalent, bearing the chiral diol unit that can be elaborated to the cryptophycins.



Cryptophycin-A (**110**): R^1 = Me, R^2 = H, X = Cl
Cryptophycin-24 (**111**): R^1 = R^2 = X = H
Cryptophycin-52 (**112**): R^1 = R^2 =Me, X = Cl
Cryptophycin-B (**113**): R^1 = Me, R^2 = H, X = H



Cryptophycin-C (**114**): R = Me, X = Cl
Cryptophycin-D (**115**): R = Me, X = Cl
Cryptophycin-29 (**116**): R = H, X = Cl



unit-**A** unit-**B** unit-**C** unit-**D**

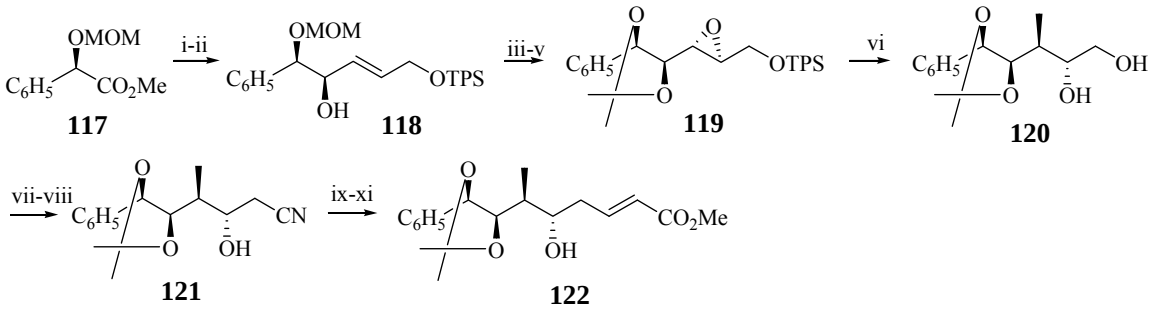
Figure IV.2.1. Precursor units for convergent synthetic approach to cryptophycins.

IV.2.2: Previous syntheses of unit-A

Among different methodologies for the synthesis of unit-**A**, besides the less-diastereoselective last step epoxidation protocol, use of Shapless asymmetric dihydroxylation (ADH) proceeded with good stereoselectivity, but moderate yield.

In the synthesis[153h] of cryptophycin-A (**111**), Li *et. al*. relied on (*R*)-mandelic acid as the sole source of asymmetry for unit-**A**. The *syn*-diol unit was introduced early in the reaction sequence and was converted to the epoxide in the last step of the synthesis.

Pousset *et al*.[155a] used *O*-protected methyl mandelate **117** for the synthesis of unit-**A**. Reaction of the Al-salt, obtained by reaction DIBAL-H with **117,** with magnesium acetylide, followed by reduction under Denmark conditions afforded **118**. Compound **118** was completely deprotected in acidic medium, and the resulting diol was selectively protected as an acetonide. This, on Sharpless epoxidation gave **119** with 90% de. Epoxide opening with trimethyl aluminum afforded diol **120**, which was converted to hydroxyl nitrile **121**. This on DIBAL-H reduction and subsequent Wittig-Horner reaction furnished the unit-**A** equivalent unsaturated ester **122** (**Scheme IV.2.1**).

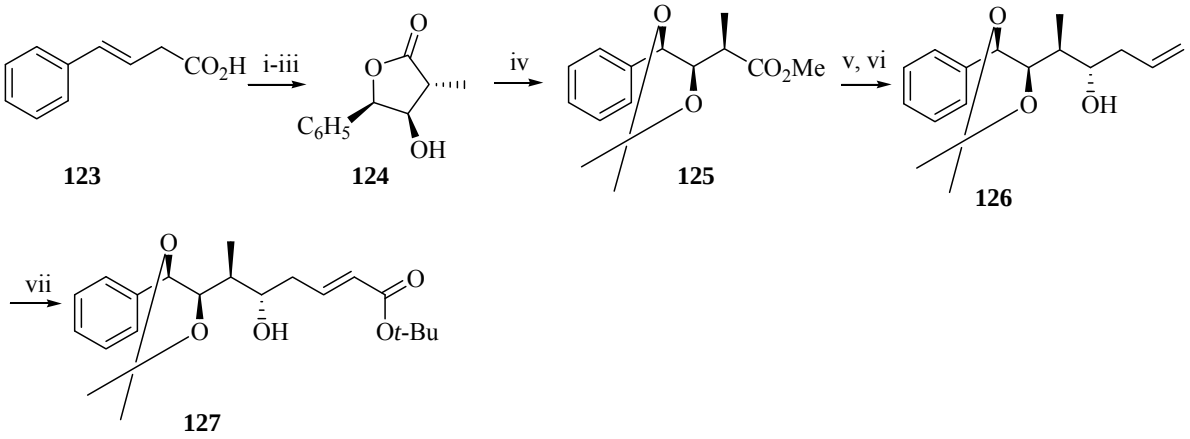


(i) (a) DIBAL-H, hexane, -78 ^{o}C, (b) Magnesium acetylide; (ii) Red-Al®, Et_2O, -20 ^{o}C; (iii) 2M HCl, MeOH, 40 ^{o}C; (iv) Acetone, $CuSO_4$, cat. PPTS; (v) *t*-BuOOH, $_L$-(+)-diisopropyl

tartrate, Ti(O-*i*-Pr)$_4$, CH_2Cl_2; (vi) Me_3Al, hexane, 25 ^oC; (vii) (a) $CH_3C(OMe)_3$, Me_3SiCl, CH_2Cl_2, 0 ^oC, (b) K_2CO_3, MeOH, 25 ^oC; (viii) KCN, $LiClO_4$, CH_3CN, 70 ^oC; (ix) *t*-$BuMe_2SiOTf$, 2,6-lutidine, CH_2Cl_2, 0 ^oC; (x) DIBAL-H, toluene, -78 ^oC; (xi) trimethylphosphonoacetate, tetramethylguanidine, THF, 30 ^oC.

Scheme IV.2.1

In a recent approach,[155b] the methyl ester of the acid **123** was subjected to ADH reaction to furnish a γ-lactone, which on base-catalyzed α-methylation afforded the lactone **124**. This on acetalization gave **125**. Conversion of **125** to the corresponding aldehyde followed by allylation gave **126** in 98% de. A cross-metathesis between **126** and *t*-butyl acrylate yielded the unit-**A** precursor **127** in 42% yield and 95% de (**Scheme IV.2.2**).



123 **124** **125** **126** **127**

(i) MeI, Cs_2CO_3, acetone, reflux; (ii) AD-mix, t-BuOH-H_2O, 0 ^oC; (iii) LDA, MeI, THF, -78 ^oC; (iv) Amberlyst-15, MeOH, $C(CH_3)_2(OMe)_2$, 25 ^oC; (v) DIBAL-H, CH_2Cl_2, -78 ^oC; (vi) CH_2=$CHCH_2Sn(n\text{-}Bu)_3$, $MgBr_2.Et_2O$, CH_2Cl_2, -78 ^oC; (vii) *t*-butylacrylate, Grubbs 2nd generation, CH_2Cl_2, 25 ^oC.

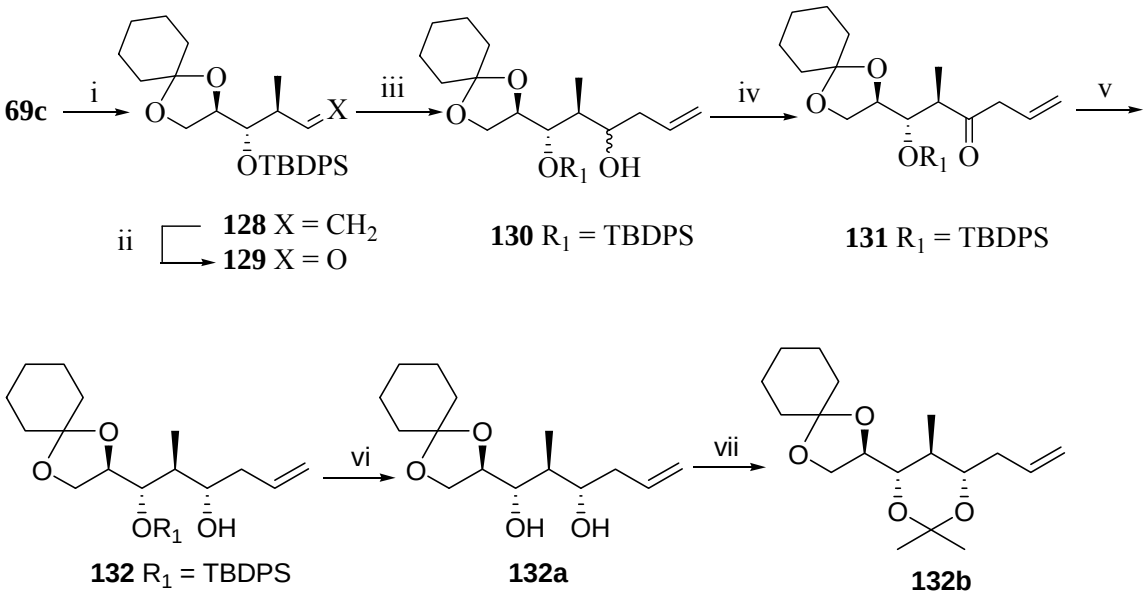
Scheme IV.2.2

IV.2.3: Present work

For the present work, it was envisaged that the alcohol stereomers **69a-c**, produced by crotylation of the aldehyde **1**, are functionally sufficiently enriched and well-suited for elaboration to the target structural motif of the unit-**A** of the cryptophycins. The *anti*,*anti* homoallylic alcohol **69c** appeared best suited for the synthesis of the target compound, because of suitable disposition of its stereogenic centres. Such a strategy would be also useful to introduce the required diol moiety in an enantioselective fashion, which would eventually produce the epoxide-containing cryptophycins.

The Ga-mediated crotylation of **1** in [bmim][Br] was very attractive for this purpose as it furnished **69a**:**69b**:**69c** in 3:5:92 ratio and 82% overall yield (**Chapter III.2.1**). For the synthesis of the cryptophycin segment (**Scheme IV.2.3**), compound **69c** was converted to the silyl derivative **128** by reacting with *tert*-butyldiphenylsilyl chloride (TBDPSCl) in the presence of imidazole as the base. Compound **128** was characterized from the absence of IR peak due to hydroxyl group, and the characteristic ^{1}H NMR peaks for the TBDPS group. This on reductive ozonolysis gave the aldehyde **129** (IR peak at 1726 cm^{-1} as well as ^{1}H and ^{13}C NMR peaks at δ 9.55 ppm and δ 204.8 ppm due to –CHO group). Its Zn-mediated allylation furnished the homoallylic alcohol **130** as a non-separable diastereomeric mixture. It was envisaged that the alcohol **130** could be obtained with better diastereomeric purity by oxidizing it to the ketone **131**, followed by hydride reduction. We anticipated that the hydride donor would form a stable complex with the β-silyloxy ketone **131** ensuring a more directional hydride transfer to the carbonyl group.

Based on this hypothesis, the alcohol **130** was oxidized with pyridinium chlorochromate (PCC) in CH_2Cl_2 to obtain the ketone **131**, which was characterized from the IR peak at 1741 cm^{-1}, and also from the ^{13}C NMR resonance at δ 206.8 ppm. The ^{1}H and ^{13}C NMR spectra of **131** are shown in **Fig. IV.2.2** and **Fig. IV.2.3** respectively. Reduction of **131** with $NaBH_4$ the alcohol **132** as a single stereomer. Alcohol **132** was characterized from the IR hydroxyl peak at 3443 cm^{-1}, the ^{1}H NMR resonances at δ 4.92-4.99 (m, 2H) and at δ 5.61-5.75 (m, 1H) as well as the ^{13}C NMR peaks at δ 116.7 and 136.1 ppm due to the olefin. The ^{13}C NMR spectrum established the diastereomeric purity of the compound **132**.

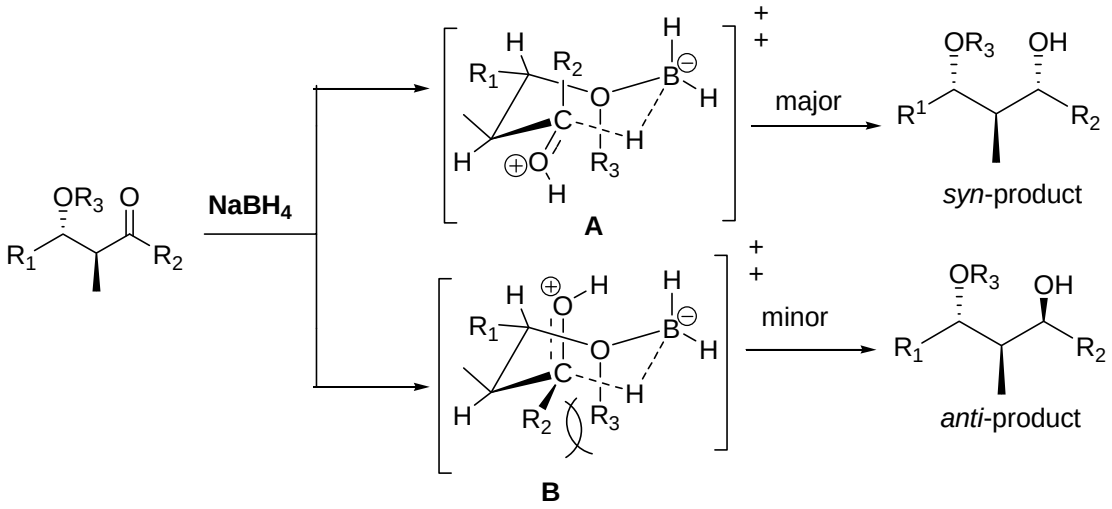


(i) TBDPSCl, imidazole, CH_2Cl_2, 25 ^{o}C; (ii) O_3, CH_2Cl_2, -78 ^{o}C; Ph_3P; (iii) Allyl bromide, Zn, THF, aqueous NH_4Cl, 25 ^{o}C; (iv) PCC, NaOAc, CH_2Cl_2, 0 ^{o}C; (v) $NaBH_4$, MeOH, 0 ^{o}C; (vi) Bu_4NF, THF, 0 ^{o}C; (ii) DMP, PPTS, 25 ^{o}C.

Scheme IV.2.3

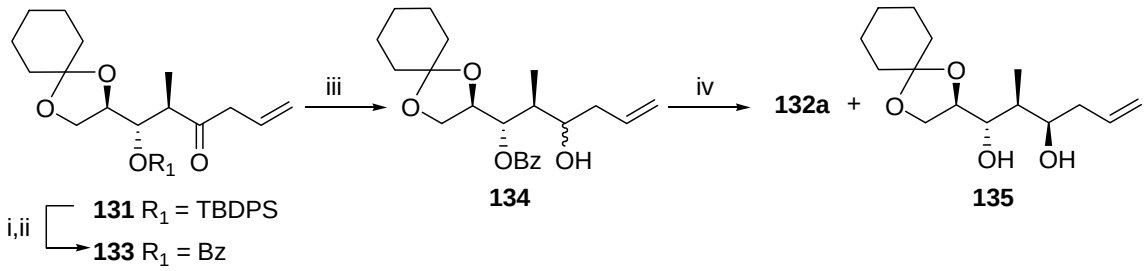
To confirm the 3,5-*syn* stereochemistry of **132**, it was converted to the acetonide derivative **132b** (**Scheme IV.2.3**). Thus, compound **132** was desilylated to the diol **132a** and subsequently converted to the cyclic acetal **132b** by reacting with 2,2′-dimethoxypropane (DMP) in the presence of pyridinium *p*-toluene sulphonate (PPTS). Its ^{13}C NMR spectrum showed peaks at δ 19.6, 29.8 and 97.7 ppm, which indicated the 3,5-*syn* stereochemistry of **132**.[156] The ^{1}H and ^{13}C NMR spectra of **132b** are shown in **Fig. IV.2.4** and **Fig. IV.2.5** respectively.

The observed selectivity in the reduction of compound **131** could be explained as follows. Presumably, the reduction proceeded through a six-membered chair like transition state **A** or **B**, both possessing the R_1 group in an equatorial position (**Scheme IV.2.4**). Of these, the bottom side approach of the H^- in the transition state **B** that would furnish the *anti*-diol is effectively hindered by the steric bulk of the axial protecting group R_3. Thus, the reaction would proceed through the transition state **A** producing the *syn*-diol, as observed in the present case. Such type of intramolecular activation of the carbonyl by a tricoordinated boron atom followed by intramolecular hydride delivery has been reported, and also the propensity of such β-hydroxy ketone boron aldolates to reduce with the opposite sense of asymmetric induction was established earlier.[157] Apparently, a bulky protecting group (R_3) like the TBDPS group, present in **131** was responsible for the exclusive formation of the *syn*-product **132**.



Scheme IV.2.4

To support this hypothesis, we desilylted the ketone **131** and the resultant hydroxyl ketone was reacted with BzCN to obtain the benzoate **133**. This was characterized from the IR peaks at 1716 and 1638 cm^{-1}, and the appearance of a peak at δ 5.42 ppm (dd, J = 9.4 and 12.2 Hz, 1H) in the ^{1}H NMR spectrum. Compound **133** was subsequently reduced with $NaBH_4$. As expected, this afforded the alcohol **134** as a mixture of chromatographically inseparable diastereomers (**Scheme IV.2.5**). Fortunately, debenzoylation of this mixture yielded the pure diols **132a** and **135** in a diastereomeric ratio of 65:35 (*syn*:*anti*). The *anti*-isomer **135** was characterized from the ^{1}H NMR [δ 5.10-5.17 (m,2H) and δ 5.57-5.75 (m,1H)] and ^{13}C NMR [δ 117.2 and δ 141.3 ppm] resonances due to presence of terminal olefin. Also the patterns of the ^{1}H NMR multiplets in the region δ 3-4 ppm due to –CH(OH) protons were completely different in case of the two diastereomeric diols **132a** and **135**. The decrease in the *syn*-selectivity in the reduction of **133** was expected, given that the less bulky R_3 (PhCO) group (**Scheme IV.2.4**) would not provide sufficient steric crowding to direct the steric course of the reduction completely.

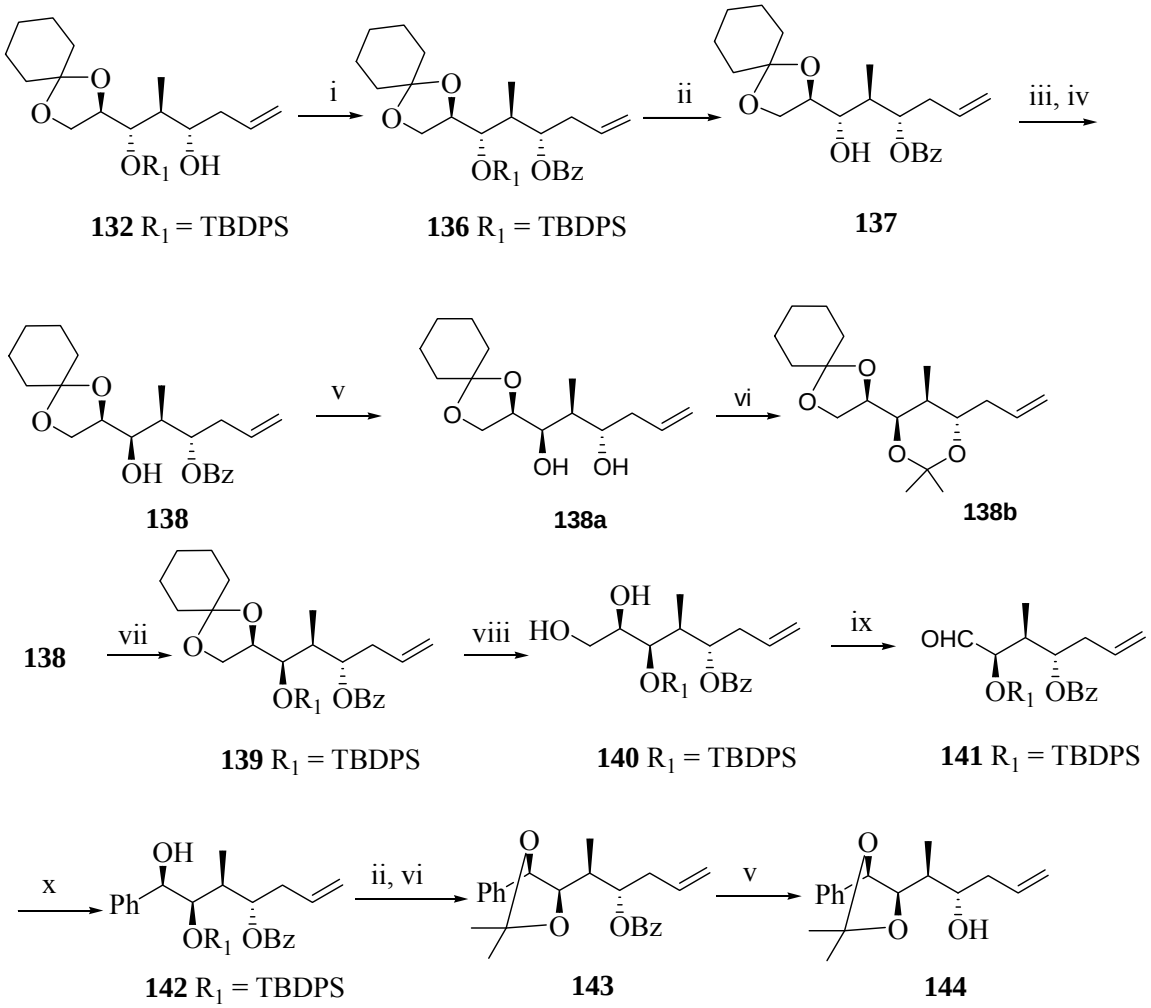


(i) Bu_4NF, THF, 0 ^oC; (ii) BzCN, Et_3N, 25 ^oC; (iii) $NaBH_4$, MeOH, 0 ^oC; (iv) K_2CO_3, MeOH, 25 ^oC.

Scheme IV.2.5

For the actual synthesis of the target compound (**Scheme IV.2.6**), the carbinol **132** was benzoylated to furnish the compound **136**, which was characterized from the IR peak at 1638 cm^{-1}, and the ^1H NMR multiplets at δ 5.45-5.52 for the –CH(OBz) group. Desilylation of **136** gave the alcohol **137**, which showed IR hydroxyl band at 3437 cm^{-1}, and absence of characteristic ^1H NMR resonances for the TBDPS group. Oxidation of the carbinol function of **137** with PCC followed by reduction with K-selectride® gave the 1,3-*anti* diol derivative **138**. As done for compound **132**, the relative 3,5-*anti* stereochemistry of **138** was ascertained by converting it (**Scheme IV.2.6**) to the cyclic acetal **138b** through the diol **138a**, followed by ^{13}C NMR analysis.[156] Appearance of the peak at δ 23.9, 24.0 and 100.3 ppm in the ^{13}C NMR spectrum confirmed its *anti*-stereochemistry. Next, the alcohol **138** was silylated with TBDPSCl and imidazole to get compound **139**, which was characterized from the appearance of ^1H and ^{13}C peaks due to –TBDPS group. Deketalization of **139** with aqueous TFA, gave the diol **140** uneventfully. The ^1H NMR (**Fig. IV.2.6**) and ^{13}C NMR (**Fig. IV.2.7**) spectra of **140** showed the absence of resonances due to cyclohexylidene moiety, while its IR spectrum revealed a broad peak at 3438 cm^{-1}

(OH). Oxidative cleavage of its α-glycol with $NaIO_4$ furnished the aldehyde **141**. It was characterized from the IR peaks at 1730 and 1712 cm^{-1}, as well as ^{1}H and ^{13}C NMR peaks at δ 9.35 ppm and δ 203.4 ppm respectively for the –CHO group. Reaction of **141** with PhMgBr proceeded with excellent diastereoselectivity (dr >98:2) to furnish the target cryptophycin unit-**A** equivalent **142** as the major product. Formation of **142** was confirmed from the appearance of IR peak at 3478 cm^{-1} and the ^{1}H NMR resonances at δ 4.88-4.97 (m, 2H) which accouted for both PhCH(OH) and -CH(OBz) protons. For further confirmation of its structure, compound **142** was converted to the known compound **144**, that has been conceived as an advanced synthon for cryptophycin **A**.[155b] Thus, compound **142** was desilylated and the resultant product converted to the acetal **143** by an acid catalyzed condensation with DMP. Formation of **143** was confirmed from the disappearance of the hydroxyl peak in its IR spectrum, as well as appearance of two singlets at δ 1.58 and 1.62 ppm in the ^{1}H NMR spectrum. Its subsequent debenzoylation finally afforded the target synthon **144**, whose spectral and optical data were in accordance with those reported.[155b]



132 R_1 = TBDPS **136** R_1 = TBDPS **137**

138 **138a** **138b**

138 **139** R_1 = TBDPS **140** R_1 = TBDPS **141** R_1 = TBDPS

142 R_1 = TBDPS **143** **144**

(i) BzCN, Et_3N, 0 ^oC-25 ^oC; (ii) Bu_4NF, THF, 0 ^oC; (iii) PCC, NaOAc, CH_2Cl_2, 0 ^oC; (iv) K-selectride®, THF, -78 ^oC; (v) K_2CO_3, MeOH, 25 ^oC; (vi) DMP, PPTS, 25 ^oC; (vii) TBDPSCl, imidazole, CH_2Cl_2, 25 ^oC; (viii) Aqueous TFA, 0 ^oC; (ix) $NaIO_4$, MeCN-H_2O, 25 ^oC; (xi) PhMgBr, THF, -30 ^oC.

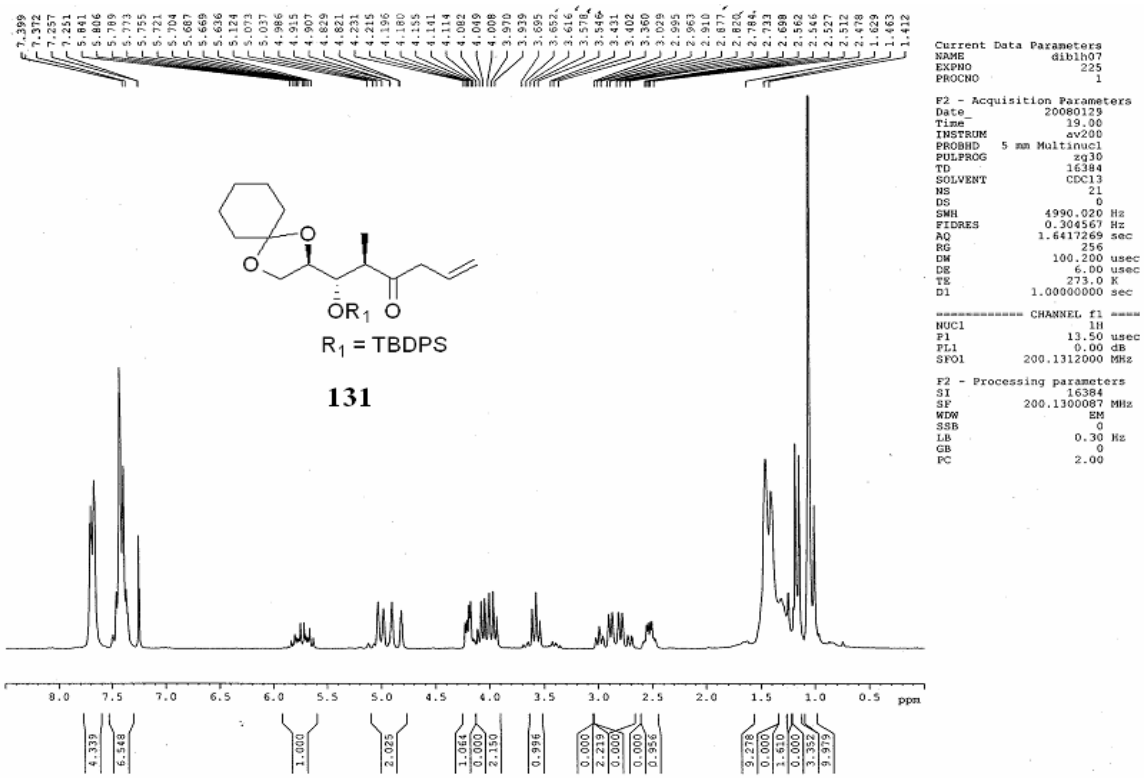


Fig. IV.2.2. ^{1}H NMR spectrum of 131

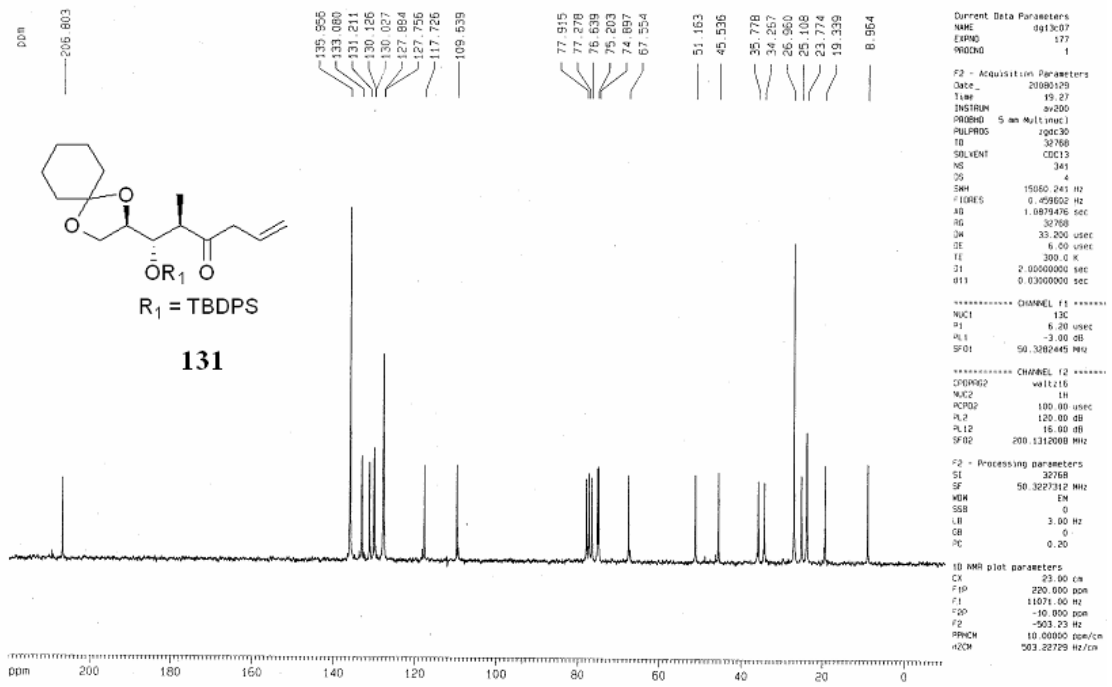


Fig. IV.2.3. ^{13}C NMR spectrum of 131

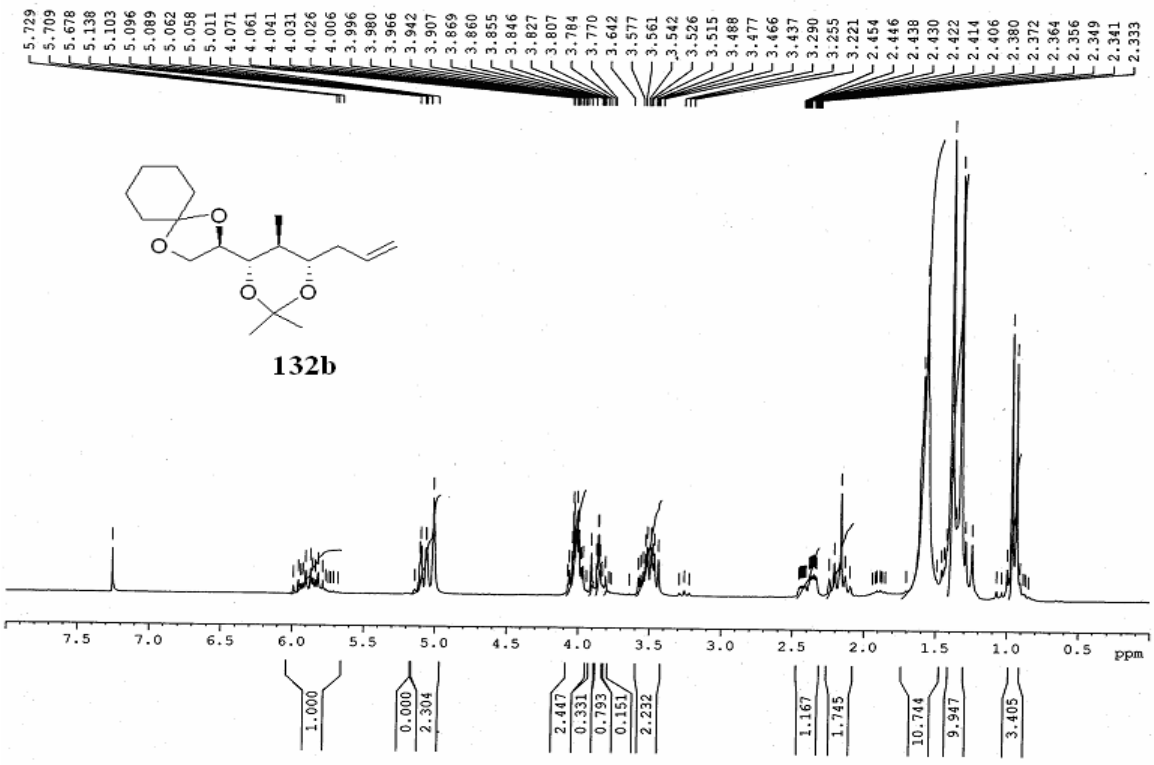


Fig. IV.2.4. ^{1}H NMR Spectrum of 132b

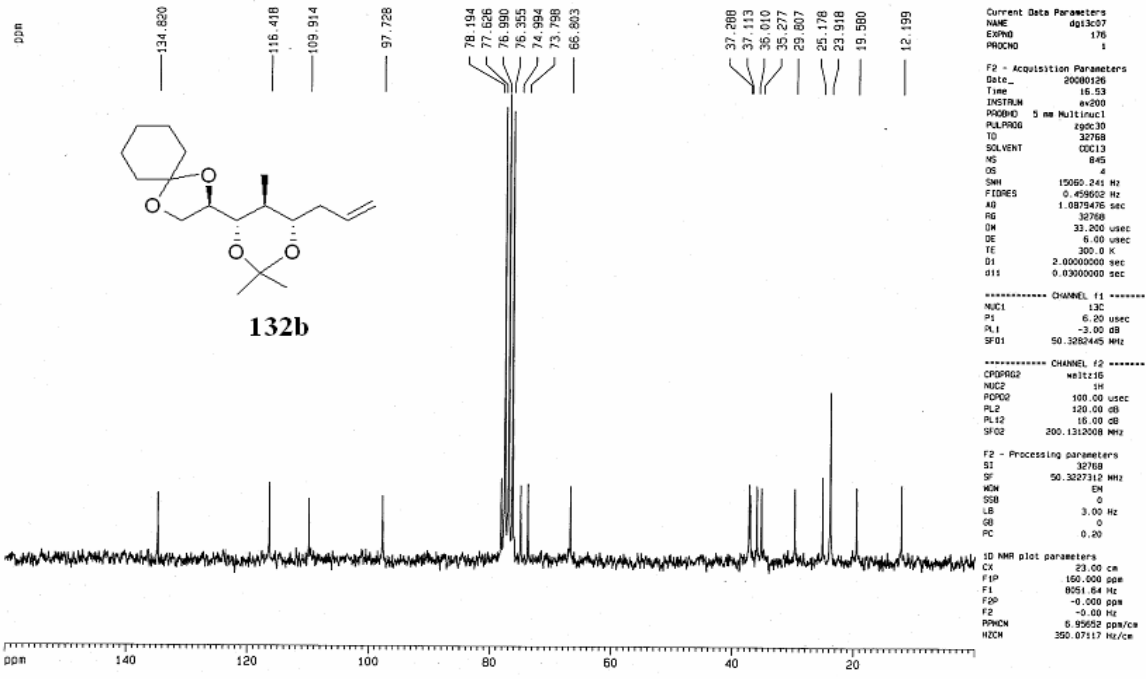


Fig. IV.2.5. ^{13}C NMR spectrum of 132b

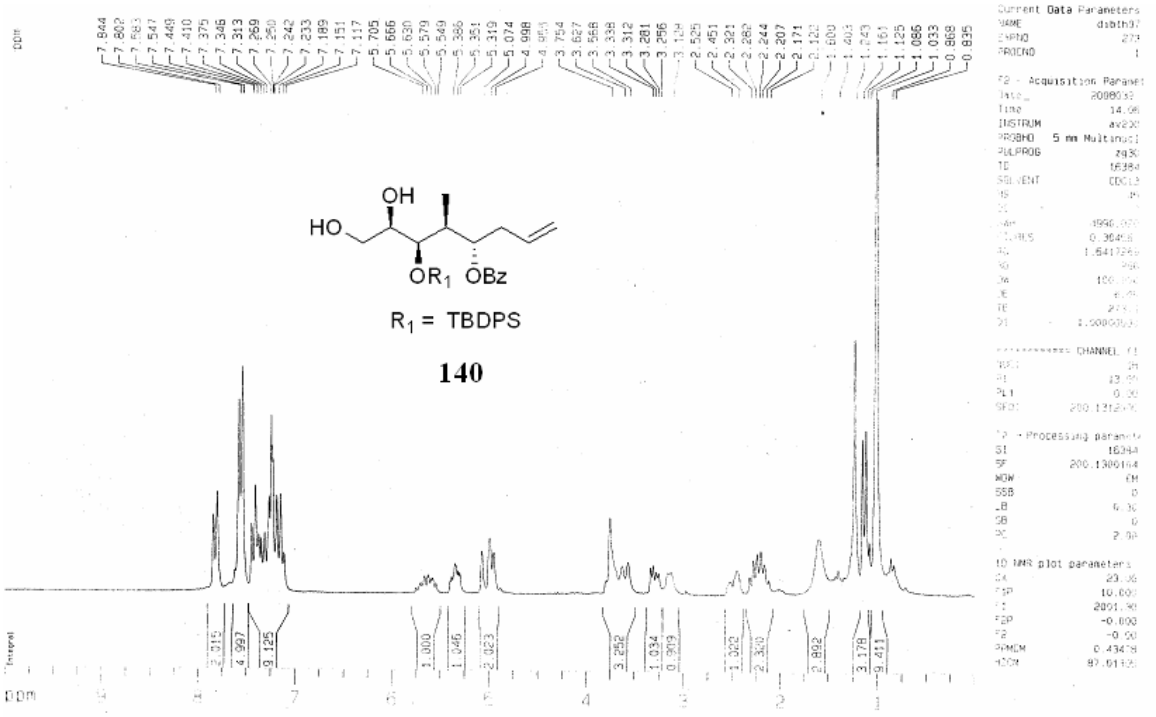


Fig. IV.2.6. ^{1}H NMR spectrum of 140

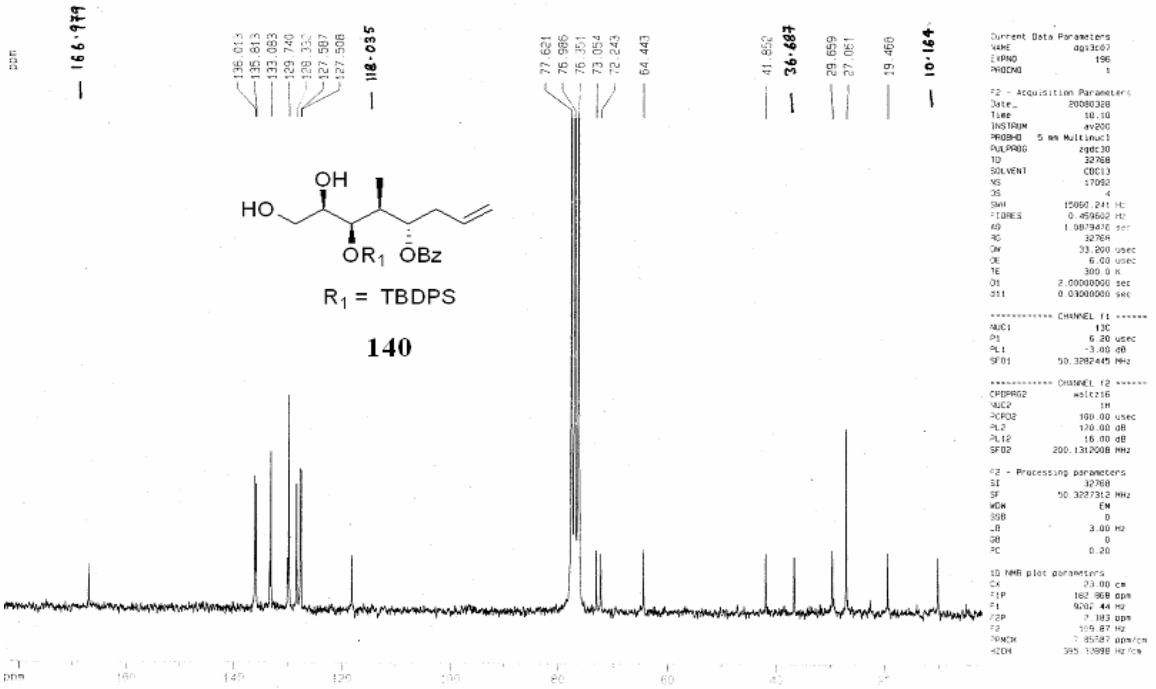


Fig. IV.2.7. ^{13}C NMR spectrum of 140

In conclusion, an efficient asymmetric synthesis of the octadienoic acid unit (unit-**A**) of cryptophycins was demonstrated from the easily available aldehyde **1**. Most of the existing synthetic routes for unit-**A** involved several reagents, which were to be prepared separately and/ or suitable for a very small scale synthesis. In comparison, all the steps in our synthesis could be carried out conveniently in multi-gram scales. Admittedly, the intermediates, **132** and **138** were prepared through a circuitous route. However, the target compound was obtained in an acceptable overall yield (11%). The synthetic strategy was based on a Ga-mediated highly diastereoselective crotylation of the easily available aldehyde **1** in [bmim][Br] as one of the key steps. The route provided an efficient alternative method for installing the cryptophycin epoxide moiety, circumventing the commonly employed last-step epoxidation, which exhibited poor diastereoselectivity. The present synthetic route is easily amenable to the synthesis of other members of the cryptophycin family.

IV.3: SYNTHESIS OF 3'-C BRANCHED 2', 3'-DIDEOXYNUCLEOSIDES

IV.3.1: Introduction

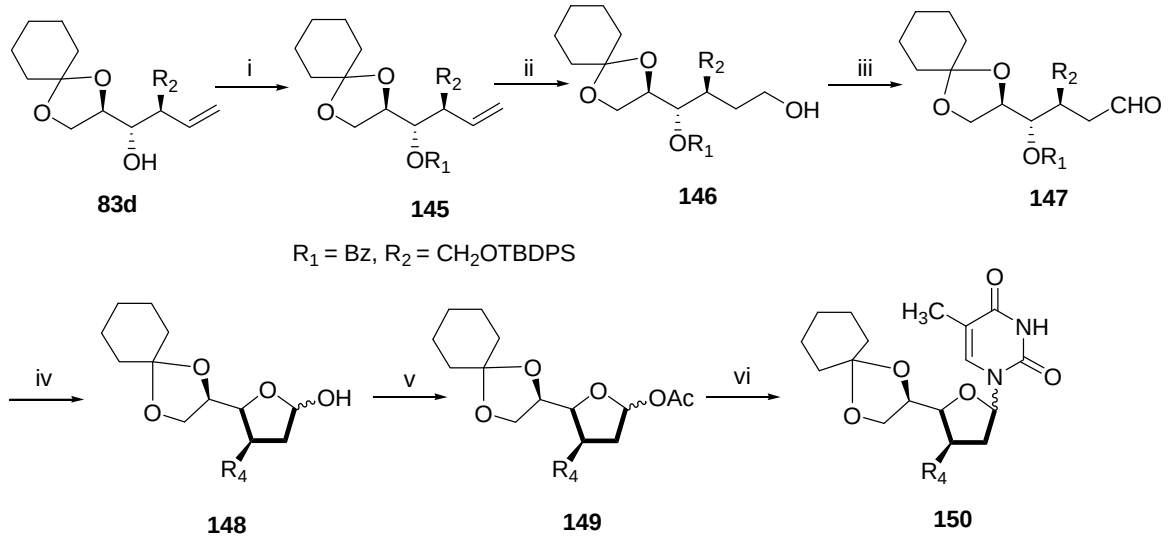
2',3'-dideoxynucleosides like ddI, ddC, AZT[158] *etc*. have been reported as potent antiviral agent against human immunodeficiency virus (HIV), and a number of 2',3'-dideoxynucleosides have been synthesized and evaluated against the virus in order to determine the structure-activity relationships.[159] Although the exact mechanism of each of these agents is not yet fully understood, in general it has been found that these compounds are pro-drugs and are sequentially phosphorylated by cellular kinases to corresponding triphospates. Unfortunately these triphospates often cause undesired side effects because of their affinity for other cellular kinases. A challenge in recent years has been to discover dideoxynucleotides or analogs which are substrates of the cellular kinases, and subsequently as the triphosphates, capable of binding to the HIV reverse transcriptase. Enormous progress has been made in the synthesis of new dideoxynucleotides and their analogs due to the urgent need for better, as well as a variety of therapeutic agents for the treatment of AIDS. Efforts have been primarily focused on the modification of the carbohydrate portion of these molecules, since the cellular kinases are more tolerant of these changes compared to changes in the base moiety. Moreover, in view of the current attention on antisense oligonuclides therapeutics[160] of varied activities viz. antiviral, anticancer, antibacterial etc., 3'-methylene branched nucleosides are used as building blocks for the preparation of the 3'-methylene-modified oligonucleotides with a view to attain better enzymatic stability against exo/endo nucleases and also enhancing membrane permeability[161]. Hence, preparation of 3'-C branched dideoxynucleotide analogs with varied stereochemical features drew attention of synthetic chemists over the ages.[162]

For the synthesis of a nucleoside analog, a convergent approach, [159a-b,163] involving the base coupling of a sugar unit with a nucleoside base using various established procedures,[164] has an inherent advantage since it provides an opportunity to carry out a desired chemical/stereochemical modification in the sugar unit prior to the coupling. Thus, designing and developing efficient synthesis of sugar units assumes considerable importance.

IV.3.2: Present work

The present work describes our endeavors to develop a very simple, efficient and stereochemically flexible strategy for the synthesis of 3-C'-branched sugars of the corresponding nucleosides (**Scheme IV.3.1**) through exploitation of the bimetallic redox strategy for crotylation, discussed in **chapter III**. To this end, the required homoallylic alcohol **83** was prepared by the coupling of the allylic bromide **82** with the aldehyde **1** (**Chapter III.1.2**) using the bi-metallic strategy. As evident from the diastereoselectivity of the reaction (discussed in the previous chapter), the strategy provided efficient routes to prepare all the four possible diastereomers **83a-d** in substantial amounts. While **83c** and **83d** could be obtained as two major diastereomers directly from the coupling reaction, the other two isomers **83a** and **83b** were prepared via an oxidation-reduction protocol. All these are suitable templates for synthesizing nucleoside analogs of diverse stereochemical feature. However, we had chosen **83d** to perform a representative synthesis of 3'-C-branched 2',3'-dideoxynucleoside analog.

For the actual synthesis, (**Scheme IV.3.1**), **83d** was chosen as a starting material. The free hydroxyl group was converted to the corresponding benzoate derivative **145** in 90% yield, by treating with BzCN in the presence of Et_3N. Compound **145** was characterized from the disappearance of a sharp band at ~3400 cm^{-1} in its IR spectrum, and presence of multiplets at δ 5.66-5.71 (1H) in the ^1H NMR spectrum (**Fig. IV.3.1**). Compound **145** was subjected to hydroboration-oxidation[165] of its terminal olefin moiety to furnish the alcohol **146** in 90% yield. Its IR band at 3466 cm^{-1} and additional signal at ~δ 3-4 in place of olefinic multiplets in the ^1H NMR spectrum (**Fig. IV.3.2**) were consistent with its structure. The hydroxyl group of **146** was oxidized with PCC[115] to give the aldehyde **147** (IR peak at 1720 cm^{-1} and ^1H NMR resonance at δ 9.75 ppm). Debenzoylation of **147** under alkaline conditions directly produced the furanose **148** possessing a protected hydroxymethyl at the 3-C position. Its IR spectrum showed characteristic hydroxyl band in place of the CHO band. The ^1H NMR spectra of **148** are shown in **Fig. IV.3.3**. The hydroxyl group of compound **148** was acetylated to produce the acetate derivative **149**. The appearance of a ^1H NMR singlet at δ 1.96 and 2.04 (2s, 3H) confirmed the acetate group. Finally, Vorbruggen coupling[163a] of **149** with silylated thymine furnished the 3'-C branched nucleoside **150**.



(i) BzCl, Et_3N, 0 ^oC; (ii) $BH_3.Me_2S$, hexane, H_2O_2, NaOH, 0 ^oC-25 ^oC; (iii) PCC, CH_2Cl_2, 25 ^oC; (iv) K_2CO_3, MeOH, 25 ^oC; (v) Ac_2O, pyridine, 0 ^oC; (vi) Thymine, HMDS, $(NH_4)_2SO_4$, TMSOTf, CH_2Cl_2, 25 ^oC.

Scheme IV.3.1

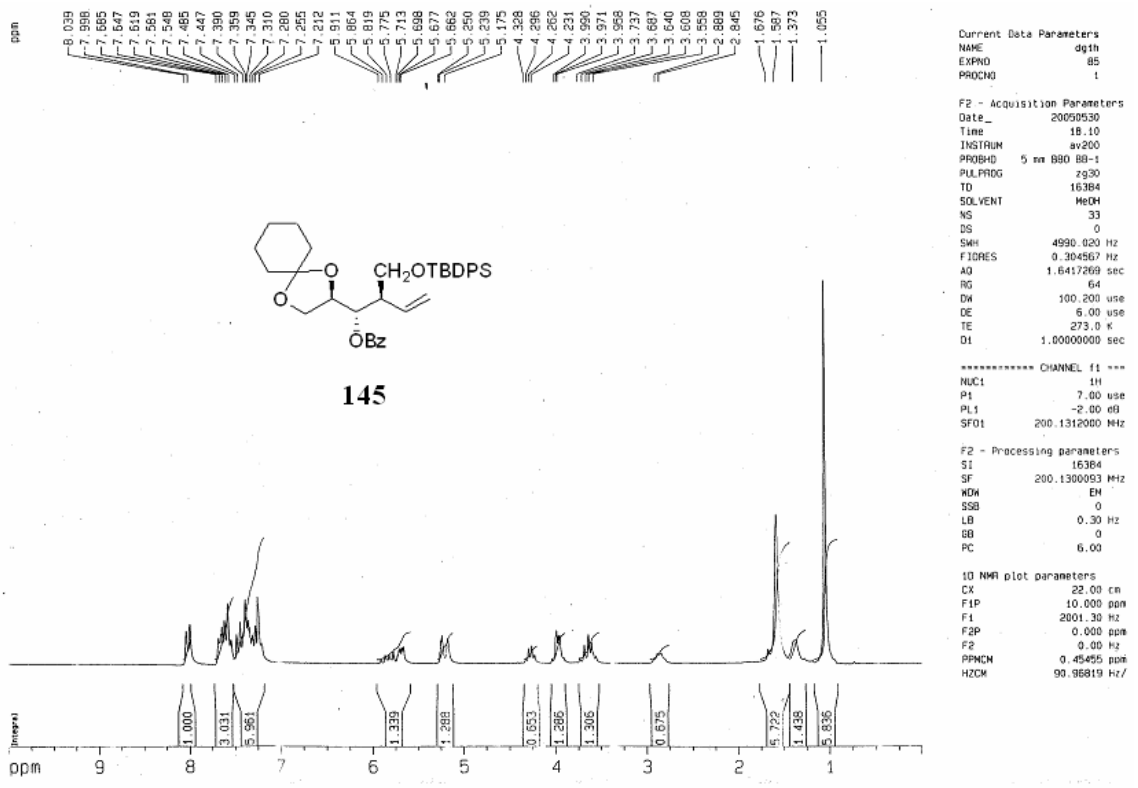


Fig. IV.3.1. ^{1}H NMR spectrum of 145

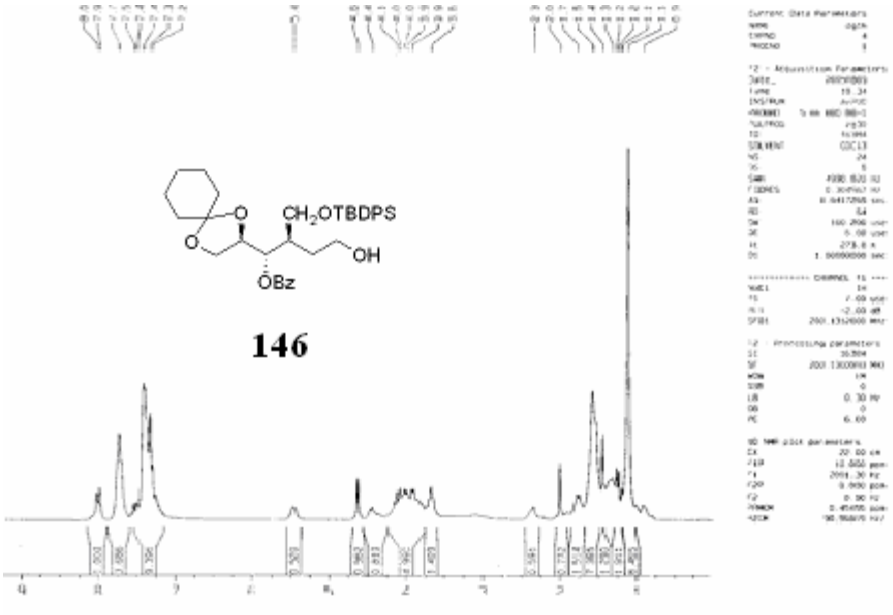


Fig. IV.3.2. ^{1}H NMR spectrum of 146

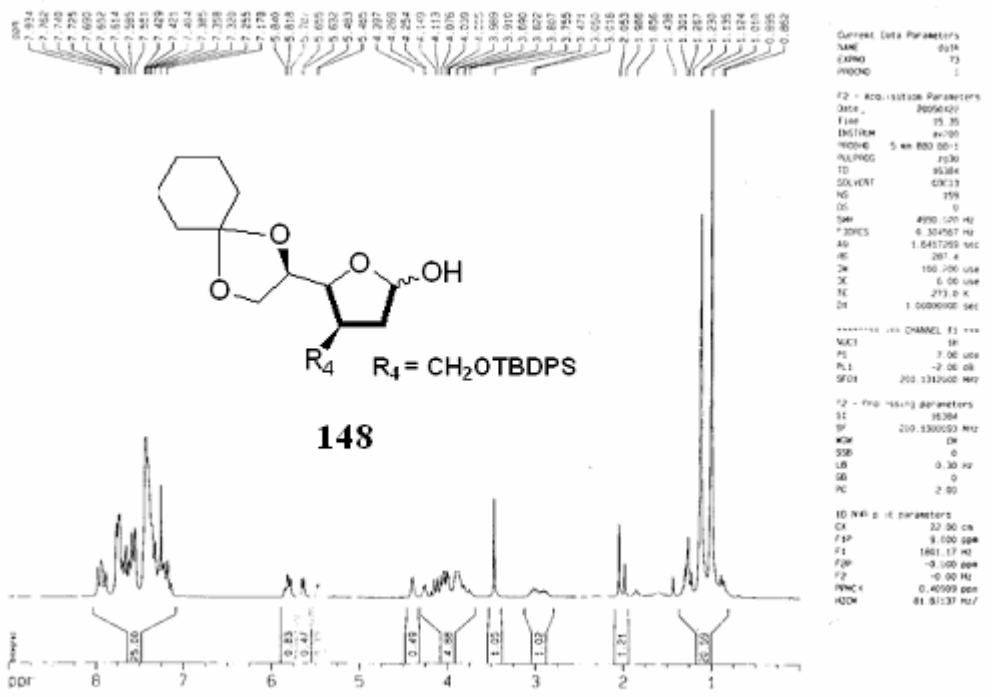


Fig. IV.3.3. ^{1}H NMR spectrum of 148

Overall, a very simple, efficient and stereochemically flexible strategy for the synthesis of 3'-C branched 2',3'-dideoxynucleosides was established. To establish the viability of our strategy, compound **150** has been synthesized as a representative target molecule. Employing a similar strategy, the other stereochemical variations at C-3 and C-4 in the sugar units could be introduced starting from the other stereomers of **83**. In hindsight, the poor 3,4-stereoselectivity for all these reactions of **1** with **82** was exploited to our advantage to have access to all four diastereomers **83a-d** starting from the same combination of substrates, and to achieve a stereodivergent synthesis of dideoxynucleosides.

IV.4: SYNTHESIS OF 2(*S*)-[1(*S*)-AZIDO-2-PHENYLETHYL] OXIRANE

IV.4.1: Introduction

The inhibition of the enzyme HIV-1 protease, which cleaves the *gag* and *gag-pol* polyproteins into the functional proteins of infectious virions, continues to be a major therapeutic target for the treatment of AIDS and related ailments.[166] These HIV-1 protease inhibitors *viz*. amprenavir, fosamprenavir etc. are important in the most frequently used regimen for the treatment of HIV/ AIDS, the highly active antiretroviral therapy (HAART).[167] Hence, it is anticipated that their demand will increase in the near future. This demand is matched by a need of technologies to produce these compounds economically on an industrial scale. Also, since these HIV protease inhibitors often exhibit complex structures equipped with multiple stereogenic centers, development of an efficient and practical synyhetic route for these inhibitors presents a challenge for synthetic organic chemists.

Regarding the synthesis of this class of inhibitors,[168] considerable attention has been focused on the preparation of protected azidoalkyl and aminoalkyl epoxides[169] primarily due to their inevitable role in the construction of ethylene and ethylamine dipeptide isosteres, which are subsequently incorporated into pseudopeptides that are potent inhibitors of HIV-1 proteases. A key epoxide synthon of this category is 2(*S*)-[1(*S*)-Azido-2phenylethyl]oxirane (**VI**), which has been prepared by several groups starting from chiral sources like (*D*)-isoascorbic acid and *D*-tartaric acid.[169d,170] However, a general synthetic methodology for the synthesis of **VI** with required stereochemical control and optical purity is still appreciated, and this prompted us to accomplish a novel and straightforward synthesis using inexpensive reagents and operationally simple procedures.

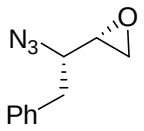
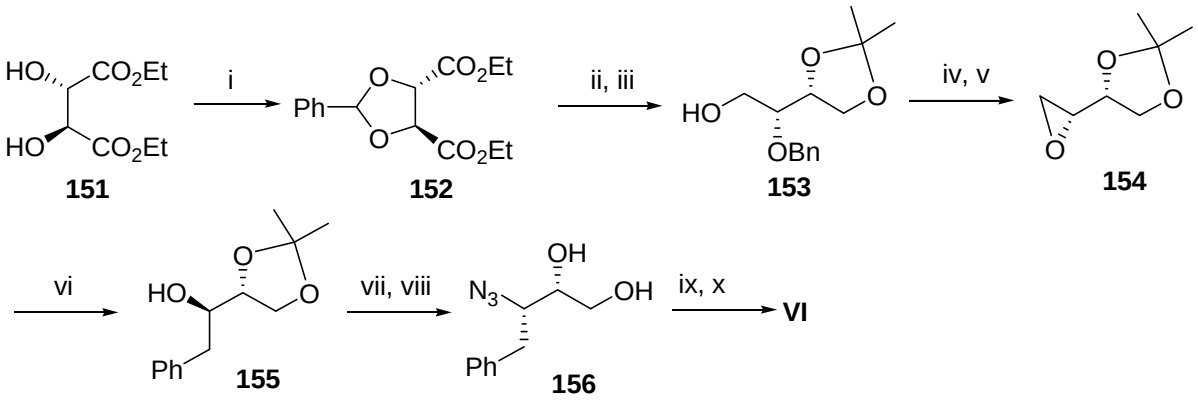


Fig. IV.4.1. Structure of 2(*S*)-[1(*S*)-Azido-2phenylethyl]oxirane (VI)

IV.4.2: Previous syntheses

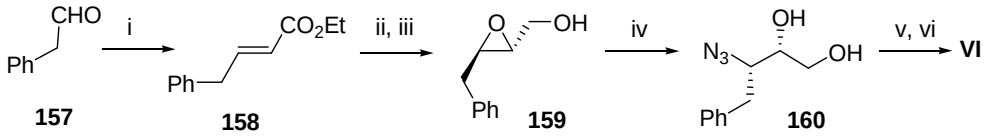
The first enantiospecific synthesis (**Scheme IV.4.1**) of the tile compound **vI** was accomplished by Ghosh *et al*.[169d] starting from optically pure and commercially available diethyl D-tartarate **151.** This was converted to benzylidene acetal **152**. Reductive cleavage of **152** by $LiAlH_4$ afforded the D-threitol derivative, which was converted to isopropylidene derivative **153**. Catalytic hydrogenation of **153** followed by treatment with triphenylphosphine and diethyl azodicarboxylate yielded the epoxide **154**, which was treated with phenylmagnesium bromide to afford **155**. Mitsonobu azidation and subsequent deketalisation of **155** yielded **156**, which was finally converted to the azido oxirane **VI** by treatment with 2-acetoxy-isobutyryl chloride in chloroform followed by exposure of the resulting chloroacetate derivative to sodium methoxide.



(i) PhCHO, triethyl orthoformate, MeC_6H_4-*p*-SO_3H, Δ; (ii) LAH, $AlCl_3$, Et_2O-CH_2Cl_2, Δ ; (iii) MeC_6H_4-*p*-SO_3H, acetone, 23 °C; (iv) H_2, $Pd(OH)_2$, 25 °C; (v) Ph_3P, $EtO_2CN{=}NCO_2Et$, benzene, Δ; (vi) PhMgBr, CuCN, THF, -40°C-0°C; (vii) $(PhO_2)_2P(O)N_3$, Ph_3P, $EtO_2CN{=}NCO_2Et$, THF, -10°C-23°C; (viii) Aqueous 40% AcOH, 90 °C; (ix) $MeCO_2C(Me)_2COCl$, $CHCl_3$, 23°C; (x) NaOMe, THF, 23°C.

Scheme IV.4.1

In another approach (**Scheme IV.4.2**), Bennet *et al.*[170a] synthesized the title compound **VI** starting from phenylacetaldehyde **157**, which was converted to the (*E*)-α,β-unsaturated ester **158**. Reduction of **158** followed by Katsuki-Sharpless asymmetric epoxidation yielded **159** with >95% e.e. Regioselective, nucleophilic azide ring opening of the epoxide **159** gave diol **160**, which after converting to primary tosylate and subsequent treatment with sodium hydride in DMF yielded **VI** in 70% overall yield.

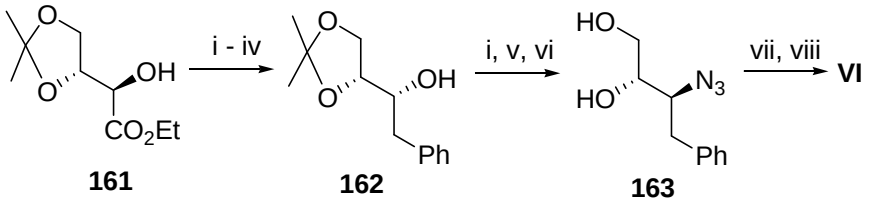


157 **158** **159** **160**

(i) *t*-BuOK, $(EtO)_2P(O)CH_2CO_2Et$, THF, -78 °C; (ii) $(Me_2CHCH_2)_2AlH$, CH_2Cl_2, -78°C-25 °C; (iii) $Ti(OPr^i)_4$, *t*-BuOOH, $_D$-(-)-DET, CH_2Cl_2, -23°C; (iv) $[Ti(OPr^i)_2(N_3)_2]$, benzene, 75°C; (v) *p*-TsCl, cat. DMAP, pyridine, 0 °C; (vi) NaH, DMF, 0 °C.

Scheme IV.4.2

More recently, Park *et al.*[170b] synthesized **VI** (**Scheme IV.4.3**) starting from the acetonide **161** derived from D-isoascorbic acid. Mesylation of **161** followed by reduction of the ester moiety yielded mesylate diol, which was subsequently converted to the oxirane. Addition of PhMgBr to the oxirane produced the alcohol **162**. This was converted to diolazide **163**, which on treatment with 2-acetoxy-isobutyryl chloride in chloroform followed by exposure of the resulting chloroacetate derivative to sodium methoxide yielded **VI** in 60% overall yield.



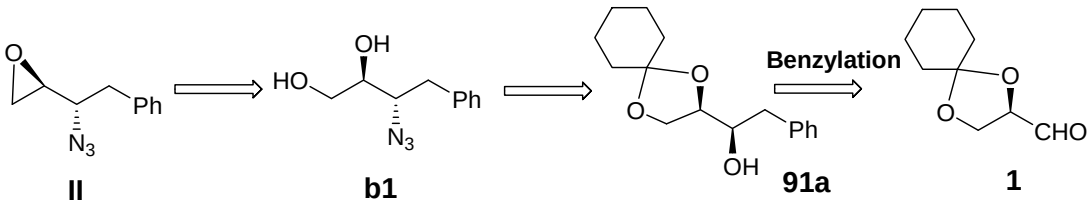
161 **162** **163**

(i) MsCl, pyridine; (ii) $NaBH_4$, MeOH; (iii) NaH, THF, -20 °C-25 °C ; iv) PhMgBr, CuI, THF, -40 °C-0 °C; (v) 1 N HCl, THF; (vi) CsN_3, 18-Cr-6, PhH, Δ; (vii) $MeCO_2C(Me)_2COCl$, $CHCl_3$; (viii) NaOMe, THF, 25 °C.

Scheme IV.4.3

IV.4.3: Present work

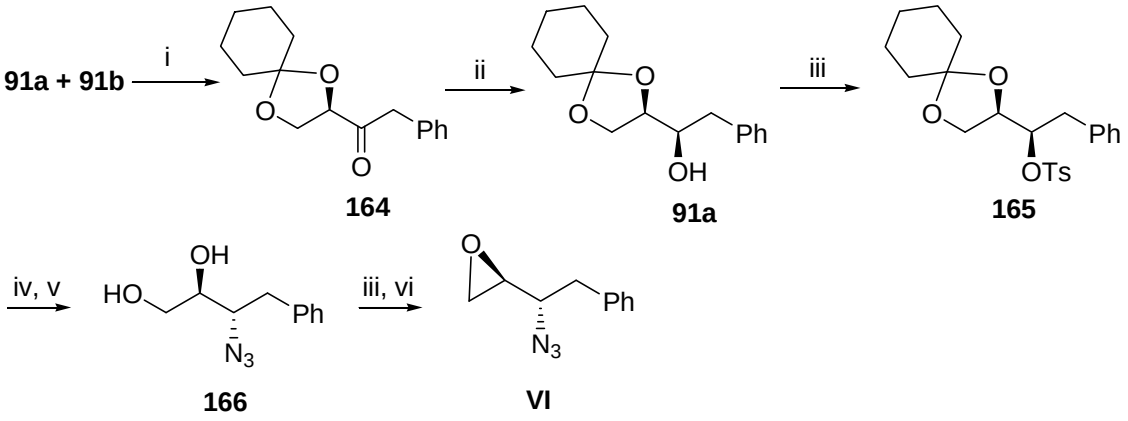
From retrosynthetic analysis of **VI** (**Scheme IV.4.4**) we envisaged that *syn*-selective benzylation of **1** could be a very straightforward approach to directly generate a carbon chain relevant to that existing in the target molecule. The homobenzylic alcohol **91a** can be converted to the azide with inversion of configuration, and ultimately to the title compound by converting its diol functionality to the epoxide. The present work describes our detailed effort in this regard with ultimate objective to synthesize **VI**.



Scheme IV.4.4

In **chapter III.1.2**, it was discussed that benzylation of **1** took place successfully using the combination of Mg and $CuCl_2$, $2H_2O$ producing **91** in moderate yield (68.4%) and much improved *syn* selectivity [*syn*-**91a** : *anti*-**91b** = 80 : 20]. However, due to the inseperability of the diastereomers **91a** and **91b**, it was necessary to develop a method in which the desired *syn*-isomer is produced exclusively. The proportion of *syn*-**91a** in this distereoisomeric mixture has been enriched (**Scheme IV.4.5**) following a known oxidation-reduction protocol.[35c] Accordingly, PCC oxidation of the diastereoismeric mixture (**91a**/**b**) afforded ketone **164.** This was characterized by the appearance of IR carbonyl peak at 1735 cm^{-1}, and also from the ^{13}C NMR peak at δ 207.9 ppm. Compound **164** was reduced with K-selectride® to yield *syn*-**91a** exclusively. **Fig IV.4.2** and **Fig. IV.4.3** represents the ^{1}H and ^{13}C NMR spectra of **91a** respectively. Tosylation of **91a** yielded **165**, which was characterized from the absence of IR peak due to hydroxyl group and also from the appearance of a singlet at δ 2.39 ppm (3H) and a multiplet at δ 4.6 ppm in the ^{1}H NMR spectrum. This was followed by deketalization of the tosylate **165** in acidic condition to afford crude diol, which was reacted with NaN_3 to give azidodiol **166** in good yield. **166** was characterized by recording the melting point and specific rotaion {m.p. 80-81^{0}C, lit.[170b] m.p. 80-82^{0}C; $[\alpha]_D^{25}$ + 30.2 (*c* 1.8, $CHCl_3$); lit.[170b]$[\alpha]_D^{25}$ 30.6 (c 2.0, $CHCl_3$)} and matching with those reported. Also it's ^{1}H and ^{13}C NMR spectra were in conformity with those reported.[170b] Regio-selective, monotosyalation at the primary

hydroxyl of **166** and base treatment of the resulting tosylate furnished the target azido epoxide **VI**. Our synthesized compound **VI** was characterized by the conformity of its spectral and optical data with the reported ones.[169c] Its ^{1}H NMR and ^{13}C NMR are shown in **Fig. IV.4.5** and **Fig. IV.4.6** respectively.



(i) PCC, CH_2Cl_2, 0°C; (ii) K-selectride®, THF, -78°C; (iii) p-TsCl, Pyridine, 0 °C; (iv) Aqueous TFA, MeCN-H_2O, 0 °C; (v) NaN_3, DMF, 90 °C; (vi) K_2CO_3, MeOH, 25 °C.

Scheme IV.4.5

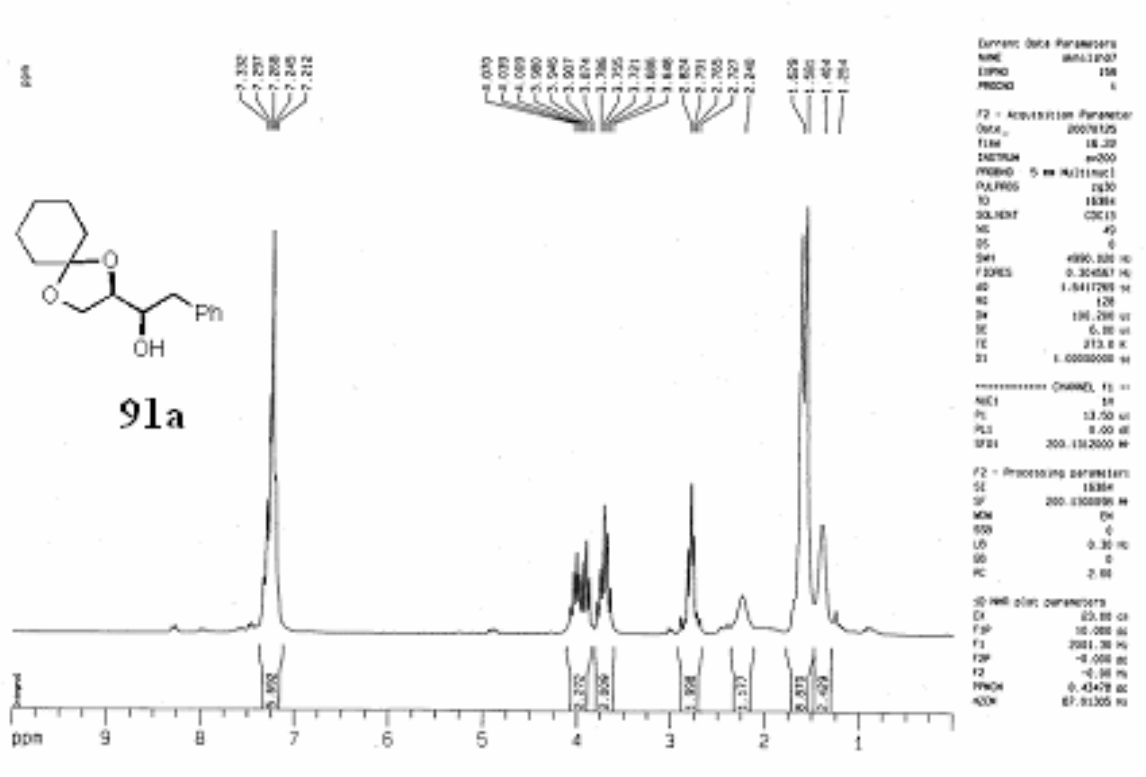


Fig. IV.4.2. ^{1}H NMR spectrum of 91a

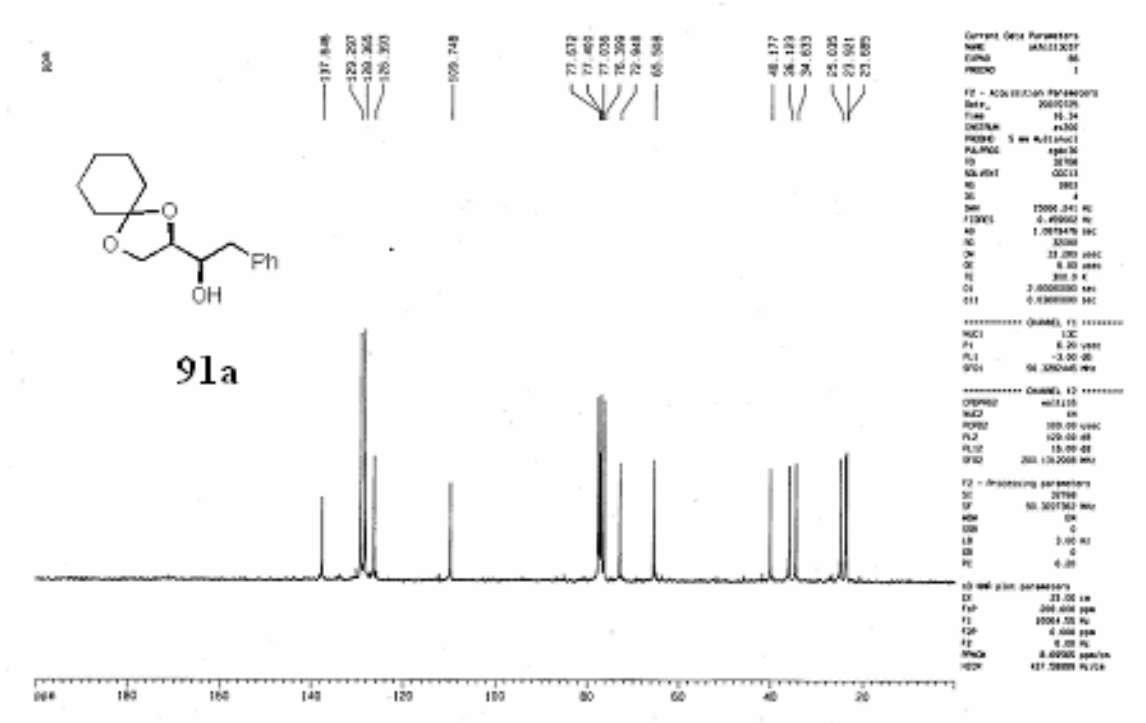


Fig. IV.4.3. ^{13}C NMR spectrum of 91a

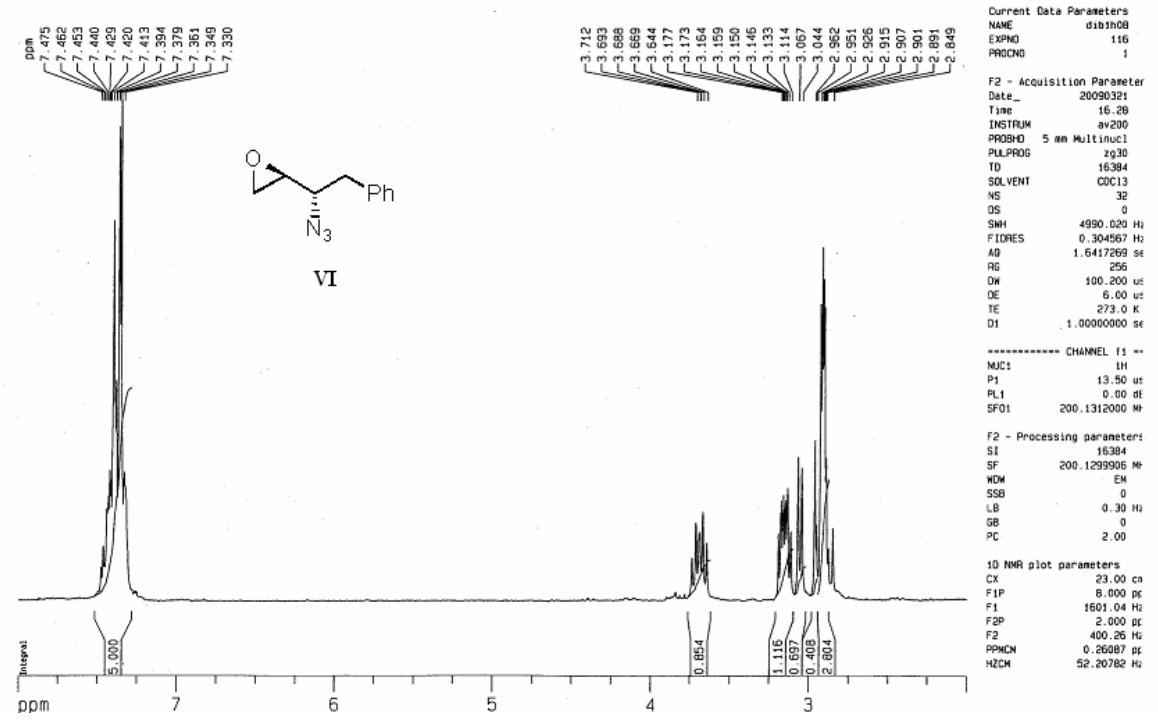


Fig. IV.4.4. ^{1}H NMR spectrum of VI

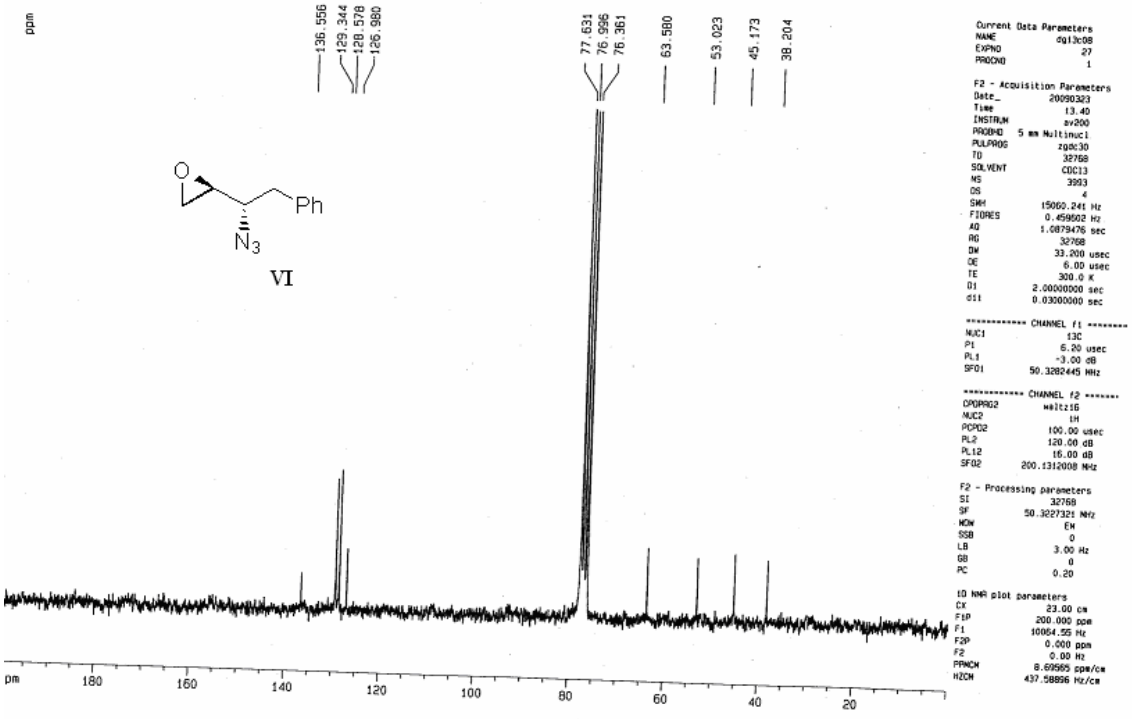


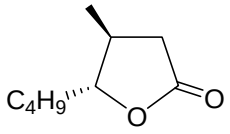
Fig. IV.4.5. ^{13}C NMR spectrum of VI

Thus, easily accessible **1** has been elegantly exploited through its benzylation to accomplish a novel and straightforward synthesis of a key synthon **VI** of protease inhibitors. The cyclohexylidene moiety in **1** played a significant role in this synthesis of **VI** as its stability and bulkiness was responsible for highly stereo-selective reduction of **164** to **91a** *via* oxidation-reduction protocol.

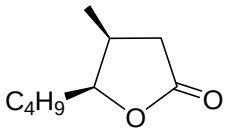
IV.5: SYNTHESIS OF *trans*-OAK LACTONE

IV.5.1: Introduction

The 4,5-disubstituted γ-lactone units are often observed in many variety of biologically relevant molecules. Two of them, the 4*S*,5*R*-(*trans*) and 4*S*,5*S*-(*cis*) isomers of 5-*n*-butyl-4-methyl-4,5-dihydro-2(3*H*)-furanone (**VII** and **VIII**) (**Fig. IV.5.1**), also known as 'oak lactone' or 'whisky lactone', are natural oak components, extracted into wine and spirits during oak barrel maturation.[171] The aroma of alcoholic beverages is believed to be due to the presence of a pure enantiomer of these lactones. The *cis*- and *trans*-configurations of the methyl and butyl groups have been determined by ^{1}H NMR spectroscopy, and the absolute configurations were assigned on the basis of an empirical correlation.[172] Hence, development of strategies to prepare **VII** and **VIII** can also be useful towards the synthesis of other biomolecules possessing a similar γ-lactone moiety.



trans-Oak lactone (**VII**)



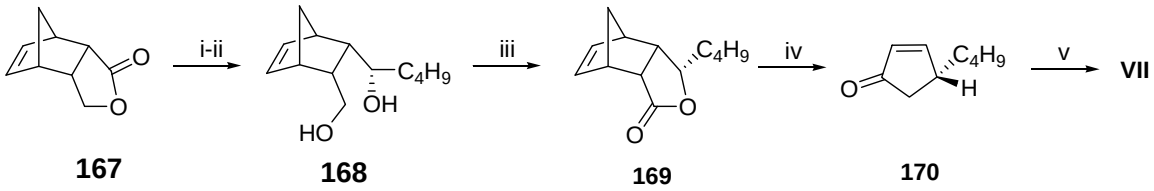
cis-Oak lactone (**VIII**)

Fig. IV.5.1. Structure of *cis*- and *trans*-Oak lactones.

IV.5.2: Previous syntheses

So far, several approaches for the synthesis of **VII** and **VIII** have been reported.[173] In one of the early synthesis,[173b] *trans*-oak lactone (**VII**) was prepared using asymmetric enzymatic reduction of ketones. Suzuki *et al.*[173d] synthesized **VII** starting from the chiral bicyclic lactone (+)-**167**, prepared from D-mannitol. Nucleophilic addition of *n*-BuLi to

167 and subsequent reduction gave **168**. A tetra-*n*-propylammonium perruthenate (TPAP) catalyzed oxidation of **168** in the presence of 4- methylmorpholine *N*-oxide (NMO) gave the diastereomeric lactone **169.** This on retro-Diels–Alder reaction in refluxing *o*-dichlorobenzene (ODCB) gave enantiomeric gave the 4-substituted butenolide (−)-**170**. Finally, stereoselective 1,4-addition of dimethylcuprate furnished **VII** (**Scheme IV.5.1**).

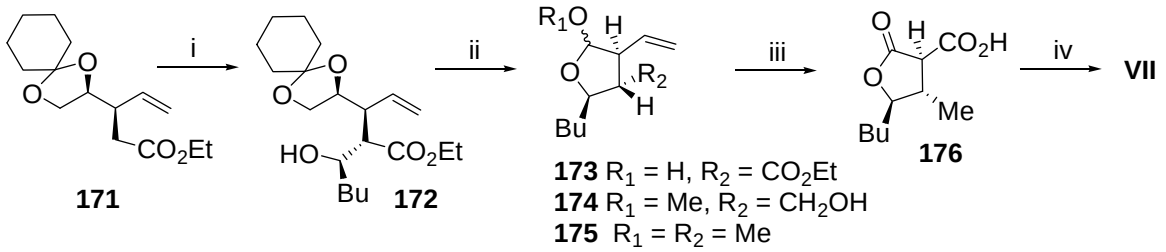


167 **168** **169** **170**

(i) *n*-BuLi, toluene, -78 ^{o}C; (ii) L-Selectride®, toluene, -78 ^{o}C; (iii) Cat. TPAP, NMO, molecular sieves, CH_2Cl_2, 25 ^{o}C; (iv) ODCB, Δ; (v) MeLi, CuI, Et_2O, -78 ^{o}C.

Scheme IV.5.1

More recently,[173e] the Li-enolate of the succinate **171** derived from D-mannitol was reacted with *n*-pentanal to afford **172** as the major isomer. Its acid-catalyzed deketalisation followed by periodate cleavage of the resulting diol produced a 1:1 anomeric mixture of the lactol **173**, which on O-methylation and $LiAlH_4$ reduction gave the alcohol **174**. Its tosylation followed by reduction produced compound **175**. Deacetalization of **175** followed by RuO_4 oxidation gave the lactone acid **176**, which on decarboxylation under heating produced **VII** (**Scheme IV.5.2**).



(i) LDA, THF, HMPA, *n*-pentanal, -70 ^{o}C; (ii) (a) AcOH-H_2O, $NaIO_4$, 25 ^{o}C; (b) MeOH, HCl, 25 ^{o}C; (c) LAH, Et_2O, 25 ^{o}C; (d) TsCl, CH_2Cl_2, pyridine, DMAP, 0 ^{o}C; (e) LAH, THF, 25 ^{o}C; (iii) (a) AcOH-H_2O, 50 ^{o}C; (b) $RuCl_3.3H_2O$, $NaIO_4$, CH_3CN, H_2O, CCl_4, 25 ^{o}C.

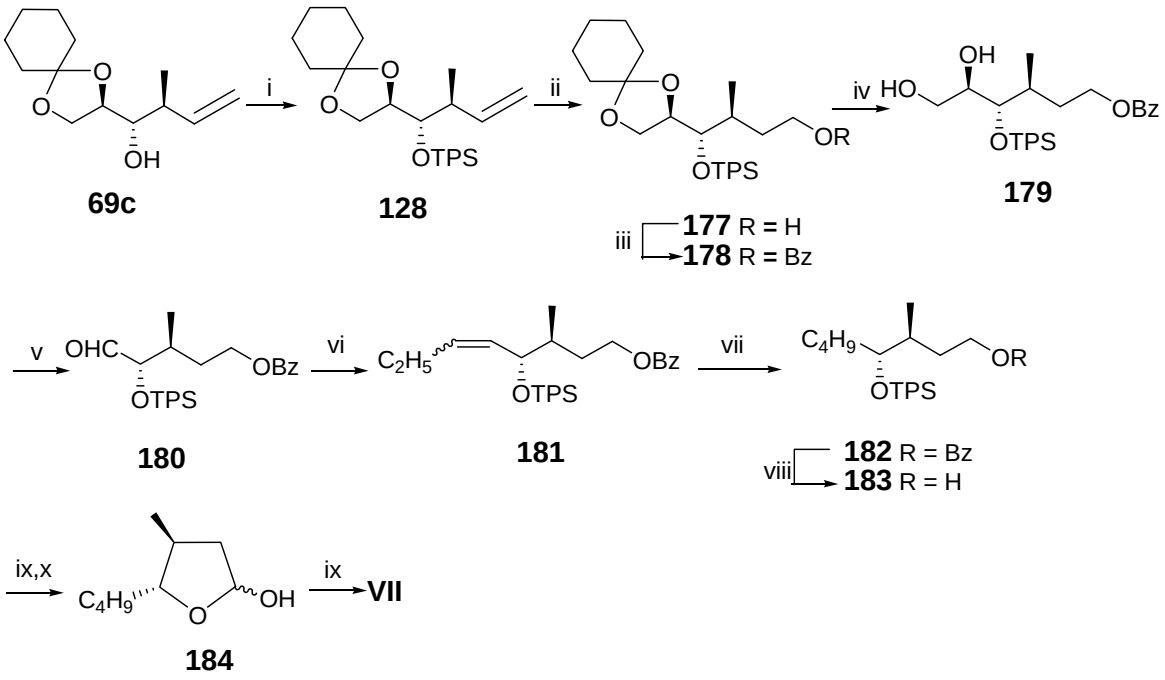
Scheme IV.5.2

IV.5.3: Present work

In spite of their elegance, the earlier protocols were not conducive, since these used reagents that are either expensive and/ or involved several steps. Hence using *trans*- oak lactone (**VII**) as a model target, we developed its shorter and simpler synthesis than those reported in literature**.**

For the synthesis (**Scheme IV.5.4**), the homoallylic alcohol **69c**, obtained as the major diastereomer via Ga-mediated crotylation of **1** in [bmim][Br] (discussed in the previous chapter) appeared suitable for its elaboration to the target compound **III**. The synthesis of **VII** started with the silyl derivative **128** of **69c**. Hydroxylation of its terminal olefin afforded the alcohol **177** in good yield. The formation of **177** was confirmed from the absence of the olefinic peaks in both ^{1}H (**Fig. IV.5.2**) and ^{13}C NMR (**Fig. IV.5.3**) spectra, as well as appearance of the IR hydroxyl peak at 3435 cm^{-1}. This was benzoylated to get **178**, which showed IR peak at 1719 cm^{-1}. The formation of **178** was also confirmed

from the appearance of ^{13}C NMR peak at δ 166.2 ppm. Compound **178** was deketalized under acidic conditions to afford diol **179**. A broad IR peak at 3448 cm^{-1}, and the absence of the NMR resonances due to cyclohexyl group confirmed its formation. $NaIO_4$ cleavage of **179** yielded the aldehyde **180**, which showed IR peak at 1723 cm^{-1}, and also ^{1}H and ^{13}C NMR resonances due to –CHO group at δ 9.61-9.66 and 204.0 ppm respectively. Subsequent Wittig olefination of the aldehyde **180** with $C_3H_7PPh_3Br$ yielded **181**, which showed the olefinic signal at δ 5.29-5.45 (m, 2H) in ^{1}H NMR spectrum. Compound **181** was catalytically hydrogenated to give **182**. Its formation was confirmed from the absence of the olefinic resonances in both ^{1}H and ^{13}C NMR spectra. A base-catalyzed debenzoylation of **182** gave the alcohol **183**. It was characterized from the presence of IR peak at 3471 cm^{-1} (OH) and ^{1}H and ^{13}C NMR spectra of **183** (**Fig. IV.5.4** and **Fig. IV.5.5** respectively). Oxidation of **183** with PCC yielded the crude aldehyde, which was desilylated to afford lactol **184**. Compound **184** was unstable, and hence was immediately oxidized with PCC to get the desired *trans*-oak lactone (**VII)**. The spectral and optical data were matching with those reported.[173e]



69c 128 179 180 181 184

(i)TBDPSCl, Et_3N, CH_2Cl_2, 25 ^oC; (ii) $Me_2S.BH_3$, hexane, NaOH-H_2O_2, 0 ^oC-25 ^oC ; (iii) BzCN, Pyridine, CH_2Cl_2, 0 ^oC; (iv) 80% aq. CF_3COOH, 0 ^oC, CH_2Cl_2; (v) $NaIO_4$, MeCN:H_2O (3:2), 25 ^oC; (vi) *n*-$C_3H_7PPh3^+Br^-$, *n*-BuLi, THF, -60 ^oC; (vii) 10% Pd-C, EtOH, 25 ^oC; (viii) K_2CO_3, MeOH, 25 ^oC; (ix) PCC, CH_2Cl_2, 25 ^oC; (x) TBAF, THF, 0 ^oC.

Scheme IV.5.4

Thus, the crotylated product (**69c**) of **1** was judiciously exploited for a simple synthesis of a oak lactone component **III**, a representative example of chiral 4,5-disubstituted γ-lactones. It is worth mentioning that our route was shorter, simpler and more straightforward compared to the reported procedures for the synthesis of the same molecule **III** staring from **1**. Understandably, following the same route the other enantiomer of **III** can be obtained starting from the other major product **69b**.

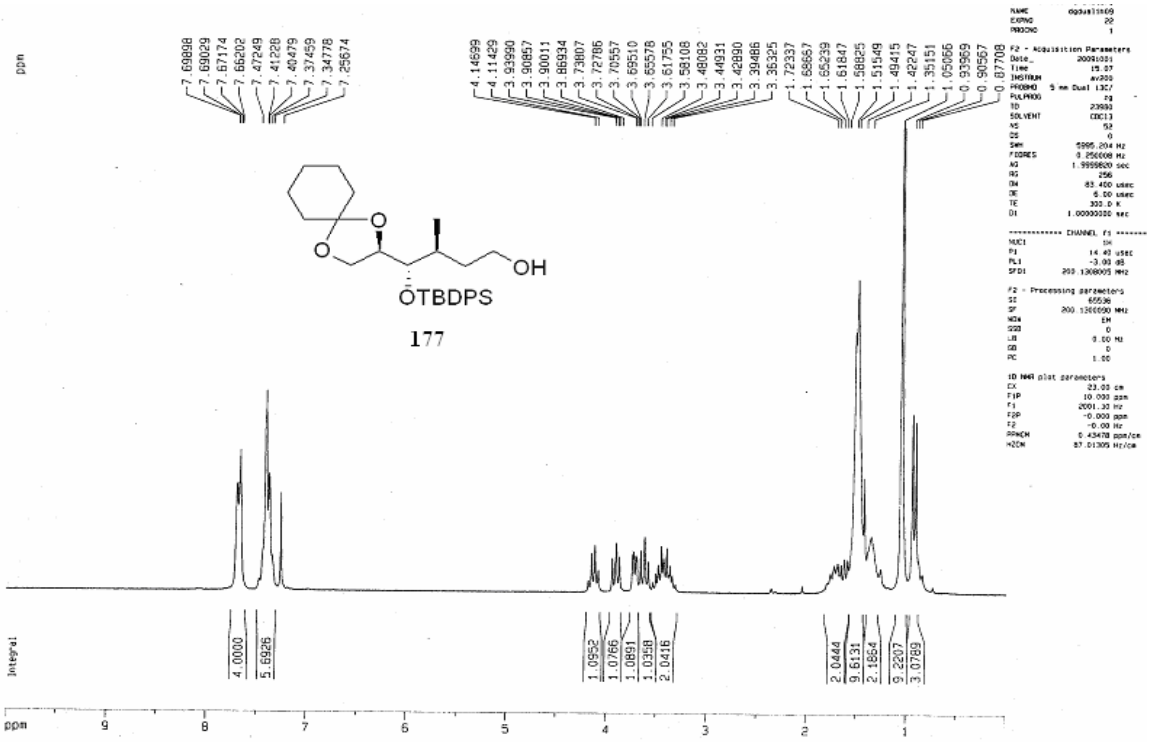


Fig. IV.5.2. ^{1}H NMR spectrum of 177

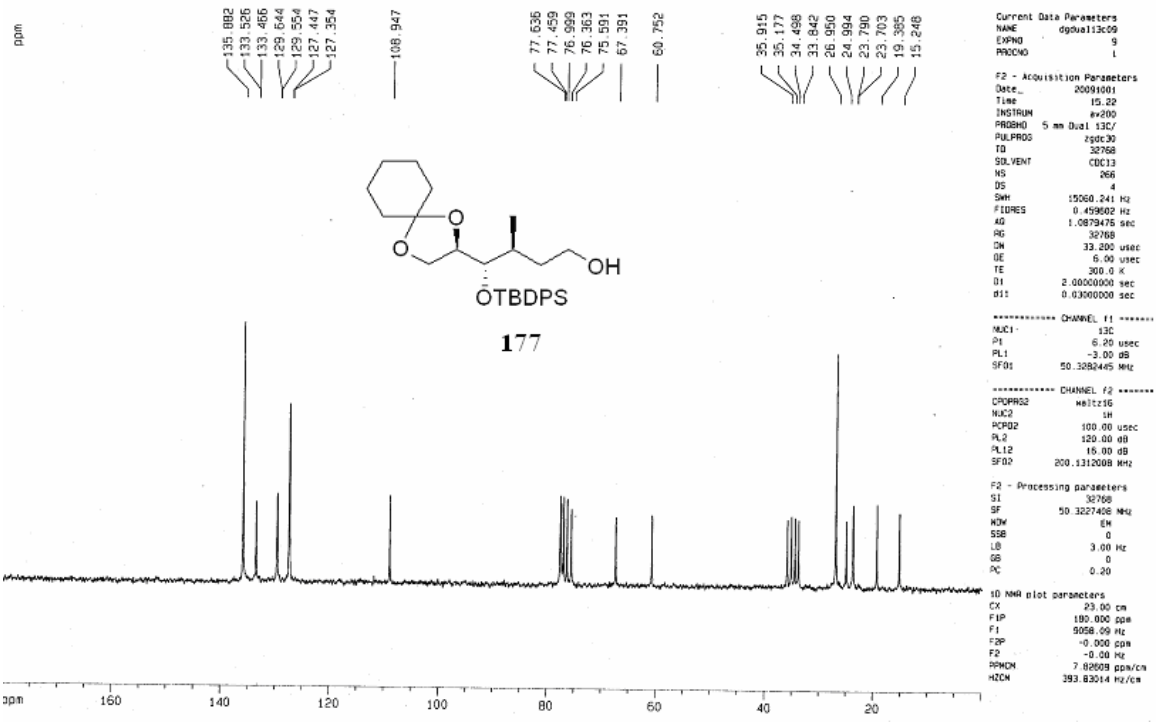


Fig. IV.5.3. ^{13}C NMR spectrum of 177

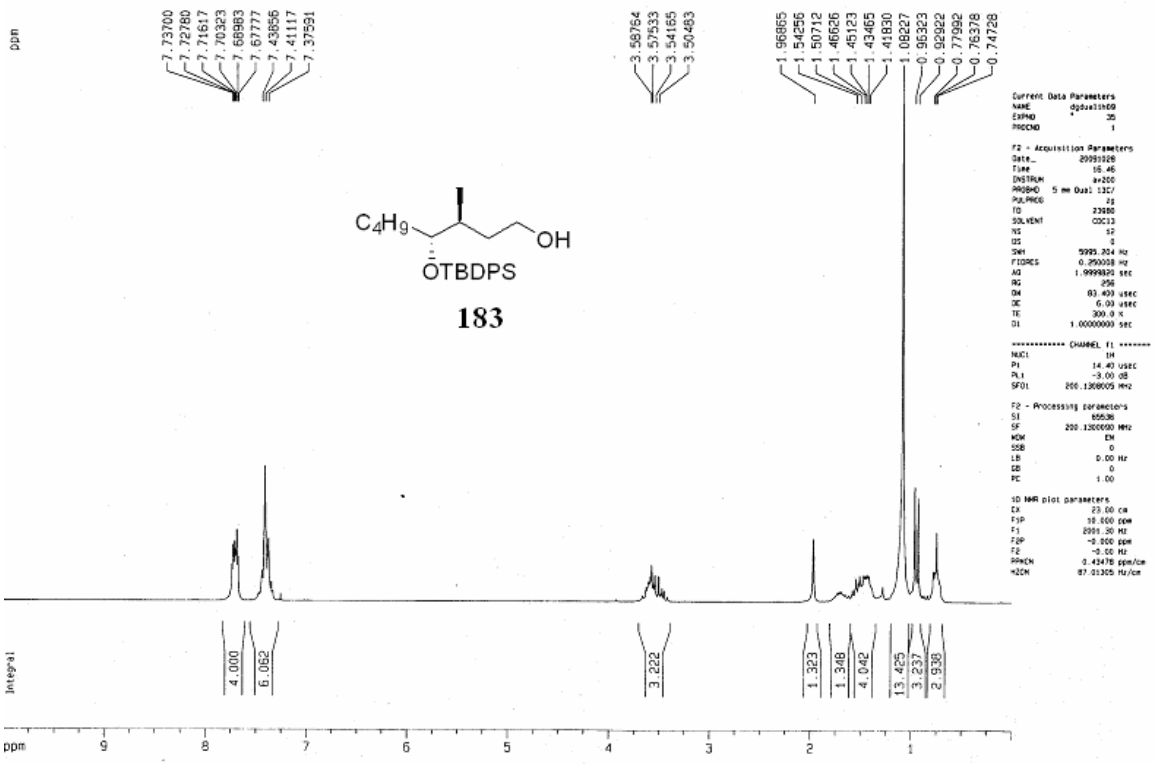


Fig. IV.5.4. ^{1}H NMR spectrum of 183

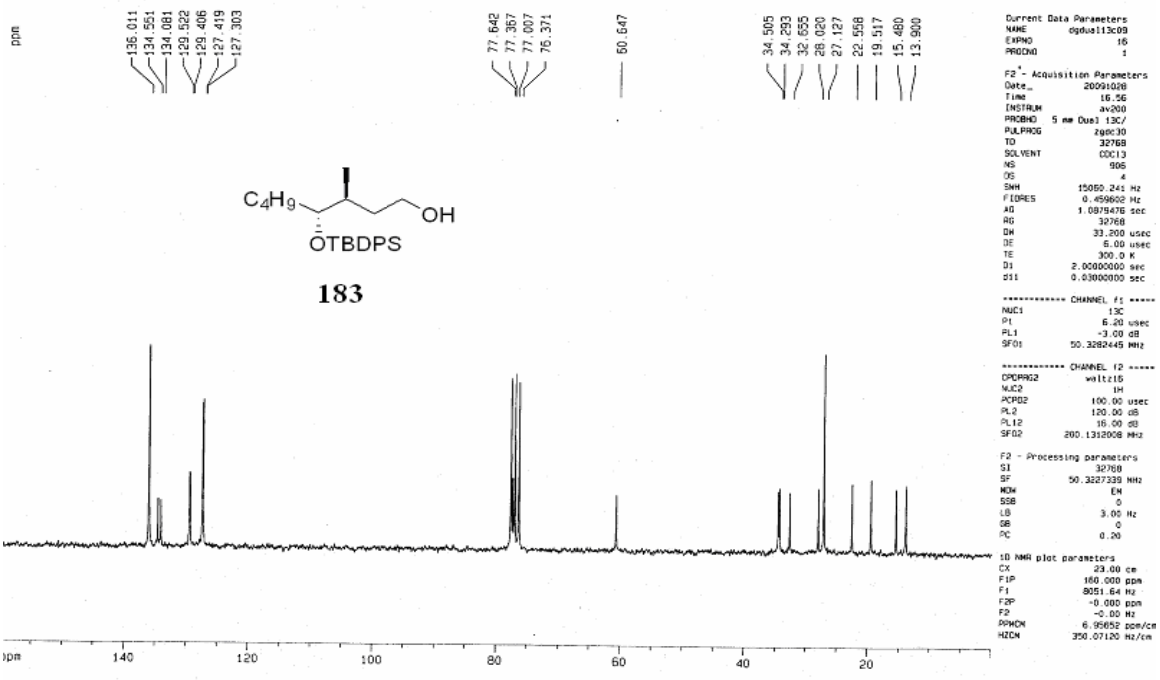


Fig. IV.5.5. ^{13}C NMR Spectrum of 183

IV.6 EXPERIMENTAL SECTION

(2*R*,3*S*,4*R*)-1,2-Cyclohexylidenedioxy-3-tosyloxy-4-vinyl-decane 105 : To a cooled (0 ^{o}C) and stirred solution of compound **79c** (3.0 g, 10.13 mmol) in pyridine (10 mL) was dropwise added a solution of *p*-TsCl (2.32 g, 12.16 mmol) in pyridine (15 mL) and the solution was stirred for 3 h (*cf*. TLC). Water and EtOAc was added to the mixture, the organic layer separated and the aqueous layer extracted with EtOAc (100 mL). The combined organic extracts were washed with aqueous HCl, water and brine, and dried. Solvent removal in vacuo and chromatographic purification (silica gel, 0-15% EtOAc/Hexane) of the crude residue afforded pure **105**. Yield: 3.65 g (80%); colourless oil; $[\alpha]_D^{24}$ +11.32 (*c* 1.2, $CHCl_3$); IR: 1365, 1177, 1096, 930 cm^{-1}; ^{1}H NMR: δ 0.85 (t, *J* = 6.6 Hz, 3H), 1.16-1.40 (m, 21H), 2.42 (s, 3H), 3.74-3.91 (m, 2H), 4.01-4.11 (m, 1H), 4.66 (dd, *J* = 7.4 and 2.2 Hz, 1H), 4.99-5.09 (m, 2H), 5.45-5.63 (m, 1H), 7.30 (d, *J* = 8.2 Hz, 2H), 7.76 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR: δ 13.8, 21.3, 22.4, 23.6, 23.7, 24.9, 26.8, 28.8, 30.5, 31.4, 34.6, 35.9, 45.7, 66.2, 74.0, 84.9, 109.5, 118.0, 127.4, 129.5, 134.4, 136.3, 144.4. Anal. Calcd. for $C_{25}H_{38}O_5S$: C, 66.63 H, 8.50 S, 7.12%. Found, C, 66.42; H, 8.61; S, 6.98%.

(2*R*,3*S*,4*R*)-3-Tosyloxy-4-vinyl-decan-1,2-diol 106 : To a cooled (0 ^{o}C) and stirred solution of **105** (3.1 g, 6.89 mmol) in CH_2Cl_2 (30 mL) was added aqueous TFA (10 mL) in portions. When the reaction was complete (~2.5 h, *cf*. TLC), the mixture was treated with $NaHCO_3$, and water, and the mixture thoroughly extracted with $CHCl_3$ (50 mL). The combined organic extracts were washed with water and brine, and dried. Removal of solvent in vacuo followed by column chromatography (silica gel, 0-5% MeOH/$CHCl_3$) of the residue afforded **106**. Yield: 1.92 g (78%); colourless oil; $[\alpha]_D^{24}$ +7.24 (*c* 1.6, CHCl3);

IR: 3417, 1358, 1175, 1045, 922 cm^{-1}; ^1H NMR: δ 0.84 (t, *J* = 7.0 Hz, 3H), 1.07-1.24 (m, 11H), 2.43 (s, 3H), 2.65 (broad s, 2H), 3.56-3.71 (m, 2H), 3.81-3.89 (m, 1H), 4.57 (dd, *J* = 8.0 and 2.2 Hz, 1H), 4.97-5.10 (m, 2H), 5.28-5.72 (m, 1H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.78 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR: δ 14.0, 21.6, 22.6, 27.0, 29.0, 31.4, 31.6, 45.0, 62.1, 70.7, 84.2, 118.5, 127.8, 129.8, 133.7, 136.4, 145.1.

(2*R*,4*R*)-4-vinyl-decan-1,2-diol 107 : To a suspension of $LiAlH_4$ (0.35 g, 9.31 mmol) in dry THF (50 mL) was added a solution of **106** (1.5 g, 4.05 mmol) in dry THF (50 mL). The reaction mixture was stirred at reflux for 3 h and gradually brought to 0 °C. The excess hydride was decomposed with aqueous saturated Na_2SO_4 solution, and the mixture extracted with Et_2O (50 mL). The combined ethereal extracts were dried, concentrated under reduced pressure, and the residue was purified by flash chromatography (silica gel, 0-20% EtOAc/hexane) to give pure **107**. Yield: 0.51 g (63%); colourless oil; $[\alpha]_D^{24}$ +1.5 (*c* 0.4, $CHCl_3$); IR: 3375 cm^{-1}; ^1H NMR: δ 0.86 (broad t, *J* = 6.6 Hz, 3H), 1.24-1.45 (m, 11H), 2.12-2.35 (m, 4H), 3.40-3.45 (m, 1H), 3.56-3.73 (m, 2H), 4.98-5.10 (m, 2H), 5.40-5.53 (m, 1H); ^{13}C NMR: δ 14.0, 22.6, 27.0, 29.3, 31.8, 35.6, 38.1, 40.5, 67.2, 70.1, 115.3, 142.5. Anal. Calcd. for $C_{12}H_{24}O_2$: C, 71.95 H, 12.08%. Found, C, 72.12; H, 12.14%.

***R*-4-vinyl-decane 109** : To a cooled (0 ^oC) and stirred solution of **107** (0.4 g, 2.0 mmol) in Et_3N (10 mL) was added mesyl chloride (0.57 g, 5.0 mmol) and the solution was stirred for 3 h. After completion of reaction (*cf*. TLC), water and EtOAc were added to the mixture, the organic layer separated and the aqueous layer extracted with EtOAc (50 mL). The combined organic extracts were washed with water and brine, and dried. Removal of solvent in vacuo afforded **108**, which was used as such for the next step.

As described earlier, compound **108** was reduced with $LiAlH_4$ (0.21 g, 5.4 mmol) in dry THF (20 mL). Usual work-up followed by flash chromatography (silica gel, 0-20% EtOAc/hexane) gave pure **109**. Yield: 0.21 g (65%); colourless oil; $[\alpha]_D^{24}$ - 4.3 (*c* 0.8, $CHCl_3$); IR: 2957, 909 cm^{-1}; ^1H NMR: δ 0.88 (t, *J* = 6.0 Hz, 6H), 1.17-1.38 (m, 14H), 1.98-2.06 (m, 1H), 4.89-5.02 (m, 2H), 5.71-5.91 (m, 1H); ^{13}C NMR: δ 14.0, 22.3, 22.6, 28.9, 29.1, 29.3, 29.5, 31.9, 33.8, 34.1, 114.0, 139.1. Anal. Calcd. for $C_{12}H_{24}$: C, 85.63 H, 14.37%. Found, C, 85.78; H, 14.29%.

(R)-2-propyloctanoic acid V : Ozone was bubbled through a cooled (-78 ^oC) solution of **109** (0.15 g, 0.89 mmol) and methanolic NaOH (1.0 mL, 2.5 M) in CH_2Cl_2 (10 mL) for 20 min. After stirring for 3 h, the mixture was diluted with $CHCl_3$ and water, and brought to room temperature. The organic layer was separated and the aqueous layer extracted with $CHCl_3$. The combined organic extracts were washed with water and brine, and dried. Removal of solvent in vacuo afforded crude ester residue.

To a solution of the ester in MeOH (10 mL) was added a methanolic NaOH (5.0 mL, 2.0 M) and the solution stirred till the ester was completely consumed (*cf*. TLC). Fter concentration under vacuum, the mixture was diluted with water and extracted with Et_2O (30 mL). The aqueous phase containing the sodium salt of the acid was separated, cooled (0 ^oC) and acidified to pH 2 with aqueous HCl. The mixture was extracted with EtOAc (30 mL). The extract was dried and the solvent was removed to afford the pure acid **V**. Yield: 0.12 g (71% in two steps); white solid; $[\alpha]_D^{24}$ -5.7 (*c* 0.7, CH_2Cl_2); IR: 2986 (broad), 1714 cm^{-1}; ^1H NMR: δ 0.89 (broad t, *J* = 6.8 Hz, 6H), 1.10-1.69 (m, 14H), 2.32-2.43 (m, 1H), 11.3 (broad s, 1H); Anal. Calcd. for $C_{11}H_{22}O_2$: C, 70.92 H, 11.90%. Found, C, 70.79; H, 11.81%.

(2*R*,3*S*,4*S*)-3-(*tert*)-Butyldiphenylsilyloxy-1,2-cyclohexylidenedioxy-4-methylhex-5-ene 128. To a solution of **69c** (1.44 g, 6.37 mmol) and imidazole (0.828 g, 12.18 mmol) in CH_2Cl_2 (30 mL) was added TBDPSCl (2.51 g, 9.15 mmol), and the mixture stirred for 12 h at room temp. After completion of the reaction (*cf*. TLC), it was poured into water (20 mL) and extracted with $CHCl_3$ (15 mL). The organic extract was washed with water and brine, dried, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 0-5% EtOAc/hexane) to give pure **128**. Yield: 2.75 g (93%); colourless oil; $[\alpha]_D^{23}$ +31.8 (*c* 2.31, $CHCl_3$); IR: 1586, 998, 909 cm^{-1}; ^1H NMR: δ 0.93 (d, *J* = 7.0 Hz, 3H), 1.05 (s, 9H), 1.23-1.51 (m, 10H), 2.28-2.37 (m, 1H), 3.70-3.86 (m, 3H), 4.01-4.10 (m, 1H), 4.96-5.01 (m, 2H), 5.81-5.98 (m, 1H), 7.22-7.26 (m, 6H), 7.68-7.77 (m, 4H); ^{13}C NMR: δ 14.2, 19.6, 23.9, 24.0, 25.3, 26.9, 27.2, 34.7, 36.2, 40.9, 66.6, 76.1, 77.8, 108.9, 114.7, 127.5, 127.6, 129.7, 129.8, 133.8, 133.9, 135.6, 136.2, 140.4. Anal. Calcd. for $C_{29}H_{40}O_3Si$: C, 74.95; H, 8.68%. Found: C, 75.10; H, 8.56%.

(2*R*,3*S*,4*R*)-3-(*tert*)-Butyldiphenylsilyloxy-4,5-cyclohexylidenedioxy-2-methylpentanal 129. Ozone was bubbled through a cooled (-78 °C) solution of **128** (2.55 g, 5.49 mmol) in CH_2Cl_2 (20 mL) till the solution turned blue. After 0.5 h, the excess O_3 was removed by purging with N_2 (gas), the mixture treated with Ph_3P (6.0 g, 22.89 mmol), and stirred for 16 h at room temperature. Most of solvent was removed in vacuo, the residue was dissolved in hexane (30 mL) and chormatographed (silica gel, 0-10% EtOAc/hexane) to furnish pure **129**. Yield: 2.08 g (81%); colourless oil; $[\alpha]_D^{22}$ +8.2 (*c* 1.00, $CHCl_3$); IR: 1726 cm^{-1}; ^1H NMR: δ 1.01 (s, 9H), 1.16-1.28 (m containing a d at δ 1.26, *J* = 7.0 Hz, 5H), 1.41-1.48 (m, 8H), 2.68-2.71 (m, 1H), 3.42-3.48 (m, 1H), 3.74-3.81 (m, 1H), 4.12-4.22 (m, 2H), 7.32-7.42 (m, 6H), 7.56-7.71 (m, 4H), 9.55 (d, *J* = 1.2 Hz, 1H); ^{13}C NMR: δ 7.4,

19.5, 23.8, 23.9, 25.1, 26.9, 34.6, 36.2, 49.9, 67.6, 73.9, 76.1, 109.6, 127.6, 127.9, 129.9, 130.2, 132.2, 133.4, 135.9, 136.2, 204.8. Anal. Calcd. for $C_{28}H_{38}O_4Si$: C, 72.06; H, 8.21%. Found: C, 71.85; H, 8.45%.

(4*R/S*,5*S*,6*S*,7*R*)-6-(*tert*)-Butyldiphenylsilyloxy-7,8-cyclohexylidenedioxy-5-methyloct-1-en-4-ol 130. To a cooled (10 °C) and stirred mixture of **129** (1.95 g, 4.17 mmol), Zn dust (0.543 g, 8.34 mmol) and allyl bromide (1.01 g, 8.34 mmol) in THF (25 mL) was dropwise added aqueous saturated NH_4Cl (8 mL) in 30 min. The mixture was stirred for 4 h at ambient temperature until the aldehyde was totally consumed (TLC). The mixture was filtered, the precipitate thoroughly washed with EtOAc, the aqueous layer separated, acidified with 5% aqueous HCl, and the clear solution extracted with EtOAc (30 mL). The organic extract was washed successively with aqueous 10% $NaHCO_3$, H_2O and brine, and dried. Solvent removal in vacuo gave a residue which was column chromatographed (silica gel, 0-25% EtOAc/ hexane) to isolate **130** as an inseparable diastereomeric mixture. Yield: 1.61 g (76%); colourless oil; IR: 3443 cm^{-1}; ^1H NMR: δ 1.06 (overlapping s and d, J = 7.2 Hz, 12H), 1.29-1.43 (m, 10H), 1.54-1.85 (m, 3H), 1.98-2.21 (m, 1H), 3.47-3.62 (m, 3H), 4.04-4.17 (m, 2H), 4.87-4.99 (m, 2H), 5.80-5.96 (m, 1H), 7.26-7.45 (m, 6H), 7.61-7.70 (m, 4H); ^{13}C NMR: δ 6.3, 11.1, 19.3, 23.8, 24.9, 27.1, 34.9, 35.0, 35.8, 39.6, 42.4, 43.5, 68.3, 68.7, 71.8, 72.7, 74.1, 74.5, 74.6, 79.9, 109.9, 110.2, 116.7, 127.6, 129.0, 133.2, 133.5, 133.6, 134.9, 135.3, 135.4, 136.0. Anal. Calcd. for $C_{31}H_{44}O_4Si$: C, 73.18; H, 8.72%. Found: C, 72.93; H, 8.63%.

(5*R*,6*S*,7*R*)-6-(*tert*)-Butyldiphenylsilyloxy-7,8-cyclohexylidenedioxy-5-methyloct-1-en-4-one 131. To a cooled (0 °C) and stirred suspension of PCC (1.02 g, 4.68 mmol) and NaOAc (0.09 g, 1.11 mmol) in CH_2Cl_2 (20 mL) was added the alcohol **130** (1.59 g, 3.12

mmol) in one lot. After stirring for 3 h, the reaction mixture was diluted with Et_2O (30 mL), and the supernatant passed through a pad of silica gel (2″ x 1″). Removal of solvent in vacuo followed by column chromatography of the residue (silica gel, 0-10% EtOAc/hexane) furnished pure **131**. Yield: 1.40 g (88%); colourless oil; $[\alpha]_D^{22}$ +2.62 (*c* 2.03, $CHCl_3$); IR: 1741 cm^{-1}; ^1H NMR: δ 1.05 (s, 9H), 1.14 (d, *J* = 7.2 Hz, 3H), 1.41-1.63 (m, 10H), 2.50-2.72 (m, 1H), 2.84 (dd, *J* = 7.2, 11.4 Hz, 2H), 3.62 (t, *J* = 7.2 Hz, 1H), 3.94-4.16 (m, 2H), 4.18-4.23 (m, 1H), 4.82-5.07 (m, 2H), 5.64-5.84 (m, 1H), 7.24-7.46 (m, 6H), 7.62-7.74 (m, 4H); ^{13}C NMR: δ 9.0, 19.3, 23.8, 25.1, 27.0, 34.3, 35.8, 45.5, 51.2, 67.6, 74.9, 75.2, 109.6, 117.7, 127.8, 127.9, 130.0, 130.1, 131.2, 133.1, 136.0, 206.8. Anal. Calcd. for $C_{31}H_{42}O_4Si$: C, 73.47; H, 8.35%. Found: C, 73.25; H, 8.53%.

(4*S*,5*S*,6*S*,7*R*)-6-(*tert*)-Butyldiphenylsilyloxy-7,8-cyclohexylidenedioxy-5-methyloct-1-en-4-ol 132. To a cooled (0 ^oC) and stirred suspension of $NaBH_4$ (0.082 g, 2.157 mmol) in MeOH (10 mL) was added **131** (1.09 g, 2.16 mmol) in MeOH (10 mL). After stirring the mixture at the same temperature for 3 h (*cf*. TLC), the mixture was brought to room temperature, the supernatant decanted and concentrated in vacuo. The residue was taken in Et_2O (25 mL), washed with H_2O (10 mL) and brine (10 mL), and dried. Removal of solvent in vacuo followed by column chromatography of the residue (silica gel, 0-10% EtOAc/hexane) furnished pure **132**. Yield: 1.04 g (95%); colourless oil; $[\alpha]_D^{22}$ +20.1 (*c* 1.2, $CHCl_3$); IR: 3443 cm^{-1}; ^1H NMR: δ 1.06 (overlapping d and s, *J* = 7.0 Hz, 12H), 1.27-1.54 (m, 10H), 1.77-1.82 (m, 1H), 1.88-2.04 (m, 2H), 2.75 (broad s, 1H), 3.55-3.63 (m, 2H), 4.02-4.17 (m, 3H), 4.92-4.99 (m, 2H), 5.61-5.75 (m, 1H), 7.34-7.44 (m, 6H), 7.64-7.70 (m, 4H); ^{13}C NMR: δ 11.1, 19.4, 23.9, 25.0, 27.1, 35.0, 35.7, 39.6, 43.6, 68.5, 72.8,

74.2, 74.4, 110.1, 116.7, 127.6, 129.8, 129.9, 133.4, 133.6, 135.4, 136.1. Anal. Calcd. for $C_{31}H_{44}O_4Si$: C, 73.18; H, 8.72%. Found: C, C, 72.95; H, 8.78%.

(4*S*,5*S*,6*S*,7*R*)-7,8-Cyclohexylidenedioxy-4,6-dihydroxy-5-methyloct-1-ene 132a. To a cooled (0 ^oC) and stirred solution of **132** (0.163 g, 0.32 mmol) in THF (10 mL) was added Bu_4NF (0.56 mL, 0.56 mmol, 1 M in THF), and the mixture stirred for ~2 h (*cf*. TLC). It was poured in water, extracted with EtOAc (15 mL). The organic extract was washed with H_2O (5 mL) and brine, and dried. Removal of solvent in vacuo followed by column chromatography (silica gel, 0-10% EtOAc/hexane) of the residue furnished pure **132a**. Yield: 0.068 g (78%); colourless oil; $[\alpha]_D^{22}$ +15.2 (*c* 1.4, $CHCl_3$); IR: 3437, 2933, 2858 cm^{-1}; ^1H NMR: δ 0.88 (d, *J* = 6.8 Hz, 3H), 1.28-1.61 (m, 10H), 2.09-2.21 (m, 2H), 2.31-2.50 (m, 1H), 3.09 (broad s, 2H), 3.71-4.03 (m, 4H), 4.18-4.25 (m, 1H), 5.09-5.16 (m, 2H), 5.72-6.03 (m, 1H); ^{13}C NMR: δ 12.6, 23.7, 23.9, 25.1, 34.8, 36.0, 38.7, 40.5, 64.3, 74.1, 74.5, 76.4, 109.6, 117.7, 134.9. Anal. Calcd. for $C_{15}H_{26}O_4$: C, 66.64; H, 9.69%. Found: C, 66.45; H, 9.75%.

(4*S*,5*S*,6*S*,7*R*)-7,8-Cyclohexanedioxy-4,6-isopropylidenedioxy-5-methyloct-1-ene 132b. A mixture of the diol **132a** (0.050 g, 0.185 mmol), DMP (1 mL) and PPTS (cat.) was stirred for 1 h. The mixture was treated with aqueous10% $NaHCO_3$, and extracted with Et_2O (10 mL). The ether layer was washed with H_2O and brine, dried, and concentrated in vacuo to give a residue which was purified by column chromatography (silica gel, 0–10% EtOAc/hexane) to afford **132b**. Yield: 0.048 g (84%); colourless oil; $[\alpha]_D^{22}$ +23.4 (*c* 1.2, $CHCl_3$); IR: 2935, 1107 cm^{-1}; ^1H NMR: δ 0.95 (d, *J* = 6.6 Hz, 3H), 1.24-1.42 (m overlapped with two s, 8H), 1.55-1.59 (m, 8H), 2.10-2.28 (m, 2H), 2.32-2.49 (m, 1H), 3.41-3.59 (m, 2H), 3.85-3.90 (m, 1H), 3.99-4.04 (m, 2H), 5.01-5.09 (m, 2H), 5.78-6.05 (m,

1H); ^{13}C NMR: δ 12.2, 19.6, 23.9, 25.2, 29.8, 35.3, 36.0, 37.1, 37.3, 66.8, 73.8, 75.0, 78.2, 97.7, 109.9, 116.4, 134.8. Anal. Calcd. for $C_{18}H_{30}O_4$: C, 69.64; H, 9.74%. Found: C, 69.75; H, 9.80%.

(5*S*,6*S*,7*R*)-6-Benzoyloxy-7,8-cyclohexylidenedioxy-5-methyloct-1-en-4-one 133. As described earlier, desilylation of **131** (0.200 g, 0.39 mmol) with Bu_4NF (0.56 mL, 0.56 mmol, 1 M in THF) in THF (5 mL), followed by work up and isolation yielded the crude hydroxy ketone (0.083 g, 79%), which was directly subjected to benzoylation as follows.

To a cooled (0 ^{o}C) and stirred solution of the hydroxy ketone (0.083 g, 0.038 mmol) in CH_2Cl_2 (10 mL) was added PhCOCN (0.077 mL, 0.065 mmol). After stirring the mixture at room temperature for 18 h, it was poured in water, the organic layer was separated, and the aqueous layer extracted with $CHCl_3$ (10 mL). The organic extract was washed with H_2O and brine, and dried. Removal of solvent in vacuo followed by column chromatography of the residue (silica gel, 0-10% EtOAc/hexane) furnished pure **133**. Yield: 0.088 g (92%); light yellow oil; $[\alpha]_D^{22}$ +11.3 (*c* 1.5, $CHCl_3$); IR: 1716, 1638 cm^{-1}; ^{1}H NMR δ 1.09 (d, *J* = 6.8 Hz, 3H), 1.28-1.57 (m, 10H), 2.42-2.60 (m, 1H), 2.82 (dd, *J* = 7.2, 11.4 Hz, 2H), 3.65-3.76 (m, 1H), 3.79-3.96 (m, 1H), 4.23-4.31 (m, 1H), 4.89-5.04 (m, 2H), 5.42 (dd, *J* = 9.4 and 12.2 Hz, 1H), 5.56-5.77 (m, 1H), 7.35-7.51 (m, 3H), 7.92-8.08 (m, 2H); ^{13}C NMR: δ 10.3, 23.4, 23.6, 24.8, 34.7, 35.7, 37.1, 41.5, 64.2, 67.8, 75.1, 109.4, 118.1, 127.4, 129.1, 130.2, 132.1, 134.1, 165.5, 200.2. Anal. Calcd. for $C_{22}H_{28}O_5$: C, 70.94; H, 7.58%. Found: C, 70.75; H, 7.39%.

(4*R/S*,5*S*,6*S*,7*R*)-6-Benzoyloxy-7,8-cyclohexylidenedioxy-5-methyloct-1-en-4-ol 134. As described earlier, reduction of **133** (0.050 g, 0.134 mmol) with $NaBH_4$ (0.021 g, 0.536

mmol) in MeOH (10 mL), work up, followed by column chromatography (silica gel, 0-25% EtOAc/hexane) led to **134** as an inseparable diastereomeric mixture. Yield: 0.038 g (76%); pale yellow oil; IR: 3423, 1718 cm^{-1}; ^{1}H NMR: δ 1.02-1.12 (overlapping d and d, *J* = 6.8 and 7.2 Hz, 3H), 1.33-1.38 (m, 2H), 1.39-1.62 (m, 8H), 2.18-2.22 (m, 1H), 2.33-2.46 (m, 2H), 2.75 (broad s, 1H), 3.37-3.46 (m, 1H), 3.79-3.87 (m, 1H), 4.06-4.13 (m, 1H), 4.41-4.47 (m, 1H), 5.01-5.17 (m, 2H), 5.44-5.48 (m, 1H), 5.82-5.96 (m, 1H), 7.39-7.59 (m, 3H), 7.98-8.02 (m, 2H); ^{13}C NMR: δ 14.2, 14.7, 23.8, 25.1, 34.9, 35.8, 36.9, 37.0, 39.9, 40.6, 65.8, 66.3, 74.4, 74.6, 75.0, 77.9, 109.6, 110.1, 115.6, 116.0, 128.4, 129.8, 130.0, 130.1, 130.2, 130.3, 132.9, 133.1, 140.1, 140.2, 165.6, 169.0. Anal. Calcd. for $C_{22}H_{30}O_5$: C, 70.56; H, 8.07%. Found: C, 70.73; H, 8.13%.

(4*S*/*R*,5*S*,6*S*,7*R*)-7,8-Cyclohexylidenedioxy-4,6-dihydroxy-5-methyloct-1-ene (**132a** + **135**)**.** A mixture of **134** (0.028 g, 0.075 mmol) and anhydrous K_2CO_3 (0.021 g, 0.15 mmol) in MeOH (5 mL) was stirred at 0 ^{o}C. After consumption of the starting material (*cf* TLC, ~2h), the mixture was concentrated in vacuo, the residue was taken in Et_2O (10 mL), the organic extract washed with H_2O and brine, and dried. Removal of solvent in vacuo and isolation by preparative thin layer chromatography of the residue (silica gel, 0-10% EtOAc/hexane) furnished the pure diasteromers **132a** and **135** (0.007 g, 32%) as a colourless oil.

132a: Yield: 0.012 g (60%).

135: Yield: 0.012 g (60%); colourless oil; $[\alpha]_D^{22}$ -1.50 (*c* 1.2, $CHCl_3$); IR: 3408, 2937, 2861 cm^{-1}; ^{1}H NMR: δ 0.93 (d, *J* = 6.4 Hz, 3H), 1.22-1.37 (m, 2H), 1.42-1.59 (m, 8H), 1.98-2.03 (m, 1H), 2.14-2.30 (m, 2H), 2.85 (broad s, 2H), 3.32-3.45 (m, 1H), 3.51-3.57 (m,

1H), 3.85-3.95 (m, 1H), 4.05-4.16 (m, 2H), 5.10-5.17 (m, 2H), 5.57-5.75 (m, 1H); ^{13}C NMR: δ 16.2, 23.9, 24.0, 25.1, 33.9, 34.9, 36.5, 42.6, 67.2, 73.9, 76.1, 77.0, 109.6, 117.2, 141.3. Anal. Calcd. for $C_{15}H_{26}O_4$: C, 66.64; H, 9.69%. Found: C, 66.43; H, 9.82%.

(4*S*,5*S*,6*S*,7*R*)-4-Benzoyloxy-6-(*tert*)-butyldiphenylsilyloxy-7,8-cyclohexylidenedioxy-5-methyloct-1-ene 136. The alcohol **132** (0.800 g, 1.58 mmol) was benzoylated with PhCOCN (0.484 mL, 4.08 mmol) in CH_2Cl_2 (15 mL) at 0 ^oC as described earlier. Work up and column chromatography (silica gel, 0-10% EtOAc/hexane) afforded pure **136**, but as a mixture of rotamers. Yield: 0.858 g (90%); light yellow oil; $[\alpha]_D^{22}$ +13.5 (*c* 2.52, $CHCl_3$); IR: 2935, 2857, 1638 cm^{-1}; ^{1}H NMR: δ 1.16 (overlapping d and s, *J* = 7.0 Hz, 12H), 1.23-1.54 (m, 10H), 1.92-2.10 (m, 1H), 2.23-2.31 (m, 2H), 3.75-3.86 (m, 2H), 3.89-3.99 (m, 1H), 4.13-4.21 (m, 1H), 4.87-5.01 (m, 2H), 5.45-5.52 (m, 1H), 5.56-5.77 (m, 1H), 7.29-7.45 (m, 9H), 7.66-7.92 (m, 5H), 7.98-8.05 (m, 1H) ; ^{13}C NMR: δ 10.6, 11.0, 19.5, 23.7, 23.8, 25.1, 27.1, 34.7, 34.9, 35.7, 36.1, 36.8, 40.1, 40.5, 64.0, 67.8, 73.5, 73.8, 75.1, 75.5, 76.5, 109.4, 109.6, 116.9, 117.0, 127.4, 127.5, 128.3, 129.1, 129.4, 129.6, 129.7, 129.8, 130.2, 132.1, 132.9, 133.8, 133.9, 134.1, 135.8, 136.0, 136.1, 165.4, 165.5. Anal. Calcd. for $C_{38}H_{48}O_5Si$: C, 74.47; H, 7.89%. Found: C, 74.28; H, 7.68%.

(2*R*,3*S*,4*S*,5*S*)-1,2-Cyclohexylidenedioxy-5-benzoyloxy-4-methyloct-7-en-3-ol 137. Desilylation of **136** (0.800 g, 1.33 mmol) with Bu_4NF (2.25 mL, 2.25 mmol, 1 M in THF) in THF (20 mL) at 0 ^oC, followed by work up and purification by column chromatography (silica gel, 0-10% EtOAc/hexane) furnished pure **137**. Yield: 0.390 g (79%); colourless oil; $[\alpha]_D^{22}$ +18.7 (*c* 1.60, $CHCl_3$); IR: 3437, 1720 cm^{-1}; ^{1}H NMR: δ 1.06 (d, *J* = 7.4 Hz, 3H), 1.20-1.36 (m, 2H), 1.48-1.57 (m, 8H), 2.01-2.13 (m, 1H), 2.35-2.52 (m, 3H), 3.72-3.89 (m, 3H), 4.03-4.21 (m, 1H), 4.97-5.13 (m, 2H), 5.43-5.50 (m, 1H), 5.72-5.93 (m, 1H), 7.35-

7.51 (m, 3H), 7.92-8.08 (m, 2H); ^{13}C NMR: δ 11.4, 23.7, 23.9, 25.1, 34.4, 34.9, 36.0, 38.9, 64.1, 71.7, 74.7, 109.4, 117.5, 128.3, 129.5, 130.5, 132.8, 134.2, 165.9. Anal. Calcd. for $C_{22}H_{30}O_5$: C, 70.56; H, 8.07%. Found: C, 70.35; H, 7.96%.

(2*R*,3*R*,4*S*,5*S*)-1,2-Cyclohexylidenedioxy-5-benzoyloxy-4-methyloct-7-en-3-ol 138. Oxidation of **137** (0.350 g, 0.95 mmol) with PCC (0.334 g, 1.52 mmol) in CH_2Cl_2 (20 mL), followed by work-up furnished the 3-keto compound. In view of its instability it was directly used for the next step. For this, K-selectride® (1.31 mL, 1.31 mmol, 1 M in THF) was injected into a cooled (-78 ^{o}C) and stirred solution of the above compound (0.290 g, 0.78 mmol) in THF (15 mL). After stirring the mixture at the same temperature till completion of the reaction (*cf*. TLC, ~ 3 h), the excess hydride was decomposed with MeOH, the supernatant decanted and concentrated in vacuo. The residue was taken in Et_2O (50 mL), the organic extract washed with H_2O and brine, and dried. Removal of solvent in vacuo followed by column chromatography of the residue (silica gel, 0-10% EtOAc/hexane) furnished pure **138**. Yield: 0.291 g (82%); colourless oil; $[\alpha]_D^{22}$ +38.8 (*c* 1.06, $CHCl_3$); IR: 3477, 1724 cm^{-1}; ^{1}H NMR: δ 1.03 (d, *J* = 7.2 Hz, 3H), 1.32-1.36 (m, 2H), 1.37-1.57 (m, 8H), 2.09-2.21 (m, 1H), 2.26-2.34 (m, 2H), 3.50-3.54 (m, 1H), 3.87-3.94 (m, 2H), 4.13-4.18 (m, 1H), 4.34-4.45 (m, 1H), 5.03-5.12 (m, 2H), 5.25-5.32 (m, 1H), 5.78-5.93 (m, 1H), 7.39-7.53 (m, 3H), 7.99-8.06 (m, 2H); ^{13}C NMR: δ 15.0, 23.7, 23.8, 25.0, 34.7, 36.1, 40.6, 64.4, 73.8, 76.2, 79.1, 109.1, 114.9, 129.4, 130.3, 133.2, 136.7, 140.4, 167.7. Anal. Calcd. for $C_{22}H_{30}O_5$: C, 70.56; H, 8.07%. Found: C, 70.71; H, 8.15%.

(2*R*,3*R*,4*S*,5*S*)-1,2-Cyclohexylidenedioxy-4-methyloct-7-en-3,5-diol 138a. A mixture of **138** (0.100 g, 0.267 mmol) and anhydrous K_2CO_3 (0.062 g, 0.454 mmol) in MeOH (10 mL) was stirred at 0 ^{o}C. After consumption of the starting material (*cf*. TLC, ~2 h), the

mixture was concentrated in vacuo, the residue was taken in Et_2O (10 mL), the organic extract washed with H_2O and brine, and dried. Removal of solvent in vacuo followed by preparative thin layer chromatography of the residue (silica gel, 10% EtOAc/hexane) furnished pure **138a**. Yield: 0.054 g (75%); colourless oil; $[\alpha]_D^{22}$ +7.3 (*c* 2.3, $CHCl_3$); IR: 3438, 2933, 2857 cm^{-1}; ^1H NMR: δ 1.03 (d, *J* = 6.0 Hz, 3H), 1.29-1.63 (m, 10H), 2.34-2.37 (m, 1H), 2.39-2.42 (m, 2H), 3.02 (broad s, 2H), 3.37-3.42 (m, 1H), 3.49-3.65 (m, 1H), 3.79-3.83 (m, 1H), 3.91-3.98 (m, 1H), 4.05-4.12 (m, 1H), 4.99-5.07 (m, 2H), 5.70-5.84 (m, 1H); ^{13}C NMR: δ 11.4, 23.8, 23.9, 25.0, 35.2, 36.1, 38.0, 40.7, 65.9, 72.3, 76.9, 77.8, 110.0, 115.8, 139.4. Anal. Calcd. for $C_{15}H_{26}O_4$: C, 66.64; H, 9.69%. Found: C, 66.42; H, 9.48%.

(2*R*,3*R*,4*S*,5*S*)-1,2-Cyclohexylidenedioxy-3,5-isopropanedioxy-4-methyloct-7-ene 138b. As described earlier, reaction of **138a** (0.030 g, 0.111 mmol) with DMP (1 mL) in the presence of PPTS (cat.) afforded **138b** after work up, and column chromatography (silica gel; 0–10% EtOAc/hexane). Yield: 0.029 g (83%); colourless oil; $[\alpha]_D^{22}$ +7.3 (*c* 2.32 in $CHCl_3$); IR: 2935, 2858, 1104 cm^{-1}; ^1H NMR: δ 1.06 (d, *J* = 6.6 Hz, 3H), 1.30 (s, 6H), 1.33-1.59 (m, 10H), 1.88-2.09 (m, 2H), 2.21-2.39 (m, 1H), 3.13-3.19 (m, 1H), 3.56-3.68 (m, 1H), 3.74-3.78 (m, 1H), 3.95-4.05 (m, 2H), 4.97-5.09 (m, 2H), 5.71-5.95 (m, 1H); ^{13}C NMR: δ 13.1, 23.5, 23.9, 24.0, 25.2, 25.3, 34.7, 34.8, 36.7, 42.0, 67.8, 70.9, 73.5, 77.9, 100.3, 109.6, 114.4, 140.8. Anal. Calcd. for $C_{18}H_{30}O_4$: C, 69.64; H, 9.74%. Found: C, 69.72; H, 9.56%.

(4*S*,5*S*,6*R*,7*R*)-4-Benzoyloxy-6-(*tert*)-butyldiphenylsilyloxy-7,8-cyclohexylidenedioxy-5-methyloct-1-ene 139. Reaction of **138** (0.120 g, 0.321 mmol) with TBDPSCl (0.149 g, 0.543 mmol) in the presence of imidazole (0.044 g, 0.641 mmol) in CH_2Cl_2 (5 mL) and

subsequent isolation afforded rotameric mixtures of **139** after purification by column chromatography (silica gel, 0-10% Et_2O/hexane). Yield: 0.189 g (94%); light yellow oil; $[\alpha]_D^{22}$ +10.9 (*c* 1.41, $CHCl_3$); IR: 1741 cm^{-1}; ^1H NMR: δ 1.06-1.16 (merged s and d, *J* = 6.8 Hz, 12H), 1.27-1.39 (m, 6H), 1.44-1.56 (m, 4H), 1.88-2.08 (m, 1H), 2.18-2.32 (m, 2H), 3.76-3.86 (m, 1H), 3.89-3.99 (m, 1H), 4.12-4.30 (m, 2H), 4.79-4.99 (m, 2H), 5.22-5.28 and 5.44-5.52 (two m, 1H), 5.57-5.75 (m, 1H), 7.25-7.48 (m, 9H), 7.62-7.77 (m, 5H), 7.89-8.05 (m, 1H); ^{13}C NMR: δ 10.6, 11.2, 19.5, 23.7, 23.8, 25.1, 27.1, 34.7, 34.9, 35.7, 36.1, 36.8, 40.1, 40.5, 64.0, 67.8, 73.5, 73.9, 75.1, 75.3, 75.5, 77.8, 109.4, 109.6, 117.0, 118.0, 127.4, 127.5, 128.3, 129.1, 129.4, 129.6, 129.7, 129.8, 130.2, 132.1, 132.9, 133.8, 133.9, 134.1, 135.8, 136.0, 136.1, 165.4, 165.5. Anal. Calcd. for $C_{38}H_{48}O_5Si$: C, 74.47; H, 7.89%. Found: C, 74.55; H, 7.76%.

(2*R*,3*R*,4*S*,5*S*)-3-(*tert*)-Butyldiphenylsilyloxy-4-methyl-5-benzoyloxyoct-1-ene-1,2-diol 140. A mixture of **139** (0.150 g, 0.244 mmol) and aqueous 80% TFA (10 mL) was stirred for 3 h at 0 °C. The mixture was diluted with water (15 mL) and extracted with $CHCl_3$ (30 mL), the organic layer separated and the aqueous layer extracted with $CHCl_3$ (10 mL). The combined organic extracts were washed successively with aqueous 2% $NaHCO_3$, H_2O and brine, and dried. Solvent removal in vacuo followed by column chromatography of the residue (silica gel, 0-40% EtOAc/hexane) furnished pure **140**. Yield**:** 0.118 g (91%); colourless oil; $[\alpha]_D^{22}$ +4.0 (*c* 1.34, $CHCl_3$); IR: 3438, 1721 cm^{-1}; ^1H NMR: δ 1.09 (s, 9H), 1.16 (d, *J* = 7.2 Hz, 3H), 1.60 (broad s, 2H), 2.12-2.28 (m, 2H), 2.32-2.51 (m, 1H), 3.25-3.39 (m, 1H), 3.54-3.75 (m, 3H), 4.96-5.07 (m, 2H), 5.32-5.39 (m, 1H), 5.55-5.71 (m, 1H), 7.12-7.41 (m, 8H), 7.45-7.58 (m, 5H), 7.80-7.84 (m, 2H); ^{13}C NMR: δ 10.2, 19.5, 27.1,

36.7, 41.9, 64.4, 72.2, 73.6, 77.8, 118.0, 127.5, 127.6, 128.3, 129.7, 133.1, 135.8, 136.0, 167.0. Anal. Calcd. for $C_{32}H_{40}O_5Si$: C, 72.14; H, 7.57%. Found: C, 72.05; H, 7.36%.

(1*R*,2R,3S,4S)-1-Phenyl-2-(*tert*)-butyldiphenylsilyloxy-3-methyl-4-benzyloxyheptan-1-ol 142. To a stirred solution of **140** (0.100 g, 0.188 mmol) in 60% aqueous CH_3CN (20 mL) was added $NaIO_4$ (0.080 g, 0.376 mmol) in portions. After stirring for 2 h, the mixture was filtered, the filtrate extracted with $CHCl_3$. The organic layer was washed with water and brine, and concentrated in vacuo to get the aldehyde **141**. Yield: 0.088 g (93%); colourless oil; $[\alpha]_D^{23}$ + 9.2 (*c* 1.22, $CHCl_3$); IR: 2710, 1730, 1712 cm^{-1}; ^1H NMR: δ 1.10 (overlapping s and d, *J* = 6.8 Hz, 12H), 1.95-2.03 (m, 1H), 2.21-2.29 (m, 2H), 4.21 (dd, *J* = 1.8, 2.4 Hz, 1H), 4.87-5.02 (m, 2H), 5.23-5.29 (m, 1H), 5.62-5.83 (m, 1H), 7.15-7.47 (m, 9H), 7.49-7.60 (m, 4H), 7.78-7.82 (m, 2H), 9.35 (d, *J* = 1.8 Hz, 1H); ^{13}C NMR: δ 11.6, 19.5, 27.4, 36.7, 42.1, 74.5, 81.1, 116.9, 127.2, 127.5, 128.1, 129.2, 132.9, 136.0, 136.2, 140.8, 169.2, 203.4. Anal. Calcd. for $C_{31}H_{36}O_4Si$: C, 74.36; H, 7.25%. Found: C, 74.24; H, 7.15%.

To a cooled (-30 °C) and stirred solution of PhMgBr [prepared from 1-bromobenzene (0.056 g, 0.353 mmol) and Mg-turnings (0.011 g, 0.441 mmol)] in THF (10 mL) was injected **141** (0.075 g, 0.150 mmol) in THF (10 mL). After stirring for 3 h, the reaction was quenched with aqueous saturated NH_4Cl (2 mL), the organic layer was separated and the aqueous portion extracted with Et_2O (30 mL). The organic extract was washed with water, brine, and dried. Solvent removal in vacuo and column chromatography of the residue (silica gel, 0-15% EtOAc/hexane) afforded pure alcohol **142**. Yield: 0.091 g (84%); white solid; $[\alpha]_D^{22}$ -5.2 (*c* 1.21, $CHCl_3$); IR: 3478, 1721 cm^{-1}; ^1H NMR: δ 1.05 (s, 9H), 1.12 (d, *J* = 7.4 Hz, 3H), 1.86-2.12 (m, 3H), 2.20-2.49 (m, 1H),

4.18 (t, *J* = 3.4 Hz, 1H), 4.75-4.84 (m, 2H), 4.88-4.97 (m, 2H), 5.37-5.54 (m, 1H), 7.03-7.17 (m, 7H), 7.25-7.43 (m, 9H), 7.55-7.65 (m, 2H), 7.74-7.78 (m, 2H); ^{13}C NMR: δ 10.6, 19.5, 27.1, 36.0, 38.9, 65.2, 74.2, 74.9, 117.3, 127.1, 128.3, 128.4, 128.6, 128.7, 129.7, 130.1, 132.9, 137.6, 139.9, 166.3. Anal. Calcd. for $C_{37}H_{42}O_4Si$: C, 76.78; H, 7.31%. Found: C, 75.98; H, 7.42%.

(4*S*,5*S*,6*R*,7*R*)-4-Benzoyloxy-5-methyl-6,7-isopropylidenedioxy-7-phenylhept-1-ene 143. As described earlier, treatment of **142** (0.150 g, 0.26 mmol) with Bu_4NF (0.30 mL, 0.30 mmol, 1 M in THF) in THF (10 mL), work up of the reaction mixture, followed by preparative thin layer chromatography (silica gel, 5% MeOH/$CHCl_3$) of the residue furnished the pure desilylated product (0.071 g, 81%). This (0.21 mmol) on stirring with PPTS (cat.) in dimethoxypropane (1 mL) for 1 h, followed by isolation and preparative thin layer chromatography (silica gel; 10% EtOAc/hexane) afforded **143**. Yield: 0.067 g (84%); colourless oil; $[\alpha]_D^{22}$ + 11.2 (*c* 1.05, $CHCl_3$); IR: 2923, 1718 cm^{-1}; ^{1}H NMR: δ 1.02 (d, *J* = 7.2 Hz, 3H), 1.28 (s, 3H), 1.35 (s, 3H), 1.82-1.89 (m, 1H), 2.15-2.26 (m, 2H), 4.15 (dd, *J* = 8.2, 3.6 Hz, 1H), 4.72-4.85 (m, 2H), 4.89-4.96 (m, 2H), 5.28-5.52 (m, 1H), 7.28-7.48 (m, 8H), 7.95-8.10 (m, 2H); ^{13}C NMR: δ 10.2, 26.8, 27.0, 35.8, 40.1, 72.8, 79.5, 83.2, 108.6, 116.8, 127.2, 127.8, 128.5, 128.9, 133.0, 136.5, 168.1. Anal. Calcd. for $C_{24}H_{28}O_4$: C, 75.76; H, 7.42%. Found: C, 75.54; H, 7.35%.

(4*S*,5*S*,6*R*,7*R*)-6,7-Isopropylidenedioxy-5-methyl-7-phenylhept-1-en-4-ol 144. Hydrolysis of **143** (0.060 g, 0.16 mmol) with K_2CO_3 (0.048 g, 0.35 mmol) in MeOH (5 mL), usual work up and column chromatography (silica gel, 0-20% EtOAc/hexane) furnished pure **144**. Yield: 0.031 g (72%); colourless oil; $[\alpha]_D^{22}$ -3.36 (*c* 1.12, $CHCl_3$) (lit.,[15b] $[\alpha]_D^{24}$ -3.34 (2.21 in $CHCl_3$)); IR: 3485, 2923 cm^{-1}; ^{1}H NMR: δ 1.05 (d, *J* = 7.2

Hz, 3H), 1.58 (s, 3H), 1.62 (s, 3H), 1.72-1.79 (m, 1H), 2.07 (broad s, 1H), 2.12-2.28 (m, 2H), 3.52-3.62 (m, 1H), 4.12 (dd, *J* = 9.2, 2.4 Hz, 1H), 4.72 (d, *J* = 9.2 Hz, 1H), 4.99-5.16 (m, 2H), 5.68-5.92 (m, 1H), 7.26-7.42 (m, 5H); ^{13}C NMR: δ 10.5, 27.0, 27.2, 36.0, 39.5, 73.5, 79.9, 82.6, 108.7, 117.5, 126.8, 127.9, 128.5, 134.8, 137.5. Anal. Calcd. for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75%. Found: C, 73.63; H, 8.61%.

(2*R*,3*S*,4*S*)-1,2-Cyclohexylidenedioxy-3-Benzoyloxy-4-C-(*ter*-*t*butyldiphenylsilyloxy)-5-hexene 145. Reaction of **83d** (2.0 g, 4.16 mmol) with BzCN (0.655 g, 5.0 mmol) and Et_3N (0.505 g, 5.0 mmol) in CH_2Cl_2 (40 mL), followed by work up, isolation and purification by column chromatography (silica gel, 5-15% EtOAc/hexane) furnished **145**. Yield: 2.18 g (90%); light yellow oil; $[\alpha]_D^{25}$ + 10.12 (*c* 1.4, $CHCl_3$); IR: 1722, 920 cm^{-1}; ^{1}H NMR: δ 1.10 (s, 9H), 1.31-1.45 (m, 10H), 2.62 (m, 1H) 3.57-3.80 (m, 2H), 3.40-4.00 (m, 2H), 4.23-4.38 (m, 1H), 5.71-5.25 (m, 2H), 5.66-5.71 (m, 1H), 5.77-5.91 (m, 1H), 7.21-7.39 (m, 10H), 7.48-7.68 (m, 3H), 7.99-78.03 (m, 2H).

(2*R*,3*S*,4*S*)-1,2-Cyclohexylidenedioxy-3-benzoyloxy-4-C-(*tert*)-butyldiphenylsilyloxy hex-1-ol 146. To well cooled (0 ^{o}C) and stirred solution of **145** (1.5 g, 2.56 mmol) was injected $BH_3.Me_2S$ (0.234 g, 3.08 mmol). After stirring for 30 min, the mixture was brought to room temperature, and stirred for an additional 3 h. Ethanol (25 mL) was added to it followed by aqueous 3N NaOH (5 mL). The solution was cooled to 0 ^{o}C, H_2O_2 (10 mL, 30% solution) added slowly, and the reaction mixture brought to room temperature. After completion of reaction (*cf*. TLC, ~2 h), the mixture was poured into ice-water and extracted with Et_2O (50 mL). The organic layer was washed with water, brine, and dried. Removal of solvent in vacuo and chromatographic purification (silica gel, 5-20% EtOAc/hexane) of the residue afforded pure **146**. Yield: 1.39 g (90%); colourless oil; $[\alpha]_D^{22}$

-4.21 (*c* 1.2, $CHCl_3$); IR: 3466, 1724, 920 cm^{-1}; ^1H NMR: δ 1.12 (s, 9H), 1.31-1.45 (m, 10H), 2.0-2.22 (m, 2H), 2.32 (m, 1H) 3.67-3.82 (m, 1H), 3.92-4.11 (m, 5H), 4.25-4.43 (m, 1H), 5.42-5.47 (m, 1H), 7.21-7.39 (m, 10H), 7.49-7.53 (m, 4H), 7.97-8.01 (m, 1H).

(2*R*,3*S*,4*S*)-1,2-Cyclohexylidenedioxy-3-benzoyloxy-4-C-(*tert*)-butyldiphenylsilyloxy hexanal 147. Oxidation of **146** (1.0 g, 1.66 mmol) with PCC (0.430 g, 1.99 mmol) and NaOAc (0.208 g, 2.98 mmol) in CH_2Cl_2 (65 mL), usual work up and column chromatography (silica gel, 0-20% EtOAc/hexane) afforded the aldehyde **147**. Yield: 0.630 g (71%); colourless oil; $[\alpha]_D^{22}$ +7.64 (*c* 1.16, $CHCl_3$); IR: 1650,1720, 920 cm^{-1}; ^1H NMR: δ 1.03 (s, 9H), 1.52-1.62 (m, 10H), 2.40-2.65 (m, 1H), 3.71-3.87 (m, 6H), 4.22-4.25 (m, 1H), 5.24-5.26 (m, 1H), 7.31-7.41 (m, 10H), 7.54-7.63 (m, 3H), 7.89-7.93 (m, 2H), 9.75 (s, 1H).

5R,6-Cyclohexylidenedioxy-3-C-(*tert*)-butyldiphenylsilyloxy-2,3-dideoxy-D-ribofuranose 148. A mixture of compound **147** (0.50 g, 0.831 mmol) and K_2CO_3 (0.172 g, 1.24 mmol) in MeOH (20 mL) was stirred for 3 h. The mixture was concentrated in vacuo, water added to it and extracted with $CHCl_3$ (50 mL). The organic layer was separated and the aqueous layer extracted with $CHCl_3$ (20 mL). The combined organic extracts were washed with water and brine, and dried. Removal of solvent in vacuo followed by chromatographic purification (silica gel, 5-30% EtOAc/hexane) afforded **148**. Yield 0.330 g (71%); colourless oil; $[\alpha]_D^{22}$ -12.6 (*c* 1.2, $CHCl_3$); IR: 3431, 920 cm^{-1}; ^1H NMR: δ 1.04 (s, 9H), 1.25-1.50 (m, 10H), 1.98-2.08 (m, 3H, H-2', H-3'), 2.25-2.45 (m, 1H, H-4') 2.65-2.73 (broad s, 1H), 3.65-4.28 (m, 6H), 7.39-7.55 (m, 6H), 7.65-7.72 (m, 4H).

5R,6-Cyclohexylidenedioxy-1-acetoxy-3-C-(*tert*)-butyldiphenylsilyloxy-2,3-dideoxy-D-ribofuranose 149. A mixture of **148** (0.3 g, 0.567 mmol), Ac_2O (0.086 g, 0.850 mmol) and

pyridine (12 mL) was stirred overnight at room temperature. Ice-cold water was added to the mixture, the mixture stirred for 1 h and extracted with $CHCl_3$ (40 mL). The organic layer was washed with dilute HCl, water and brine, and dried. Removal of solvent and chromatographic purification (silica gel, 5-20% EtOAc/Hexane) afforded pure **149**. Yield 0.291 g (91%); white solid; $[\alpha]_D^{25}$ -2.3 (*c* 1.4, $CHCl_3$); ^{1}H NMR: δ 1.05 (s, 9H), 1.4-1.6 (m, 10H), 1.96 and 2.04 (2s, 3H), 2.1-2.3 (m, 2H, H-2), 2.6 (m, 1H, H-3), 3.6-3.8 (m, 2H), 3.9-4.1 (m, 4H), 6.24 (m, 1H, H-1), 7.40 (m, 6H), 7.65 (m, 4H). Anal. Calcd. For $C_{31}H_{42}O_6Si$: C, 69.11; H, 7.86. Found, C, 69. 29; H, 8.04.

5R,6-Cyclohexylidenedioxy-1-thymine-3-C-(*tert*)-butyldiphenylsilyloxy-2,3-dideoxy-D-ribofuranose 150. To a well stirred suspension of **149** (0.250 g, 0.451 mmol) and thymine (0.085 g, 0.678 mmol) uhder Ar in dry CH_3CN (40 mL) at room temperature was drop-wise added bis(trimethylsilylacetamide (0.189 g). This reaction mixture was stirred for 3 h, cooled to -30 ^oC, and treated with trifluromethanesulphonate (1 mL). After stirring for 7 days at room temperature, the mixture was diluted with CH_2Cl_2 and water. The organic layer was separated and aqueous layer washed with $CHCl_3$. The organic extract were washed with aqueous saturated $NaHCO_3$, water and brine, and dried. Removal of solvent in vacuo followed by preparative TLC (silica gel, 25% EtOAc/hexane) afforded **150**. Yield: 0.153 g (63%); $[\alpha]_D^{25}$ -15.03 (*c* 1.4, $CHCl_3$); ^{1}H NMR: δ 1.05 (s, 9H), 1.4-1.7 (m, 10H, overlapped with a s at δ 1.7, 3H), 1.9-2.6 (m, 3H, H-2', H-3'), 3.6-4.0 (m, 3H), 4.1-4.3 (m, 2H), 4.45 (m, 1H, H-4), 6.38 (m, 1H, H-1), 7.3-7.5 (m, 6H), 7.6-7.7 (m, 4H, overlapped with a m, 1H, H-6), 8.1 (broad s, 1H, NH); Anal. Calcd. For $C_{31}H_{42}O_6N_2Si$: C, 70.79; H, 7.68%. Found, C, 70. 55; H, 7.44%.

(3*R*)- 3,4-O-Cyclohexylidene-2-oxo-1-phenyl-butane-3,4-diol 164. Oxidation of a diastereomeric mixture of **91a** and **91b** (2.1 g, 8.0 mmol) with PCC (2.6 g, 12 mmol) in CH_2Cl_2 (60 mL), followed by usual work-up, solvent removal under vacuo followed by colum chromatography of the residue (silica gel, 0-15 % EtOAc/hexane) afforded pure **164**. Yield: 1.56 g (74.3%); colourless oil; $[\alpha]_D^{26}$ +10.40 (*c* 2.0, $CHCl_3$); IR: 1735, 910 cm^{-1}; ^1H NMR: δ 1.2-1.6 (m, 10H), 3.7-4.3 (m, 4H), 4.4-4.5 (m, 1H), 7.1-7.3 (m, 5H); ^{13}C NMR: δ 23.6, 23.9, 24.9, 34.3, 35.6, 45.3, 66.0, 79.4, 111.6, 126.8, 128.4, 129.6, 133.2, 207.9. Anal. Calcd. for $C_{16}H_{20}O_3$: C, 73.81; H, 7.74%. Found: C, 73.99; H, 7.55%.

(2*R*,3*R*)-3,4-O-Cyclohexylidene-1-phenyl-butane-2,3,4-triol 91a. Following the earlier procedure, a solution of **164** (1.4 g, 5.38 mmol) in THF (30 mL) was reduced with K-selectride® (5.5 mL, 1 M in THF) at -78 ^oC**.** Usual work up, solvent removal under vacuo followed by column chromatography (silica gel, 0-20 % EtOAc/hexane) of the residue afforded pure **91a**. Yield: 1.32 g (93.6%); colourless oil; $[\alpha]_D^{25}$ +9.12 (*c* 1.2, $CHCl_3$); IR: 3464, 2937 cm^{-1}; ^1H NMR: δ 1.2-1.6 (m, 10H), 2.40 (broad s, 1H), 2.7-2.8 (m, 2H), 3.64-3.78 (m, 2H), 3.87-4.0 (m, 2H), 7.2-7.3 (m, 5H); ^{13}C NMR: δ 23.6, 23.9, 25.0, 34.6, 36.1, 40.1, 65.5, 72.9, 77.4, 109.7, 126.3, 128.3, 129.2, 137.6 Anal. Calcd. for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45%. Found: C, 73.38; H, 8.62%.

(2*R*,3*R*)-3,4-O-Cyclohexylidene-2-O-*p*-toluenesulphonyl-1-phenyl-butane-2,3,4-triol 165. To a cooled (0 ^oC) and stirred solution of compound **91a** (0.786 g, 3.0 mmol) in pyridine (10 mL) was dropwise added a solution of *p*-TsCl (0.575 g, 3.0 mmol) in pyridine (15 mL) and the solution was stirred for 3 h (*cf*. TLC). Water and EtOAc was added to the mixture, the organic layer separated and the aqueous layer extracted with EtOAc (40 mL).

The organic extracts were washed with aqueous HCl, water and brine, and dried. Solvent removal in vacuo and chromatographic purification (silica gel, 0-15% EtOAc/Hexane) of the crude residue afforded pure **165**. Yield: 1.14 g (91.1%); colourless oil; $[\alpha]_D^{25}$ +32.8 (*c* 3.2, $CHCl_3$); IR: 1168, 1103 cm^{-1}; ^1H NMR: δ 1.4-1.6 (m, 10H), 2.39 (s, 3H), 2.78 (q, J = 7.2 Hz, 1H), 3.10 (dd, J = 13.8, 6.4 Hz, 1H), 3.7-3.9 (m, 2H), 4.2 (m, 1H), 4.6 (m, 1H), 7.04-7.25 (m, 7H), 7.58 (d, J= 8.2 Hz, 2H); ^{13}C NMR: δ 21.3, 23.5, 23.6, 24.9, 34.2, 35.4, 36.5, 64.4, 74.1, 82.1, 110.0, 126.4, 127.4, 128.2, 129.3, 129.4, 133.3, 135.5, 144.2. Anal. Calcd. for $C_{23}H_{28}O_5S$: C, 66.32; H, 6.72; S, 7.69%. Found: C, 66.14; H, 6.65; S, 7.89%.

(2*S*, 3*R*)- 2-Azido -1-phenyl-butane-3,4-diol 166. A mixture of **165** (0.832 g, 2.0 mmol) in CH_2Cl_2 (40 mL) and 80% aqueous TFA (10 mL) was stirred for 3 h at 0 °C. The mixture was diluted with water (15 mL) and extracted with $CHCl_3$ (30 mL), the organic layer separated and the aqueous layer extracted with $CHCl_3$ (10 mL). The combined organic extracts were washed successively with aqueous 2% $NaHCO_3$, H_2O and brine, and dried. Solvent removal in vacuo followed by column chromatography of the residue (silica gel, 0-5% MeOH/$CHCl_3$) furnished pure **166**. Yield: 0.308 g (74.1%); white solid; mp 80-81°C [lit.[32b] mp 80-82 °C]; $[\alpha]_D^{25}$ +30.2 (*c* 1.8, $CHCl_3$) [lit.[32b] $[\alpha]_D^{25}$ +30.6 (*c* 2.0, $CHCl_3$)]; IR: 3397, 2112 cm^{-1}; ^1H NMR: δ 1.26 (broad s, 2H), 2.72-2.83 (m, 1H), 2.92-3.09 (m, 1H), 3.6-3.8 (m, 4H), 7.29 (m, 5H); ^{13}C NMR: δ 36.9, 63.1, 65.5, 73.0, 126.9, 128.6, 129.2, 137.2.

2*S*-[1(S)-Azido-2-phenylethyl]oxirane (VI). To a cooled (0 °C) and stirred solution of compound **166** (0.207 g, 1.0 mmol) in pyridine (4 mL) was dropwise added a solution of *p*-TsCl (0.20 g, 1.05 mmol) in pyridine (5 mL) and the solution stirred for 3 h (*cf*. TLC).

Water and EtOAc was added to the mixture, the organic layer separated and the aqueous layer extracted with $CHCl_3$ (20 mL). The combined organic extracts were washed with aqueous HCl, water and brine, and dried. Solvent removal in vacuo afforded the crude tosylate which was dissolved in MeOH (10 mL). K_2CO_3 (500 mg, 3.6 mmol) was added to it and the mixture stirred for 4 h at room temperature. Solvent was evaporated under reduced pressure, water and EtOAc added, organic layer seperated and washed successively with water, brine and then dried. Solvent removal under reduced pressure and column chromatography of the residue (silica gel, 0-10 % EtOAc/hexane) afforded **VI**. Yield: 0.145 g (77.1%); colourless oil; $[\alpha]_D^{26}$ +12.9 (*c* 1.0, $CHCl_3$) [lit.[31c] $[\alpha]_D^{25}$ +12.9 (*c* 1.15, $CHCl_3$)]; IR: 2936, 1738 cm^{-1}; ^1H NMR: δ 2.84-2.96 (m, 3H), 3.05 (d, *J* = 4.6 Hz, 1H), 3.11-3.17 (m, 1H), 3.64-3.71 (m, 1H), 7.33-7.47 (m, 5H). ^{13}C NMR: δ 38.2, 45.1, 53.0, 63.5, 126.9, 128.5, 129.3, 136.5.

(3S,4S,5R)-3-Methyl-4-*O*-(*tert*)-butyldiphenylsilyl-5,6-*O*-Cyclohexylidene-1-hexanol 177. To well cooled (0 ^oC) and stirred solution of **128** (4.0 g, 8.62 mmol) was injected $BH_3.Me_2S$ (1 M in hexane, 3mL). After stirring for 30 min, it was gradually brought to room temperature, and stirred for an additional 3 h. Ethanol (10 mL) was added dropwise followed by 3N aqueous NaOH (3 mL). The solution was cooled to 0 ^oC, H_2O_2 (4 mL, 30% solution) added slowly, and the reaction mixture brought to room temperature. After completion of reaction (*cf*. TLC, ~2 h), the mixture was poured into ice-water and extracted with Et_2O (70 mL). The organic layer was washed with water and brine, and dried. Removal of solvent in vacuo and chromatographic purification (silica gel, 5-15% EtOAc/hexane) afforded pure **177**. Yield: 2.99 g (72%); colourless oil; $[\alpha]_D^{24}$ +23.2 (*c* 1.60, $CHCl_3$); IR: 3435 cm^{-1}; ^1H NMR: δ 0.91 (d, *J* = 6.8 Hz, 3H), 1.05 (s, 9H), 1.35-1.52

(m, 12H), 1.61-1.72 (m, 2H), 3.36-3.48 (m, 2H), 3.62 (t, *J*=7.2Hz, 1H), 3.71 (dd, *J* = 2.2 and 6.4 Hz, 1H), 3.86-3.93 (m, 1H), 4.09-4.16 (m, 1H), 7.25-7.47 (m, 6H), 7.66-7.73 (m, 4H); ^{13}C NMR: δ 15.2, 19.3, 23.7, 23.8, 25.0, 26.9, 33.8, 34.5, 35.2, 35.9, 60.7, 67.4, 75.6, 77.5, 108.9, 127.3, 127.4, 129.5, 129.6, 133.4, 133.5, 135.8. Anal. Calcd. for $C_{29}H_{42}O_4Si$: C, 72.15; H, 8.77%. Found: C, 72.34; H, 8.52%.

(2*R*,3*S*,4*S*)-1,2-*O*-Cyclohexylidene-3-*O*-(*tert*)-butyldiphenylsilyl-4-Methyl-6-benzyloxyhexane 178. Reaction of **177** (2.80 g, 5.81 mmol) with BzCN (0.83 mL, 6.97 mmol) and Et_3N (1.2 mL, 8.71 mmol) in CH_2Cl_2 (15 mL), followed by work up, isolation and purification by column chromatography (silica gel, 0-10% EtOAc/hexane) furnished pure **178**. Yield: 3.06 g (90%); light yellow oil; $[\alpha]_D^{24}$ -8.7 (*c* 1.2, $CHCl_3$); IR: 1719, 909 cm^{-1}; ^{1}H NMR: δ 1.04 (d merged with s, 12H), 1.31-1.49 (m, 10H), 1.59-1.65 (m, 1H), 1.85-1.93 (m, 2H), 3.54-3.62 (m, 1H), 3.70 (dd, *J* = 1.8 and 7.0 Hz, 1H), 3.87-3.95 (m, 1H), 4.09-4.20 (m, 3H), 7.25-7.38 (m, 9H), 7.50-7.66 (m, 4H), 7.90-7.99 (m, 2H); ^{13}C NMR: δ 14.7, 19.3, 23.7, 25.0, 26.7, 26.9, 31.3, 34.4, 34.6, 35.9, 63.2, 67.6, 75.4, 77.3, 190.0, 127.4, 128.1, 129.4, 129.6, 130.3, 132.5, 133.3, 133.5, 135.8, 166.2.

(2*R*,3*S*,4*S*)-3-*O*-(*tert*)-butyldiphenylsilyl-4-Methyl-6-*O*-benzoyl-1,2,3,6-tetrahydroxy-hexane 179. A mixture of **178** (2.8 g, 4.78 mmol) in CH_2Cl_2 (25 mL) and aqueous 80% TFA (10 mL) was stirred for 3 h at 0 °C. The mixture was diluted with water (50 mL) and extracted with $CHCl_3$ (50 mL), the organic layer separated and the aqueous layer extracted with $CHCl_3$ (20 mL). The organic extract was washed successively with aqueous 2% $NaHCO_3$ (10 mL), H_2O (20 mL) and brine, and dried. Solvent removal in vacuo followed by column chromatography of the residue (silica gel, 0-5% MeOH/$CHCl_3$) furnished pure

179. Yield: 1.49 g (77.5%); colouless oil; $[\alpha]_D^{24}$ +6.72 (*c* 1.61, $CHCl_3$); IR: 3448, 1717 cm^{-1}; ^1H NMR: δ 1.03 (d, *J* = 6.98 Hz, 3H), 1.09 (s, 9H), 1.61-1.66 (m, 1H), 1.9-2.0 (m, 2H), 2.42 (broad s, 2H), 3.53-3.61 (m, 1H), 3.69-3.80 (m, 3H), 4.13-4.19 (m, 2H), 7.25-7.45 (m, 9H), 7.65-7.71 (m, 4H), 7.92-7.97 (m, 2H); ^{13}C NMR: δ 15.1, 19.4, 27.0, 31.3, 34.0, 63.4, 63.9, 72.8, 77.4, 127.4, 127.6, 128.1, 129.3, 129.7, 130.1, 132.6, 133.2, 135.8, 166.5. Anal. Calcd. for $C_{30}H_{38}O_5Si$: C, 71.11; H, 7.56%. Found: C, 71.33; H, 7.39%.

(3*S*,4*S*)-1-O-Benzoyl-3-methyl-4-O-tert-butyldiphenylsilyl-oct-5-ene 181. To a stirred solution of **179** (1.37 g, 2.7 mmol) in 60% aquous acetonitrile (25 mL) at room temperature was added $NaIO_4$ (1.16 g, 5.4 mmol). The mixture was stirred for ~2 h (*cf*. TLC), filtered, washed with EtOAc, and the organic layer was washed with water, brine and dried. Solvent was removed under reduced pressure to afford crude aldehyde **180**. Yield: 1.15 g (91%); $[\alpha]_D^{24}$ +30.50 (*c* 0.8, $CHCl_3$); IR: 1723 cm^{-1}; ^1H NMR: δ 1.16 (s merged with d, 12H), 1.68-1.72 (m, 1H), 1.90-2.12 (m, 2H), 3.98-4.02 (m, 1H), 4.24-4.32 (m, 2H), 7.33-7.42 (m, 8H), 7.63-7.98 (m, 5H), 7.97-7.99 (m, 2H), 9.61-9.66 (m, 1H); ^{13}C NMR: δ 15.3, 19.3, 26.9, 30.4, 34.9, 62.7, 81.1, 127.7, 128.2, 129.4, 129.9, 132.7, 135.6, 166.2, 204.0.

To a cooled (-60 ^oC) suspension of *n*-$C_3H_7PPh_3Br$ (1.4 g. 3.6 mmol) in THF (50 mL) was added *n*-BuLi (3.6 mL of 1 M in hexane). The resultant orange mixture was stirred for an additional 1 h. To it was added a solution of the aldehyde **180** (1.0 g, 2.12 mmol) in THF (20 mL) over a period of 45 min. The mixture was stirred for an additional 2 h at -60 ^oC, gradually brought to 0 ^oC and stirred further for 30 min. The reaction was quenched by adding aqueous saturated NH_4Cl and extracted with EtOAc (50 mL). The

organic layer was separated and the aqueous layer extracted with EtOAc (20 mL). The combined organic extracts were washed successively with H_2O and brine, and dried. Removal of solvent under reduced pressure and column chromatography (silica gel, 0-5% EtOAc/hexane) of the residue afforded pure **181**. Yield: 0.760 g (71.8%); colourless oil; $[\alpha]_D^{24}$ +17.2 (*c* 1.64, $CHCl_3$); IR: 1720 cm^{-1}; ^1H NMR: δ 0.74 (t, *J* = 7.6 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 3H), 1.09 (s, 9H), 1.44-1.62 (m, 2H), 1.62-1.88 (m, 3H), 4.23-4.30 (m, 2H), 4.35-4.42 (m, 1H), 5.29-5.45 (m, 2H), 7.33-7.48 (m, 9H), 7.66-7.71 (m, 4H), 8.00-8.05 (m, 2H); ^{13}C NMR: δ 13.7, 14.2, 19.2, 20.9, 26.8, 31.1, 37.0, 63.2, 72.4, 127.1, 127.3, 128.1, 128.3, 128.9, 129.2, 129.3, 130.3, 132.6, 132.8, 134.1, 135.7, 135.8, 166.4. Anal. Calcd. for $C_{32}H_{40}O_3Si$: C, 76.75; H, 8.05%. Found: C, 76.98; H, 7.86%.

(3*S*,4*S*)- 3-Methyl-4-O-tert-butyldiphenylsilyl-octan-1,4-diol 183. A mixture of **181** (0.70 g, 1.40 mmol) and 10% Pd-C (0.03 g) in EtOH (10mL) was magnetically stirred under a positive pressure of H_2 gas. After stirring for ~8 h, the mixture was diluted with Et_2O (15 ml), and the supernatant was passed through a 5 cm pad of silica gel. Removal of solvent under reduced pressure afforded crude **182** in almost quantitative yield. $[\alpha]_D^{24}$ + 12.6 (*c* 1.2, $CHCl_3$); colourless oil; IR: 1722 cm^{-1}; ^1H NMR: δ 0.71 (t, *J* = 6.6 Hz, 3H), 1.05 (s merged with d, 12H), 1.10-1.14 (m, 2H), 1.25-1.35 (m, 2H), 1.37-1.40 (m, 1H), 1.79-1.92 (m, 4H), 3.56-3.63 (m, 1H), 4.17-4.31 (m, 2H), 7.32-7.44 (m, 9H), 7.63-7.94 (m, 4H), 7.95-7.98 (m, 2H); ^{13}C NMR: δ 13.7, 15.2, 19.4, 22.4, 26.9, 27.8, 30.6, 32.3, 34.6, 63.4, 76.8, 127.1, 127.2, 128.1, 129.2, 129.3, 130.2, 132.6, 134.5, 135.8, 166.4.

Hydrolysis of **182** (0.60 g, 1.19 mmol) with K_2CO_3 (0.42 g, 2.98 mmol) in MeOH (5 mL), usual work up and column chromatography (silica gel, 0-10% EtOAc/hexane)

furnished pure **183**. Yield: 0.37 g (78.1%); colourless oil; $[\alpha]_D^{24}$ + 4.6 (*c* 1.4, $CHCl_3$); IR: 3471 cm^{-1}; ^1H NMR: δ 0.76 (t, *J* = 3.2 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H), 1.08 (m merged with s, 13H), 1.41-1.46 (m, 4H), 1.50-1.54 (m, 1H), 1.97 (broad s, 1H), 3.50-3.58 (m, 3H), 7.37-7.44 (m, 6H), 7.68-7.73 (m, 4H); ^{13}C NMR: δ 13.9, 15.5, 19.5, 22.5, 27.1, 28.0, 32.6, 34.3, 34.5, 60.6, 77.4, 127.3, 127.4, 129.4, 129.5, 124.1,134.5, 136.0. Anal. Calcd. for $C_{25}H_{38}O_2Si$: C, 75.32; H, 9.61%. Found: C, 75.11; H, 9.77%.

***trans*-Oak lactone VII:** Oxidation of **183** (0.350 g, 0.88 mmol) with PCC (0.218 g, 1.49 mmol) and NaOAc (0.041 mg, 0.50 mmol) in CH_2Cl_2 (30 mL), and work-up followed by removal of solvent in vacuo yielded crude aldehyde (0.310 g). This was desilylated with Bu_4NF (1.3 mL, 1.3 mmol, 1 M in THF) in THF (10 mL) at 0 °C. Usual work-up and removal of solvent in vacuo yielded relatively unstable lactol **184** (0.080 g), which on oxidation with PCC (0.185 g, 0.860 mmol) in CH_2Cl_2 (10 mL), followed by usual work-up and colum chromatography (silica gel, 0-15 % EtOAc/hexane) afforded pure **VII**. Yield: 0.065 g (47.7% overall yield in three steps); colourless oil; $[\alpha]_D^{24}$ + 93.5 (*c* 0.25, $CHCl_3$) [lit.[36e] $[\alpha]_D^{24}$ + 93 (c 0.2, $CHCl_3$)]; ^1H NMR: δ 0.91 (t, *J* = 7.2 Hz, 3H), 1.02 (d, *J* = 6.8 Hz, 3H), 1.19-1.65 (m, 6H), 2.16-2.21 (m, 2H), 2.62-2.71 (m. 1H), 3.96-4.02 (m, 1H); ^{13}C NMR: δ 14.3, 17.2, 22.7, 27.5, 33.8, 36.0, 37.9, 87.6, 176.7.

REFERENCES

1. Wender, P. A. *Chem. Rev.* **1996**, *96*, 1.

2. (a) Ward, R. S. In: *Selectivity in Organic Synthesis*, Wiley, 1999. (b) Hoz, A. D. L.; Diaz-Ortiz, A.; Moreno, A. *Curr. Org. Chem*. **2004**, *8*, 903.

3. (a) Chattopadhyay, A.; Mamdapur, V. R. *J. Org. Chem*. **1995**, *60*, 585. (b) Chattopadhyay, A. *J. Org. Chem*. **1996**, *61*, 6104.

4. Bentley, R. *Stereochemistry*, Tam, C. H. ed., Elsevier: Amsterdam, 1982.

5. (a) Stinson, S. C. *Chem. Eng. News*. **1992**, *70*, 46. b) Chan, A. S. C. *Chem. Tech*. **1993**, *23*, 46.

6. Tombo, R. G. M.; Bellus, D. *Angew. Chem. Intl. Ed. Engl.* **1991**, *30*, 1193.

7. Tessier, J.; Herve, J. J. *Deltamethrine*, Roussel Uclaf ed., 1982, 25.

8. Ariens, E.J. *Proc. 1st Int. Pharmacol. Meet*. Vol 7, Pergamon Press, Oxford, 1963, 247.

9. Renynolds, G. P.; Elsworth, J. D.; Blau, K.; Sandler, M.; Lees, A. J.; Stern, G. M. *Br. J. Clin. Pharmacol*. **1978**, *6*, 542.

10. (a) Hanessian, S. *Total Synthesis of Natural Products: The Chiron Approach*, Pergamon Press, Oxford, 1986. (b) Mori, K. *The Total Synthesis of Natural Products*, Apsimon, J., ed., John Wiley & Sons, 1992. (c) Hanessian, S. *Pure Appl. Chem*. **1993**, *65*, 1189.

11. Arnold, L.D.; Drover, J. C.; Vederas, G. J. C. *J. Am. Chem. Soc*. **1987**, *109*, 4649.

12. (a) Blaschke, G. *Angew. Chem. Intl. Ed. Engl*. **1980**, *19*, 13. (b) Pirkle, W. H.; Hoekstra, M. S. *J. Org. Chem.* **1974**, *39*, 3904. (c) Dobashi, A.; Oka, K.; Hara,

S. *J. Am. Chem. Soc.* **1980**, *102*, 7122. (d) Wilen, S. H.; Collet, A.; Jaques, J. *J. Am. Chem. Soc*., **1977**, *33*, 2725.

13. *Asymmetric Synthesis*, Atiken, A.; Kilenyi, S. N. eds., Blackie Academic & Professional, Glasgow, 1994, 85.

14. (a) Wong, C. H.; Whitesides, G. M. In: *Enzymes in Synthetic Organic Chemistry*, Elsevier Sci., 1994. (b) Santiniello, E.; Ferraboschi, P.; Grisenti, P.; Manzocchi, A. *Chem. Rev*. **1992**, *92*, 1071.

15. (a) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 2. (b) Stephenson, G. R., *Advanced Asymmetric Synthesis*, Chapman & Hall, 1996. (c) Van Draanen, N. A.; Arseniayadis, Crimmins, M. T.; Heathcock, C. H. *J. Org. Chem*. **1991**, *56*, 2499. (d) Mulzer, J.; Altenbach, H. J.; Braun M. Krohn, K.; Reissig, H. U. *Organic Synthesis Highlights*, VCH: Weinheim, 1991, pp-1. (e) *Asymmetric Synthesis*, Morrison, J. D., ed., Academic Press: New York, 1983, pp-1. (f) Mukaiyama, T. *Org. React*. **1982**, *28*, 203. (g) Marshall, J. A. *Chem. Rev*. **1996**, *96*, 31. (h) Hoffman, R. W. *Angew. Chem. Int. Ed. Engl*. **1987**, *26*, 489. (i) Heathcock, C. H. *Comprehensive Organic Synthesis*, Trost, B. M., ed., Pergamon Press: Oxford, 1991, Vol. 2, pp-181. (j) Elliel, E. L.; Otsuka, S. *Asymmetric Reactions and Processes in Chemistry*, ACS Symposium Series 185, pp-982. (k) Masamune, S.; Choy, W.; Peterson, J. S.; Sita, L. R. *Angew. Chem. Int. Ed. Engl*. **1985**, 24, 1. (l) Garcý´a-Fortanet, J.; Murga, J.; Carda, M.; Marco, J. A. *Org. Lett.* **2003,** *5*, 1447**,** and references cited therein.

16. Fischer, E. *Berchite* **1894**, *27*, 3210.

17. Hanessian, S.; Maji, D. K.; Govindan, S.; Matera, R.; Tintelnot-Blomley, M. *J. Org. Chem.* **2010**, *75*, 2861.

18. Myers, A.G.; Yang, B.H.; Chen, H.; Gleason, J.L. *J. Am. Chem. Soc*. **1994**, *116*, 9361.

19. Chan, P. C. M.; Chong, J. M. *J. Org. Chem.* **1988**, *53*, 5584.

20. Hills, I. D.; Fu, G. C. *Angew. Chem. Int. Ed. Engl.* **2003**, *42***,** 3921.

21. Mengel, A.; Reiser, O. *Chem. Rev*. **1999**, *99*, 1191.

22. (a) Cram, D. J.; Wilson, D. R. *J. Am. Chem. Soc*. **1963**, *85*, 1245. (b) Cram, D. J.; Elhafez, F. A. A. *J. Am. Chem. Soc*. **1952**, *74*, 5828. (c) Cram, D. J.; Greene, F. D. *J. Am. Chem. Soc*. **1953**, *75*, 6004.

23. First direct observation of Cram-Chelate transition states: (a) Rettz, M. T.; Huellmann, M.; Seitz, T. *Angew. Chem*. **1987**, *99*, 478. (b) Rettz, M. T.; Huellmann, M.; Seitz, T. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 477. (c) Rettz, M. T.; Raguse, B.; Seitz, T. *Tetrahedron* **1993**, *49*, 8561. (d) Rettz, M. T. *Acc. Chem. Res.* **1993**, *26*, 462.

24. (a) Che´rest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *18*, 2199. (b) Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145. (c) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61. (d) Anh, N. T.; Eisenstein, O. *Tetrahedron Lett.* **1976**, *3*, 155.

25. (a) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920. (b) Denmark, S. E.; Henke, B. R. *J. Am. Chem.Soc.* **1991**, *113*, 2177.

26. (a) Cahn, R. S.; Ingold, C. K.; Prelog, V. *Angew. Chem. Intl. Ed. Engl*. **1966**, *5*, 385. (b) Eliel, E. L. *Tetrahedron* **1974**, *30*, 1503.

27. (a) Lee, V. J. *In: Comprehensive Organic Synthesis*. Trost, B. M.; Fleming, I. eds.; Pergamon Press: Oxford, 1991, Vol. 4, pp-69. (b) Lee, V. J. In: *Comprehensive Organic Synthesis*. Trost, B. M.; Fleming, I. eds.; Pergamon Press: Oxford, 1991, Vol. 4, pp-139. (c) Kitamura, M., Miki, T., Nakano, K., Noyori, R. *Bull. Chem. Soc. Jpn*. **2000**, *73*, 999.

28. (a) In: *Asymmetric Synthesis*. Morrison, J. D. ed.; Academic Press: NY, 1983, Vol. 2, Chapter 2. (b) Singh, V. K. *Synthesis* **1992**, 605.

29. (a) Daview-Colmen, M. T.; Rivett, D. E. A. *Fortschr. Chem. Org. Naturst.* **1989**, *55*, 1. (b) Ohloff, G. *Fortschr. Chem. Org. Naturst.* **1978**, *35*, 431. (c) Chattopadhyay, A.; Hassarajani, S. A.; Dhotare, B. *J. Org. Chem*. **1999**, *64*, 6874. (d) Chattopadhyay, A. *Tetrahedron: Asymmetry* **1997**, *8*, 2727. (e) Chattopadhyay, A.; Salaskar, A. *Perkin Trans. I* **2002**, 785. (f) Dhotare, B.; Hassarajani, S. A.; Chattopadhyay, A. *Enantiomer* **1999**, *4*, 431. (g) Dhotare, B.; Chattopadhyay, A. *Tetrahedron Lett.* **2005**, *46*, 3103. (h) Chattopadhyay, A.; Vichare, P.; Dhotare, B. *Tetrahedron Lett.* **2007**, *48*, 2871.

30. (a) Ohkuma, T.; Noyori, R. In: *Comprehensive Asymmetric Catalysis*. Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. eds.; Springer: Berlin, 1999, Vol. I, and 2004, Supplement I. (b) Blaser, H. U.; Spindler, F.; Studer, M. *Appl. Catal. A: Gen.* **2001**, *221*, 119.

31. (a) Nakamura, K.; Matsuda, T. *Curr. Org. Chem*. **2006**, *10*, 1217. (b) Panke, S.; Wubbolts, M. *Curr. Opin. Chem. Biol*. **2005**, *9*, 188. (c) Kroutil, W.; Mang, H.; Edegger, K.; Faber, K. *Curr. Opin. Chem. Biol*. **2004**, *8*, 120.

32. For some selective references see: (a) Kaluzna, I. A.; Matsuda, T.; Sewell, A. K.; Stewart, J. D. *J. Am. Chem. Soc*. **2004**, *126*, 12827. (b) Poessl, T. M.; Kosjek, B.; Ellmer, U.; Gruber, C. C.; Edegger, K.; Faber, K.; Hildebrandt, P.; Bornscheuer, U. T.; Kroutil, W. *Adv. Synth. Catal*. **2005**, *347*, 1827. (c) Edegger, K.; Stampfer, W.; Seisser, B.; Faber, K.; Mayer, S. F.; Oehrlein, R.; Hafner, A.; Kroutil, W. *Eur. J. Org. Chem*. **2006**, 1904. (d) Ema, T.; Yagasaki, H.; Okita, N.; Takeda, M.; Sakai, T. *Tetrahedron* **2006**, *62*, 6143. (e) *Modern reduction methods,* Andersson, P.G.; Munslow, I. J. ed. Wiley-VCH, 2008. (f) Chartrain, M.; Greasham, R.; Moore, J.; Reider, P.; Robinson, D.; Buckland, B. *J. Mol. Catal. B: Enzym.* **2001**, *11*, 503. (g) Moore, J. C.; Pollard, D. J.; Kosjek, B.; Devine, P. N. *Acc. Chem. Res.* **2007**, *40*, 1412.

33. (a) Bawa, R. A.; Ajjabou, F.; Shalfooh, E. *J. Phy. Sc.* **2008**, *19*, 1. (b) Patel R. N.; Goswami, A.; Chu, L.; Donovan, M. J.; Nanduri, V.; Goldberg, S, Johnston, R.; Siva, P. J.; Nielsen, B.; Fan, J.; He, W.; Shi, Z.; Wang, K. Y.; Eiring, R.; Cazzulino, D.; Singh, A.; Mueller, R. *Tetrahedron: Asymmetry* **2004**, *15*, 1247.

34. (a) Daverio, P.; Zanda, M. *Tetrahedron: Asymmetry* **2001**, *12*, 2225. (b) Corey, E. J.; Helal, C. J. *Angew*. *Chem., Int*. *Ed*. **1998**, 37, 1987.

35. (a) Brown, H. C.; Krishnamurthy, S. *Tetrahedron* **1979**, *35*, 567. (b) Brown, H. C.; Ramachandran, P. V. In: *Reductions in Organic Synthesis*, ACS Symposium Series, Chapter 1, pp-1. (c) Dhotare, B.; Salaskar, A.; Chattopadhyay, A. *Synthesis*, **2003**, *16*, 2571.

36. (a) Hirao, A.; Nakahama, S.; Mochizuki, D.; Itsuno, S.; Ohowa, M.; Yamazaki, N. *J. Chem. Soc., Chem. Commun*. **1979**, 807. (b) Itsuno, S.; Sakurai, Y.;

Shimizu, K.; Ito, K. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1859. (c) Corey, E. J.; Helal, C. J. *Angew. Chem. Int. Ed. Engl*. **1998**, *37*, 1986. (d) Nagata, T.; Yorozu, K.; Yamada, T.; Mukaiyama, T. *Angew. Chem. Int. Ed. Engl*. **1995**, *34*, 2145. (e) Cordes, D. B.; Nguyen, T. M.; Kwong, T. J.; Suri, J. T. ; Luibrand, R. T.; Singaram, B. *Eur. J. Org. Chem.* **2005**, 5289.

37. (a) Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed*. **2001**, *40*, 40. (b) Frèchet, J. M.; Bald, E.; Lecavalier, P. *J. Org. Chem*. **1986**, *51*, 3642. (c) Yamaguchi, S.; Mosher, H. S. *J. Org. Chem*. **1973**, *38*, 1870. (d) Beck, A. K.; Dahinden, R.; Kühnle, F. N. M. *Am. Chem. Soc. Symp. Ser*. **1996**, *641*, 52. (e) Ren, Y.; Tian, X.; Sun, K.; Xu, J.; Xu, X.; Lu, S. *Tetrahedron Lett*. **2006**, *47*, 463. (f) Midland, M. M.; Nguyen, N. H. *J. Org. Chem*. **1981**, *46*, 4107.

38. (a) Noyori, R. 'Nobel Lecture', *Angew. Chem. Int. Ed*. **2002**, *41*, 2008. (b) Noyori, R.; Kitamura, M.; Ohkuma, T. *Proc. Natl. Acad. Sci*. **2004**, *101*, 5356.

39. Hu, A.; Lin, W. *Org. Lett.* **2005**, *7*, 455.

40. (a) Woodward, S. S.; Finn, M. G.; Sharpless, K. B. *J. Am. Chem. Soc*. **1991**, *113*, 106. (b) Jacobsen, E. N.; Marko, I.; France, M. B.; Svendsen, J. S.; Shrpless, K. B. *J. Am. Chem. Soc*. **1989**, *111*, 737.

41. (a) Criegee, R. *Angew. Chem.* **1937**, *50*, 153. (b) Schroder, M. *Chem. Rev.* **1980**, *80*, 187. (c) Sharpless, K. B.; Akashi, K. J. *J. Am. Chem. Soc*. **1976**, 98, 1986. (d) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett*. **1976**, 1973. (e) Minato, M.; Yamamoto, K.; Tsuji. J. *J. Org. Chem*.**1990**, *55*, 766.

42. Hentges, S. G.; Sharpless, K. B. *J. Am. Chem. Soc*. **1980**, *102*, 4263.

43. (a) Cleare, M. J.; Hydes, P. C.; Griffth, W. P.; Wright, M. J. *J. Chem. Soc. Dalton Trans*. **1977**, 941. (b) Griffith, W. P.; Shapski, A. C.; Woode, K. A.; Wright, M. J. *J. Inorg. Chim. Acta*. **1978**, *31*, L413.

44. (a) Oishi, T.; Hirama, M. *Tetrahedron Lett*. **1992**, *33*, 639. (b) Imada, Y.; Saito, T.; Kawakami, T.; Murahishi, S. -I. *Tetrahedron Lett*. **1992**, *33*, 5081.

45. Hanessian, S.; Meffre, P.; Girard, M.; Beaudoin, S.; Sanceau, J. Y.; Bennani, Y. L. *J. Org. Chem*. **1993**, *58*, 1991.

46. (a) Jacobsen, E. N.; Marko, L.; Mungall, W. S.; Schroder, G.; Sharpless, K. B. *J. Am. Chem. Soc*. **1988**, *110*, 1968. (b) Wai. J. S. M.; Marko, I.; Sevendsen, J. S.; Finn, M. G.; Jacobsen, E. N.; Sharpless, K. B. *J. Am. Chem. Soc*. **1989**, *111*, 1123. (c) Kwong, H. –L.; Sorato, C.; Ogino, Y.; Chen, S.; Sharpless, K. B. *Tetrahedron Lett*. **1990**, *31*, 2999. (d) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. –S.; Kwong, H. –L.; Morikawa, K.; Wang, Z. –M.; Xu, D.; Zang, X. –L. *J. Org. Chem*. **1992**, *57*, 2768. (e) Crispino, G. A.; Jeong, K. –S.; Kolb, H. C.; Wang, Z. –M.; Xu, D.; Sharpless, K. B. *J. Org. Chem*. **1993**, *58*, 3785. (f) Sharpless, K. B.; Amberg, W.; Beller, M.; Chen, H.; Hartung, J.; Kawanami, Y.; Lubben, D.; Manoury, E.; Ogino, Y.; Shibata, T.; Ukita, T. *J. Org. Chem*. **1991**, *56*, 4585. (g) Vanhessche, K. P.M.; Wang, Z. –M.; Sharpless, K. B. *Tetrahedron Lett*. **1994**, *35*, 3469.

47. Soai, K.; Niwa, S. *Chem. Rev*. **1992**, *92*, 883.

48. Goldfuss, B.; Steigelmann, M.; Khan, S. J; houk, K. N. *J. Org. Chem*., **2000**, *65*, 77.

49. (a) Noyori, R.; Kitamura, M. *Angew. Chem. Intl. Ed. Engl.* **1991**, *30*, 49. (b) Soai, K.; Niwa, S. *Chem. Rev*. **1992**, *92*, 833. (c) Arnold, L. A.; Imbos, R.; Mandoli, A.; De Vries, A. H. M.; Naaz, R.; Feringa, B. L. *Tetrahedron*, **2000**, *56*, 2865.

50. Ko, D,-H.; Kim, K. H.; Ha, D, -C. *Org. Lett*. **2002**, *4*, 3759.

51. (a) Bolm, C.; Ewald, M. *Tetrahedron Lett*. **1990**, *31*, 5011. (b) Jansen, J. F. G. A.; Feringa, B. L. *Tetrahedron:Asymmetry* **1992**, *3*, 581. (c) Uemura, M.; Miyaki, R.; Nakayama, K.; Hayashi, I. *Tetrahedron:Asymmetry* **1992**, *3*, 713. (d) Asami, M.; Usui, K.; Higuchi, S.; Inoue, S. *Chem. Lett*. **1994**, 297. (e) Corma, A.; Iglesias, M.; Martin, V.; Rubio, J.; Sanchez, F. *Tetrahedron:Asymmetry* **1992**, *3*, 845.

52. (a) McNeill, A. H.; Thomas, E. J. *Tetrahedron Lett.* **1990**, *31*, 6239. (b) Carey, J. S.; Thomas, E. J. *J. Chem. Soc., Chem. Commun.* **1994**, 283. (c) Carey, J. S.; Thomas, E. J. *Synlett* **1992**, 585. (d) Carey, J. S.; Thomas, E. J. *Tetrahedron Lett*. **1993**, *34*, 3935. (e) Stanway, S. J.; Thomas, E. J. *J. Chem. Soc., Chem. Commun.* **1994**, 285. (f) McNeill, A. H.; Thomas, E. J. *Synthesis* **1994**, 322. (g) Hallet, D. J.; Thomas, E. J. *Tetrahedron:Asymmetry* **1995**, *6*, 2575. (h) Thomas, E. J. *J. Chem. Soc., Chem. Commun*. **1997**, 411. (i) Hobson, L. A.; Vincent, M. A.; Thomas, E. J.; Hillier, I. H. *J. Chem. Soc., Chem. Commun*. **1998**, 899. (j) Nishigaichi, Y.; Kuramoto, M.; Takuwa, A. *Tetrahedron Lett*. **1995**, *36*, 3353. (k) Nishigaichi, Y.; Yoshikawa, M.; Takigawa, Y.; Takuwa, A. *Chem. Lett*. **1996**, *25*, 961.

53. Marshall, J. A. *Chem. Re*v. **1996**, *96*, 31.

54. Barbero, A.; Pulido, F. J.; Rincoń, J. A. *J. Am. Chem. Soc.* **2003**, *125*, 12049.

55. (a) Yamamoto, Y.; Asao, N. *Chem. Rev.* **93**, 2207. (b) Cheng, H. –S.; Loh, T-. P. *Pure Appl. Chem.* **2005**, *77*, 1199.

56. (a) Nicolaou, K. C.; Kim, D. W.; Baati, R. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 3701. (b) Nicolaou, K. C.; Ninkovic, S.; Sarabia, F.; Vourloumis, D.; He, Y.; Vallberg, H.; Finlay, M. R. V.; Yang, Z. *J. Am. Chem. Soc.* **1997**, *119*, 7974. (c) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 2. (d) Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569. (e) Germay, O.; Kumar, N.; Thomas, E. J. *Tetrahedron Lett*. **2001**, *42*, 4969. (f) Romo, D.; Meyer, S. D.; Johnson, D. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 7906. (g) Kobayashi, J.; Ishibashi, M. *Chem. Rev*. **1993**, *93*, 1753. (h) Doi, Y.; Ishibashi, M.; Kobayashi, J. *Tetrahedron* **1996**, *52*, 4573, and references cited therein.

57. (a) Okachi, T.; Onaka, M. *J. Am. Chem. Soc.* **2004**, *126*, 2306. (b) Wadamoto, M.; Yamamoto, H. *J. Am. Chem. Soc.*, **2005**, *127*, 14556. (c) Inoue, M.; Suzuki, T.; Nakada, M. *J. Am. Chem. Soc.*, **2003**, *125*, 1140.

58. (a) Panek, J. S. In: *Comprehensive Organic Synthesis*. Schreiber, S. L. ed.; Pergamon: Oxford, 1991, vol. 1, 595. (b)Yamamoto, Y.; Asao, N. *Chem. Rev*. **1993**, *93*, 2207. (c) Marshall, J. A. *Chem. Rev*. **1996**, *96*, 31. (d) *Organic Synthesis in Water*. Grieco, P. A. ed.; Blackie, London, 1998, and references therein. (e) Yamaguchi, M. In: *Main Group Metals in Organic Synthesis*. Yamamoto, H.; Oshima, K. eds., Wile-VCH: Weinheim, 2004, vol. 1, pp-307. (f) Kim, E.; Gordon, D. M.; Schmid, W.; Whitesides, G. M. *J. Org. Chem.*

1993, *58*, 5500. (g) McCluskey, A. *Green Chem*. **1999**, 167. (h) Fukuma, T.; Lock, S.; Miyoshi, N.; Wada, M. *Chem. Lett*. **2002**, 376.

59. (a) Blomborg, C. In: *The Barbier Reactions and Related One Step Processes*, Springer, Berlin, 1993. (b) Lindstrom, U. M. *Chem. Rev.* **2003**, *103*, 2751 and references cited therein. (c) Li. C.J. *Chem. Rev.* **1993**, *93*, 2023. (d) Mulzer, J.; Altembach, H. J.; Braun, M.; Krohn, K.; Reissig, H.U. *Organic Synthesis Highlights*; VCH: Weinheim, 1991, 71. (e) Welton, T. *Chem. Rev*. **1999**, *99*, 2071.

60. (a) Petrier, C.; Luche, J. L. *J. Org. Chem*. **1985**, *50*, 910. (b) Einhorn, C.; Luche, J. L. *J. Organomet. Chem*. **1987**, *322*, 177. (c) Petrier, C. J.; Luche, J. L. *Tetrahedron Lett*. **1985**, *26*, 1449. (d) Luche, J. L.; Cintas, P. *Active Metals*, Furstner, A. ed.; VCH publishers; New York, 1996, pp-133.

61. (a) Li, C. J.; Meng, Y.; Xiang-Hui Y. *J. Org. Chem.* **1997**, *62*, 8632-8633. (b) Nokami, J.; Otera, J.; Sudo, T.; Okawara, R. *Organometallics* **1983**, *2*, 191. (c) Nokami, J.; Wakabayashi, S.; Okawara, R. *Chem. Lett.* **1984**, 869. (d) Zhou, J. Y.; Chen, Z. G.; Wu, S. H. *Chem. Commun.* **1994**, 2783. (e) Li, X. R.; T. P. Loh, *Tetrahedron:Asymmetry* **1996**, *7*, 1535. (f) Wang, Z. Y.; Zha, Z. G.; Zhou, C. L. *Org. Lett*. **2002**, *4*, 1683. (g) Zha, Z. G.; Wang, Y. S.; Yang, G..; Zhang, L.; Wang, Z. Y. *Green Chem.* **2002**, *4*, 578. (h) Tan, K. T.; Chng, S. S.; Cheng, H. S.; Loh, T. P. *J Am. Chem. Soc*. **2003**, *125*, 2958.

62. (a) Akiyama, T.; Iwai, J. *Tetrahedron Lett.* **1997**, *38*, 853. (b) LaRonde, F. J.; Brook, M. A. *Can. J. Chem.* **2003**, *81*, 1206. (c) Fargeas, V.; Zammattio, F.; Chrétien, J. M.; Bertrand, M, J.; Paris, M.; Quintard, J. P. *Eur. J. Org. Chem.*

2008, 1681. (d) Fargeas, V.; Zammattio, F.; Chrétien, J. M.; Bertrand, M, J.; Paris, M.; Quintard, J. P. *Eur. J. Org. Chem.* **2008**, 1681.

63. (a) Araki, S.; Ito, H.; Butsugan, Y. *J. Organomet. Chem*. **1988**, *347*, 5. (b) Smith, K.; Lock, S.; El-Hiti, G. A.; Wada, M.; Miyoshi, M. *Org. Biomol. Chem*. **2004**, *2*, 935. (c) Li, L,-H.; Chan, T. H. *Can. J. Chem*. **2001,** *79*, 1536.

64. (a) Nair, V.; Ros, S.; Jayan, C. N.; Pillai, B. S. *Tetrahedron* **2004**, *60*, 1959. (b) Augé, J.; Lubin-Germain, N. Uziel, J. *Synthesis* **2007**, 1739.

65. (a) Araki, S.; Ito, H.; Butsugan, Y. *J. Org. Chem*. **1988**, *53*, 1831. (b) Chan, Y. H.; Yang, Y. *J. Am. Chem. Soc*. **1999**, *121*, 3228. (c) Gordon, C. M.; Ritchie, C. *Green Chem*. **2002**, 124. (d) Hirashita, T.; Kamei, T.; Satake, M.; Horie, T.; Shimizu, H.; Araki, S. *Org. Biomol. Chem*. **2003**, *21*, 3799. (e) Paquette, L. A.; Mitzel, T. M. *J. Am. Chem. Soc*. **1996**, *118*, 1931-1937. (f) Paquette, L. A.; Mitzel, T. M. *J. Org. Chem*. **1996**, *61*, 8799-8804. (g) Loh, T.-P.; Tan, K.-T.; Yang, J.-Y.; Xiang, C.-L. *Tetrahedron Lett*. **2001**, *42*, 8701.

66. (a) Araki, S.; Ito, H.; Butsugan, Y. *Appl. Organomet. Chem*. **1988**, *2*, 475. (b) Wang, Z.; Yuan, S.; Li, C. –J. *Tetrahedron Lett*. **2002**, *43*, 5097. (c) Han, Y.; Chi, Z.; Huang, Y.-Z. *Synth. Commun*. **1999**, *43*, 1287. (d) Andrews, P. C.; Peatt, A. C.; Raston, C. L. *Tetrahedron Lett*. **2004**, *45*, 243. (e) Tsuji, T.; Usugi, S.-I.; Yorimitsu, H.; Shinokubo, H.; Matsubara, S.; Oshima, K. *Chem. Lett*. **2002**, 2. (f) Han, Y.; Huang, Y.-Z. *Tetrahedron Lett*. **1994**, *35*, 9433. (g) Lee, P. H.; Kim, H.; Lee, K. *Adv. Synth. Catal*. **2005**, *347*, 1219. (h) Gohain, M.; Prajapati, D. *Chem. Lett*. **2005**, 90. (i) Laskar, D. D.; Gohain, M.; Prajapati, D.; Sandhu, J. S. *New J. Chem*. **2002**, *26*, 193. (j) Yamaguchi, M.; Sotokawa,

T.; Hirama, M. *Chem. Commun*. **1997**, 743. (k) Usugi, S.-I.; Yorimitsu, H.; Oshima, K. *Tetrahedron Lett*. **2001**, *42*, 4535.

67. (a) Nokami, J.; Ohga, M.; Nakamoto, H.; Matsubara, T.; Hussain, I.; Kataoka, K. *J. Am. Chem. Soc*. **2001**, *123*, 9168. (b) Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *Org. Lett*. **2005**, *7*, 3577. (c) Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *J. Organometallic Chem*. **2007**, *692*, 505.

68. Wasserscheid, P.; Kiem, W. *Angew. Chem. Int. Ed*. **2000**, *39*, 3772.

69. (a) Chauvin, Y.; Einloft, S.; Olivier, H. *Ind. Eng. Chem. Res*. **1995**, *34*, 1149. (b) Gilbert, B.; Chauvin, Y.; Olivier, H.; Di Macro-Van Tiggelen, F. *J. Chem. Soc. Dalton Trans*. **1995**, 3867. (c) Gui, J.; Deng, Y.; Hu, Z.; Sun, Z. *Tetrahedron Lett*. **2004**, *45*, 2681. (d) Yeung, K, -S.; Farkas, M, E.; Qiu, Z.; Yang, Z. *Tetrahedron Lett*. **2002**, *43*, 5793. (e) Xu, L.; Chen, W.; Xiao, J. *Organometallics*, **2000**, *19*, 1123, and references cited therein. (f) Tait, S.; Osteryoung, R.A. *Inorg. Chem*. **1984**, *23*, 4352. (g) Jiang, T.; Gao, H.; Han, B.; Zhao, G.; Chang, Y.; Wu, W.; Gao, L.; Yang, G. *Tetrahedron Lett*. **2004**, *45*, 2699. (h) Gordon, C. M.; McCluskey, A. *Chem. Commun*. **1999**, 1431. (i) Chen, W.; Xu, L.; Chatterton, C.; Xiao, J. *Chem. Commun.* **1999**, 1247. (j) Song, C. E.; Shim, W. H.; Roh, E. J.; Choi, J. H. *Chem. Commun.* **2000**, 1695.

70. (a) Wilkes, J.S.; Levisky, J.A.; Wilson, R.A.; Hussey, C.L. *Inorg. Chem*. **1982**, *21*, 1263. (b) Carlin, R.T.; Wilkes, J.S. In: *Chemistry of Nonaqueous Solutions* Mamantov, G.; Popov, A. I. eds., VCH, Weinheim, 1994, pp.277. (c) Chan, B.K.M.; Chang, N.H.; Grimmet, R.M. *Aust.J.Chem*.**1977**, *30*, 2005.

71. Freemantle, M. *Chem. Eng. News* **1998**, *76*, 32.

72. Karodia, N.; Guise, S.; Newlands, J.; Anderson, -A. *Chem. Commun*. **1998**, 2341.

73. (a) Cintas, P. *Synlett* **1995**, 1087. (b) Podlech, J; Maier, T. C. S*ynthesis* **2003**, 633.

74. (a) Li, C. J.; Chan, T. H. *Tetrahedron Lett.* **1991**, *32*, 7017. (b) Li, C. J.; Chan, T. H. *Tetrahedron* **1999**, *55*, 11149.

75. (a) For reviews see: Araki, S.; Hirashita, T. *Indium in Organic Synthesis* In: Yamamoto, H. and Oshima, K. Ed., *Main Group Metals in Organic Synthesis*, Wiley-VCH, Weinheim 2004, pp-323. (b) Paquette, L.A. *Synthesis* **2003**, 765–774. (c) Loh, T.-P.; Yin, Z.; Song, H.-Y.; Tan, K.L. *Tetrahedron Lett.* **2003**, *44*, 911. (d) Augé, J.; Lubin-Germain, N.; Marque, S.; Seghrouchni, L. *J. Organomet. Chem.* **2003**, *679*, 79. (e) Loh, T.-P.; Zhou, J.-R. *Tetrahedron Lett.* **2000**, *41*, 5261. (f) Loh, T.-P.; Zhou, T.-P. *Tetrahedron Lett.* **1999**, *40*, 9115.

76. (a) Fujita, S.; Kanamaru, H.; Senboku, H.; Arai, M. *Int. J. Mol. Sci.* **2006**, *7*, 438. (b) Shaabani, A.; Soleimani, E.; Darvishi, M. *Monatsh Chem*. **2007**, *138*, 43. (c) Boovanahalli, S. K.; Kim, D. W.; Chi, D. Y. *J. Org. Chem.* **2004**, *69*, 3340.

77. (a) Law, M. C.; Cheung, T. W.; Wong, K. Y.; Chan, T. K. *J. Org. Chem.* **2007**, *72*, 923. (b) Law, M. C.; Wong, K. Y.; Chan, T. H. *Green Chem*. **2002**, *4*, 161.

78. Miao, W.; Chung, L. W.; Wu, Y. –D.; Chan, T. H. *J. Am. Chem. Soc*. **2004**, *126*, 13326.

79. (a) Chan, T. H.; Li, C. J.; Lee, M. C.; Wei, Z. Y. *Can. J. Chem*. **1994**, *72*, 1181. (b) Wasserscheid, P.; Welton, T. In: *Ionic Liquids in Synthesis*, Chap 6, Endres, F.; Welton, T. eds., Wiley-VCH Verlag GmbH & Co. KGaA, 2002, pp-289. (c) Dai, J. C.; Wu, X. T.; Hu, S. M.; Fu, Z. Y.; Zhang, J. J.; Du, W. X.; Zhang, H. H.; Sun, R. Q. *Eur. J. Inorg. Chem.* **2004**, 2096.

80. (a) Walborsky, H. M. *Acc. Chem. Res*. **1990**, *23*, 286. (b) Walling, C. *Acc. Chem. Res*. **1991**, *24*, 255. (c) Li, C.-J.; Zhang, W.-C. *J. Am. Chem. Soc*. **1998**, *120*, 9102.

81. (a) Bini, R.; Chiappe, C.; Marmugi, E.; Pieraccini, D. *Chem. Commun*. **2006**, 897. (b) Dai, J. C.; Wu, X. T.; Hu, S. M.; Fu, Z. Y.; Zhang, J. J.; Du, W. X.; Zhang, H. H.; Sun, R. Q. *Eur. J. Inorg. Chem.* **2004**, 2096. (c) Choi, D. S.; Kim, D. H.; Shin, U. S.; Deshmukh, R. R.; Lee, S.-g.; Song, C. E. *Chem.. Commun*. **2007**, 3467.

82. Kim, Y.J.; Varma, R. S. *J. Org. Chem.* **2005**, *70*, 7882-7891.

83. (a) Dronskowski, R. *Inorg. Chem.* **1994**, *33*, 5960-5963. (b) Hepler, L. G.; Hugus, Z. Z., Jr.; Latimer, W. M. *J. Am. Chem. Soc.* **1953**, *75*, 5652.

84. Zhao, L.; Zhang, C.; Zhuo, L.; Zhang, Y.; Ying, J. Y. *J. Am. Chem. Soc*. **2008**, *130*, 12586.

85. (a) Schoenebeck, F.; Murphy, J. A.; Zhou, S.-Z.; Uenoyama, Y.; Miclo, Y.; Tuttle, T. *J. Am. Chem. Soc.* **2007**, *129*, 13368. (b) Ames, J. R.; Houghtaling, M. A.; Terrian, D. L.; Mitchell, T. A. *Can. J. Chem.* **1997**, *75*, 28. (c) Thummel, R. P.; Goulle, V.; Chen, B. *J. Org. Chem.* **1989**, *54*, 3057. (d) Taton, T. A.; Chen, P. *Angew. Chem., Int. Ed.* **1996**, *35*, 1011. (e) Goldwhite, H.;

Kaminski, J.; Millhauser, G.; Ortiz, J.; Vargas, M.; Vertal, L.; Lappert, M. F.; Smith, S. J. *J. Organomet. Chem.* **1986**, *310*, 21. (f) Cetinkaya, B.; Cetinkaya, E.; Chamizo, J. A.; Hitchcock, P. B.; Jasim, H. A.; Kucukbay, H.; Lappert, M. F. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2047. (g) Mery, D.; Aranzaes, J. R.; Astruc, D. *J. Am. Chem. Soc.* **2006**, *128*, 5602.

86. Rettig, S. J.; Storr, A.; Trotter, J. *Can. J. Chem*. **1976**, *54*, 1278.

87. (a) Andrews, P. C.; Peatt, A. C.; Raston, C. L. *Green Chem*. **2001**, *3*, 313. (b) Andrews, P. C.; Peatt, A. C.; Raston, C. L. *Tetrahedron Lett*. **2002**, *43*, 5097.

88. $(CH_2CH=CH_2)_2GaCl$ was prepared by reacting $CH_2CH=CH_2MgBr$ with $GaCl_3$ in 2:1 molar ratio. Kovar, R. A.; Loaris, G.; Derr, H.; Callaway, J. O. *Inorg. Chem*. **1974**, *13*, 1476.

89. (a) Yamane, H.; Mikawa, Y.; Yokoyama, C. *Acta Cryst*. **2007**, *E63*, 59. (b) Coates, G. E.; Downs, A. J. *J. Chem. Soc.* **1964**, 3353. (c) Rickard, C. E. F.; Taylor, M. J.; Kilner, M. *Acta Cryst.* **1999**, *C55*, 1215.

90. The imidazolium ionic liquids are known to dissolve substantial amount of O_2. Husson-Borg, P.; Majer, V.; Gomes, M. F. C. *J. Chem. Engg. Data*. **2003**, *48*, 480.

91. (a) Fukuzumi, S.; Mori, H.; Imahori, H.; Suenobu, T.; Araki, Y.; Ito, O.; Kadish, K. M. *J. Am. Chem. Soc*. **2001**, *123*, 12458. (b) Kim, Y.- J.; Steritwieser, A. *J. Am. Chem. Soc*. **2002**, *124*, 5757. (c) Fukuzumi, S.; Yuasa, J.; Miyagawa, T.; Suenobu, T. *J. Phys. Chem. A* **2005**, *109*, 3174.

92. Chianese, A. R.; Crabtree, R. H. In: *Activation and functionalization of C-H bonds* Goldberg, K. I.; Goldman, A. S. eds., Am. Chem. Soc. 2004, pp-169.

93. Ott, L. S.; Cline, M. L.; Deetlefs, M.; Sheddon, K. R.; Finke, R. G. *J. Am. Chem. Soc*. **2005**, *127*, 5758.

94. McGuinness, D. S.; Cavell, K. J.; Yates, B. F. *Chem. Commun*. **2001**, 353.

95. (a) Wanzlick, H. W.; Kleiner, H. J. *Angew. Chem.* **1961**, *73*, 493. (b) Wanzlick, H. W. *Angew. Chem*. **1962**, *74*, 129. (c) Wanzlick, H. W.; Esser, T.; Kleiner, H. J. *Chem. Ber*. **1963**, *96*, 1208. (d) Arduengo, A. J.; Dais, R. L.; Harlow, R.; Kline, M. *J. Am. Chem. Soc*. **1991**, *113*, 361. (e) Arduengo, A. J.; Dais, R. L.; Harlow, R.; Kline, M. *J. Am. Chem. Soc*. **1992**, *114*, 5530. (f) Arduengo, A. J. *Acc. Chem. Res*. **1999**, *32*, 913.

96. (a) Bourissou, D.; Guerret, O.; Gabbaï, F. P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39. (b) Herrmann, W. A.; Köcher, C. *Angew. Chem. Int. Edit.* **2002**, *41*, 1290.

97. Carmalt, C. J.; Cowley, A. H. *Adv. Inorg. Chem.* **2000**, *50*, 1.

98. (a) Francis, M. D.; Hibbs, D. E.; Hursthouse, M. B.; Jones, C.; Smithies, N. A. *J. Chem. Soc., Dalton Trans.* **1998**, 3249. (b) Raston, C. L. *J. Organomet. Chem.* **1994**, *475*, 15. (c) Francis, M. D.; Hibbs, D. E.; Hursthouse, M. B.; Jones, C.; Smithies, N. A. *J. Chem. Soc. Dalton Trans.* **1998**, 3249. (d) Stasch, A.; Singh, S.; Roesky, H. W.; Noltemeyer, M.; Schmidt, H. –G. *Eur. J. Inorg. Chem*. **2004**, 4052.

99. (a) Hermann, W. A.; Köcher, C. *Angew. Chem. Int. Ed. Engl*. **1997**, *36*, 2163. (b) Öfele, K. *J. Organomet. Chem*. **1968**, *12*, 42. (c) Wanzlick, H. W.; Schönerr, H. -J. *Angew. Chem. Int. Ed. Engl*. **1968**, *7*, 141. (d) Hermann, W. A.;

Böhm, V. P. W.; Reisinger, C. *J. Organomet. Chem*. **1999**, *576*, 23. (e) Zhang, C.; Huang, J.; Trudell, M. L.; Nolan, S. P. *J. Org. Chem*. **1999**, *64*, 3804.

100. Schlosser, M. (Ed.), Organometallics in Synthesis, Wiley, Chichester, 1994.

101. Barbier, P. *C. R. Acad. Sci.* **1899**, *128*, 110.

102. Li, C.-J. ; Haberman, J. X.; Keh, C. C. K.; Yi, X. -H.; Meng, Y.; Hua, X. –G.; Venkatraman, S.; Zhang, W. –C.; Nguyen, T.; Wang, D.; Huang, T.; Zhang, J. *Organic Reactions in Water and Other Alternative Media: Metal-Mediated Carbon—Carbon Bond Formations*, *ACS Symposium Series* 2002, *819*, Chapter 13, pp-178.

103. (a) Dam, J. H.; Fristrup, P.; Madsen, R. *J. Org. Chem.* **2008**, *73*, 3228. (b) Blomberg, C.; Hartog, F. A. *Synthesis* **1977**, 18.

104. (a) Killinger, T. A.; Boughton, N. A.; Runge, T. A.; Wolinsky, J. *J. Organomet. Chem.* **1977**, *124*, 131. (b) Nokami, J.; Otera, J.; Sudo, T.; Okawara, R. *Organometallics* **1983**, *2*, 191. (c) Pe´trier, C.; Luche, J. -L. *J. Org. Chem.* **1985**, *50*, 910. (d) Li, C. J.; Chan, T. H. *Tetrahedron Lett.* **1991**, *32*, 7017. (e) Wada, M.; Ohki, H.; Akiba, K. -Y. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1738. (f) Li, C.-J.; Meng, Y.; Yi, X. -H.; Ma, J.; Chan, T.-H. *J. Org. Chem.* **1998**, *63*, 7498. (g) Zhang, W. -C.; Li, C.-J. *J. Org. Chem.* **1999**, *64*, 3230. (h) Li, L -H.; Chan, T. H. *Tetrahedron Lett.* **2000**, *41*, 5009.

105. Chattopadhyay, A.; Salaskar, A. *Synthesis* **2000**, 561.

106. (a) Petrier, C.; Luche, J.L. *Tetrahedron Lett.* **1987**, *28*, 2347. (b) Petrier, C.; Dupuy, J. L.; Luche, J. L. *Tetrahedron Lett*. **1986**, *27*, 3149. (c) Hegarty, P.; Mann, J. *Synlett.* **1993**, 553.

107. (a) Reike, R. D.; Sell, M. S.; Klein, W. R.; Chen, T.; Brown, J. D.; Hanson, M. V. *Active Metals*, Furstner, A. Ed.; VCH Publishers; New York, 1996, pp-1.

108. (a) Davies, S. C.; Klabunde, K. J. *Chem. Rev*. **1982**, *82*, 152. (b) Kavaliunas A. V.; Taylor A.; Rieke R. D. *Organometallics* **1983**, *2*, 377.

109. (a) Krabetz, R.; Mross, W. D. *Ullmanns Encykl. Techn. Chem., Vol. 13.* 4th Edition, VCH Weinheim, 1977, pp-517.

110. Reetz. M. T.; Helbig, W.; Quaiser, S. A. *Active Metals*, Furstner, A. Ed.; VCH Publishers; New York, 1996, pp-279.

111. Chattopadhyay, A.; Goswami, D.; Dhotare, B. *Tetrahedron Lett.* **2010**, *51*, 3893.

112. (a) Cherest, M.; Felkin, H. *Tetrahedron Lett.* **1968**, *9*, 2205. (b) Anh, N. T. *Top. Curr. Chem*. **1980**, *88*, 145.

113. Evans, D. A.; Takacs, J. M.; McGee, L. R.; Ennis, M. D.; Mathre, D. J.; Bartroli, J. *Pure Appl. Chem.* **1981**, *53*, 1109, and references cited therein.

114. (a) Mulzer, J.; Lasalle, P.; Freibler, A. *Leibigs Ann. Chem.* **1986**, 1152. (b) Roush, W. R.; Adams, M. A.; Walts, A. E.; Harries, D. J. *J. Am. Chem. Soc*. **1986**, *108*, 3422.

115. Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.

116. Marshall, J. A.; Garofalo, A. W. *J. Org. Chem*. **1993**, *58*, 3675.

117. Goswami, D.; Chattopadhyay, A.; Chattopadhyay, S. *Tetrahedron: Asymmetry* **2009,** *20*, 1957.

118. Goswami, D.; Chattopadhyay, A. *Lett. Org. Chem.* **2006**, *3*, 922.

119. Wender, P. A.; Holt, D. A.; Sieburth, S. Mc. N. *Organic Synth.* 1990, Coll. Vol. *7*, pp-456.

120. Brown, C. A.; Ahuja, V. K. *J. Chem. Soc. Chem. Commun*. **1973**, 553.

121. Chattopadhyay, A.; Goswami, D.; Dhotare, B. *Tetrahedron Lett.* **2006**, *47*, 4701.

122. Allred, E. A.; Sonnenberg, J.; Winstein, S. *J. Org. Chem.* **1960**, *25*, 26, and references cited therein.

123. (a) Tanida, H.; Ishitobi, H.; Irie T.; Tsushima, T. *J. Am. Chem. Soc.* **1969**, *91*, 4512. (b) Tanida, H.; Ysuji, T.; Ishitobi, H.*J. Am. Chem. Soc.* **1964**, *86*, 4904.

124. Ley, S. V.; Stewart-Liddon, A. J. P.; Pears, D.; Perri, R. H.; Treacher, K. *Beilst. J. Org. Chem*. **2006**, *2*, 1.

125. (a) Li, C. J. *Chem. Rev.* **2005**, *105*, 3095, and references cited therein. (b) Li, C. J.; Chan, T. H. *Organic reactions in Aqueous Media*; Wiley: New York, 1997. (c) Grieco, P. Ed. *Organic Reactions in Water*; Chapman & Hall: London, 1998. d) Mulzer, J.; Attenbach,; Braun, M.; Reissig, H. *Organic Synthesis Highlights*; VCH:Weinheim, 1991, pp-71. (e) Li, C. J. *Chem. Rev.* **1993**, *93*, 2023, and references cited therein.

126. (a) Zhou, C.; Jiang, J.; Zhou, Y.; Miao, Q.; Wang, Z. *Lett. Org. Chem.* **2005,** *2*, 61. (b) Zhou, C.; Wang, Z. *Synthesis*, **2005**, 1649. (c) Biebar, L. W.; Storch, E. C.; Malvestiti, I.; Da Silva, M. F. *Tetrahedron Lett.* **1998,** *39*, 9393.

127. Barczak, N. T.; Jarvo, E. R. *Eur. J. Chem* **2008,** 5507.

128. Dubey, A. K.; Goswami, D.; Chattopadhyay, A. *Arkivoc* **2010,** *ix*, 137.

129. Sato, F.; Kobayashi, Y.; Takahashi, O.; Chiba, T.; Takeda, Y.; Kusukabe, M. *J. Chem. Soc. Chem. Commun.* **1985**, 1636.

130. (a) Dhotare, B.; Chattopadhyay, A. *Tetrahedron Lett.* **2005,** *46*, 3103. (b) Vichare, P.; Chattopadhyay, A. *Tetrahedron:Asymmetry* **2010** (*in press*, doi:10.1016/j.tetasy.2010.06.024).

131. Rübsam, F.; Seck, S.; Giannis, A. *Tetrahedron* **1997**, *53*, 2823.

132. (a) Wang, Z.; Yuan, S.; Li, C. –J. *Tetrahedron Lett*. **2002**, *43*, 5097. (b) Andrews, P. C.; Peatt, A. C.; Raston, C. L. *Tetrahedron Lett*. **2004**, *45*, 243.

133. Suzuki, H.; Matano, Y. Ed. *Organobismuth Chemistry*, Elsevier: Amsterdam, 2001, Ch. 1.

134. Wada, M.; Akiba, K. –Y. *Tetrahedron Lett.* **1985**, *26*, 4211.

135. Miyamoto, H.; Daikawa, N.; Tanaka, K. *Tetrahedron Lett.* **2003**, *44*, 6963.

136. (a) Cram, D. J.; Wilson, D. R. *J. Am. Chem. Soc*. **1963**, *85*, 1245. (b) Reetz, M. T. *Angew. Chem., Int. Ed. Engl*. **1984**, *23*, 556.

137. Isaac, M. B.; Chan, T. -H. *Tetrahedron Lett*. **1995**, *36*, 8957.

138. (a) Makoto, W.; Hidenori, O.; Kinya, A. *Tetrahedron Lett*. **1986**, *27*, 4771. (b) Makoto, W.; Munekazu, H.; Yoshihiro, K.; Norikazu, M. *Bull. Chem. Soc. Jpn*. **1997**, *70*, 2265. (c) Xu, X.; Zha, Z.; Wang, Z. *Synlett* **2004**, 1171.

139. (a) Thompson, A.; Corley, E. G.; Huntington, M. F.; Grabowski, E. J. J.; Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc*. **1998**, *120*, 2028. (b) McGarrity, J. F.; Ogle, C. A. *J. Am. Chem. Soc*. **1985**, *107*, 1805. (c) Haeffner, F.; Sun, C.; Williard, P. G. *J. Am. Chem. Soc*. **2000**, *122*, 12542.

140. (a) Chemler, S. R.; Roush, W. R. *J. Org. Chem.* **2003**, *68*, 1319. (b) Hu, T.; Takenaka, N.; Panek, J. S. *J. Am. Chem. Soc.* **2002**, *124*, 12806.

141. Batey, R. A.; Thadani, A. N.; Smil, D. V.; Lough, A. J. *Synthesis* **2000**, 990.

142. Liozzi, F.J.; Lasek, R.J. *Science* **1987**, *237*, 642. (b) Uchida, Y.; Tomonaga, M. *Brain Res*. **1989**, *481*, 191. (c) Moumdijian, R.A.; Antel, J. P.; Yong, V. W. *Brain Res*. **1991**, *547*, 223.

143. Sorbera, l. A.; Castaner, J.; Castaner, R. M. *Drugs Future* **2004**, *29*, 441.

144. (a) Lambert, C.; Utimoto, K.; Nozaki, H. *Tetrahedron Lett.* **1984,** *25*, 5323. (b) Kishimoto, K.; Nakai, H. *Japan Patent* 7-98328, 1995; *Chem. Abstr*. **1997**, *126*, 74487. (c) Kishimoto, K.; Nakai, H. *Japan Patent* 7-102693, 1995; *Chem. Abstr*. **1997**, *126*, 74488. (d) Hasegawa, T.; Yamamoto, H. *Bull. Chem. Soc. Jpn*. **2000**, *73*, 423. (e) Hasegawa, T**.;** Kawanaka, Y.; Kasamatsu, E.; Iguchi, Y.; Yonekawa, Y.; Okamoto, M.; Ohta, C.; Hashimoto, S.; Ohuchida, S. *Org. Process. Res. Dev*. **2003**, *7*, 168. (f) Hasegawa, T.; Yamamoto, H. *Synthesis* **2003**, 1181. (g) Pelotier, B.; Holmes, T.; Piva, O. *Tetrahedron: Asymmetry* **2005**, *16*, 1513. (h) Hasegawa, T.; Kawanaka, Y.; Kasamatsu, E.; Ohta, C.; Nakabayashi, K.; Okamoto, M.; Hamano, M.; Takahashi, K.; Ohuchida, S.; Hamada, Y. *Org. Process. Res. Dev*. **2005**, *9*, 774. (i) Garcia, J. M.; Odriozola, J.M.; Lecumberri, A.; Razkin, J.; Gonjalez, A. *Tetrahedron* **2008**, *64*, 10664. (j) Fernandes, R. A.; Dhall, A.; Ingle, A. B. *Tetrahedron Lett*. **2009**, *50*, 5903.

145. Jurczac, J.; Stanslaw, P.; Bauer, T. *Tetrahedron* **1984**, *42*, 447.

146. For review: Jordan, M. A. *Curr. Med. Chem. Anti-Cancer Agents* **2002**, *2*, 1.

147. For reviews: (a) Moore, R. E.; Corbett, T. H.; Patterson, G. M. L.; Valeriote, F. A. *Curr. Pharm. Des*. **1996**, *2*, 317. (b) Corbett, T. H.; Valeriote, F. A.; Demchik, L.; Lowichik, N.; Polin, L.; Panchapor, C.; Pugh, S.; White, K.; Kushner, J.; Rake, J.; Wentland, M.; Golakoti, T.; Hetzel, C.; Ogino, J.; Patterson, G.; Moore, R. *Invest. New Drugs* **1997**, *15*, 207. (c) Polin, L.; Valeriote, F.; White, K.; Panchapor, C.; Pugh, S.; Knight, J.; LoRusso, P.; Hussain, M.; Liversidge, E.; Peltier, N.; Golakoti, T.; Patterson, G.; Moore, R.; Corbett, T. H. *Invest. New Drugs* **1997**, *15*, 99. (d) Shih, C.; Al-Awar, R. S.; Fray, A. H.; Martinelli, M. J.; Moher, E. D.; Norman, B. H.; Patel, V. F.; Shultz, R. M.; Toth, J. E.; Varie, D. L.; Corbett, T. H.; Moore, R. E. *Anticancer Agents*: *Frontiers in Cancer Chemotherapy*, ed. Ojima, I.; Vite, G. D.; Altmann, K. American Chemical Society, Washington, DC, 2001; Vol. 796, pp. 171. (e) Eggen, M.; Georg, G. I. *Med. Res. Rev*. **2002**, ***22***, 85. (f) Tius, M. A. *Tetrahedron* **2002**, *58*, 4343. (g) Eissler, S.; Stoncius, A.; Nahrwold, M.; Sewald, N. *Synthesis* **2006**, 3747.

148. (a) Schwartz, R. E.; Hirsch, C. F.; Sesin, D. F.; Flor, J. E.; Chartrain, M.; Fromtling, R. E.; Harris, G. H.; Salvatore, M. J.; Liesch, J. M.; Yudin, K. *J. Ind. Microbiol*. **1990**, *5*, 113. (b) Trimurtulu, G.; Ohtani, I.; Patterson, G. M. L.; Moore, R. E.; Corbett, T. H.; Valeriote, F. A.; Demchik, L. *J. Am. Chem. Soc*. **1994**, *116*, 4729. (c) Subbaraju, G. V.; Golakoti, T.; Patterson, G. M. L.; Moore, R. E. *J. Nat. Prod*. **1997**, *60*, 302.

149. (a) Kerksiek, K.; Mejillano, M.; Schwartz, R. E.; Georg, G. I.; Himes, R. *FEBS Lett*. **1995**, *377*, 59. (b) Mooberry, S. L.; Taoka, C. R.; Busquets, L. *Cancer*

Lett. **1996**, *107*, 53. (c) Smith, C. D.; Zhang, X. *J. Biol. Chem*. **1996**, *271*, 6192. (d) Bai, R.; Schwartz, R. E.; Kepler, J. A.; Pettit, G. R.; Hamel, E. *Cancer Res*. **1996**, *56*, 4398. (e) Panda, D.; Himes, R. H.; Moore, R. E.; Wilson, L.; Jordan, M. A. *Biochemistry* **1997**, *36*, 12948.

150. (a) Kobayashi, M.; Aoki, S.; Ohyabu, N.; Kuroso, M.; Wang, W.; Kitagawa, I. *Tetrahedron Lett*. **1994**, *35*, 7969. (b) Kobayashi, M.; Kuroso, M.; Ohyabu, N.; Wang, W.; Fujii, S.; Kitagawa, I. *Chem. Pharm. Bull*. **1994**, *42*, 2196. (c) Golakoti, T.; Ogino, J.; Heltzel, C. E.; Husebo, T. L.; Jensen, C. M.; Larsen, L. K.; Patterson, G. M. L.; Moore, R. E.; Mooberry, S. L.; Corbett, T. H.; Valeriote, F. A. *J. Am. Chem. Soc*. **1995**, *117*, 12030. (d) Koiso, Y.; Morita, K.; Kobayashi, M.; Wang, W.; Ohyabu, N.; Iwasaki, S. *Chem.-Biol. Interact*. **1996**, *102*, 183.

151. Golakoti, T.; Ogino, J.; Heltzel, C. E.; Husrebo, T. L.; Jensen, C. M.; Larsen, L. K.; Patterson, G. M. L.; Moore, R. E.; Moobery, S. L.; Corbett, T. H.; Valeriote, F. A. *J. Am. Chem. Soc*. **1995**, *117*, 12030.

152. (a) Ali, S. M.; Georg, G. I. *Tetrahedron Lett*. **1997**, *38*, 1703. (b) Eggen, M.; Georg, G. I. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 3177. (c) Varie, D. L.; Brennan, J.; Briggs, B.; Cronin, J. S.; Hay, D. A.; Rieck, J. A. I.; Zmijewski, M. J. *Tetrahedron Lett*. **1998**, *39*, 8405. (d) Fray, A. H. *Tetrahedron*: *Asymmetry* **1998**, *9*, 2777. (e) Liang, J.; Hoard, D. W.; Khau, V. V.; Martinelli, M. J.; Moher, E. D.; Moore, R. E.; Tius, M. A. *J. Org. Chem*. **1999**, *64*, 1459. (f) Liang, J.; Moher, E. D.; Moore, R. E.; Hoard, D. W. *J. Org. Chem*. **2000**, *65*, 3143, and references cited therein.

153. (a) Kobayashi, M.; Wang, W.; Ohyabu, N.; Kurosu, M.; Kitagawa, I. *Chem. Pharm. Bull*. **1995**, *43*, 1598. (b) Barrow, R. A.; Hemscheidt, T.; Liang, J.; Paik, S.; Moore, R. E.; Tius, M. A. *J. Am. Chem. Soc*. **1995**, *117*, 2479. (c) de Muys, J. -M.; Rej, R.; Nguyen, D.; Go, B.; Fortin, S.; Lavallee, J. -F. *Bioorg. Med. Chem. Lett*. **1996**, *6*, 1111. (d) Dhokte, U. P.; Khau, V. V.; Hutchison, D. R.; Martinelli, M. J. *Tetrahedron Lett*. **1998**, *39*, 8771. (e) White, J. D.; Hong, J.; Robarge, L. A. *J. Org. Chem*. **1999**, *64*, 6206. (f) Eggen, M.; Mossman, C. J.; Buck, S. B.; Nair, S. K.; Bhat, L.; Ali, S. M.; Reiff, E. A.; Boge, T. C.; Georg, G. I. *J. Org. Chem*. **2000**, *65*, 7792. (g) Eggen, M.; Nair, S. K.; Georg, G. I. *Org. Lett*. **2001**, *3*, 1813. (h) Li, L. -H.; Tius, M. A. *Org. Lett*. **2002**, *4*, 1637. (i) Hoard, D. W.; Moher, E. D.; Martinelli, M. J.; Norman, B. H. *Org. Lett*. **2002**, *4*, 1813. (j) Vidya, R.; Eggen, M. J.; Georg, G. I.; Himes, R. H. *Bioorg. Med. Chem. Lett*. **2003**, *13*, 757. (k) Sammet, B.; Radzey, H.; Neumann. B.; Stammler, H.-G.; Sewald, N. *Synlett* **2009**, 417.

154. Furuyama, M.; Shimizu, I. *Tetrahedron: Asymmetry* **1998**, *9*, 1351.

155. (a) Pousset, C.; Haddad, M.; Larcheveque, M. *Tetrahedron* **2002**, *57*, 7163. (b) Eissler, S.; Nahrwold, M.; Neumann, B.; Stammler, H.-G.; Sewald, N. *Org. Lett*. **2007**, *9*, 817, and references cited therein.

156. (a) Richnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett*. **1990**, *31*, 945. (b) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett*. **1990**, *31*, 7099.

157. (a) Pai, K.; Narasaka, H. C. *Chem. Lett.* **1980**, 1415. (b) Narasaka, K.; Pai, F. -C. *Tetrahedron* **1984**, *40*, 2233. (c) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc*. **1988**, *110*, 3560.

158. Mitsuya, H.; Weinhold, K. J.; Furman, P.A.; St. Clair, M.H.; Lehrman, S.N.; Gallo, R.C.; Bolognesi, D.; Barry, D.W; Broder, S. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 7096.

159. (a) Huryn, D. M.; Okabe, M. *Chem Rev*. **1992**, *92*, 1745, and references cited therein. (b) Duelhom, K. L.; Pedersen, E. B. *Synthesis* **1992**, 1, and references cited therein. (c) Yokoyama, M.; Momotake, A. *Synthesis* **1999**, 1541.

160. Ulhmann, E.; Peyman, A. *Chem Rev*. **1990**, *90*, 543. (b) Crooke, S.T. *Biochim. Biophys. Acta* **1999**, *31*, 1489. (c) Ou, X.; Tan, T.; He, L.; Li, Y.; Li, J.; Kuang, A. *Cancer Gene Therapy* **2005**, *12*, 313. (d) James A. H. Inkster, J. A. H.; Adam, M. J.; Storr, T.; Ruth, T. J. *Nucleosides, Nucleotides and Nucleic Acids* **2009**, *28*, 1131.

161. Heinmann, U.; Rudolph, L.N.; Alings, C.; Morr, M.; Heikens, W.; Frank, R.; Blocker, H. *Nucleic Acids Res*. **1991**, *19*, 427.

162. (a) Svansson, L.; Kvarnstrom, I. *J. Org. Chem*. **1991**, 56, 2993, and references cited therein. (b) Hossain, N.; Plavec, J; Chattopadhyay, J. *Tetrahedron* **1994**, *50*, 4167. (c) Aguste, S. P.; Young, D. W. *J. Chem. Soc. Perkin 1*, **1995**, 395. (d) Robins, M. J.; Doboszewski, B.; Timoshchuk, V. A.; Peterson, M. A. *J. Org. Chem*. **2000**, *65*, 2939.

163. (a) Wilson, L.J.; Hager, M.W.; EI-Kattan, Y. A.; Liotta, D.C. *Synthesis* **1992**, 1465, and references cited therein. (b) Yokoyama, M. *Synthesis* **2000**, 1637.

164. (a) Vorbruggen, H. *Acc. Chem. Res.* **1995**, *28*, 509. (b) Martin, P. *Helv. Chim.Acta*. **1996**, *79*, 1930. (c) Saneyoshi, M.; Satoh, E. *Chem. Pharm. Bull*. **1979**, *27*, 2518.

165. Lane, C. F. *J. Org. Chem*. **1974**, *39*, 1437.

166. (a) Kohl, N. E.; Emini, E. A.; Schleif, W.A.; Davis, L. J.; Heimbach, J. C.; Dixon, R. A. F.; Scholnick, E. M.; Sigal, I. S. *Proc. Natl. Acad. Of Sci. U.S.A.* **1988**, *85*, 4686. (b) Flexner, C. *New. Engl. J. Med.* **1998**, *338*, 1281. (c) Huff, J. R. *J. Med. Chem*., **1991**, *34*, 2305. (d) Martin, J. A. *Antiviral. Res.* **1992**, *17*, 265. (e) Tomasselli, A. G.; Heinrikson, R. L. *Biochim. Biophys. Acta.* **2000**, 189. (f) Wlodwer, A.; Erickson, J. W. *Annu. Rev. Biochem.* **1993**, 543. (g) Meek, T. D. *J. Enzymol. Inhib.* **1992**, *5*, 65.

167. Glushakova, S.; Dubrovsky, L.; Grivel, J. –C.; Haffer, O.; Bukrinsky, M. *Antiviral Res*. **2000**, *47*, 89, and references cited therein.

168. (a) Pearl, L. H.; Taylor, W. R. *Nature*, **1987**, *329*, 351. (b) Parkes, K. E. B.; Bushnall, D. J.; Cracjeff, P. H.; Dunsdon, S. J.; Freeman, A.; Gun, M. P.; Popkin, R. A.; Lambert, R. W.; Thomas, G. J. *J. Org. Chem.* **1994**, *59*, 3656. (c) Rieger, D. L. *J. Org. Chem.* **1997**, *62*, 8546. (d) Yanada, R.; Koh, Y.; Nishimori, N.; Matsumura, A.; Obika, S.; Mitsua, H.; Fuji, N.; Takemoto, Y. *J. Org. Chem.* **2004**, *69*, 3417. (e) Honda, Y.; Katayama, S.; Kojima, M.; Suzuki, M.; Kishibata, N.; Izawa, K. *Org. Biomol. Chem*. **2004**, *69*, 3417.

169. (a) Izaw, K.; Onishi, T. *Chem. Rev*. **2006**, *106*, 2811. (b) Ghosh, A. K.; Bilcer, G.; Sciltz, G. *Synthesis* **2001**, 2203, and references cited therein. (c) Ghosh, A. K.; McKee, S. P.; Lee, H. Y.; Thompson, W. J. *J. Chem. Soc. Chem. Commun*. **1992**, 273. (d) Ghosh, A. K.; Thompson, W. J.; Holloway, M. K.; McKee, S. P.; Duong, T. T.; Lee, H. Y.; Munson, P. M.; Smith, A. M.; Wei, J. M.; Dark, P.

L.; Zugay, J. A. *J. Med. Chem*. **1993**, *36*, 2300. (e) Kim, B. M.; Bae, S. J.; So, S. M.; Yoo, H. T.; Chang, S. K.; Lee, J. H.; Kang, J. *Org. Lett.* **2001**, *3*, 2349.

170. (a) Bennet, F., Girijavallabhan, V. M., Patel, N. *J. Chem. Soc. Chem. Commun*. **1993**, 737. (b) Park, S.; Lee, S.; Kang, H-J. *Bull Korean Chem. Soc*. **2008**, *29*, 1073.

171. (a) Gunther, C.; Mosandi, A. *Liebigs Ann. Chem*. **1986**, 2112, and refernces cited therein. (b) Wilkinson, K.; Esley, G. M.; Prager, R. H.; Tanaka, T.; Sefton, M. A. *Tetrahedron* **2004**, *60*, 6091.

172. Masuda, M.; Nishimura, K. *Chem*. *Lett*. **1981**, 1333.

173. (a) Chartchouk, T.; Ollivier, J.; Salaun, J. *Tetrahedron: Asymmetry* **1997**, *8*, 1011. (b) Tsuboi, S.; Sakamoto, J.; Yamashita, H.; Sakai, T.; Utaka. M. *J. Org. Chem.* **1998**, *63*, 1102. (c) Schlapbach, A.; Hoffman, R. W.; *Eur. J. Org. Chem.* **2001**, 323. (d) Suzuki, K.; Shoji, M.; Kobayashi, E.; Inomata, K. *Tetrahedron: Asymmetry* **2001**, *12*, 2789. (e) Ghosh, M.; Bose, S.; Ghosh, S. *Tetrahedron Lett.* **2008**, *49*, 5424, and references cited therein.

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LIST OF PUBLICATIONS

1. **Goswami, D.**; Chattopadhyay, A.; Chattopadhyay, S. A convenient synthesis of unit-A of Cryptophycins. (*commumnicated*).

2. **Goswami, D.**; Chattopadhyay, A.; Chattopadhyay, S. [bmim][Br], A new solvent and activator for the Ga-mediated barbier allylation of aldehydes and ketones: direct formation of a *N*-heterocyclic carbene from Ga-metal. (*commumnicated*).

3. Chattopadhyay, A.; **Goswami, D.**; Dhotare, B. Crotylation of (R)-2,3-O-cyclohexylideneglyceraldehyde: a simple synthesis of (+)-trans-oak lactone. *Tetrahedron Lett*. **2010,** *51*, 3893-3896.

4. Dubey, A. K.; **Goswami, D.**; Chattopadhyay, A. A simple and inexpensive procedure for low valent copper mediated benzylation of aldehydes in wet medium. *Arkivoc* **2010,** *ix*, 137-145.

5. **Goswami, D.**; Chattopadhyay, A.; Chattopadhyay, S. Metal-dependent modulation of diastereoselectivity in the Barbier-type crotylation of (R)-cyclohexylideneglyceraldehyde. *Tetrahedron: Asymmetry* **2009**, *20*, 1957-1961.

6. Sharma, A.; Gamre, S.; Roy, S.; **Goswami, D.**; Chattopadhyay, A.; Chattopadhyay, S. A convenient asymmetric synthesis of the octalactin lactone. *Tetrahedron Lett*. **2008,** *49*, 3902-3905.

7. Sharma, A.; Roy, S.; **Goswami, D.**; Chattopadhyay, A.; Chattopadhyay, S. An asymmetric synthesis of the β-hydroxy acid segment of hapalosin. *Lett. Org. Chem.* **2006**, *3*, 741-743.

8. **Goswami, D.**; Chattopadhyay, A. Crotylation of (R)-2,3-cyclohexylideneglyceraldehyde: A simple strategy for the synthesis of

enantiopure anti-alzheimer (R)-arundic acid. *Lett. Org. Chem.* **2006**, *3*, 922-925.

9. Chattopadhyay, A.; **Goswami, D.**; Dhotare, B. A simple and stereodivergent strategy for the synthesis of 3′-C-branched 2′,3′-dideoxynucleosides exploiting (Z)-but-2-en-1,4-diol and (R)-2,3-cyclohexylideneglyceraldehyde. *Tetrahedron Lett*. **2006,** *47*, 4701-4705.

10. Dhotare, B.; **Goswami, D.**; Chattopadhyay, A. (R)-2,3-Cyclohexylideneglyceraldehyde, a novel template for stereoselective preparation of functionalized δ-lactones: Synthesis of mosquito oviposition pheromone. *Tetrahedron Lett*. **2005,** *46*, 6219-6221.