Tetrahedron 69 (2013) 1881–1896

Contents lists available at SciVerse ScienceDirect

Tetrahedron

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

Metal-mediated alkynediol cycloisomerization: first and second generation formal total syntheses of didemniserinolipid B

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ARTICLE INFO

Article history:
Received 3 October 2012
Received in revised form 14 December 2012
Accepted 20 December 2012
Available online 29 December 2012

Keywords:
Alkynol-cycloisomerization
Bicyclic ketal
Palladium catalysis
Gold catalysis
Zipper reaction

ABSTRACT

A formal total synthesis of didemniserinolipid B was developed by employing a regioselective metal-mediated 6-*endo*-dig alkynol-cycloisomerization reaction. Two routes for the synthesis of key Burke's intermediate have been developed. Our initial approach involved the introduction of a C_{17}-alkynol followed by Pd-mediated cycloisomerization and then coupling with the serinol unit prior to the introduction of an α,β-unsaturated ester unit through selective oxidation of 1°-OH followed by a two-carbon Wittig homologation. Alternatively, the second generation strategy featuring the serinol coupling with the C_{17}-alkynol followed by alkyne addition to the epoxide and subsequent Au-mediated cycloisomerization of an acetonide protected alkynediol unit has been executed. This approach has avoided several late stage protection–deprotection events.

1. Introduction

Bicyclic ketal, a common structural unit present in many natural products has received substantial synthetic *attention* in *recent* years, due to the isolation of several new natural products having a bicyclic ketal unit as an integral part of their structures and the diverse biological activities reported such as anti-fungal, anti-cancer, and anti-HIV.[1] An intramolecular acetal formation from a suitable keto-diol is a commonly employed method used for the construction of the bicyclic ketal core.[2] The synthesis of a bicyclic ketal through cycloisomerization of ω-alkynediols reported initially using a Pd-complex by Utimoto,[3] has caught the attention of several groups in recent years and various transition metals like palladium, silver, gold, platinum, iridium, and mercury have been employed as catalysts for this key transformation.[4,5] In recent years, the metal-mediated alkynediol cycloisomerization has been used as one of the key skeletal construct in the synthesis of complex natural products.[6] The key issue in these cycloisomerization reactions is the mode of cyclization i.e. *exo*-dig versus *endo*-dig.[5t,7,8] In order to address the regioselectivity issues, a systematic investigation dealing with the influence of electronic and steric factors over competitive 5-*exo*-dig versus 6-*endo*-dig cyclizations and over the 6-*exo*-dig versus 7-*endo*-dig modes of cyclizations mediated by $Pd[CH_3CN]_2Cl_2$ complex has been carried out by our group.[5t,8] In case of competitive 5-*exo*-dig versus 6-*endo*-dig cyclizations these investigations have revealed that the regioselectivity of the cyclization was in line with electronic control.[5t] However, in case of competitive 6-*exo*-dig versus 7-*endo*-dig cyclizations, a complete 6-*exo*-dig selectivity without any electronic interference has been observed.[8b] Based on these findings, we have recently documented the total synthesis of cephalosporolides E and F,[6d] a formal total synthesis of didemniserinolipid B,[6e] and the central 6,8-dioxabicyclo[3,2,1]octane core of cyclodidemniserinol trisufate[6f] featuring selective 5-*exo*-dig, 6-*endo*-dig, and 6-*exo*-dig alkynol cyclization, respectively. In our previous communication, dealing with the didemniserinolipid B (**1**), we synthesized the key Burke's intermediate **2**.[6e] The assembly of the central carbon skeleton has been addressed by employing alkyne–epoxide coupling and the serniol unit has been appended after the construction of the key bicyclic ketal (via a regioselective Pd-mediated alkynol-cycloisomerization of an alkyne triol). Herein, we provide the complete details of our basic investigations related to the acyclic stereocontrol over the regiochemistry of these cyclizations, which ultimately led us to arrive at the designing of the key alkyne triol that has served as the advanced intermediate in our formal total synthesis of didemniserinolipid B (**1**) and we also provide details of two closely related approaches for the formal total syntheses of didemniseriniolipid B.

Didemniserinolipids A–C (Fig. 1) were isolated in 1999 by González et al. from the methanol extract of *didemnum* sp., with the aim of finding new cytotoxic agents against P388, A549, and HT29 tumor cell lines.[9] Didemniseriniolipids are characterized by their

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http://dx.doi.org/10.1016/j.tet.2012.12.045

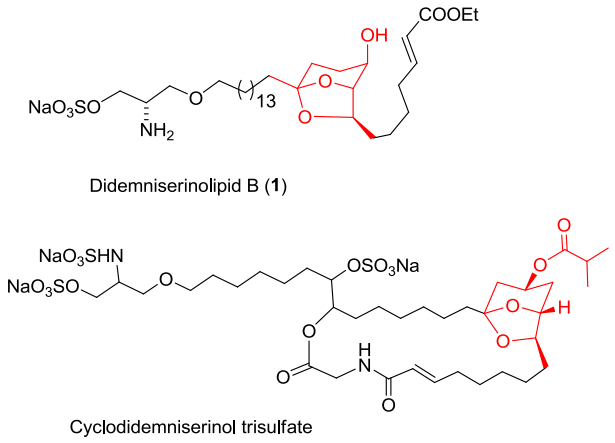


Fig. 1. Structures of didemniserinolipid B and cyclodidemniserinol trisulfate.

unusual serinolipid structure, which has been proposed with the help of extensive NMR analysis. The related macrocycle containing serinolipid cyclodidemniserinol sulfate was subsequently isolated from Palauan ascidian *Didemnum guttatumas* by Faulkner and co-workers and showed promising HIV-integrase inhibitory activity,[10] thus attracting considerable synthetic interest.[11–14] In 2002, Steven Ley's group reported the synthesis of didemniserinolipid B and revised its structure as **1** by amending the stereochemistry of the serinol fragment and they proposed the position of *O*-sulfate at C(31).[11] Later, Burke and co-workers reported the second total synthesis of **1** by employing ketalization and ring closing metathesis as the key strategy for constructing the central bridged bicyclic core.[12]

Our interest in this regard was to extend the synthetic potential of alkynediol cycloisomerization for the construction of the central bicyclic ketal core unit and apply it in the total synthesis of the didemniserinolipids. The key features of our retro synthesis are depicted in Fig. 2. The target molecule has been visualized from **2**, a key protected derivative of **1** that has been synthesized by Burke and co-workers.[12] The selective oxidation of the 1°-OH in diol **3** and subsequent two-carbon Wittig homologation has been planned as the final event in the synthesis of **2**. The next disconnection is the ether link that combines the central lipid carbon framework **4** and the serinol unit **5**.

The key bicyclic ketal intermediate **4** was planned by the cycloisomerization of the alkynol **6**. Keeping the knowledge that we acquired with the model cycloisomerization reactions of sugar alkynols in mind, the alkyne group has been positioned favorably for 6-*endo*-*dig* cyclization. Based upon these key disconnections compounds **5**, **6**, and **8** were identified as important coupling partners representing the serinol, the central bicyclic core, and long-chain alcohol portions, respectively. The alkynol **6** can be obtained from the opening of the epoxide **9** with the alkyne **8**.[15] After the stereochemical comparisons, epoxide **9** synthesis was intended from D-mannitol. The synthesis of alkynol **8** has been envisioned from propargyl alcohol via alkylation with the requisite 14-carbon long-chain halide and a subsequent acetylenic Zipper reaction.[16] The synthesis of serinol derivative **5** has been already reported from D-serine.[17] Considering our observations in the synthesis of central bicyclic core of cyclodidemniserinol trisulfate, where we noticed an exclusive 5-*exo*-dig over the 6-*endo*-dig cyclization,[5t] we have initially designed the epimeric alkynols **11**, **13**, and their benzoates **12**, **14** as model substrates in the context of the present total synthesis to learn about the possible acyclic stereocontrol over the regioselectivity of the alkynol-cycloisomerization. The synthesis of **13** and its benzoate **14** was planned from the epoxide **15**, which, in turn, can be made from the penultimate intermediate that has been planned for preparing the original epoxide **9**. In our earlier communication, we documented the details about the synthesis of didemniserinolipid B, featuring the alkynol-cycloisomerization of a free 1,2,3-triol unit. The cycloisomerization is completely selective toward the desired 6-*endo* product even if the spectator homopropargylic –OH (of the 1,2,3-triol) group could possibly participate in a 5-*exo*-dig fashion.[6e]

2. Results and discussion

2.1. Synthesis and cycloisomerization of model substrates 11–14

The synthesis of epoxide **9** started from the known diacetonide **10**[18] by oxidative diol cleavage using $NaIO_4$, subsequent Wittig reaction of the intermediate aldehyde with the ylide generated from the phosphonium salt **A**[19] by using KO^{t}Bu as the base (Scheme 1). The optimized reaction conditions involve the addition of ylide generated in THF to a solution of the aldehyde in ether at 0 °C, which gave the olefin **16** in a *Z*/*E* ratio of 9:1. Hydrogenation of the olefin **16** using Raney-Ni gave the saturated dicetonide **17**. Selective deprotection of the terminal acetonide group using *p*-TSA in MeOH afforded the diol **18** in 80% yield. The diol **18** was transformed to the key epoxide **9** at 83% overall yield following a two-step sequence involving selective tosylation of the primary hydroxyl group using tosyl chloride, dibutyltin oxide, and triethylamine and subsequent treatment of the resulting tosylate **19** with K_2CO_3. The protons attached to the oxirane ring in compound **9** resonated at relatively up-field [δ 2.63 (dd), 2.80 (dd), 2.94 (ddd)] in the ^{1}H NMR spectrum, while a triplet and doublet at 45.1 and 51.5 ppm in the ^{13}C NMR spectrum confirmed the formation of the epoxide. Next, the epimeric epoxide **15** was prepared from **18** following a three-step sequence—i. selective 1°-OH benzoylation, ii. mesylation of the 2°-OH, and subsequent iii. LiOH treatment. After having the epoxides **9** and **15** in hand, we next proceeded for their opening and the preparation of model substrates. Thus, the opening of epoxide **9** with the lithiated 1-heptyne under Yamaguchi conditions[15] gave the alkynol **20**, which, upon acetonide deprotection by using 60% AcOH in water, gave the parent model compound **11**. Protection of the free –OH of **20** as its benzoate **21** followed by acetonide hydrolysis gave the model substrate **12**. Similarly, the opening of the epimeric epoxide **15** through the Yamaguchi protocol afforded the alkynol **24**, which, upon acetonide deprotection, gave the model substrate **13**. The model compound **14** was prepared by the benzoylation of **24** and the acetonide hydrolysis of the resulting benzoate **25**.

The cycloisomerization of model compounds **11**, **12**, **13**, and **14** was carried out under the optimized conditions. The results are given in Scheme 2. In all the cases, the reactions proceeded in a 6-*endo*-dig mode of cyclization and the corresponding [3,2,1]bicyclic ketals were obtained in good yields. These results indicate that the stereochemistry as well as bulkiness of the substituent at the β-position to the alkyne seems to be not having much influence over the regioselectivity of the cycloisomerization. The cyclization of acetonides **20** and **24** having the free alcohol β- to the alkyne is facile and gave the corresponding bicyclic ketals in moderate yields.[20] On the other hand, the benzoates **21** and **25** are intact under similar reaction conditions, which indicate that the acetonide hydrolysis might be facilitated by the presence of an adjacent free-OH (Table 1).

2.2. Synthesis of C_{17}-alkynol fragment 8

Having completed the model studies and established the construction of the requisite bicyclic ketal core with complete

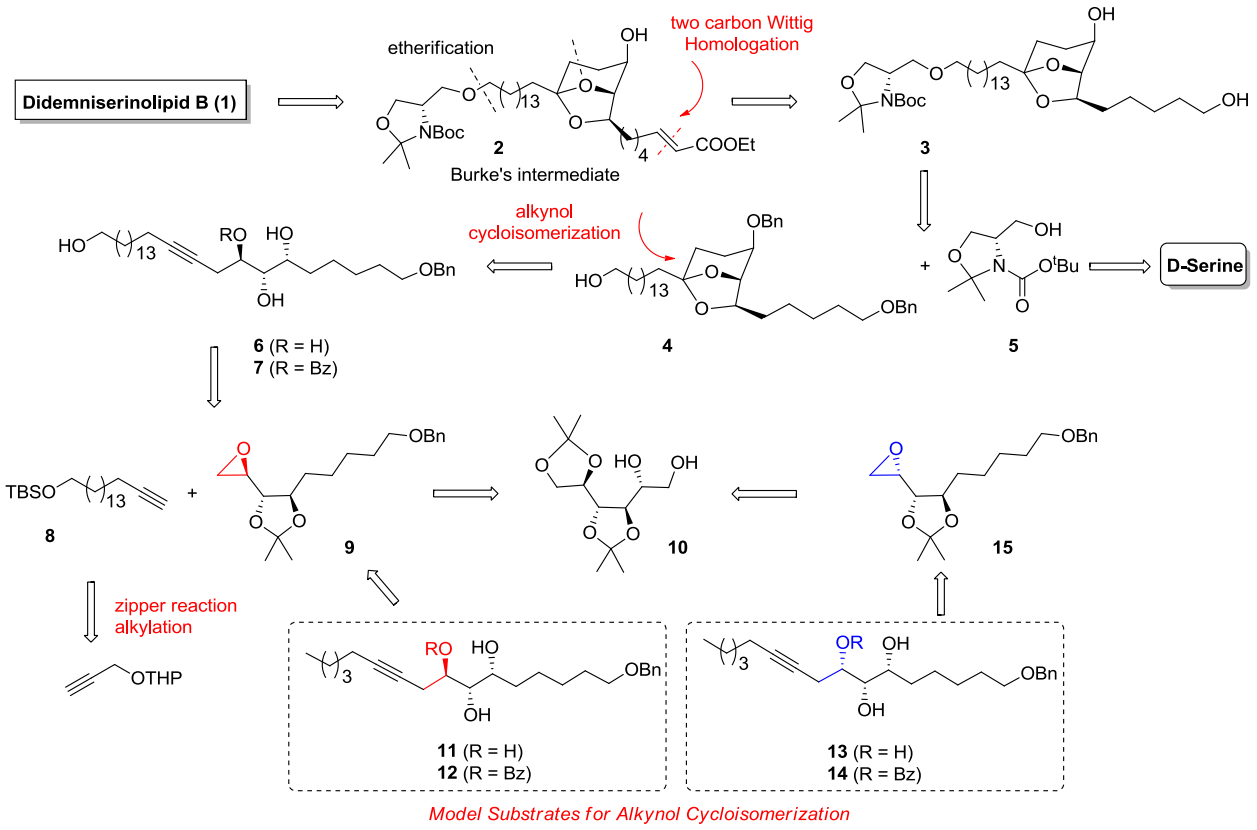


Fig. 2. Retrosynthetic strategy for didemniserinolipid B (**1**) and the model substrates **11**–**14** designed for understanding the acyclic stereocontrol over the regioselectivity of the alkynol cyclization.

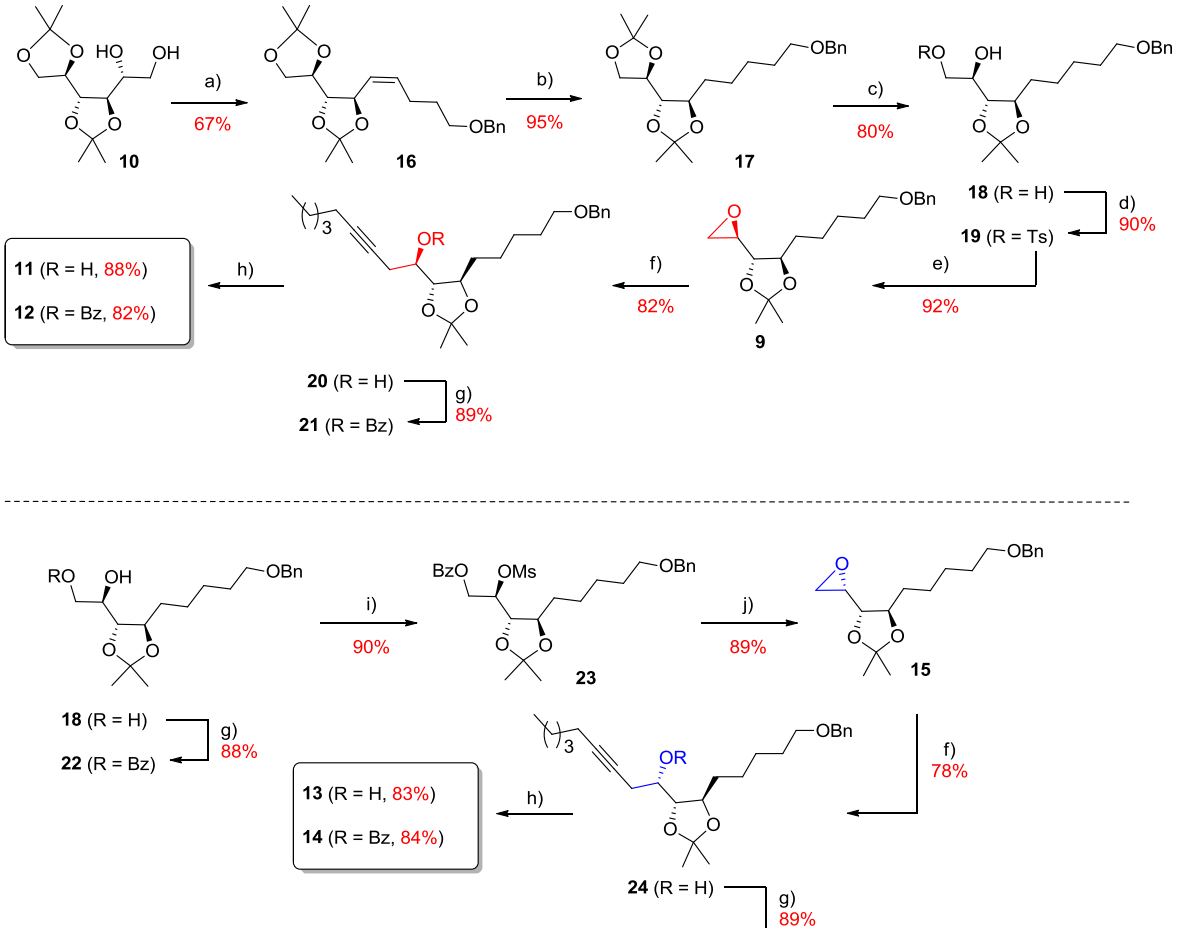
regioselectivity, we next proceeded for the synthesis of C_{17}-alkynol **8**. The acetylenic Zipper reaction[16] that involves the isomerization of an internal alkyne to the terminal alkyne in the presence of a base has been selected in this regard. The known THP ether of propargyl alcohol was alkylated with tetradecyl bromide using *n*-butyl lithium as a base to afford the substituted alkyne **30** (Scheme 3). The deprotection of the THP ether **30** was effected by using *p*-TSA and methanol to afford the alkylated propargyl alcohol **31**. After exploring a variety of bases and reaction conditions (Table 2) we concluded that the isomerization of alcohol **31** to the requisite heptadec-16-yn-1-ol (**32**) could be conducted successfully by employing lithium metal in combination with potassium *tert*-butoxide in 1,3-diaminopropane as the solvent/base.[21] The ^{1}H and ^{13}C NMR spectra of **32** evidenced the presence of terminal acetylene. For example, in the ^{1}H spectrum of **32**, the acetylenic-H resonated as a triplet at 1.88 and the propargylic protons resonated as dt at δ 2.16 ppm. The acetylenic carbons resonated as a doublet and a singlet at 68.2 and 84.6 ppm, respectively, in the ^{13}C NMR spectrum. Subsequently, the free –OH group in compound **32** was protected as its TBS ether to obtain the key fragment **8**.

2.3. First generation formal total synthesis of didemniserinolipid B

The coupling of the oxirane **9** with the alkyne **8** resulted in the formation of homopropargylic alcohol **33**, which was protected as its benzoate **34** (Scheme 4). The hydrolysis of the acetonide group in compounds **33** and **34** using cat. *p*-TSA in methanol afforded the alkynol **6** and its benzoate **7**. The intended cycloisomerization of alkynols **6** and **7** proceeded smoothly with $Pd(CH_3CN)_2Cl_2$ as the catalyst, and afforded, respectively, the bicyclic ketals **35** and **36** in good yield. The constitution of the bicyclic ketal unit present in **36** was investigated with the help of spectral data analysis. In the ^{1}H NMR spectrum of **36**, the three characteristic methine protons of the ketal are present at δ 3.97, 4.28 and 4.89. The protons of the CH_2–CH_2 unit present in the bicyclic ketal were found to resonate separately from the rest of the alkane-H as multiplets at downfield. The presence of the characteristic ketal carbon at 109.4 ppm in the ^{13}C NMR spectrum and two CH_2s as triplets separately in the downfield at 35.1 and 37.8 ppm indicated the presence of a [3.2.1] bicyclic ketal. Similarly, in the ^{1}H NMR spectrum of **35**, the three characteristic methine protons of the bicyclic ketal resonated at δ 3.58, 3.86, 4.04 ppm and in the ^{13}C NMR spectrum a singlet corresponding to the ketal carbon at 109.5 ppm and the two triplets corresponding to ring CH_2 at 35.2 and 37.5 ppm were seen. Selective protections of the 1°-OH in compound **35** as its TBS ether **37** followed by the benzylation of 2°-OH and subsequent deprotection of the silyl group in resulting **38** gave the key bicyclic ketal fragment **4**.

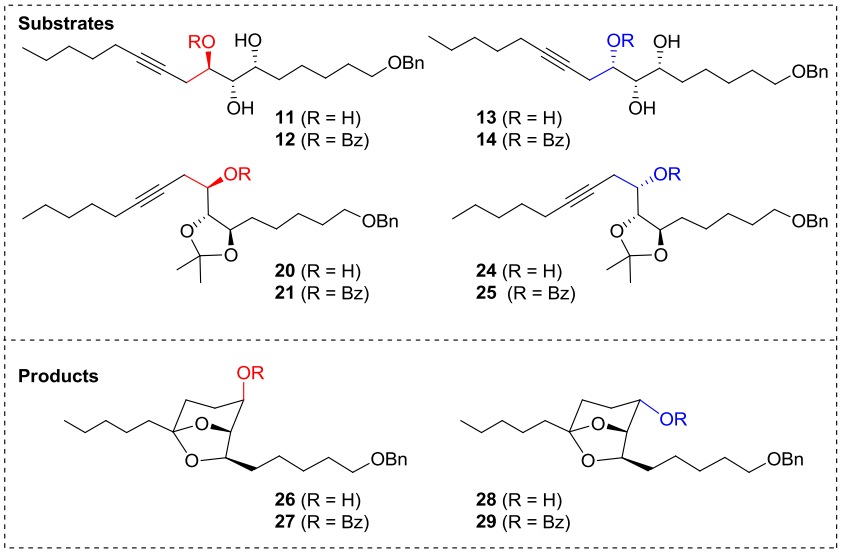
Burke's group has earlier showed that the serinol coupling was effective with the mesylate of the bicyclic ketal and the serinol **5** using sodium hydride as the base, and importantly with DMSO as solvent. Accordingly, compound **4** was subjected for mesylation to obtain the key mesylate **39**. The coupling of the mesylate **39** with the serinol **5** needs a special mention (Scheme 5).[12] The control of the reaction temperature during the addition has substantial influence on the outcome of the reaction. When the reaction was conducted below 0 °C, the required ether **40** was obtained in 65% yield along with an unidentified mixture of products comprising an olefin, probably obtained by demesylation. However, when the temperature was above 0 °C, the elimination of mesylate was the major event.

Having executed the key cycloisomerization and serinol coupling events successfully, our next concern was the two-carbon



Scheme 1. *Reagents and conditions*: (a) *i*. $NaIO_4$, CH_2Cl_2/H_2O (9:1), 0 °C→rt, 4 h; *ii*. $BnOC_4H_8PPh_3I$, KOtBu, THF, 0 °C, 2 h; (b) Raney-Ni, H_2, EtOH, rt, 30 min; (c) cat. *p*-TSA, MeOH, 0 °C, 20 h; (d) TsCl, Et_3N, cat. Bu_2SnO, cat. DMAP, CH_2Cl_2, 0 °C→rt, 4 h; (e) K_2CO_3, MeOH, 0 °C, 1 h; (f) hept-1-yne, *n*-BuLi, THF, $BF_3{\cdot}Et_2O$, −78 °C, 1 h; (g) BzCl, Et_3N, CH_2Cl_2, 0 °C→rt, 2 h; (h) 60% AcOH, 85 °C, 4 h; (i) MsCl, Et_3N, CH_2Cl_2, 0 °C→rt, 4 h; (j) LiOH, MeOH/THF (1:1), rt, 4 h.

homologation. Compound **40** was subjected to debenzylation to afford the diol **3**. The diol **3** was oxidized selectively to the aldehyde using DMP as the oxidizing agent and the resulting aldehyde was used as such for the next step without further purification.[22] The Wittig olefination of the intermediate aldehyde using the stable ylide $Ph_3P{=}CHCO_2Et$ in refluxing benzene afforded the desired α,β-unsaturated ester **2**. The ^1H NMR spectrum revealed the presence of the olefinic protons at δ 5.80 (d) and 6.94 (dt) with a coupling



Scheme 2. Cycloisomerization of model substrates.

Table 1
Pd-mediated cycloisomerization of alkynediols and their acetonides conditions: 5 mol% $Pd[CH_3CN]_2$, CH_3CN, rt, 2–6 h

Entry	Substrate	Product	Yield (%)
1	**11**	**26**	67
2	**12**	**27**	80
3	**13**	**28**	81
4	**14**	**29**	73
5	**20**	**26**	65
6	**21**	—	—
7	**24**	**28**	71
8	**25**	—	—

constant of 15.6 Hz indicative of a trans double bond. Also, the quartet at δ 4.17 was suggestive of the methylene group of the ethyl ester. The ^{13}C NMR spectrum showed doublets at 121.5 and 148.9 ppm corresponding to the olefinic carbons and the ester carbonyl resonated at 166.7 ppm. All other data were in total agreement with the reported values by the Burke group. The specific rotation of the synthetic sample was found to be $[\alpha]_D^{25}$ +24.6 (*c* 0.5, $CHCl_3$) [lit.[12] $[\alpha]_D^{25}$ +37.6 (*c* 0.98, $CHCl_3$)].

2.4. Second generation formal total synthesis of didemniserinolipid B

Next, to make the synthetic scheme more convergent, to provide the step-economy, and to demonstrate the substrate flexibility, we have devised an alternative strategy (Fig. 3) featuring the serinol coupling with the C_{17}-alkynol followed by alkyne addition to the epoxide and subsequent cycloisomerization of the resulting acetonide **41**. This approach should thus avoid the several intermediate protection–deprotection events.

The execution of the second generation strategy started with the preparation of mesylate **43** by treatment of alkynol **32** with mesyl chloride and triethylamine in dichloromethane (Scheme 6). The coupling of the mesylate **43** and the serinol **5** proceeded smoothly to provide the key alkyne **42** in 71% yield. The addition of alkyne **42** to epoxide **9** was carried out under established conditions to obtain the key cycloisomerization substrate **41** in 71% yield. The cycloisomerization of **41** needed substantial catalyst optimization. Under the standard conditions using the $Pd[CH_3CN]_2Cl_2$ complex, a complex mixture resulting from the formation of requisite bicyclic ketal, corresponding ketone, along with the deprotection of the acetonide group present in the serinol unit was noticed. Pd $[PhCN]_2Cl_2$ was found to be ineffective for this transformation. Next, various electrophilic [Au]-complexes such as $AuCl_3$, $AuBr_3$, and $Au(PPh_3)_3Cl$ have been screened for the cycloisomerization of **41**.[23] To this end, the best results were obtained when $Au(PPh_3)_3Cl$ (5 mol %) was employed in combination with $AgSbSF_6$ (5 mol %) in CH_2Cl_2. With this catalyst combination, the cycloisomerization of **41** gave compound **44** (in 85% yield) resulting from the requisite cycloisomerization followed by the deprotection of serinol acetonide.[23c] Initially, to provide alternative final events in the total synthesis, we converted compound **44** to the corresponding diacetate **45** and subsequently carried out its debenzylation. The oxidation of the resulting alcohol **46** and Wittig homologation gave **47**. However, the deacetylation of compound **47** has turned out to be a difficult proposition. In this context, the intermediate ketal **44** was subjected for the acetonide protection to obtain compound **48**, which subsequently transformed to **2** following the established three-step sequence—i. debenzylation, ii. oxidation, and iii. Wittig homologation.

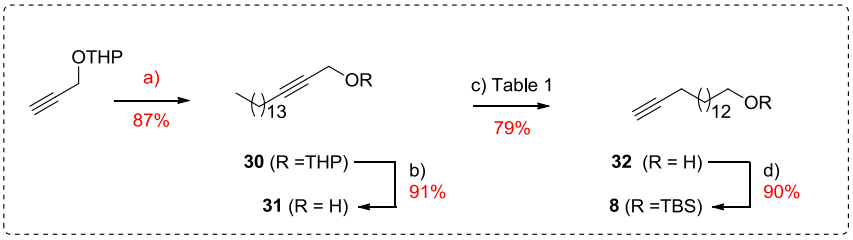
3. Conclusions

To conclude, a formal total synthesis of didemniserinolipid B was developed by employing a highly regioselective metal-mediated 6-*endo*-dig alkynol-cycloisomerization reaction. The Pd-mediated cycloisomerization of model alkynols revealed that the regioselectivity of the alkynol-cycloisomerization was not influenced by stereochemistry and the protecting group present on the homopropargylic –OH. Two routes for the synthesis of the key Burke's intermediate have been developed. The first approach features a sequential coupling of epoxide and alkyne followed by cycloisomerization and then serinol coupling. Whereas in the second approach, the alkynol and serinol are coupled prior to the epoxide alkyne coupling and subsequent alkynol-cycloisomerization. The later approach is characterized by its modular nature and avoided several protection–deprotection events. Thus, the strategy reported here is characterized by flexibility at different stages and has the potential to synthesize didemniserinolipid analogs by incorporating changes at either end of the chain.

4. Experimental

4.1. General methods

All solvents were dried according to the standard methods prior to use. Commercial reagents were used without purification. Column chromatography was carried out by using spectrochem silica gel (60–120, 100–200, 230–400 mesh). ^1H and ^{13}C NMR spectroscopy measurements were carried out on Bruker AC 200 MHz or Bruker DRX 400 and Bruker DRX 500 MHz spectrometers, and TMS was used as an internal standard. ^1H and ^{13}C NMR chemical shifts are reported in parts per million (ppm) downfield from chloroform-*d* (δ=7.25) or TMS and coupling constants (*J*) are reported in hertz (Hz). The following abbreviations are used to designate signal multiplicity: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, b=broad. The multiplicity of ^{13}C NMR signals was assigned with the help of DEPT spectra and the abbreviations used: s=singlet, d=doublet, t=triplet, q=quartet, represent C (quaternary), CH, CH_2, and CH_3, respectively. The LCMS and HRMS mass spectra were taken in a Hybrid Quadruple–TOF LC/MS and MALDI-TOF, respectively. Elemental analysis data were obtained on a Thermo Finnigan Flash EA 1112 Series CHNS Analyzer.



Scheme 3. Reagents and conditions: (a) *n*-BuLi, HMPA, *n*-$C_{14}H_{29}Br$, THF, –10 °C, 1 h; (b) cat. *p*-TSA, MeOH, rt, 1h; (c) Li, KO^{t}Bu, 1,3-diaminopropane, 0 °C→rt, 1 h; (d) TBSCl, CH_2Cl_2, Et_3N, 0 °C, 1 h.

Table 2
Conditions explored for the Zipper reaction

Entry	Reaction conditions	Results obtained
1	KH, 1,3-diaminopropane, 0 °C→rt	<5% Conversion
2	KO^{t}Bu, DMSO, rt	Starting material recovered
3	Na, liq. NH_3, −78 °C	Starting material recovered
4	Li, liq. NH_3, −78 °C	Starting material recovered
5	KO^{t}Bu, DMSO, 80 °C	Starting material recovered
6	Li, KO^{t}Bu, 1,3-diaminopropane, rt	Isomerization with 79% yield

4.2. (4*S*,4′*R*,5*R*)-5-((*Z*)-5-(Benzyloxy)pent-1-enyl)-2,2,2′,2′-tetramethyl-4,4′-bi(1,3-dioxolane) (16)

At 0 °C, a solution of the aldehyde (4.0 g, 17.4 mmol) in ether (20 mL) was treated with a solution of the ylide [generated from $BnO(CH_2)_4P^+Ph_3I^-$ (28.8 g, 52.2 mmol) using KO^{t}Bu (4.9 g, 43.5 mmol) in THF (50 mL) at 0 °C] and stirred for 30 min. The reaction mixture was quenched with saturated NH_4Cl (25 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2×25 mL). The combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated. Purification of the crude product by column chromatography (90:10 petroleum ether/EtOAc) gave **16** (4.4 g, 67%) as colorless syrup: R_f (10% EtOAc/petroleum ether) 0.5; $[\alpha]_D^{25}$ +10.7 (*c* 1.3, $CHCl_3$); IR ($CHCl_3$) ν: 2986, 1448, 1243, 1048, 847, 634, 467 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.31 (s, 3H), 1.36 (s, 3H), 1.38 (s, 3H), 1.41 (s, 3H), 1.67–1.75 (m, 2H), 2.22–2.31 (m, 2H), 3.48 (t, *J*=6.4 Hz, 2H), 3.70 (dd, *J*=6.4, 7.6 Hz, 1H), 3.89–3.95 (m, 1H), 4.01–4.10 (m, 2H), 4.50 (s, 2H), 4.68 (ddd, *J*=0.7, 7.6, 8.7 Hz, 1H), 5.42 (tt, *J*=1.5, 10.7 Hz, 1H), 5.64 (tt, *J*=7.7, 10.9 Hz, 1H), 7.27–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 24.4 (t), 25.2 (q), 26.6 (q), 26.9 (q), 27.2 (q), 29.3 (t), 66.8 (t), 69.5 (t), 72.8 (t), 74.9 (d), 76.3 (d), 81.1 (d), 109.2 (s), 109.4 (s), 127.4 (d, 2C), 127.5 (d, 2C), 128.3 (d, 2C), 134.9 (d), 138.5 (s) ppm; MS (ESI) *m*/*z*=399 $[M+Na]^+$; HRMS (ESI) calcd for $C_{22}H_{32}O_5Na$ $[M+Na]^+$ 399.2147, found 399.2148.

4.3. (4*S*,4′*R*,5*R*)-5-(5-(Benzyloxy)pentyl)-2,2,2′,2′-tetramethyl-4,4′-bi(1,3-dioxolane) (17)

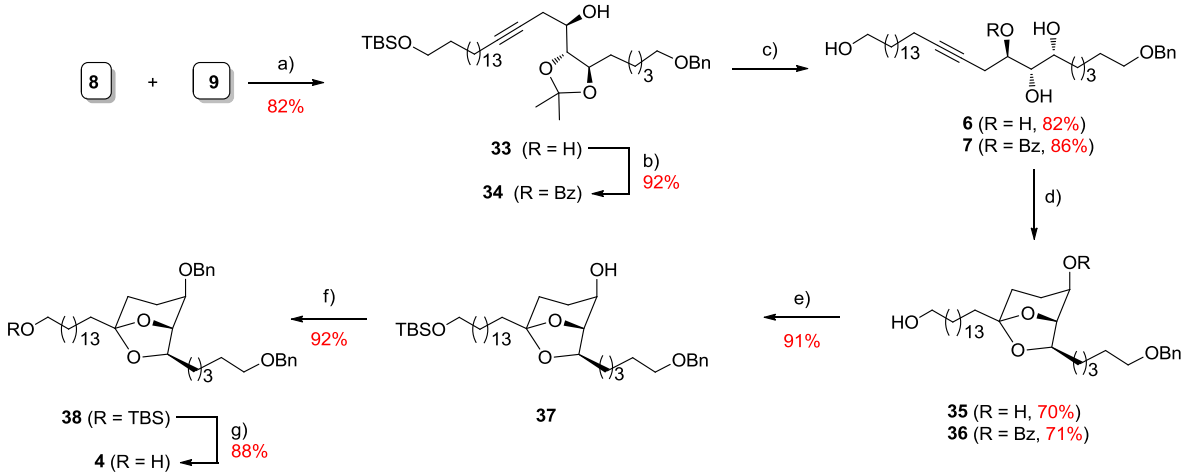
A suspension of the diacetonide **16** (2.1 g, 5.6 mmol), Raney-Ni (50 mg) in ethanol (20 mL) was flushed with hydrogen gas and stirred under hydrogen (20 psi) atmosphere for 30 min. The reaction mixture was filtered through Celite, concentrated, and the crude product was purified by column chromatography (90:10 petroleum ether/EtOAc) to procure **17** (2.0 g, 95%) as colorless syrup: R_f (10% EtOAc/petroleum ether) 0.52; $[\alpha]_D^{25}$ +18.7 (*c* 0.6, $CHCl_3$); IR ($CHCl_3$) ν: 3018, 1496, 1372, 1216, 1064, 758, 668 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.32 (s, 6H), 1.36 (s, 3H), 1.38 (s, 3H), 1.41–1.72 (m, 8H), 3.45 (t, *J*=6.4 Hz, 2H), 3.45 (t, *J*=7.7 Hz, 1H), 3.82–4.12 (m, 4H), 4.48 (s, 2H), 7.21–7.32 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 25.4 (q), 26.0 (t), 26.3 (t), 26.8 (q), 27.1 (q), 27.4 (q), 29.7 (t), 33.7 (t), 67.7 (t), 70.3 (t), 72.8 (t), 77.3 (d), 80.5 (d), 81.2 (d), 108.7 (s), 109.5 (s), 127.4 (d), 127.6 (d, 2C), 128.3 (d, 2C), 138.6 (s) ppm; MS (ESI) *m*/*z*=401 $[M+Na]^+$; HRMS (ESI) calcd for $C_{22}H_{34}O_5Na$ $[M+Na]^+$ 401.2304, found 401.2271.

4.4. (*R*)-1-((4*R*,5*R*)-5-(5-(Benzyloxy)pentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethane-1,2-diol (18)

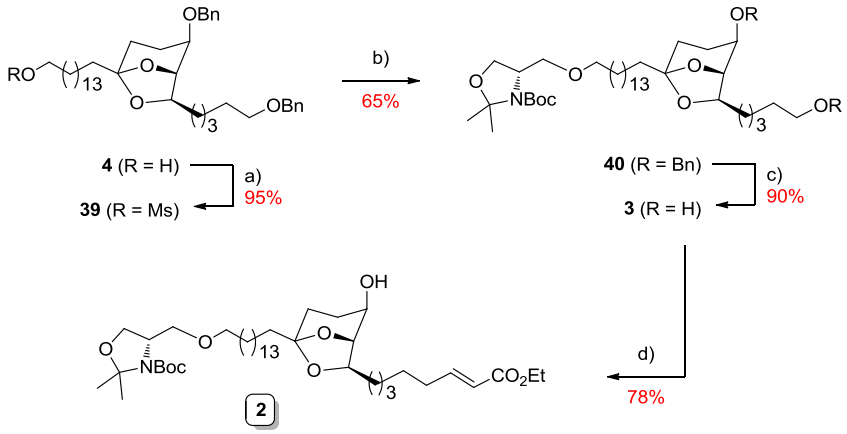
To a solution of the diacetonide **17** (1.4 g, 3.7 mmol) in MeOH (10 mL), catalytic *p*-TSA (5 mg, 0.03 mmol) was added and the reaction mixture was stirred at 0 °C for 20 h. The reaction mixture was quenched by the addition of few drops of triethylamine and the solvent was evaporated. The crude residue was purified by column chromatography (65:35 petroleum ether/EtOAc) to obtain **18** (1.0 g, 80%) as a colorless oil: R_f (50% EtOAc/petroleum ether) 0.3; $[\alpha]_D^{25}$ +30.8 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) ν: 3433, 2936, 1415, 1373, 1216, 1069, 759, 669 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.35 (s, 3H), 1.37 (s, 3H), 1.40–1.49 (m, 2H), 1.45 (br s, 1H), 1.56–1.69 (m, 5H), 2.16 (br s, 1H), 2.53 (d, *J*=4.0 Hz, 1H), 3.45 (t, *J*=6.4 Hz, 2H), 3.57–3.78 (m, 4H), 3.92 (dt, *J*=3.5, 7.7 Hz, 1H), 4.48 (s, 2H), 7.24–7.33 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 25.9 (t), 26.0 (t), 27.0 (q), 27.3 (q), 29.5 (t), 33.9 (t), 63.8 (t), 70.2 (t), 72.7 (d), 72.7 (t), 79.3 (d), 80.8 (d), 108.6 (s), 127.4 (d), 127.5 (d, 2C), 128.2 (d, 2C), 138.4 (s) ppm; MS (ESI) *m*/*z*=361 $[M+Na]^+$; HRMS (ESI) calcd for $C_{19}H_{30}O_5Na$ $[M+Na]^+$ 361.1991, found 361.1972.

4.5. (*R*)-2-((4*R*,5*R*)-5-(5-(Benzyloxy)pentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-hydroxyethyl 4-methyl-benzenesulfonate (19)

To an ice-cooled solution of the diol **18** (500 mg, 1.48 mmol) in CH_2Cl_2 (15 mL), were added Bu_2SnO (10 mg), DMAP (10 mg), and Et_3N (0.3 mL, 2.22 mmol) and stirred for 0.5 h at rt. The reaction mixture was cooled to 0 °C and treated with *p*-TsCl (280 mg, 1.48 mmol) and stirring was continued for 4 h at rt. Solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (80:20 petroleum ether/EtOAc) to yield **19** (655 mg, 90%) as colorless syrup: R_f (30% EtOAc/petroleum



Scheme 4. Reagents and conditions: (a) *n*-BuLi, $BF_3{\cdot}Et_2O$, THF, −78 °C, 1 h; (b) BzCl, Et_3N, CH_2Cl_2, 0 °C, 2 h; (c) cat. *p*-TSA, MeOH, rt, 1 h; (d) 5 mol % $Pd(CH_3CN)_2Cl_2$, CH_3CN, rt, 2 h; (e) TBSCl, NEt_3, CH_2Cl_2, 0 °C, 2 h; (f) BnBr, NaH, THF, 0 °C, 1 h (g) cat. *p*-TSA, MeOH, rt, 30 min.



Scheme 5. Reagents and conditions: (a) MsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h; (b) **5**, NaH, DMSO, 0 °C→rt, 16 h; c) cat. 20% $Pd(OH)_2$, EtOAc, H_2 (1 atm), rt, 30 min; (d) *i*. DMP, CH_2Cl_2, 0 °C→rt, 6 h; *ii*. $Ph_3P{=}CHCO_2Et$, benzene, reflux, 1 h.

ether) 0.46; $[\alpha]_D^{25}$ +33.0 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) ν: 3434, 2984, 1560, 1375, 1247, 1047, 757, 668 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.28 (s, 3H), 1.32 (s, 3H), 1.35–1.44 (m, 3H), 1.48–1.69 (m, 5H), 2.45 (s, 3H), 2.47 (br s, 1H), 3.45 (t, *J*=6.4 Hz, 2H), 3.48 (t, *J*=3.4 Hz, 1H), 3.72–3.83 (m, 1H), 3.91 (dd, *J*=3.2, 7.4 Hz, 1H), 4.01 (dd, *J*=6.9, 10.5 Hz, 1H), 4.25 (dd, *J*=2.8, 10.5 Hz, 1H), 4.48 (s, 2H), 7.23–7.32 (m, 5H), 7.34 (d, *J*=8.2 Hz, 2H), 7.79 (d, *J*=8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 21.7 (q), 25.9 (t), 26.1 (t), 27.0 (q), 27.4 (q), 29.6 (t), 34.0 (t), 70.3 (t), 71.5 (d), 72.1 (t), 72.8 (t), 79.4 (d), 80.1 (d), 109.9 (s), 127.5 (d), 127.6 (d, 2C), 128.1 (d, 2C), 128.3 (d, 2C), 129.9 (d, 2C), 132.7 (s), 138.6 (s), 144.9 (s) ppm; MS (ESI) *m*/*z*=515 $[M+Na]^+$. Anal. calcd for $C_{26}H_{36}O_7S$: C, 63.39; H, 7.37; S, 6.51%, found C, 63.28; H, 7.20; S, 6.12%.

4.6. (4*R*,5*S*)-4-(5-(Benzyloxy)pentyl)-2,2-dimethyl-5-((*R*)-oxiran-2-yl)-1,3-dioxolane (9)

A suspension of the tosylate **19** (500 mg, 1.02 mmol) and K_2CO_3 (210 mg, 1.52 mmol) in MeOH (10 mL) was stirred at 0 °C under argon atmosphere for 1 h. The reaction mixture was filtered, concentrated, and the residue was purified by silica gel chromatography (80:20 petroleum ether/EtOAc) to obtain **9** (300 mg, 92%) as colorless oil: R_f (30% EtOAc/petroleum ether) 0.5; $[\alpha]_D^{25}$ +4.5 (*c* 1.2, $CHCl_3$); IR ($CHCl_3$) ν: 2937, 2861, 1455, 1371, 1217, 1099, 876, 756, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.40 (s, 6H), 1.42–1.53 (m, 3H), 1.57–1.71 (m, 5H), 2.64 (dd, *J*=2.5, 5.0 Hz, 1H), 2.80 (dd, *J*=3.9, 5.0 Hz, 1H), 2.95 (ddd, *J*=2.5, 3.9, 6.3 Hz, 1H), 3.28 (dd, *J*=6.3, 7.8 Hz, 1H), 3.47 (t, *J*=6.5 Hz, 2H), 3.96 (dt, *J*=4.7, 7.8 Hz, 1H), 4.49 (s, 2H), 7.22–7.34 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 25.6 (t), 26.1 (t), 26.6 (q), 27.1 (q), 29.5 (t), 33.1 (t), 45.1 (t), 51.5 (d), 70.2 (t), 72.7 (t), 79.5 (d), 81.1 (d), 109.0 (s), 127.4 (d), 127.5 (d, 2C), 128.2 (d, 2C), 138.6 (s) ppm; MS (ESI) *m*/*z*=343 $[M+Na]^+$; HRMS (ESI) calcd for $C_{19}H_{28}O_4Na$ $[M+Na]^+$ 343.1886, found 343.1860.

4.7. (*R*)-2-((4*R*,5*R*)-5-(5-(Benzyloxy)pentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-hydroxyethyl benzoate (22)

At 0 °C, to a cooled solution of the diol **18** (4 g, 11.8 mmol) in CH_2Cl_2 (50 mL), Bu_2SnO (50 mg), DMAP (50 mg), and Et_3N (5 mL, 35.5 mmol) were added and stirred for 30 min at the same temperature. To this, benzoyl chloride (1.51 mL, 13.0 mmol) was added dropwise and the reaction mixture was further stirred for 8 h while warming to rt. Reaction mixture was poured into water (25 mL) and the aqueous layer was extracted with CH_2Cl_2 (2×25 mL). Combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated under reduce pressure. The residue was purified by column chromatography (85:15 petroleum ether/EtOAc) to obtain **22** (4.6 g, 88%) as colorless syrup: R_f (10% EtOAc/petroleum ether) 0.46; $[\alpha]_D^{25}$ +36.0 (*c* 3.1, $CHCl_3$); IR ($CHCl_3$) ν: 3444, 3019, 1719, 1372, 1276, 1215, 1047, 758, 668 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz):δ 1.39 (s, 3H), 1.4 (s, 3H), 1.45–1.79 (m, 8H), 2.93 (br s, 1H), 3.45 (t, *J*=6.6 Hz, 2H), 3.69 (t, *J*=7 Hz, 1H), 3.91–4.1 (m, 2H), 4.39 (dd, *J*=6.6, 11.8 Hz, 1H), 4.48 (s, 2H), 4.58 (dd, *J*=3.2, 11.8 Hz, 1H), 7.23–7.32 (m, 5H), 7.34 (d, *J*=8.2 Hz, 2H), 7.57 (tt, *J*=1.4, 6.1 Hz, 1H), 7.79 (d, *J*=8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 25.9 (t), 26.1 (t), 27.0 (q), 27.4 (q), 29.5 (t), 34.1 (t), 66.8 (t), 70.3 (t), 71.6 (d), 72.8 (t), 79.3 (d), 80.3 (d), 108.9 (s), 127.4 (d), 127.6 (d, 2C), 128.3 (d, 2C), 128.4 (d, 2C), 129.6 (s), 129.7 (d, 2C), 133.2 (d), 138.5 (s), 167.0 (s); MS (ESI) *m*/*z*=465 $[M+Na]^+$; HRMS (ESI) calcd for $C_{26}H_{34}O_6Na$ $[M+Na]^+$ 465.2253, found 465.2258.

4.8. (*R*)-2-((4*S*,5*R*)-5-(5-(Benzyloxy)pentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-(methylsulfonyloxy)ethyl benzoate (23)

To an ice-cooled solution of benzoate **22** (1.5 g, 3.4 mmol) in CH_2Cl_2 (15 mL) and Et_3N (1.43 mL, 10.2 mmol) was added MsCl (0.4 mL, 5.1 mmol) and it was further stirred for 4 h at rt. Reaction

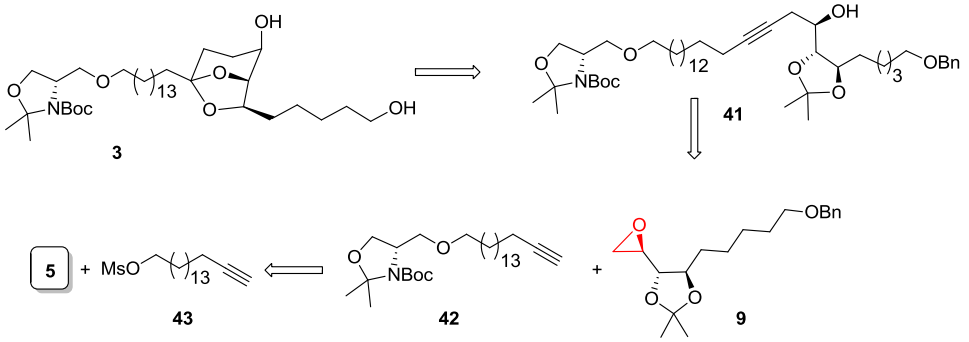
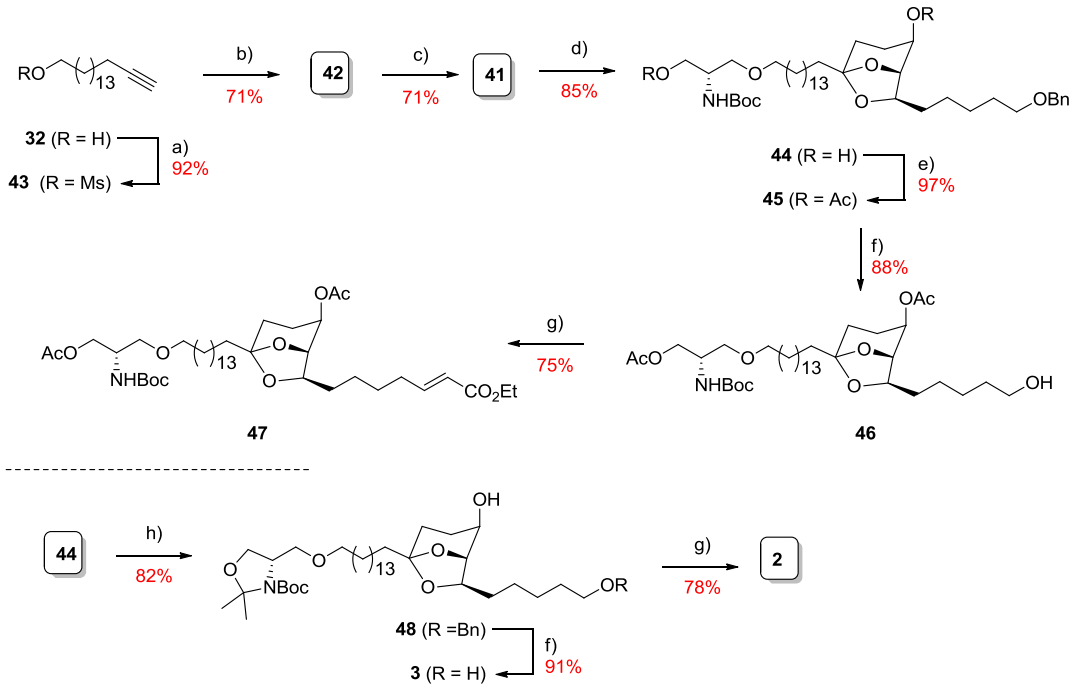


Fig. 3. Alternative retrosynthetic strategy for didemniserinolipid B.



Scheme 6. Reagents and conditions: (a) MsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h; (b) **5**, NaH, DMSO, 0 °C→rt, 16 h; (c) *n*-BuLi, $BF_3{\cdot}Et_2O$, THF, −78 °C, 1 h; (d) $Au(PPh_3)_3Cl$ (5 mol %), $AgSbSF_6$ (5 mol %), CH_2Cl_2, 0→rt, 3 h; (e) AC_2O, Et_3N, cat. DMAP, CH_2Cl_2, 0 °C, 2 h; (f) cat. Pd–C, EtOAc, rt, 30 min; (g) *i*. DMP, CH_2Cl_2, 0 °C→rt, 6 h; *ii*. $Ph_3P{=}CHCO_2Et$, benzene, reflux, 1 h; (h) 2,2-dimethoxypropane, cat. *p*-TSA, acetone, 0 °C→rt, 16 h; (i) cat. 20% $Pd(OH)_2$, EtOAc, H_2 (1 atm), rt, 30 min.

mixture was diluted with CH_2Cl_2 (15 mL) and washed with water, brine, dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. The resulting residue was purified by column chromatography (75:25 petroleum ether/EtOAc) to yield **23** (1.6 g, 90%) as colorless solid: R_f (20% EtOAc/petroleum ether) 0.5; $[\alpha]_D^{25}$ +28.4 (*c* 8.8, $CHCl_3$); IR ($CHCl_3$) ν: 2934, 1723, 1560, 1366, 1274, 1177, 925, 758, 667 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.41 (s, 6H), 1.45–1.77 (m, 8H), 3.05 (s, 3H), 3.45 (t, *J*=7.4 Hz, 2H), 3.89 (t, *J*=6.7 Hz, 1H), 4.12 (ddd, *J*=2.9, 8.2, 10.1 Hz, 1H), 4.43 (d, *J*=7.1 Hz, 1H), 4.46 (s, 2H), 4.75 (d, *J*=12.5 Hz 1H), 5.01 (t, *J*=6.6 Hz 1H), 7.23–7.32 (m, 5H), 7.42 (d, *J*=8.2 Hz, 2H), 7.54 (d, *J*=1.4,6.1 Hz, 1H), 8.06 (d, *J*=8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.6 (t), 25.8 (t), 26.6 (q), 27.1 (q), 29.3 (t), 33.6 (t), 38.6 (q), 63.2 (t), 69.9 (t), 72.5 (t), 78.4 (d), 78.5 (d), 78.9 (d), 109.4 (s), 127.2 (d), 127.3 (d, 2C), 128.0 (d, 2C), 128.3 (d, 2C), 129.1 (s), 129.4 (d, 2C), 133.2 (d), 138.4 (s), 165.7 (s) ppm; MS (ESI) *m*/*z*=543 $[M+Na]^+$; HRMS (ESI) calcd for $C_{27}H_{36}O_8SNa$ $[M+Na]^+$ 543.2029, found 543.2015.

4.9. (4*R*,5*S*)-4-(5-(Benzyloxy)pentyl)-2,2-dimethyl-5-((*S*)-oxiran-2-yl)-1,3-dioxolane (15)

A solution of the mesylate **23** (2 g, 3.8 mmol), $LiOH{\cdot}H_2O$ (483 mg, 11.5 mmol) in MeOH/THF (2:3, 10 mL) was stirred at rt for 4 h. The reaction mixture was concentrated and dissolved in ethyl acetate (25 mL), washed with brine, dried, and concentrated under reduce pressure. The crude residue thus obtained was purified by silica gel chromatography (85:15 petroleum ether/EtOAc) to obtain **15** (1.1 g, 89%) as colorless oil: R_f (20% EtOAc/petroleum ether) 0.53; $[\alpha]_D^{25}$ +6.2 (*c* 0.9, $CHCl_3$); IR ($CHCl_3$) ν: 2935, 2859, 1455, 1370, 1216, 1101, 878, 737, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.38 (s, 6H), 1.42–1.66 (m, 8H), 2.69 (dd, *J*=2.6, 5.2 Hz, 1H), 2.79 (dd, *J*=4.4, 5.2 Hz, 1H), 2.99 (ddd, *J*=2.7, 4.2, 6.8 Hz, 1H), 3.47 (m, 3H), 3.95 (dt, *J*=4.9, 8.2 Hz, 1H), 4.49 (s, 2H), 7.22–7.34 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.8 (t), 26.2 (t), 26.6 (q), 27.2 (q), 29.6 (t), 33.0 (t), 43.9 (t), 51.4 (d), 70.2 (t), 72.9 (t), 77.8 (d), 81.2 (d), 109.2 (s), 127.5 (d), 127.6 (d, 2C), 128.3 (d, 2C), 138.6 (s) ppm; MS (ESI) *m*/*z*=343 $[M+Na]^+$; HRMS (ESI) calcd for $C_{19}H_{28}O_4Na$ $[M+Na]^+$ 343.1886, found 343.1821.

4.10. General procedure for epoxide opening (A)

At −78 °C, to a solution of 1-alkyne (4 mmol) in THF (15 mL) were added *n*-BuLi (4 mmol) and $BF_3{\cdot}Et_2O$ (4 mmol) followed by a solution of the epoxide (1 mmol) in THF (8 mL) with a 15 min interval. The stirring was continued for another 30 min at −78 °C and then quenched with NH_4Cl (5 mL). The reaction mixture was allowed to reach rt and partitioned between ethyl acetate (25 mL) and water (25 mL). The aqueous layer was extracted with ethyl acetate (2×25 mL) and the combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Purification of the crude alkynol product was carried out by column chromatography.

4.11. (*R*)-1-((4*R*,5*R*)-5-(5-(Benzyloxy)pentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)non-3-yn-1-ol (20)

1-Heptyne (594 mg, 6.2 mmol), *n*-BuLi (3.9 mL, 6.2 mmol, 1.6 M in hexane), $BF_3{\cdot}Et_2O$ (0.77 mL, 6.2 mmol), and epoxide **9** (0.5 g, 1.6 mmol) were subjected to general procedure A. The crude product was purified by silica gel chromatography (85:15 petroleum ether/EtOAc) to afford **20** (530 mg, 82%) as a colorless syrup: R_f (10% EtOAc/petroleum ether) 0.57; $[\alpha]_D^{25}$ +37.3 (*c* 2.5, $CHCl_3$); IR ($CHCl_3$) ν: 3546, 2934, 2861, 2401, 1455, 1370, 1217, 1101, 878, 769, 668 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.90 (t, 3H), 1.27–1.33 (m, 4H), 1.35 (s, 3H), 1.38 (s, 3H), 1.40–1.70 (m, 10H), 2.11–2.16 (m, 2H), 2.16 (br s, 1H), 2.45–2.50 (m, 2H), 3.46 (t, *J*=6.6 Hz, 2H), 3.60–3.77 (m, 2H), 3.98 (dt, *J*=3.5, 7.0 Hz, 1H), 4.49 (s, 2H), 7.24–7.33 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 14.0 (q), 18.7 (t), 22.2 (t), 24.3 (t), 26.1 (t), 26.3 (t), 27.1 (q), 27.5 (q), 28.6 (t), 29.7 (t), 31.1 (t), 34.5 (t), 70.4 (t), 70.9 (d), 72.9 (t), 74.9 (s), 78.9 (d), 81.9 (d), 84.0 (s), 108.6 (s), 127.5 (d), 127.7 (d, 2C), 128.4 (d, 2C), 138.7 (s) ppm; MS (ESI) *m*/*z*=439 $[M+Na]^+$; HRMS (ESI) calcd for $C_{26}H_{40}O_4Na$ $[M+Na]^+$ 439.2825, found 439.2826.

4.12. (*R*)-1-((4*R*,5*R*)-5-(5-(Benzyloxy)pentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)non-3-yn-1-ol (24)

Epoxide **15** (400 mg, 1.25 mmol), 1-heptyne (480 mg, 5.0 mmol), $BF_3{\cdot}Et_2O$ (0.63 mL, 5.0 mmol), and *n*-BuLi (3.1 mL, 5.0 mmol, 1.6 M in hexane) were subjected to general procedure A. The crude product was purified by silica gel chromatography (85:15 petroleum ether/EtOAc) to obtain alkynol **24** (410 mg, 78%) as a colorless syrup: R_f (10% EtOAc/petroleum ether) 0.58; $[\alpha]_D^{25}$ +55.8 (*c* 1.6, $CHCl_3$); IR ($CHCl_3$) ν: 3431, 2935, 1453, 1380, 1276, 1068, 879, 714 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.90 (t, *J*=6.9 Hz, 3H), 1.22–1.33 (m, 4H), 1.39 (s, 3H), 1.40 (s, 3H), 1.44–1.70 (m, 10H), 2.14 (tt, *J*=2.2, 4.5, 6.9 Hz, 2H), 2.31–2.53 (m, 3H), 3.46 (t, *J*=6.6 Hz, 2H), 3.61 (br s 1H), 3.75 (dd, *J*=2.8, 8.1 Hz, 1H), 3.96 (dt, *J*=3.5, 7.0 Hz, 1H), 4.49 (s, 2H), 7.24–7.33 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 14.0 (q), 18.7 (t), 22.2 (t), 25.3 (t), 25.9 (t), 26.3 (t), 26.9 (q), 27.5 (q), 28.6 (t), 29.6 (t), 31.0 (t), 33.1 (t), 69.0 (d), 70.2 (t), 72.8 (t), 75.5 (s), 77.8 (d), 81.8 (d), 83.0 (s), 108.8 (s), 127.5 (d), 127.6 (d, 2C), 128.3 (d, 2C), 138.6 (s) ppm; MS (ESI) *m*/*z*=439 $[M+Na]^+$; HRMS (ESI) calcd for $C_{26}H_{40}O_4Na$ $[M+Na]^+$ 439.2824, found 439.2810.

4.13. (*R*)-1-((4*S*,5*R*)-5-(5-(Benzyloxy)pentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)non-3-ynyl benzoate (21)

To an ice-cooled solution of **20** (500 mg, 1.2 mmol), Et_3N (0.5 mL, 3.60 mmol), and DMAP (20 mg) CH_2Cl_2 (10 mL) was added benzoyl chloride (0.21 mL, 1.8 mmol) and stirred for 2 h at rt. The reaction mixture was poured into water (10 mL) and extracted with CH_2Cl_2 (2×10 mL). The combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The resulting crude product was purified by column chromatography (90:10 petroleum ether/EtOAc) to afford the benzoate **21** (560 mg, 89%) as colorless syrup: R_f (10% EtOAc/petroleum ether) 0.5; $[\alpha]_D^{25}$ +51.2 (*c* 1.1, $CHCl_3$); IR ($CHCl_3$) ν: 3019, 1717, 1214, 1111, 757, 711, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.82 (t, *J*=7.1 Hz, 3H), 1.19–1.34 (m, 8H), 1.36 (s, 3H), 1.41 (s, 3H), 1.46–1.70 (m, 6H), 2.09 (tt, *J*=2.1, 6.8 Hz, 2H), 2.63–2.75 (m, 2H), 3.39 (t, *J*=6.5 Hz, 2H), 3.96–4.07 (m, 2H), 4.45 (s, 2H), 5.23 (dd, *J*=5.8,11.6 Hz, 1H), 7.26–7.35 (m, 5H), 7.41–7.45 (m, 2H),7.53–7.57 (m, 1H), 8.04 (d, *J*=7.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.9 (q), 18.6 (t), 21.6 (t), 22.1 (t), 25.9 (t), 26.1 (t), 27.0 (q), 27.5 (q), 28.5 (t), 29.5 (t), 30.9 (t), 34.2 (t), 70.2 (t), 72.8 (t), 72.9 (d), 74.6 (s), 78.8 (d), 80.3 (d), 82.9 (s), 109.2 (s), 127.5 (d), 127.6 (d, 2C), 128.3 (d, 2C), 128.4 (d, 2C), 129.7 (d, 2C), 129.9 (s), 133.1 (d), 138.6 (s), 165.6 (s) ppm; MS (ESI) *m*/*z*=543 $[M+Na]^+$; HRMS (ESI) calcd for $C_{33}H_{44}O_5Na$ $[M+Na]^+$ 543.3087, found 543.3043.

4.14. (*S*)-1-((4*S*,5*R*)-5-(5-(Benzyloxy)pentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)non-3-ynyl benzoate (25)

To a solution of **24** (600 mg, 1.40 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added triethylamine (0.6 mL, 4.3 mmol), DMAP (10 mg) and stirred for 15 min. Benzoyl chloride (0.25 mL, 2.2 mmol) was added at 0 °C and stirred further for 2 h. Usual workup followed by purification of the crude product by column chromatography (90:10 petroleum ether/EtOAc) gave the benzoate **25** (665 mg, 89%) as colorless syrup: R_f (7% EtOAc/petroleum ether) 0.5; $[\alpha]_D^{25}$ 50.8 (*c* 1.2, $CHCl_3$); IR ($CHCl_3$) ν: 3448, 2933, 1717, 1453, 1271, 1111, 877, 758, 666 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.83 (t, *J*=7.1 Hz, 3H), 1.21–1.3 (m, 6H), 1.40 (s, 3H), 1.42 (s, 3H), 1.48–1.7 (m, 8H), 2.09 (tt, *J*=2.4, 6.9 Hz, 2H), 2.67 (ddd, *J*=2.3, 6.8, 9.1 Hz, 2H), 3.44 (t, *J*=6.6 Hz, 2H), 3.84 (dt, *J*=3.8, 8.1, 11.9 Hz, 1H), 4.01 (dd, *J*=2.8, 8.7 Hz, 1H), 4.48 (s, 2H), 5.23 (dt, *J*=2.7, 6.8, 9.5 Hz, 1H), 7.26–7.33 (m, 5H), 7.43 (tt, *J*=1.5, 7.9 Hz, 2H), 7.56 (tt, *J*=2.6, 7.3 Hz, 1H), 8.07 (tt, *J*=1.5, 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.0 (q), 18.6 (t), 22.0 (t), 22.2 (t), 25.9 (t), 26.3 (t), 26.8 (q), 27.5 (q), 28.5 (t), 29.6 (t), 30.9 (t), 33.0 (t), 70.3 (t), 70.6 (d), 72.8 (t), 74.8 (s), 77.2 (d), 80.5 (d), 83.0 (s), 108.8 (s), 127.5 (d), 127.6 (d, 2C), 128.3 (d, 2C), 128.4 (d, 2C), 129.8 (d, 2C), 129.9 (s), 133.2 (d), 138.7 (s), 165.9 (s) ppm; MS (ESI) *m*/*z*=543 $[M+Na]^+$; HRMS (ESI) calcd for $C_{33}H_{44}O_5Na$ $[M+Na]^+$ 543.3086, found 543.3096.

4.15. General procedure for acetonide deprotection (B)

A solution of acetonide (1 mmol) in 60% AcOH in water (5 mL) was stirred at 80 °C for 2–4 h. The reaction mixture was evaporated. The crude residue was washed with toluene (10 mL) three times. Then it was purified by column chromatography.

4.16. (6*R*,7*S*,8*R*)-1-(Benzyloxy)tetradec-10-yne-6,7,8-triol (11)

Acetonide **20** (150 mg, 0.36 mmol) was subjected to general procedure B and the crude product was purified by silica gel chromatography (15:85 petroleum ether/EtOAc) to obtain **11** (120 mg, 88%) as a white solid: R_f (80% EtOAc/petroleum ether) 0.35; mp: 51–52 °C; $[\alpha]_D^{31}$ +3.1 (*c* 2.9, $CHCl_3$); IR ($CHCl_3$) ν: 3400, 2933, 2859, 1603, 1495, 1455, 1216, 1098, 756, 697, 666 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz):δ 0.9 (t, *J*=7.0, 3H), 1.28–1.35 (m, 5H), 1.37–1.44 (m, 3H), 1.46–1.55 (m, 3H), 1.59–1.65 (m, 3H), 2.14 (tt, *J*=2.3, 7.1 Hz, 2H), 2.48–2.50 (m, 2H), 2.96–3.02 (m, 2H), 3.17 (br s, 1H), 3.47 (t, *J*=6.6 Hz, 3H), 3.81 (q, *J*=6.6 Hz, 1H), 3.98 (br s, 1H), 4.49 (s, 2H), 7.26–7.34 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.9 (q), 18.6 (t), 22.1 (t), 23.9 (t), 25.5 (t), 26.1 (t), 28.6 (t), 29.6 (t), 31.0 (t), 33.5 (t), 70.3 (d), 70.4 (t), 71.8 (d), 72.8 (t), 73.9 (d), 75.4 (s), 83.6 (s), 127.5 (d), 127.6 (d, 2C), 128.3 (d, 2C), 138.5 (s) ppm; MS (ESI) *m*/*z*=399 $[M+Na]^+$; HRMS (ESI) calcd for $C_{23}H_{36}O_4Na$ $[M+Na]^+$ 399.2513, found 399.2512.

4.17. (6*R*,7*S*,8*R*)-1-(Benzyloxy)-6,7-dihydroxyhexadec-10-yn-8-yl benzoate (12)

Acetonide **21** (200 mg, 0.38 mmol) was subjected to general procedure B. The crude product was purified by silica gel chromatography (40:60 petroleum ether/EtOAc) to obtain **12** (152 mg, 82%) as a colorless thick syrup: R_f (50% EtOAc/petroleum ether) 0.5; $[\alpha]_D^{25}$ +20.2 (*c* 7.1, $CHCl_3$); IR ($CHCl_3$) ν: 3443, 2932, 1721, 1452, 1272, 1113, 757, 712, 640, 668 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.81 (t, *J*=7.2 Hz, 3H), 1.12–1.67 (m, 14H), 2.03 (m, 2H), 2.55 (br d, *J*=8.1 Hz, 1H), 2.74–2.82 (m, 2H), 2.9 (br s, 1H), 3.43 (t, *J*=6.5 Hz, 2H), 3.55–3.65 (m, 2H), 4.46 (s, 2H), 5.08 (ddd, *J*=4.6, 6.1, 10.7 Hz, 1H), 7.24–7.32 (m, 5H), 7.43 (dd, *J*=1.4, 7.2 Hz, 1H), 7.46 (dd, *J*=1.4, 7.7 Hz, 1H), 7.59 (tt, *J*=2.5, 8.7 Hz, 1H), 8.07 (tt, *J*=1.6, 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 13.9 (q), 18.6 (t), 21.7 (t), 22.1 (t), 25.7 (t), 26.2 (t), 28.5 (t), 29.6 (t), 30.9 (t), 33.0 (t), 69.3 (d), 70.2 (t), 72.8 (t), 73.2 (d), 73.5 (d), 75.1 (s), 82.7 (s), 127.4 (d), 127.6 (d, 2C), 128.3 (d, 2C), 128.4 (d, 2C), 129.5 (s), 129.9 (d, 2C), 133.4 (d), 138.6 (s), 167.1 (s) ppm; MS (ESI) *m*/*z*=481 $[M+H]^+$; HRMS (ESI) calcd for $C_{30}H_{40}O_5Na$ $[M+Na]^+$ 503.2773, found 503.2799.

4.18. (6*R*,7*S*,8*S*)-1-(Benzyloxy)tetradec-10-yne-6,7,8-triol (13)

Acetonide **24** (140 mg, 0.34 mmol) was subjected to general procedure B. The crude product was purified by silica gel chromatography (15:85 petroleum ether/EtOAc) to obtain **13** (105 mg, 83%) as a white solid: R_f (80% EtOAc/petroleum ether) 0.36; mp: 40–42 °C; $[\alpha]_D^{31}$ +8.1 (*c* 2.8, $CHCl_3$); IR ($CHCl_3$) ν: 3422, 2932, 2859, 1719, 1602, 1453, 1275, 1070, 755, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz):δ 0.9 (t, *J*=7.1 Hz, 3H), 1.27–1.34 (m, 4H), 1.35–1.42 (m, 3H), 1.44–1.49 (m, 3H), 1.51–1.58 (m, 2H), 1.59–1.65 (m, 2H), 2.13 (tt, *J*=2.3, 7.1 Hz, 2H), 2.42–2.5 (m, 2H), 2.89 (br s, 2H), 3.4 (br s, 1H), 3.46 (t, *J*=6.6 Hz, 3H), 3.69 (br s, 1H), 3.79 (br s, 1H), 4.48 (s, 2H), 7.24–7.34 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.9 (q), 18.6 (t),

22.1 (t), 24.3 (t), 25.3 (t), 26.1 (t), 28.6 (t), 29.6 (t), 31.0 (t), 33.6 (t), 70.3 (t), 72.4 (d), 72.8 (t), 73.2 (d), 73.4 (d), 75.6 (s), 83.3 (s), 127.5 (d), 127.6 (d, 2C), 128.3 (d, 2C), 138.5 (s) ppm; MS (ESI) m/z=399 $[M+Na]^+$; HRMS (ESI) calcd for $C_{23}H_{36}O_4Na$ $[M+Na]^+$ 399.2512. found 399.2516.

4.19. (6*R*,7*S*,8*S*)-1-(Benzyloxy)-6,7-dihydroxyhexadec-10-yn-8-yl benzoate (14)

Acetonide **25** (200 mg, 0.38 mmol) was subjected to general procedure B. The crude product was purified by silica gel chromatography (30:70 petroleum ether/EtOAc) to obtain **14** (155 mg, 84%) as a white syrup: R_f (60% EtOAc/petroleum ether) 0.43; $[\alpha]_D^{25}$ +4.7 (*c* 2.7, $CHCl_3$); IR ($CHCl_3$) ν: 3448, 2932, 1718, 1451, 1273, 1114, 758, 668, 617 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz):δ 0.9 (t, *J*=7.1 Hz, 3H), 1.27–1.36 (m, 4H), 1.42–1.49 (m, 6H), 1.59–1.62 (m, 2H), 1.80–1.83 (m, 2H), 2.12 (tt, *J*=2.2, 7.1 Hz, 2H), 2.50 (m, 3H), 2.74 (br s, 1H), 3.44 (t, *J*=6.6 Hz, 2H), 3.77 (br s, 2H), 4.47 (s, 2H), 5.26 (ddd, *J*=4.4, 6.1, 10.4 Hz, 1H), 7.24–7.34 (m, 5H), 7.43 (tt, *J*=1.5, 7.1 Hz, 2H), 7.56 (tt, *J*=2.3, 7.3 Hz, 1H), 8.06 (tt, *J*=1.5, 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.9 (q), 18.6 (t), 22.1 (t), 24.5 (t), 25.2 (t), 26.0 (t), 28.6 (t), 29.5 (t), 30.7 (t), 31.1 (t), 70.0 (d), 70.2 (t), 72.8 (t), 73.6 (d), 75.2 (s), 75.3 (d), 83.7 (s), 127.4 (d), 127.6 (d, 2C), 128.3 (d, 2C), 128.4 (d, 2C), 129.7 (d, 2C), 130.1 (s), 133.1 (d), 138.6 (s), 166.6 (s) ppm; MS (ESI) m/z=481 $[M+H]^+$; HRMS (ESI) calcd for $C_{30}H_{40}O_5Na$ $[M+Na]^+$ 503.2773. found 503.2781.

4.20. General procedure for cycloisomerization (procedure C)

A solution of the alkynol (1 equiv) and Pd $(CH_3CN)_2Cl_2$ (0.05 equiv) in acetonitrile (30 mL/1 mmol substrate) was stirred at rt under argon atmosphere for 3–6 h. The reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure and the residue obtained was purified by silica gel chromatography.

4.21. (1*R*,2*R*,5*S*,7*R*)-7-(5-(Benzyloxy)pentyl)-5-pentyl-6,8-dioxabicyclo[3.2.1]octan-2-ol (26)

Triol **11** (200 mg, 0.53 mmol) and Pd $(CH_3CN)_2Cl_2$ (7 mg, 0.03 mmol) were subjected to general procedure C. The crude product was purified by silica gel chromatography (80:20 petroleum ether/EtOAc) to obtain **26** (134 mg, 67%) as colorless syrup: R_f (15% EtOAc/petroleum ether) 0.4; $[\alpha]_D^{25}$ +25.0 (*c* 0.9, $CHCl_3$); IR ($CHCl_3$) ν: 3444, 2930, 2857, 1722, 1455, 1216, 1100, 892, 753, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.87 (t, *J*=6.7, 3H), 1.24–1.34 (m, 5H), 1.36–1.44 (m, 6H), 1.61–1.65 (m, 9H), 1.90 (br s, 1H), 3.46 (t, *J*=6.5 Hz, 2H), 3.90 (ddd, *J*=5.5, 9.6, 18.2 Hz, 1H), 3.93 (m, 1H), 4.19 (dd, *J*=5.6, 6.7 Hz, 1H), 4.49 (s, 2H), 7.26–7.34 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.0 (q), 22.6 (t), 22.9 (t), 25.4 (t), 26.0 (t), 26.6 (t), 29.6 (t), 31.9 (t), 33.7 (t), 35.2 (t), 36.7 (t), 66.5 (d), 70.3 (t), 72.8 (t), 75.7 (d), 80.8 (d), 108.5 (s), 127.5 (d), 127.6 (d, 2C), 128.3 (d, 2C), 138.6 (s) ppm; MS (ESI) m/z=399 $[M+Na]^+$; HRMS (ESI) calcd for $C_{23}H_{36}O_4Na$ $[M+Na]^+$ 399.2513, found 399.2495.

4.22. (1*R*,2*R*,5*S*,7*R*)-7-(5-(Benzyloxy)pentyl)-5-pentyl-6,8-dioxabicyclo[3.2.1]octan-2-ol (27)

Diol **12** (200 mg, 0.42 mmol) and Pd$(CH_3CN)_2Cl_2$ (5 mg, 0.02 mmol) were subjected to general procedure C. The crude product was purified by silica gel chromatography (78:22 petroleum ether/EtOAc) to procure **27** (161 mg, 80%) as colorless syrup: R_f (15% EtOAc/petroleum ether) 0.43; $[\alpha]_D^{25}$ +32.9 (*c* 1.7, $CHCl_3$); IR ($CHCl_3$) ν: 3448, 2929, 1717, 1274, 1273, 1113, 712, 617 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 0.86 (t, *J*=6.7 Hz, 3H), 1.26–1.32 (m, 5H), 1.35–1.43 (m, 4H), 1.45–1.5 (m, 2H), 1.56–1.65 (m, 3H), 1.67–1.71 (m, 2H), 1.8–1.85 (m, 2H), 1.86–1.9 (dd, *J*=6.9, 9.7 Hz 2H), 3.42 (t, *J*=6.5 Hz, 2H), 3.76 (d, *J*=5.4 Hz, 1H), 4.46 (s, 2H), 4.66 (d, *J*=4.6 Hz 1H), 5.08 (ddd, *J*=5.5, 7.3, 12.8 Hz, 1H), 7.26–7.33 (m, 5H), 7.42 (dd, *J*=1.6, 7.6 Hz, 2H), 7.53 (tt, *J*=1.5, 8.7 Hz, 1H), 8.05 (tt, *J*=1.6, 6.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 14.0 (q), 22.5 (t), 23.8 (t), 25.4 (t), 26.1 (t), 28.8 (t), 29.6 (t), 30.2 (t), 32.0 (t, 2C), 34.5 (t), 70.3 (t), 72.9 (t), 74.3 (d), 77.2 (d), 81.4 (d), 110.7 (s), 127.5 (d), 127.6 (d, 2C), 128.2 (d, 2C), 128.32 (d, 2C), 129.7 (d, 2C), 130.5 (s), 132.7 (d), 138.6 (s), 166.3 (s) ppm; MS (ESI) m/z=481 $[M+H]^+$; HRMS (ESI) calcd for $C_{30}H_{40}O_5Na$ $[M+Na]^+$ 503.2773, found 503.2774.

4.23. (1*R*,2*R*,5*S*,7*R*)-7-(5-(Benzyloxy)pentyl)-5-pentyl-6,8-dioxabicyclo[3.2.1]octan-2-ol (28)

Triol **13** (150 mg, 0.36 mmol) and Pd $(CH_3CN)_2Cl_2$ (5 mg, 0.02 mmol) were subjected to general procedure C. The crude product was purified by silica gel chromatography (80:20 petroleum ether/EtOAc) to obtain **28** (125 mg, 81%) as colorless syrup: R_f (15% EtOAc/petroleum ether) 0.42; $[\alpha]_D^{28}$ +71.8 (*c* 0. 4, $CHCl_3$); IR ($CHCl_3$) ν: 3421, 2932, 1602, 1456, 1029, 697, 617 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 0.90 (t, *J*=7.0 Hz, 3H), 1.26–1.34 (m, 6H), 1.37–1.44 (m, 7H), 1.59–1.70 (m, 7H), 1.80–1.92 (m, 1H), 3.46 (t, *J*=6.6 Hz, 2H), 3.90 (m, 1H), 3.94 (dd, *J*=4.5, 7.1 Hz, 1H), 4.20 (dd, *J*=5.5, 7.3 Hz, 1H), 4.49 (br s, 2H), 7.25–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 14.0 (q), 22.6 (t), 22.9 (t), 25.4 (t), 26.1 (t), 26.7 (t), 29.7 (t), 32.0 (t), 33.8 (t), 35.2 (t), 36.7 (t), 66.6 (d), 70.4 (t), 72.9 (t), 75.7 (d), 80.8 (d), 108.5 (s), 127.5 (d), 127.6 (d, 2C), 128.3 (d, 2C), 138.7 (s) ppm; MS (ESI) m/z=399 $[M+Na]^+$; HRMS (ESI) calcd for $C_{23}H_{36}O_4Na$ $[M+Na]^+$ 399.2512, found 399.2498.

4.24. (1*S*,2*S*,5*S*,7*R*)-7-(5-(Benzyloxy)pentyl)-5-pentyl-6,8-dioxabicyclo[3.2.1]octan-2-yl benzoate (29)

Diol **14** (150 mg, 0.31 mmol) and Pd $(CH_3CN)_2Cl_2$ (4 mg, 0.02 mmol) were subjected to general procedure C. The crude product purified by silica gel chromatography (80:20 petroleum ether/EtOAc) gave **29** (110 mg, 73%) as colorless syrup: R_f (10% EtOAc/petroleum ether) 0.45; $[\alpha]_D^{25}$ +36.8 (*c* 0.6, $CHCl_3$); IR ($CHCl_3$) ν: 3418, 2930, 1716, 1602, 1274, 1112, 990, 712, 617 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz):δ 0.85 (t, *J*=7.0 Hz, 3H), 1.27–1.30 (m, 4H), 1.35–1.42 (m, 4H), 1.44–1.52 (m, 2H), 1.58–1.71 (m, 6H), 1.79–1.83 (m, 2H), 1.86–1.90 (m, 2H), 3.42 (t, *J*=6.5 Hz, 2H), 3.76 (d, *J*=5.3, Hz, 1H), 4.46 (br s, 2H), 4.66 (d, *J*=4.4 Hz, 1H), 5.08 (dt, *J*=5.6, 7.1, 11.5 Hz, 1H), 7.26–7.34 (m, 5H), 7.42 (tt, *J*=1.5, 6.9 Hz, 2H), 7.53 (tt, *J*=1.5, 7.1 Hz, 1H), 8.05 (dt, *J*=1.6, 6.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.0 (q), 22.5 (t), 23.8 (t), 25.4 (t), 26.1 (t), 28.8 (t), 29.6 (t), 30.2 (t), 32.1 (t), 34.5 (t, 2C), 70.3 (t), 72.8 (t), 74.3 (d), 77.2 (d), 81.4 (d), 110.7 (s), 127.5 (d), 127.6 (d, 2C), 128.3 (d, 2C), 128.3 (d, 2C), 129.7 (d, 2C), 130.5 (s), 132.8 (d), 138.6 (s), 166.3 (s) ppm; MS (ESI) m/z=503 $[M+Na]^+$; HRMS (ESI) calcd for $C_{30}H_{40}O_5Na$ $[M+Na]^+$ 503.2773, found 503.2628.

4.25. 2-(Heptadec-2-ynyloxy)tetrahydro-2*H*-pyran (30)

At −10 °C, a solution of the THP ether of the propargyl alcohol (1 g, 7.1 mmol) in THF (10 mL) was treated with *n*-BuLi (3.66 mL, 8.6 mmol) (2.34 M in hexane) and stirred for 30 min. HMPA (1.53 mL, 8.6 mmol) was added and the reaction mixture was stirred at −10 °C for another 30 min. Myristyl bromide (2.37 g, 8.6 mmol) was dissolved in THF (20 mL) and stirred at −10 °C to which the solution of alkynyl lithium in THF was added and stirred for further 30 min. The reaction mixture was quenched with saturated NH_4Cl. The organic layer was separated and the aqueous layer was washed with ethyl acetate, the combined organic layers were washed with ethyl acetate, brine, dried, and concentrated. Purification of the crude product by column chromatography

(90:10 petroleum ether/EtOAc) afforded **30** (2.1 g, 87%) as colorless oil: R_f (7% EtOAc/petroleum ether) 0.6; IR ($CHCl_3$)ν: 2926, 1466, 1345, 1216, 1118, 1022, 903, 759, 668 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.88 (t, J=6.7 Hz, 3H), 1.24–1.34 (m, 24H), 1.46–1.88 (m, 6H), 2.11–2.23 (m, 2H), 3.44–3.55 (m, 1H), 3.81 (ddd, J=3.3, 8.5, 11.7 Hz, 1H), 4.14 (dt, J=2.1, 15.3 Hz, 1H), 4.25 (dt, J=2.1, 15.3 Hz, 1H), 4.79 (t, J=2.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 14.2 (q), 18.4 (t), 18.9 (t), 19.1 (t), 22.7 (t), 25.5 (t), 28.5 (t), 28.6 (t), 28.8 (t), 28.9 (t), 29.2 (t), 29.4 (t), 29.6 (t), 29.7 (t), 29.7 (t), 30.3 (t), 32.0 (t), 54.5 (t), 61.8 (t), 75.8 (s), 86.6 (s), 96.4 (d) ppm; MS (ESI) m/z=359 $[M+Na]^+$. Anal. calcd for $C_{22}H_{40}O_2$: C, 78.51; H, 11.98%, found C, 78.40; H, 12.13%.

4.26. Heptadec-2-yn-1-ol (31)

To a solution of **30** (400 mg, 1.1 mmol) in MeOH (10 mL), *p*-TSA (7 mg) was added and the reaction mixture was stirred at rt for 30 min. The reaction mixture was quenched by the addition of few drops of triethylamine and the solvent was evaporated. The crude residue was purified by column chromatography (80:20 petroleum ether/EtOAc) to obtain **31** (275 mg, 91%) as a white solid: R_f (10% EtOAc/petroleum ether) 0.4; mp: 48–49 °C; IR ($CHCl_3$) ν: 3539, 2944, 2254, 1631, 1444, 1376, 1040, 918, 759 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.87 (t, J=6.7 Hz, 3H), 1.25–1.42 (m, 24H), 2.18 (tt, J=2.1, 6.9 Hz, 2H), 4.22 (t, J=2.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 14.2 (q), 18.8 (t), 22.7 (t), 28.6 (t), 28.9 (t), 29.2 (t), 29.4 (t), 29.6 (t), 29.7 (t, 5C), 32.0 (t), 51.3 (t), 78.4 (s), 86.5 (s) ppm; MS (ESI) m/z=275 $[M+Na]^+$. Anal. calcd for $C_{17}H_{32}O$: C, 80.88; H, 12.78%, found C, 80.60; H, 12.73%.

4.27. Heptadec-16-yn-1-ol (32)

Lithium (3.3 g, 475.4 mmol) was added to freshly distilled 1,3-diaminopropane (250 mL) and stirred at rt till the reaction mixture turns into a deep purple suspension. The suspension was heated at 80 °C till the blue color disappeared. The reaction mixture was cooled to rt and KO^{t}Bu (35.6 g, 316.9 mmol) was added and stirred for 30 min. Alkynol **31** (20 g, 79.2 mmol) was added to the reaction mixture and stirred at rt for 1 h. The reaction mixture was poured slowly on ice and partitioned between CH_2Cl_2 and water. The aqueous layer was extracted with CH_2Cl_2 and combined CH_2Cl_2 layer was washed with brine, dried (Na_2SO_4), and concentrated. Purification of the residue by column chromatography (80:20 petroleum ether/EtOAc) afforded **32** (15.8 g, 79%) as white solid: R_f (10% EtOAc/petroleum ether) 0.45; mp: 50–51 °C; IR ($CHCl_3$) ν: 3308, 2928, 1603, 1466, 1216, 1049, 758, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.25–1.41 (m, 22H), 1.48–1.58 (m, 4H), 1.88 (t, J=2.5 Hz, 1H), 2.15 (dt, J=2.5, 6.8 Hz, 2H), 3.61 (t, J=6.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 18.4 (t), 25.8 (t), 28.5 (t), 28.8 (t), 29.1 (t), 29.4 (t), 29.5 (t), 29.6 (t, 3C), 29.6 (t, 3C), 32.8 (t), 62.9 (t), 68.2 (d), 84.6 (s) ppm; HRMS (ESI) calcd for $C_{17}H_{32}ONa$ $[M+Na]^+$ 275.2350, found 275.2305.

4.28. *tert*-Butyl(heptadec-16-ynyloxy)dimethylsilane (8)

To a solution of **32** (1 g, 3.9 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added Et_3N (0.83 mL, 5.9 mmol), DMAP (10 mg) and stirred for 15 min. TBSCl (890 mg, 5.9 mmol) was added at 0 °C and stirred further for 1 h. The reaction mixture was diluted with CH_2Cl_2 (15 mL) and washed with brine, dried (Na_2SO_4), and concentrated. The resulting crude product was purified by column chromatography (95:5 petroleum ether/EtOAc) to afford silyl ether **8** (1.3 g, 90%) as colorless oil: R_f (5% EtOAc/petroleum ether) 0.4; IR ($CHCl_3$) ν: 2944, 2253, 1444, 1376, 1040, 918, 751, 648 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.03 (s, 6H), 0.88 (s, 9H), 1.25 (m, 20H), 1.46–1.55 (m, 5H), 1.77 (t, J=2.5 Hz, 1H), 1.92 (t, J=2.7 Hz, 1H), 2.16 (dt, J=2.7, 6.9 Hz, 2H), 3.58 (t, J=6.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ −5.3 (q, 2C), 18.4 (t), 18.7 (s), 25.8 (t), 26.0 (q, 3C), 28.5 (t), 28.8 (t), 29.1 (t), 29.5 (t), 29.5 (t), 29.6 (t, 3C), 29.7 (t, 3C), 32.9 (t), 63.3 (t), 68.0 (d), 84.7 (s); MS (ESI) m/z=389 $[M+Na]^+$; HRMS (ESI) calcd for $C_{23}H_{46}OSiNa$ $[M+Na]^+$ 389.3216, found 389.3222.

4.29. (*R*)-1-((4*R*,5*R*)-5-(5-(Benzyloxy)pentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-19-(*tert*-butyldimethylsilyloxy)nonadec-3-yn-1-ol (33)

Alkyne **8** (2.97 g, 8.12 mmol), *n*-BuLi (3.47 mL, 8.12 mmol, 2.34 M in hexane), $BF_3{\cdot}Et_2O$ (1.1 mL, 8.12 mmol), epoxide **9** (650 mg, 2.03 mmol) were subjected to general procedure C. The crude product was purified by silica gel chromatography (85:15 petroleum ether/EtOAc) to obtain **33** (1.0 g, 82%) as a colorless syrup: R_f (10% EtOAc/petroleum ether) 0.52; $[\alpha]_{25}D$ $_{+9.5\ (c\ 0.6,\ MeOH);\ IR\ (CHCl3)}$ ν: 3439, 2929, 1463, 1370, 1254, 1101, 836, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.03 (s, 6H), 0.88 (s, 9H), 1.22–1.29 (m, 24H), 1.34 (s, 3H), 1.37 (s, 3H), 1.40–1.53 (m, 10H), 2.11–2.19 (m, 2H), 2.16 (br s, 1H), 2.43–2.49 (m, 2H), 3.45 (t, J=6.6 Hz, 2H), 3.58 (t, J=6.6 Hz, 2H), 3.59 (t, J=6.7 Hz, 1H), 3.63–3.75 (m, 1H), 3.96 (dt, J=3.5, 7.0 Hz, 1H), 4.48 (s, 2H), 7.24–7.33 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ −5.3 (q, 2C), 18.3 (s), 18.7 (t), 23.3 (t), 24.3 (t), 25.8 (t), 26.0 (q, 3C), 26.0 (t), 26.0 (t), 26.1 (t), 26.2 (t), 27.1 (q), 27.4 (q), 28.9 (t, 2C), 29.1 (t), 29.4 (t), 29.5 (t), 29.6 (t, 4C), 32.9 (t), 34.4 (t), 63.3 (t), 70.3 (t), 70.8 (d), 72.8 (t), 74.9 (s), 78.8 (d), 81.9 (d), 84.0 (s), 108.6 (s), 127.4 (d), 127.6 (d, 2C), 128.3 (d, 2C), 138.6 (s) ppm; MS (ESI) m/z=709 $[M+Na]^+$. Anal. calcd for $C_{42}H_{74}O_5Si$: C, 73.42; H, 10.86%, found C, 73.38; H, 10.92%.

4.30. (*R*)-1-((4*S*,5*R*)-5-(5-(Benzyloxy)pentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-19-(*tert*-butyldimethylsilyloxy) nonadec-3-ynyl benzoate (34)

To a solution of **33** (700 mg, 1.02 mmol) in CH_2Cl_2 (10 mL) at 0 °C were added Et_3N (0.21 mL, 1.5 mmol), DMAP (10 mg) and stirred for 15 min. To this, benzoyl chloride (0.18 mL, 1.5 mmol) was added at 0 °C and stirred further for 2 h. The reaction mixture was diluted with CH_2Cl_2 (25 mL) and washed with brine, dried (Na_2SO_4), and concentrated. The resulting crude product was purified by column chromatography (90:10 petroleum ether/EtOAc) to afford the benzoate **34** (741 mg, 92%) as colorless syrup: R_f (10% EtOAc/petroleum ether) 0.6; $[\alpha]_{25}D$ $_{-4.1\ (c\ 1.0,\ CHCl3)}$; IR ($CHCl_3$) ν: 2928, 1725, 1495, 1369, 1268, 1100, 836, 710 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.04 (s, 6H), 0.89 (s, 9H), 1.15–1.30 (m, 26H), 1.36 (s, 3H), 1.41 (s, 3H), 1.46–1.80 (m, 8H), 2.04–2.11 (m, 2H), 2.67–2.70 (m, 2H), 3.39 (t, J=6.4 Hz, 2H), 3.59 (t, J=6.6 Hz, 2H), 3.95–4.09 (m, 2H), 4.45 (s, 2H), 5.23 (q, J=5.7 Hz, 1H), 7.27–7.34 (m, 5H), 7.38–7.46 (m, 2H), 7.55 (tt, J=1.4, 7.3 Hz, 1H), 8.04 (dt, J=1.3, 6.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ −5.3 (q, 2C), 18.4 (s), 18.7 (t), 21.6 (t), 25.8 (t), 25.9 (t), 26.0 (q, 3C), 26.1 (t), 27.0 (q), 27.5 (q), 28.8 (t), 29.2 (t), 29.4 (t), 29.5 (t), 29.5 (t), 29.7 (t, 7C), 32.9 (t), 34.2 (t), 63.3 (t), 70.2 (t), 72.8 (t), 72.8 (d), 74.6 (s), 78.8 (d), 80.3 (d), 82.9 (s), 109.2 (s), 127.4 (d), 127.6 (d, 2C), 128.3 (d, 2C), 128.4 (d, 2C), 129.7 (d, 2C), 129.9 (s), 133.1 (d), 138.6 (s), 165.6 (s) ppm; MS (ESI) m/z=813 $[M+Na]^+$. Anal. calcd for $C_{49}H_{78}O_6Si$: C, 74.38; H, 9.94%, found C, 74.10; H, 9.78%.

4.31. (19*R*,20*S*,21*R*)-26-(Benzyloxy)hexacos-16-yne-1,19,20,21-tetraol (6)

To a solution of the acetonide **33** (200 mg, 0.29 mmol) in MeOH (5 mL), *p*-TSA (5 mg, 0.03 mmol) was added and the reaction mixture was stirred at rt for 2 h. The reaction mixture was quenched by the addition of few drops of triethylamine and the solvent was evaporated. The crude residue was purified by column chromatography (40:60 petroleum ether/EtOAc) to obtain **6**

(130 mg, 82%) as a white syrup: R_f (40% EtOAc/petroleum ether) 0.42; $[\alpha]_D^{25}$ −3.2 (*c* 0.5, MeOH); IR (Nujol) ν: 3438, 2923, 1462, 1377, 1111, 1058, 737, 648 cm^{-1}; ^1H NMR (methanol-d_4, 200 MHz): δ 1.22 (m, 18H), 1.35–1.59 (m, 16H), 2.10–2.16 (m, 2H), 2.38 (ddt, *J*=2.5, 5.8, 16.8 Hz, 1H), 2.54 (ddt, *J*=2.5, 4.7, 16.9 Hz, 1H), 3.32 (dt, *J*=1.6, 7.1 Hz, 1H), 3.48 (t, *J*=6.6 Hz, 2H), 3.52 (t, *J*=6.4 Hz, 2H), 3.70 (ddd, *J*=4.7, 6.3, 10.5 Hz, 1H), 3.74–3.80 (m, 1H), 4.43 (s, 2H), 7.22–7.28 (m, 5H); ^{13}C NMR (methanol-d_4, 50 MHz): δ 19.1 (t), 21.5 (t), 24.3 (t), 26.0 (t), 26.1 (t), 26.5 (t), 29.3 (t), 29.4 (t), 29.5 (t), 29.8 (t), 29.9 (t), 30.0 (t, 6C), 32.7 (t), 33.7 (t), 62.8 (t), 70.5 (d), 70.8 (t), 71.6 (d), 73.3 (t), 74.3 (s), 76.4 (d), 83.0 (s), 128.0 (d), 128.1 (d, 2C), 128.7 (d, 2C), 138.6 (s) ppm; MS (ESI) *m*/*z*=555 $[M+Na]^+$. Anal. calcd for $C_{33}H_{56}O_5$: C, 74.39; H, 10.59%. Found: C, 74.17; H, 10.44%.

4.32. (6*R*,7*S*,8*R*)-1-(Benzyloxy)-6,7,26-trihydroxyhexacos-10-yn-8-yl benzoate (7)

To a solution of the acetonide **34** (400 mg, 0.51 mmol) in MeOH (10 mL), *p*-TSA (5 mg, 0.03 mmol) was added and the reaction mixture was stirred at rt for 2 h. The reaction mixture was quenched by the addition of few drops of triethylamine and the solvent was evaporated. The crude residue was purified by column chromatography (50:50 petroleum ether/EtOAc) to obtain **7** (280 mg, 86%) as colorless syrup: R_f (30% EtOAc/petroleum ether) 0.4; $[\alpha]_D^{25}$ −3.9 (*c* 0.8, $CHCl_3$); IR ($CHCl_3$) ν: 3427, 2929, 1706, 1453, 1276, 1116, 757, 668 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz):δ 1.24–1.40 (m, 26H), 1.45–1.67 (m, 8H), 2.08 (tt, *J*=2.0, 6.7 Hz, 2H), 2.54 (br d, *J*=8.3 Hz, 1H), 2.65–2.81 (m, 2H), 2.92 (br s, 1H), 3.42 (t, *J*=6.6 Hz, 2H), 3.55–3.65 (m, 2H), 3.62 (t, *J*=6.6 Hz, 2H), 4.46 (s, 2H), 5.06 (ddd, *J*=4.4, 6.3, 10.3 Hz, 1H), 7.23–7.31 (m, 5H), 7.44 (tt, *J*=1.5, 7.1 Hz, 2H), 7.59 (tt, *J*=2.3, 7.3 Hz, 1H), 8.06 (tt, *J*=1.5, 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 18.6 (t), 21.7 (t), 25.7 (t), 25.8 (t), 26.2 (t), 28.8 (t), 28.8 (t), 29.1 (t), 29.4 (t), 29.5 (t), 29.6 (t, 6C), 29.6 (t), 32.7 (t), 33.0 (t), 63.0 (t), 69.2 (d), 70.2 (t), 72.8 (t), 73.2 (d), 73.6 (d), 75.1 (s), 82.7 (s), 127.4 (d), 127.6 (d, 2C), 128.3 (d, 2C), 128.4 (d, 2C), 129.5 (s), 129.9 (d, 2C), 133.5 (d), 138.6 (s), 167.1 (s) ppm; MS (ESI) *m*/*z*=659 $[M+Na]^+$. Anal. calcd for $C_{40}H_{60}O_6$: C, 75.43; H, 9.50%, found C, 75.70; H, 9.63%.

4.33. (1*S*,2*R*,5*S*,7*R*)-7-(5-(Benzyloxy)pentyl)-5-(15-hydroxypentadecyl)-6,8-dioxabicyclo[3.2.1]octan-2-ol (35)

Tetrol **6** (500 mg, 0.94 mmol) and $Pd(CH_3CN)_2Cl_2$ (12 mg, 0.05 mmol) were subjected to general procedure C. The crude product was purified by silica gel chromatography (50:50 petroleum ether/EtOAc) to obtain **35** (350 mg, 70%) as colorless syrup: R_f (40% EtOAc/petroleum ether) 0.4; $[\alpha]_D^{25}$ +14.4 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) ν: 3437, 2929, 1639, 1560, 1416, 1216, 757, 668 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.24–1.32 (m, 23H), 1.35–1.44 (m, 5H), 1.49–1.58 (m, 4H), 1.60–1.69 (m, 6H), 1.77 (dt, *J*=5.5, 12.3 Hz, 1H), 1.92–2.01 (m, 1H), 3.45 (t, *J*=6.5 Hz, 2H), 3.58 (t, *J*=1.5 Hz, 1H), 3.62 (t, *J*=6.8 Hz, 2H), 3.86 (dd, *J*=5.5, 7.4 Hz, 1H), 4.04 (br s, 1H), 4.48 (s, 2H), 7.26–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.9 (t), 25.0 (t), 25.3 (t), 25.7 (t), 26.0 (t), 29.4 (t), 29.5 (t), 29.6 (t), 29.6 (t, 6C), 29.7 (t), 29.8 (t), 30.1 (t), 32.8 (t), 35.2 (t), 37.5 (t), 63.0 (t), 66.3 (d), 70.3 (t), 72.9 (t), 77.8 (d), 82.3 (d), 109.5 (s), 127.5 (d), 127.6 (d, 2C), 128.3 (d, 2C), 138.6 (s) ppm; MS (ESI) *m*/*z*=555 $[M+Na]^+$. Anal. calcd for $C_{33}H_{56}O_5$: C, 74.39; H, 10.59%, found C, 74.20; H, 10.46%.

4.34. (1*S*,2*R*,5*S*,7*R*)-7-(5-(Benzyloxy)pentyl)-5-(15-hydroxypentadecyl)-6,8-dioxabicyclo[3.2.1]octan-2-yl benzoate (36)

Triol **7** (500 mg, 0.79 mmol) and Pd $(CH_3CN)_2Cl_2$ (11 mg, 0.04 mmol) were subjected to general procedure C. The crude product was purified by silica gel chromatography (60:40 petroleum ether/EtOAc) to obtain **36** (355 mg, 71%) as colorless syrup: R_f (30% EtOAc/petroleum ether) 0.42; $[\alpha]_D^{25}$ +15.0 (*c* 2.5, $CHCl_3$); IR ($CHCl_3$) ν: 3406, 2928, 1711, 1277, 1216, 758, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.25 (m, 22H), 1.37–1.72 (m, 14H), 1.80–1.96 (m, 2H), 2.06–2.21 (m, 2H), 3.45 (t, *J*=6.4 Hz, 2H), 3.62 (t, *J*=6.6 Hz, 2H), 3.97 (dd, *J*=4.5, 7.1 Hz, 1H), 4.28 (br s, 1H), 4.48 (s, 2H), 4.89 (br s, 1H), 7.25–7.32 (m, 5H), 7.43 (tt, *J*=1.5, 6.9 Hz, 2H), 7.55 (tt, *J*=1.5, 7.1 Hz, 1H), 8.08 (dt, *J*=1.6, 6.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz):δ 22.7 (t), 22.8 (t), 25.4 (t), 25.8 (t), 26.1 (t), 29.5 (t), 29.7 (t), 29.7 (t), 29.7 (t, 7C), 29.8 (t), 30.8 (t), 32.8 (t), 35.1 (t), 37.5 (t), 63.0 (t), 68.9 (d), 70.2 (t), 72.9 (t), 77.8 (d), 79.7 (d), 109.4 (s), 127.5 (d), 127.6 (d), 128.3 (d, 3C), 128.4 (d), 129.8 (d), 130.2 (d), 130.4 (s), 133.0 (d), 133.5 (d), 138.6 (s), 166.1 (s) ppm; MS (ESI) *m*/*z*=659 $[M+Na]^+$. Anal. calcd for $C_{40}H_{60}O_6$: C, 75.43; H, 9.50%, found C, 75.14; H, 9.42%.

4.35. (1*R*,2*R*,5*S*,7*R*)-7-(5-(Benzyloxy)pentyl)-5-(15-(*tert*-butyldimethylsilyloxy)pentadecyl)-6,8-dioxabicyclo[3.2.1]octan-2-ol (37)

To a solution of **35** (500 mg, 0.94 mmol) in CH_2Cl_2 (5 mL) at 0 °C were added imidazole (130 mg, 1.9 mmol), DMAP (10 mg) and stirred for 15 min. To this, TBSCl (210 mg, 1.41 mmol) was added at 0 °C and stirred further for 1 h. The reaction mixture was diluted with CH_2Cl_2 (25 mL) and washed with brine, dried (Na_2SO_4), and concentrated. The resulting crude product was purified by column chromatography (90:10, 75:25 petroleum ether/EtOAc) to afford **37** (550 mg, 91%) and the disilyl ether **37-OTBS** (50 mg, 7%) as colorless syrups.

*4.35.1. Characterization data of **37**.* R_f (30% EtOAc/petroleum ether) 0.42; $[\alpha]_D^{25}$ +21.4 (*c* 0.9, $CHCl_3$); IR ($CHCl_3$) ν: 3428, 3019, 2929, 1464, 1216, 1097, 758, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.03 (s, 6H), 0.88 (s, 9H), 1.24–1.32 (m, 24H), 1.36–1.44 (m, 6H), 1.46–1.56 (m, 3H), 1.58–1.69 (m, 4H), 1.64 (br s, 1H), 1.77 (dt, *J*=5.8, 12.3 Hz, 1H), 1.92–2.03 (m, 1H), 2.39 (br s, 1H), 3.46 (t, *J*=6.5 Hz, 2H), 3.58 (t, *J*=6.8 Hz, 2H), 3.58 (s, 1H), 3.87 (dd, *J*=5.8, 7.5 Hz, 1H), 4.04 (br s, 1H), 4.49 (s, 2H), 7.24–7.28 (m, 1H), 7.29–7.35 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ −5.3 (q, 2C), 18.4 (s), 23.0 (t), 25.1 (t), 25.4 (t), 25.8 (t), 26.0 (q, 3C), 26.0 (t), 29.4 (t), 29.6 (t), 29.6 (t), 29.7 (t, 7C), 29.8 (t), 30.1 (t), 32.9 (t), 35.2 (t), 37.5 (t), 63.3 (t), 66.3 (d), 70.3 (t), 72.9 (t), 77.9 (d), 82.4 (d), 109.5 (s), 127.5 (d), 127.6 (d, 2C), 128.3 (d, 2C), 138.6 (s) ppm; MS (ESI) *m*/*z*=669 $[M+Na]^+$. Anal. calcd for $C_{39}H_{70}O_5Si$: C, 72.39; H, 10.90%, found: C, 71.95; H, 10.75%.

*4.35.2. Characterization data of **37-TBS**.* R_f (10% EtOAc/petroleum ether) 0.6; $[\alpha]_D^{25}$ +14.6 (*c* 1.2, $CHCl_3$); IR ($CHCl_3$) ν: 2929, 1471, 1216, 1098, 836, 759, 668 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.03 (s, 6H), 0.06 (s, 3H), 0.06 (s, 3H), 0.88 (s, 9H), 0.90 (s, 9H), 1.24–1.32 (m, 28H), 1.40–1.43 (m, 4H), 1.48–1.54 (m, 2H), 1.60–1.69 (m, 4H), 1.83 (dt, *J*=5.5, 12.3 Hz, 1H), 1.90–2.00 (m, 1H), 3.46 (t, *J*=6.5 Hz, 2H), 3.58 (t, *J*=6.8 Hz, 2H), 3.58 (br s, 1H), 3.78 (dd, *J*=5.2, 7.3 Hz, 1H), 3.92 (br s, 1H), 4.49 (s, 2H), 7.27–7.33 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ −5.3 (q, 2C), −4.7 (q), 18.3 (s), 18.4 (s), 22.9 (t), 25.5 (t), 25.8 (t), 25.9 (q, 3C), 26.0 (q, 3C), 26.1 (t), 29.4 (t), 29.6 (t, 5C), 29.7 (t, 5C), 29.8 (t), 30.3 (t), 32.9 (t), 35.2 (t), 37.6 (t), 63.3 (t), 66.9 (d), 70.3 (t), 72.9 (t), 77.7 (d), 83.0 (d), 109.2 (s), 127.5 (d), 127.6 (d, 2C), 128.3 (d, 2C), 138.6 (s) ppm; MS (ESI) *m*/*z*=783 $[M+Na]^+$. Anal. calcd for $C_{45}H_{84}O_5Si_2$: C, 70.99; H, 11.12%, found C, 70.75; H, 10.95%.

4.36. (15-((1*R*,2*R*,5*S*,7*R*)-2-(Benzyloxy)-7-(5-(benzyloxy)pentyl)-6,8-dioxabicyclo[3.2.1]octan-5-yl)pentadecyloxy)(*tert*-butyl)dimethylsilane (38)

To an ice-cooled solution (0 °C) of alcohol **37** (0.2 g, 0.31 mmol) in DMF (10 mL) was added NaH (11 mg, 0.46 mmol) and stirred for 30 min. Benzyl bromide (0.06 mL, 0.46 mmol) was added to the reaction mixture at 0 °C and the reaction mixture was stirred for

1 h. The reaction mixture was quenched with ice, partitioned between ethyl acetate, water and the organic layer was separated, washed with ethyl acetate, brine, dried (Na_2SO_4), and concentrated. Purification of the residue by column chromatography (90:10 petroleum ether/EtOAc) afforded **38** (0.21 g, 92%) as colorless syrup: R_f (7% EtOAc/petroleum ether) 0.6; $[\alpha]_D^{25}$ +20.2 (*c* 1.8, $CHCl_3$); IR ($CHCl_3$) ν: 2926, 1455, 1361, 1347, 1254, 1099, 836, 758, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.04 (s, 6H), 0.89 (s, 9H), 1.24–1.25 (m, 28H), 1.34–1.44 (m, 4H), 1.49–1.53 (m, 4H), 1.63–1.67 (m, 2H), 1.79–1.87 (m, 2H), 3.28 (br s, 1H), 3.45 (t, *J*=6.5 Hz, 2H), 3.59 (d, *J*=6.5 Hz, 2H), 3.78 (dd, *J*=4.8, 7.3 Hz, 1H), 4.17 (br s, 1H), 4.49 (s, 2H), 4.58 (d, *J*=12.8 Hz, 1H), 4.62 (d, *J*=12.5 Hz, 1H), 7.27–7.36 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ −5.3 (q, 2C), 18.4 (s), 21.9 (t), 22.7 (t), 25.4 (t), 25.8 (t), 26.0 (q, 3C), 29.4 (t), 29.6 (t), 29.7 (t, 8C), 29.8 (t), 30.7 (t), 31.9 (t), 32.9 (t), 35.2 (t), 37.4 (t), 63.3 (t), 70.3 (t, 2C), 72.3 (d), 72.9 (t), 77.7 (d), 80.0 (d), 109.3 (s), 127.5 (d, 2C), 127.6 (d, 2C), 127.6 (d, 2C), 128.3 (d, 2C), 128.4 (d, 2C), 138.5 (s), 138.6 (s) ppm; MS (ESI) *m*/*z*=760 $[M+Na]^+$. Anal. calcd for $C_{46}H_{76}O_5Si$: C, 74.95; H, 10.39%, found C, 74.80; H, 10.43%.

4.37. 15-((1*R*,2*R*,5*S*,7*R*)-2-(Benzyloxy)-7-(5-(benzyloxy)pentyl)-6,8-dioxabicyclo[3.2.1]octan-5-yl)pentadecan-1-ol (4)

To a solution of **38** (200 mg, 0.27 mmol) in MeOH (10 mL), *p*-TSA (5 mg, 0.03 mmol) was added and the reaction mixture was stirred at rt for 30 min. The reaction mixture was quenched by the addition of few drops of triethylamine and the solvent was evaporated. The crude residue was purified by column chromatography (60:40 petroleum ether/EtOAc) to obtain **4** (152 mg, 88%) as a colorless oil: R_f (20% EtOAc/petroleum ether) 0.4; $[\alpha]_D^{25}$ +23.8 (*c* 1.4, $CHCl_3$); IR ($CHCl_3$) ν: 3437, 2927, 1596, 1384, 1217, 1027, 759, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.24 (m, 26H), 1.35–1.46 (m, 4H), 1.49–1.70 (m, 8H), 1.79–1.87 (m, 2H), 3.28 (s, 1H), 3.45 (t, *J*=6.5 Hz, 2H), 3.61 (d, *J*=6.5 Hz, 2H), 3.78 (dd, *J*=4.8, 7.3 Hz, 1H), 4.17 (br s, 1H), 4.49 (s, 2H), 4.59 (d, *J*=12.5 Hz, 1H), 4.62 (d, *J*=12.5 Hz, 1H), 7.25–7.28 (m, 2H), 7.32–7.37 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.9 (t), 22.7 (t), 22.7 (t), 25.4 (t), 25.7 (t), 26.0 (t), 29.3 (t), 29.4 (t), 29.5 (t), 29.6 (t, 4C), 29.7 (t), 29.8 (t), 30.7 (t), 31.9 (t), 32.8 (t), 35.2 (t), 37.4 (t), 63.0 (t), 70.3 (t, 2C), 72.2 (d), 72.8 (t), 77.7 (d), 80.0 (d), 109.3 (s), 127.4 (d, 2C), 127.5 (d, 2C), 127.6 (d, 2C), 128.3 (d, 2C), 128.3 (d, 2C), 138.5 (s), 138.6 (s) ppm; MS (ESI) *m*/*z*=645 $[M+Na]^+$. Anal. calcd for $C_{40}H_{62}O_5$: C, 77.13; H, 10.03%, found C, 77.01; H, 9.86%.

4.38. *tert*-Butyl-4-((15-((1*R*,2*R*,5*S*,7*R*)-2-(benzyloxy)-7-(5-(benzyloxy)pentyl)-6,8-dioxabicyclo[3.2.1]octan-5-yl)pentadecyloxy)methyl)-2,2-dimethyloxazolidine-3-carboxylate (40)

At 0 °C, triethylamine (0.06 mL, 0.48 mmol) was added to a solution of **4** (0.2 g, 0.32 mmol) in CH_2Cl_2 and stirred for 30 min. MsCl (0.03 mL, 0.38 mmol) was added at 0 °C and stirred for 30 min. The reaction mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried (Na_2SO_4), concentrated and the resulting crude mesylate **39** (208 mg, 93%) was used as such for the next step without purification.

Serinol derivative **5** (65 mg, 0.28 mmol) was dissolved in dry DMSO (3 mL) and treated with NaH (5 mg, 60% dispersion in mineral oil, 0.21 mmol) and mesylate **39** (100 mg, 0.14 mmol) was added sequentially. The reaction immediately changed color from nearly colorless to orange red. The reaction was stirred at room temperature for 16 h, and was then quenched by the ice and diluted with ethyl acetate. The two layers were separated and the aqueous layer extracted with ethyl acetate (5×15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Purification by flash column chromatography (70:30 petroleum ether/EtOAc) yielded the serinol ether **40** (105 mg, 65%) as colorless oil: R_f (30% EtOAc/petroleum ether) 0.4; $[\alpha]_D^{25}$ +12.6 (*c* 0.2, $CHCl_3$); IR ($CHCl_3$) ν: 3017, 2928, 1690, 1454, 1393, 1216, 1092, 757, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.23–1.28 (m, 28H), 1.38 (s, 3H), 1.40 (s, 3H), 1.46 (m, 9H), 1.51–1.71 (m, 10H), 1.79–1.89 (m, 2H), 3.28 (br s, 1H), 3.28–3.30 (br s, 1H), 3.37 (t, *J*=6.5 Hz, 1H), 3.45 (t, *J*=6.5 Hz, 2H), 3.78 (dd, *J*=4.8, 7.5 Hz, 1H), 3.89–3.92 (m, 1H), 3.97–4.00 (m, 2H), 4.03–4.07 (m, 1H), 4.16 (br s, 1H), 4.48 (s, 2H), 4.58 (d, *J*=12.5 Hz, 1H), 4.62 (d, *J*=12.5 Hz, 1H), 7.25–7.28 (m, 3H), 7.32–7.37 (m, 7H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.9 (t), 22.7 (t), 22.7 (t), 24.4, 24.7 (2q, 1C), 25.4 (t), 26.0 (t), 26.1 (t), 26.2 (t), 26.7, 27.4 (2q, 1C), 28.4, 28.4 (2q, 3C), 29.3 (t), 29.5 (t), 29.6 (t, 2C), 29.7 (t, 4C), 29.8 (t), 30.7 (t), 31.9 (t), 35.2 (t), 37.4 (t), 56.3, 56.5 (2d, 1C), 65.4, 65.7 (2t, 1C), 69.2, 70.0 (2t, 1C), 70.3 (t, 2C), 71.4 (t), 72.3 (d), 72.9 (t), 77.7 (d), 79.7, 80.2 (2s, 1C), 80.0 (d), 93.2, 93.7 (2s, 1C), 109.3 (s), 127.5 (d), 127.6 (d, 3C), 127.6 (d, 2C), 128.3 (d, 2C), 128.4 (d, 2C), 138.5 (s), 138.6 (s), 151.7, 152.2 (2s, 1C) ppm; MS (ESI) *m*/*z*=858 $[M+Na]^+$. Anal. calcd for $C_{51}H_{81}NO_8$: C, 73.25; H, 9.76; N, 1.68%, found C, 72.80; H, 9.83; N, 1.42%.

4.39. (*S*)-*tert*-Butyl-4-((15-((1*R*,2*R*,5*S*,7*R*)-2-hydroxy-7-(5-hydroxypentyl)-6,8-dioxabicyclo[3.2.1]octan-5-yl)pentadecyloxy)methyl)-2,2-dimethyloxazolidine-3-carboxylate (3)

A suspension of **40** (50 mg, 0.06 mmol), $Pd(OH)_2$ (5 mg) in ethyl acetate (5 mL) was flushed with hydrogen gas and stirred under hydrogen (20 psi) atmosphere for 30 min. The reaction mixture was filtered through Celite, concentrated and the crude product was purified by column chromatography (60:40 petroleum ether/EtOAc) to yield **3** (35 mg, 90%) as colorless oil: R_f (40% EtOAc/petroleum ether) 0.4; $[\alpha]_D^{25}$ +36.3 (*c* 0.2, $CHCl_3$); IR ($CHCl_3$) ν: 3436, 2928, 1690, 1406, 1394, 1216, 758, 668 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.24–1.35 (m, 24H), 1.40–1.46 (m, 6H), 1.46 (s, 9H), 1.51–1.70 (m, 14H), 1.77 (dt, *J*=5.5, 12.3 Hz, 1H), 1.92–2.04 (m, 1H), 3.23–3.50 (m, 2H), 3.39 (dd, *J*=2.7, 8.1 Hz, 1H), 3.46 (dd, *J*=2.9, 8.1 Hz, 1H), 3.60–3.66 (m, 1H), 3.63 (t, *J*=6.44 Hz, 2H), 3.85–4.00 (m, 3H), 3.97–4.05 (m, 1H), 4.05 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.7 (t), 22.9 (t), 23.1, 24.4 (2q, 1C), 25.0 (t), 25.3 (t), 25.6 (t), 26.1 (t), 26.7, 27.5 (2q, 1C), 28.4, 28.5 (2q, 3C), 29.1 (t), 29.3 (t), 29.4 (t), 29.6 (t, 2C), 29.6 (t, 3C), 29.8 (t), 30.1 (t), 31.9 (t), 32.6 (t), 35.2 (t), 37.5 (t), 56.3, 56.5 (2d, 1C), 62.8 (t), 65.4, 65.7 (2t, 1C), 66.3 (d), 69.3, 70.0 (2t, 1C), 71.4 (t), 77.8 (d), 79.7, 80.2 (2s, 1C), 82.4 (d), 93.3, 93.7 (2s, 1C), 109.6 (s), 151.7, 152.2 (2s, 1C) ppm; MS (ESI) *m*/*z*=678 $[M+Na]^+$. Anal. calcd for $C_{37}H_{69}NO_8$: C, 67.75; H, 10.60; N, 2.14%, found C, 67.60; H, 10.43; N, 2.02%.

4.40. (*S*)-*tert*-Butyl-4-((15-((1*R*,2*R*,5*S*,7*R*)-7-((*E*)-7-ethoxy-7-oxohept-5-enyl)-2-hydroxy-6,8-dioxabicyclo[3.2.1]octan-5-yl)pentadecyloxy)methyl)-2,2-dimethyloxazolidine-3-carboxylate (2)

To an ice-cooled solution of the diol **3** (35 mg, 0.05 mmol) in CH_2Cl_2 (2 mL), DMP (22 mg, 0.06 mmol) was added in small portions and stirred for 6 h. The reaction mixture was quenched with ice, partitioned between CH_2Cl_2, water and the organic layer was separated, washed with CH_2Cl_2, brine, dried (Na_2SO_4), and concentrated to afford the aldehyde (29 mg, 85%) as colorless syrup. The crude aldehyde was used for the next step without purification.

To a solution of the aldehyde (29 mg, 0.04 mmol) in benzene (2 mL), the ylide [(carbethoxymethylene) triphenyl phosphorane] (42 mg, 0.12 mmol) was added and refluxed for 1 h. The solvent was evaporated under reduced pressure and the crude residue was purified by column chromatography (80:20 petroleum ether/EtOAc) to yield **2** (25 mg, 78%) as colorless oil: R_f (15% EtOAc/petroleum ether) 0.45; $[\alpha]_D^{25}$ +24.6 (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) ν: 3451, 2928, 1732, 1693, 1465, 1393, 1247, 1046, 758, 667 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.24–1.34 (m, 24H), 1.39–1.42 (m, 6H), 1.46 (s, 9H), 1.51–1.59 (m, 10H), 1.63–1.70 (m, 4H), 1.77 (dt, *J*=5.5, 12.5 Hz,

1H), 1.92–2.05 (m, 1H), 2.20 (q, J=6.5 Hz, 2H), 2.30–2.44 (m, 1H), 3.26–3.32 (m, 1H), 3.37–3.49 (m, 3H), 3.54–3.60 (m, 1H), 3.60 (br s, 1H), 3.66–3.92 (m, 3H), 3.97–3.99 (m, 1H), 4.05 (br s, 1H), 4.17 (q, J=7.0 Hz, 2H), 5.80 (br d, J=15.6 Hz, 1H), 6.94 (dt, J=7.0, 15.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.3 (q), 22.7 (t), 23.0 (t), 23.1, 24.4 (2q, 1C), 25.0 (t), 25.1 (t), 26.1 (t), 26.7, 27.5 (2q, 1C), 27.8 (t), 28.4, 28.5 (2q, 3C), 29.3 (t), 29.5 (t), 29.7 (t, 7C), 29.8 (t), 30.1 (t), 31.9 (t), 35.0 (t), 37.5 (t), 56.5, 56.3 (2d, 1C), 60.2 (t), 65.4, 65.7 (2t, 1C), 66.2 (d), 69.3, 70.0 (2t, 1C), 71.4 (t), 77.7 (d), 79.7, 80.2 (2s, 1C), 82.4 (d), 93.2, 93.7 (2s, 1C), 109.6 (s), 121.5 (d), 148.9 (d), 166.7 (s) ppm; MS (ESI) m/z=746 $[M+Na]^+$. Anal. calcd for $C_{41}H_{73}NO_9$: C, 68.01; H, 10.16; N, 1.93%, found C, 67.90; H, 10.03; N, 1.72%.

4.41. (*S*)-*tert*-Butyl 4-((heptadec-16-ynyloxy)methyl)-2,2-dimethyloxazolidine-3-carboxylate (42)

At 0 °C, triethylamine (6.7 mL, 47.5 mmol) was added to a solution of **32** (4 g, 15.8 mmol) in CH_2Cl_2 and stirred for 30 min. MsCl (1.9 mL, 23.8 mmol) was added at 0 °C and stirred for 30 min. The reaction mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried (Na_2SO_4), concentrated and the resulting crude mesylate **43** (4.8 g, 92%) was used as such for the next step without purification.

Serinol derivative **5** (2.8 g, 12.1 mmol) was dissolved in dry DMSO (30 mL) and treated with NaH (582 mg, 60% dispersion in mineral oil, 14.5 mmol) and mesylate **43** (4.8 g, 14.5 mmol) was added sequentially. The reaction immediately changed color from nearly colorless to orange red. The reaction was stirred at room temperature for 16 h, and was then quenched by the ice and diluted with ethyl acetate. The two layers were separated and the aqueous layer extracted with ethyl acetate (5×15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Purification by flash column chromatography (85:15 petroleum ether/EtOAc) yielded the serinol ether **42** (4.01 g, 71%) as colorless oil: R_f (10% EtOAc/petroleum ether) 0.4; $[\alpha]_D^{25}$ +20.9 (c 1.1, $CHCl_3$); IR ($CHCl_3$) ν: 3311, 2928, 2856, 1694, 1466, 1392, 1260, 1090, 847, 758, 629 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.23 (s, 24H), 1.45 (s, 9H), 1.43–1.49 (m, 2H), 1.50 (s, 3H), 1.55 (s, 3H), 1.92 (t, J=2.7 Hz, 1H), 2.15 (dt, J=2.6, 6.8 Hz, 2H), 3.22–3.36 (m, 1H), 3.42 (dd, J=6.4, 12.1 Hz, 2H), 3.48–3.60 (m, 1H), 3.86–4.07 (m, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 18.4 (t), 23.1, 24.4 (2q, 1C), 26.1 (t), 26.8, 27.5 (2q, 1C), 28.5 (2q, 3C), 28.5 (t), 28.8 (t), 29.1 (t), 29.5 (t), 29.5 (t), 29.6 (t, 4C), 29.7 (t, 3C), 56.3, 56.5 (2d, 1C), 65.4, 65.7 (2t, 1C), 68.1 (d), 69.3, 70.1 (2t, 1C), 71.4 (t), 79.7, 80.2 (2s, 1C), 84.8 (s), 93.3, 93.7 (2s, 1C), 151.7, 152.2 (2s, 1C) ppm; MS (ESI) m/z=488 $[M+Na]^+$; HRMS (ESI) calcd for $C_{28}H_{51}NO_4Na$ $[M+Na]^+$ 488.3716, found 488.3706.

4.42. (*S*)-*tert*-Butyl 4-(((*R*)-19-((4*R*,5*R*)-5-(5-(benzyloxy)pentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-19-hydroxynonadec-16-ynyloxy)methyl)-2,2-dimethyloxazolidine-3-carboxylate (41)

Alkyne **43** (3.2 g, 6.9 mmol), n-BuLi (4.6 mL, 6.9 mmol, 1.6 M in hexane), $BF_3\cdot Et_2O$ (0.9 mL, 6.9 mmol), epoxide **9** (550 mg, 1.7 mmol) were subjected to general procedure A. The crude product was purified by silica gel chromatography (80:20 petroleum ether/EtOAc) to obtain **41** (960 mg, 71%) as a colorless syrup: R_f (15% EtOAc/petroleum ether) 0.46; $[\alpha]_D^{25}$ +91.7 (c 0.9, $CHCl_3$); IR ($CHCl_3$) ν: 3019, 2930, 1691, 1456, 1393, 1216, 1173, 759, 668 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.23 (s, 24H), 1.34 (s, 3H), 1.38 (s, 3H), 1.40–1.44 (m, 6H), 1.46 (s, 9H), 1.51 (s, 3H), 1.55 (s, 3H), 1.58–1.62 (m, 4H), 2.14 (tt, J=2.7, 6.8 Hz, 2H), 2.23 (d J=4.2 Hz, 1H), 2.43–2.48 (m, 2H), 3.25–3.38 (m, 1H), 3.41–3.48 (m, 4H), 3.54–3.76 (m, 3H), 3.86–4.03 (m, 4H), 4.48 (s, 2H), 7.24–7.34 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 18.7 (t), 23.0, 24.3 (q, 2C), 24.3 (t), 26.0 (t, 3C), 26.2 (t), 27.1, 27.4 (q, 2C), 28.4 (q, 3C), 28.9 (t, 3C), 29.1 (t), 29.4 (t), 29.6 (t, 7C), 34.4 (t), 56.3, 56.4 (2d, 1C), 65.4, 65.6 (2t, 1C), 69.2, 70.0 (2t, 1C), 70.3 (t), 70.8 (d), 71.3 (t), 72.8 (t), 74.9 (s), 78.8 (d), 79.7, 80.2 (2s, 1C), 81.8 (d), 83.9 (s), 93.2, 93.6 (2s, 1C), 108.6 (s), 127.4 (d), 127.6 (d, 2C), 128.3 (d, 2C), 138.6 (s), 151.7, 152.2 (2s, 1C) ppm; MS (ESI) m/z=808 $[M+Na]^+$; HRMS (ESI) calcd for $C_{47}H_{79}NO_8Na$ $[M+Na]^+$ 808.5704, found 808.5649.

4.43. *tert*-Butyl (*R*)-1-(15-((1*R*,2*R*,5*S*,7*R*)-7-(5-(benzyloxy)pentyl)-2-hydroxy-6,8-dioxabicyclo[3.2.1]octan-5-yl)pentadecyloxy)-3-hydroxypropan-2-ylcarbamate (44)

A solution of the acetonide **41** (120 mg, 0.15 mmol) in dry CH_2Cl_2 was degassed properly. Then $(C_6H_5)_3PAuCl$ (4 mg, 0.008 mmol) followed by $AgSbF_6$ (3 mg, 0.008 mmol) were added at 0 °C and stirred at rt under argon atmosphere for 3 h. The reaction mixture was concentrated under reduce pressure and the obtained residue was purified by silica gel chromatography (40:60 petroleum ether/EtOAc) to obtain **44** (92 mg, 85%) as colorless syrup: R_f (40% EtOAc/petroleum ether) 0.4; $[\alpha]_D^{25}$ +20.8 (c 3.6, $CHCl_3$); IR ($CHCl_3$) ν: 3444, 2927, 2856, 1695, 1455, 1366, 1246, 1172, 1092, 755, 697 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.23 (s, 24H), 1.35–1.41 (m, 4H), 1.43 (s, 9H), 1.48–1.55 (m, 4H), 1.60–1.67 (m, 6H), 3.53 (dt, J=5.6, 18.7 Hz, 1H), 1.91–2.00 (m, 1H), 2.59 (br s, 1H), 3.40 (t, J=6.7 Hz, 2H), 3.44 (t, J=6.5 Hz, 2H), 3.53 (dd, J=3.9, 9.5 Hz, 1H), 3.57 (dd, J=3.6, 9.3 Hz, 2H), 3.65 (dd, J=3.7, 10.2 Hz, 1H), 3.75–3.78 (m, 2H), 3.85 (dd, J=5.4, 7.1 Hz, 1H), 4.03 (br s, 1H), 3.92 (br s, 1H), 4.47 (s, 2H), 5.19 (d, J=5.5 Hz, 1H), 7.24–7.33 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.9 (t), 25.0 (t), 25.3 (t), 26.0 (t), 28.3 (q, 3C), 29.4 (t), 29.5 (t), 29.5 (t, 3C), 29.6 (t, 7C), 29.7 (t), 30.1 (t), 35.2 (t), 37.5 (t), 51.4 (d), 64.2 (t), 66.2 (d), 70.2 (t), 71.4 (t), 71.7 (t), 72.8 (t), 77.8 (d), 79.6 (s), 82.3 (d), 109.5 (s), 127.4 (d), 127.6 (d, 2C), 128.3 (d, 2C), 138.5 (s), 156.0 (s) ppm; MS (ESI) m/z=728 $[M+Na]^+$; HRMS (ESI) calcd for $C_{41}H_{71}NO_8Na$ $[M+Na]^+$ 728.5078, found 728.5030.

4.44. (1*S*,2*R*,5*S*,7*R*)-5-(15-((*S*)-3-Acetoxy-2-(*tert*-butoxycarbonylamino)propoxy)pentadecyl)-7-(5-(benzyloxy)pentyl)-6,8-dioxabicyclo[3.2.1]octan-2-yl acetate (45)

To a solution of **44** (80 mg, 0.11 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added Et_3N (0.1 mL, 0.7 mmol), DMAP (2 mg) and stirred for 15 min. To this, acetic anhydride (0.032 mL, 0.34 mmol) was added at 0 °C and stirred further for 2 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The resulting crude product was purified by column chromatography (60:40 petroleum ether/EtOAc) to afford the diacetate **45** (87 mg, 97%) as colorless syrup: R_f (30% EtOAc/petroleum ether) 0.43; $[\alpha]_D^{25}$ 19.6 (c 5.5, $CHCl_3$); IR ($CHCl_3$) ν: 3447, 2928, 2855, 1739, 1497, 1366, 1244, 1114, 925, 756, 666 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.23 (s, 24H), 1.35–1.41 (m, 4H), 1.42 (s, 9H), 1.48–1.54 (m, 4H), 1.57–1.62 (m, 3H), 1.64–1.71 (m, 3H), 1.77 (dt, J=5.6, 18.7 Hz, 2H), 2.03 (s, 3H), 2.09 (s, 3H), 3.38 (t, J=6.7 Hz, 2H), 3.44 (t, J=6.6 Hz, 2H), 3.38–3.49 (m, 2H), 3.88 (dd, J=4.8, 7.3 Hz, 1H), 3.97 (br s, 1H), 4.09 (dd, J=5.5, 10.8 Hz, 1H), 4.15 (dd, J=6.2, 11.0 Hz, 2H), 4.47 (s, 2H), 4.66 (t, J=2.3 Hz, 1H), 4.89 (d, J=8.1 Hz, 1H), 7.24–7.33 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.8 (q), 21.3 (q), 22.5 (t), 22.7 (t), 25.3 (t), 26.0 (t), 26.0 (t), 28.3 (2q, 3C), 29.4 (t), 29.5 (t), 29.6 (t, 3C), 29.6 (t, 2C), 29.6 (t, 5C), 29.7 (t), 30.6 (t), 35.0 (t), 37.3 (t), 49.0 (d), 63.7 (t), 68.3 (d), 69.3 (t), 70.2 (t), 71.5 (t), 72.8 (t), 77.8 (d), 79.5 (s), 79.6 (d), 109.2 (s), 127.4 (d), 127.6 (d, 2C), 128.3 (d, 2C), 138.6 (s), 155.3 (s), 170.8 (s) ppm; MS (ESI) m/z=812 $[M+Na]^+$; HRMS (ESI) calcd for $C_{45}H_{75}NO_{10}Na$ $[M+Na]^+$ 812.5289, found 812.5244.

4.45. (1*S*,2*R*,5*S*,7*R*)-5-(15-((*S*)-3-Acetoxy-2-(*tert*-butoxycarbonylamino)propoxy)pentadecyl)-7-(5-hydroxypentyl)-6,8-dioxabicyclo[3.2.1]octan-2-yl acetate (46)

A suspension of **45** (200 mg, 0.3 mmol), Pd/C (5 mg) in ethyl acetate (5 mL) was flushed with hydrogen gas and stirred under

hydrogen (20 psi) atmosphere for 30 min. The reaction mixture was filtered through Celite, concentrated and the crude product was purified by column chromatography (50:50 petroleum ether/EtOAc) to yield **46** (175 mg, 88%) as colorless oil: R_f (30% EtOAc/petroleum ether) 0.4; $[\alpha]_D^{25}$ −47.4 (*c* 1.3, $CHCl_3$); IR ($CHCl_3$) ν: 3448, 2928, 2855, 1735, 1499, 1366, 1244, 1043, 756, 665 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.23 (s, 22H), 1.35–1.41 (m, 6H), 1.43 (s, 9H), 1.51–1.58 (m, 6H), 1.61–1.72 (m, 5H), 1.78 (dt, *J*=5.6, 18.4 Hz, 1H), 2.04 (s, 3H), 2.10 (s, 3H), 3.38 (t, *J*=6.4 Hz, 2H), 3.41–3.49 (m, 2H), 3.63 (t, *J*=6.4 Hz, 2H), 3.91 (t, *J*=5.5 Hz, 1H), 3.97 (br s, 1H), 4.10 (dd, *J*=5.3, 10.1 Hz, 1H), 4.13–4.18 (m, 2H), 4.67 (br s, 1H), 4.88 (d, *J*=7.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.8 (q), 21.3 (q), 22.5 (t), 22.7 (t), 25.3 (t), 25.5 (t), 26.0 (t), 28.3 (q, 3C), 29.4 (t), 29.5 (t), 29.6 (t, 3C), 29.6 (t, 2C), 29.7 (t, 5C), 29.7 (t), 30.6 (t), 32.6 (t), 35.0 (t), 37.3 (t), 49.0 (d), 62.8 (t), 63.7 (t), 68.4 (d), 69.3 (t), 71.6 (t), 77.8 (d), 79.6 (d), 109.3 (s), 155.4 (s), 170.9 (s) ppm; MS (ESI) *m*/*z*=722 $[M+Na]^+$; HRMS (ESI) calcd for $C_{38}H_{69}NO_{10}Na$ $[M+Na]^+$ 722.4819, found 722.4765.

4.46. (*E*)-Ethyl 7-((1*S*,2*R*,5*S*,7*R*)-2-acetoxy-5-(15-((*S*)-3-acetoxy-2-(*tert*-butoxycarbonylamino)propoxy)pentadecyl)-6,8-dioxabicyclo[3.2.1]octan-7-yl)hept-2-enoate (47)

To an ice-cooled solution of the alcohol **46** (50 mg, 0.07 mmol) in CH_2Cl_2 (2 mL), DMP (36 mg, 0.08 mmol) was added in small portions and stirred for 6 h. The reaction mixture was quenched with ice, partitioned between CH_2Cl_2, water and the organic layer was separated, washed with CH_2Cl_2, brine, dried (Na_2SO_4), and concentrated to afford the aldehyde (40 mg, 80%) as colorless syrup. The crude aldehyde was used for the next step without purification.

To a solution of the aldehyde (35 mg, 0.05 mmol) in benzene (2 mL), the ylide [(carbethoxymethylene) triphenyl phosphorane] (52 mg, 0.15 mmol) was added and refluxed for 1 h. The solvent was evaporated under reduced pressure and the crude residue was purified by column chromatography (80:20 petroleum ether/EtOAc) to yield **47** (29 mg, 75%) as colorless oil: R_f (10% EtOAc/petroleum ether) 0.4; $[\alpha]_D^{25}$ −83.4 (*c* 0.98, $CHCl_3$); IR ($CHCl_3$) ν: 3367, 2927, 2854, 1720, 1500, 1465, 1244, 1042, 971, 775 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.23 (s, 24H), 1.27 (t, *J*=7.2 Hz, 3H), 1.36–1.41 (m, 4H), 1.43 (s, 9H), 1.47–1.56 (m, 6H), 1.65–1.72 (m, 3H), 1.79 (dt, *J*=5.8, 8.2 Hz, 1H), 2.05 (s, 3H), 2.10 (s, 3H), 2.19 (dd, *J*=6.8, 13.6 Hz, 2H), 3.39 (t, *J*=6.7 Hz, 2H), 3.42–3.50 (m, 2H), 3.89 (dd, *J*=5.1, 7.8 Hz, 1H), 3.97 (br s, 1H), 4.09 (dd, *J*=5.6, 11.1 Hz, 1H), 4.14–4.18 (m, 2H), 4.17 (q, *J*=7.3 Hz, 2H), 4.67 (t, *J*=2.0 Hz, 1H), 4.87 (d, *J*=7.4 Hz, 1H), 5.80 (d, *J*=15.6 Hz, 1H), 6.93 (dt, *J*=7.0, 15.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.3 (q), 20.9 (q), 21.3 (q), 22.5 (t), 22.8 (t), 25.1 (t), 26.1 (t), 27.8 (t), 28.3 (q, 3C), 29.5 (t), 29.5 (t), 29.6 (t, 3C), 29.6 (t, 2C), 29.7 (t, 5C), 29.7 (t), 30.6 (t), 32.1 (t), 34.9 (t), 37.4 (t), 60.1 (t), 63.7 (t), 68.3 (d), 69.3 (t), 71.6 (t), 77.7 (d), 79.7 (d), 109.4 (s), 121.5 (d), 148.9 (d), 152.7 (s), 166.7 (s), 170.9 (s, 2C) ppm; MS (ESI) *m*/*z*=790 $[M+Na]^+$; HRMS (ESI) calcd for $C_{42}H_{73}NO_{11}Na$ $[M+Na]^+$ 790.5082, found 790.5037.

4.47. (4*S*)-*tert*-Butyl 4-((15-((1*R*,2*R*,5*S*)-7-(5-(benzyloxy)pentyl)-2-hydroxy-6,8-dioxabicyclo[3.2.1]octan-5-yl)pentadecyloxy)methyl)-2,2-dimethyloxazolidine-3-carboxylate (48)

To a solution of diol **44** (100 mg, 0.14 mmol) in acetone, were added DMP (0.07 mL, 0.6 mmol) and *p*-TSA (5 mg) at 0 °C. The reaction mixture was stirred at rt for 2.5 h when TLC analysis indicates the reaction was complete then was treated with few drops of triethylamine and the solvent was removed under reduced pressure and the resulting crude product was purified by column chromatography (70:30 petroleum ether/EtOAc) to obtain **48** (87 mg, 82%) as a colorless thick syrup: R_f (35% EtOAc/petroleum ether) 0.4; $[\alpha]_D^{25}$ +28.7 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) ν: 3404, 2925, 2854, 1702, 1459, 1388, 1103, 847, 770, 732, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.24 (s, 24H), 1.38–1.44 (m, 6H), 1.46 (s, 9H), 1.51 (s, 3H), 1.55 (s, 3H), 1.53–1.54 (m, 2H), 1.60–1.69 (m, 6H), 1.76 (dt, *J*=5.6, 18.4 Hz, 1H), 1.93–2.00 (m, 1H), 2.37 (d, *J*=6.3 Hz, 1H), 3.29 (dd, *J*=9.5, 21.4 Hz, 1H), 3.41 (t, *J*=6.7 Hz, 2H), 3.45 (t, *J*=6.4 Hz, 2H), 3.37–3.49 (m, 1H), 3.59 (br s, 1H), 3.85–3.92 (m, 3H), 3.98 (br s, 1H), 4.04 (br s, 1H), 4.49 (s, 2H), 7.24–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 23.0 (t), 23.1, 24.4 (2q, 1C), 25.1 (t), 25.4 (t), 26.0 (t), 26.1 (t), 26.7, 27.5 (2q, 1C), 28.4, 28.5 (2q, 3C), 29.5 (t), 29.6 (t, 5C), 29.7 (t, 4C), 29.8 (t), 30.1 (t), 35.2 (t), 37.5 (t), 56.3, 56.5 (2q, 1C), 65.4, 65.7 (2t, 1C), 66.3 (d), 69.3, 70.0 (2t, 1C), 70.3 (t), 71.4 (t), 72.9 (t), 77.9 (d), 79.7, 80.2 (2s, 1C), 82.3 (d), 93.2, 93.7 (2s, 1C), 109.5 (s), 127.5 (d), 127.6 (d, 2C), 128.3 (d, 2C), 138.6 (s), 151.7, 152.2 (2s, 1C) ppm; MS (ESI) *m*/*z*=768 $[M+Na]^+$; HRMS (ESI) calcd for $C_{44}H_{75}NO_8Na$ $[M+Na]^+$ 768.5391, found 768.5352.

4.48. (4*S*)-*tert*-Butyl-4-((15-((1*R*,2*R*,5*S*)-2-hydroxy-7-(5-hydroxypentyl)-6,8-dioxabicyclo[3.2.1]octan-5-yl)pentadecyloxy)methyl)-2,2-dimethyloxazolidine-3-carboxylate (3)

A suspension of **48** (50 mg, 0.07 mmol), 20% $Pd(OH)_2/C$ (5 mg) in ethyl acetate (5 mL) was flushed with hydrogen gas and stirred under hydrogen (20 psi) atmosphere for 30 min. The reaction mixture was filtered through Celite, concentrated and the crude product was purified by column chromatography (60:40 petroleum ether/EtOAc) to yield **3** (40 mg, 91%) as colorless oil: R_f (40% EtOAc/petroleum ether) 0.4; $[\alpha]_D^{25}$ +36.3 (*c* 0.2, $CHCl_3$); IR ($CHCl_3$) ν: 3436, 2928, 1690, 1406, 1394, 1216, 758, 668 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.24–1.35 (m, 24H), 1.37–1.44 (m, 6H), 1.46 (s, 9H), 1.51–1.59 (m, 11H), 1.62–1.71 (m, 3H), 1.77 (dt, *J*=5.5, 12.3 Hz, 1H), 1.92–2.01 (m, 1H), 2.37 (d, *J*=9.2 Hz, 1H), 3.26–3.50 (m, 2H), 3.39 (dd, *J*=2.7, 8.1 Hz, 1H), 3.46 (dd, *J*=2.9, 8.1 Hz, 1H), 3.60–3.66 (m, 1H), 3.63 (t, *J*=6.4 Hz, 2H), 3.85–4.00 (m, 3H), 3.97–4.05 (m, 1H), 4.05 (br s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 22.7 (t), 22.9 (t), 23.1, 24.4 (2q, 1C), 25.0 (t), 25.3 (t), 25.6 (t), 26.1 (t), 26.7, 27.5 (2q, 1C), 28.4, 28.5 (2q, 3C), 29.1 (t), 29.3 (t), 29.4 (t), 29.6 (t, 2C), 29.6 (t, 3C), 29.8 (t), 30.1 (t), 31.9 (t), 32.6 (t), 35.2 (t), 37.5 (t), 56.3, 56.5 (2d, 1C), 62.8 (t), 65.4, 65.7 (2t, 1C), 66.3 (d), 69.3, 70.0 (2t, 1C), 71.4 (t), 77.8 (d), 79.7, 80.2 (2s, 1C), 82.4 (d), 93.3, 93.7 (2s, 1C), 109.6 (s), 151.7, 152.2 (2s, 1C) ppm; MS (ESI) *m*/*z*=678 $[M+Na]^+$; HRMS (ESI) calcd for $C_{37}H_{69}NO_8Na$ $[M+Na]^+$678.4921, found 678.4874.

4.49. (4*S*)-*tert*-Butyl 4-((15-((1*R*,2*R*,5*S*)-7-((*E*)-7-ethoxy-7-oxohept-5-enyl)-2-hydroxy-6,8-dioxabicyclo[3.2.1]octan-5-yl) pentadecyloxy)methyl)-2,2-dimethyloxazolidine-3-carboxylate (2)

To an ice-cooled solution of the diol **3** (35 mg, 0.05 mmol) in CH_2Cl_2 (2 mL), DMP (27 mg, 0.6 mmol) was added in small portions and stirred for 6 h. The reaction mixture was quenched with ice, partitioned between CH_2Cl_2, water and the organic layer was separated, washed with CH_2Cl_2, brine, dried (Na_2SO_4), and concentrated to afford the aldehyde (30 mg, 85%) as colorless syrup. The crude aldehyde was used for the next step without purification.

To a solution of the aldehyde (30 mg, 0.05 mmol) in benzene (2 mL), the ylide ((carbethoxymethylene) triphenyl phosphorane) (56 mg, 0.16 mmol) was added and refluxed for 1 h. The solvent was evaporated under reduced pressure and the crude residue was purified by column chromatography (80:20 petroleum ether/EtOAc) to yield **2** (26 mg, 78%) as colorless oil: R_f (15% EtOAc/petroleum ether) 0.45; $[\alpha]_D^{25}$ +26.6 (*c* 0.4, $CHCl_3$); MS (ESI) *m*/*z*=746 $[M+Na]^+$; HRMS (ESI) calcd for $C_{41}H_{73}NO_9Na$ $[M+Na]^+$ 746.5183. found 746.5129.

Acknowledgements

We thank the Ministry of Science and Technology for funding through the Department of Science and Technology under the

Green Chemistry Program (No. SR/S5/GC-20/2007). Financial support from CSIR (New Delhi) in the form of research fellowships to SD and BI is gratefully acknowledged.

Supplementary data

NMR spectra. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.12.045.

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