ABSTRACT

The thesis entitled “Application of self-metathesis in the synthesis of bis-tetrahydrofurans, 1,6-dioxaspiro(4,5)decane spiroketal, ritonavir and lopinavir core unit using $C_2$-symmetric approach and synthesis of 8-methoxygoniodiol” is divided into three chapters.

Chapter I: It describes “Stereoselective synthesis of bis-hydroxy tetrahydrofurans using cross-metathesis”.

Chapter II: It is further divided into two sections.

   Section A: It deals with “A short approach to the synthesis of ritonavir and lopinavir core and its C-3 epimer via cross metathesis”.

   Section B: It deals with the “Stereoselective synthesis of 1, 6-dioxaspiro(4,5)decane chiral spiroketal skeleton via $C_2$-symmetric approach using cross-metathesis”.

Chapter III: It describes the “stereoselective synthesis of 8-methoxygoniodiol”.

CHAPTER I

It describes the “Stereoselective synthesis of bis-hydroxy tetrahydrofurans using cross-metathesis”. The annonaceous acetogenins are a family of almost 400 natural products, which have been found in 37 different species of annonaceous plants. A remarkably broad spectrum of biological activity has been reported for these agents, including cytotoxic, antitumor, antimalarial, pesticidal, antifeedent and most importantly, in vivo antitumor behavior. They have also been shown to be active against multidrug-resistant tumors. Biogenetically, the acetogenins are characterized by a long lipophilic tail, a central polyoxygenated core, and a terminal $\alpha,\beta$-unsaturated $\gamma$-lactone. Diversity within this family arises principally from variations in stereochemistry, the location of the THF and THP units and various hydroxylation patterns.

An important structural feature that appears in most of the annonaceous acetogenins having high biological activity is a $C_{10}$ fragment containing two adjacent bis-THF groups, flanked by two hydroxy groups. Usually the two THF rings are linked in a
Figure 1:

General structure of acetogenins

*threo* arrangement with *trans* substituents at the 1,5-positions. The crucial component in the synthesis of any of these natural products is the stereoselective preparation of the polyoxygenated central fragment, *i.e.*, the adjacent dihydroxy bis-THF unit (figure 1). Taking the above into consideration we undertook the synthesis of polyoxygenated central bis tetrahydrofuran motif 1, by employing self cross-metathesis, Sharpless asymmetric dihydroxylation and acid catalyzed cyclisation reactions as key steps.

The general features of our approach to bis tetrahydrofuran core 1 is illustrated in retro synthetic format in **Scheme 1**.

**Scheme 1:**
Accordingly, our synthesis commenced from readily available \( p \)-anisaldehyde 7. The Grignard reaction of anisaldehyde with homoallylmagnesium bromide in THF afforded the free hydroxy compound 8. Here to our dismay the self metathesis of olefin 8 was unsuccessful with Grubbs’ I and II generation catalysts. Then we tried to explore the self metathesis by protecting the free hydroxy function in compound 8. Thus, the hydroxy compound 8 was treated with acetic anhydride, TEA in DCM yielded the acetate derivative 6. Now the acetate compound underwent self metathesis with Grubbs’ I generation catalyst in DCM to afford the dimer compound 5 exclusively as \( E \) isomer. This dimer olefin 5 subjected to Sharpless asymmetric dihydroxylation conditions with AD Mix \( \beta \) in tert-BuOH-H\(_2\)O afforded the dimeric \( \text{syn} \) diol 4. The crucial cyclisation of 4 was carried out with trifluoroacetic acid in dichloromethane at 0 °C for 4 h to give single isomer 3 via \( \text{SN}^1 \) fashion. The oxidative cleavage of aromatic ring in 3 to its corresponding acid derivative 9 was unsuccessful with RuO\(_4\) under different conditions (scheme 2).

**Scheme 2:**

\[
\begin{align*}
p\text{-Anisaldehyde} & \quad \xrightarrow{\text{a}} \quad \text{MeO} \quad \xrightarrow{\text{b}} \quad \text{OH} \\
7 & \quad \text{MeO} \quad \xrightarrow{\text{c}} \quad \text{MeO} \\
8 & \quad \text{MeO} \\
6 & \quad \text{OAc} \\
5 & \quad \text{MeO} \\
4 & \quad \text{OH} \\
3 & \quad \text{MeO} \\
9 & \quad \text{COOH} \\
\end{align*}
\]
Abstract

**Reagents and conditions:** (a) \( \text{CH}_2=\text{CH}-\text{CH}_2\text{MgBr}, \text{THF}, 0 \, ^\circ\text{C}-\text{rt}, 5 \, \text{h}, 80\% \); (b) \((\text{CH}_3\text{CO})_2\text{O}, \text{TEA, DMAP, DCM, 0 \, ^\circ\text{C} \text{ to rt}, 3 \, \text{h}, 90\% \); (c) 10 mol\% Grubbs’ 1st generation catalyst, DCM, 40 \, ^\circ\text{C}, 12 \, \text{h}, 85\% ; (d) AD mix-\(\beta\), H\(_2\)O: t-BuOH (1:1) 0 \, ^\circ\text{C}, 12 \, \text{h}, 75\% ; (e) TFA, DCM, rt, 4 \, \text{h}, 72\% ; (f) RuCl\(_3\), NaIO\(_4\), CCl\(_4\): EA:H\(_2\)O, rt, 12 h.

The conformation of the THF unit 3 is fixed by considering the observed coupling constants and NOEs. The \( J_{\text{H}2-\text{H}3b} = 11.3 \, \text{Hz} \) and the weak NOE between these protons confirms that they are in trans to each other. Furthermore the strong NOE cross peaks between \( \text{H}2-\text{H}4a \), \( \text{H}2-\text{H}5 \) and \( \text{H}5-\text{H}4a \) suggested that these protons are in same plane. In addition to these NOEs other NOE cross-peaks, \( \text{H}o-\text{H}3b \), \( \text{H}o-\text{H}3a \), \( \text{H}o-\text{H}2 \) and \( \text{H}m-\text{CH}3 \) confirms the structure of the molecule as shown in figure 2.

**Figure 2:** NOE observations of compound 3

In order to overcome the difficulty of [scheme 2](#) we changed our strategy to complete the bis hydroxy tetrahydrofuran unit 2 using self metathesis, Sharpless asymmetric dihydroxylation and \( S_N^2 \) cyclisation as shown in [scheme 3](#).

We envisaged that the bis- tetrahydrofuran unit 3 can be prepared from \( C_2 \)-symmetric diol 10 via nucleophilic substitution reaction (\( S_N^2 \)). This \( C_2 \)-symmetric diol 10 can obtained from dimer olefin 11 compound by applying Sharpless asymmetric dihydroxylation protocol using AD Mix \( \beta \). The dimer olefin compound 11 can be derived from single olefin monomer unit 12 by subjecting to Grubbs’ olefin metathesis conditions using first generation catalyst. The olefin compound 12 can be obtained from epoxide 13, by regioselective opening with allyl magnesium bromide. This oxirane 13 can obtained from L-Ascorbic acid 14 in six steps using standard conditions.
Scheme 3:

The synthesis commenced from L-Ascorbic acid (vitamin C) 14. The saturated diol function of ascorbic acid 14 was easily protected as acetonide 15 by dissolving 14 in excess acetone containing catalytic amount of acetyl chloride.

Scheme 4:

Reagents and conditions: (a) AcCl, acetone 0 °C-rt, 14 h; (b) H₂O₂, K₂CO₃, H₂O, 0 °C-rt ,12 h; (c) EtI, ACN, reflux, 15 h, 85 % (for three steps); (d) LiAlH₄, THF, 0 °C-rt, 1 h, 95 %; (e) i, p-TsCl, Py, 0 °C, 12 h, ii, K₂CO₃, MeOH, 0 °C-rt, 2 h, 75 % (for two steps).
The enone moiety in acetonide 15 was cleaved using H$_2$O$_2$, K$_2$CO$_3$ to afford potassium salt 16, which on treatment with ethyl iodide in acetonitrile at reflux conditions afforded ester 17 in good yield. In the presence of LAH in THF the ester functionality was reduced to diol 18. The primary hydroxy in diol 18 selectively converted to its tosyl derivative using p-TsCl, TEA in DCM and was used as such with out purification. This tosyl compound treated with K$_2$CO$_3$ in MeOH afforded the epoxide 13 smoothly (scheme 4).

Regioselective opening of epoxide 13 using allylmagnesium bromide gave homoallylic alcohol 19 in good yield. The key cross metathesis reaction of olefin 19 using Grubbs’ first-generation olefin metathesis catalyst (10 mol %) afforded the C$_2$ symmetric compound 11b as an inseparable E, Z mixture of isomers in a ratio of 85:15. In order to improve the E-selectivity, the cross metathesis reaction was carried out with substrates 20 and 21 which possesses electron withdrawing groups to give compounds 11a and 11c in good yields with E:Z isomer ratios of 93:7 and 70:30, respectively. From the above comparative study it was interesting to note that acetate protection gave the best E/Z isomer ratios (in favour of the E – isomer).

Scheme 5:
**Abstract**

Reagents and conditions: (a) CH$_2$=CH-CH$_2$MgBr, CuI, ether, -20 °C, 12 h, 85%; (b) (CH$_3$CO)$_2$O, TEA, DMAP, DCM, 0 °C to rt, 3 h, 90%; (c) p-TsCl, TEA, DMAP, DCM, 0 °C to rt, 24 h, 87%; (d) 10 mol% Grubbs’ 1$^{st}$ generation catalyst, DCM, 40 °C, 12 h, for 11a 90%, for 11b 85%, for 11c 82%; (e) K$_2$CO$_3$, methanol, 0 °C to rt, 2 h, 85%; (f) p-TsCl, TEA, DMAP, DCM, 0 °C to rt, 36 h, 87%; (g) AD mix-β, H$_2$O: t-BuOH (1:1) 0 °C, 12 h, 85%; (h) NaH, THF, 0 °C to rt, 6 h, 80%.

Accordingly, compound 11a upon treatment with K$_2$CO$_3$ in MeOH gave $C_2$-symmetric diol 11b which was converted to di-tosylate 11c using $p$-toluenesulphonyl chloride and triethylamine in DCM. Compound 11c upon Sharpless asymmetric dihydroxylation (SAD) using AD-mix-β afforded diol 10. Finally cyclisation of 10 using NaH in THF furnished the desired compound 2 after column chromatography as light yellow syrup in 80% yield (scheme 5).

In conclusion, we have demonstrated a short asymmetric approach for the synthesis of a dihydroxy bis-tetrahydrofuran unit via cross-metathesis. It was also observed in the above case that the presence of an acetate protecting group gave a better $E/Z$ isomer ratio in comparison to a tosyl group and the unprotected hydroxy group in cross metathesis.

**CHAPTER II**

**Section A:**

It deals with “A short approach to the synthesis of ritonavir and lopinavir core and its C-3 epimer via cross metathesis”. Acquired immunodeficiency syndrome (AIDS), a degenerative disease of the immune system, is one of the most challenging problems in the medicine. Among various strategies to combat this disease, therapeutic inhibition of the virally encoded HIV protease became an attractive target. The treatment of HIV and AIDS was revolutionalized by the introduction of peptidomimetic aspartyl protease inhibitors.

Even though there are six protease inhibitors the ritonavir 22 (trade name “norvir”, ABT-538) and lopinavir 23 (trade name “aluviran”, ABT-378) are FDA approved clinically effective peptidomimetic HIV protease inhibitors from Abbott laboratories with high oral bioavailability (figure 3).
In addition to above inhibitors, specially, the recognition of HIV protease exists in its active form as a $C_2$-symmetric homodimer has prompted interest in the potential utility of $C_2$-symmetric compounds as novel inhibitors (the symmetric molecule inhibited both protease activity and acute HIV-1 infection *in vitro*, was at least 10,000-fold more potent against HIV-1 protease than against related enzymes and appeared to be stable to degradative enzymes). Accordingly, the $C_2$ symmetric diaminodiol core containing inhibitors such as A-76928 24 is under clinical trials (figure 4).

Due to high biological importance we paid attention to undertake a stereoselective synthesis of both Phe-Phe hydroxyethylene core unit 25 of ritonavir 22 and lopinavir 23, its C-2 epimer 26 and diamino diol core unit 27 of A-76928 24 (figure 4). Inspite of many
synthesis reported for these core units, almost all are fraught with long reaction sequence. In order to circumvent these large step strategies coupled with an objective to device a simple protocol, a new synthetic approach for these units was undertaken and here in we describe a short and simple approach for these core units from commercially available L-Phenylalanine via self cross-metathesis and Sharpless asymmetric dihydroxylation protocols.

**Figure 5:**

The general features of our approach to Phe-Phe hydroxyethylene core unit 25 its C-2 epimer 26 and diamino diol core unit 27 are illustrated in retro synthetic format in scheme 6.

**Scheme 6:**

We envisioned that the diamino alcohols 25, 26 and diamino diol 27 units can be obtained from by using appropriate reagents as shown in scheme 6. The compound 28 can be obtained by dimerisation of olefin 29 a single monomer unit under self cross metathesis conditions with Grubbs’ catalyst.
This olefin 29 can be obtained from corresponding aldehyde, which can be prepared from L-phenylalaninol 30. The L-phenylalaninol 30 can be easily derived from natural amino acid L-phenylalanine 31 by using established procedure. The diamino diol 27 can be derived from C₂-symmetric olefin 28 with Sharpless asymmetric dihydroxylation conditions.

Accordingly, the synthesis commenced from commercially available amino acid L-phenylalanine 31. Reaction of L-phenylalanine 31 (scheme 7) with acetyl chloride in refluxing methanol afforded its methylester hydrochloride 32. The crude ester 32 on treatment with triethylamine in THF at 0 °C generated the free amine, which was in situ derivatized as its N-Boc ester 33 in quantitative yield. The ester functionality in compound 33 was reduced using LiBH₄ (prepared in situ from anhydrous LiCl and NaBH₄ in ethanol) in THF to give alcohol 30 in 82 % as a white solid.

**Scheme 7:**

![Scheme 7](image)

**Reagents and conditions:** (a) AcCl, MeOH, reflux, 3 h; (b) (Boc)₂O, Et₃N, THF, rt, 7 h (95% for two steps); (c) LiCl, NaBH₄, EtOH, THF, rt, 16 h, 82%.

This alcohol 30 was subjected to Swern oxidation conditions using (COCl)₂, DMSO in DCM to give aldehyde, which was taken as such to the next step without purification. To our dismay, one carbon extension of aldehyde to olefin compound was unsuccessful under standard Wittig protocol. Finally olefin 29 was obtained by Takai-Nozaki olefination conditions in 55% overall yield (for two steps). The key cross metathesis reaction of olefin 29 using Grubbs’ second generation olefin metathesis catalyst (10 mol %) afforded C₂-symmetric dimer 28 as E isomer exclusively, where as with first generation Grubbs’ catalyst failed to give the product in our hand. Although alkene 28 was reported in literature and synthesized using Julia olefination but it involves
more no of steps and reagents like n-butyllithium, Na/Hg amalgam and Na liq. NH₃, which resulted in low yields of the product. Therefore their approach has limitation to large scale synthesis. Hydroboration of olefin 28 with BH₃.DMS in THF gave the required alcohols 27 and 26 in 3.8:1 ratio as separable mixture and its spectral data were in good agreement with reported values (scheme 8).

Scheme 8:

![Scheme 8](image)

**Reagents and conditions:** (a) i) DMSO, (COCl)₂, DCM, -78 °C, 2 h then TEA; ii) Zn, CH₃I, Ti (O⁻Pr)₄, THF, rt, 1 h, 55% (for two steps); (b) 10 mol% Grubbs' II⁺ Generation catalyst, DCM, 40 °C, 14 h, 87%; (c) BH₃-DMS, H₂O₂, NaOH, THF, 0 °C to rt, 8 h, 70%.

In order to get exclusively either of the isomers, oxidation and reduction protocol was applied on mixture of 25 and 26 (scheme 9). Dess-Martin periodinane oxidation of the secondary alcohol function of 25 and 26 in DCM led to the keto compound 34. Reduction of the keto compound 34 with NaBH₄ in MeOH gave anti alcohol 26 as major isomer in 9:1 ratio, where as reduction with ZnBH₄ in THF afforded syn alcohol 25 as major isomer in 8:2 ratio. To get the C₂ symmetric diol we subjected the olefin compound 28 was subjected to dihydroxylation under Sharpless asymmetric conditions with AD Mix-β in t-BuOH:H₂O (1:1) which afforded the anti diol 27 exclusively and its spectral data were in good agreement with reported values.
Abstract

Scheme 9:

Reagents and conditions: (a) Dess-Martin periodinane, DCM, 0 °C to rt, 3 h, 80%; (b) ZnBH₄, THF, 0 °C to rt, 5 h, 75%; (c) NaBH₄, MeOH, 0 °C to rt, 3 h, 80%; (d) AD mix-β, H₂O: t-BuOH (1:1) 0 °C, 12 h, 85%.

In conclusion, we demonstrated here a short and common approach for the synthesis of phe-phe hydroxyethylene isostere 25 a core unit of ritonavir and lopinavir, its C-3 epimer 26 and diol 27 from C₂ symmetric dimer 28, which was obtained from a single monomer using self-metathesis.

Section B:

It deals with the “Stereoselective synthesis of 1, 6-dioxaspiro(4.5)decane chiral spiroketal skeleton via C₂- symmetric approach using cross-metathesis”. Spiroketals are widely distributed in nature and exists in a wide range of natural products of varying complexity. Spiroketals particularly 1,7-dioxaspiro(5.5)undecane and the 1,6-dioxaspiro(4.5)decane systems are subunits of many biologically active compounds such as polyether ionophores, insect pheromones and antibiotic macrolides. The source of these is includes insects, microbes, plants, fungi and marine organisms. The novel structural features of these spiroketals attracted the attention of both biologists and synthetic organic chemists all over the world and several approaches have been developed for their synthesis. A recent report reveals that even poorly substituted spiroketals exhibit biological effects such as tublin modulation (Spiket P) and cytotoxicity against tumor cell lines (figure 6).
Abstract

Figure 6:

Although approaches for the synthesis of 1,6-dioxaspiro(4.5)decane 35 system are reported earlier but most of them had long reaction sequence and does not involve good selectivities. Therefore we developed a new approach having concise, versatile reaction sequences, which involve cross-metathesis and acid catalyzed cyclisation reactions via C₂-symmetric substrate. This strategy of making C₂-symmetric compounds from a single substrate in a single step has an advantage over conventional approach, which requires more than one substrate thus leading to more number of manipulations. Infact the self metathesis strategy falls under the one of the principles of green chemistry.

The general features of our approach to 1,6-dioxaspiro(4.5)decane spiroketal unit 35 is illustrated in retro synthetic format in scheme 10.

As shown in the retrosynthetic analysis (scheme 10), we envisaged that 1,6-dioxaspiro(4.5)decane unit 35, could be synthesized from spiroketalisation of pseudo C₂ symmetric keto compound 36. This keto compound can be derived from its corresponding alcohol 37, which in turn can be prepared from C₂ symmetric olefin 38 under hydroboration conditions. The key intermediate in our synthesis that is the dimer olefin compound 38, which can be obtained from self cross-metathesis of single monomer olefin 39 using Grubbs’ olefin metathesis catalyst. This olefin compound 39 can be prepared easily from chiral oxirane 40 in two steps.
Accordingly, the synthesis (scheme 11) of 1, 6-dioxaspiro(4.5)decane unit 35 commenced from commercially available benzylglycidyl ether 41. The racemic terminal epoxide was subjected to solvent free hydrolytic kinetic resolution by employing 0.005 mol% (salen)Co(III)(OAc) complex (Jacobson catalyst) to afford the chiral oxirane 40 in good yield. The regioselective opening of epoxide 40 using allylmagnesiumbromide gave alcohol 42, the alcohol functionality in 42 was protected as methoxymethyl ether to get the olefin 39 using methoxymethyl chloride and diisopropylethylamine in DCM. The key cross metathesis reaction of olefin 39 using Grubbs’ first generation olefin metathesis catalyst (10 mol %) afforded C2-symmetric dimer compound 38 as inseparable E, Z mixture with ratio of E:Z = 9:1, which was identified by proton integration values in 1H NMR and carried to the next step without their separation. Hydroboration of olefin 38 yielded the alcohol 37. This was converted to keto compound 36 using Dess-Martin periodinane. The spiroketalization of ketone 36 by treating with conc. HCl in MeOH gave cyclised compound 43. Finally the deprotection of benzyl group was achieved by applying Li/liq NH3 conditions to afford the desired compound 35, as colorless liquid in 90% yield, whose physical and spectral data were in good agreement with reported values.
Abstract

Scheme 11:

Reagents and conditions: (a) (R,R)-(salen)Co(III)(OAc) complex, H$_2$O, toluene, rt, 12 h, 42%; (b) CH$_2$=CH-CH$_2$MgBr, Cul, Ether,-20 °C, 12 h, 87%; (c) MOM-Cl, DIPEA, DMAP, DCM, 0 °C to rt, 4 h, 90%; (d) 10 mol% Grubbs 1$^{st}$ Generation catalyst, DCM, 40 °C, 12 h, 94%; (e) BH$_3$-DMS, H$_2$O$_2$, NaOH, THF, 0 °C to rt, 8 h, 85%; (f) Dess-Martin periodinane, DCM, 0 °C to rt, 3 h, 88%; (g) Conc. HCl, MeOH, 40 °C, 10 min 92%; (h) Na in liq. NH$_3$, THF, -78 °C, 5 h, 85%.

In conclusion, we demonstrated here a short asymmetric and common approach for the synthesis of 1, 6-dioxaspiro(4.5)decane chiral spiroketal system from only one starting material using self-metathesis and acid catalyzed cyclisation.

CHAPTER III

It describes the “Stereoselective synthesis of 8-methoxygoniodiol”. Lactone rings are the structural features of many natural products. Of the naturally occurring lactones, which all display a wide range of pharmacological activities, those bearing a 5,6-dihydropyran-2-one moiety are relatively common in various types of natural sources. 5,6-dihydropyran-2-ones of both natural and non-natural origin have been found to be
cytotoxic. The pyranone units are widely distributed in all parts of plants (Lamiaceae, Piperaceae, Lauraceae, and Annonaceae families) including leaves, stems, flowers, and fruits. Styrylactones with pyronones unit are common feature of Goniothalamus family.

Thirty-one bioactive styryl-lactones, with six different basic skeletons, have been isolated from Goniothalamus species till now, 8-methoxygoniodiol 44 is one among them (figure 7).

**Figure 7:**

![8-Methoxygoniodiol 44](image)

Intriguing biological profiles and impressive molecular structure of 44 attracted us to synthesise the 8-methoxygoniodiol 44, isolated from stems and leaves of Goniothalamus amuyon. The seeds of Goniothalamus amuyon are reported to be useful for the treatment of edema and rheumatism. In addition to that this 8-methoxygoniodiol found to possess significant cytotoxicity against several human tumors. The key features of our approach to 8-methoxygoniodiol 44 are illustrated in the retro synthetic format (scheme 12).

We envisioned that the 8-methoxygoniodiol 44 can be prepared from cis α,β-unstaurated ester compound 45 via acid mediated, acetonide deprotection followed by lactonisation in one pot. The ester can be obtained from its corresponding alcohol 46 by DMP oxidation and Horner-Wadsworth-Emmons reaction. This alcohol 46 in turn can be prepared from hydroxy compound 47 by usual protection and deprotection process. The hydroxyl compound 47 can obtained from diol 48 in four steps. This diol can be prepared from compound 49 by employing Sharpless asymmetric dihydroxylation protocol. This olefine can be derived from propanediol 50 using standard reactions.
Accordingly, our synthesis of 8-methoxygoniodiol 44 commenced from commercially available propanediol 50. One of the hydroxy group in 50 was protected as its benzyl ether using BnBr, NaH in DMF to give compound 51. The alcohol compound 51 was subjected to Swern oxidation using DMSO, (COCl)$_2$ and Et$_3$N to give aldehyde, this aldehyde was subjected to Wittig protocol with phenacyl triphenylphosphorane (PhCOCHPPh$_3$) in DCM to give stereoselectively trans $\alpha,\beta$-unsaturated ketone 49 as a yellow colour liquid along with cis isomer as separable mixture in 8:2 ratio. This trans compound 49 was subjected to modified Sharpless asymmetric dihydroxylation conditions using AD Mix $\beta$ in tert-BuOH-H$_2$O to afford the syn diol 48. The diol compound 48 underwent acetonide protection using 2,2-DMP and $p$-TSA (cat) in DCM to give acetonide protected compound 52 (scheme 13).
Scheme 13:

Reagents and conditions: (a) NaH, BnBr, DMF, 0 °C-rt, 8 h, 70%; (b) i. DMSO, (COCl)$_2$, DCM, -78 °C, 2 h then Et$_3$N; ii. PhCOCHPPh$_3$, DCM, rt, 6 h, 78%; (c) AD Mix β, tert-BuOH-H$_2$O,NaHCO$_3$, 0 °C, 8 h, 82%; (d) 2,2-DMP, p-TSA, DCM, rt, 4 h, 90 %.

The keto functionalty in 52 was reduced with NaBH$_4$ but the diastereoselectivity was not good (6:4 ratio). In order to get good selectivity the compound 52 with K-selectride in THF to afford the syn hydroxy compound 53 in excellent selectivity. The outcome was explained based on the Crams chelation model. To get the required anti alcohol, we conducted Mitsunobu inversion on 54, with DIAD, in presence of p-nitro benzoic acid, TPP in THF to yield the ester compound 54 with inversion configuration. The ester 54 was underwent hydrolysis with K$_2$CO$_3$ in MeOH to give the anti alcohol compound 47. The alcohol functionality was converted to its methyl ether using methyl iodide and NaH in THF to give the methoxy derivative 55 in good yield (scheme 14).

Schem 14.

Reagents and conditions: (a) K-Selectride, THF, -78 °C, 3 h, 70%; (b) DIAD, TPP, p-NBA, rt, 6 h, 80%; (c) K$_2$CO$_3$, MeOH, 0 °C-rt, 3 h, 83%; (d) Mel, NaH, 0 °C-rt, 4 h, 90 %.
The benzyl protection in compound 55 was removed by using Pd/C, ethylacetate in presence of H₂ gas to give the primary hydroxy compound 46. The free hydroxy group in 46 was oxidized using Swern oxidation conditions to afford the aldehyde, which was used to next step as such. To this aldehyde, ylide was added slowly at -78 °C, (ylide was generated freshly by treatment of bis-2, 2, 2 trifluromethyl (methoxy carbonyl methyl) phosphonate with NaH at 0 °C) affording the cis α,β-unstaurated ester 45 as exclusively z-isomer. When the α,β-unstaurated ester compound 45 was treated with p-TSA (Cat) in benzene, acetonide deprotection followed by lactonisation occurred in one pot to give desired product 8-methoxygoniodiol 44. The spectral data of 44 was in good agreement with the reported values (scheme 15).

Scheme 15:

Reagents and conditions: (a) Pd/C, H₂, ethylacetate, 12 h, 89 %; (b) i, DMSO, (COCl)₂, DCM, -78 °C, 2 h then Et₃N; ii. (CF₃CH₂O)₂P(O)CH₂CO₂Me, NaH, THF, 0 °C-rt, 2 h, 63 % (for two steps); (c) p-TSA, benzene, rt, 6 h, 80 %.

In conclusion we have developed an enantioselective synthesis of 8-methoxygoniodiol 44 using Sharpless asymmetric dihydroxylation and the strategy is very much useful to prepare the different analogues of 8-methoxygoniodiol for more therapeutic values.