Tetrahedron: *Asymmetry* xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

A diversity oriented synthesis of D-*erythro*-sphingosine and siblings

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ARTICLE INFO

Article history:
Received 5 July 2017
Revised 26 July 2017
Accepted 7 August 2017
Available online xxxx

ABSTRACT

An efficient building block-based synthetic protocol has been developed for the synthesis of 3-ketosphingoids with various chain lengths using cross metathesis of a Garner's aldehyde-derived α,β-unsaturated ketone as the key step. Stereoselective reduction of the biomimetic precursors thus obtained provided D-*erythro*-sphingosine and truncated anaogues in good overall yields.

1. Introduction

Sphingolipids of the general structure **1** (Fig. 1) are known to be involved in nearly all aspects of cellular regulation and hence are implicated in a myriad of disease related events including apoptosis, cell growth, cell differentiation and inflammation.[1] Sphingosine **2**, the basic structural core of the sphingolipids, is also important in kinase regulation, cell signaling and in the studies of dermatitis.[2] For this and other reasons, sphingosines have received considerable attention from chemists and biologists over decades.[3,4] In addition to the synthesis of the naturally occurring ones, design and synthesis of analogues for biological understanding has remained the major focus.[5] In many of these synthetic studies, the L-serine derived Garner's aldehyde **3** has served as an important starting material as metal-mediated stereoselective alkynylation or alkenylation of the latter has provided useful building blocks, such as **4a**–**b** for the synthesis of D-*erythro*-sphingosine and its analogues.[6,7] Classical Wittig or sulfone-alkylation based strategies for the installation of the pendant alkyl chain is now being supplemented by metal-mediated coupling strategies.[8] In particular, the cross metathesis reaction of the suitably protected allyl alcohol **4b** has been thoroughly utilized[9] for the synthesis of the D-*erythro*-sphingoids, a minor limitation being the *E/Z*-selectivity and occasional dwindling of the chemical yield, mostly due to use of two class-I type olefins in the cross-metathesis approaches. On the other hand, the unsaturated ketone **5** has remained unexplored as cross metathesis partner for the synthesis of 3-keto-sphingoids as bio-mimetic precursor[10] of sphingosines. We opted to use **5** as a type-II olefin in a cross metathesis reaction with the expectation that some of the general problems associated with cross metathesis of **4b** may be avoided due to proven utility of electron deficient alkenes as one of the partners in cross metathesis reaction. Herein, we report a successful application of compound **5** as a building block in cross-metathesis mediated modular synthesis of *N*,*O*,*O*-triacetyl-D-*erythro*- sphingosine and three chain truncated analogues.

2. Results and discussion

The unsaturated ketone **5** (Scheme 1) was prepared by oxidation of the known allyl alcohol **7**, obtained by non-selective vinylation of the L-serine derived Garner's aldehyde **3**. Previously, the oxidation was carried out[11] under Swern conditions at low temperature. We have found that the oxidation could conveniently be carried out at room temperature using IBX as oxidant with little compromise in chemical yield or the stereochemical integrity. Moreover, the unsaturated ketone **5** could be stored at 4 °C for weeks with only a negligible loss of enantiomeric purity. With access to a gram scale synthesis of **5**, we next focused on its utility along the projected line. After some initial explorations, it was quickly realized that the cross metathesis of **5** with 1-pentadecene proceeded rapidly (~1 h) when Grubbs' 2nd generation catalyst (1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro (phenyl-methylene)(trichlorohexylphosphne)ruthenium (Grubb-II) was used, as all attempts using Grubbs' 1st generation catalysts met with limited success. The cross metathesis product **6a** was obtained as a single isomer in good yield (91%) using only one equivalent of the second olefin, thus obviating the need of an excess of partner olefin as generally observed in similar situations.[12] Stereoselective reduction of α-aminoketones of type **6** to the corresponding *anti*-amino alcohols is well documented and various reagents have provided useful levels of selectivity in demanding situtations.[13] The $NaBH_4/CeCl_3$ system has worked consistently but under varied conditions with somewhat varying stereoselectivity. We have found that the stereoselectivity in the

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http://dx.doi.org/10.1016/j.tetasy.2017.08.006
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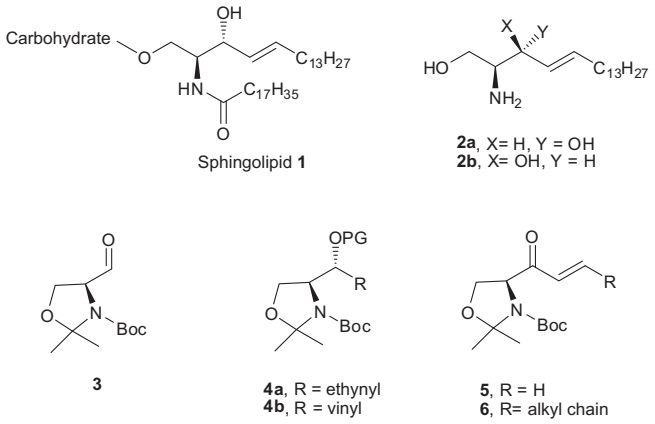
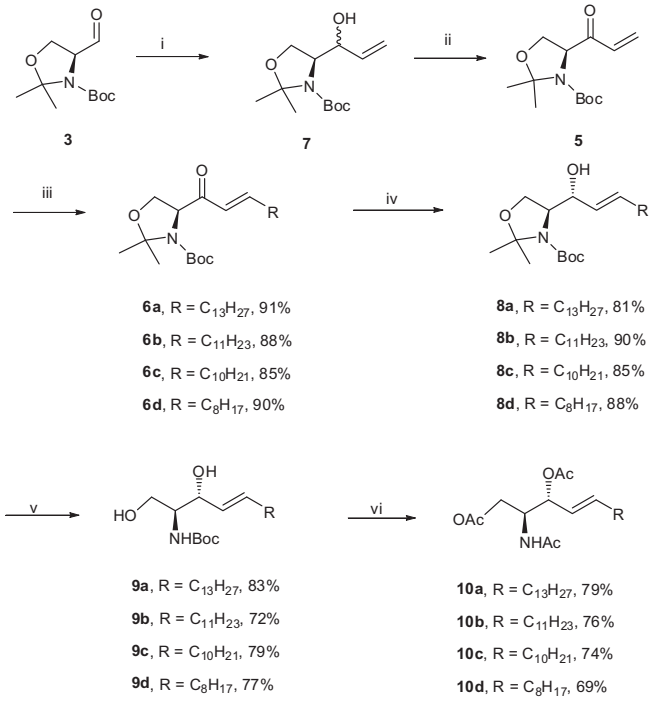


Figure 1. Sphingosines and building blocks for their synthesis.



Scheme 1. Synthesis of *N,O,O*-triacetyl-D-*erythro*-sphingoids **10a–d**. *Reagents and conditions:* (i) vinylmagnesium bromide, THF, 0 °C, 1 h, 92%; (ii) IBX, DMSO, rt, 1 h, 85%; (iii) G-II (1 mol %), appropriate olefin, CH_2Cl_2, reflux, 1 h, 79–91%; (iv) $NaBH_4$, $CeCl_3$, THF–MeOH, −15 °C, 2 h, 81–90%; (v) *p*-TSA, MeOH, 1 h, 77–83%; (vi) MeOH, HCl (3 M), 50 °C, 3 h, 69–79%.

reduction of **6a** to **8a** is influenced by the temperature as well as by the solvent. The optimum result was obtained when a mixture of THF and MeOH (1:5) was used as the solvent and the reduction was conducted at −15 °C. The desired *anti*-product **8a** was obtained in 81% isolated yield together with the minor *syn*-isomer (8%), which could be separated. The deprotection of the oxazolidine unit in the allyl alcohol **8a** was smoothly achieved under conventional conditions and the known Boc-protected aminodiol **9a** was obtained in good yield (83%). A one-pot deprotection of the Boc-group in the latter followed by exhaustive acetylation resulted in the formation of **10a** in an overall yield of 48% over four steps from the building block **5.** The spectroscopic and analytical data of **10a** were found to be in agreement with the known[4d] *N,O,O*-triacetyl-D-*erythro*-sphingosine.

Sphingosine derivatives with truncated alkyl chains have recently been biologically evaluated with encouraging results.[15] Thus, we opted to prepare sphingoids with C16, C15 and C13 chain length to demonstrate the utility of **5** as a building block. Thus, cross metathesis of **5** with shorter chain alkenes such as tridecene, dodecene or decene proceeded with similar facility provided the corresponding cross metathesis products **6b–d**, respectively. Chelation-controlled reduction of each of these enones under the developed conditions provided the corresponding *anti*-diols **8b–d** with good overall yield and stereoselectivity. In each of these reductions, the corresponding *syn*-isomers were obtained as minor products (8–14%) which could be separated. The diastereomeric ratio for the reduction reaction in each case was as follows: **8a** (81:8), **8b** (90:8), **8c** (85:14), and **8d** (88:11). The stereochemical assignment of the products **8b–d** was based on the Felkin-Anh cyclic transition state model with additional support from comparison of available data for the two compounds further along the synthetic sequence (vide experimental). Thus, each of the allylic alcohols **8b–d** were subjected to deprotection of the oxazolidine ring leading to the *N*-Boc-protected amino diols **9b–d** and thence to further deprotection-acetylation events leading to the triacetyl derivatives **10b–d**.

3. Conclusion

In conclusion, we have demonstrated a short and efficient diversity oriented biomimetic synthetic approach towards the synthesis of the biologically important D-*erythro*-sphingosine derivatives involving **5** as a building block in good overall yields (40–48%). The present methodology may be used to supplement existing methodologies[13b,f] for the preparation of 3-keto-sphingoids.[14] Further applications of this general strategy appear feasible. The utility of **5** in this regard will be pursued in our laboratory.

4. Experimental

4.1. General

Column chromatography was performed on silica gel, Merck grade 230–400 mesh and neutral alumina. Reactions were monitored by thin-layer chromatography; TLC plates were visualized with UV, in an iodine chamber, or with vanillin solution, unless noted otherwise. Optical rotations were measured on a Rudolph Autopol-IV polarimeter purchased from a DST grant. IR spectra were recorded on a Perkin–Elmer Spectrum-1 instrument using KBr disks, chloroform solution or as neat. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer, operating at 400 and 100 MHz, respectively. Chemical shifts (δ) are given from TMS (0 ppm) as the internal standard for ^{1}H NMR and $CDCl_3$ (77.0 ppm) for ^{13}C NMR. The following abbreviations were used to denote the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = double doublet, ddd = doublet of double doublet, dt = doublet of triplet, br = broad, etc. The data in the parentheses indicate those for rotamers. Mass spectra were recorded in Water Xevo-QTOF instrument purchased through a DST-PURSE grant. THF, toluene, benzene and ether were freshly distilled under argon from a purple solution of sodium benzophenone ketyl. Unless stated otherwise, all reagents were purchased from commercial sources and used without additional purification.

4.1.1. (4 *R,S*)-*tert*-Butyl 4-(1-hydroxyallyl)-2,2-dimethyloxazolidine-3-carboxylate 7

Vinyl magnesium bromide (1.0 M in THF, 4.4 ml, 4.4 mmol) was added dropwise to a stirred solution of the Garner's aldehyde **3** (1 g, 4.4 mmol) in THF (8 mL) at 0 °C under nitrogen over 10 min

and stirring was continued for an hour at the same temperature. The reaction was quenched by the slow addition of saturated aqueous NH_4Cl solution (10 mL). The reaction mixture was diluted with ethyl acetate (50 ml), and the combined organic extract was washed with water (2 × 25 mL) and brine (25 mL), and then dried (Na_2SO_4). It was filtered and the filtrate was concentrated in *vacuo*. The residual mass was then purified by chromatography over silica gel using a mixture of ethyl acetate/petroleum ether (3:7) as the eluent to afford an epimeric mixture of the allyl alcohol **7** (1.04 mg, 92%) as a colourless viscous liquid. IR (KBr): 3408, 2978, 2928, 1697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.79–5.75 (m, 1H), 5.31–5.25 (m, 1H), 5.17–5.12 (m, 1H), 4.26–4.08 (m, 2H), 3.96–3.81 (m, 3H), 1.49 (d, J = 14 Hz, 3H), 1.41 (br s, 13H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.2 (155.1), 136.7 (137.6), 116.2 (117.8), 94.5, 81.1 (81.4) 74.1 (73.3), 64.7 (64.4), 61.9 (61.8), 28.3, 26.3 (27.1), 24.5 (24.2). HRMS (QTOF) calcd for $C_{13}H_{23}NNaO_4$ $(M+Na)^+$ 280.1525; obs 280.1510.

4.1.2. (*S*)-*tert*-Butyl 4-acryloyl-2,2-dimethyloxazolidine-3-carboxylate 5

At first, IBX (446 mg, 1.56 mmol) was added in portions to a stirred solution of alcohol **7** (200 mg, 0.77 mmol) in DMSO (5 mL) and the resulting reaction mixture was stirred at room temperature for one hour. It was then quenched with saturated aqueous NH_4Cl solution (10 mL) and filtered. The filtrate was diluted with ethyl acetate (25 mL) and the combined organic extract was washed with water (2 × 25 mL) and brine (20 mL), and then dried ($MgSO_4$). It was then filtered and the filtrate was concentrated in vacuo to give a pale yellow liquid, which was purified by chromatography over silica gel using ethyl acetate/petroleum ether (2:8) as the eluent to afford the unsaturated ketone **5** (170 mg, 85%) as a colourless viscous liquid. R_f: 0.5 [EA/PE (2:8)]; $[\alpha]_D$ = −58.5 (*c* 0.4, $CHCl_3$, {Lit.[11] *ent*. **5** $[\alpha]_D$ = +54.1 (*c* 1.21, $CHCl_3$)}; IR (KBr): 2979, 2936, 1702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.44–6.56 (m, 1H): 6.25–6.35 (m, 1H), 5.79 (d, J = 10.4 Hz, 1H), 4.50 (dd, J = 3.6, 7.4 Hz, 1H), [4.69–4.67 (m, 1H)], 4.11 (dd, J = 10.8, 18.2 Hz, 1H), 3.85 (dd, J = 3.6, 9.2 Hz, 1H) [3.90 (dd, 1H, J = 9.0, 2.8)], 1.63 (s, 3H) [1.58 (s, 3H)], 1.42 (s, 3H) [1.45 (s, 3H)], 1.30 (br s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.3 (195.6), 150.8, 129.4 (131.2), 94.7 (94.0), 80.1 (80.4), 65.1 (64.7), 63.4 (63.1), 27.7 (27.8), 25.5, 24.7 (24.5), 23.6. HRMS (QTOF): calcd for $C_{13}H_{21}NNaO_4$ $(M+Na)^+$ 278.1368; obs.278.1361.

4.1.3. General procedure for cross metathesis

A solution of the unsaturated ketone **5** (220 mg, 0.863 mmol), 1-pentadecene (0.2 mL, 0.863 mmol) in anhydrous and degassed dichloromethane (3 mL) was treated with Grubbs' II catalyst (7 mg, 1 mol %) and the reaction mixture was heated at reflux for 1 h under argon. It was then allowed to return to rt and then concentrated in vacuo. The residual brownish mass was chromatographed over silica gel using a mixture of ethyl acetate and petroleum ether (1:9) as eluent to provide the corresponding cross metathesis product **6a** (307 mg, 91%) as a viscous, colorless oil.

4.1.3.1. (*S,E*)-*tert*-Butyl 4-(hexadec-2-enoyl)-2,2-dimethyloxazolidine-3-carboxylate 6a. $[\alpha]_D$ = −30.4 (*c* 0.15, $CHCl_3$) [Lit.[13b] $[\alpha]_D$ = −30.0 (*c* 0.85 $CHCl_3$)]; IR (KBr): 2926, 2854, 1711, 1701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.86–6.94 (m, 1H), 6.23 (d, J = 15.6 Hz, 1H), 4.44 (dd, J = 8.0, 4.0 Hz, 1H), (4.62, dd, J = 7.2, 2.8 Hz, 1H), 4.09 (dd, J = 17.0, 9.0 Hz, 1H), 3.84 (dd, J = 9.0, 4.0 Hz, 1H), (3.89, dd, J = 9.0, 2.8 Hz, 1H), 2.16 (td, J = 14.8, 7.5 Hz, 2H), 1.63 (s, 3H) (1.58, s, 3H), 1.42 (s, 3H), (1.48, s, 3H), 1.30 (br s, 9H), 1.19 (br s, 22H), 0.80 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.7 (195.8), 149.7 (151.4), 125.2 (125.8), 95.1 (94.4), 80.5 (80.7), 65.9 (65.4), 64.1 (63.8), 32.7, 31.9, 29.6, 29.5, 29.4, 29.3, 29.2, 28.3, 28.2, 28.0, 27.9, 26.1 (25.2), 25.1 (24.1), 22.7, 14.1. HRMS (QTOF): calcd for $C_{26}H_{47}NNaO_4$ $(M+Na)^+$ 460.3403; obs. 460.3466.

4.1.3.2. (*S,E*)-*tert*-Butyl 2,2-dimethyl-4-(tetradec-2-enoyl)oxazolidine-3-carboxylate 6b. Colorless oil. Yield: 88%. $[\alpha]_D$ = −12.3 (*c* 0.1, $CHCl_3$); IR (KBr):3010, 2924, 2853, 1710 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.94–6.88 (m, 1H), 6,24 (d, J = 16.0 Hz, 1H), 4.44 (dd, J = 7.4, 3.6 Hz, 1H) (4.63–4.61, m, 1H), 4.13–4.08 (m, 1H), 3.83 (dd, J = 8.0, 3.2 Hz, 1H) (3.88 (dd, J = 9.2, 2.4 Hz, 1H), 2.14–2.19 (m, 2H), 1.64 (s, 3H) (1.58, s, 3H), 1.42 (s, 3H) (1.48, s, 3H), 1.42–1.48 (m, 9H), 1.30 (br s, 9H), 1.18 (br s, 18H), 0.80 (t, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.5 (195.6), 149.5 (151.3), 125.2 (125.8), 94.9 (94.3), 80.3 (80.6), 65.8 (65.4), 64.0 (63.8), 32.6, 31.9, 29.5, 29.4, 29.2 (29.3), 29.1, 28.2, 28.1 (28.2), 27.9 (27.8), 25.9, 25.1 (25.0), 24.1, 22.6, 14.0. HRMS (QTOF): calcd for $C_{24}H_{43}NNaO_4$ $(M+Na)^+$ 432.3090; obs. 432.3101.

4.1.3.3. (*S,E*)-*tert*-Butyl 2,2-dimethyl-4-(tridec-2-enoyl)oxazolidine-3-carboxylate 6c. Colorless oil (85%). $[\alpha]_D$ = −36.0 (*c* 0.05, $CHCl_3$); IR (KBr): 2927, 2856, 1710 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.87–6.94 (m, 1H), 6,23 (d, J = 16.0 Hz, 1H), 4.44 (dd, J = 8.0, 3.2 Hz, 1H) (4.63–4.61, m, 1H), 4.09 (dd, J = 16.0, 8.8 Hz, 1H), 3.82 (dd, J = 9.2, 3.6 Hz, 1H) (3.88, J = 8.8, 2.4 Hz, dd), 1.63 (s, 3H) (1.57 s, 3H), 1.42 (s, 3H) (1.47, s, 3H), 1.29 (br s, 9H), 1.29 (br s, 7H), 1.19 (br s, 16H), 0.80 (t, J = 6.8 Hz, 3H): ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.5 (195.7), 149.6 (151.3), 125.2 (125.8), 94.9 (94.3), 80.3 (80.6), 65.8 (65.4), 64.0 (63.8), 32.6, 31.8, 29.4 (29.5), 29.2 (29.3), 28.1 (28.3), 28.0, 27.9 (27.8), 26.0, 25.1 (25.0), 24.0, 22.6, 14.1. HRMS (QTOF): calcd for $C_{23}H_{41}NNaO_4$ $(M+Na)^+$ 418.2933. obs 418.2943.

4.1.3.4. (*S,E*)-*tert*-Butyl 2,2-dimethyl-4-(undec-2-enoyl)oxazolidine-3-carboxylate 6d. Colorless oil. Yield: 90%. $[\alpha]_D$ = −47.6 (*c* 0.1, $CHCl_3$). IR (KBr): 2928, 2856, 1710 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.87–6.94 (m, 1H), 6.23 (d, J = 16.0 Hz, 1H), 4.44 (dd, J = 7.2, 3.6 Hz, 1H) (4.63–4.61, m, 1H), 4.10 (dd, J = 17.0, 9.2 Hz, 1H), 3.83 (dd, J = 7.0, 3.6 Hz, 1H), 3.88 (dd, J = 9.2, 2.4 Hz, 1H), 2.16 (td, J = 14.5, 7.2 Hz, 2H), 1.63 (s, 3H) (1.58, s, 3H), 1.42 (s, 3H) (1.48, s, 3H), 1.30 (br s, 9H), 1.19(br s, 12H), 0.81 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, 196.6 (195.7), 149.7 (151.3), 125.2 (125.8), 95.0 (94.4), 80.4 (80.8), 65.8 (65.5), 64.0 (63.8), 32.7, 31.8, 29.3 (29.6), 29.2, 28.3, 28.2, 27.9 (27.8), 25.2 (25.1), 24.1, 22.6, 14.0. HRMS (QTOF): calcd for $C_{21}H_{37}NNaO_4$ (M+Na)+ 390.2620; obs 390.2632.

4.1.4. General procedure for anti-selective reduction of the ketones

At first, $CeCl_3$ (221 mg, 0.59 mmol) was added in portions to a stirred solution of compound **6a** (260 mg, 0.59 mmol) in THF-methanol (1:5, 5 mL) at −15 °C under nitrogen and stirred for 10 min. Next, $NaBH_4$ (21 mg, 0.59 mmol) was added portion wise over 5 min and stirring was continued for 2 h. It was then quenched with saturated NH_4Cl solution (5 mL) and stirred at room temperature for 15 min. The solvent was concentrated under reduced pressure and the resulting suspension was diluted with ethyl acetate (50 ml). It was then washed with water (20 mL), brine (20 mL), dried ($MgSO_4$) and then filtered. The filtrate was concentrated in vacuo to leave a residual mass, which was purified through chromatography over silica gel using a mixture of ethyl acetate and petroleum ether (2:8) as the eluent to afford compound **8a** (211 mg, 81%) as a colourless viscous liquid. The corresponding *syn*-isomer (23 mg, 8%) eluted later which was slightly contaminated with the *anti*-isomer.

4.1.4.1. (*S*)-*tert*-Butyl 4-((*R*,*E*)-1-hydroxyhexadec-2-en-1-yl)-2,2-dimethyloxazolidine-3-carboxylate 8a. $[\alpha]_D = -25.4$ (*c* 0.5, $CHCl_3$). IR (KBr): 3427, 2924, 2853, 1701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.70–5.63 (m, 1H), 5.36 (dd, *J* = 15.2, 4.8 Hz, 1H), 4.14–4.05 (m, 2H), 3.97–3.94 (m, 1H), 3.78–3.75 (m, 1H), 1.96 (td, *J* = 7.2, 4.0 Hz, 2H), 1.41 (br s, 15H), 1.18 (br s, 22H), 0.81 (t, *J* = 6.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.2, 133.4, 128.1, 94.3, 81.1, 74.1, 64.9, 62.3, 32.4 (32.3), 31.9, 29.7, 29.6, 29.5, 29.3, 29.2, 29.1, 29.0, 28.3, 26.2, 24.6, 22.7, 14.1. HRMS (QTOF): calcd for $C_{26}H_{49}NNaO_4$ $(M+Na)^+$ 462.3559; obs. 462.3656.

4.1.4.2. (S)-*tert*-Butyl 4-((*R*,*E*)-1-hydroxytetradec-2-en-1-yl)-2,2-dimethyloxazolidine-3-carboxylate 8b. Yield: 90%. R_f: 0.5 (EA/PE::3:7). $[\alpha]_D = -19.5$ (*c* 0.2, $CHCl_3$). IR (KBr): 3432, 2925, 2854, 1699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.67–5.64 (m, 1H), 5.37 (dd, 1H, *J* = 14.5, 5.2 Hz), 4.13–4.05 (m, 2H), 3.94–3.77 (m, 2H), 1.99–194 (m, 2H), 1.41 (br s, 15H), 1.18 (br s, 18H), 0.80 (t, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.8, 133.3, 128.1, 94.3, 80.9, 74.0, 64.9, 62.3, 32.4 (32.3), 31.9, 29.7 (29.6), 29.5, 29.4, 29.3, 29.2, 29.1, 29.0 (28.9), 28.3, 26.2, 22.7, 14.1. HRMS (QTOF): calcd for $C_{24}H_{45}NNaO_4$ $(M+Na)^+$ 434.3246; obs. 434.3246.

4.1.4.3. (*S*)-*tert*-Butyl 4-((*R*,*E*)-1-hydroxytridec-2-en-1-yl)-2,2-dimethyloxazolidine-3-carboxylate 8c[15d]. Yield: 85%. $[\alpha]_D = -42.0$ (*c* 0.1, $CHCl_3$). IR (KBr): 3417, 2925, 2854, 1701 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.68–5.64 (m, 1H), 5.37 (dd, *J* = 16.0, 5.6 Hz, 1H), 4.12–4.06 (m, 2H), 3.95 (br s, 1H), 3.87–3.77 (m, 1H), 1.96 (td, *J* = 8.0, 6.8 Hz, 2H), 1.41 (br s, 15H), 1.18 (br s, 16H), 0.81 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 133.4, 128.1, 94.4, 81.0, 74.0, 64.9, 62.3, 32.4, 32.3, 31.9, 29.6, 29.5, 29.3, 29.2, 29.1 (29.0), 28.4 (26.2), 24.6, 22.7, 14.1. HRMS (QTOF): calcd for $C_{23}H_{43}NNaO_4$ $(M+Na)^+$ 420.3090; obs. 420.3131.

4.1.4.4. (*S*)-*tert*-Butyl 4-((*R*,*E*)-1-hydroxyundec-2-en-1-yl)-2,2-dimethyloxazolidine-3-carboxylate 8d. Yield: 88%. $[\alpha]_D = -19.6$ (*c*, 0.25, $CHCl_3$). IR (KBr): 3441, 2925, 2854, 1701 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.68–5.62 (m, 1H), 5.37 (dd, *J* = 15.4, 5.6 Hz, 1H), 4.12–4.05 (m, 2H), 4.00–3.95 (m, 1H), 3.82–3.77 (m, 1H), 1.96 (dt, *J* = 8.0, 6.8 Hz, 2H), 1.42–1.41 (m, 15H), 1.19 (br s, 12H), 0.81 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.2, 132.4, 128.1, 94.4, 81.0, 74.0, 64.9 (64.2), 62.3, 32.4 (32.3), 31.9, 29.6 (29.7), 29.4 (29.3), 29.2 (29.1), 28.9 (28.3), 26.2 (27.1), 24.6 (24.3), 22.7, 14.1. HRMS (QTOF): calcd for $C_{21}H_{39}NNaO_4$ $(M+Na)^+$ 392.2777; obs. 392.2791.

4.1.5. General procedure for the deprotection of the oxazolidine ring

A solution of alcohol **8a** (40 mg, 0.09 mmol) in MeOH (2 mL) was added dropwise to a magnetically stirred suspension of *p*-toluenesulfonic acid (2 mg) in MeOH (2 mL) at room temperature. The reaction mixture was stirred for 1 h and then quenched with saturated $NaHCO_3$ solution (2 mL). It was then diluted with water (20 mL) and extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layer was dried ($MgSO_4$), filtered, and the filtrate was concentrated. The residual mass was purified by chromatography over silica gel using a mixture (1:1) of EA/PE to give diol **9a** (33 mg, 83%) as a colorless viscous liquid.

4.1.5.1. *tert*-Butyl ((2*S*,3*R*,*E*)-1,3-dihydroxyoctadec-4-en-2-yl)-carbamate 9a. R_f: $[\alpha]_D = -6.0$ (*c* 0.35, $CHCl_3$) [Lit.[9d] $[\alpha]_D = -2.3$ (*c* 0.88, $CHCl_3$)]; IR (KBr) ν_{max} 3343, 2920, 2850, 1689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.69 (dt, 1H, *J* = 15.6, 7.2 Hz), 5.44 (dd, 1H, *J* = 15.4, 6.8 Hz), 5.30 (d, 1H, *J* = 8.4 Hz), 4.21 + (br s, 1H), 3.84 (dd, 1H, *J* = 11.2, 3.8 Hz), 3.61 (dd, 2H, *J* = 7.8, 3.2 Hz), 3.52 (br s, 1H), 3.19 (br s, 1H), 1.97 (td, 2H, *J* = 7.2, 6.8 Hz) 1.37 (br s, 9H), 1.19 (br s, 22H), 0.80 (t, 3H *J* = 6.8 Hz): ^{13}C NMR (100 MHz, CDCl3) δ 156.3, 134.1, 128.9, 79.8, 74.5, 62.5, 55.4, 32.3, 31.9, 29.7, 29.6, 29.5, 29.3, 29.2, 29.1, 28.4, 22.7, 14.1. HRMS (QTOF) calcd for $C_{23}H_{45}NNaO_4$ $(M+Na)^+$ 422.3246; obs. 422.3201.

4.1.5.2. *tert*-Butyl ((2*S*,3*R*,*E*)-1,3-dihydroxyhexadec-4-en-2-yl)-carbamate 9b[15f]. Yield: 72%. $[\alpha]_D = -7.1$ (*c* 0.45, $CHCl_3$); IR (KBr): 3418, 2924, 2853, 1692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.71–5.66 (m, 1H), 5.44 (dd, *J* = 16, 6.8 Hz, 1H), 5.30(d, *J* = 8.4 Hz, 1H), 4.22 (br s, 1H), 3.84 (dd, *J* = 11, 2.8 Hz, 1H), 3.69–3.52 (m, 2H), 3.09 (br s, 2H), 2.00–1.95 (m, 2H), 1.37 (br s, 9H), 1.18 (br s, 18H), 0.80 (t, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.2, 134.2, 128.8, 79.8, 74.6, 64.1, 62.6, 55.4, 32.3, 31.9, 29.7, 29.6, 29.5, 29.3, 29.2, 29.1, 28.4, 22.7, 14.1. HRMS (QTOF): calcd for $C_{21}H_{41}NNaO_4$ $(M+Na)^+$ 394.2933; obs. 394.2901.

4.1.5.3. *tert*-Butyl ((2*S*,3*R*,*E*)-1,3-dihydroxypentadec-4-en-2-yl)-carbamate 9c. Yield: 79%. $[\alpha]_D = -4.5$ (*c* 0.45, $CHCl_3$); $[\alpha]_D = -4.0$ (*c* 1.1, CH_2Cl_2) {Lit.[15e] $[\alpha]_D = -4.1$ (*c* 1.48, CH_2Cl_2)}. IR (KBr): 3386, 2925, 2854, 1690 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.74–5.67 (m, 1H), 5.45 (dd, *J* = 16, 6.4 Hz, 1H), 5.26–5.25 (br s, 1H), 4.25–4.24 (br s, 1H), 3.86 (dd, *J* = 11.2, 3.6 Hz, 1H), 3.72–3.53 (m, 2H), 2.82–2.72 (br s, 2H), 1.98 (q, *J* = 7.2 Hz, 2H), 1.38 (br s, 9H), 1.19 (br s, 16H), 0.81 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.8, 134.2, 128.8, 79.8, 74.8, 62.6, 55.4, 32.3, 31.9, 29.6, 29.5, 29.3, 29.2, 29.1, 28.3, 22.7, 14.1. HRMS (QTOF): calcd for $C_{20}H_{39}NNaO_4$ $(M+Na)^+$ 380.2777; obs. 380.2802.

4.1.5.4. *tert*-Butyl ((2*R*,3*R*,*E*)-1,3-dihydroxytridec-4-en-2-yl)carbamate 9d. Yield: 77%. $[\alpha]_D = -2.0$ (*c* 0.2, $CHCl_3$). IR (KBr): 3439, 2925, 2854, 1701 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.66–5.73 (m, 1H), 5.45 (dd, *J* = 14.8, 6.4 Hz, 1H), 5.31 (d, *J* = 8.0 Hz, 1H), 4.22–4.23 (br s, 1H), 3.85 (dd, *J* = 7.6, 3.2 Hz, 1H), 3.54–3.69 (m, 2H), 3.13 (br s, 2H), 1.95–1.99 (m, 2H), 1.38 (br s, 9H), 1.19 (br s, 11H), 0.80 (t, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.3, 134.1, 128.9, 79.8, 74.6, 64.1, 62.5, 54.4, 32.3, 31.8, 29.7, 29.4, 29.3, 29.2, 29.1, 28.4, 22.6, 14.1. HRMS (QTOF): calcd for $C_{18}H_{35}NO_4$ $(M)^+$ 329.2566; obs. 329.2604.

4.1.6. General procedure for the preparation of triacetate derivative

A solution of diol **9a** (25 mg, 0.06 mmol) in a mixture of MeOH (5 mL) and 3 (M) HCl (5 mL) was heated at 50 °C for 3 h. The resulting solution was allowed to return to rt and then concentrated under reduced pressure to afford the hydrochloride salt of the corresponding amino alcohol as a foam. The crude residue was dissolved in dry pyridine (5 mL), and a catalytic amount of DMAP and acetic anhydride (0.1 mL) were added to it. The reaction mixture was allowed to stir at room temperature for 12 h. It was then diluted with ethyl acetate (25 mL), washed with HCl (1 M, 2 × 20 mL), water (20 mL), brine (25 mL), and then dried ($MgSO_4$). It was then filtered and the filtrate was evaporated in vacuo to afford a residue, which was purified by chromatography over silica gel using a mixture (1:1) of ethyl acetate and petroleum ether to obtain compound **10a** (21 mg, 79%) as a colourless solid.

4.1.6.1. (2*S*,3*R*,*E*)-2-Acetamidooctadec-4-ene-1,3-diyl diacetate 10a. $[\alpha]_D = -13.2$ (*c* 1.2, $CHCl_3$), Lit.[4d] $[\alpha]_D = -12.0$ (*c* 1.0, $CHCl_3$). IR (KBr): 2921, 2850, 1736, 1692 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.67–5.75 (m, 2 H); 5.32 (dd, *J* = 14.8, 7.6 Hz, 1H), 5.21 (t, *J* = 7.2 Hz, 1H), 4,33–4.39 (m, 1H), 4.22 (dd, *J* = 9.8, 6.0 Hz, 1H), 3.97 (dd, *J* = 11.0, 4.0 Hz, 1H), 2.00 (s, 3H) 1.99 (s, 3H), 1.91 (s, 3H), 1.18–1.27 (br s, 24H), 0.81 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 170.0, 169.8, 137.5, 124.1, 73.9, 62.6, 50.6, 32.3, 31.9, 29.7, 29.6, 29.5, 29.4, 29.2, 28.9, 23.3, 22.7,

21.1, 20.8, 14.1. HRMS (QTOF): calcd for $C_{24}H_{43}NNaO_5$ $(M+Na)^+$ 448.3039; obs 448.3002.

4.1.6.2. (2*S*,3*R*,*E*)-2-Acetamidohexadec-4-ene-1,3-diyl diacetate 10b. Colourless solid. Yield: 76%. $[\alpha]_D = -12.7$ (*c* 1.2, $CHCl_3$), Lit.[15g] $[\alpha]_D = -12.3$ (*c* 0.3). IR (KBr): 2920, 2850, 1736, 1655 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.75–5.68 (m, 2H), 5.32 (dd, *J* = 14.0, 6.4 Hz, 1H), 5.21 (t, *J* = 6.0 Hz, 1H), 4,38–4.33 (m, 1H), 4.22 (dd, *J* = 10.2, 6.0 Hz, 1H), 3.97 (dd, *J* = 11.6, 4.0 Hz, 1H), 2.00 (s, 3H), 1.99 (s, 3H), 1.91 (s, 3H), 1.18 (br s, 20H), 0.81 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 170.1, 169.7, 137.4, 124.1, 73.8, 62.5, 50.6, 32.2, 31.9, 29.6, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 28.9, 23.3, 23.2, 22.6, 21.1, 20.8, 14.1. HRMS (QTOF): calcd for $C_{22}H_{39}NNaO_5$ $(M+Na)^+$ 420.2726; obs 420.2734.

4.1.6.3. (2*S*,3*R*,*E*)-2-Acetamidopentadec-4-ene-1,3-diyl diacetate 10c. Colourless solid. Yield: 74% yield. $[\alpha]_D = -21.0$ (*c* 0.2, $CHCl_3$). IR (KBr): 2922, 2851, 1736, 1655 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.74–5.69 (m, 1H), 5.62 (d, *J* = 9.2 Hz, 1H), 5.32 (dd, *J* = 12.0, 7.2 Hz, 1H), 5.21 (t, *J* = 7.2 Hz, 1H), 4,38–4.33 (m, 1H), 4.24 (dd, *J* = 11.6, 6.4 Hz, 1H), 3.96 (dd, *J* = 11.4, 4.0 Hz, 1H), 2.00 (s, 3H), 1.99 (s, 3H), 1.91 (s, 3H), 1.18 (br s, 18H), 0.80 (t, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 170.1, 169.8, 137.5, 124.1, 73.8, 62.6, 50.6, 32.3, 31.9, 29.7, 29.6, 29.5, 29.3, 29.2, 28.9, 23.4, 22.7, 20.9, 20.8, 14.1. HRMS (QTOF): calcd for $C_{21}H_{37}NNaO_5$ $(M+Na)^+$ 406.2569; obs. 406.2578.

4.1.6.4. (2*S*,3*R*,*E*)-2-Acetamidotridec-4-ene-1,3-diyl diacetate 10d. Colourless solid. Yield: 69%. $[\alpha]_D = -21.7$ (*c* 0.35, $CHCl_3$). IR (KBr): 2923, 2852, 1736, 1656 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.75–5.68 (m, 1H), 5.65 (d, *J* = 9.2 Hz, 1H), 5.32 (dd, *J* = 14.8, 7.2 Hz, 1H), 5.20 (t, *J* = 6.4 Hz, 1H), 4.38–4.33 (m, 1H), 4.23 (dd, *J* = 11.2, 5.6 Hz, 1H), 3.97 (dd, *J* = 11.2, 3.6 Hz, 1H), 2.01 (s, 3H), 1.99 (s, 3H), 1.92 (s, 3H), 1.18 (br s, 13H), 0.81 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 169.5, 169.3, 136.9, 123.6, 73.3, 62.1, 50.1, 31.8, 31.3, 29.2, 28.9, 28.8, 28.7, 28.4, 22.9, 22.2, 20.7, 20.4, 13.6. HRMS (QTOF): calcd for $C_{19}H_{33}NNaO_5$ $(M+Na)^+$ 378.2256; obs. 378.2266.

Acknowledgements

We are thankful to CSIR (Govt. of India) and University of Kalyani for funds and UGC, New Delhi, for a post-doctoral fellowship to one of us (A.G.).

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