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The formal synthesis of 3-*epi* jaspine B using stereoselective intramolecular oxa-Michael addition

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ABSTRACT

The formal synthesis of 3-e*pi* jaspine B was achieved by using a stereoselective intramolecular oxa-Michael addition. The diacetate derivative of 3-e*pi* jaspine B was also synthesized.

1. Introduction

Sponges of the genus *Jaspis* (family Coppatiidae) have received considerable attention from scientists in recent times because of the interesting pharmacological properties of their chemical components. Among these, modified peptides,[1] nucleosides,[2] sterols and other triterpene derivatives,[3] cytotoxic macrolides,[4] and brominated tyrosine derivatives[5] are particularly worth mentioning. Recent studies on the marine sponge *pachastrissa* sp. by Higa and co-workers[6] led to the isolation of a cyclic anhydrophyto sphingosine, which they named as pachastrissamine **1**. Later Debitus et al.[7] independently reported the isolation of pachastrissamine **1** from the marine sponge *Jaspis* sp., which they named as jaspine B **1** (Fig. 1).

Jaspine B **1** showed remarkable cytotoxicity (IC_{50} 0.24 μM) against A549 human lung carcinoma cell line using the ATP lite assay and also proved to be the most potent compound yet to be isolated from the *Jaspis* genus on this cell line, cf. pectenotoxin II (IC_{50} >10 μM),[8] bengamide Y (IC_{50} = 12.8 μM),[9] bengamide Z (IC_{50} = 10.5 μM).[10] Canels et al. reported that 3-*epi* jaspine B **2** also showed comparable activity with that of jaspine B **1**.[11] Because of the presence of a tri-substituted THF ring in jaspine B **1**, a common structural motif present in a large number of bioactive compounds, jaspine B **1** attracted the attention of many synthetic chemists and biologists. Many synthetic approaches have been developed for jaspine B **1** and its isomers.[12] Our group published the first total synthesis of jaspine B **1** and its C2 epimer **4**.[13a] Recently we also published the synthesis of the C2 and C3 epimer **5** and an enantiomer of jaspine B **3** and their biological activity in comparison to jaspine B **1**.[13b] In continuation of our work in the synthesis of bioactive heterocycles using the intramolecular hetero-Michael addition,[14] herein we report the stereoselective synthesis of 3-*epi* jaspine B **2** using an intramolecular oxa-Michael addition reaction for building the tri-substituted furan moiety.

As per the retro-synthesis (Scheme 1), compound **6** is the key precursor for the synthesis of 3-*epi* jaspine B **2**. The tri substituted furan moiety **6** can be prepared from **7** by an intramolecular oxa-Michael addition reaction. The compound **7** was envisaged to derive from **8**, which in turn can be prepared from D-(−)-isoascorbic acid. One of the key aspects of the synthesis is to study the stereochemical outcome of the intramolecular oxa-Michael addition in the construction of the THF skeleton and it was anticipated that the major compound will have the acetate group in a *trans* position to the benzyloxy group.

2. Results and discussion

As shown in Scheme 2, enantiomerically pure (*R*)-ethyl 2-(benzyloxy)-2-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)acetate **8**, the starting precursor of our strategy was prepared from D-(−)-isoascorbic acid using a standard literature procedure.[15] The ester functionality of compound **8** was reduced to an alcohol using $LiAlH_4$ in THF to yield compound **9**. The compound **9** was oxidized under Swern conditions, followed by Wittig reaction with $PPh_3CHCOOEt$ at 0 °C, and gave the compound **10** as separable *trans* and *cis* isomers mixture in a 9:1 ratio with 92% yield. Deprotection of the acetonide group in compound **10** was achieved using 80% aqueous acetic acid to give diol **7**, which on further treatment with NaH in THF at −40 °C, underwent *5-exo-trig* intramolecular oxa-Michael addition[16] regio-selectively to give the inseparable cyclic compounds **6a** and **6b** in a ratio of 10:1 (approximately) and the ratio was confirmed by ^1H NMR integrations.

The alcohol functionality of compound **6** was converted into the corresponding mesylate, which upon treatment with NaN_3 in DMF at 120 °C afforded inseparable azido compounds **11a** and **11b** in a ratio of 10:1 (approximately) and the ratio was confirmed by ^1H NMR integrations (Scheme 2). The ester and azide functionality

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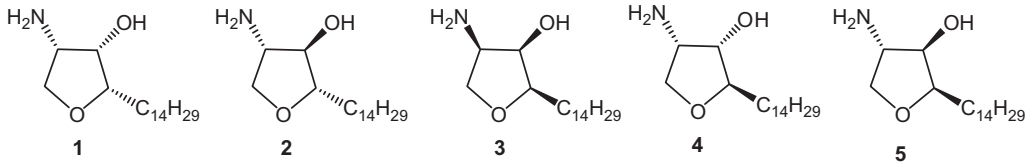
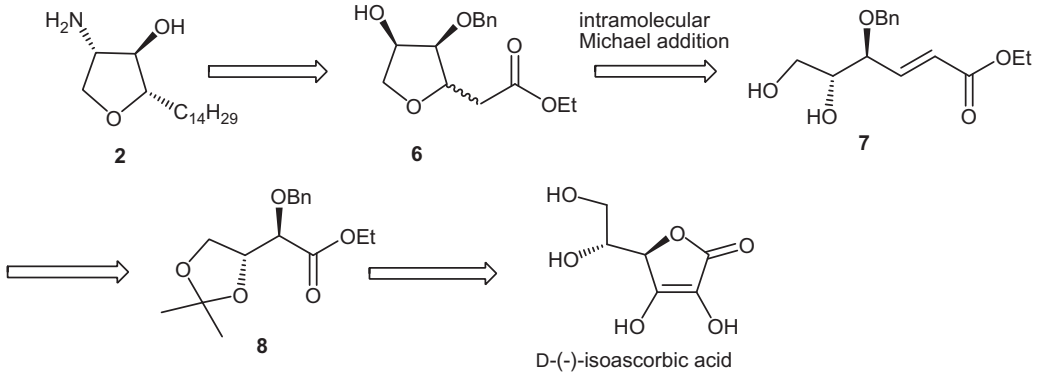
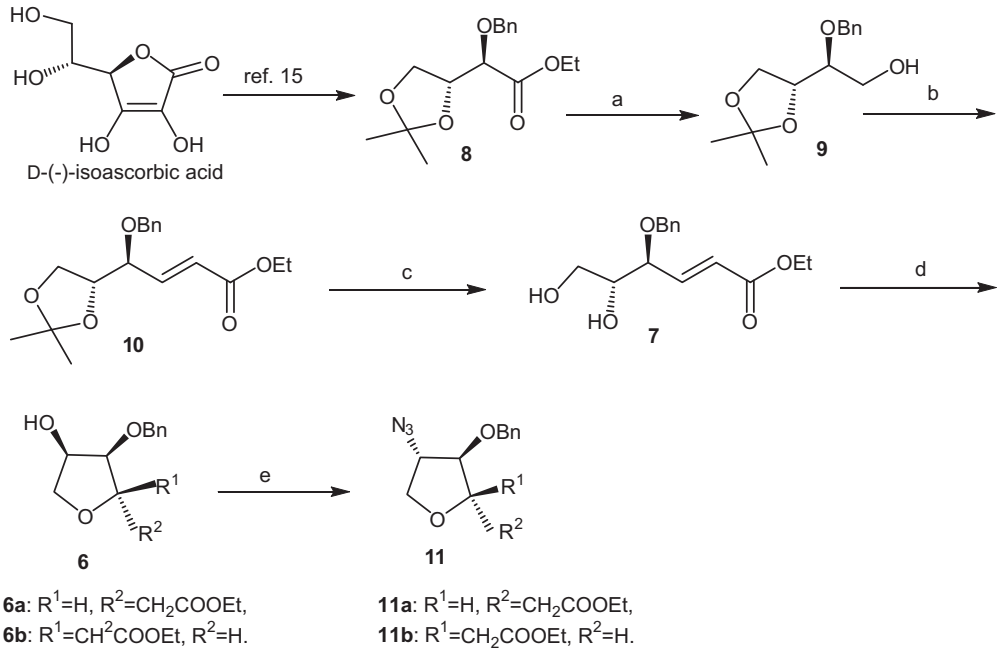


Figure 1. Jaspine B and its stereoisomers.



Scheme 1. Retrosynthetic analysis.



Scheme 2. Reagents and conditions: (a) $LiAlH_4$, THF, 0 °C to rt, 2 h, 95%; (b) (i) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, 2 h then DIPEA; (ii) $PPh_3CHCOOEt$, CH_2Cl_2, 0 °C, 1 h, (92% for two steps); (c) (i) 80% aq AcOH, 0 °C to rt, 8 h, 98%; (d) NaH, THF, 0.5 h, −40 °C, 96% (**6a**/**6b** = 10:1 ratio); (e) (i) MsCl, Et_3N, CH_2Cl_2, DMAP (cat), 0 °C to rt, 1 h; (ii) NaN_3, DMF, 120 °C, 8 h, (90% for two steps) (**11a**/**11b** = 10:1 ratio).

in compound **11** was reduced with $LiAlH_4$ in THF and the crude amine was treated with $(Boc)_2O$ to give chromatographically separable compounds **12** and **13** in the ratio of 10:1. The confirmation of structures **12** and **13** was achieved by detailed 1D and 2D NMR studies including DQFCOSY and NOESY experiments. For **12** NOE cross peaks were observed between N*Ha*-Hf, N*Ha*-OH and Ph*CH*$_2$-He, whereas for **13** the NOE cross peaks were observed between N*Ha*-Hd, N*Ha*-He, N*Ha*-Hc[1] and Hc-Hf (Fig. 2).

The compound **12** was oxidized under TEMPO/BAIB conditions and the resultant aldehyde was treated with excess Wittig reagent $C_{12}H_{25}PPh_3^+Br^-$ in THF at −78 °C to give *cis* olefin **14** exclusively with 23% overall yield (for two steps). When compound **13** was subjected under similar conditions of oxidation and Wittig reaction it also gave the same compound **14** with 21% overall yield (Scheme 3). The confirmation of the structure **14** was achieved by detailed 1D and 2D NMR studies including DQFCOSY and NOESY experiments and NOE cross peaks were observed between Ha-He, Hd-Hf and He-Ph*CH*$_2$ (Fig. 2).

The formation of **14** from **13** can be explained on the basis of a mechanism proposed by Davies et al. (Scheme 4).[17] Oxidation of **13**

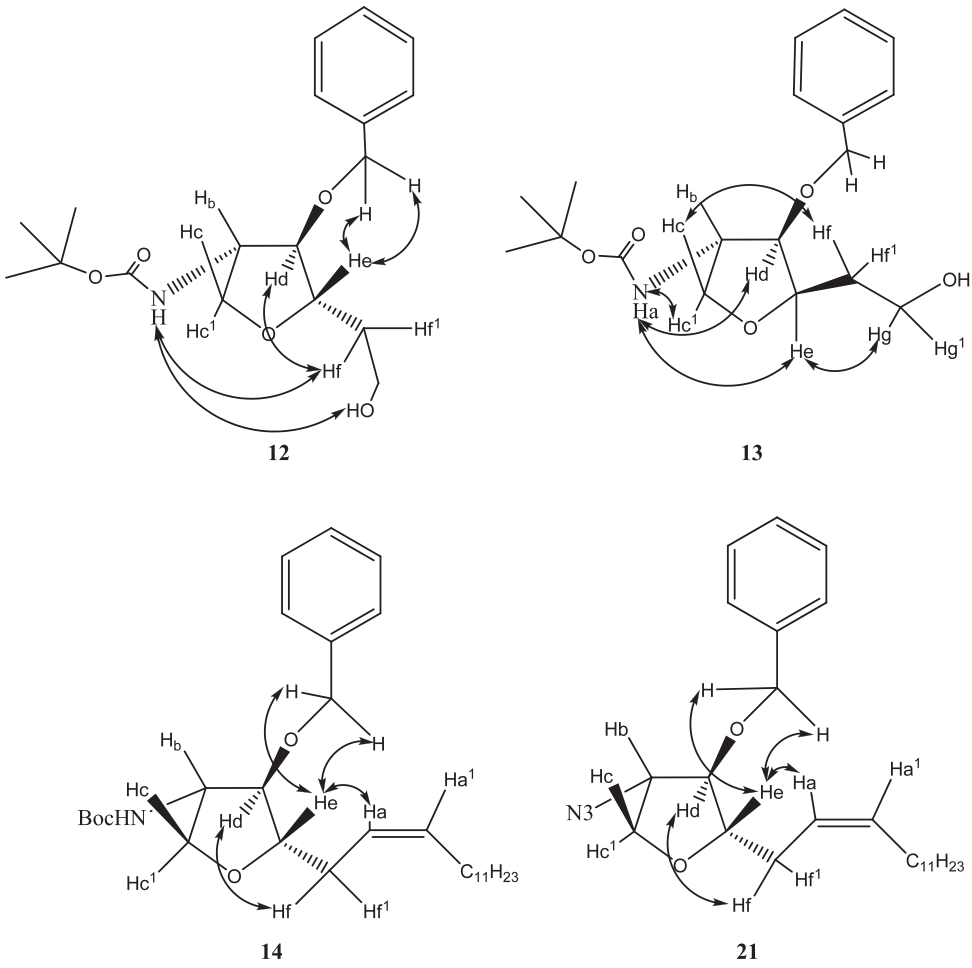
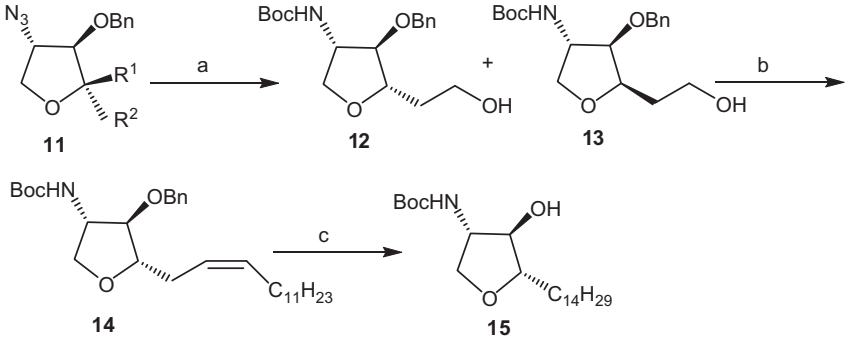


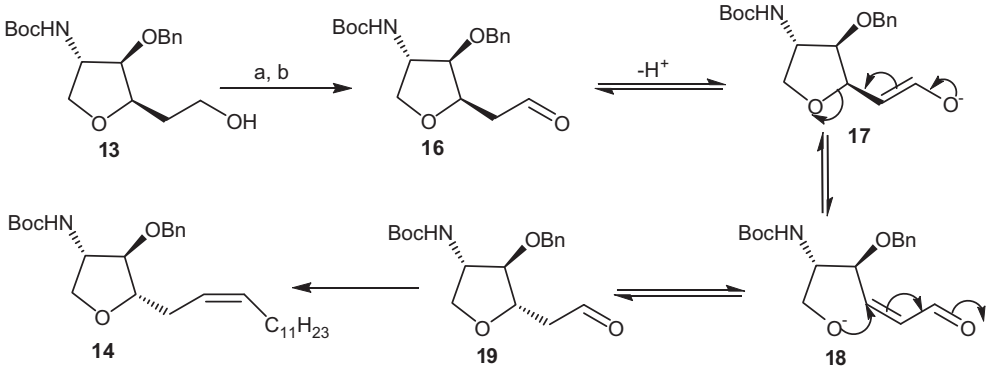
Figure 2. NOE correlations.



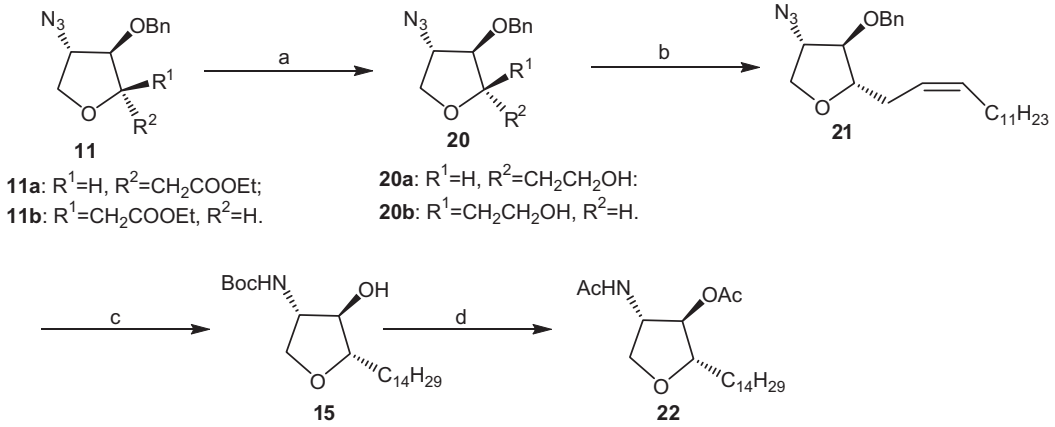
Scheme 3. Reagents and conditions: (a) (i) $LiAlH_4$, THF, 0 °C to rt, 1 h, aq NaOH then $(Boc)_2O$, 0 °C, 2 h, 90% (**12** compound 82% and **13** compound 8%); (b) (i) BAIB, TEMPO (cat), CH_2Cl_2, rt, 2 h; (ii) $C_{12}H_{25}PPh_3^+Br^-$, KO^{t}Bu, THF, −40 °C, 1 h (23% from **12** and 21% from **13** for two steps); (c) 10% Pd/C, H_2, EtOH, 12 h, 95%.

gave aldehyde **16** which might have undergone 1,2-elimination via enolate **17** to give **18**. Re-cyclisation of the resultant compound **18** would generate the thermo-dynamically favored 2,3-*anti* aldehyde **19** (C2 epimer of **16**), which was trapped by the twelve carbon Wittig ylide to give the olefin **14**. Hydrogenation of **14** under Pd/C–H_2 conditions gave **15**, whose spectral data are in good agreement with the reported values; conversion of **15** to 3-*epi* jaspine B **2** was recently reported by Canels et al.[11a] Very recently another synthesis of 3-*epi* jaspine B **2** was reported by Yoshimitsu et al.[11b] (Scheme 3). In an attempt to improve the yield, a modified protocol was envisaged from **11** based on the above strategy. Reduction of the ester in diastereomeric mixture **11** with DIBAL-H gave alcohol **20** as a diastereomeric mixture. Oxidation of **20** followed by reaction with 12 carbon chain Wittig reagent gave **21** as a single stereoisomer (Scheme 5).

The confirmation of the structure **21** was achieved by detailed 1D and 2D NMR studies including DQFCOSY and NOESY experiments and NOE cross peaks were observed between Ha-He, Hd-Hf and He-PhCH_2 (Fig. 2). Hydrogenation of **21** under Pd/C–H_2 condition followed by $(Boc)_2O$ treatment gave **15.** Boc deprotection of the compound **15** with TFA/CH_2Cl_2 followed by acetylation with $(Ac)_2O/CH_2Cl_2$ gave the compound **22** (Scheme 5) and the stereo-



Scheme 4. Reagents and conditions: (a) (i) BAIB, TEMPO (cat), CH_2Cl_2, rt, 2 h; (ii) $C_{12}H_{25}PPh_3{}^+Br^-$, KO^{t}Bu, THF, −40 °C, 1 h, (21% for two steps).



Scheme 5. Reagents and conditions: (a) DIBAL-H, CH_2Cl_2, 0 °C to rt, 2 h, 98%; (b) (i) BAIB, TEMPO (cat), CH_2Cl_2, rt, 2 h, (ii) $C_{12}H_{25}PPh_3{}^+Br^-$, KO^{t}Bu, THF, −40 °C, 1 h, (55% for two steps); (c) 10% Pd/C, H_2, EtOH, 12 h then $(Boc)_2O$, 1 h, (96% for two steps); (d) (i) TFA, CH_2Cl_2, 0 °C; (ii) $(Ac)_2O$, CH_2Cl_2, 0 °C, (92% for two steps).

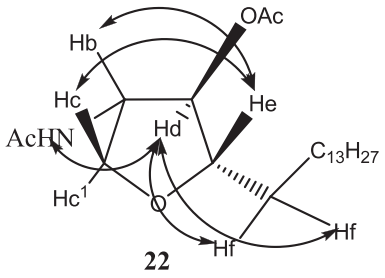


Figure 3. NOE correlation.

chemistry was confirmed by detailed 1D and 2D NMR studies including DQFCOSY and NOESY experiments and NOE cross peaks were observed between Hd-Hf, Hb-He, and N*H*Ac-Hd (Fig. 3).

3. Conclusions

In conclusion, we have developed a strategy for the synthesis of 3-*epi* jaspine B **2** using a base-induced intramolecular oxa-Michael addition reaction, which is also useful to make some other analogs of jaspine B with high stereoselectivity.

4. Experimental

TLC was performed on Merck Kiesel gel 60, F254 plates (layer thickness 0.25 mm). Column chromatography was performed on silica gel (60–120 mesh) using ethyl acetate and hexane mixture as eluent. Melting points were determined on a Fisher John's melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer RX-1 FT-IR system. ^{1}H NMR and ^{13}C NMR spectra were recorded using Varian Gemini-200 MHz or Bruker Avance-300 MHz spectrometer. ^{1}H NMR data are expressed as chemical shifts in ppm followed by multiplicity (s-singlet; d-doublet; t-triplet; q-quartet; m-multiplet), number of proton(s) and coupling constant(s) *J* (Hz). ^{13}C NMR chemical shifts are expressed in ppm. Optical rotations were measured with Horiba-SEPA-300 digital polarimeter. Accurate mass measurement was performed on Q STAR mass spectrometer (Applied Biosystems, USA).

4.1. (*S*)-2-(Benzyloxy)-2-((*R*)-2,2-dimethyl-1,3-dioxo-an-4-yl) ethanol 9

To a suspension of $LiAlH_4$ (0.36 g, 10.2 mmol) in dry THF (10 mL) was added a solution of ester **8** (1.50 g, 5.10 mmol) in THF (15 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. The mixture was treated with water and 15% NaOH solution. The fine white precipitate, which was formed, was washed with ethyl acetate and discarded. The filtrate was concentrated and the residue was purified by column chromatography with ethyl acetate/hexane (1:4) to give alcoholic compound **9** (1.23 g, 95%) as a syrup. $[\alpha]_D^{25} = +23.3$ (*c* 1.1, $CHCl_3$); IR (KBr): ν_{max} 3455, 2986, 2933, 2881, 1455, 1376, 1214, 1072, 851, 742, 699 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.30 (m, 5H), 4.62 (s, 2H), 4.07 (m, 2H), 3.81 (dd, 1H, *J* = 6.0, 8.3 Hz), 3.75 (t, 1H, *J* = 4.5 Hz), 3.63 (m, 1H), 3.47 (m, 1H,), 1.96 (q, 1H, *J* = 5.3 Hz), 1.39 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ:

137.9, 128.5, 127.9, 127.8, 109.2, 79.6, 75.8, 72.6, 66.8, 61.8, 26.6, 25.1; MS (ESI) *m*/*z* 275 (M^++Na); HRMS (ESI) calcd for $C_{14}H_{20}O_4Na$ (M^++Na) *m*/*z* 275.1264 found 275.1259.

4.2. (*S*,*E*)-Ethyl 4-(benzyloxy)-4-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)but-2-enoate 10

To a solution of $(COCl)_2$ (0.83 mL, 9.52 mmol) in CH_2Cl_2 (10 mL) was added DMSO (1.35 mL, 19.05 mmol) at −78 °C, and the mixture was stirred for 10 min. A solution of alcohol **9** (1.20 g, 4.76 mmol) in CH_2Cl_2 was added to the resulting mixture, and stirring was continued for another 1 h at −78 °C. Then DIPEA (6.75 mL, 38.09 mmol) was added at −78 °C and the reaction mixture was warmed to 0 °C and stirred for 20 min, water (20 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (2 × 20 mL), dried over anhydrous Na_2SO_4. Evaporation of the solvent provided the crude aldehyde, which was directly used in the next step.

To a solution of aldehyde in CH_2Cl_2 (15 mL), $PPh_3CHCOOEt$ (2.49 g, 7.14 mmol) was added at 0 °C and stirred for 1 h. The reaction mixture was quenched with water and extracted with CH_2Cl_2 (2 × 20 mL). The organic layer was washed with water and brine and dried over anhydrous Na_2SO_4. The solvent was removed under vacuo and the residue was purified by column chromatography with ethyl acetate/hexane (1:5) to give the compound **10** as *trans* (1.26 g, 83%) and *cis* (0.14 g, 9%) isomers in the ratio of 9:1 (1.40 g, 92% for two steps) as colorless liquids.

4.2.1. Spectral data of *trans* compound

$[\alpha]_D^{25} = +11.0$ (*c* 1.3, $CHCl_3$); IR (KBr): ν_{max} 3480, 2985, 2936, 2878, 1720, 1657, 1455, 1373, 1269, 1174, 1074, 850 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 7.28 (m, 5H), 6.85 (dd, 1H, *J* = 6.0, 15.9 Hz), 6.04 (dd, 1H, *J* = 1.1, 15.5 Hz), 4.62 (d, 1H, *J* = 11.7 Hz), 4.41 (d, 1H, *J* = 11.7 Hz), 4.20 (q, 2H, *J* = 6.8 Hz), 4.02 (m, 2H), 3.92 (t, 1H, *J* = 6.0 Hz), 3.81 (m, 1H), 1.35 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.6, 144.5, 137.3, 128.3, 127.7, 123.9, 109.6, 78.7, 77.1, 71.6, 66.5, 60.4, 26.4, 25.0, 14.1; MS (ESI) *m*/*z* 343 (M^++Na); HRMS (ESI) calcd for $C_{18}H_{24}O_5Na$ (M^++Na) *m*/*z* 343.1538 found 343.1521.

4.3. (4*S*,5*R*,*E*)-Ethyl 4-(benzyloxy)-5,6 dihydroxyhex-2-enoate 7

A solution of compound **10** (1.20 g, 3.75 mmol) in 80% aqueous acetic acid (15 mL) was stirred for 8 h. The reaction mixture was neutralized by the addition of saturated $NaHCO_3$ solution and extracted with EtOAc (2 × 20 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo and the residue was purified by column chromatography with ethyl acetate/hexane (2:3), to give **7** (1.00 g, 96%) as a colorless liquid. $[\alpha]_D^{25} = +48.6$ (*c* 1.6, $CHCl_3$); IR (KBr): ν_{max} 3418, 2924, 2936, 2854, 1719, 1657, 1457, 1372, 1275, 1176, 1098, 1036, 986, 712 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.35 (m, 5H), 6.92 (dd, 1H, *J* = 6.4, 15.9 Hz), 6.11 (dd, 1H, *J* = 1.1, 15.9 Hz), 4.68 (d, 1H, *J* = 11.7 Hz), 4.41 (d, 1H, *J* = 11.7 Hz), 4.23 (q, 2H, *J* = 6.8 Hz), 4.15 (m, 1H), 3.68 (m, 3H), 2.64 (br, 1H), 2.10 (br, 1H), 1.32 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.0, 144.7, 137.2, 128.4, 127.9, 124.0, 79.4, 73.2, 71.6, 63.0, 60.6, 14.1; MS (ESI) *m*/*z* 303 (M^++Na); HRMS (ESI) calcd for $C_{18}H_{24}O_5Na$ (M^++Na) *m*/*z* 303.1209 found 303.1208.

4.4. Ethyl 2-((2*S*(*R*),3*R*,4*R*)-3-(benzyloxy)-4-hydroxytetrahydrofuran-2-yl)acetate 6a/6b

To a suspension of NaH (0.11 g, 60% w/w, 2.75 mmol) in anhydrous THF (4 mL), compound **7** (0.50 g, 1.79 mmol) in anhydrous THF (10 mL) was slowly added at −40 °C. The mixture was stirred at the same temperature for about 30 min, quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc (2 × 20 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo and the residue was purified by column chromatography with ethyl acetate/hexane (2:3), to give the inseparable mixture **6** as **6a** and **6b** in 10:1 ratio (0.49 g, 98%) as a colorless liquid.

4.4.1. Spectral data of major compound

$[\alpha]_D^{25} = -33.1$ (*c* 1.2, $CHCl_3$); IR (KBr): ν_{max} 3420, 2932, 1716, 1656, 1453, 1370, 1274, 1180, 1096, 1036, 986, 744, 704 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.32 (m, 5H), 4.62 (s, 2H), 4.13 (m, 4H), 4.00 (dd, 1H, *J* = 4.9, 9.4 Hz), 3.78 (t, 1H, *J* = 5.7 Hz), 3.69 (dd, 1H, *J* = 4.2, 9.4 Hz), 2.50 (m, 2H), 1.25 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.5, 137.0, 128.5, 128.1, 127.9, 81.9, 76.6, 73.1, 72.5, 69.2, 60.5, 38.1, 14.0.

MS (ESI) *m*/*z* 303 (M^++Na); HRMS (ESI) calcd for $C_{15}H_{20}O_5Na$ (M^++Na) *m*/*z* 303.1202 found 303.1208.

4.5. Ethyl 2-((3*R*,4*S*)-4-azido-3-(benzyloxy)tetrahydrofuran-2-yl)acetate 11a/11b

To a solution of compound **6** (0.60 g, 2.14 mmol) in dry CH_2Cl_2 (8 mL), at 0 °C were added Et_3N (0.75 mL, 5.36 mmol), mesyl chloride (0.20 mL, 2.57 mmol), and DMAP (3 mg). The reaction mixture was then stirred at room temperature for 45 min. It was then poured into water (10 mL) and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Evaporation of solvent provided the crude mesylate, which was directly used for the next step.

To a stirred solution of the crude mesylate in dry DMF (6 mL) was added NaN_3 (0.28 g, 4.29 mmol). The mixture was heated at 120 °C under stirring for 4 h. Then the mixture was diluted with water and extracted with EtOAc (3 × 40 mL), the organic phase was dried over anhydrous Na_2SO_4, concentrated in vacuo and the residue was purified by column chromatography with ethyl acetate/hexane (1:12) to give the non-separable azido compound **11** as **11a** and **11b** in the ratio 10:1 (0.59 g, 90% for two steps) as a syrup.

4.5.1. Spectral data of major compound

$[\alpha]_D^{25} = +15.4$ (*c* 1.1, $CHCl_3$); IR (KBr): ν_{max} 3031, 2926, 2871, 2102, 1739, 1664, 1497, 1437, 1257, 1171, 1081, 1020, 846, 742, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.30 (m, 5H), 4.60 (s, 2H), 4.13 (m, 3H), 3.96 (m, 2H), 3.78 (d, 1H, *J* = 4.0 Hz), 3.66 (dd, 1H, *J* = 3.0, 9.6 Hz), 2.62 (m, 2H), 1.26 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.2, 137.0, 128.4, 127.9, 127.6, 86.8, 80.0, 72.0, 70.6, 65.6, 60.5, 38.1, 14.0; MS (ESI) *m*/*z* 328 (M^++Na); HRMS (ESI) calcd for $C_{15}H_{19}N_3O_4Na$ (M^++Na) *m*/*z* 328.1259 found 328.1273.

4.6. *tert*-Butyl-(3*S*,4*R*,5*S*)-4-(benzyloxy)-5-(2-hydroxyethyl)-tetrahydrofuran-3-ylcar-bamate 12 and *tert*-butyl-(3*S*,4*R*,5*R*)-4-(benzyloxy)-5-(2-hydroxyethyl)-tetrahydro-furan-3-ylcarbamate 13

To a suspension of $LiAlH_4$ (0.13 g, 3.61 mmol) in dry THF (5 mL) was added a solution of azide **11** (0.50 g, 1.64 mmol) in THF (10 mL) at 0 °C. The reaction mixture was brought to room temperature and stirred for 2 h. The mixture was treated with water and 15% NaOH solution and stirred for 1 h and to it was then added $(Boc)_2O$ (0.37 mL, 1.6 mmol) and stirred for 1 h. The reaction mixture was washed with ethyl acetate. The filtrate was concentrated and the residue was purified by column chromatography with ethyl acetate/hexane (3:7) to give pure compounds **12** (0.46 g, 82%) and **13** (0.04 g, 8%) with an overall yield 90% ,as white solids.

4.6.1. Spectral data of compound 12

Mp: 73–75 °C; $[\alpha]_D^{25} = -75.6$ (*c* 1.2, $CHCl_3$); IR (KBr): ν_{max} 3542, 3442, 2940, 2883, 1682, 1537, 1458, 1368, 1315, 1272, 1167, 1104, 1081, 1043, 996, 892, 755, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.31 (m, 5H), 5.07 (d, 1H, *J* = 7.5 Hz), 4.79 (d, 1H, *J* = 12.1 Hz), 4.59 (d, 1H, *J* = 12.1 Hz), 4.09 (m, 1H), 3.91 (m, 1H), 3.79 (m, 2H), 3.68 (m, 2H), 3.55 (d, 1H, *J* = 3.4 Hz), 2.43 (br, 1H), 1.81 (m, 2H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 155.0 137.6, 128.3, 127.9, 127.7, 88.9, 83.7, 79.7, 72.0, 71.6, 60.6, 56.4, 35.8, 28.3. MS (ESI) *m*/*z* 360 (M^++Na); HRMS (ESI) calcd for $C_{18}H_{27}NO_5Na$ (M^++Na) *m*/*z* 360.1425 found 360.1420.

4.6.2. Spectral data of compound 13

Mp: 84–86 °C; $[\alpha]_D^{25} = -56.6$ (*c* 1.5, $CHCl_3$);IR (KBr): ν_{max} 3540, 3442, 2942, 2883, 1685, 1532, 1460, 1368, 1315, 1270, 1167, 1081, 996, 892, 755, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.32 (m, 5H), 4.79 (m, 2H), 4.58 (d, 1H, *J* = 12.1 Hz), 4.19 (m, 2H), 4.07 (m, 1H), 3.78 (d, 1H, *J* = 4.2 Hz), 3.71 (t, 2H, *J* = 5.7 Hz), 3.53 (m, 1H), 2.25 (br, 1H), 1.98 (m, 1H), 1.71 (m, 1H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 155.0, 137.8, 128.3, 127.8, 127.6, 83.8, 79.8, 79.2, 71.1, 70.8, 60.6, 55.7, 31.3, 28.3. MS ESI) *m*/*z* 360 (M^++Na); HRMS (ESI) calcd for $C_{18}H_{27}NO_5Na$ (M^++Na) *m*/*z* 360.1425 found 360.1420.

4.7. *tert*-Butyl-(3*S*,4*R*,5*S*)-4-(benzyloxy)-5-((*Z*)-tetradec-2-enyl) tetrahydrofuran-3-yl-carbamate 14 from 12

To a solution of compound **12** (0.06 g, 0.18 mmol) in dry CH_2Cl_2 (2 mL), at 0 °C were added (diacetoxyiodo) benzene (0.09 g, 0.27 mmol) and TEMPO free radical (2 mg), the reaction mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was quenched with saturated sodium thiosulphate solution, the aqueous mixture was extracted with CH_2Cl_2 (2 × 20 mL), the organic layer was washed with saturated $NaHCO_3$ solution and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent provided the crude aldehyde, which was directly used for the next step.

To a pre-cooled (−40 °C) solution of the Wittig salt $C_{12}H_{25}PPh_3{}^+Br^-$ (0.45 g, 0.90 mmol) in anhydrous THF (20 mL) was added KO^{t}Bu (0.10 g, 0.81 mmol) in THF (5 mL) under N_2 protection. The orange colored solution was stirred for about 1 h. The reaction mixture was allowed to settle down, the upper layer was canulated slowly to the solution of aldehyde in THF (2 mL) at −40 °C and stirred for another 30 min. The reaction was then quenched by saturated NH_4Cl solution and washed with EtOAc (3 × 10 mL) followed by brine. The combined organic layer was dried over anhydrous Na_2SO_4. The solvent was removed under vacuo and the residue was purified by column chromatography with ethyl acetate/hexane (1:7) to give the compound **14** (0.02 g, 23% for two steps) as a syrupy liquid. $[\alpha]_D^{25} = -15.2$ (*c* 1.2, $CHCl_3$); IR (KBr): ν_{max} 3445, 2925, 2854, 1711, 1500, 1460, 1367, 1335, 1251, 1170, 1078, 857, 736, 698 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 7.28 (m, 5H), 5.40 (m, 1H), 5.30 (m, 1H), 4.75 (d, 1H, *J* = 12.2 Hz), 4.66 (d, 1H, *J* = 7.9 Hz), 4.57 (d, 1H, *J* = 12.2 Hz), 4.04 (m, 1H), 3.89 (dd, 1H, *J* = 4.3, 9.4 Hz), 3.70 (m, 2H), 3.46 (d, 1H, *J* = 2.8 Hz), 2.29 (m, 2H), 1.88 (m, 2H), 1.45 (s, 9H), 1.30 (m, 18H), 0.88 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 133.0, 128.3, 128.0, 127.7, 124.0, 87.8, 84.4, 71.9, 71.6, 56.6, 32.0, 31.3, 29.6, 29.5, 29.3, 28.4, 27.3, 22.7, 14.0; MS (ESI) *m*/*z* 510 (M^++Na); HRMS (ESI) calcd for $C_{30}H_{49}NO_4Na$ (M^++Na) *m*/*z* 510.3560 found 510.3559.

4.8. *tert*-Butyl (3*S*,4*R*,5*S*)-4-(benzyloxy)-5-((*Z*)-tetradec-2-enyl)tetrahydrofuran-3-yl-carbamate 14 from 13

To a solution of compound **13** (0.03 g, 0.09 mmol) in dry CH_2Cl_2 (2 mL), at 0 °C were added (diacetoxyiodo) benzene (0.05 g, 0.09 mmol) and TEMPO free radical (2 mg) and the reaction mixture was warmed to room temperature for 1 h. The reaction mixture was quenched with saturated sodium thiosulphate solution, the aqueous mixture was extracted with CH_2Cl_2 (2 × 20 mL), the organic layer was washed with saturated $NaHCO_3$ solution and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent provided the crude aldehyde, which was directly used for the next step. To a pre-cooled (−40 °C) solution of the Wittig salt $C_{12}H_{25}PPh_3{}^+Br^-$ (0.15 g, 0.30 mmol) in anhydrous THF (10 mL) was added KO^{t}Bu (0.03 g, 0.27 mmol) in THF (5 mL) under N_2 protection. The orange colored solution was stirred for about 1 h. The reaction mixture was allowed to settle down, the upper layer was canulated slowly to the solution of aldehyde in THF (2 mL) at −40 °C and stirred for another 30 min. The reaction was then quenched by saturated NH_4Cl solution and washed with EtOAc (3 × 10 mL) followed by brine. The combined organic layer was dried over anhydrous Na_2SO_4. The solvent was removed under vacuo and the residue was purified by column chromatography with ethyl acetate/hexane (1:7) to give the compound **14** (0.01 g, 21% for two steps) as a syrup.

4.9. *tert*-Butyl-(3*S*,4*R*,5*S*)-4-hydroxy-5-tetradecyltetrahydrofuran-3-ylcarbamate 15 from 14

The suspension of Pd/C (10% on carbon) (5 mg) in an ethanolic solution of olefin **14** (0.06 g, 0.12 mmol, 5 mL) was stirred under an H_2 atmosphere at room temperature for about 20 h. The Pd/C was filtered and the solvent was concentrated under vacuo and the residue was purified by column chromatography with ethyl acetate/hexane (1:4) to give the compound **15** (0.05 g, 95%) as a white solid. Mp: 94–96 °C; $[\alpha]_D^{25} = -30.2$ (*c* 1.3, $CHCl_3$) {Lit.[11] $[\alpha]_D^{25} = -31.7$ (*c* 1.09, $CHCl_3$)}; IR (KBr): ν_{max} 3351, 2920, 2850, 1688, 1533, 1469, 1391, 1367, 1172, 1078, 1013, 858, 718, 619 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 4.78 (d, 1H, *J* = 4.5 Hz), 4.04 (dd, 1H, *J* = 6.7, 9.6 Hz), 3.90 (m, 1H), 3.77 (dd, 1H, *J* = 3.8, 5.7 Hz), 3.64 (m, 2H), 1.60 (m, 2H), 1.45 (s, 9H), 1.28 (m, 24H), 0.87 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 156.4, 85.0, 82.5, 80.2, 70.4, 60.2, 33.7, 32.0, 31.9, 29.7, 29.3, 28.3, 26.0, 22.7, 14.1; MS (ESI) *m*/*z* 422 (M^++Na); HRMS (ESI) calcd for $C_{23}H_{45}NO_4Na$ (M^++Na) *m*/*z* 422.3244 found 422.3246.

4.10. 2-((3*R*,4*S*)-4-Azido-3-(benzyloxy)-tetrahydrofuran-2-yl)-ethanol 20

To a solution of the azide compound **11** (0.12 g, 0.39 mmol) in dry CH_2Cl_2 (2 mL), at −78 °C was added DIBAL-H (0.56 mL, 0.79 mmol) and the reaction mixture was warmed to room temperature, stirred for 1 h, the reaction mixture was quenched with saturated suspension of NH_4Cl solution followed by saturated sodium potassium tartarate solution and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The filtrate was concentrated and the residue was purified by column chromatography with ethyl acetate/hexane (3:7) to give the inseparable mixture **20** (0.09 g, 92%) as an oily liquid.

4.10.1. Spectral data for major compound

$[\alpha]_D^{25} = +4.5$ (*c* 2.6, $CHCl_3$); IR (KBr): ν_{max} 3424, 2932, 2874, 2101, 1455, 1256, 1081, 743, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.32 (m, 5H), 4.63 (d, 1H, *J* = 11.8 Hz), 4.54 (d, 1H, *J* = 11.8 Hz), 3.90 (m, 4H), 3.71 (m, 3H), 1.93 (m, 1H), 1.85 (q, 2H, *J* = 6.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 137.0, 128.6, 128.1, 127.8, 88.0, 83.1, 72.4, 70.9, 65.7, 60.5, 35.3; MS (ESI) *m*/*z* 286 (M^++Na); HRMS (ESI) calcd for $C_{13}H_{17}N_3O_3Na$ (M^++Na) *m*/*z* 286.1159 found 286.1167.

4.11. ((2*S*,3*R*,4*S*)-4-Azido-3-(benzyloxy)-2-((*Z*)-tetradec-2-enyl) tetrahydrofuran 21

To a solution of alcoholic compound **20** (0.05 g, 0.19 mmol) in dry CH_2Cl_2 (2 mL), at 0 °C was added (diacetoxy iodo) benzene (0.09 g, 0.27 mmol) and TEMPO free radical (2 mg) and the reaction mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was quenched with saturated sodium thiosulphate solution, the aqueous mixture was extracted with CH_2Cl_2 (2 × 20 mL), the organic layer was washed with saturated $NaHCO_3$ solution, brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent provided the crude aldehyde, which was directly used in the next step.

To a pre-cooled (−40 °C) solution of the Wittig salt $C_{12}H_{25}PPh_3{}^+Br^-$ (0.47 g, 0.95 mmol) in dry THF (20 mL) was added slowly KO^{t}Bu (0.09 g, 0.85 mmol) in THF (5 mL) under N_2 protection. The orange color solution was stirred for 1 h and stirring was stopped to allow the reaction mixture to settle down. The upper layer was canulated slowly to the solution of aldehyde in THF (2 mL) at −40 °C and stirred for another 30 min and then allowed to warm to room temperature. The reaction was then quenched by saturated NH_4Cl solution at −40 °C and washed with EtOAc (3 × 10 mL), followed by brine. The combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed under vacuo and the residue was purified by column chromatography with ethyl acetate/hexane (1:19) to give the compound **21** (0.04 g, 55% for two steps) as a syrup. $[\alpha]_D^{25} = +6.7$ (*c* 2.8, $CHCl_3$); IR (KBr): ν_{max} 3444, 2926, 2854, 2100, 1728, 1632, 1460, 1400, 1256, 1081, 737, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.31 (m, 5H), 5.44 (m, 1H), 5.34 (m, 1H), 4.63 (d, 1H, *J* = 11.3 Hz), 4.53 (d, 1H, *J* = 12.1 Hz), 4.16 (dd, 1H, *J* = 6.0, 9.8 Hz), 3.99 (m, 1H), 3.84 (m, 2H), 3.64 (dd, 1H, *J* = 3.0, 9.8 Hz), 2.45 (m, 2H), 2.02 (m, 2H), 1.33 (m, 18H), 0.88 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 137.2, 133.0, 128.5, 128.0, 127.8, 123.9, 87.2, 84.0, 72.2, 70.7, 65.9, 31.9, 30.9, 29.6, 29.5, 29.3, 27.4, 22.7, 14.8; MS (ESI) *m*/*z* 436 (M^++Na); HRMS (ESI) calcd for $C_{25}H_{39}N_3O_4Na$ (M^++Na) *m*/*z* 436.1543 found 436.1538.

4.12. *tert*-Butyl-(3*S*,4*R*,5*S*)-4-hydroxy-5-tetradecyltetrahydrofuran-3-ylcarbamate 15 from 21

The suspension of Pd/C (10% on carbon, 5 mg) in an ethanolic solution of olefin **21** (0.05 g, 0.12 mmol, 5 mL) was stirred under an H_2 atmosphere at room temperature for about 20 h. The Pd/C was filtered and the filtrate was dried over anhydrous Na_2SO_4. The solvent was removed under vacuo and to it were added CH_2Cl_2 (5 mL), NEt_3 (0.05 mL, 0.36 mmol), $(Boc)_2O$ (0.03 mL, 0.12 mmol) at 0 °C and then stirred for 1 h. The reaction mixture was quenched with saturated NH_4Cl solution washed with CH_2Cl_2 (3 × 10 mL) followed by brine. The combined organic layers were concentrated under vacuo and the residue was purified by column chromatography with ethyl acetate/hexane (1:4) to give the compound **15** (0.05 g, 96%) as a white solid.

4.13. (2*S*,3*R*,4*S*)-4-Acetamido-2-tetradecyl-tetrahydrofuran-3-yl acetate 22

To an ice-cooled, stirred solution of compound **15** (0.020 g, 0.05 mmol) in CH_2Cl_2 (1 mL) was added TFA (1 mL). The reaction was allowed to room temperature and stirred for 6 h. The volatiles were removed on a rotary evaporator and the next reaction proceeded without further purification.

To an ice-cooled, stirred solution of TFA salt of 3-*epi* jaspine B in dry CH_2Cl_2 (4 mL), were added Et_3N (0.03 mL, 0.21 mmol), Ac_2O (0.02 mL, 0.23 mmol), and DMAP (2 mg). After the completion of addition, the reaction was allowed to room temperature and stirred for 4 h. The reaction mixture was diluted with CH_2Cl_2 (30 mL) and the organic layer was washed with saturated aq NH_4Cl solution, water and brine, dried over anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator and the residue was purified by column chromatography on silica gel using ethyl acetate/hexane (1:2) as the eluant to afford the acetate derivative of 3-*epi* jaspine B **22** (0.018 g, 94%) as a thick syrup. $[\alpha]_D^{25} = +11.2$ (*c* 1.1, $CHCl_3$); IR (KBr): ν_{max} 3279, 2923, 2854, 1742, 1654, 1548, 1461, 1372, 1236, 1043, 722 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.88 (d, 1H, *J* = 6.6 Hz), 4.64 (dd, 1H, *J* = 3.2, 5.1 Hz), 4.32 (m, 1H), 4.00 (dd, 1H, *J* = 5.6, 7.8 Hz), 3.70 (dd, 1H, *J* = 3.0, 9.8 Hz), 3.64 (dt, 1H, *J* = 4.9, 8.6 Hz), 2.02 (s, 3H), 1.92 (s, 3H), 1.64 (m, 1H), 1.50 (m, 1H), 1.36 (m, 1H), 1.2 (m, 23 H), 0.88 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.7, 169.9, 83.0, 81.8, 71.8, 56.5, 33.5, 31.9, 29.6, 29.6, 29.5, 29.5, 29.3, 25.9, 23.1, 22.7, 21.0, 14.1; MS (ESI) *m*/*z* 406 (M^++Na); HRMS (ESI) calcd for $C_{25}H_{39}N_3O_4Na$ (M^++Na) *m*/*z* 406.2950 found 406.2933.

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