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Graphical Abstract

Stereoselective Addition of Grignard Reagents to Sulfinimines Derived from Tartrate Diol (threitol): Generation of Chiral Building Blocks for the Collective Total Synthesis of Lentiginosine, Conhydrine and Methyldihydropalustramate **Kavirayani R. Prasad* and Vipin Ashok Rangari**

HO HC HO Ėt (+)- α -conhydrine Lentiginosine ^tBu <u>RMgX</u> NHS(O)^tBu steps OBn HO, Et Ĥ Ph N Boc ŌН ĊO₂Me methyldihydropalustramate JUR

Stereoselective Addition of Grignard Reagents to Sulfinimines Derived from Tartrate Diol (threitol): Generation of Chiral Building Blocks for the Collective Total Synthesis of Lentiginosine, Conhydrine and Methyldihydropalustramate

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Abstract: A systematic investigation of the addition of Grignard reagents to sulfinimines derived from tartaric acid diol was undertaken. It was observed that the chirality of the inherent tartrate moiety influences the diastereoselectivity of the resultant sulfinamides formed in the reaction. The formed products serve as excellent building blocks for the synthesis of natural products. This has been demonstrated in the collective total synthesis of lentiginosine, (+)- α -conhydrine and methyldihydropalustramate.

Key words: Sulfinimines, Chiral pool, Stereoselective addition, Total synthesis, Alkaloids

Introduction:

Polyhydroxy functionalized pyrrolidines, piperidines are important class of compounds ubiquitously present in aza-sugars and other therapeutically important molecules.¹ Owing to the fact that a large number of polyhydroxy functionalized piperidines, pyrrolidines and other bicyclic analogues display excellent glycosidase inhibitory activity, there has been a continuing interest in the development of synthetic strategies for their synthesis.² The readily available chiral pool compounds such as carbohydrates and tartaric acid were widely utilized for the synthesis of these polyhydroxy amine containing compounds. Extensive protection/ deprotection of the functional groups was required in the synthesis of aza-sugars from carbohydrates,³ while, approaches from tartaric acid generally involved the stereoselective addition of nucleophiles such as Grignard reagents to imines or imine equivalents derived from tartrate diol (threitol). Terashima's group was the first to study the addition of Grignard reagents to imines derived from tartaric acid. They found that the addition of cyclohexylmethylmagnesium bromide to the benzylimine 1 derived from tartaric acid does not form the required product, while, an organocerium reagent prepared from the Grignard reagent and CeCl₃ afforded the product with excellent selectivity.⁴ Later, Dondoni's group studied the nucleophilic addition reactions of nitrones 2 derived from tartrate.⁵ We reasoned that the formation of sulfinimines **3-4** from the aldehydes derived from tartaric acid would serve as excellent start point for the synthesis of polyhydroxy functionalized amine compounds. Sulfinimines are proven reagents for the synthesis of chiral amines with perfect stereocontrol⁶ and the ease of deprotection of the sulfinamide group allows the generation of free amine and further transformations involving the amine functionality. The process would be beneficial from the conventional use of imine equivalents which involve cumbersome deprotection of the amine protecting groups. Also, a systematic examination of the addition of organometallic reagents such as Grignard reagents and organolithium compounds would give the insight in to the diastereoselectivity associated with the match, mis-match situation of the chiral sulfinimine and tartrate components. Prior to our work, few examples concerning the addition of CN^7 and MeP(O)(OMe)₂⁸ on sulfinimine **3** derived from p-toluenesulfinamide and tartrate was recorded in literature. It is important to note that except for allyl Grignard reagents, the addition of other Grignard reagents is not possible on the imines derived from *p*-tolunesulfinamide. Addition of iodomethyllithium and vinylmagnesium bromide to structurally similar sulfinimine **4**^{9,10} prepared from Ellman's sulfinamide has also been reported. Herein, we describe in detail our efforts concerning the study of various alkyl/aryl Grignard reagents to the sulfinimine 4 and

application of the formed products in the collective total synthesis of natural products lentiginosine **5**, (+)- α -conhydrine **6**, methyldihydropalustramate **7** and the piperidine **8**; a key intermediate for the synthesis of CP,99,994, CP-122,721 and LP-733,060, molecules of therapeutic significance (Fig-1).



Fig.1: Chiral imines derived from tartrate diol (threitol).

Results and Discussion

Accordingly, the study commenced with the synthesis of the sulfinimine from the diol derived from tartaric acid analogus to a procedure described earlier.¹⁰ Addition of MeMgI to the imine produced the addition product **9a** in 92% yield and in >99:1 diastereomeric ratio.¹¹ The addition of ^{*n*}BuMgBr, PhCH₂MgBr also proceeded smoothly to afford the addition products **9b-c** in >99:1 diastereomeric in good yields. The addition of ^{*i*}BuMgBr formed the product **9d** in 52% yield (71% based on the recovery of the starting material) while, the addition of ^{*i*}PrMgBr afforded the product **9e** in 68% yield (dr >99:1) along with 14% of the imine reduction product originating from the addition of the β-hydride of the Grignard reagent. The addition of PhMgBr and 4-OMePhMgBr also furnished the products **9f-g** with excellent diastereoselectivity (>99:1). The addition of pent-4-enylmagnsium bromide as well as 4-benzyloxybutylmagnesium bromide also gave the products **9h-i** with more than >99:1 diastereoselectivity. The addition of vinylmagnesium bromide produced the product **9j** in 74% yield and in >99:1 *dr*. All these results are summarized in chart-1.



Chart-1: Stereoselective addition of Grignard reagents to the sulfinimine 4

Stereochemistry at the newly formed amine center is established by the following. Deprotection of the sulfinyl group in **9a** with methanolic HCl followed by protection as Cbz carbamate funrnished the Cbz protected amine **10** in 87% yield. Deprotection of the acetonide in **10** yielded the diol in 75% yield. Treatment of **11** with NaIO₄ produced the aldehyde the reduction of which with NaBH₄ afforded the amino alcohol **12** in 86% yield. Comparison of the optical rotation¹² of **12** with that obtained from natural amino acid alanine clearly established the stereochemistry as (*S*) at the newly formed center bearing the amine group (Scheme-1).



Scheme-1: Determination of the absolute stereochemistry of the amine center in 9a

The sense of induction in the addition reaction was governed by the tartrate moiety rather than the sulfinimine. Similar outcome was observed by Wang in the addition of vinylmagnesium bromide to structurally similar sulfinimine.¹⁰ It is evident that the major products formed in the addition of nucleophiles to imine **4** originate from the addition of nucleophiles from a face opposite to the sulfinyl oxygen of the sulfinimine. Formation of the major products **9a-j** can be explained by a model proposed by Davis¹³ for the addition of organometallic reagents to sulfinimines derived from ethylglyoxalate (fig-2).



Fig. 2: Proposed model for the observed selectivity

To investigate the effect of *match-mismatch* situation in the reaction, sulfinimine **4a** derived from D-tartaric acid and S_s -*tert*-butanesulfinamide was reacted with MeMgI. The formation of both possible diastereomers **13a** and **13b** was observed in 3:1 ratio, which were isolated in 59% and 14% respectively (Scheme-2), indicating a *mis-match* situation. Following a procedure described in scheme-1, stereochemistry at the newly formed amine center in the major diastereomer **13a** was found to be *R*.



Scheme-2: Addition of MeMgI to sulfinimine 4a.

After optimizing the conditions for the addition of Grignard reagents and the stereochemistry of the newly formed stereogenic center, application of the resultant compounds is exemplified in the synthesis of bio-active natural products. The total synthesis of lentiginosine 5 and conhydrine 6 was accomplished from the sulfinamide as depicted in Scheme-3. Lentiginosine is the smallest azasugar natural product that displayed potent glycosidase inhibitory activity. A plethora of publications about the synthesis of lentiginosine¹⁴ have appeared in literature including the synthesis originating from tartaric acid.¹⁵ In the present sequence, the synthesis of lentiginosine started with the debenzylation of both benzyl groups in 9i using Li/ naphthalene to furnish the free diol which was transformed to the bis-tosylate 14 in 61% yield for two steps. Deprotection of the acetonide as well as the sulfinyl group in 14 was accomplished by reaction with saturated methanolic HCl. Neutralization of the formed amine hydrochloride with K₂CO₃ resulted in the concomitant displacement of both tosyl groups with amine to furnish lentiginosine in 60% yield (26% overall yield from the sulfinimine in 4 steps). The sulfinamide 9i was also utilized in the synthesis (+)- α -conhydrine **6**, an alkaloid natural product isolated from the seeds and leaves of *Conium maculatum L* which was also shown to exhibit glycosidase inhibitory activity.¹⁶ For the synthesis of conhydrine the sulfinyl group in 9i was deprotected and the amine was protected as the Boc carbamate to yield 15 in 84% yield. Debenzylation of the benzylethers in 15 afforded the diol **16** which on tosylation of the free hydroxy groups furnished the *bis*-tosylate **17** in 83% yield. Reaction of the bis-tosylate 17 with NaH furnished the piperidine 18 in 81% yield. Conversion of the tosylate **18** to the iodide and subsequent reaction with Zn in EtOH cleanly furnished the allyl alcohol **19** in 71% yield. Hydrogenation of the olefin in **19** followed by the deprotection of the Boc group afforded conhydrine 6 in 73% for two steps (Scheme-3). The spectral and physical data of which is in complete agreement with that reported in literature.¹⁷



Scheme-3: Total Synthesis of lentiginosine **5** and (+)- α -conhydrine **6** from sulfinamide **9i**

After accomplishing the synthesis of lentiginosine and conhydrine, application of the sulfinamide **9f** in the synthesis of **8**; a key intermediate for the synthesis of therapeutically important piperidines **21-23^{18ab}** (which are shown to act as neurokinin substance P antagonists receptors) was undertaken. Thus, removal of the sulfinyl group in **9f** and further protection of the free amine as the Boc carbamate furnished **24** in 63% yield. Debenzylation of the benzylether in **24** afforded the free alcohol **25** (97% yield) which was converted to the tosylate **26** using standard conditions. *N*-allylation of the carbamate furnished the product **27** in 60% yield. Conversion of the tosylate in **27** to the iodide and further reaction with zinc in methanol afforded the diene **28** in 91% yield. Ring closing metathesis (RCM) of the diene **28** with Grubbs' 2nd generation catalyst and further hydrogenation of the formed dihydropiperidine with H₂/Pd furnished 2-phenyl,3-hydroxy-N-Boc piperidine **8** in 80% yield. Since conversion of **8** to LP-733,060, CP-99,994 and CP-122,721 is reported in literature,^{18a,c} the present sequence constitutes a formal synthesis of **21-23** (Scheme-4).



Scheme-4: Formal synthesis of LP-733,060, CP-99,994 and CP-122,721

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In another application, total synthesis of methyldihydropalustramate 7,¹⁹ a degradation product of the natural product palustrine and also considered as the intermediate for the synthesis of palustrine was accomplished from the sulfinamide **9h** as depicted in scheme-5. Accordingly, debenzylation of the benzyl ether in **9h** furnished the free alcohol which was converted to the tosylate 29 under standard reaction conditions in 56% yield for two steps. The tosylate in 29 was transformed to the iodide which on deprotection of the N-sulfinyl group and further protection of the free amine with Boc anhydride afforded the Boc-carbamate **30** in 71% yield for two steps. Elaboration of the olefin in **30** to the unsaturated ester **31** was accomplished by a two-step process involving ozonolysis of the olefin and subsequent Horner-Wadsworth-Emmons olefination. Although, olefin cross metathesis of **30** with ethylacrylate also rendered the required unsaturated ester 31, we preferred the ozonolysis/HWE olefination sequence because of the better yield. Reaction of 31 with NaH underwent the intramolecular aza Michael addition to form the 2,6-disubstituted piperidine **32** in 78% yield. Treatment of **32** with zinc in ethanol yielded the allyl alcohol 33 in 77% yield. K₂CO₃ mediated trans esterification of the ethyl ester in 33 to the methyl ester 34 (80% yield) and further hydrogenation formed the Boc-protected epimethyldihydropalustramate **35** in almost quantitative yield. Dess-Martin periodinane²⁰ oxidation of the alcohol in 35 afforded the ketone which on reduction with NaBH₄ furnished the Bocprotected methyldihydropalustramate 36 in 77% yield. TFA mediated deprotection of Boc group in 36 furnished (-)-methyldihydropalustramate 7 in 72% yield. The spectral and physical data is in complete agreement with that reported in literature (Scheme-5).^{19d}



Scheme-5: Total synthesis of (–)-methyldihydropalustramate

In conclusion, a systematic study on the addition of Grignard reagents to the sulfinimines derived from tartaric acid was reported. It was observed that the diastereoselectivity in the addition reaction is controlled by inherent tartrate moiety and the sulfinamide group acts as a bulky group. Slight influence of the match-mismatch like situation was observed in the addition reaction. The formed sulfinamides serve as excellent building blocks for the synthesis of a number of amine containing natural products. This was demonstrated in the collective total synthesis of natural

products lentiginosine, (+)- α -conhydrine, dihydromethylpalustramate and a key intermediate in the synthesis of therapeutically important piperidines LP-733,060, CP-99,994 and CP-122,721.

Experimental:

General Information: Column chromatography was performed on silica gel, Acme grade 100–200 mesh. TLC plates were visualized either with UV in an iodine chamber or with phosphomolybdic acid spray unless noted otherwise. All reagents were purchased from commercial sources and used without additional purification. THF was freshly distilled over Na-benzophenone ketyl. Melting points were recorded using melting point apparatus in capillary tubes and are uncorrected. Unless stated otherwise, ¹H (400 MHz) and ¹³C (100 MHz) spectra were recorded on 400 MHz machine in CDCl₃ as solvent with TMS as reference. High-resolution mass spectra (HRMS) were recorded on a Q-TOF micromass spectrometer using electron spray ionization mode.

Preparation of 4: To a stirred solution of ((4S,5S)-5-((benzyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol [4-O-Benzyl-23-O-isopropylidene-L-threotol]²¹ (1.0 g, 3.96 mmol) dissolved in EtOAc (15 mL) was added IBX (3.35 g, 11.9 mmol) and the reaction mixture was refluxed for 3 h. After completion of the reaction (TLC), it was filtered through a short pad of celite, and the solvent was evaporated off to obtain the crude aldehyde as a colorless oil. The resulting oil was dissolved in dry THF (10 mL), (S)-tert-butanesulfinamide (0.574 g, 4.75 mmol), and anhydrous Ti(OEt)₄ (1.4 mL, 6.6 mmol), were added successively under argon atmosphere and the resulting reaction mixture was allowed to reflux for 3 h. After completion of the reaction (TLC), it was quenched by addition of saturated solution of brine (5 mL) and was stirred at rt for 15 min. The resulting solid cake was filtered through a short pad of celite and was washed with EtOAc (2×20 mL). The solvent was evaporated off, to obtain crude residue which was purified by silica gel column chromatography using EtOAc:hexane (2:8) as eluent to obtain the imine **4** (1.05 g, 75%) as a colourless oil. $\left[\alpha\right]_{D}^{24}$ +130.6 (c 1.0, CHCl₃); IR (neat): 3251, 2985, 1625, 1370, 1080 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 8.08 (d, J = 4.8 Hz, 1H), 7.37-7.27 (m, 5H), 4.66 - 4.52 (m, 3H), 4.25-4.16 (m, 1H), 3.72 - 3.58 (m, 2H), 1.48 (s, 3H), 1.43 (s, 3H), 1.12 (s, 9H), ¹³C NMR (100 MHz, CDCl₃).δ: 167.3, 137.6, 128.4 (2C), 127.8 (3C), 111.3, 79.1, 78.2, 73.6, 69.5, 57.0, 26.9, 26.5, 22.3 (3C) HRMS ESI m/z calcd for C₁₈H₂₇NO₄SNa, 376.1558; found 376.1557.

Preparation of **4a**: Following a similar procedure described above, [4-O-Benzyl-23-O-isopropylidene-D-threotol] furnished the imine **4a** (0.73 g, 66%) as colourless oil $[\alpha]_D^{24}$ + 172.6 (*c* 0.95, CHCl₃); IR (neat): 3432, 2985, 1633, 1372 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): **δ** 8.10 (d, *J* = 4.4 Hz, 1H), 7.40–7.25 (m, 5 H), 4.65–4.55 (dd, *J* = 6.8 Hz, 5.6 Hz, 3H), 4.30 – 4.22 (m, 1H), 3.70 (ddd, *J* = 14.4 Hz, 10.4 Hz, 4.0 Hz, 2H), 1.50 (s, 3H), 1.44 (s, 3H), 1.19 (s, 9H), ¹³C NMR (100 MHz, CDCl₃).δ: 166.7, 137.7, 128.3 (2C), 127.7 (2C), 127.6, 111.2, 78.8, 78.0, 73.5, 69.4, 57.2, 26.8, 26.5, 22.4 (3C), HRMS ESI *m/z* calcd for C₁₈H₂₇NO₄SNa, 376.1558; found 376.1556.

General Procedure for the Addition of Grignard reagents to Sulfinimine 4: The following procedure for the preparation of **9a** by the addition of MeMgI to sulfinimine **4** is representative: To

a stirred solution of the imine **4** (0.08 g, 0.24 mmol) in THF (5 mL) at -78 °C, was added dropwise methylmagnesium iodide (0.5 M in Et₂O, 0.63 mL, 0.33 mmol) under argon atmosphere for 2 min. The reaction mixture was stirred for 45 min at the same temperature. Progress of reaction was monitored by TLC, and after completion of the reaction, it was quenched cautiously by addition of sat. aqueous NH₄Cl (5 mL) solution and allowed to warm to room temperature and extracted with EtOAc (2×10 mL). The combined organic layer was washed with brine (5 mL), dried over Na₂SO₄ and concentrated. The crude residue thus obtained was purified by silica gel column chromatography using (1:1) EtOAc:hexane as eluent to yield the compound **9a** (0.084 g, 92%) (dr 99:1). as a colourless oil. [α]_D²⁴ + 20.6 (*c* 1.4, CHCl₃); IR (neat): 3274, 3232, 2927, 1063 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.37 – 7.29 (m, 5 H), 4.58 (s, 2H), 4.12 (dd, *J* = 12 Hz, 6 Hz 1H), 3.97 (s, 1H), 3.92 (t, *J* = 6.4 Hz, 1H) 3.64 – 3.61 (m, 2H), 3.52 (dd, *J* =10, Hz, 5.6 Hz, 1H), 1.41 (s, 3H), 1.38 (s, 3H), 1.20 (s, 3H), 1.18 (s, 9H), ¹³C NMR (100 MHz, CDCl₃). δ 137.5, 128.4 (2C), 127.8 (3C), 109.3, 82.0, 76.6, 73.6, 71.3, 55.4, 51.0, 27.1, 26.9, 22.6 (3C), 16.8; HRMS ESI *m/z* calcd for C₁₉H₃₁NO₄SNa, 392.1872; found 392.1872.

Preparation of **9b**: Following the general procedure, addition of *n*-butyImagnesium bromide (0.25 M in THF, 1.7 mL, 0.43 mmol) to the imine **4** (0.102 g, 0.29 mmol) afforded the compound **9b** (0.098 g, 82%) (dr >99:1) as a colourless oil. $[\alpha]_D^{24}$ + 32.7 (*c* 0.85, CHCl₃); IR (neat): 3415, 2924, 1649, 1219, 1119, cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.38 – 7.26 (m, 5 H), 4.58 (s, 2H), 4.17 (q, *J* = 6.0 Hz, 1H), 4.07 (t, *J* = 6.4 Hz, 1H) 3.86 (d, *J* = 5.6 Hz, 1H), 3.67 (dd, *J* = 9.6 Hz, 5.6 Hz, 1H), 3.53 – 3.46 (m, 1H), 3.41 (t, *J* = 5.6 Hz, 1H) 1.69 – 1.51 (m, 2H), 1.41 (s, 3H), 1.38 (s, 3H) 1.35 – 1.25 (m, 4H), 1.18 (s, 9H), 0.9 (t, *J* = 6.4 Hz, 3H), ¹³C NMR (100 MHz, CDCl₃). δ 137.5, 128.3 (2C), 127.72, 127.70 .127.5, 109.2, 81.0, 76.6, 73.5, 71.2, 56.8, 55.7, 30.8, 27.2, 26.9, 26.8, 22.6 (3C), 22.4, 13.9 HRMS ESI *m/z* calcd for C₂₂H₃₇NO₄SNa, 434.2341; found 434.2340.

Preparation of 9c: Following the general procedure addition of benzylmagnesium bromide (0.65 M in THF, 0.46 mL, 0.33 mmol) to the imine **4** (0.09 g, 0.25 mmol) afforded the compound **9c** (0.104g, 92%) (dr 99:1) as colourless oil. $[\alpha]_D^{24}$ + 8.4 (*c* 1.0, CHCl₃); IR (neat): 3244, 2925, 1375, 1067 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.35 – 7.09 (m, 10H), 4.55 (s, 2H), 4.28 (q, *J* = 6.4 Hz, 2H), 4.05 (t, *J* = 6.4, Hz, 1H), 3.85 – 3.65 (m, 3H), 3.51 (dd, *J* = 9.2 Hz, 7.2 Hz, 1H), 2.98 (dd, *J* = 14.0, 4.0 Hz, 1H), 2.85 (dd, *J* = 14.0 Hz, 7.6 Hz, 1H) 1.46 (s, 3H) 1.4 (s, 3H), 1.0 (s, 9H), ¹³C NMR (100 MHz, CDCl₃).δ: 137.7, 137.5, 129.8 (2C), 128.3 (2C), 128.1, 127.8 (2C), 127.7 (2C), 126 2, 109.5, 81.1, 76.7, 73.5, 71.1, 58.9, 55.8, 37.6, 27.0, 26.9, 22.4 (3C) HRMS ESI *m/z* calcd for C₂₅H₃₅NO₄SNa, 468.2185; found 468.2185.



Preparation of **9***d*: Following the general procedure addition of 2-methyl-propylmagnesium bromide (0.2 M in THF, 1.0 mL, 0.20 mmol) to the imine **4** (0.049 g, 0.13 mmol) afforded a compound **9d** as a colourless oil in 52% yield (0.030 g,) (dr 99:1) $[\alpha]_D^{24}$ + 20.64 (*c* 1.4., CHCl₃); IR (neat): 3246, 2928, 1371, 1071 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.34 – 7.27 (m, 5 H), 4.58 (s, 2H), 4.16 – 4.09 (m, 2H), 3.74 (d, *J* = 6.8, Hz, 1H), 3.67 (dd, *J* = 9.6 Hz, 4.8 Hz, 1H), 3.58 – 3.42 (m, 2H), 1.80 – 1.70 (m, 1H), 1.42 (s, 3H) 1.38 (s, 3H), 1.34 – 1.27 (m, 2H), 1.19 (s, 9H), 0.93 (d, *J* = 6.4 Hz, 3H); 0.83 (d, *J* = 6.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃). δ : 137.7, 128.4 (2C), 127.8 (2C), 127.7, 109.3, 81.9, 76.3, 73.6, 71.3, 56.0, 55.2, 40.3, 27.0, 26 9, 24.2, 23.4, 22.7 (3C), 21.5; HRMS ESI *m/z* calcd for C₂₂H₃₇NO₄SNa, 434.2341; found 434.2341.



Preparation of 9e: Following the general procedure addition of isopropylmagnesium chloride (0.3 M in THF, 2.0 mL, 0.61 mmol) to the imine **4** (0.144 g, 0.4 mmol) afforded the compound **9e** (0.110 g, 68%) (dr >99:1) as a colourless solid. $[\alpha]_{D}^{24}$ + 55.2 (*c* 1.55, CHCl₃); mp = 53 °C, IR (KBr): 3261, 2960, 1367, 1055, cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.32 – 7.30 (m, 5 H), 4.57 (s, 2H), 4.42 (q, *J* = 4.8 Hz, 1H), 3.96 – 3.89 (m, 2H); 3.80 (dd, *J* = 9.2, Hz, 4.4 Hz, 1H), 3.46 – 3.42 (m, 1H), 3.25 (t, *J* =6.8 Hz, 1H), 2.10 – 2.03 (m, 1H), 1.41 (s, 3H), 1.37 (s, 3H) 1.13 (s, 9H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃). δ 137.4, 128.4 (2C), 127.9 (2C), 127.87, 109.5, 79.7, 77.2, 73.6, 71.3, 63.3, 56.1, 30.1, 27.1, 26.9, 22.9 (3C), 20.2, 15.5; HRMS ESI *m/z* calcd for C₂₁H₃₅NO₄SNa, 420.2185; found 420.2185. The product **9e'** from the reduction of the imine was also formed in 14% yield. $[\alpha]_{D}^{24}$ +12.67 (*c* 0.6, CHCl₃); IR (neat): 3420, 2924, 1612, 1371 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.40 – 7.24 (m, 5 H), 4.58 (s, 2H), 4.03 (s, 2H), 3.74 – 3.62 (m, 2H), 3.54 (dd, *J* = 10.8, Hz, 2.4 Hz, 1H), 3.49 (s, 1H), 3.19 (t, *J* =11.2 Hz, 1H), 1.40 (s, 3H), 1.39 (s, 3H) 1.2 (s, 9H), ¹³C NMR (100 MHz, CDCl₃). δ 137.6, 128.5 (2C), 127.8 (2C), 127.7, 109.4, 78.7, 73.6, 70.4, 56.1, 46.4, 29.7, 27.1, 26.9, 22.7 (3C); HRMS ESI *m/z* calcd for C₁₈H₂₉NO₄SNa, 378.1718; found 378.1718.

Preparation of **9***f*: Following the general procedure, addition of phenylmagnesium bromide (0.5 M in THF, 1.2 mL, 0.6 mmol) to the imine **4** (0.144 g, 0.4 mmol) afforded the compound **9***f* in 87% yield (0.150 g,) (dr >99:1) as a colourless oil. $[\alpha]_D^{24}$ + 52.0 (*c* 1, CHCl₃); IR (neat): 3231, 2980, 1372, 1073 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.37 – 7.22 (m, 10H), 4.69 (d, *J* = 5.2 Hz, 1H), 4.44 – 4.36 (m, 3H), 4.20 – 4.16 (m, 1H), 4.14 – 4.08 (m, 1H), 3.18 (dd, *J* = 9.6 Hz, 5.6 Hz, 1H), 3.0 (dd, *J* = 9.6 Hz, 4.4 Hz, 1H) 1.39 (s, 3H), 1.36 (s, 3H) 1.22 (s, 9H); ¹³C NMR (100 MHz, CDCl₃). δ 137.5, 137.3, 128.4 (2C), 128.3 (2C), 128.2 (2C), 127.7 (2C), 127.2 (2C), 109.6, 81.1, 76.4 73.5, 70.8, 58.2, 55.7, 27.0, 26.9, 22.6 (3C); HRMS ESI *m/z* calcd for C₂₄H₃₃NO₄SNa, 454.2028; found 454.2028.



Preparation of **9***g*: Following the general procedure addition of 4-methoxyphenylmagnesium bromide (0.47 M in THF, 0.91 mL, 0.42 mmol) to the imine **4** (0.1 g, 0.28 mmol), afforded the compound **9**g in 93% yield (0.120 g) (*dr* >99:1) as a colourless oil. $[\alpha]_D^{24}$ + 67.0 (*c* 0.8, CHCl₃); IR (neat): 3234, 2925, 1512, 1072 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.36 – 7.18 (m, 7H), 6.83 (s, 1H), 6.81 (s, 1H), 4.64 (d, *J* = 4.8 Hz, 1H), 4.50 – 4.40 (m, 2H), 4.33, (s, 1H), 4.17 (q, *J* = 5.6 Hz, 1H) 4.07 (t, *J* = 6.8 Hz, 1H), 3.78 (s 3H), 3.22 (dd, *J* = 10 Hz, 5.6 Hz, 1H), 3.06 (dd, *J* =10 Hz, 4.8 Hz, 1H), 1.38 (s, 3H), 1.35 (s, 3H) 1.20 (s, 9H), ¹³C NMR (100 MHz, CDCl₃). δ 159.2, 137.4, 129.3 (2C), 129.0, 128.3 (2C), 127.6 (3C), 113.7 (2C), 109.4, 81.1, 76.3, 73.4, 70.8, 57.6, 55.5, 55.0, 27.0, 26.8, 22.5 (3C), HRMS ESI *m/z* calcd for C₂₅H₃₅NO₅SNa, 484.2134; found 484.2136.

Preparation of **9***h*: Following the general procedure addition of pent-4-enyl-1-magnesium bromide (0.3 M in THF, 1.41 mL, 0.42 mmol) to the imine **4** (0.1 g, 0.28 mmol) afforded the compound **9***h* (0.100 g, 83%) with (dr 99:1). as a colourless oil. $[\alpha]_D^{24}$ + 35.5 (*c* 1.5, CHCl₃); IR (neat): 3231, 2931, 1370, 1074 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.40 – 7.20 (m, 5 H), 5.05–4.90 (m, 1H), 4.58 (s, 2H), 4.58 (s, 2H), 4.16 (q, *J* = 6.0 Hz, 1H), 4.10 – 4.02 (m, 1H), 3.86 (d, *J* = 5.2 Hz, 1H), 3.68 (dd, *J* = 9.6 Hz, 5.2 Hz, 1H), 3.50 (dd, *J* = 9.6 Hz, 6.8 Hz, 1H), 3.49 – 3.34 (m, 1H), 2.04 (m, 2H), 1.70–1.5 (m, 3H), 1.49–1.40 (m, 1H) 1.41 (s, 3H), 1.37 (s, 3H),1.18 (s, 9H), ¹³C NMR (100 MHz, CDCl₃). δ : 138.2, 137.4, 128.3 (2C), 127.74 (2C), 127.71, 114.7, 109.3, 81.1, 76.6, 73.5, 71.2, 56.8, 55.7, 33.7, 30.6, 26.9, 26.8, 24.3, 22.6 (3C); HRMS ESI *m/z* calcd for C₂₃H₃₇NO₄S+H, 424.2522; found 424.2523.

Preparation of **9***i*: Following the general procedure addition of 4-benzyloxybutylmagnesium bromide (0.2 M in THF, 18 mL, 3.6 mmol) to the imine **4** (0.85 g, 2.4 mmol) in THF (10 mL) at -78 °C, afforded the compound **9***i* as a colourless oil in 72% yield (0.9 g,) (dr >99:1). $[\alpha]_D^{24}$ + 20.3 (*c* 1.1, CHCl₃); IR (neat): 3264, 3030, 2932, 1454, cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.37 - 7.29 (m, 8H), 7.28 - 7.22 (m, 2H), 4.56 (s, 2H), 4.48 (s, 2H), 4.15 (dd, *J* = 12 Hz, 6 Hz, 1H), 4.10 - 4.02 (m,1H), 3.87 (d, *J* = 5.6 Hz, 1H), 3.69 (dd, *J* = 9.6 Hz, 4.8 Hz, 1H), 3.53 - 3.38 (m, 4H), 1.70 - 1.54 (m, 6H), 1.40(s, 3H), 1.36 (s, 3H), 1.17 (s, 9H), ¹³C NMR (100 MHz, CDCl₃). δ 138.5, 137.5, 129.8 (2C), 128.3 (2C), 128.2, 127.75 (2C), 127.71, 127.3, 124.4, 109.3, 81.1, 73.5, 72.7, 71.2, 70.0, 56.9, 55.7, 31.1, 29.5, 27.0, 26.8, 22.6 (3C), 22.4, 21.8 HRMS ESI *m/z* calcd for C₂₉H₄₃NO₅SNa, 540.2760; found 540.2757.



Preparation of **9***j*: Following the general procedure addition of vinyImagnesium bromide (0.28 M in THF, 1.6 mL, 0.45 mmol), to the imine **4** (0.108 g, 0.30 mmol) afforded the compound **9***j* in 74% yield (0.084 g) (dr 99:1). as colourless oil. $[\alpha]_D^{24}$ + 52.2 (*c* 1.1, CHCl₃); IR (neat): 3236, 2984, 1455, 1370, 1074 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.36 – 7.27 (m, 5H), 5.63 (ddd, 17.2 Hz, 10.4 Hz, 8.0 Hz, 1H), 5.34 (d, *J* = 16.8 Hz, 1H), 5.27 (d, *J* = 10.8 Hz, 1H), 4.60 (s, 2H), 4.18 (td, *J* = 7.6 Hz, 5.2 Hz, 1H), 4.09 – 4.05 (m, 1H), 4.02 – 3.97 (m, 2H), 3.59 (dd, *J* = 10.0, 5.2 Hz, 1H), 3.52 (dd, *J* = 10.4 Hz, 5.2 Hz, 1H) 1.41 (s, 3H), 1.38 (m, 3H), 1.21 (s, 9H); ¹³C NMR (100 MHz, CDCl₃). δ : 137.5, 134.2, 128.3 (2C), 127.7 (3C), 120.0, 109.4, 80.6, 76.3, 73.5, 71.0, 58.1, 55.5, 27.0, 26.8, 22.6 (3C); HRMS ESI *m/z* calcd for C₂₀H₃₁NO₄SNa, 404.1872; found 404.1872.



Preparation of **13a**: Following the general procedure, addition of methylmagnesium iodide (0.5 M in Et₂O, 4.3 mL, 2.15 mmol) to the imine **4a** (0.560 g, 1.58 mmol) afforded the separable mixture of diastereomers **13a** and **13b**. Data for **13a** $[\alpha]_{D}^{24}$ + 34.4 (*c*, 1.0 CHCl₃);, IR (neat): 3401, 2981, 2927, 1456, 1070 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.39 – 7.22 (m, 5H), 4.60 (s, 2H), 4.19 (dd, *J* = 17.2 Hz, 5.2 Hz, 1H), 4.02 (d, *J* = 4.8 Hz, 1H), 3.82 (t, *J* = 6.8 Hz, 1H) 3.64 – 3.58 (m, 2H), 3.51 (td, *J* = 12.4 Hz, 6.4 Hz, 1H), 1.42 (s, 3H), 1.40 (s, 3H) 1.19 (s, 9H), 1.15 (d, 4.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃). δ 137.8, 128.4 (2C), 127.7 (3C), 109.4, 81.8, 76.5, 73.5, 70.4, 55.4, 52.1, 27.2 (2C), 22.5 (3C), 18.5; HRMS ESI *m/z* calcd for C₁₉H₃₁NO₄SNa, 392.1872; found 392.1874. Data for **13b** $[\alpha]_{D}^{24}$ +60.63 (*c*, 1.0 CHCl₃); IR (neat): 3441,2986, 2863, 1370 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.38 – 7.25 (m, 5H), 4.57 (s, 2H), 4.06 (dd, *J* = 12 Hz, 5.6 Hz, 1H), 3.75(t, *J* = 6.8 Hz, 1H), 3.58 (d, *J* = 4.4 Hz, 1H), 3.44 (td, *J* = 13.6 Hz, 6.4 Hz, 2H), 3.12 (d, *J* = 8.8 Hz, 1H), 1.40 (s, 6H), 1.37 (d, *J* = 6.4 Hz, 3H) 1.15 (s, 9H), ¹³C NMR (100 MHz, CDCl₃). δ 137.7, 128.4 (2C), 127.79 (2C), 127.77, 109.6, 82.0, 78.0, 73.5, 71.1, 56.1, 55.0, 27.14, 27.10, 22.5 (3C), 19.2; HRMS ESI *m/z* calcd for C₁₉H₃₁NO₄SNa, 392.1872; found 392.1871. Me

NHCbz Omega OBn

Preparation of **10**: To a stirred solution of the compound **9a** (0.08 g, 0.21 mmol) in THF (2 mL) was added a saturated solution of methanolic HCl (1 mL) at 0 °C and stirred at the same temperature for 20 min, After completion of the reaction (TLC), it was quenched by addition of solid NaHCO₃. The reaction mixture was filtered through a short pad of celite, and the solvent was evaporated off. The residue was dissolved in CH₂Cl₂ (5 ml), Et₃N (0.16 mL, 0.57 mmol), and CbzCl (0.1 mL, 0.57 mmol) were added successively at 0 °C and the reaction mixture was stirred for 4 h at room temperature. After completion of the reaction (TLC), the reaction mixture was diluted with EtOAc (10 mL) and washed with water (5 mL) and brine (5 mL). The organic layer dried over Na₂SO₄, solvent was evaporated off, and the residue thus obtained was purified by silica gel column chromatography using EtOAc:hexane (2:8) as eluent to furnish the compound **10** (0.075 g, 87%). [α]_D²⁴–16.8 (*c* 0.9, CHCl₃); IR (neat): 3333, 3202, 1717, 1529 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.40 – 7.20 (m, 10H), 5.07 (s, 2H), 4.98 (d, *J* = 6 Hz, 1H), 4.55 (s, 2H), 4.03 (d, *J* = 4.8 Hz, 1H), 3.90 – 3.75 (m, 2 H), 3.65 – 3.48 (m, 2H), 1.39 (s, 6H), 1.20 (d, *J* = 6.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃)δ 155, 137.7, 136.5, 128.5 (3C), 128.4, 128.07, 128.05 (3C), 127.71, 127.69, 109.5, 81.0, 77.5, 73.5, 70.8, 66.6, 48.6, 27.0, 26.9, 16.5; HRMS ESI *m/z* calcd for C₂₃H₂₉NO₅Na, 422.1943; found 422.1943.

Me

HO HO HO

1

Preparation of **11***:* To a stirred solution of the compound **10** (0.09 g, 0.22 mmol) in CH₂Cl₂ (3 mL) was added TFA (0.3 mL) at 0 °C and stirred at rt for 2 h. After completion of the reaction (TLC), the solvent was evaporated off and the residue thus obtained was purified by column chromatography using EtOAc:hexane (1:1) as eluent to furnish the compound **11** (0.06 g, 75%) as colourless white solid. $[\alpha]_D^{24}$:-2.38 (*c* 1.05, CHCl₃); m.p. 84–87 °C. IR (KBr): 3311, 2870, 1659, 1156 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.33 – 7.28 (m, 10H), 5.16–5.02 (m, 3H), 4.54 (s, 2H), 3.88 –3.81 (m, 1H), 3.77 (dd, *J* = 14.4 Hz, 7.3 Hz, 1H), 3.59 (d, *J* = 5.2 Hz, 2H), 3.40 (m, 1H), 3.25–2.50 (m, 2H), 1.22 (d, *J* = 6.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃). δ 156.8, 137.7, 136.2, 128.5 (3C), 128.4, 128.17, 127.12, 127.83, 127.80 (3C), 74.35, 73.6, 71.8, 69.03, 66.98, 49.2, 16.9; HRMS ESI *m/z* calcd for C₂₀H₂₅NO₅Na, 382.1630; found 382.1631.

Preparation of 12: To a stirred solution of the compound 11 (0.060 g, 0.16 mmol) in MeOH:H₂O (2:1) (6 mL) was added NaIO₄ (0.143 g, 0.66 mmol) and was stirred at rt for 2 h. After completion of the reaction (TLC), most of the solvent was evaporated off and the residue thus obtained was dissolved in CH₂Cl₂ (10 mL) and washed with sat. aq. NaHCO₃ (2 mL) brine (2 mL) and dried over Na₂SO₄. Solvent was evaporated off and the residue thus obtained was dissolved in MeOH (2 mL), and NaBH₄ (0.019 g 0.50 mmol) was added and stirred for 1 h at 0 °C. After completion of the reaction (TLC) acetone (1mL) was added, and the reaction mixture was stirred at rt for 5 min, most of the volatile were evaporated off, and the residue thus obtained was dissolved in EtOAc (10 mL) and washed with sat. NaHCO₃ (2 mL), and brine (2 mL), successively, dried over sodium Na₂SO₄. After the solvent was evaporated off and residue obtained was purified by silica gel column chromatography using EtOAc:hexane (3:2) as eluent to afford 12 (0.03 g, 86%) as a colourless oil $[\alpha]_{D}^{24}$ -8.23 (c 0.85, CHCl₃); lit¹² $[\alpha]_{D}^{23}$ -10.7 (c 0.55, CHCl₃), IR (neat): 3309, 2931, 1684, 1532 cm^{-1} ; ¹H NMR (400 MHz, CDCl₃): δ 7.40 – 7.23 (m, 5 H), 5.09 (s, 2H), 4.98 (d, J = 5.6 Hz, 1H), 3.82 (d, J = 4.8 Hz, 1H), 3.64 (dd, J = 11.2 Hz, 3.6 Hz, 1H), 3.51 (dd, J = 10.8 Hz, 6.0 Hz, 1H), 2.55 (bs, 1H), 1.15 (d, J = 6.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃). δ 156.6, 136.3, 136.1, 128.5, 128.5, 128.13, 128.0, 66.8 (2C), 49.0, 17.2; HRMS ESI *m*/*z* calcd for C₁₁H₁₅NO₃Na, 232.0950 found 232.0948.



Preparation of **14**: To a suspension of lithium (0.1 g) in THF (20 mL) was added naphthalene (3.5 g) under argon atmosphere and the reaction mixture was stirred at rt for 2h which resulted in the dark green colour solution. To a stirred solution of the compound **9**i (0.2 g, 0.38 mmol) dissolved in THF (5 mL) was added the above Li/Napthalide solution at 0 °C, till dark green colour persisted and the reaction was stirred at rt for 3h. After completion of the reaction (TLC), MeOH (5 mL) was added dropwise and the solvent was evaporated off. The resulting residue was purified by silica gel column chromatography using MeOH:EtOAc (5:95) as eluent to obtain the crude diol which was used as such in the next step. To a solution of the crude diol (obtained above) in dry CH₂Cl₂ (5 mL), Et₃N (0.33 mL, 2.28 mmol), *p*-toluenesulfonyl chloride (0.36 g, 1.9 mmol) and DMAP (5 mg,

0.038 mmol) were added and the reaction mixture was stirred at rt for 6h. After completion of the reaction (TLC), it was poured into water (5 mL) and was extracted with CH_2Cl_2 (2×5 mL). Combined organic layer was washed with brine (5 mL), dried over Na₂SO₄. Evaporation of solvent gave the residue which was purified by column chromatography using EtOAc:hexane (7:3) as eluent to furnish **14** (0.150 g, 61% for 2 steps) as a colourless oil. $[\alpha]_D^{24}$: +31 (*c* 0.8, CHCl₃), IR (KBr): 3128, 2956, 1739, 1598 cm^{-1 1} H NMR (400 MHz, CDCl₃): δ 7.85 – 7.76 (m, 4H), 7.34 (d, *J* = 7.6 Hz, 4H), 4.46 (dd, *J* = 11.6 Hz, 3.2 Hz, 1H) 4.22 – 4.11 (m, 1H), 4.11 – 4.39 (m, 4H), 3.76 (d, *J* = 8.4 Hz, 1H), 3.32 – 3.15 (m, 1H), 2.43 (s, 6H), 1.60 – 1.45 (m, 6H), 1.37 (s, 3H), 1.35 (s, 3H), 1.22 (s, 9H); ¹³C NMR (100 MHz, CDCl₃). δ 145.1, 145.7, 133.0, 132.5, 129.2 (2C), 129.8 (2C), 127.8 (4C), 109.4, 78.3, 76.8, 70.1, 69.5, 58.9, 56.5, 32.2, 28.5, 27.0, 26.5, 22.8 (3C), 21.58, 21.56, 21.3; HRMS ESI *m/z* calcd for C₂₉H₄₃NO₉S₃Na, 668.1998; found 668.2000.

(+)-Lentiginosine (5): To a stirred solution of 14 (0.070 g, 0.11 mmol) in THF (2 mL) was added saturated methanolic HCl (2 mL) at 0 °C and stirred at rt for 10 h. After completion of the reaction (TLC), the solvent was evaporated off and the residue thus obtained was dissolved in CH₃CN (3 mL), and K₂CO₃ (0.14 g, 1.0 mmol) was added to the reaction mixture and stirred at 70 °C for 6 h. The solvent was evaporated off and residue obtained was dissolved in EtOAc (20 mL) and was filtered through a short pad of celite. The solvent was evaporated off and the residue thus obtained was dissolved in the residue thus obtained was purified by silica gel column chromatography using MeOH:CH₂Cl₂ (2:8) as eluent to yield lentiginosine **5** (9 mg, 60%) as a white solid. $[\alpha]_D^{24}$ +2.3 (c 0.3, MeOH), lit^{22a} +2.2 (c.0.28, MeOH); m.p. 99–103 °C, lit^{22b} 104 °C; IR (KBr): 3387, 2926, 1446, 1134 cm^{-1 1} H NMR (400 MHz, CD₃OD): δ 3.98 (dd, *J* = 7.2 Hz, 3.2 Hz, 1H), 3.63 (dd, *J* = 8.4 Hz, 3.2 Hz, 1H), 3.01(d, *J* = 10.8 Hz, 1H), 2.90 (d, *J* = 10.4 Hz, 1H), 2.61(t, *J* = 9.2 Hz, 1H), 2.08 (t, *J* = 10.8 Hz, 1H) 2.05 – 1.95 (m, 1H), 1.95 – 1.76 (m, 2H), 1.75–1.45 (m, 2H), 1.45 – 1.18 (m, 2H); ¹³C NMR (100 MHz, CD₃OD). δ 84.9, 77.4, 71.1, 62.6, 54.3, 29.1, 25.5, 24.7; HRMS ESI *m/z* calcd for C₈H₁₅NO₂H, 158.1181; found 158.1182.



Preparation of **15**: To a stirred solution of **9i** (0.437 g, 0.84 mmol) in THF (5 mL) was added saturated methanolic HCl (2 mL) at 0 °C and stirred for 20 min. The residue obtained after evaporation of solvent was dissolved in 1,4-dioxan (10 mL) and (Boc)₂O (0.4 mL, 1.52 mmol), NaOH (1M, 2.1 mL, 2.10 mmol), were added at 0 °C. The reaction mixture was stirred at rt for 12 h and was poured into EtOAc (10 mL), and was washed with water (5 mL) and brine (5 mL). The organic layer was dried over Na₂SO₄ and the solvent was evaporated off. The residue obtained after evaporation of solvent was purified by column chromatography using (1:10) EtOAc:hexane to furnish the compound **15** (0.365 g, 84%) as a colourless oil. $[\alpha]_D^{24} - 2.40$ (*c* 0.75, CHCl₃); IR (neat): 3401, 2923, 1655, 1018 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.36 – 7.30 (m, 8H), 7.39 – 7.20 (m, 2H), 4.57 (dd, *J* = 21.6 Hz, 12.0 Hz, 2H), 4.48 (s, 2H), 4.41 (d, *J* = 8.4 Hz, 1H), 4.11 (s, 1H), 3.80 – 3.60 (m, 1H), 3.60 (dd , *J* = 10.4 Hz, 4.0 Hz, 1H), 3.54 (dd , *J* = 10.4 Hz, 5.2 Hz, 2H), 3.45 (t, *J* = 6.4 Hz, 2H), 1.81 – 1.48 (m, 4H), 1.41–1.39 (m, 17H).; ¹³C NMR (100 MHz, CDCl₃). δ : 155.6, 138.6, 137.9, 128.3 (2C), 128.2 (2C), 127.6(2C), 127.59, 127.56 (2C), 127.4, 109.3, 80.1, 79.2, 78.1, 73.4, 72.8, 70.9, 70.0, 52.7, 31.3, 29.5, 28.3 (3C), 27.1, 26.9, 22.2.;HRMS ESI *m/z* calcd for C₃₀H₄₃NO₆Na, 536.2987; found 536.2988.



Preparation of **16**: To a stirred solution of the compound **15** (0.365 g, 0.71 mmol) dissolved in MeOH (5 mL) was added 10% Pd/C (0.07 g) and stirred under H₂ atmosphere for 30 h. After completion of the reaction (TLC), most of the solvent was evaporated off, and the residue obtained was dissolved in EtOAc (20 mL) and was passed through a short pad of celite. The residue obtained after evaporation of solvent was purified by silica gel column chromatography using (8:2) EtOAc:hexane to furnish **16** (0.2 g, 84%) as a white solid. $[\alpha]_D^{24}$: – 24.3 (*c*, 0.6 acetone); lit²³ – 6.9 (*c* 0.6 acetone). m.p. = 76–80 °C; lit²³. m.p. 75 –76 °C.; IR (KBr): 3360, 2928, 1683, 1502, 1072 cm⁻¹.;¹H NMR (400 MHz, CDCl₃): δ 4.59 (d, *J* = 8.8 Hz, 1H), 4.06 (t, *J* = 3.6 Hz, 1H), 3.83 – 3.70 (m, 3H), 3.66 – 3.60 (m, 3H), 2.43 (bs, 1H), 2.04 (bs, 1H), 1.75 – 1.30 (m, 21 H), ;¹³C NMR (100 MHz, CDCl₃). δ 155.9, 109.8, 79.7, 79.5, 79.3, 62.7, 62.4, 52.7, 32.3, 31.1, 28.3 (3C), 27.1, 27.0, 21.7. HRMS ESI *m/z* calcd for C₁₆H₃₁NO₆Na, 356.2049; found 356.2043.



Preparation of **17**: To a stirred solution of the compound **16** (0.174 g, 0.52 mmol) dissolved in CH₂Cl₂ (5 mL) was added Et₃N (0.3 mL, 2.08 mmol), *p*-toluenesulfonyl chloride (0.298 g, 1.57 mmol) and DMAP (0.032 g, 0.26 mmol). The reaction mixture was stirred at rt for 3 h and after completion of the reaction (TLC), it was washed with aq. citric acid (aq. 10%) and the aq. layer was extracted with CH₂Cl₂ (2×5 mL). Organic layer washed with water (5 mL) and brine (5 mL), and dried over anhydrous Na₂SO₄. The residue obtained after evaporation of the solvent was purified by column chromatography using (3:7) EtOAc:hexane to furnish the compound **17** (0.280 g, 83%) as a white solid. $[\alpha]_D^{24} - 33.3$ (*c* 0.6 acetone); mp = 96 –97 °C.; IR (KBr): 3377, 2949, 1608, 1166 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 7.80 – 7.77 (m, 4H), 7.36 –7.34 (m, 4H), 4.40 (d, *J* = 9.6 Hz, .1H) 4.16 – 4.13 (m, 2H), 4.04 – 4.0 (m, 3H), 3.70 – 3.63 (m, 2H), 2.45 (s, 6H), 1.77 – 1.58 (m, 4H), 1.43 (s, 9H), 1.38 – 1.21 (m, 8H), ¹³C NMR (100 MHz, CDCl₃).δ 155.6, 144.9, 144.7, 133.0, 132.7, 129.84 (2C), 129.80 (2C), 127.9 (2C), 127.8 (2C), 109.6, 79.7, 78.8, 70.2 (2C), 69.3, 52.7, 31.4, 28.5, 28.2 (3C), 27.0, 26.7, 21.5 (2C), 21.2.; HRMS ESI *m/z* calcd for C₃₀H₄₃NO₁₀S₂Na, 664.2226; found 664.2230.



Preparation of **18**: To the compound **17** (0.165 g, 0.25 mmol) dissolved in THF (5 mL) was added NaH (15 mg, 0.37 mmol) at 0 °C and the reaction mixture was stirred at rt for 1 h. After completion of the reaction (TLC), it was quenched by addition of sat. aq. NH₄Cl (2 mL). and was extracted with EtOAc (2×10 mL). Organic layer was washed with brine (5 mL), and dried over anhydrous Na₂SO₄. The residue obtained after evaporation of solvent was purified by column chromatography using (2:8) EtOAc:hexane to furnish the compound **18** (0.098 g, 81%) as a colourless oil. $[\alpha]_D^{24} - 51.2$ (*c* 1.3, CHCl₃), IR (neat): 2980, 1685, 1367, 1132 cm^{-1; 1}H NMR (400 MHz, CDCl₃): δ 7.77 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 4.50 - 3.98 (m, 5H), 3.89 (dd, *J* = 10.8 Hz, 3.6 Hz, 2H), 2.43 (s, 3H), 1.94 (d, *J* = 12.4 Hz, 1H), 1.65 - 1.45 (m, 5H), 1.42 (s, 9H), 1.35 (s, 3H), 1.32 (s, 3H); ¹³C NMR (100 MHz,

CDCl₃) δ 155.0, 144.9, 132.6, 129.8 (2C), 128.0 (2C), 109.5, 80.0, 77.2, 73.3, 68.9, 52.3, 40.8, 28.3 (3C), 27.1, 26.9, 25.4, 25.1, 21.6, 19.0; HRMS ESI *m/z* calcd for C₂₃H₃₅NO₇SNa, 492.2032; found 492.2032.

Preparation of 19: To a stirred solution of the compound 18 (0.09 g, 0.19 mmol) in acetone (5 ml) was added Nal (0.285 g, 1.92 mmol) at rt and refluxed for 24 h. After completion of the reaction (TLC), the solvent was evaporated off, and the residue obtained was dissolved in EtOAc (10 mL), and was washed with water (5 mL), brine (5 mL) and dried over anhydrous Na₂SO₄. The residue obtained after evaporation of the solvent was purified by short path silica gel column using EtOAc:hexane (1:9). The crude iodide (obtained above) was dissolved in MeOH (5 ml) and zinc dust was added (0.123 g, 1.92 mmol). It was refluxed for 6 h and after completion of the reaction most of the solvent was evaporated off and the residue was dissolved in EtOAc (10 mL). It was passed through a short pad of celite. Evaporation of the solvent followed by purification by silica gel column chromatography of the residue using EtOAc:hexane (3:7) as eluent, furnished the compound **19** (0.032 g,71%) as a colourless oil. $[\alpha]_{D}^{24}$ – 53.3 (c 0.4, CHCl₃), IR (neat): 3443, 2903, 1663, 1419 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): 5.90 (ddd, *J* = 17.2 Hz, 10 Hz, 7.2 Hz, 1H), 5.27 (d, *J* = 17.2 Hz, 1H), 5.14 (d, J = 10.4 Hz, 1H), 4.45 - 4.30 (m, 1H), 4.15 - 4.06 (m, 1H), 3.97 (d, J = 12 Hz, 1H), 2.85 – 2.65 (m, 1H), 2.01 (d, J = 12.8 Hz, 2H), 1.70 – 1.50 (m, 5H), 1.44 (s, 9H); ¹³C NMR (100 MHz, CDCl₃):δ 155.4, 138.7, 116.6, 79.6, 72.1, 54.9, 40.3, 28.4 (3C), 25.0, 24.3, 19.3. HRMS ESI m/z calcd for C₁₃H₂₃NO₃Na, 264.1576; found 264.1572.



Preparation of **20**: To a stirred solution of the compound **19** (25 mg 0.1 mmol) in dry EtOAc (2 mL) was added 10% Pd/C (5 mg) and the reaction mixture was stirred under H₂ atmosphere for 4 h. After completion of the reaction (TLC), it was passed through a short pad of celite pad. The solvent was evaporated off to furnish the compound **20** in quantitative yield (0.025g). $[\alpha]_D^{24} - 28.7$ (*c* 0.4, CHCl₃); IR (Neat): 3427, 2923, 1664, 1420 cm⁻¹; ¹H NMR (400 MHz, CDCl₃):4.10–3.90 (m, 2H) 3.81 (bs, 1H), 2.72 (t, *J* = 12.4 Hz, 1H), 2.01 (d, *J* = 12.4 Hz, 1H), 1.70–1.50 (m, 6H), 1.45 (s, 9H), 1.24 (s, 2H), 0.99 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): 155.2, 79.5, 71.0, 55.4, 40.3, 28.5 (3C), 26.5, 25.2, 24.5, 19.5, 10.1.; HRMS ESI *m/z* calcd for C₁₃H₂₅NO₃Na, 266.1732; found 266.1729.

(+)-
$$\alpha$$
-conhydrine 6

(+)- α -conhydrine (**6**): To a stirred solution of the compound **20** (0.025 g, 0.1 mmol), in CH₂Cl₂ (2 mL) was added TFA (0.5 mL) at 0 °C, and the reaction mixture was stirred for 6 h at room temperature. After completion of the reaction (TLC), sat. aq. NaHCO₃, was added to the reaction mixture and was extracted with EtOAc (10 mL×3). Organic layer was dried over anhydrous Na₂SO₄. The residue obtained after evaporation of the solvent was purified by silica gel column chromatography using EtOAc:MeOH (8:2) to furnish α -(+)-conhydrine **6** as a white solid (11 mg, 73%). [α]_D²⁴ + 7.7 (*c* 0.35, EtOH); lit.¹⁷ [α]_D²⁴ + 8.0 (*c* 1.85, EtOH). mp; 109–113 °C; IR (neat): 3538, 3289, 2924, 1452 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): 3.50–3.39 (m, 1H) 3.20–3.09 (m, 1H), 2.71(dt, *J*

= 11.6 Hz, 2.8 Hz, 1H), 2.61 (td, J = 10.8 Hz, 3.2 Hz, 1H), 2.40 (bs, 2H), 1.89–1.80 (m, 1H), 1.67–1.25 (m, 7H), 0.98 (t, J = 7.6 Hz, 3H). ; ¹³C NMR (100 MHz, CDCl₃): 75.6, 60.2, 46.9, 26.2, 25.4, 24.9, 24.3, 10.5. ;HRMS ESI m/z calcd for C₈H₁₇NO+H, 144.1388; found 144.1383.



Preparation of **24**: To a stirred solution of the compound **9f** (0.312 g, 0.72 mmol) in THF (2 mL) was added saturated methanolic HCl (1 mL) at 0 °C and stirred for 20 min. After completion of the reaction, most of the solvent was evaporated off and the residue thus obtained was dissolved in 1,4-dioxane (10 mL). NaOH (1N, 1.8 mL, 1.8 mmol), (Boc)₂O (0.3 mL, 1.30 mmol) were added at 0 °C and the reaction mixture was stirred at rt for 18 h. After completion of the reaction (TLC), it was diluted with EtOAc (20 mL), washed with water (5 mL), brine (5 mL), and dried over anhydrous Na₂SO₄. The residue obtained after evaporation of solvent was purified by column chromatography using EtOAc:hexane (1:9) as eluent to furnish the compound **24** (0.192 g, 63%) as a white solid. $[\alpha]_D^{24}$ -12.42 (*c* 0.95, CHCl₃); m.p. 102–106 °C; IR (KBr): 3370, 2930, 1691, 1165 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.35 – 7.20 (m, 10 H), 5.52 (d, *J* = 7.6 Hz, 1H), 4.78 (bs, 1H), 4.54 (s, 2 H), 4.12 (t, *J* = 7.2 Hz, 1H), 3.86 (dt, *J* = 10 Hz, 5.2 Hz, 1H), 3.57 – 3.45 (m, 2H) 1.38 (s, 9 H), 1.35 (s, 3H) 1.21 (s, 3H); ¹³C NMR (100 MHz, CDCl₃). δ 154.9, 137.6, 128.2 (3C), 127.95, 127.79 (2C), 127.52 (2C), 127.48 (2C), 127.38, 109.5, 80.4, 79.6, 73.5 (2C), 70.2, 55.8, 28.1(3C), 26.8, 26.5; HRMS ESI *m/z* calcd for C₂₅H₃₃NO₅Na, 450.2256 found 450.2256.



Preparation of **25***:* To a stirred solution of **24** (0.250 g, 0.58 mmol) in MeOH (5 mL) was added 10% Pd/C (50 mg) and the reaction was stirred under H₂ atmosphere for 36 h. After completion of the reaction (TLC), most of the solvent was evaporated off and residue thus obtained was dissolved in EtOAc (20 mL) and passed through a short pad of celite to furnish the compound **25** (0.190 g, 97%) as a colourless oil. $[\alpha]_D^{24}$ + 11.19 (*c* 1.05, CHCl₃); IR (neat): 3317, 2942, 1659, 1020 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.34 – 7.24 (m, 5 H), 5.34 (s, 1H), 4.81 (s, 1H), 4.22(t, *J* = 7.2 Hz, 1H), 3.83 (dd, *J* = 8.0 Hz, 4.0 Hz, 1H), 3.75 (d, *J* = 10.4 Hz, 1H), 3.59 (dd, *J* = 11.6 Hz, 3.2 Hz, 1H), 2.32 (bs, 1H), 1.40 – 1.38 (s, 12 H), 1.23 (s, 3H); ¹³C NMR (100 MHz, CDCl₃).δ 155.2, 128.3 (2C), 127.9 (2C), 127.8 (2C), 109.3, 79.9, 79.0, 78.5, 62.2, 55.9, 28.7 (3C), 27.1, 26.8; HRMS ESI *m/z* calcd for C₁₈H₂₇NO₅Na, 360.1787 found 360.1785.



Preparation of **26**: To a stirred solution of **25** (0.163 g, 0.48 mmol) dissolved in CH₂Cl₂ (5 mL) was added Et₃N (0.1 mL, 0.72 mmol), DMAP (0.006 g, 0.048 mmol), and *p*-toluenesulfonyl chloride (0.139 g, 0.72 mmol), at rt and the resulting reaction mixture was stirred for 16 h. After completion of the reaction (TLC), it was quenched by addition of water (3 mL). The organic layer was separated and the water layer was extracted with CH₂Cl₂ (2×5 mL). The combined organic layer was washed with brine (5 mL), and dried over anhydrous Na₂SO₄. The residue obtained after evaporation of solvent was purified by silica gel column chromatography using EtOAc:hexane (2:8) to give compound **26** (0.186 g, 78%), as a white solid. $[\alpha]_D^{24} - 5.52$ (*c* 0.85, CHCl₃); m. p. = 125–130

°C.; IR (KBr): 3320, 2942, 1661, 1020 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.81 (s, 1H), 7.79 (s, 1H), 7.38 – 7.23 (m, 7H), 5.61 (d, *J* = 8.4 Hz, 1H), 4.74 (s, 1H), 4.16 – 4.13 (m, 1H), 4.07(d, *J* = 10 Hz, 1H), 4.02 – 3.98 (m, 1H), 3.92 (s, 1H), 2.46 (s, 3H), 1.40 (s, 9H), 1.30 (s, 3H), 1.23 (s, 3H); ¹³C NMR (100 MHz, CDCl₃). δ 155.1, 145.1, 140.2, 138.3, 129.9 (3C), 128.4, 128.0 (2C), 127.9, 127.7 (2C), 110.0, 80.0, 78.9, 77.2, 69.0, 67.1, 28.3 (3C), 26.8, 26.8, 21.6; HRMS ESI *m/z* calcd for C₂₅H₃₃NO₇Na, 514.1875 found 514.1875.

Preparation of 27 : To a stirred solution of the compound 26 (0.138 g, 0.28 mmol) in DMF (5 mL) was added NaH (0.021 g, 0.84 mmol) at 0 °C and stirred at the same temp for 10 min. Allyl bromide (0.15 mL, 1.68 mmol) was added to the reaction mixture and was stirred for 3 h at rt. After completion of the reaction (TLC), it was quenched by addition of sat. NH₄Cl (1mL) and was extracted with EtOAc (2×10 mL). The combined organic layer was washed with brine (3 mL), dried over Na₂SO₄. The residue obtained after evaporation of solvent was purified by silica gel column chromatography using EtOAc:hexane (1:9) as eluent to give compound 27 (0.09 g, 60%) as a colourless oil. $[\alpha]_{D}^{24}$ +11.25 (c 0.8 , CHCl₃); IR (neat): 3469, 2981, 1688, 1386, 1177 cm⁻¹; NMR exhibited rotamers. ¹H NMR (400 MHz, CDCl₃): δ 7.83 (s, 1H), 7.81 (s, 1H), 7.38 – 7.24 (m, 7H), 5.48 - 5.18 (m, 1H), 4.90 - 4.79 (m, 3H), 4.58 (t, J = 8.0 Hz, 1H), 4.31 (bs, 1H), 4.23 (d, J = 10.4 Hz, 1H), 4.01 (d, J = 6.8 Hz, 1H), 3.64 (bs, 1H), 3.44 (bs, 1H), 2.45 (s, 3H), 1.42 (s, 9H), 1.33 (s, 3H), 1.30 (s, 3H); ¹H NMR (400 MHz, DMSO at 80 °C): δ 7.79 (s, 1H), 7.77 (s, 1H), 7.49 (s, 1H), 7.47 (s, 1H), 7.40 – 7.20 (m, 5H), 5.40 (m, 1H), 5.10 (d, J = 8.8 Hz, 1H), 4.92 - 4.80 (m, 1H), 4.61 (dd, J = 8.8 Hz, 1H), 4.25 – 4.12 (m, 2H), 4.04 (dd, J = 10.8 Hz, 6.4 Hz, 1H), 3.63 (dd, J = 15.6 Hz, 6.4 Hz, 1H), 3.52 (dd, J = 15.6 Hz, 6.0 Hz, 1H), 2.41 (s, 3H), 1.3 (s, 9H), 1.27 (s, 3H), 1.24 (s, 3H); ¹³C NMR (100 MHz, CDCl₃).δ 144.9, 134, 132.6, 132.7, 129.8 (3C), 128.2 (3C), 128.0 (3C), 127.7, 69.3, 28.2 (3C), 26.8, 27.1, 27.0, 21.6. ¹³C NMR (100 MHz, DMSO at 80 °C).δ 154.7, 145.0 (2C), 137.8, 134.4, 132.3, 129.99, 129.94, 128.5, 127.9, 127.4 (3C), 116.4, 109,6, 79.8, 76.6, 75.3, 70.2, 61.1, 47.7, 27.72 (3C) and 27.68 (3C, rotamer), 26.9 and 26.8 (rotamer), 26.7 and 26.69 (rotamer), 20.9 and 20.8 (rotamer); HRMS ESI *m*/z calcd for C₂₈H₃₇NO₇Na, 554.2188 found 554.2187.



Preparation of **28**: To a stirred solution of **27** (0.118 g, 0.24 mmol) in acetone (10 mL) was added NaI (0.663 g, 4.44 mmol) and was refluxed for 16 h. After completion of the reaction (TLC), the solvent was evaporated off, and the residue thus obtained was dissolved in EtOAc (10 mL) and was washed with water (5 mL), brine (5 mL) and dried over anhydrous Na₂SO₄. Residue obtained after evaporation of solvent was purified by silica gel column chromatography using EtOAc:Hexane (1:9) as eluent to give the corresponding iodide (0.1 g, 93%) as a colourless oil. $[\alpha]_D^{24}$ + 23.52 (*c* 0.85, CHCl₃) IR (neat): 3399, 3300, 2924, 1688 cm⁻¹; NMR exhibited peaks for a mixture of rotamers) ¹H NMR (400 MHz, CDCl₃) δ 7.43 – 7.24 (m, 5H), 5.75 – 5.20 (m, 2H), 5.10 – 4.60 (m, 2H), 4.54 – 5.30 (m, 1H), 4.04 (m, 1H), 3.90 – 3.60 (m, 2H), 3.46 (dd, *J* = 10.8 Hz, 4.0 Hz, 1H), 3.22 (dd, *J* = 10.8 Hz, 4.8 Hz, 1H), 1.48 (s, 9H), 1.46 (s, 3H), 1.35 (s, 3H); ¹³C NMR (100 MHz, CDCl₃). δ 134.3 (2C), 128.3 (2C), 127.8, 109.7, 79.4, 78.0, 28.3 (3C), 27.6, 27.4 ⁻¹H NMR (400 MHz, DMSO at 80 °C): δ 7.42 – 7.21 (m, 5H), 5.44 (ddd, *J* = 16.4 Hz, 11.2 Hz, 6.4 Hz, 1H), 4.04 (dd, *J* = 10 Hz, 6.4 Hz, 1H), 5.0 – 4.8

(m, 2H), 4.55 (dd, J = 8.8 Hz, 6.4 Hz, 1H), 4.04 (dd, J = 10, 6.4 Hz, 1H), 3.84 (dd, J = 16.8 Hz, 6.0 Hz, 1H), 3.68 (dd, J = 15.6 Hz, 6.0 Hz, 1H), 3.47 (dd, J = 10.8 Hz, 3.6 Hz, 1H), 3.30 (dd, J = 10.8 Hz, 6.4 Hz, 1H), 1.42 (s, 9H); ¹³C NMR (100 MHz, DMSO at 80 °C). δ 154.3, 137.6, 134.3, 128.3 (2C), 127.6 (2C), 127.0, 115.9, 108.5, 79.5, 78.7, 78.1, 60.7, 27.6 (3C), 27.0, 26.8, 7.7; HRMS calcd for C₂₁H₃₀INO₄Na, 510.1117 found 510.1114.

To a stirred solution of the iodide (0.097 g, 0.19 mmol) (obtained above) dissolved in MeOH (5 mL) was added Zn dust (0.260 g, 3.98 mmol) and refluxed for 6 h. After completion of the reaction, the solvent was evaporated off, and the residue thus obtained was dissolved in EtOAc (10 mL) and was passed through a short pad of celite. The residue obtained after evaporation of the solvent was purified by silica gel column chromatography using EtOAc:hexane (2:8) as eluent to furnish the diene **28** (0.052 g, 91%), as a colourless oil. $[\alpha]_D^{24}$ + 31.3 (c 1.15, CHCl₃); IR (neat): 3432, 2927, 2924, 1650, 1170 cm⁻¹; NMR exhibited rotamers. ¹H NMR (400 MHz, CDCl₃): δ 7.45 (s, 1H), 7.42 (s, 1H), 7.40 – 7.24 (m, 3H), 5.99 (ddd, J = 16.4 Hz, 10.4 Hz, 5.6 Hz, 1H), 5.69 – 5.51 (m, 1H), 5.34 (d, J = 17.2 Hz, 1H), 5.23 (d, J = 10.4 Hz, 1H), 4.99 (s, 1H), 4.96 (d, J = 4.4 Hz, 1H), 4.84 (s, 1H), 3.79 (dd, J = 15.6 Hz, 6.0 Hz, 1H), 3.6 (bs,1H), 1.46 (s, 9H); ¹³C NMR (100 MHz, CDCl₃).δ 138.2, 137.5, 134.9, 129.0, 128.4 (2C), 127.7 (2C), 117.1, 116.2, 80.3, 29.6, 28.4 (3C); HRMS calcd for C₁₈H₂₅NO₃Na, 326.1732 found 322.1732 , ¹H NMR (400 MHz, DMSO at 80 °C): 7.45 (s, 1H), 7.43 (s, 1H), 7.35 -7.25 (m, 2H), 7.26 – 7.20 (m, 1H), 5.94 (ddd, J = 17.2 Hz, 10.4 Hz, 6.4 Hz, 1H), 5.56 – 3.68 (m, 1H), 5.29 (d, J = 16.8 Hz, 1H), 5.11 (d, J = 10.4 Hz, 1H), 4.95–4.77 (m, 4H), 4.72 (dd, J = 4.8 Hz, 6.4 Hz, 1H), 3.70 (dd, J = 16.0 Hz, 6.4 Hz, 1H), 3.63 (dd, J = 15.6 Hz, 5.6 Hz, 1H), 1.4 (s. 9H),; ¹³C NMR (100 MHz, DMSO at 80 °C).δ 154.4, 139.68, 139.65, 139.0, 135.1, 128.6, 127.3 (2C), 126.4, 115.1, 114.9, 78.6, 70.8, 63.1, 47.4, 27.7 (3C).



Preparation of 8: To a stirred solution of 28 (0.050 g, 0.16 mmol) in CH₂Cl₂ (0.02 M, 8 mL) was added Grubb's 2nd generation catalyst (7 mg, 0.0082 mmol) and the reaction mixture was stirred at rt for 4 h. After completion of the reaction (TLC), the solvent was evaporated off and the residue thus obtained was purified by silica gel column chromatography using EtOAc:hexane (3:7) as eluent to furnish the tetrahydropyridine (0.035g, 80%) as a colourless oil. $[\alpha]_D^{24}$: – 10.0 (*c* 1.1, CHCl₃); IR (neat): 3432, 2927, 2924, 1650, 1170 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.34 – 7.20 (m, 5H), 6.18 – 6.12 (m, 1H), 5.94 (d, J = 9.6 Hz, 1H), 5.23 (s, 1H), 4.51 (s, 1H), 4.36 (d, J = 19.2 Hz, 1H), 3.45 (d, J = 19.2 Hz, 1H), 2.25 (bs, 1H), 1.51 (s, 9H), ¹³C NMR (100 MHz, CDCl₃). δ 155.8, 138.3, 128.8, 128.4, 127.4 (3C), 126.8, 125.3, 80.5, 77.2, 65.7, 40.7, 28.4 (3C). HRMS ESI m/z calcd for C₁₆H₂₁NO₃Na, 298.1419 found 298.1414. To a stirred solution of the tetrahydropyridine (obtained above) (0.026 g, 0.094 mmol) dissolved in dry EtOAc (2 mL), was added 10% Pd/C (5 mg) and was stirred under H₂ atmosphere for 4 h. After completion of the reaction (TLC), it was passed through a short pad of celite, and the solvent was evaporated off to furnish the compound 8 (0.021 g, 80%) as a colourless oil. $[\alpha]_{D}^{24}$ + 53.1 (c 1.0, CHCl₃). lit²⁴ $[\alpha]_{D}^{20}$ + 49.4 (c 1.33, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.40 - 7.32 (m, 2H), 7.28 - 7.15, (m, 3H), 5.37 (s, 1H), 4.52 (s, 1H), 4.09 (dd, J = 13.6 Hz, 4.0 Hz, 1H), 2.87 (td, J = 13.2 Hz, 3.2 Hz, 1H), 2.25 (d, J = 5.2 Hz, 1H), 2.00 - 1.80 (m, 1H), 1.77 -1.74 (m, 2H), 1.65–1.56 (m, 1H), 1.38 (s, 9H); ¹³C NMR (100 MHz, CDCl₃).δ 156.7, 138.1, 128.7 (2C), 126.8 (2C), 126.3, 80.1, 67.5, 60.2, 39.9, 28.3 (3C), 25.9, 18.8; HRMS ESI m/z calcd for C₁₆H₂₃NO₃Na, 300.1576 found 300.1578.



Preparation of 29: To a stirred solution of the compound 9h (0.09 g, 0.21 mmol), in THF (10 mL) was added solution of Li/naphthalide (2 mL) dropwise till the green colour persisted and the reaction mixture was stirred at rt for 1 h. After completion of the reaction (TLC), it was quenched by addition of MeOH (4 mL). Most of the solvent was evaporated off and residue thus obtained was purified by short path silica gel column chromatography using EtOAc:hexane (7:3) to give the alcohol. The primary alcohol (obtained above) was dissolved in CH₂Cl₂ (5 mL) and *p*-toluenesulfonyl chloride (0.06 g, 0.1 mmol), Et₃N (0.1 mL, 0.63 mmol), DMAP (3 mg, 0.021 mmol), were added at 0 °C. The reaction mixture was stirred at rt for 3 h. After completion of the reaction, it quenched by addition of water (5 mL) after extraction with EtOAc (2×10 mL) and dried over anhydrous Na₂SO₄. Removal of solvent followed by silica gel column chromatography of the residue obtained using EtOAc:hexane (1:1) yielded the compound **29** (0.06 g, 56% for 2 steps) as colourless oil. $[\alpha]_D^{24}$ +27.8 (c 1.5, CHCl₃); IR (neat): 3314, 2926,1604, 1364; ¹H NMR (400 MHz, CDCl₃) δ 7.79 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 5.79 (dddd, J = 24.0 Hz, 17.2 Hz, 6.8 Hz, 3.2 Hz, 1H), 5.02 (dd, J = 17.2 Hz, 2.0 Hz, 1H), 4.96 (d, J= 10.0, Hz, 1H), 4.22 (dd, J = 10.4 Hz, 3.6 Hz, 1H), 4.19 – 4.15 (m, 1H), 4.06 (dd, J = 10.4 Hz, 5.2 Hz, 1H), 3.81 (t, J = 6.8 Hz, 1H), 3.34 (ddd, J = 14.8 Hz, 7.2 Hz, 3.6 Hz, 1H), 3.24 (d, J = 7.2 Hz, 1H), 2.45 (s, 3H), 2.15 – 1.95 (m, 2H), 1.82 – 1.72 (m, 1H), 1.69 – 1.54 (m, 2H), 1.53 – 1.42 (m, 1H), 1.36 (s, 3H), 1.3 (s, 3H), 1.21 (s, 9H).; ¹³C NMR (100 MHz, CDCl₃) δ 145.0, 138.1, 132.6, 129.8 (2 C), 127.9 (2C), 114.9, 110.0, 79.6, 76.6, 69.8, 58.6, 56.2, 33.3, 31.8, 27.2, 26.9, 24.1, 22.6 (3C), 21.5.; HRMS ESI *m*/*z* calcd for C₂₃H₃₇NO₆S₂H 488.2141 found 488.2139.



Preparation of compound 30: To a stirred solution of the compound 29 (0.095 g) in acetone (10 mL), was added NaI (0.48 g, 3.21 mmol), and the resulting solution was refluxed for 48 h. After completion of the reaction (TLC), most of the solvent was evaporated off, and the residue obtained was dissolved in water (5 mL), extracted with EtOAc (2×10 mL), washed with sat. sodium thiosulfate solution (5 mL), water (5 mL) and brine (5 mL) and dried over anhydrous Na₂SO₄. The residue obtained after evaporation of solvent was dissolved in THF (2 mL) and saturated ethereal HCl solution (2 mL), was added dropwise at 0 °C and stirred for 30 min at the same temperature. The solvent was evaporated off, and the residue thus obtained was dissolved in THF:H₂O (5 mL, 4:1) and NaHCO₃ (0.084 g, 1.05 mmol), (Boc)₂O (0.07 mL, 0.31 mmol), were added successively and stirred at rt for 8 h. After completion of the reaction (TLC), it was extracted with EtOAc (2×10 mL), and dried over anhydrous Na₂SO₄. Residue obtained after evaporation of solvent was purified by silica gel column chromatography using EtOAc:hexane (1:9) to obtain the compound 30 in 71% yield (0.065 g) for two steps. $[\alpha]_{D}^{24}$ –26.6 (*c* 0.75, CHCl₃), IR (neat): 3351, 2924,1681, 1528, 1020.; (¹H NMR (400 MHz, CDCl₃); δ 5.72 (dddd, J = 23.6 Hz, 16.8 Hz, 6.4 Hz, 3.2 Hz, 1H), 4.86 (d, J = 17.2Hz, 1H), 4.90 (d, J = 10.4 Hz, 1H), 4.32 (d, J = 9.6 Hz, 1H), 3.95 - 3.82 (m, 1H), 3.76 - 3.63 (m, 1H), 3.53 (t, J = 7.2 Hz, 1H), 3.30 (dd, J = 10.8 Hz, 4.8 Hz, 1H), 3.16 (dd, J = 10.8 Hz, 5.2 Hz, 1H), 2.15 -1.92 (m, 2H), 1.80 – 1.63 (m, 1H), 1.52 – 1.20 (m, 18H).; 13 C NMR (100 MHz, CDCl₃) δ 155.6, 138.3, 114.9, 109.6, 83.7, 79.7, 78.1, 52.7, 33.4, 31.0, 28.4 (3C), 27.6, 27.4, 24.7, 7.9; HRMS ESI m/z calcd for C₁₇H₃₀INO₄+Na 462.1117 found 462.1120.

Preparation of **31**: A solution of compound **30** (0.06 g, 0.13 mmol) in CH₂Cl₂:MeOH (4:1, 5 mL), was cooled to -78 °C, and a stream of O₃/O₂ was passed for 5 min. The reaction mixture was warmed to 0 °C and Me₂S (0.05 mL, 0.65 mmol) was added and stirred for further 1.5 h. The residue obtained after evaporation of solvent was dissolved in toluene (5 mL), and the ylide (ethyl 2-(triphenyl- λ^5 -phosphanylidene)acetate) (0.07 g, 0.2 mmol) was added and refluxed for 6 h. Most of the solvent was evaporated off and the residue thus obtained was purified by silica gel column chromatography using EtOAc:hexane (2:8) to obtain **31** (0.061 g, 88%), as a white solid. [*α*]₀²⁴ - 33.1 (*c* 1.4, CHCl₃); m.p. 75–78 °C. IR (neat): 3434, 2923,1715, 1605 cm^{-1;} (¹H NMR (400 MHz, CDCl₃) δ 6.94 (ddd, *J* = 15.6 Hz, 14.0 Hz, 7.2 Hz, 1H), 5.84 (d, *J* = 15.6 Hz, 1H), 4.45 (d, *J* = 9.6 Hz, 1H), 4.34 (q, *J* = 7.2 Hz, 2H), 3.95 (dd, *J* = 11.2 Hz, 5.2 Hz, 1H), 3.84 – 3.72 (m, 1H), 3.65 – 3.57 (m, 1H), 3.37 (dd, *J* = 10.8 Hz, 4.8 Hz, 1H), 3.23 (dd, *J* = 10.8 Hz, 5.2 Hz, 1H), 2.40 – 2.10 (m, 2H), 1.90 – 1.75 (m, 1H), 1.55 – 1.45 (m, 15 H), 1.40 (s, 3H). 1.29 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 166.6, 155.6, 148.4, 121.8, 109.6, 83.6, 79.8, 78.1, 60.1, 52.6, 31.7, 31.1, 28.3 (3C), 27.5, 27.4, 23.9, 14.2, 7.8; HRMS ESI *m/z* calcd for C₂₀H₃₄INO₆+Na 534.1329 found 534.1327.



Preparation of 32: To a stirred solution of the compound **31** (0.060 g, 0.11 mmol) in THF (2 mL) was added NaH (60%, 10 mg, 0.23 mmol) at 0°C and was stirred for 10 min and was slowly warmed to rt and stirred at rt for 45 min. After completion of the reaction, it was quenched by addition of NH₄Cl (2 mL) and was extracted with EtOAc (2×10 mL). The organic layer was washed with water (5 ml), brine (5 mL) and dried over anhydrous Na₂SO₄. Evaporation of the solvent gave the crude residue, which was purified by silica gel chromatography using EtOAc:hexane (5:95) to furnish the compound **32** (0.047 g, 78%), as a colourless oil. $[\alpha]_D^{24}$: -68.0 (*c* 1.4, CHCl₃).; IR (Neat): 2979, 1733,1686, 1169 cm⁻¹; (¹H NMR (400 MHz, CDCl₃) δ 4.63 (bs, 1H), 4.40 – 4.00 (m, 3H), 3.85 – 3.15 (m, 2H), 3.55 – 3.45 (m, 1H), 3.24 (dd, *J* = 10.0 Hz, 5.6 Hz, 1H), 2.65 (bs, 2H), 1.93 (d, *J* = 12.8 Hz, 1H), 1.87 – 1.77 (m, 1H), 1.65 (bs, 2H), 1.55 – 1.40 (m, 17H), 1.27 (t, *J* = 7.2 Hz, 3H).; ¹³C NMR (100 MHz, CDCl₃) δ 171.7, 155.1, 109.3, 83.8, 80.4, 78.4, 60.4, 48.9, 47.6, 38.7, 28.4 (3C), 28.0, 27.4, 27.3, 23.9, 15.3, 14.2, 7.0; HRMS ESI *m/z* calcd for C₂₀H₃₄INO₆+Na 534.1329 found 534.1330.



Preparation of **33**: The iodide **32** (0.075 g, 0.14 mmol) was dissolved in EtOH (5 mL), and Zn dust (0.095 g, 1.46 mmol) was added at rt and further stirred under reflux for 6 h. After completion of the reaction (TLC), the solvent was evaporated off and the residue was suspended in EtOAc (20 mL) it was filtered through a short pad of celite and the solvent was evaporated off. The residue thus obtained was purified by silica gel column chromatography using EtOAc:hexane (1:3), to yield **33** (0.037 g, 77%) as a colourless oil. $[\alpha]_D^{24}$ –29.8 (*c* 0.8, CHCl₃); IR (neat): 3436, 2923,1376, 1609, 1370 cm⁻¹ (¹H NMR (400 MHz, CDCl₃) δ 5.93 (ddd, *J* = 16.8 Hz, 10.4 Hz, 6.0 Hz, 1H), 5.30 (d, *J* = 17.2 Hz, 1H), 5.18 (d, *J* = 10.4 Hz, 1H), 4.73 – 4.58 (m, 1H), 4.34 (dd, *J* = 10.0 Hz, 5.2 Hz, 1H), 4.25 – 4.00 (m, 3H), 2.83 (bs, 1H), 2.65 (dd, *J* = 14.0 Hz, 6.0 Hz, 1H), 2.54 (dd, *J* = 13.6 Hz, 8.8 Hz, 1H), 2.05 – 1.94 (m, 1H), 1.80 – 1.65 (m, 2H), 1.55 – 1.35 (m, 12H), 1.27 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (100 MHz,

CDCl₃) δ 172.4, 155.4, 138.9, 116.2, 79.9, 74.1, 60.7, 57.8, 47.1, 40.1, 28.3 (3 C), 28.1, 22.6, 15.6, 14.1; HRMS ESI *m/z* calcd for C₁₇H₂₉NO₅+Na 350.1943 found 350.1940.



Preparation of **34**: To a stirred solution of the ester **33** (0.035 g, 0.1 mmol) dissolved in MeOH (5 mL) was added K₂CO₃ (0.063 g, 4.5 mmol) at rt and stirred for 8 h. After completion of the reaction, the solvent was evaporated off and the residue was suspended in EtOAc (10 mL). It was passed through a short pad of celite. The solvent was evaporated off and the residue thus obtained was purified by silica gel column chromatography using EtOAc:hexane (1:3), to yield the compound **34** (0.025 g, 80%) as a colourless oil. $[\alpha]_D^{24} - 28.5$ (*c* 1.25, CHCl₃); IR (neat): 3435, 2931,1738, 1688, 1170 cm⁻¹. (¹H NMR (400 MHz, CDCl₃) δ 5.91 (ddd, *J* = 17.2 Hz, 10.8 Hz, 6.0 Hz, 1H), 5.28 (d, *J* = 17.2 Hz, 1H), 5.16 (d, *J* = 12.0 Hz, 1H), 4.62 (dd, *J* = 12.0 Hz, 6.0 Hz, 1H), 4.37 – 4.30 (m, 1 H), 4.10 – 4.00 (m, 1H), 3.65 (s, 3H), 2.90 (bs, 1H), 2.66 (dd, *J* = 14.0 Hz, 6.8 Hz, 1H), 2.53 (dd, *J* = 14.0 Hz, 8.8 Hz, 1H), 2.05 – 1.90 (m, 1H), 1.78 – 1.65 (m, 2H), 1.50 – 1.35 (m, 12 H).; ¹³C NMR (100 MHz, CDCl₃) δ 172.8, 155.4, 138.9, 116.1, 80.0, 74.2, 54.8, 51.8, 47.1, 39.9, 28.34 (3C), 28.3, 22.6, 15.6.; HRMS ESI *m/z* calcd for C₁₆H₂₇NO₅+Na 336.1787 found 336.1789.



Preparation of **35**: Pd/C (5 mg) was added to a solution of **34** (0.035 g, 0.1 mmol) dissolved in EtOAc (2 mL) and stirred under H₂ atmosphere for 3 h. After completion of the reaction, it was filtered through a short pad of celite. The residue obtained after evaporation of solvent was purified by silica gel column chromatography using EtOAc:hexane (3:7) to obtain **35** (0.035 g) in quantitative yield as a colourless oil. $[\alpha]_D^{24} - 22.8$ (*c* 1.25, CHCl₃); IR (neat): 3432, 2928,1739, 1688, 1172 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 4.67 (ddd, *J* = 14.0 Hz, 7.2 Hz, 2.0 Hz, 1H), 3.98 – 3.90 (m, 1H), 3.72 (dd, *J* = 9.2 Hz, 4.8 Hz, 1H), 3.69 (s, 3H), 2.92 (bs, 1H), 2.68 (dd, *J* = 13.6 Hz, 8.0 Hz, 1H), 2.50 (dd, *J* = 13.6 Hz, 7.6 Hz, 1H), 2.02 – 1.90 (m, 1H), 1.87 – 1.68 (m, 2H), 1.60 – 1.35 (m, 14H), 1.00 (t, *J* = 7.6 Hz, 3H).; ¹³C NMR (100 MHz, CDCl₃) δ 173.1, 155.6, 79.8, 74.4, 55.3, 51.9, 47.1, 40.2, 28.6, 28.3 (3C), 26.8, 22.3, 16.0, 10.9.; HRMS ESI *m/z* calcd for C₁₆H₂₉NO₅+Na 338.1943 found 338.1945.

Preparation of **36**: To a stirred solution of **35** (0.110 g, 0.33 mmol) in CH₂Cl₂ was added Dess-Martin Periodinane (0.222 g, 0.52 mmol) and NaHCO₃ (0.086 g, 1.0 mmol) sequentially at rt. The resulting reaction mixture was stirred at rt for 1.5 h and after completion of the reaction (TLC), it was quenched by addition of aqueous sodium thiosulfate solution (10 mL). The aqueous layer was extracted with Et₂O (2×10 mL) and the combined organic layer was dried over anhydrous Na₂SO₄. The residue obtained after evaporation of solvent was used as such in next step. To a suspension of NaBH₄ (0.02 g, 0.52 mmol) in THF (2 mL) was added a solution of the crude ketone (obtained above) dissolved in THF (2 mL). The reaction mixture was cooled to 0 °C and MeOH (4 mL) was added dropwise and stirred at rt for 1 h. After completion of the reaction, most of the solvent was evaporated off, and the residue was dissolved in water and was extracted with Et₂O (2×10 mL). The combined organic layer was dried over anhydrous Na₂SO₄. Residue obtained after evaporation of solvent was purified by silica gel column chromatography using EtOAc:hexane (1:3) to yield the compound **36** (0.085 g, 77%) as a colourless oil. $[\alpha]_{D}^{24}$ -30.1 (*c* 0.6, CHCl₃); IR (neat): 3463, 2932,1737, 1684, 1174 cm⁻¹ (¹H NMR (400 MHz, CDCl₃) δ 4.75 - 4.55 (m, 1H), 4.15 - 4.00 (m, 1H), 3.66 (s, 3H), 3.58 - 3.48 (m, 1H), 2.80 - 2.60 (m, 1H), 2.55 - 2.48 (m, 1H), 1.75 - 1.48 (m, 6H), 1.46 - 1.38 (m, 10H), 1.37 - 1.25 (m, 1H), 1.00 (t, *J* = 7.2 Hz, 3H).; ¹³C NMR (100 MHz, CDCl₃) δ 172.7, 157.6, 80.2, 74.5, 54.2, 51.2, 47.4, 38.7, 28.3 (4C), 25.6 (2C), 14.7. 9.7.; HRMS ESI *m/z* calcd for C₁₆H₂₉NO₅+Na 338.1943 found 338.1946.

(–)*Methyldihydropalustramate* (**7**):Compound **36** (0.015 g, 0.047 mmol) was dissolved in CH₂Cl₂ (2 mL) and TFA (0.5 mL), was added dropwise to it at 0 °C, and stirred for 6 h at rt. After completion of the reaction (TLC), the solvent was evaporated off. The residue obtained was dissolved in water and was neutralized with aq. sat. NaHCO₃ (2 mL) and was extracted with EtOAc (3×10 mL). The combined organic layer was dried over anhydrous Na₂SO₄. The residue obtained after evaporation of solvent was purified by silica gel column chromatography using MeOH:EtOAc (1:4), to yield the compound **7** (8 mg, 72%) as a colourless oil. $[\alpha]_D^{24}$ –25.4 (*c* 0.4, MeOH); lit.^{19b} $[\alpha]_D^{24}$ =-26.4 (*c* 0.014, MeOH), lit.^{19d} $[\alpha]_D^{24}$ +26 0 (*c* 1.35 in MeOH) for the enantiomer; IR (neat) 3401,3370,2921, 1729, 1018 cm⁻¹; (¹H NMR (400 MHz, CDCl₃) δ 3.66 (s, 3H), 3.22 (ddd, *J* = 8.4 Hz, 6.8 Hz, 3.6 Hz, 1 H), 3.01 – 2.87 (m, 1H), 2.46 (ddd, *J* = 11.2 Hz, 6.8 Hz, 2.4 Hz, 1H), 2.42 – 2.35 (m, 2H), 1.82 (td, *J* = 12.4 Hz, 1H), 1.67 – 1.50 (m, 3H), 1.47 – 1.30 (m, 2H), 1.17–1.02 (m, 2H), 0.97 (t, *J* = 7.2 Hz, 3H);¹³C NMR (100 MHz, CDCl₃) δ 172.7, 75.6, 60.6, 53.1, 51.5, 41.3, 32.1, 28.4, 26.6, 24.2, 10.0; HRMS ESI *m/z* calcd for C₁₁H₂₁NO₃+H 216.1600 found 216.1604.

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Highlights of the present work:

- Systematic study of the addition of Grignard reagents to Sulfinimines derived from tartaric acid
- Outcome of the diastereoselectivity of the formed product is dependent on the inherent chirality of the tartrate rather on the sulfinimine.
- The formed products are excellent building blocks for the synthesis of natural products: lentiginosing, methyldihydropalustramate, conhydrine and for the formal synthesis of Formal synthesis of LP-733,060, CP-99,994 and CP-122,721

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