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STERIOCHEMICAL ASSIGNMENT OF ALCOHOLS –A VERSATILE CHIRAL BUILDING BLOCKS STUDIES TOWARDS TOTAL SYNTHESIS OF (-)-AUREONETOL

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ABSTRACT

A novel and interesting synthetic strategies. However, there is enough scope to develop a more efficient synthetic approach for the synthesis of (-) -Aureonetol. Wittig olefination of the aldehydes or ketones to get allyl vinyl ethers followed by a Claisen rearrangement for the generation of 4-pentenal. This method has been extensively studied and applied to the synthesis of (-) –Aureonetol.

KEYWORDS: Dicyclohexylidene protection, Oxidative cleavage, Wittig reaction and Claisen rearrangement.

INTRODUCTION

With the growing global threat of multidrug-resistant microbes and increasing economical and environmental concerns about synthetic production of natural products and their analogs, there is an increasing interest in developing alternate platforms for discovery, development, and production of pharmaceutically valuable compounds.[1–3] The presence of a tetrahydrofuran sub-unit in many natural products makes their accessibility a continuing challenge.[4,5] Fungi are considered as a potential repository that we depend on in

our endeavors for the discovery of pharmacologically important molecules with notable bioactivities or drug ability to some extent.

Chaetomium genus, containing more than 100 species, is a common fungal genus that ubiquitously inhabited in soil and decomposed plant materials. A large number of structurally diverse metabolites have recently been characterized from *Chaetomium* species, including chaetoglobosins, xanthones, anthraquinones, azaphilones, terpenoids, and steroids. These structures display a wide range of biological activities, such as anticancer, antimicrobial, enzyme inhibitory, antimalarial, and antioxidant.[6,7]

Burrows in 1967 from the fungus *Chaetomium coarctatum*.[8,9] structurally similar compound was isolated. Substituted tetrahydrofurans are attractive synthetic targets owing to their frequent occurrence in natural products. Of the range of substitution patterns that are available, the 2,3,4-trisubstitution pattern is found in a number of natural products; some examples are shown in Figure 1.

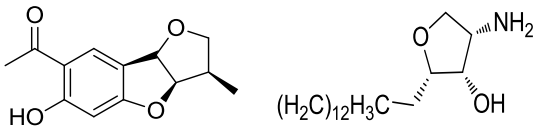


Figure 1: Bioactive natural products containing 2,3,4-trisubstituted THF ring.

Pachastrissamine (jaspine B) exhibits anti-cancer activity, whilst (+)-gynunone, which contains the core motif within a tricyclic framework, displays anti platelet aggregation activity. Aureonitol is a fungi-derived tetrahydrofuran, inhibits influenza replication by targeting its surface glycoprotein hemagglutinin.[10] In 1979, Bohlmann isolated a tetrahydrofuran metabolite from the plant *Helichrysum aureonitens*.[9] He named the compound aureonitol.

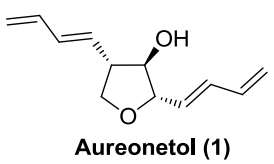
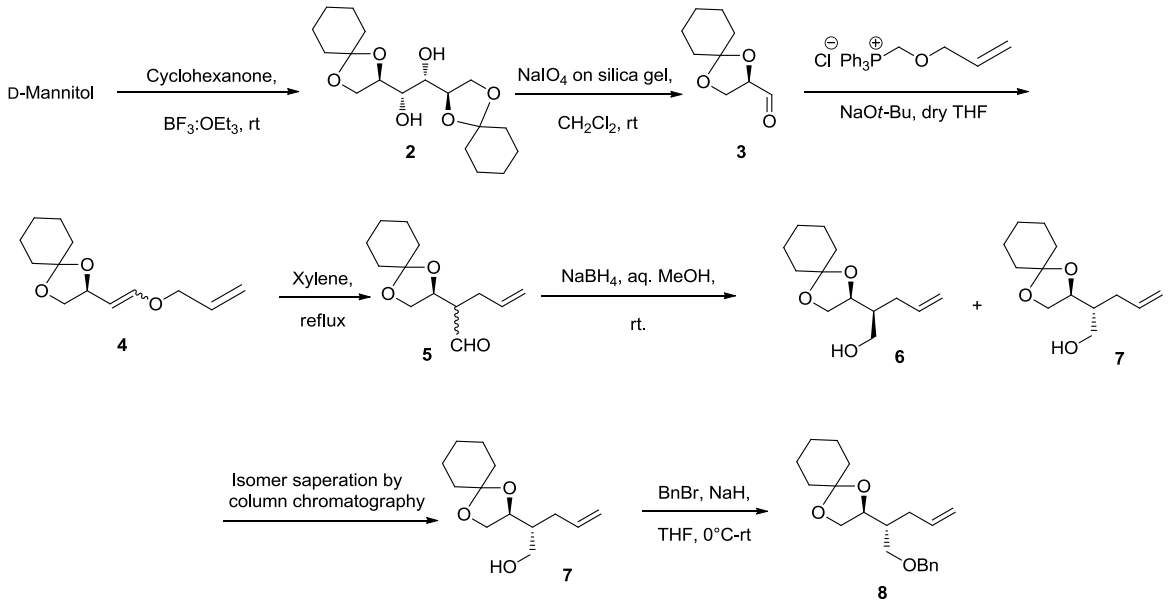


Figure 2: Bioactive natural products containing 2,3,4-trisubstituted THF ring Aureonitol.

Chaetomium Kuntze ex Fries (Chaetomiaceae) is a cosmopolitan fungus found in soil and cellulose-containing substrates.[11] Members of this genus are rich sources of bioactive

secondary metabolites with different chemical structures, such as alkaloids, esters and polyketides. Among the secondary metabolites produced by this genus, aureonitol, a tetrahydrofuran (THF) derivative, is an abundant metabolite.

Using the fungus Chaetomium globosum as a model organism, it has been shown that aureonitol acts as a transcriptional regulator for the synthesis of other secondary metabolites in this species. Aureonitol has been isolated from different species of the genus Chaetomium, from pure cultures in vitro and in association with the plant Helichrysum aureonitens in nature.[12] Although it has been demonstrated that other THF derivatives are endowed with antiviral activity, including against influenza[14], the effects of aureonitol on influenza replication have not been characterized. We show here that aureonitol inhibits influenza replication by targeting conserved residues on HA. It was more effective against influenza A(H3N2), with an EC50 of 100 nM. Aureonitol cytoxicity was also very low, with a CC50 value of 1426 µM. Aureonitol inhibited influenza hemagglutination and, consequently, signifi cantly impaired virus adsorption. Aureonitol is promising for future anti-influenza drug design.[10,13]



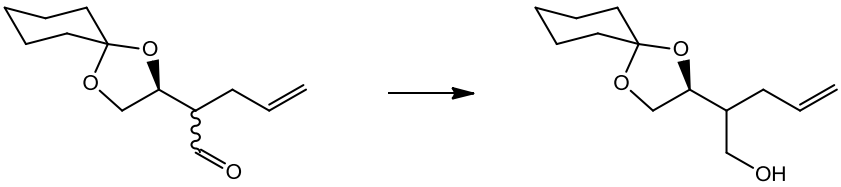
Scheme 1

RESULT AND DISCUSSION

The starting material, D-mannitol is very cheap and readily available. The synthesis begins with the preparation of the 1, 2: 5, 6-di-*O*-cyclohexylidene-D-mannitol by stirring the D-mannitol in dry DMSO in presence of cyclohexanone, triethyl orthoformate and catalytic

amount of BF_3:OEt_2 at room temperature for 12- 15 hours. After aqueous workup, dicyclohexylidene-D-mannitol **2** was isolated as a white solid.

The dicyclohexylidene-D-mannitol **2** was stirred with silica supported sodium metaperiodate in CH_2Cl_2 at room temperature for 10-12 hours. After complete consumption of starting material, the reaction mixture was filtered to get the required (*R*)-2, 3-*O*-cyclohexylideneglyceraldehyde **3**. To apply the Wittig olefination-Claisen rearrangement protocol to the aldehyde **3**, it was treated with allyloxymethylenetriphenylphosphorane in dry THF at 50-55°C. Corresponding allyl vinyl ether **4** was obtained in 78% yield. We started our synthesis using of 4-pentenal **5** obtained from 2,3-*O*-cyclohexylidene-D-glyceraldehyde employing Wittig olefination-Claisen rearrangement protocol as reported.[3] Diastereomeric mixture of 4-pentenal **5** was reduced with sodium borohydride in aqueous methanol at room temperature. The resulting alcohols appeared separately on TLC and were separated through flash column chromatography using ethyl acetate/pet ether (5:95) as an eluent, giving less polar alcohol **6** and more polar alcohol **7** in the ratio of 1:2.7 .



5

6- Less Polar- Minor alcohol

7- More Polar- Major alcohol

Scheme 2.

In the IR spectrum of less polar alcohol **6**, a strong absorption band at 3450 cm^{-1} corresponded to the hydroxyl group. Two sharp signals at 1641 and 922 cm^{-1} were due to terminal olefin. ^1H NMR spectrum of the alcohol **6** showed broad signals between δ 1.40-1.65, integrating together for ten protons were attributed to the methylene protons of cyclohexyl group. The homoallylic methyne proton showed a multiplet between δ 1.72- 1.82. A triplet at δ 2.03, integrating for two protons and with a coupling constant of 6.9 Hz, was assigned to the allylic methylene protons.

A broad exchangeable singlet between δ 2.83- 3.10 and integrating for one proton was assigned to proton of hydroxyl group. Two protons of hydroxy methylene group and one of the methylene protons of the dioxolane ring together gave a multiplet between δ 3.65- 3.77. The second methylene proton of the dioxolane ring and the methyne proton of the dioxolane

ring together showed a multiplet between δ 4.02- 4.12. A multiplet between δ 5.00- 5.10 and integrating for two protons was attributed to the terminal protons of olefin. The internal proton of the terminal olefin showed a multiplet between δ 5.60- 5.83.

In the ^{13}C NMR spectrum, signals at δ 23.7, 23.9, 24.9, 34.9 and 36.1 assigned to five methylene carbons of the cyclohexyl group. The homoallylic methyne carbon resonated at δ 32.7. Allylic methylene carbon showed a signal at δ 43.7. Remaining methylene carbons showed signals at δ 64.0 and 68.1. Methyne carbon of the dioxolane ring showed a peak at δ 78.6. A signal at δ 109.5 assigned to the quaternary carbon. Terminal and internal olefinic carbons resonated at δ 116.9 and 135.4, respectively. The specific optical rotation for alcohol **6** was found to be $[\alpha]_D^{30}$ = -0.51 (*c* 1.34, $CHCl_3$). Elemental analysis supported the molecular formula $C_{13}H_{22}O_3$. This data confirmed the gross structure of the alcohol **6**.

The IR spectrum of the more polar alcohol **7** showed a strong absorption band at 3444 cm^{-1} indicating the presence of hydroxyl group. Also, two sharp signals at 1641 and 927 cm^{-1} corresponded to terminal olefin. ^1H NMR spectrum showed broad signals between δ 1.38- 1.64, integrating together for ten protons were attributed to the methylene protons of cyclohexyl group. The homoallylic methyne proton showed a multiplet between δ 1.81- 1.93. A multiplet at δ 2.01- 2.26, integrating for two protons was assigned to the allylic methylene protons. A broad D_2O exchangeable singlet arising between δ 2.55- 2.66 and integrating for one proton was assigned to proton of hydroxyl group. Two protons of hydroxy methylene group and one of the methylene protons of the dioxolane ring together gave a multiplet between δ 3.53- 3.77. The second methylene proton of the dioxolane ring appeared as a multiplet between δ 3.93- 4.05. The methyne proton of the dioxolane ring showed multiplet between δ 4.09- 4.24. A multiplet between δ 4.95- 5.12 and integrating for two protons was assigned to the terminal protons of olefin. The internal proton of the terminal olefin showed a multiplet between δ 5.68- 5.89. In the ^{13}C NMR spectrum signals appearing at δ 23.7, 23.9, 25.0, 34.6 and 36.0 were assigned to five methylene carbons of the cyclohexyl group. The homoallylic carbon resonated at δ 31.7. Allylic methylene carbon showed a signal at δ 43.4. Remaining methylene carbons showed signals at δ 62.7 and 66.3. Methyne carbon of the dioxolane ring showed a peak at δ 77.0.

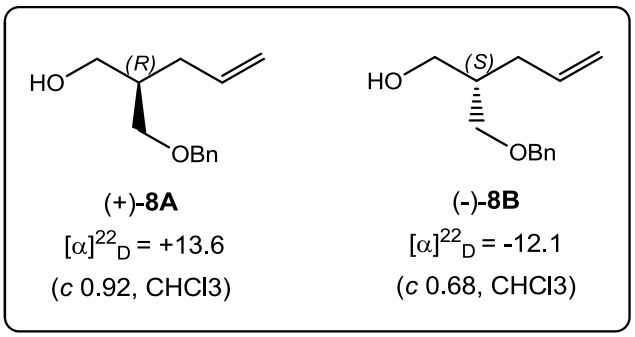
A signal appearing at δ 109.0 was assigned to a quaternary carbon. Terminal and internal olefinic carbons resonated at δ 116.5 and 136.2 respectively. The specific optical rotation for

alcohol **7** was found to be $[\alpha]_D^{30}$ = +0.72 (*c* 3.1, $CHCl_3$). The elemental analysis was in tune with the molecular formula $C_{13}H_{22}O_3$. The NMR and analysis data confirmed the gross structure of the alcohol **7**.

Steriochemical assignment of alcohols 6 and 7

Before proceeding further, it was essential to establish the absolute stereochemistry of newly generated chiral centre and thus the complete stereostructure of the alcohols **6** and **7**. Of the various possible methods for determining the absolute stereochemistry of the newly formed chiral center, chemical correlation of the respective compound or its derivative to the known compound was thought to be more simple, reliable and a convenient method.

Kishi et al[5] have prepared the alcohols (+)-**8A** and (-)-**8B** and reported their optical rotations**.** It was a rather straightforward job to transform alcohols **6** and **7** to known alcohols (+)-**8A** and (-)-**8B**, without disturbing the newly generated chiral centre, and thus the absolute stereochemistry of the alcohols **6** and **7** could be assign by comparing their specific optical rotations with those of the known alcohols (+)-**8A** and (-)-**8B**.



Scheme 3.

After analyzing above results of allylic oxidations we decided to protect alcohol **7** with relatively stable and inert protecting group and then check the allylic oxidation reaction on it. For this reason alcohol **7** was converted to benzyl ether **8** in good yield by typical reaction procedure.[6]

Finally, the syntheses discussed above employed varied, novel and interesting synthetic strategies. However, there is enough scope to develop a more efficient synthetic approach for the synthesis of (-) -Aureonetol. Wittig olefination of the aldehydes or ketones to get allyl vinyl ethers followed by a Claisen rearrangement for the generation of 4-pentenal. This method has been extensively studied and applied in the synthesis of (-) -Aureonetol.

EXPERIMENTAL

MATERIALS AND METHODS

1,2 : 5,6-Di-*O*-cyclohexylidene-D-mannitol (2)

2,3-*O*-Cyclohexylidene-D-glyceraldehyde, The starting material D-mannitol is very cheap and readily available. The synthesis begins with the preparation of the 1, 2: 5, 6-di-*O*-cyclohexylidene-D-mannitol by stirring the D-mannitol in dry DMSO in presence of cyclohexanone, triethyl orthoformate and catalytic amount of BF_3:OEt_2 at room temperature for 12- 15 hours. After aqueous workup, dicyclohexylidene-D-mannitol **2** was isolated as a white solid. M.P.: 104-105 ^oC (Lit.[1] 105-106 ^oC) in 61% yield. $[\alpha]_D^{29}$ = +1.80 (*c* 4.6, MeOH), {Lit.[1] $[\alpha]_D^{20}$ = +2.1 (*c* 5.0, MeOH)}. The IR and ^1H NMR data was in accordance with the reported values.[1]

Procedure

To a mixture of D-mannitol (10 g, 54.89 mmol), cyclohexanone (17.10 mL, 164.68 mmol), triethyl orthoformate (9.22 mL, 55.44 mmol) in dry DMSO (35 mL) at room temperature boron trifluoride etherate (0.68 mL, 5.49 mmol) was added. This reaction mixture was then stirred overnight at room temperature. The mixture was then poured into ice-cooled sodium hydrogen carbonate solution and extracted with ether (3 x 50 mL). The combined extract was washed with water, brine and dried over anhydrous sodium sulfate. Evaporation of the solvent afford crude product containing excess cyclohexanone. The residual syrup was crystallized from hexane and further recrystallized from hexane-ether (2:1) to give fine needles of product **2**. (11.50 g, 61% yield).

M.P.: 104-105 ^oC, (Lit.[47] 105-106^oC).

$[\alpha]_D^{29}$ = +1.80 (*c* 4.6, MeOH), {Lit.[47] $[\alpha]_D^{20}$ = +2.1 (*c* 5.0, MeOH)}.

IR (KBr): 3405, 2855, 1444, 1110 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ 1.31-1.69 (m, 20H, C**H**$_2$ x 10), 2.70 (bs, 2H, -O**H** x 2, exchangeable with D_2O), 3.74 (m, 2H, C3-**H** and C4-**H**), 3.95- 4.27(m, 6H, C1-**H**$_2$, C2-**H**, C5-**H**, C6-**H**$_2$).

Anal. calcd. for $C_{18}H_{30}O_6$: C, 63.14; H, 8.83. Found: C, 63.26; H, 8.70.

2, 3-*O*-Cyclohexylidene-D-glyceraldehyde (3)

The dicyclohexylidene-D-mannitol **2** was stirred with silica supported sodium metaperiodate in CH_2Cl_2 at room temperature for 10-12 hours. After complete consumption of starting

material, the reaction mixture was filtered to get the required (*R*)-2, 3-*O*-cyclohexylideneglyceraldehyde **3**.

The aldehyde was obtained in near quantitative yield and was sufficiently pure for further use. The specific optical rotation for aldehyde **3** was found to be $[\alpha]_D^{29}$ = +60.30 (*c* 3.1, Benzene), {Lit.[1] $[\alpha]_D^{20}$ = +61.2 (*c* 3.4, Benzene)}. The IR and ^{1}H NMR data of the crude product confirmed this and was in agreement with the reported data.[2]

Procedure

To the solution of 1,2: 5,6-di-*O*-cyclohexylidene-D-mannitol (**2**) (11 g, 32.16 mmol) in CH_2Cl_2 (150 mL) at room temperature was added silica supported sodium meta periodate (8.25 g, 38.60 mmol, adsorbed on 33 g of silica gel) and reaction mixture was stirred for 10-12 hours. After completion of reaction (TLC check), the reaction mixture was filtered and residue was washed with CH_2Cl_2. After evaporation of solvent the glyceraldehyde derivative **3** was obtained as a colorless liquid in sufficient pure form and was used for further reaction without any purification. (10.7 g, 98% yield).

$[\alpha]_D^{29}$ = +60.30 (*c* 3.1, Benzene), {Lit.[47] $[\alpha]_D^{20}$ = +61.2 (*c* 3.4, Benzene)}.

IR (film): 2940, 2720, 1741, 1454, 1341, 1182, 921 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.41- 1.65 (m, 10H, C**H$_2$** x 5), 4.07 (1H, dd, *J*= 8.5, 5.5, C3-**H**), 4.18 (dd, 1H, *J* = 8.5, 6.3 Hz, C3-**H**), 4.36 (m, 1H, C2-**H**), 9.72 (d, 1H, *J* = 2.0 Hz, C1-**H**).

^{13}C NMR: (75 MHz, $CDCl_3$): δ 23.7, 23.8, 24.9, 34.6, 38.5, 62.5, 79.5, 111.9, 202.1.

Anal. calcd. for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.66; H, 8.12.

(*S*)-2-(2-(Allyloxy)-vinyl)-1,4-dioxospiro[4.5]-decane (4)

To apply the Wittig olefination-Claisen rearrangement protocol to the aldehyde **3**, it was treated with allyloxymethylenetriphenylphosphorane in dry THF at 50-55°C. Corresponding allyl vinyl ether **4** was obtained in 78% yield.[3]

IR spectrum of this enol ether showed strong peaks at 1693 and 927 cm^{-1} corresponding to the olefin and a signal appearing at 1097 cm^{-1} was due to enol ether linkage. In ^{1}H NMR spectrum, a doublet of a doublet at δ 4.77 with coupling constants of 12.2 and 8.5 Hz, integrating for 0.4 proton and another doublet of a doublet at δ 5.05 with coupling constants of 8.6 and 7.3 Hz, integrating for 0.6 proton, together were attributed to the *β*-proton of the

enol ether. The doublet at δ 6.12 with coupling constant of 7.3 Hz, integrating for 0.6 proton and a doublet at δ 6.55 with coupling constant of 12.2 Hz, integrating for 0.4 proton together were attributed to the *α*-proton of the enol ether. These two sets of signals clearly indicated that the resulting allyl vinyl ether **4**, though appeared homogeneous on TLC, was actually an inseparable mixture of *E* and *Z* isomers in the ratio of 1:1.5. Broad signals between δ 1.39-1.62, integrating together for ten protons were attributed to the methylene protons of cyclohexyl group.

Two triplets resonating very closely at δ 3.49 and 3.52 with coupling constant of 8.5 Hz and integrating together for one proton were assigned to one of the methylene proton of the dioxolane ring. Second proton of this methylene group showed two doublet of doublets at δ 4.03 and 4.08 together integrating for one proton, with coupling constants of 8.6 and 6.1 Hz. This further confirmed that the compound in hand was a mixture of *E* and *Z* isomers. Allylic methylene protons showed a multiplet between δ 4.24- 4.28 for two protons. The methyne protons of the dioxolane ring appeared as two doublet of doublets at δ 4.42 and 4.48 with coupling constants of 8.5 and 6.1 Hz. Olefinic methylene protons showed a multiplet between δ 5.21- 5.34. A multiplet observed between δ 5.83- 5.97 and integrating for one proton corresponded to internal proton of the terminal olefin. ^{13}C NMR spectrum showed two sets of signals which further confirmed the presence of *E* and *Z* isomers in the product. Signals at δ 23.6, 25.0, 33.3 and 36.3 corresponded to methylene carbons of the cyclohexyl group. Allylic methylene carbon and methylene carbon of dioxolane ring gave two signals, each for the *E* and *Z* isomers, at δ 69.0, 69.4, 69.5 and 70.0. Methyne carbon of the dioxolane ring gave two signals at δ 72.9 and 74.5 for the *E* and *Z* isomers. The quaternary carbon of the dioxolane ring gave two signals at δ 101.6 and 104.6 for the *E* and *Z* isomers.

The *β*-carbon of the enol ether showed signals at δ 109.0 and 109.2. Terminal carbon gave peaks at δ 117.6 and 117.7 while the internal olefinic carbon gave peaks at 132.3 and 132.7. The *α*-carbon of the enol ether showed signals at δ 147.7 and 150.1. From ^{13}C NMR signals it was confirmed that the allyl vinyl ether **4** was obtained as an inseparable mixture of *E* and *Z* isomers. The elemental analysis was in agreement with molecular formula $C_{13}H_{20}O_3$. Spectral values and analytical data were in accord with the structure of compound **4**.

Procedure

To a suspension of 2, 3-*O*-Cyclohexylidene-D-glyceraldehyde (**3**) (10 g, 58.82 mmol) and allyloxymethylenetriphenylphosphoniumchloride (28.22 g, 76.47 mmol) in dry THF (150

mL), Sodium *tert*-butoxide (7.34 g, 76.47 mmol) was added portion wise over the period of 10 min. at 50- 55 °C. The reaction was stirred for 1h at the same temperature. After the completion of reaction (TLC check), THF was removed under reduced pressure and the crude product was extracted with ethyl acetate (3 x 50 mL). The combine organic layer was washed with water, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using pet ether as a mobile phase, gave pure allyl vinyl ether **4** as coloueless thick liquid. The product in hand was the inseparable mixture of *E* and *Z* isomers in 1:1.5 ratio (10.3 g, 78% yield).

IR (film): 2935, 1693, 1097, 927 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.39- 1.62 (m, 10H, C**H$_2$** x 5), 3.49 & 3.52 (2t, 1H, *J* = 8.5 Hz, OC**H$_{2A}$**CH-O), 4.03 & 4.08 (2dd, 1H, *J* = 8.6 & 6.1 Hz, -OC**H$_{2B}$**CH-O), 4.24- 4.28 (m, 2H, -OC**H$_2$**CH=CH_2), 4.42 & 4.48 (2dd, 1H, *J* = 8.5 & 6.1 Hz, OC**H**CH_2O), 4.77 (dd, 0.4H, *J* = 12.2 & 8.5 Hz, C**H**=CH-O), 5.05 (dd, 0.6H, *J* = 8.6 & 7.3 Hz, C**H**=CH-O), 5.21- 5.34 (m, 2H, C**H$_2$**=CH-), 5.83- 5.97 (m, 1H, , CH_2=C**H**), 6.12 (d, 0.6H, *J* = 7.3 Hz, CH=C**H**-O), 6.55 (d, 0.4H, *J* = 12.2 Hz, CH=C**H**-O).

^{13}C NMR: (75 MHz, $CDCl_3$): δ 23.6, 25.0, 33.3, 36.3, 69.0, 69.4, 69.5, 70.0, 72.9, 74.5, 101.6, 104.6, 109.0, 109.2, 117.6, 117.7, 132.3, 132.7, 147.7, 150.1.

MS (m/z): 225(M^++1), 183, 167, 141, 83, 57, 41, 27.

Anal. calcd. for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.77; H, 8.82.

(*S*)-2-(1,4-Dioxaspiro[4.5]-decan-2-yl)-pent-4-enal (5)

The isomeric mixture of allyl vinyl ether **4** as such was refluxed in xylene to effect the Claisen rearrangement.[3] After Claisen rearrangement we expected to observe two diastereoisomers of the corresponding aldehyde **5** separately on TLC. However, the TLC showed a homogeneous single spot. IR spectrum showed strong absorption bands at 2937 and 1724 cm^{-1} indicating the presence of aldehyde functional group. The peaks appearing at 1640 and 910 cm^{-1} corresponded to terminal olefin. In ^{1}H NMR a doublet at δ 9.77, integrating for 0.27 proton with coupling constant of 3 Hz and a singlet at δ 9.74 integrating for 0.73 proton were together assigned to the proton of aldehyde group. Two very closely spaced doublet of doublets at δ 3.64 and 3.73, having coupling constants of 8.2 and 7.0 Hz and integrating for 0.27 and 0.73 proton respectively were together assigned to one of the methylene proton of dioxolane ring.

These two signals indicated that the resulting aldehyde **5**, though appeared homogeneous on TLC, was actually an inseparable mixture of diastereomers in the ratio of 1:2.7. Broad signals between δ 1.40- 1.67, integrating together for ten protons were attributed to the methylene protons of cyclohexyl group. Multiplets between δ 2.22- 2.27 integrating for three protons were due to the allylic methylene protons and homoallylic methyne proton. A multiplet resonating between δ 4.07- 4.17 and integrating for one proton was assigned to the remaining methylene proton of the dioxolane ring. The methyne proton of the dioxolane ring showed a multiplet between δ 4.25- 4.35. Terminal olefinic protons showed a multiplet between δ 5.04- 5.17 whereas internal olefinic proton showed a multiplet between δ 5.66- 5.89. The ^{13}C NMR spectrum showed two sets of signals which further confirmed that the compound was a mixture of diastereomers. Signals at δ 23.6, 23.8, 23.9, 25.0, 34.5, 34.7, 36.0 and 36.1 corresponded to methylene carbons of the cyclohexyl group for two diasereomers. Allylic methylene carbon showed signals at δ 30.0 and 30.5 for two diastereomers, while the homoallylic carbon resonated at δ 54.4. The signals at δ 67.1 and 67.2 were assigned to the methylene carbon of the dioxolane ring. Methyne carbon of the dioxolane ring gave two signals at δ 73.6 and 74.7 for two diastereomers. The quaternary carbon of the dioxolane ring gave two signals at δ 109.4 and 109.9 for the diastereomers.

The terminal carbon of the olefin resonated at δ 117.6 and the internal olefinic carbon gave peaks at δ 134.2 and 134.4. The carbonyl carbon showed peaks at δ 202.9 and 203.0 corresponding to the two diastereomers. This spectral data confirmed that the resulting aldehyde **5** was a mixture of two inseparable diastereomers.

Procedure

The isomeric mixture of allyl vinyl ether **4** (10 g, 44.6 mmol) as such was dissolved in xylene (25 mL) and solution was refluxed for 6-7 hours. After the completion of reaction (TLC check), xylene was removed under reduced pressure. The crude product was purified through silica gel column chromatography using pet ether as an eluent to afford pure 4-pentenal **5** as coluorless viscous liquid. The product in hand was the mixture of two inseparable diastereoisomers in the ratio of 1: 2.7. (9.7 g, 97% yield).

IR (film): 2937, 1724, 1640, 1101, 910 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.40- 1.67 (m, 10H, C**H$_2$** x 5), 2.22- 2.27 (m, 3H, C**H**-C**H$_2$**-CH=CH$_2$), 3.64 (dd, 0.27H, *J* = 8.2 & 7.0 Hz, OC**H$_{2A}$**CH-O), 3.73 (dd, 0.73H, *J* = 8.2 & 7.0 Hz, OC**H$_{2A}$**CH-O), 4.07- 4.17 (m, 1H, OC**H$_{2B}$**CH-O), 4.25- 4.35 (m, 1H, OCH$_2$C**H**-O), 5.04-

5.17 (m, 2H, C**H**$_2$=CH-), 5.66- 5.89 (m, 1H, CH$_2$=C**H**-), 9.74 (s, 0.73H, -C**H**O), 9.77 (d, 0.27H, *J* = 3 Hz, -C**H**O).

^{13}C NMR: (75 MHz, CDCl$_3$): δ 23.6, 23.8, 23.9, 25.0, 30.0, 30.5, 34.5, 34.7, 36.0, 36.1, 54.4, 67.1, 67.2, 73.6, 74.7, 109.4, 109.9, 117.6, 134.2, 134.4, 202.9, 203.0.

(*S* & *R*)-2-((*S*)-1,4-Dioxaspiro[4.5]decan-2-yl)-pent-4-en-1-ol (6 and 7)

We started our synthesis using of 4-pentenal **5** obtained from 2,3-*O*-cyclohexylidene-D-glyceraldehyde employing Wittig olefination-Claisen rearrangement protocol as reported.[4] Diastereomeric mixture of 4-pentenal **5** was reduced with sodium borohydride in aqueous methanol at room temperature. The resulting alcohols appeared separately on TLC and were separated through flash column chromatography using ethyl acetate/pet ether (5:95) as an eluent, giving less polar alcohol **6** and more polar alcohol **7** in the ratio of 1:2.7.

In the IR spectrum of less polar alcohol **6**, a strong absorption band at 3450 cm^{-1} corresponded to the hydroxyl group. Two sharp signals at 1641 and 922 cm^{-1} were due to terminal olefin.

^{1}H NMR spectrum of the alcohol **6** showed broad signals between δ 1.40- 1.65, integrating together for ten protons were attributed to the methylene protons of cyclohexyl group. The homoallylic methyne proton showed a multiplet between δ 1.72- 1.82. A triplet at δ 2.03, integrating for two protons and with a coupling constant of 6.9 Hz, was assigned to the allylic methylene protons. A broad exchangeable singlet between δ 2.83- 3.10 and integrating for one proton was assigned to proton of hydroxyl group. Two protons of hydroxy methylene group and one of the methylene protons of the dioxolane ring together gave a multiplet between δ 3.65- 3.77. The second methylene proton of the dioxolane ring and the methyne proton of the dioxolane ring together showed a multiplet between δ 4.02- 4.12. A multiplet between δ 5.00- 5.10 and integrating for two protons was attributed to the terminal protons of olefin. The internal proton of the terminal olefin showed a multiplet between δ 5.60- 5.83. In the ^{13}C NMR spectrum, signals at δ 23.7, 23.9, 24.9, 34.9 and 36.1 assigned to five methylene carbons of the cyclohexyl group. The homoallylic methyne carbon resonated at δ 32.7. Allylic methylene carbon showed a signal at δ 43.7. Remaining methylene carbons showed signals at δ 64.0 and 68.1. Methyne carbon of the dioxolane ring showed a peak at δ 78.6. A signal at δ 109.5 assigned to the quaternary carbon. Terminal and internal olefinic carbons resonated at δ 116.9 and 135.4, respectively. The specific optical rotation for alcohol **6** was

found to be $[\alpha]_D^{30}$ = -0.51 (*c* 1.34, $CHCl_3$). Elemental analysis supported the molecular formula $C_{13}H_{22}O_3$. This data confirmed the gross structure of the alcohol **6**.

The IR spectrum of the more polar alcohol **7** showed a strong absorption band at 3444 cm^{-1} indicating the presence of hydroxyl group. Also, two sharp signals at 1641 and 927 cm^{-1} corresponded to terminal olefin. ^1H NMR spectrum showed broad signals between δ 1.38-1.64, integrating together for ten protons were attributed to the methylene protons of cyclohexyl group. The homoallylic methyne proton showed a multiplet between δ 1.81- 1.93.

A multiplet at δ 2.01- 2.26, integrating for two protons was assigned to the allylic methylene protons. A broad D_2O exchangeable singlet arising between δ 2.55- 2.66 and integrating for one proton was assigned to proton of hydroxyl group. Two protons of hydroxy methylene group and one of the methylene protons of the dioxolane ring together gave a multiplet between δ 3.53- 3.77. The second methylene proton of the dioxolane ring appeared as a multiplet between δ 3.93- 4.05. The methyne proton of the dioxolane ring showed multiplet between δ 4.09- 4.24. A multiplet between δ 4.95- 5.12 and integrating for two protons was assigned to the terminal protons of olefin. The internal proton of the terminal olefin showed a multiplet between δ 5.68- 5.89. In the ^{13}C NMR spectrum signals appearing at δ 23.7, 23.9, 25.0, 34.6 and 36.0 were assigned to five methylene carbons of the cyclohexyl group. The homoallylic carbon resonated at δ 31.7. Allylic methylene carbon showed a signal at δ 43.4. Remaining methylene carbons showed signals at δ 62.7 and 66.3. Methyne carbon of the dioxolane ring showed a peak at δ 77.0. A signal appearing at δ 109.0 was assigned to a quaternary carbon. Terminal and internal olefinic carbons resonated at δ 116.5 and 136.2 respectively.

The specific optical rotation for alcohol **7** was found to be $[\alpha]_D^{30}$ = +0.72 (*c* 3.1, $CHCl_3$). The elemental analysis was in tune with the molecular formula $C_{13}H_{22}O_3$. The NMR and analysis data confirmed the gross structure of the alcohol **7**.

Steriochemical assignment of alcohols 6 and 7

Before proceeding further, it was essential to establish the absolute stereochemistry of newly generated chiral centre and thus the complete stereostructure of the alcohols **6** and **7**. Of the various possible methods for determining the absolute stereochemistry of the newly formed chiral center, chemical correlation of the respective compound or its derivative to the known compound was thought to be more simple, reliable and a convenient method.

Kishi et.al[5] have prepared the alcohols (+)-**8A** and (-)-**8B** and reported their optical rotations**.** It was a rather straightforward job to transform alcohols **6** and **7** to known alcohols (+)-**8A** and (-)-**8B**, without disturbing the newly generated chiral centre, and thus the absolute stereochemistry of the alcohols **6** and **7** could be assign by comparing their specific optical rotations with those of the known alcohols (+)-**8A** and (-)-**8B**.

Procedure

To the solution of aldehyde **5** (9.80 g, 43.75 mmol) in 5% aqueous methanol (70 mL), sodium borohydride (1.66 g, 43.75 mmol) was added portion wise over a period of 10 min. The reaction mixture was stirred at room temperature for 30-40 min. After completion of reaction (TLC check) the methanol was removed under reduced pressure, and the crude residue was partitioned between ethyl acetate and water. Layers were separated and aqueous layer was extracted with ethyl acetate (3 x 40 mL). Combined organic layer was washed with water, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude product was purified by flash column chromatography using ethyl acetate/pet ether (5:95) as an eluent to give the less polar alcohol **6** (2.56 g) and more polar alcohol **7** (6.92 g) as colorless liquids in the ratio of 1:2.7. (9.48 g, 96% yield).

(*S*)-2-((*S*)-1,4-Dioxaspiro[4.5]decan-2-yl)-pent-4-en-1-ol (6)

$[\alpha]_D^{30}$ = -0.51 (*c* 2.34, $CHCl_3$).

IR (film): 3450, 2937, 1641, 1446, 1105, 922 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.40- 1.65 (m, 10H, C**H$_2$** x 5), 1.72- 1.82 (m, 1H, -C**H**CH_2OH), 2.03 (t, 2H, *J* = 6.9 Hz, -C**H$_2$**$CH{=}CH_2$), 2.83- 3.10 (bs, 1H, exchangeable with D_2O, -O**H**), 3.65- 3.77 (m, 3H, -C**H$_2$**OH & -OC**H$_{2A}$**CH-), 4.02- 4.12 (m, 2H, -OC**H$_{2B}$**CH- & -CH_2C**H**-O), 5.00- 5.10 (m, 2H, C**H$_2$**=CH-), 5.60- 5.83 (m, 1H, CH_2=C**H**-).

^{13}C NMR: (75 MHz, $CDCl_3$): δ 23.7, 23.9, 24.9, 32.7, 34.9, 36.1, 43.7, 64.0, 68.1, 78.6, 109.5, 116.9, 135.4.

MS (m/z): 227(M^+ +1), 210, 197, 183, 171, 141, 99.

Anal. calcd. for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 69.08; H, 9.69.

(*R*)-2-((*S*)-1,4-Dioxaspiro[4.5]decan-2-yl)-pent-4-en-1-ol (7)

$[\alpha]_D^{30}$ = +0.72 (*c* 3.1, $CHCl_3$).

IR (film): 3444, 2937, 1641, 1444, 1103, 927 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.38- 1.64 (m, 10H, C**H$_2$** x 5), 1.81- 1.93 (m, 1H, -C**H**CH_2OH), 2.01- 2.26 (m, 2H, -C**H$_2$**$CH{=}CH_2$), 2.55- 2.66 (bs, 1H, exchangeable with D_2O, -O**H**), 3.53- 3.77 (m, 3H, -C**H$_2$**OH & -OC**H$_{2A}$**CH-), 3.93- 4.05 (m, 1H, -OC**H$_{2B}$**CH-) 4.09- 4.24 (m, 1H, -CH_2C**H**-O), 4.95- 5.12 (m, 2H, C**H$_2$**=CH-), 5.68- 5.89 (m, 1H, CH_2=C**H**-).

^{13}C NMR: (75 MHz, $CDCl_3$): δ 23.7, 23.9, 25.0, 31.7, 34.6, 36.0, 43.4, 62.7, 66.3, 77.0, 109.0, 116.5, 136.2.

MS (m/z): 227(M^+ +1), 210, 197, 183, 141, 99, 43.

Anal. calcd. for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 69.08; H, 9.68.

(*S*)-2-((*R*)-1-(Benzyloxy)pent-4-en-2-yl)-1,4-dioxaspiro[4.5]decane(8)

After analyzing above results of allylic oxidations we decided to protect alcohol **7** with relatively stable and inert protecting group and then check the allylic oxidation reaction on it. For this reason alcohol **7** was converted to benzyl ether **8** in good yield by typical reaction procedure.[6]

IR spectrum of compound **8** showed sharp signals at 1641 and 912 cm^{-1} for terminal olefin. Absorption bands at 1448 and 737 cm^{-1} showed presence of aromatic group. Stretching at 1103 cm^{-1} corresponded to ether linkage. In ^{1}H NMR spectrum multiplet integrating for ten protons between δ 1.39- 1.67 was attributed to methylene protons of cyclohexyl group. Homoallylic methyne proton showed multiplet between δ 1.84- 1.94. Multiplet between δ 2.12- 2.22 was due to one of the allylic methyne protons while remaining allylic methyne proton exhibited multiplet between δ 2.36- 2.44. Doublet of a doublet at δ 3.37 with coupling constants of 9.4 and 6.7 Hz attributed to one of the methylene protons of carbon carrying benzyl ether whereas another doublet of doublet at δ 3.45 with coupling constants of 9.5 and 4.6 Hz was due to remaining methylene proton.

One of the methylene protons of dioxolane ring appeared as multiplet between δ 3.66- 3.72. Remaining methylene proton and methyne proton of dioxolane ring together exhibited a multiplet between δ 4.00- 4.11. Singlet for two protons at δ 4.45 was due to benzylic methylene protons. Doublet at δ 5.01 with coupling constant of 8.2 Hz attributed to one of the terminal olefinic protons while another terminal olefinic proton showed doublet at δ 5.04 with coupling constant of 15.4 Hz. Internal proton of olefine appeared as multiplet between δ 5.74- 5.88. A multiplet integrating for five protons at δ 7.25- 7.36 was attributed to aromatic protons of benzyl group.

In ^{13}C NMR signals at δ 23.9, 24.0, 25.2, 35.2 and 36.3 attributed to methylene carbons of cyclohexyl group. Homoallylic methyne carbon exhibited signal at δ 32.7 whereas allylic methylene carbon showed peak at δ 42.0. Methylene and methyne carbons of dioxolane ring gave signals at δ 67.9 and 76.7 respectively. Methylene carbon bearing benzyl ether appeared at δ 70.1. Benzylic methylene carbon exhibited signal at δ 73.2. Peaks resonating at δ 116.4 and 138.3 were due to terminal and internal olefinic carbons respectively. Aromatic carbons showed signals at δ 127.4, 127.5, 128.3 and 136.5. The specific optical rotation of benzyl ether **8** was found to be $[\alpha]_D^{21}$ = -1.51 (*c* 1.53, $CHCl_3$). The elemental analysis was toning with molecular formula $C_{20}H_{28}O_3$. The spectroscopic and elemental analysis data confirmed the structure of compound **8**.

Procedure

To the suspension of sodium hydride (60% in mineral oil, 1.09 g, 27.17 mmol) in dry THF (30 mL) at 0 °C, the solution of alcohol **7** (5.12 g, 22.64 mmol) in dry THF (30 mL) was added slowly over the period of 15 min. The solution was stirred at same temperature for 10 min. and benzyl bromide (2.96 mL, 24.90 mmol) was added dropwise in it. Reaction mixture was allowed to come at room temperature and stirred for 7-8 hours. After completion of reaction (TLC check), the mixture was cooled in ice bath and reaction was quenched by adding water. Layers were saperated and aqueous layer was extracted ethyl acetate (3 x 40 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography using ethyl acetate/pet ether (5:95) mobile phase to give benzyl ether **8** as colourless thick liquid (6.74 g, 94% yield).

$[\alpha]_D^{21}$ = -1.51 (*c* 1.53, $CHCl_3$).

IR (film): 2933, 2858, 1641, 1448, 1103, 912, 737 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.39- 1.67 (m, 10H, C**H**$_2$ x 5), 1.84- 1.94 (m, -C**H**CH_2OBn), 2.12- 2.22 (m, 1H, -C**H$_{2A}$**$CH=CH_2$), 2.36- 2.44 (m, 1H, -C**H$_{2B}$**$CH=CH_2$), 3.37 (dd, 1H, *J* = 9.4 & 6.7 Hz, -C**H$_{2A}$**OBn), 3.45 (dd, 1H, *J* = 9.5 & 4.6 Hz, -C**H$_{2B}$**OBn), 3.66- 3.72 (m, 1H, -OC**H$_{2A}$**CHO-), 4.00- 4.11 (m, 2H, -OC**H$_{2B}$**C**H**O-), 4.45 (s, 2H, -OC**H$_2$**Ph), 5.01 (d, 1H, *J* = 8.2 Hz, -CH=C**H$_{2A}$**), 5.04 (d, 1H, *J* = 15.4 Hz, -CH=C**H$_{2B}$**), 5.74- 5.88 (m, 1H, -C**H**=CH2), 7.25- 7.36 (m, 5H, Ar-**H** x 5).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.9, 24.0, 25.2, 32.7, 35.2, 36.3, 42.0, 67.9, 70.1, 73.2, 76.7, 108.6, 116.4, 127.4, 127.5, 128.3, 136.5, 138.3.

Anal. calcd. for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found C, 75.80; H, 8.98.

CONCLUSION

The syntheses discussed above employed varied, novel and interesting synthetic strategies. However, there is enough scope to develop a more efficient synthetic approach for the synthesis of (-) -Aureonetol. Wittig olefination of the aldehydes or ketones to get allyl vinyl ethers followed by a Claisen rearrangement for the generation of 4-pentenal. This method has been extensively studied and applied in the synthesis of different natural products. Also application of this protocol to the synthesis of (-) –Aureonetol.

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