DOI: 10.1002/ejoc.200800680

First Asymmetric Total Synthesis of Penarolide Sulfate A_1

Debendra K. Mohapatra,*[a][‡] Debabrata Bhattasali,[a] Mukund K. Gurjar,[a] M. Islam Khan,[b] and K. S. Shashidhara[b]

Keywords: Macrocycles / Asymmetric synthesis / C–C coupling / Dihydroxylation / Epoxidation / Total synthesis / Regioselectivity

Penarolide sulfate A_1, with three contiguous stereogenic centers on a macrocyclic skeleton, affords promise as an α-glucosidase inhibitor. Herein, we describe the first asymmetric total synthesis of this natural product. A stereoselective strategy for rapid assembly of the complete framework of the 30-membered macrocyclic core is delineated herein. Sequential amidation and intramolecular Sonogashira cross-coupling reactions were pivotal to the success of our efforts.

Introduction

In 2000, Fusetani and coworkers reported the isolation, structure elucidation, and biological activity of new α-glucosidase inhibitors Penarolide sulfate A_1 (**1**) and A_2 (**2**) (Figure 1) from the marine sponge *Penares* sp., with IC_{50} values of 1.2 and 1.5 μg mL^{-1}, respectively.[1] The constitution and relative stereochemistry of Penarolide sulfate A_1 and A_2 were elucidated by chemical degradation and extensive 2D NMR spectroscopic studies; the absolute configuration was established by application of Mosher's method. Penarolide sulfate A_1 and A_2 are 30- and 31-membered macrolides encompassing a proline residue and three sulfate groups.

The intriguing structural features, noteworthy biological profiles, and limited availability make Penarolide sulfate A_1 and A_2 attractive targets for total synthesis. No report has yet appeared on the total synthesis of any of these natural products. We report, herein, a novel convergent strategy for the total synthesis of Penarolide sulfate A_1; efficient assembly of its 30-membered macrolide core is realized through sequential amidation[2] and macrocyclization by an intramolecular Sonogashira cross-coupling reaction.[3]

Retrosynthesis of **1** into three segments **4**, **5** and **8** provided the impetus for our work. The assembly of the 30-membered macrocyclic core was envisioned to be a sequence of amidation between the C1–C18 acid and amine segments (**8** and **4**) followed by intramolecular Sonogashira reaction of the amide thus formed. Key segment **4** would be elaborated from chiral building block **6** by a simple esterification[4] reaction with commercially available *N*-Boc-L-proline. Our plan for the synthesis of the C1–C18 subunit is founded upon the regioselective Sharpless asymmetric dihydroxylation[5] and Sharpless asymmetric epoxidation reactions[6] (Scheme 1).

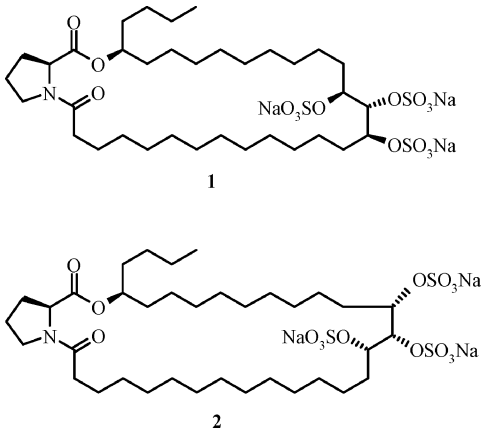
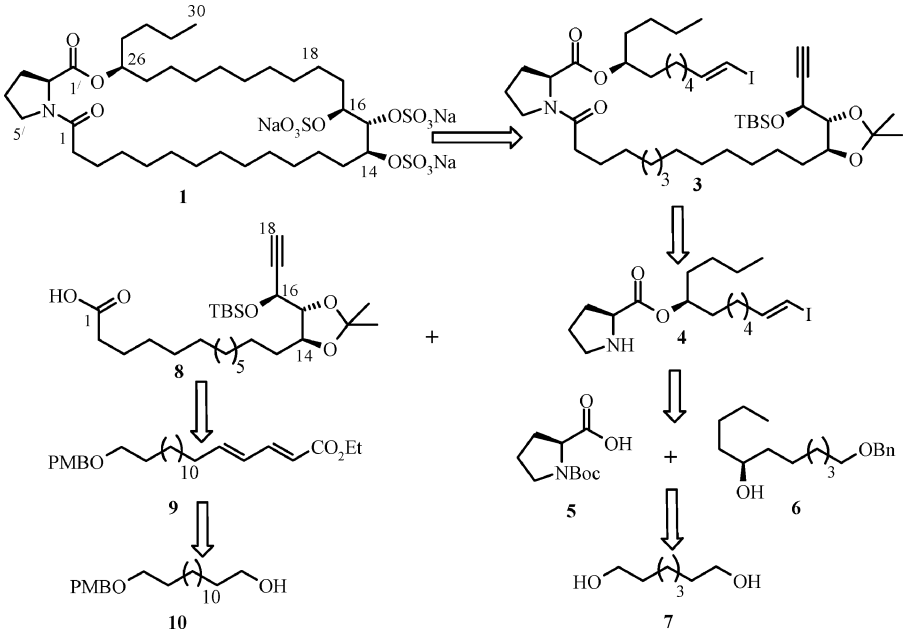


Figure 1. Penarolide sulfate A_1 (**1**) and A_2 (**2**).

Results and Discussion

The synthesis of C1–C18 segment **8** was initiated with the introduction of the diene appendage at C14 of aldehyde **12** through a Horner–Wadsworth–Emmons reaction[7] (produced exclusive *E*,*E* diastereomer **9** in 83% yield). Asymmetric dihydroxylation of **9** (*E*,*E*-dienoate) by using $(DHQ)_2$-PHAL (= hydroquinine 1,4-phthalazinediyl diether) as the chiral ligand at 0 °C for 6 h gave exclusively the regioselec-

[a] Division of Organic Chemistry, National Chemical Laboratory, Dr. Homi Bhabha Road, Pune 411008, India
Fax: +91-40-27160512
E-mail: mohapatra@iict.res.in
dkm_77@yahoo.com
[b] Division of Biochemical Sciences, National Chemical Laboratory, Dr. Homi Bhabha Road, Pune 411008, India
[‡] Current Address: Division of Organic Chemistry, Indian Institute of Chemical Technology, Tarnaka, Hyderabad 500007, India
Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.

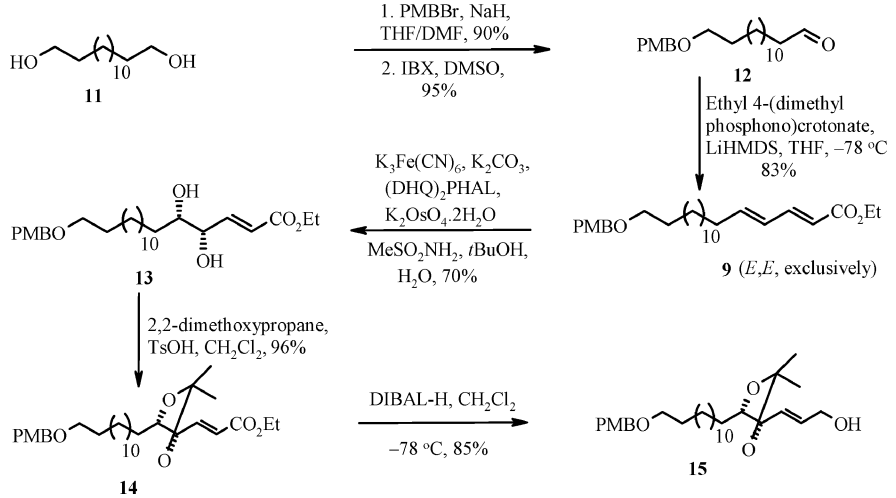


Scheme 1. Retrosynthetic analysis of penarolide sulfate A_1 (**1**).

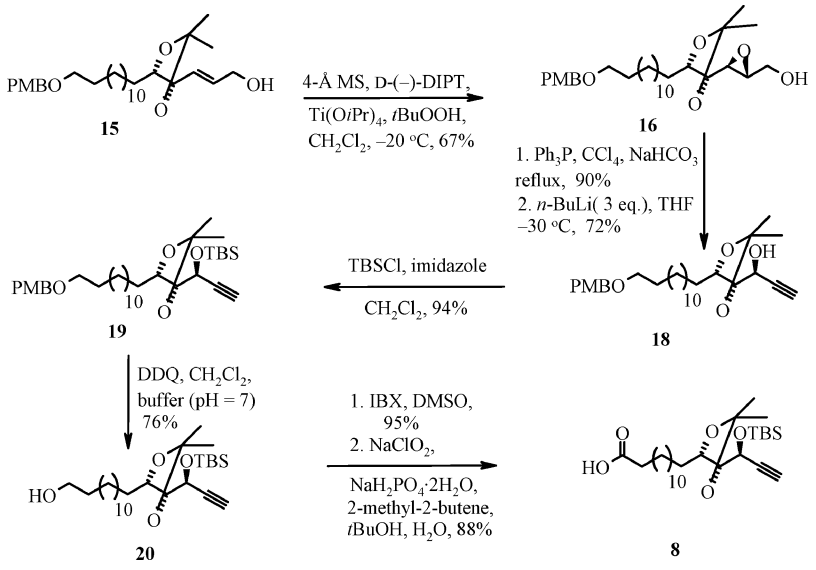
tive dihydroxy derivative **13** (*ee* = 98.4%)[8] in 70% yield. Protection of the diol group present in compound **13** as an isopropylidene derivative followed by reduction with DIBAL-H gave alcohol **15** (Scheme 2). Sharpless asymmetric epoxidation of **15** produced **16** as a single diastereomer (confirmed from its ^{13}C NMR spectra). Epoxy chloride **17** was then prepared from **16** by treatment with Ph_3P and CCl_4 at reflux. Compound **17**, upon treatment with an excess amount of *n*BuLi (3 equiv.), afforded alkynol **18**.[9] Protection of the secondary alcohol as its TBS ether followed by oxidative removal of the PMB ether with DDQ[10] yielded the penultimate C_{18} alcohol **20**. Oxidation of **20** to the corresponding aldehyde with IBX followed by further oxidation with $NaClO_2$ in *t*BuOH at 0 °C gave the required C_{18} acid **8** in 88% yield[11] (Scheme 3).

We next turned our attention to the preparation of amine building block **4**. Reaction of known aldehyde **21**[12] under Corey–Chakovsky reaction[13] conditions produced racemic terminal epoxide **22**. Compound **22** was then subjected to hydrolytic kinetic resolution (HKR)[14] by using (*R*,*R*)-salen-Co^{III}OAc (0.5 mol-%) and distilled water (0.55 equiv.) at 0 °C to afford chiral epoxide **23** with 98.8% *ee*[15] along with diol **24** with 93.3% *ee*.[16] Unrequired diol **24** was converted into required epoxide **23** following a known strategy[17] (Scheme 4).

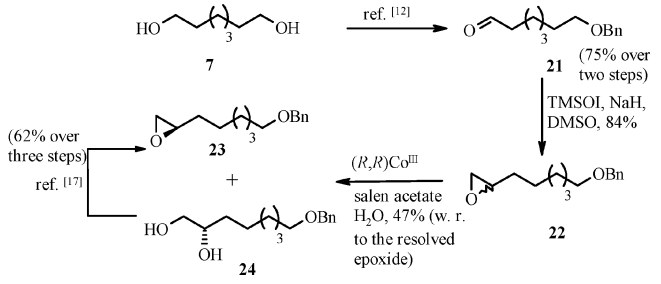
Secondary alcohol **6** was derived by the regioselective ring opening[18] of **23** with propylmagnesium bromide in the presence of catalytic CuCN in dry THF. Esterification with commercially available *N*-Boc-L-proline under standard EDC/DMAP {EDC = 1-ethyl-3-[3′-(dimethylamino)propyl]-



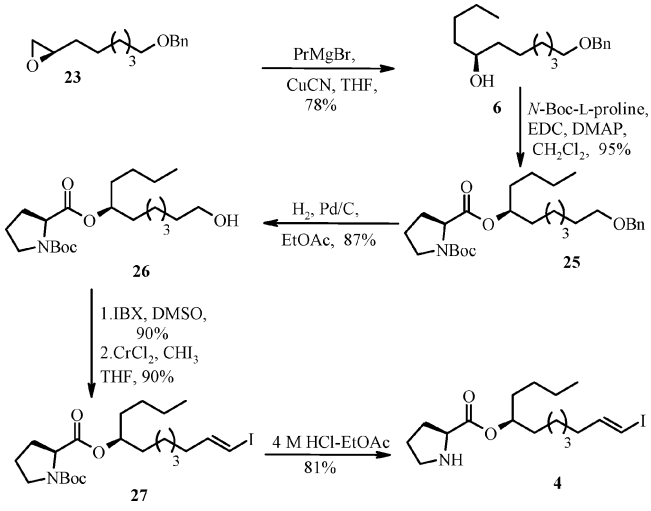
Scheme 2. Synthesis of allylic alcohol **15**.



Scheme 3. Synthesis of C_{18} acid **7**.



Scheme 4. Synthesis of chiral epoxide **23**.



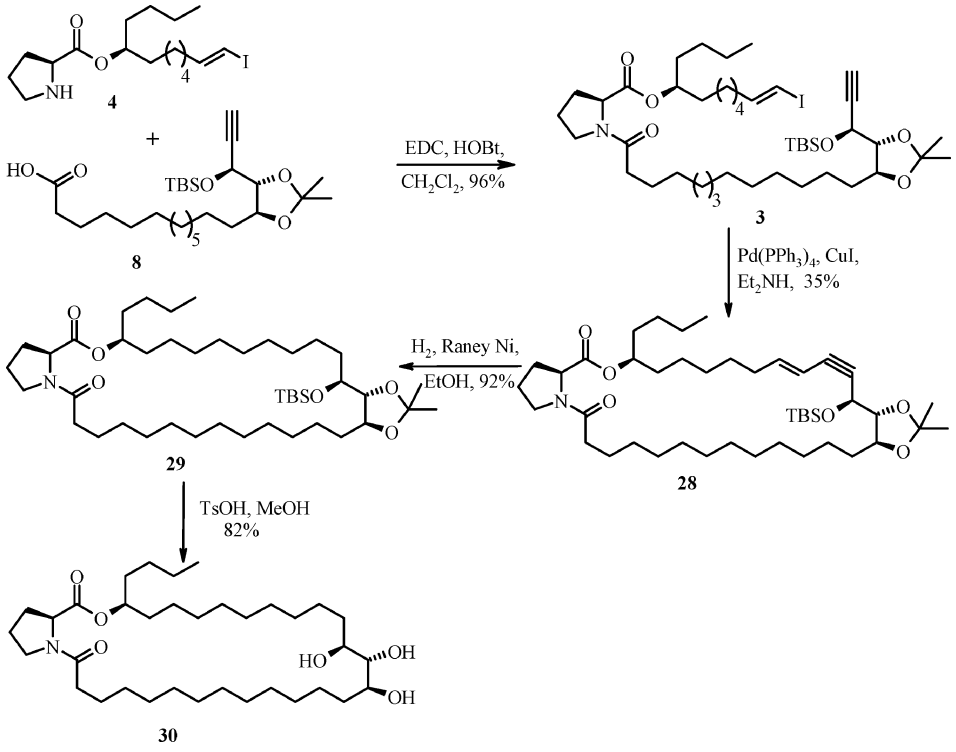
Scheme 5. Synthesis of amine **4**.

carbodiimide} conditions afforded **25**. In a sequence of three simple chemical transformation, viz., hydrogenolysis,[19] IBX oxidation, and Takai olefination,[20] **25** was transformed into **27**. Deprotection of the *tert*-butoxycarbonyl protecting group under acidic conditions[21] gave target amine building block **4** in 81% yield (Scheme 5).

Assembly of fragments **4** and **8** to target molecule **1** became our next task. EDC/HOBt-mediated (HOBt = 1-hydroxybenzotriazole) coupling of amine **4** with carboxylic acid **8** was facile and afforded coupled product **3**. Formation of the 30-membered macrocyclic ring following an intramolecular Sonogashira cross-coupling reaction was our next goal; several reaction conditions to tune the macrocyclization under Sonogashira coupling conditions were attempted. Finally, the reagent combination of tetrakis(triphenylphosphane)palladium(0) and CuI in anhydrous diethylamine at 0 °C for 30 min gave the best result. Reduction of both the double and triple bonds present in the macrocycle by Raney Ni[22] in ethanol under a hydrogen atmosphere and complete deprotection by using TsOH[23] in methanol led to the formation of triol **30**. The spectral as well as analytical data of synthetic **30** was in good agreement with the assigned structure (Scheme 6).

Finally, we tried persulfation[24] on compound **30** under various standard persulfation reaction conditions (mentioned in Table 1), but we were dismayed to obtain complex, intractable reaction mixtures in all cases. However, we were delighted to see that modification of procedure 1 (Table 1) for persulfation of **30** as depicted in Scheme 7 yielded trisulfated natural product **1** (Penarolide sulfate A_1) in 84% yield. The spectral and analytical data of synthetic **1** completely matched that of the natural product isolated by Fusetani et al.[1]

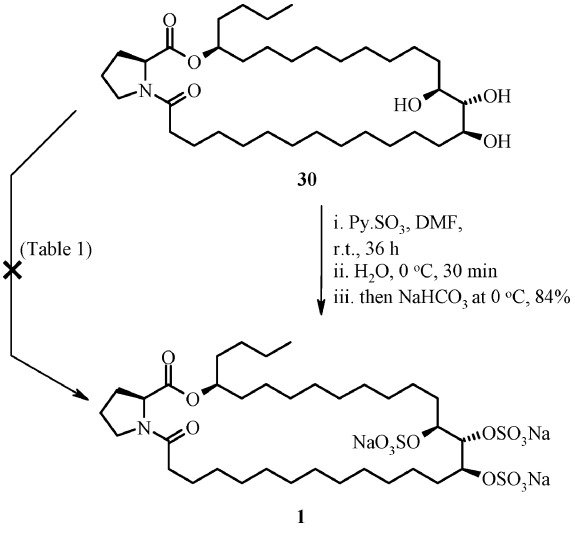
At this stage, we thought it would be pertinent to evaluate also the enzyme inhibition activity of **30**, because then we would be able to rationalize the importance of the sulfate groups toward biological activity for this class of molecules.



Scheme 6. Synthesis of desulfated penarolide sulfate A_1 (**30**).

Table 1. Various persulfation reaction conditions.

Conditions for Persulfation of **30**	Observation
1. (a) Py·SO_3, DMF, r.t., 36 h; (b) $NaHCO_3$, 0 °C	complex intractable reaction mixture
2. Py·SO_3, Na_2SO_4, microwave, 10 min	complex intractable reaction mixture
3. (a) Py·SO_3, DMF, r.t., 20 h; (b) acetone/methanol (9:1), H_2O, 0 °C; (c) then 1 N NaOH, 0 °C	complex intractable reaction mixture



Scheme 7. Synthesis of penarolide sulfate A_1.

Enzyme Inhibition Study of 30

Thus, desulfated penarolide sulfate also acts as an α-glucosidase inhibitor (IC_{50} = 166 μM); the extent of inhibition is much less than that of parent molecule **1**. Compound **30** inhibits β-glucosidase, β-mannosidase, and β-galactosidase, but the extent of inhibition towards the corresponding α-analogs is negligible at 1 mM inhibitor concentration (Table 2, Figure 2).

Table 2. Inhibition of various glycosides by desulfated penarolide sulfate A_1 (**30**) as the inhibitor.[a]

Glycosidases	K_i [μM]
α-Glucosidase	160
β-Glucosidase	21.0%[b]
α-Galactosidase	7.5%[b]
β-Galactosidase	30.0%[b]
α-Mannosidase	2.4%[b]
β-Mannosidase	35%[b]

[a] The enzyme inhibition study was carried out under similar conditions to those reported in ref.[25] and the same is detailed in the Experimental Section. [b] Percentage inhibition at 1 mM inhibitor concentration.

As compound **30** was found to be weakly active in comparison to compound **1**, we attempted the preparation of the partially sulfated derivatives of **30**. For this endeavor, controlled deprotection of compound **29** by using TBAF in THF resulted in the formation of compound **31** in 94% yield (Scheme 8). Following our earlier method of sulfation, compound **31** afforded a number of products that we failed

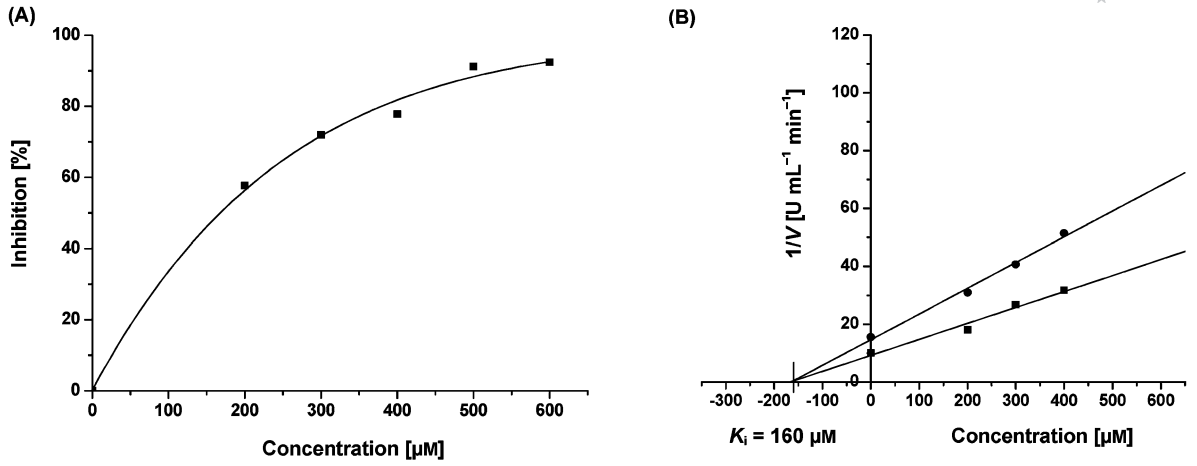
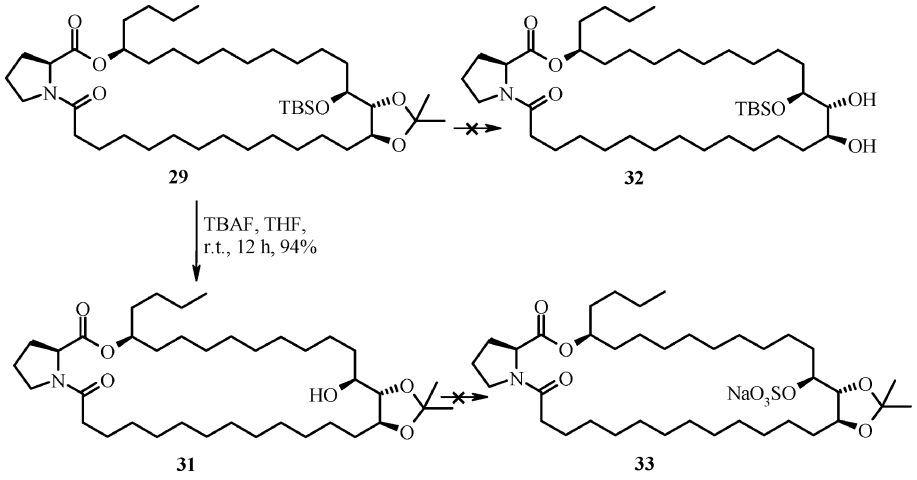


Figure 2. Binding of **30** to α-glucosidase and kinetics of inhibition. (A) The sigmoidal curve indicates the best fit for the percentage inhibition data obtained, and the IC_{50} value was calculated from the graph. (B) Enzymatic activity of the α-glucosidase was estimated by using the substrate *p*-nitrophenyl-α-D-glucopyaranoside 250 μM (■) and 500 μM (●) at different concentrations of **30**. K_i was determined by following the method of Dixon.[26]



Scheme 8. Selective deprotection and partial sulfation.

to characterize. Similarly, controlled deprotection of the isopropylidene group present in compound **29** in the presence of the TBS group was attempted to obtain dihydroxy derivative **32**. Various Lewis acid [$Zn(NO_3)_2{\cdot}6H_2O$,[27] $CuCl_2{\cdot}2H_2O$ in ethanol,[28] $FeCl_3{\cdot}6H_2O/SiO_2$[29]] mediated reaction conditions at room temperature were found to be futile, and we ended up with unreacted starting material. However, employment of harsh reaction conditions (heating from 70 to 110 °C in the presence of earlier-mentioned Lewis acids) furnished completely deprotected triol **30**. TMSOTf[30] mediated opening of the isopropylidene group also failed to furnish desired product **32**. Because we were unable to prepare the partially sulfated derivatives of **30**, their bioevaluation was not possible and the role of the sulfate groups toward biological activity remained inconclusive for this class of natural product.

Conclusions

In conclusion, the first total synthesis of penarolide sulfate A_1 is documented. The cornerstone of our synthetic protocol was intramolecular Sonogashira cross-coupling reaction for the construction of the key 30-membered macrocyclic ring. Regioselective Sharpless asymmetric dihydroxylation, Sharpless asymmetric epoxidation, and Jacobsen HKR were employed for the generation of the four asymmetric centers present in the molecule. A biological activity profile of the desulfated penarolide sulfate A_1 (**30**) was also disclosed. The reported approach is convergent in nature and provides considerable flexibility for the synthesis of related unnatural analogs.

Experimental Section

General Remarks: Air- and/or moisture-sensitive reactions were carried out with anhydrous solvents under an atmosphere of argon in oven/flame-dried glassware. All anhydrous solvents were distilled prior to use: THF, benzene, toluene, and diethyl ether from Na and benzophenone; CH_2Cl_2 from CaH_2; MeOH, EtOH from Mg cake. Commercial reagents were used without purification. Column chromatography was carried out by using silica gel (60–120 mesh) and (230–400 mesh). Specific optical rotations $[\alpha]_D$ are given in

10^{-1}° $cm^2 g^{-1}$. Infrared spectra were recorded in $CHCl_3$/neat (as mentioned) and reported in wave number (cm^{-1}). ^1H and ^{13}C NMR chemical shifts are reported in ppm downfield from tetramethylsilane 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, quint. = quintet, m = multiplet, br. = broad.

14-(4-Methoxybenzyloxy)tetradecan-1-ol (10): To a stirred solution of tetradecane-1,14-diol (**11**; 26.8 g, 116.3 mmol) in THF/DMF (7:3, 200 mL) at 0 °C was added NaH (4.67 g, 116.3 mmol) portionwise followed by the addition of PMBBr (16.41 mL, 116.3 mmol). After 12 h, the reaction was quenched by the addition of ice-cold water (130 mL), and the reaction mixture was concentrated under reduced pressure. The residue thus obtained was diluted with water and extracted with ethyl acetate (3 × 100 mL). The combined organic fraction was washed with water (150 mL), brine, and dried with anhydrous Na_2SO_4, and the solvent was evaporated. The residue was purified on silica gel (light petroleum/ethyl acetate, 4:1) to afford **10** (36.7 g, 90%) as a white solid. M.p. 63 °C. IR (liquid film, $CHCl_3$): $\tilde{\nu}$ = 3421, 1612, 1248, 1036 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.25 (d, J = 8.7 Hz, 2 H), 6.86 (d, J = 8.7 Hz, 2 H), 4.42 (s, 2 H), 3.80 (s, 3 H), 3.62 (t, J = 6.6 Hz, 2 H), 3.42 (t, J = 6.6 Hz, 2 H), 1.62–1.52 (m, 4 H), 1.25 (m, 20 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 159.0, 130.6, 129.1, 113.7 (2 C), 72.4, 70.1, 62.8, 55.1, 32.7, 29.7, 29.6 (2 C), 29.4 (2 C), 26.2, 25.7 ppm. $C_{22}H_{38}O_3$ (350.54): calcd. C 75.38, H 10.93; found C 75.16, H 11.21.

14-(4-Methoxybenzyloxy)tetradecanal (12): Iodoxybenzoic acid (IBX; 28.12 g, 100.4 mmol) in DMSO (100 mL) was stirred at room temperature for 30 min, till it become a clear solution. Compound **10** (35.2 g, 100.4 mmol) in THF (100 mL) was added to the clear solution, and the mixture was stirred at room temperature for 4 h. The reaction mixture was then diluted with water (100 mL) and filtered. THF was removed under reduced pressure, and the reaction mixture was extracted with diethyl ether (3 × 75 mL), washed with $NaHCO_3$, water, brine, dried with anhydrous Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (light petroleum/ethyl acetate, 9:1) to afford **12** (33.2 g, 95%) as a yellow oil. IR (liquid film, $CHCl_3$): $\tilde{\nu}$ = 2926, 1726, 1613, 1247, 1099 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 9.75 (t, J = 1.9 Hz, 1 H), 7.24 (d, J = 8.7 Hz, 2 H), 6.86 (d, J = 8.7 Hz, 2 H), 4.42 (s, 2 H), 3.79 (s, 3 H), 3.42 (t, J = 6.6 Hz, 2 H), 2.41 (dt, J = 7.3, 1.9 Hz, 2 H), 1.65–1.52 (m, 4 H), 1.25 (m, 18 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 202.4, 159.0, 130.7, 129.1, 113.6, 72.4, 70.1, 55.0, 43.8, 29.7, 29.5, 29.4 (2 C), 29.3, 29.1, 26.1, 22.0 ppm. $C_{22}H_{36}O_3$ (348.52): calcd. C 75.82, H 10.41; found C 75.59, H 10.29.

(2*E*,4*E*)-Ethyl-18-(4-methoxybenzyloxy)octadeca-2,4-dienoate (9): To a solution of ethyl 4-(dimethylphosphono)crotonate (29.45 g, 132.6 mmol) in anhydrous THF (250 mL) at –78 °C was added LiHMDS (1.0 M in THF, 132.55 mL). After 1 h, this solution was transferred by cannula into a solution of **12** (30.8 g, 88.4 mmol) in THF (70 mL) maintained at –78 °C. The reaction mixture was warmed to room temperature, stirred for 1 h, quenched with saturated aqueous NH_4Cl solution (100 mL), and concentrated. The aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic fraction was washed with water and brine and dried with anhydrous Na_2SO_4, and the solvent was evaporated. The residue was purified by silica gel column chromatography (light petroleum/ethyl acetate, 9:1) to afford **9** (32.6 g, 83%) as a light-yellow oil. IR (liquid film, $CHCl_3$): $\tilde{\nu}$ = 2926, 1715, 1247, 1036 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.29 (dd, J = 15.4, 9.5 Hz, 1 H), 7.28 (d, J = 8.7 Hz, 2 H), 6.89 (d, J = 8.7 Hz, 2 H), 6.21–6.11 (m, 2 H), 5.81 (d, J = 15.4 Hz, 1 H), 4.45 (s, 2 H), 4.22 (q, J = 7.1 Hz, 2 H), 3.82 (s, 3 H), 3.45 (t, J = 6.7 Hz, 2 H), 2.18 (q, J = 6.9 Hz, 2 H), 1.62 (quint., J = 6.9 Hz, 2 H), 1.45–1.42 (m, 2 H), 1.38–1.32 (m, 4 H), 1.31–1.28 (m, 17 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.3, 159.0, 145.1, 144.7, 130.8, 129.2, 128.3, 119.1, 113.7, 72.4, 70.2, 60.1, 55.2, 33.0, 29.7, 29.6, 29.5 (2 C), 29.4 (2 C), 29.1, 28.7, 26.2, 14.3 ppm. $C_{28}H_{44}O_4$ (444.65): calcd. C 75.63, H 9.97; found C 75.89, H 10.11.

(4*S*,5*S*,*E*)-Ethyl-4,5-dihydroxy-18-(4-methoxybenzyloxy)octadec-2-enoate (13): To a vigorously stirred mixture of $K_3[Fe(CN)_6]$ (56.02 g, 170.2 mmol), K_2CO_3 (23.52 g, 170.2 mmol), $(DHQ)_2$-PHAL (442 mg, 0.57 mmol), $MeSO_2NH_2$ (5.4 g, 56.7 mmol), and $K_2OsO_4{\cdot}2H_2O$ (84 mg, 0.23 mmol) in *t*BuOH/H_2O (1:1, 300 mL) at 0 °C was added compound **9** (25.2 g, 56.7 mmol). After 6 h, the reaction was quenched with sodium sulfite (50 g) and *t*BuOH was evaporated under reduced pressure. The aqueous phase was extracted with ethyl acetate (3 × 100 mL). The combined organic fraction was washed with 2 N KOH, water, and brine, dried with anhydrous Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (light petroleum/ethyl acetate, 4:1) to afford **13** (19.0 g, 70%) as a white solid. M.p. 67 °C. $[\alpha]_D^{25}$ = –17.1 (c = 1.2, $CHCl_3$). IR (liquid film, $CHCl_3$): $\tilde{\nu}$ = 3308, 2927, 1713, 1464, 1251 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.31 (d, J = 8.7 Hz, 2 H), 6.99 (dd, J = 15.6, 5.0 Hz, 1 H), 6.93 (d, J = 8.7 Hz, 2 H), 6.19 (d, J = 15.6 Hz, 1 H), 4.49 (s, 2 H), 4.27 (q, J = 7.2 Hz, 2 H), 4.16 (m, 1 H) 3.87 (s, 3 H), 3.59 (m, 1 H), 3.49 (t, J = 6.7 Hz, 2 H), 2.73 (br. s, 2 H), 1.66 (quint., J = 6.9 Hz, 2 H), 1.60–1.51 (m, 2 H), 1.39–1.33 (m, 23 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.3, 159.1, 147.1, 130.7, 129.2, 122.3, 113.7, 74.1, 74.0, 72.5, 70.2, 60.5, 55.2, 33.1, 29.7, 29.6, 29.5, 26.2, 25.6, 14.2 ppm. $C_{28}H_{46}O_6$ (478.66): calcd. C 70.26, H 9.69; found C 70.37, H 9.84.

(*E*)-Ethyl-3-{(4*S*,5*S*)-5-[13-(4-methoxybenzyloxy)tridecyl]-2,2-dimethyl-1,3-dioxolan-4-yl}acrylate (14): To a solution of **13** (16.6 g, 34.7 mmol) and 2,2-dimethoxypropane (5.11 mL, 41.6 mmol) in CH_2Cl_2 (125 mL) was added TsOH (250 mg). The reaction mixture was stirred at room temperature for 1 h. After completion of the reaction (monitored by TLC), the reaction mixture was washed with $NaHCO_3$ (75 mL), water and brine, dried with anhydrous Na_2SO_4, and concentrated. The residue was purified on silica gel (light petroleum/ethyl acetate, 9.5:0.5) to afford acetonide derivative **14** (17.3 g, 96%) as a colorless oil. $[\alpha]_D^{25}$ = –8.1 (c = 1.7, $CHCl_3$). IR (liquid film, $CHCl_3$): $\tilde{\nu}$ = 2854, 1724, 1513, 1247 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.32 (d, J = 8.7 Hz, 2 H), 6.93 (d, J = 8.7 Hz, 2 H), 6.92 (dd, J = 15.7, 5.6 Hz, 1 H), 6.18 (dd, J = 15.7, 1.5 Hz, 1 H), 4.49 (s, 2 H), 4.28 (q, J = 7.2 Hz, 2 H), 4.22–4.18 (m, 1 H), 3.87 (s, 3 H), 3.79 (dt, J = 8.3, 5.9 Hz, 1 H), 3.49 (t, J = 6.7 Hz, 2 H), 1.68–1.63 (m, 4 H), 1.58–1.53 (m, 2 H), 1.50 (s, 3 H), 1.48 (s, 3 H), 1.39–1.33 (m, 21 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.9, 159.1, 144.2, 130.8, 129.2, 122.6, 113.7, 109.3, 80.6, 80.3, 72.5, 70.2, 60.5, 55.2, 32.1, 29.8, 29.7, 29.6 (2 C), 29.5, 27.3, 26.7, 26.2, 26.0, 14.3 ppm. $C_{31}H_{50}O_6$ (518.73): calcd. C 71.78, H 9.72; found C 71.62, H 9.63.

(*S*)-1-{(4*S*,5*S*)-5-[13-(4-Methoxybenzyloxy)tridecyl]-2,2-dimethyl-1,3-dioxolan-4-yl}prop-2-yn-1-ol (15): To a solution of **14** (15.9 g, 30.7 mmol) in CH_2Cl_2 (150 mL) at –78 °C was added DIBAL-H (1.3 M in toluene, 51.91 mL, 67.5 mmol). After 1 h, excess of DIBAL-H was quenched with a saturated solution of sodium potassium tartrate. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The organic layer was washed with water, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column

chromatography (light petroleum/ethyl acetate, 4:1) to give **15** (12.5 g, 85%) as a colorless oil. $[\alpha]_D^{25}$ = –3.6 (*c* = 1.2, $CHCl_3$). IR (liquid film, $CHCl_3$): $\tilde{\nu}$ = 3436, 2854, 1464, 1217 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.17 (d, *J* = 8.7 Hz, 2 H), 6.79 (d, *J* = 8.7 Hz, 2 H), 5.88 (dt, *J* = 15.4, 5.1 Hz, 1 H), 5.62 (dd, *J* = 15.4, 7.3 Hz, 1 H), 4.35 (s, 2 H), 4.09 (d, *J* = 5.1 Hz, 2 H), 3.93 (t, *J* = 8.1 Hz, 1 H), 3.73 (s, 3 H), 3.59 (dt, *J* = 8.1, 5.9 Hz, 1 H), 3.35 (t, *J* = 6.7 Hz, 2 H), 1.54–1.49 (m, 2 H), 1.47–1.44 (m, 2 H), 1.33 (s, 3 H), 1.33 (s, 3 H), 1.28–1.18 (m, 20 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.1, 133.9, 130.8, 129.2, 128.2, 113.8, 108.4, 81.7, 80.8, 72.5, 70.2, 62.7, 55.2, 31.9, 29.8, 29.7, 29.6 (3 C), 29.5, 27.3, 27.0, 26.2, 26.1 ppm. $C_{29}H_{48}O_5$ (476.69): calcd. C 73.07, H 10.15; found C 73.26, H 10.29.

[(2*R*,3*S*)-3-{(4*R*,5*S*)-5-[13-(4-Methoxybenzyloxy)tridecyl]-2,2-dimethyl-1,3-dioxolan-4-yl}oxiran-2-yl]methanol (16): To a solution of titanium tetrakis(isopropoxide) (7.30 mL, 24.8 mmol) and D-(–)-DIPT (= diisopropyl tartrate) (6.31 mL, 24.8 mmol) in CH_2Cl_2 (125 mL) carrying activated molecular sieves (4 Å, 12.0 g) at –22 °C was added *t*-butylhydroperoxide (3.3 M in toluene, 15.01 mL, 49.5 mmol) dropwise. After 15 min a solution of allylic alcohol **15** (11.8 g, 24.8 mmol) in CH_2Cl_2 (75 mL) was added dropwise. The reaction mixture was kept at that temperature for 16 h; aqueous tartaric acid (10%) was added followed by stirring for 1 h. The reaction mixture was filtered, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 75 mL), and the combined CH_2Cl_2 extract was concentrated under reduced pressure and then taken up in diethyl ether (125 mL). This solution was then treated with 1 M NaOH solution (60 mL) and stirred for another 1 h and then extracted with diethyl ether (3 × 50 mL). The combined organic fraction was washed with water and brine, dried with anhydrous Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (230–400 mesh; light petroleum/ethyl acetate, 3:1) to afford epoxy alcohol **16** (8.2 g, 67%) as a colorless oil. $[\alpha]_D^{25}$ = +2.3 (*c* = 1.1, $CHCl_3$). IR (liquid film, $CHCl_3$): $\tilde{\nu}$ = 3447, 2926, 1513, 1248 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 8.7 Hz, 2 H), 6.85 (d, *J* = 8.7 Hz, 2 H), 4.41 (s, 2 H), 3.96–3.91 (m, 2 H), 3.79 (s, 3 H), 3.66 (dd, *J* = 12.8, 4.3 Hz, 1 H), 3.41 (t, *J* = 6.7 Hz, 2 H), 3.39 (dd, *J* = 7.8, 6.3 Hz, 1 H), 3.09 (quint., *J* = 2.3 Hz, 1 H), 3.01 (dd, *J* = 6.3, 2.3 Hz, 1 H), 2.02 (br. s, 1 H), 1.62–1.55 (m, 4 H), 1.40 (s, 3 H), 1.39 (s, 3 H), 1.33–1.26 (m, 20 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.1, 130.8, 129.2, 113.7, 109.2, 80.4, 79.8, 72.5, 70.2, 61.0, 56.7, 55.2, 55.0, 33.2, 29.8, 29.7, 29.6, 29.5, 27.3, 26.7, 26.2, 25.9 ppm. $C_{29}H_{48}O_6$ (492.69): calcd. C 70.70, H 9.82; found C 70.53, H 9.96.

(4*R*,5*S*)-4-[(2*R*,3*S*)-3-(Chloromethyl)oxiran-2-yl]-5-[13-(4-ethoxybenzyloxy)tridecyl]-2,2-dimethyl-1,3-dioxolane (17): Sodium hydrogen carbonate (3.5 g) was added to a solution of **16** (7.5 g, 15.2 mmol) and triphenylphosphane (7.98 g, 30.5 mmol) in CCl_4 (100 mL), and the reaction mixture was heated at reflux for 2 h. Removal of solvent under reduced pressure and residue purification by silica gel column chromatography (light petroleum/ethyl acetate, 9.5:0.5) gave **17** (7.0 g, 90%) as a colorless oil. $[\alpha]_D^{25}$ = +1.3 (*c* = 1.5, $CHCl_3$). IR (liquid film, $CHCl_3$): $\tilde{\nu}$ = 2928, 1612, 1465, 1216 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.26 (d, *J* = 8.7 Hz, 2 H), 6.87 (d, *J* = 8.7 Hz, 2 H), 4.43 (s, 2 H), 4.00–3.90 (m, 1 H), 3.80 (s, 3 H), 3.67 (dd, *J* = 11.9, 4.7 Hz, 1 H), 3.55 (dd, *J* = 11.9, 6.2 Hz, 1 H), 3.43 (t, *J* = 6.7 Hz, 2 H), 3.42–3.39 (m, 1 H), 3.23 (ddd, *J* = 6.2, 4.7, 1.9 Hz, 1 H), 2.97 (dd, *J* = 5.8, 1.9 Hz, 1 H), 1.63–1.52 (m, 4 H), 1.40 (s, 6 H), 1.26 (m, 20 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 159.0, 130.8, 129.1, 113.7, 109.3, 79.8, 79.7, 72.4, 70.1, 57.9, 55.4, 55.1, 43.9, 33.1, 29.7, 29.6, 29.4, 27.2, 26.6, 26.2, 25.8 ppm. $C_{29}H_{47}ClO_5$ (511.13): calcd. C 68.14, H 9.27; found C 68.27, H 9.47.

(*S*)-1-{(4*S*,5*S*)-5-[13-(4-Methoxybenzyloxy)tridecyl]-2,2-dimethyl-1,3-dioxolan-4-yl}prop-2-yn-1-ol (18): *n*-Butyllithium (1.6 M in hexane, 22.78 mL, 36.5 mmol) was added dropwise to a solution of **17** (6.2 g, 12.2 mmol) in dry THF (70 mL) at –78 °C under a nitrogen atmosphere. After stirring for 1 h at –78 °C, the reaction mixture was gradually warmed to room temperature over a period of 1 h, quenched with aqueous NH_4Cl solution (50 mL), and concentrated. The residue was extracted with ethyl acetate (3 × 50 mL), washed with water and brine, dried with anhydrous Na_2SO_4, and evaporated. The residue was purified by silica gel column chromatography (light petroleum/ethyl acetate, 4:1) to afford **18** (5.2 g, 72%) as a colorless oil. $[\alpha]_D^{25}$ = –8.8 (*c* = 1.7, $CHCl_3$). IR (liquid film, $CHCl_3$): $\tilde{\nu}$ = 3425, 2926, 1612, 1465, 1247 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 8.7 Hz, 2 H), 6.86 (d, *J* = 8.7 Hz, 2 H), 4.47 (dd, *J* = 3.8, 2.2 Hz, 1 H), 4.42 (s, 2 H), 4.05 (ddd, *J* = 8.0, 7.8, 3.8 Hz, 1 H), 3.80 (s, 3 H), 3.75 (dd, *J* = 7.8, 3.8 Hz, 1 H), 3.42 (t, *J* = 6.6 Hz, 2 H), 2.51 (d, *J* = 2.2 Hz, 1 H), 1.69–1.48 (m, 4 H), 1.42 (s, 6 H), 1.25 (m, 20 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 159.1, 130.7, 129.2, 113.7, 109.0, 82.4, 81.1, 77.4, 75.0, 72.5, 70.1, 62.3, 55.1, 34.1, 29.8, 29.7, 29.6, 29.5, 27.6, 27.0, 26.2, 26.0 ppm. $C_{29}H_{46}O_5$ (474.67): calcd. C 73.38, H 9.77; found C 73.63, H 9.55.

***tert*-Butyl[(*S*)-1-{(4*R*,5*S*)-5-[13-(4-methoxybenzyloxy)tridecyl]-2,2-dimethyl-1,3-dioxolan-4-yl}prop-2-ynyloxy]dimethylsilane: (19)**. To a solution of **18** (4.7 g, 9.9 mmol) and imidazole (877 mg, 12.9 mmol) in CH_2Cl_2 (40 mL) was added TBSCl (1.79 g, 11.9 mmol) in portions, and the resulting mixture was stirred at room temperature for 2 h. After completion of the reaction (monitored by TLC), the reaction mixture was poured on ice, diluted with water, and extracted with ethyl acetate (3 × 50 mL). The combined organic layer was washed with brine, dried with anhydrous Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (light petroleum/ethyl acetate, 9:1) to furnish **19** (5.52 g, 94%) as a colorless oil. $[\alpha]_D^{25}$ = +2.1 (*c* = 1.1, $CHCl_3$). IR (liquid film, $CHCl_3$): $\tilde{\nu}$ = 2855, 1614, 1513, 1249, 1097 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.7 Hz, 2 H), 6.86 (d, *J* = 8.7 Hz, 2 H), 4.42 (s, 2 H), 4.39 (dd, *J* = 5.7, 2.2 Hz, 1 H), 4.01 (ddd, *J* = 8.0, 7.2, 3.3 Hz, 1 H), 3.80 (s, 3 H), 3.70 (dd, *J* = 7.2, 5.7 Hz, 1 H), 3.42 (t, *J* = 6.6 Hz, 2 H), 2.45 (d, *J* = 2.2 Hz, 1 H), 1.62–1.54 (m, 4 H), 1.41 (s, 3 H), 1.39 (s, 3 H), 1.38–1.25 (m, 20 H), 0.91 (m, 9 H), 0.17 (s, 3 H), 0.13 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 159.0, 130.8, 129.2, 113.7, 108.9, 83.0 (2 C), 78.5, 73.9, 72.5, 70.2, 63.9, 55.2, 34.5, 29.8, 29.7, 29.6 (2 C), 29.5 (2 C), 27.6, 27.1, 26.2, 25.7, 18.2, –4.7, –5.0 ppm. $C_{35}H_{60}O_5Si$ (588.93): calcd. C 71.38, H 10.27; found C 71.47, H 10.08.

13-{(4*S*,5*R*)-5-[(*S*)-1-(*tert*-Butyldimethylsilyloxy)prop-2-ynyl]-2,2-dimethyl-1,3-dioxolan-4-yl}tridecan-1-ol (20): To a stirred solution of **19** (3.47 g, 5.9 mmol) in CH_2Cl_2/buffer (pH = 7) (18:1, 30 mL) was added DDQ (1.61 g, 7.1 mmol) at 0 °C. After 3 h, the reaction was quenched by the addition of saturated $NaHCO_3$ solution (50 mL) and extracted with CH_2Cl_2 (3 × 75 mL). The combined organic fraction was washed with water and brine, dried with anhydrous Na_2SO_4, and evaporated. The residue was purified by silica gel column chromatography (light petroleum/ethyl acetate, 3:1) to furnish **20** (2.1 g, 76%) as a light-yellow oil. $[\alpha]_D^{25}$ = +2.4 (*c* = 1.0, $CHCl_3$). IR (liquid film, $CHCl_3$): $\tilde{\nu}$ = 3311, 2856, 2117, 1464, 1253, 1167 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 4.40 (dd, *J* = 5.7, 2.2 Hz, 1 H), 4.02 (ddd, *J* = 8.0, 7.2, 3.3 Hz, 1 H), 3.72 (dd, *J* = 7.2, 5.7 Hz, 1 H), 3.64 (t, *J* = 6.5 Hz, 2 H), 2.46 (d, *J* = 2.2 Hz, 1 H), 1.63–1.50 (m, 4 H), 1.42 (s, 3 H), 1.39 (s, 3 H), 1.27 (m, 20 H), 0.92 (m, 9 H), 0.18 (s, 3 H), 0.14 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 108.9, 83.1, 83.0, 78.4, 74.0, 63.9, 63.0, 34.5, 32.8, 29.7 (2 C), 29.6, 29.5, 27.6, 27.1, 26.2, 25.8, 18.2, –4.6, –4.9 ppm.

$C_{27}H_{52}O_4Si$ (468.78): calcd. C 69.18, H 11.18; found C 69.24, H 11.33.

13-{(4*S*,5*R*)-5-[(*S*)-1-(*tert*-Butyldimethylsilyloxy)prop-2-ynyl]-2,2-dimethyl-1,3-dioxolan-4-yl}tridecanoic Acid (8): Iodoxybenzoic acid (IBX; 1.17 g, 4.2 mmol) in DMSO (15 mL) was stirred at room temperature for 30 min till it become a clear solution. Compound **20** (1.96 g, 4.2 mmol) in THF (10 mL) was added to the clear solution, and the mixture was stirred for 4 h at room temperature. The reaction mixture was then diluted with water (40 mL) and filtered. The filtrate was extracted with diethyl ether (3 × 50 mL), washed with $NaHCO_3$, water, and brine, dried with anhydrous Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (light petroleum/ethyl acetate, 9:1) to afford **20ald** (1.9 g, 95%) as a yellow oil. $[\alpha]_D^{25}$ = +3.6 (*c* = 1.4, $CHCl_3$). IR (liquid film, $CHCl_3$): $\tilde{\nu}$ = 2855, 2117, 1711, 1463, 1252, 1132 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 9.77 (t, *J* = 1.9 Hz, 1 H), 4.40 (dd, *J* = 5.7, 2.2 Hz, 1 H), 4.02 (ddd, *J* = 8.3, 7.2, 3.3 Hz, 1 H), 3.72 (dd, *J* = 7.2, 5.7 Hz, 1 H), 2.47 (d, *J* = 2.2 Hz, 1 H), 2.42 (dt, *J* = 7.3, 1.9 Hz, 2 H) 1.77–1.46 (m, 6 H), 1.46 (s, 3 H), 1.42 (s, 3 H), 1.39–1.26 (m, 16 H), 0.92 (m, 9 H), 0.17 (s, 3 H), 0.13 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 202.9, 108.9, 83.1, 83.0, 78.5, 73.9, 63.9, 43.9, 34.5, 29.7, 29.6, 29.4 (2 C), 29.2, 27.6, 27.1, 26.2, 25.8, 22.1, 18.2, –4.6, –5.0 ppm. $C_{27}H_{50}O_4Si$ (466.77): calcd. C 69.48, H 10.80; found C 69.32, H 10.98.

To a solution of the above aldehyde (1.43 g, 3.1 mmol), $NaH_2PO_4{\cdot}2H_2O$ (1.45 g, 9.3 mmol), and 2-methyl-2-butene (2 mL) in *t*BuOH (20 mL) was added a solution of $NaClO_2$ (840 mg, 9.3 mmol) in water (10 mL) dropwise. After 2 h, the reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (3 × 25 mL). The combined organic layer was washed with brine, dried with anhydrous Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (light petroleum/ethyl acetate, 4:1) to give **8** (1.3 g, 88%) as a light yellow oil. $[\alpha]_D$ = +4.3 (*c* = 1.0, $CHCl_3$). IR (liquid film, $CHCl_3$): $\tilde{\nu}$ = 3310, 2928, 1712, 1463, 1217 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.40 (dd, *J* = 5.5, 2.3 Hz, 1 H), 4.02 (ddd, *J* = 8.3, 7.3, 3.3 Hz, 1 H), 3.73 (dd, *J* = 7.3, 5.5 Hz, 1 H), 2.45 (d, *J* = 2.3 Hz, 1 H), 2.34 (t, *J* = 7.3 Hz, 2 H) 1.77–1.51 (m, 6 H), 1.42 (s, 3 H), 1.39 (s, 3 H), 1.26 (m, 16 H), 0.91 (m, 9 H), 0.17 (s, 3 H), 0.13 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 179.8, 108.9, 83.1, 83.0, 78.5, 73.9, 63.9, 34.5, 34.0, 29.7, 29.6, 29.5 (2 C), 29.4, 29.2, 29.0, 27.6, 27.1, 26.1, 25.7, 24.7, 18.2, –4.7, –5.0 ppm. $C_{27}H_{50}O_5Si$ (482.77): calcd. C 67.17, H 10.44; found C 67.08, H 10.30.

7-(Benzyloxy)heptan-1-ol (7a): To a solution of heptane-1,7-diol (**7**; 21.23 g, 160.6 mmol) in THF/DMF (7:3, 200 mL) at 0 °C was slowly added sodium hydride (60% in dispersion oil, 6.42 g, 160.6 mmol). The reaction mixture was stirred at 0 °C for 30 min. Benzyl bromide (19.06 mL, 160.6 mmol) in THF was added dropwise. After being stirred for 30 min at that temperature, the reaction mixture was allowed to warm to room temperature. The reaction mixture was stirred overnight at room temperature and quenched with water. After removal of THF under reduced pressure, the residue was partitioned between ether (250 mL) and water (300 mL). The organic layer was dried with anhydrous Na_2SO_4 and concentrated, and the residue was purified by silica gel column chromatography (light petroleum/ethyl acetate, 7:3) to give **7a** (30.7 g, 86%) as a colorless oil. IR (liquid film, $CHCl_3$): $\tilde{\nu}$ = 3433, 2853, 1613, 1586, 1464, 1247 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.34–7.25 (m, 5 H), 4.49 (s, 2 H), 3.59 (t, *J* = 6.7 Hz, 2 H), 3.45 (t, *J* = 6.6 Hz, 2 H), 1.85 (br. s, 1 H), 1.68–1.48 (m, 4 H), 1.33 (m, 6 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 138.4, 128.2, 127.5, 127.4, 72.7, 70.2, 62.5, 32.5, 29.5, 29.1, 26.1, 25.6 ppm. $C_{14}H_{22}O_2$ (222.32): calcd. C 75.63, H 9.97; found C 75.76, H 10.08.

7-(Benzyloxy)heptanal (21): To a stirred solution of 7-benzyloxyheptan-1-ol (**7a**; 21.13 g, 95.0 mmol) in CH_2Cl_2 (250 mL) was added PCC (40.97 g, 190.1 mmol), and the resulting mixture was stirred at room temperature for 2 h. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with diethyl ether (200 mL) and filtered. The filtrate was concentrated under reduced pressure, and the residue thus obtained was purified by silica gel column chromatography (light petroleum/ethyl acetate, 4:1) to give **21** (18.22 g, 87%) as a colorless oil. IR (liquid film, $CHCl_3$): $\tilde{\nu}$ = 2926, 1725, 1614, 1462, 1301 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 9.74 (t, *J* = 1.7 Hz, 1 H), 7.34–7.25 (m, 5 H), 4.49 (s, 2 H), 3.45 (t, *J* = 6.6 Hz, 2 H), 2.41 (dt, *J* = 7.2, 1.7 Hz, 2 H), 1.70–1.55 (m, 4 H), 1.46–1.26 (m, 4 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 202.3, 138.5, 128.2, 127.5, 127.4, 72.7, 70.0, 43.7, 29.4, 28.9, 25.9, 21.9 ppm. $C_{14}H_{20}O_2$ (220.31): calcd. C 76.33, H 9.15; found C 76.19, H 9.33.

2-[6-(Benzyloxy)hexyl]oxirane (22): To a suspension of NaH (60% dispersion in oil, 4.33 g, 108.3 mmol) and trimethylsulfoxonium iodide (23.84 g, 108.3 mmol) in DMSO (150 mL) under an atmosphere of argon at 10 °C was added **21** (15.9 g, 72.2 mmol) in DMSO (100 mL) over a period of 30 min. After 3 h, the reaction was quenched with ice-cold water and extracted with ethyl acetate (3 × 125 mL). The combined organic layer was washed with water and brine, dried with anhydrous Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (light petroleum/ethyl acetate, 9:1) to afford **22** (14.22 g, 84%) as a yellow oil. IR (liquid film, $CHCl_3$): $\tilde{\nu}$ = 2929, 1603, 1454, 1258 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.33–7.28 (m, 5 H), 4.49 (s, 2 H), 3.46 (t, *J* = 6.6 Hz, 2 H), 2.90–2.84 (m, 1 H), 2.73 (dd, *J* = 5.1, 4.0 Hz, 1 H), 2.44 (dd, *J* = 5.1, 2.7 Hz, 1 H), 1.63–1.30 (m, 10 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 138.5, 128.2, 127.5, 127.3, 72.7, 70.2, 52.1, 46.8, 32.3, 29.6 (2 C), 29.2, 26.1, 25.9 ppm. $C_{15}H_{22}O_2$ (234.33): calcd. C 76.88, H 9.46; found C 76.71, H 9.31.

(*R*)-2-[6-(Benzyloxy)hexyl]oxirane (23) and (*S*)-8-(Benzyloxy)octane-1,2-diol (24): (*R*,*R*)-Salen-Co^{III}OAc (172 mg, 0.26 mmol) was added to (*R*/*S*)-epoxide **22** (12.18 g, 52.0 mmol), followed by the dropwise addition of water (0.51 mL, 28.6 mmol) over 1 h at 0 °C. The reaction mixture was allowed to come to room temperature and then stirred for 36 h. The reaction mixture was filtered, and the filtrate was concentrated. The residue was purified by column chromatography (light petroleum/ethyl acetate, 9:1) to afford **23** (5.7 g, 47%) as a light-yellow oil. $[\alpha]_D^{25}$ = +5.6 (*c* = 2.0, $CHCl_3$). IR (liquid film, $CHCl_3$): $\tilde{\nu}$ = 2933, 1603, 1454, 1216 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.33–7.28 (m, 5 H), 4.49 (s, 2 H), 3.46 (t, *J* = 6.6 Hz, 2 H), 2.90–2.84 (m, 1 H), 2.73 (dd, *J* = 5.1, 4.0 Hz, 1 H), 2.44 (dd, *J* = 5.1, 2.7 Hz, 1 H), 1.63–1.30 (m, 10 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 138.5, 128.2, 127.5, 127.3, 72.7, 70.2, 52.2, 46.9, 32.4, 29.6 (2 C), 29.2, 26.1, 25.9 ppm. $C_{15}H_{22}O_2$ (234.33): calcd. C 76.88, H 9.46; found C 76.97, H 9.29.

Further elution (petroleum ether/ethyl acetate, 1:1) gave diol **24** (5.5 g, 42%) as a yellow oil. $[\alpha]_D^{25}$ = +2.9 (*c* = 1.0, $CHCl_3$). IR (liquid film, $CHCl_3$): $\tilde{\nu}$ = 3392, 2932, 1454, 1216, 1028 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.26 (m, 5 H), 4.49 (s, 2 H), 3.67 (m, 2 H), 3.46 (t, *J* = 6.6 Hz, 2 H), 3.41–3.39 (m, 1 H), 2.53 (br. s, 2 H), 1.64–1.58 (m, 2 H), 1.42–1.33 (m, 8 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 138.4, 128.3, 127.5, 127.4, 72.8, 72.1, 70.3, 66.5, 33.0, 29.6, 29.4, 26.0, 25.5 ppm. $C_{15}H_{24}O_3$ (252.35): calcd. C 71.39, H 9.59; found C 71.68, H 9.37.

(*S*)-8-(Benzyloxy)-1-(*tert*-butyldiphenylsilyloxy)octan-2-ol (24a): To a solution of **24** (5.32 g, 21.1 mmol), imidazole (1.87 g, 27.4 mmol), and DMAP (103 mg, 0.8 mmol) in CH_2Cl_2 (75 mL) was added TBDPSCl (6.95 g, 25.3 mmol) in portions. The resulting mixture

was stirred at room temperature for 3 h. After completion of the reaction (monitored by TLC), the reaction mixture was poured on ice, diluted with water, and extracted with diethyl ether (3 × 75 mL). The combined organic layer was washed with brine, dried with anhydrous Na_2SO_4, and concentrated. The residue was purified on silica gel by (light petroleum/ethyl acetate, 9:1) to produce **24a** (9.21 g, 89%) as a colorless oil. $[\alpha]_D^{25}$ = +0.9 (*c* = 1.3, $CHCl_3$). IR (liquid film, $CHCl_3$): $\tilde{\nu}$ = 3467, 2857, 1589, 1427, 1362 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.68–7.24 (m, 15 H), 4.48 (s, 2 H), 3.74–3.60 (m, 2 H), 3.50–3.41 (m, 1 H), 3.43 (t, *J* = 6.7 Hz, 2 H), 2.27 (br. s, 1 H), 1.62–1.52 (m, 2 H), 1.37–1.26 (m, 8 H), 1.06 (m, 9 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 138.6, 135.5, 133.1 (2 C), 129.8, 128.3, 127.7, 127.5, 127.4, 72.8, 71.8, 70.3, 68.0, 32.7, 29.7, 29.4, 26.9, 26.1, 25.4, 19.2 ppm. $C_{31}H_{42}O_3Si$ (490.75): calcd. C 75.87, H 8.63; found C 75.93, H 8.41.

(*S*)-8-(Benzyloxy)-1-(*tert*-butyldiphenylsilyloxy)octan-2-yl-methanesulfonate (24b): To a solution of alcohol **24a** (8.94 g, 18.2 mmol) and triethylamine (3.81 mL, 27.3 mmol) at 0 °C in CH_2Cl_2 (75 mL) was added methanesulfonyl chloride (2.5 g, 21.9 mmol) in CH_2Cl_2 (20 mL) dropwise. The reaction mixture was stirred for 2 h. After completion of the reaction (monitored by TLC), the reaction mixture was washed successively with aqueous sodium hydrogen carbonate and water, dried with anhydrous Na_2SO_4, and concentrated. The residue thus obtained was purified by silica gel column chromatography (light petroleum/ethyl acetate, 4:1) to afford **24b** (9.43 g, 91%) as a colorless oil. $[\alpha]_D^{25}$ = –5.7 (*c* = 0.5, $CHCl_3$). IR (liquid film, $CHCl_3$): $\tilde{\nu}$ = 2858, 1962, 1589, 1458, 1428, 1242 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.68–7.25 (m, 15 H), 4.75–4.64 (m, 1 H), 4.48 (s, 2 H), 3.83–3.68 (m, 2 H), 3.44 (t, *J* = 6.7 Hz, 2 H), 2.97 (s, 3 H), 1.68–1.52 (m, 4 H), 1.39–1.16 (m, 6 H), 1.06 (m, 9 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 138.6, 135.5, 135.4, 132.8, 132.6, 130.0, 129.9, 128.3, 127.8, 127.6, 127.4, 83.8, 72.8, 70.2, 65.3, 38.5, 31.4, 29.6, 29.1, 26.8, 25.9, 24.8, 19.2 ppm. $C_{32}H_{44}O_5SSi$ (568.84): calcd. C 67.57, H 7.80; found C 67.73, H 7.74.

(*S*)-11-(Benzyloxy)undecan-5-ol (6): To a suspension of magnesium (1.5 g, 61.8 mmol) in dry THF (100 mL) at 0 °C was added a solution of *n*-propyl bromide (5.62 mL, 61.8 mmol) in THF (30 mL). After 30 min, CuCN (2.22 g, 24.7 mmol) and **23** (4.83 g, 20.6 mmol) were added, and the mixture was stirred for 1 h at 0 °C. The reaction mixture was quenched with saturated NH_4Cl solution, and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (2 × 50 mL). The organic layer was dried with anhydrous Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (light petroleum/ethyl acetate, 4:1) to afford **6** (4.5 g, 78%) as a colorless oil. $[\alpha]_D^{25}$ = +1.5 (*c* = 1.3, $CHCl_3$). IR (liquid film, $CHCl_3$): $\tilde{\nu}$ = 3437, 2933, 1454, 1278, 1216 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.33–7.25 (m, 5 H), 4.49 (s, 2 H), 3.57–3.54 (m, 1 H), 3.45 (t, *J* = 6.5 Hz, 2 H), 1.64–1.58 (m, 2 H), 1.45–1.30 (m, 14 H), 0.91 (t, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.7, 128.3, 127.6, 127.5, 72.9, 71.9, 70.4, 37.5, 37.2, 29.7, 29.6, 27.9, 26.2, 25.6, 22.8, 14.1 ppm. $C_{18}H_{30}O_2$ (278.43): calcd. C 77.65, H 10.86; found C 77.46, H 10.69.

(*S*)-2-[(*S*)-11-(Benzyloxy)undecan-5-yl]-1-*tert*-butylpyrrolidine-1,2-dicarboxylate (25): To a solution of *N*-Boc-L-proline (4.0 g, 18.6 mmol), EDCI (3.86 g, 20.1 mmol), and DMAP (946 mg, 7.7 mmol) in CH_2Cl_2 (60 mL), was added **6** (4.31 g, 15.5 mmol) at 0 °C. After 12 h at room temperature, the reaction mixture was quenched with water, and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layer was washed with brine, dried with anhydrous Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (light petroleum/ethyl acetate, 4:1) to afford **25** (7.0 g, 95%) as a light-yellow oil. $[\alpha]_D^{25}$ = –34.5 (*c* = 1.2, $CHCl_3$). IR (liquid film, $CHCl_3$): $\tilde{\nu}$ = 2932, 1736, 1692, 1406, 1163 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.33–7.25 (m, 5 H), 4.92–4.80 (m, 1 H), 4.49 (s, 2 H), 4.34–4.20 (m, 2 H), 3.61–3.47 (m, 1 H), 3.44 (t, *J* = 6.6 Hz, 2 H), 2.21–1.87 (m, 4 H), 1.62–1.48 (m, 4 H), 1.45 and 1.42 (rotamers, s, s, 9 H), 1.30–1.22 (m, 12 H), 0.89 (t, *J* = 6.5 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.5 and 172.4 (rotamers), 153.9 and 153.6 (rotamers), 138.5, 132.6, 129.3, 128.1, 127.3, 127.2, 79.5 and 79.2 (rotamers), 74.7 and 74.5 (rotamers), 72.6, 70.1 and 70.1 (rotamers), 58.9, 46.3 and 46.1 (rotamers), 33.8 and 33.7 (rotamers), 33.6, 30.9, 29.6 and 29.5 (rotamers), 29.1 and 29.0 (rotamers), 28.5 and 28.2 (rotamers), 27.3 and 27.2 (rotamers), 25.9 and 25.8 (rotamers), 25.1 and 24.9 (rotamers), 24.1, 23.1, 22.4, 13.8 and 13.7 (rotamers) ppm. $C_{28}H_{45}NO_5$ (475.66): calcd. C 70.70, H 9.54, N 2.94; found C 70.88, H 9.41, N 2.79.

(*S*)-1-*tert*-Butyl-2-[(*S*)-11-hydroxyundecan-5-yl]pyrrolidine-1,2-dicarboxylate (26): A solution of **25** (6.71 g, 14.1 mmol) in ethyl acetate (60 mL) was stirred in the presence of 10% Pd/C (750 mg, 5 mol-%) under a hydrogen atmosphere. After 6 h, the reaction mixture was filtered through a pad of Celite and concentrated. The residue was purified by silica gel column chromatography (light petroleum/ethyl acetate, 3:2) to provide **26** (4.7 g, 87%) as a light-yellow oil. $[\alpha]_D^{25}$ = –43.8 (*c* = 1.6, $CHCl_3$). IR (liquid film, $CHCl_3$): $\tilde{\nu}$ = 3455, 2934, 1736, 1690, 1406, 1215 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 4.92–4.79 (m, 1 H), 4.32–4.20 (m, 1 H), 3.62 (t, *J* = 6.5 Hz, 2 H), 3.56–3.35 (m, 2 H), 2.25–1.86 (m, 4 H), 1.81–1.68 (m, 2 H), 1.55–1.49 (m, 4 H), 1.46 and 1.42 (rotamers, s, s, 9 H), 1.32–1.26 (m, 10 H), 0.89 (t, *J* = 6.5 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.7 and 172.6 (rotamers), 154.1 and 153.8 (rotamers), 79.7 and 79.4 (rotamers), 74.9 and 74.6 (rotamers), 62.5, 59.1, 46.4 and 46.2 (rotamers), 33.8 and 33.7 (rotamers), 32.5, 30.9, 30.0, 29.1 and 29.0 (rotamers), 28.4, 28.3, 27.4 and 27.3 (rotamers), 25.5, 25.1 and 25.0 (rotamers), 24.2, 23.3, 22.5, 13.9 and 13.8 (rotamers) ppm. $C_{21}H_{39}NO_5$ (385.54): calcd. C 65.42, H 10.20, N 3.63; found C 65.67, H 10.01, N 3.45.

(*S*)-1-*tert*-Butyl-2-[(*S*,*E*)-12-iodododec-11-en-5-yl]pyrrolidine-1,2-dicarboxylate (27): Iodoxybenzoic acid (IBX; 3.56 g, 12.7 mmol) in DMSO (50 mL) was stirred at room temperature for 30 min till it become a clear solution. Compound **26** (4.08 g, 10.6 mmol) in THF (30 mL) was added to the clear solution, and the mixture was stirred for 4 h at room temperature. The reaction mixture was then diluted with water (70 mL) and filtered. THF was removed under reduced pressure, and the reaction mixture was extracted with diethyl ether (3 × 50 mL), washed with $NaHCO_3$, water, and brine, dried with anhydrous Na_2SO_4, and concentrated. The residue was purified on silica gel (light petroleum/ethyl acetate, 9:1) to afford **26ald** (3.7 g, 90%) as a yellow oil. $[\alpha]_D^{25}$ = –39.1 (*c* = 2.0, $CHCl_3$). IR (liquid film, $CHCl_3$): $\tilde{\nu}$ = 2934, 1733, 1694, 1405, 1215, 1163 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 9.74 (m, 1 H), 4.90–4.81 (m, 1 H), 4.29–4.21 (m, 1 H), 3.56–3.35 (m, 2 H), 2.43–2.39 (m, 2 H), 2.32–1.86 (m, 4 H), 1.65–1.50 (m, 6 H), 1.44 and 1.41 (rotamers, s, s, 9 H), 1.31–1.24 (m, 8 H), 0.87 (t, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 202.2 and 202.0 (rotamers), 172.7 and 172.6 (rotamers), 154.2 and 153.8 (rotamers), 79.7 and 79.5 (rotamers), 74.8 and 74.5 (rotamers), 59.2, 46.5 and 46.3 (rotamers), 43.7, 33.9 and 33.9 (rotamers), 33.9 and 33.8 (rotamers), 31.0 and 30.1 (rotamers), 29.7 and 29.0 (rotamers), 28.4 (2 C), 27.5 and 27.3 (rotamers), 25.1 and 24.9 (rotamers), 24.5 and 24.3 (rotamers), 23.4, 22.5, 21.9, 14.0 and 13.9 (rotamers) ppm. $C_{21}H_{37}NO_5$

(383.52): calcd. C 65.77, H 9.72, N 3.65; found C 65.65, H 9.84, N 3.73.

Anhydrous $CrCl_2$ (4.93 g, 40.1 mmol) was suspended in THF (80 mL) under an argon atmosphere. A solution of the above aldehyde (2.56 g, 6.7 mmol) and iodoform (5.28 g, 13.4 mmol) in THF (50 mL) was added dropwise to the suspension at 0 °C. After stirring at 0 °C for 3 h, the reaction mixture was poured into water (150 mL) and extracted with diethyl ether (3 × 75 mL). The combined extract was washed with brine, dried with anhydrous Na_2SO_4, and concentrated. The residue was purified on silica gel (light petroleum/ethyl acetate, 9:1) to provide **27** (3.1 g, 90%) as a light-yellow oil. $[\alpha]_D^{25}$ = –35.4 (*c* = 1.2, $CHCl_3$). IR (liquid film, $CHCl_3$): $\tilde{\nu}$ = 2400, 1737, 1690, 1405, 1162 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 6.48 (dt, *J* = 14.3, 7.2 Hz, 1 H), 5.98 (d, *J* = 14.3 Hz, 1 H), 4.91–4.82 (m, 1 H), 4.32–4.21 (m, 1 H), 3.58–3.35 (m, 2 H), 2.22–1.92 (m, 6 H), 1.61–1.49 (m, 4 H), 1.46 and 1.43 (rotamers, s, s, 9 H), 1.29 (m, 10 H), 0.89 (t, *J* = 6.5 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.7 and 172.6 (rotamers), 154.1 and 153.8 (rotamers), 146.4 and 146.3 (rotamers), 79.7 and 79.4 (rotamers), 74.8 and 74.6 (rotamers), 74.5 and 74.4 (rotamers), 60.3 and 59.1 (rotamers), 46.4 and 46.2 (rotamers), 35.9, 33.9, 33.7, 31.0 and 30.0 (rotamers), 28.9 and 28.7 (rotamers), 28.4 (2 C), 28.2 and 27.8 (rotamers), 27.4 and 27.3 (rotamers), 25.0 and 24.9 (rotamers), 24.3, 23.4, 22.6, 14.0 and 13.9 (rotamers) ppm. $C_{22}H_{38}INO_4$ (507.45): calcd. C 52.07, H 7.55, N 2.76; found C 52.25, H 7.43, N 3.03.

(*S*)-[(*S*,*E*)-12-Iodododec-11-en-5-yl]-1-(13-{(4*S*,5*R*)-5-[(*S*)-1-(*tert*-butyldimethylsilyloxy)prop-2-ynyl]-2,2-dimethyl-1,3-dioxolan-4-yl}tridecanoyl)pyrrolidine-2-carboxylate (3): A suspension of compound **27** (2.45 g, 4.8 mmol) and HCl (4 M in ethyl acetate, 25 mL) was stirred for 3 h at room temperature. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with ethyl acetate and neutralized with saturated sodium hydrogen carbonate solution (55 mL). The aqueous phase was extracted with ethyl acetate (3 × 75 mL). The combined organic layer was washed with brine, dried with anhydrous Na_2SO_4, and concentrated. The residue was purified on neutral alumina (ethyl acetate) to provide free amine **4** (1.59 g, 81%) as a yellow oil. $[\alpha]_D^{25}$ = –10.4 (*c* = 3.5, $CHCl_3$). IR (liquid film, $CHCl_3$): $\tilde{\nu}$ = 3343, 2930, 1730, 1605, 1459, 1377, 1215 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 6.49 (dt, *J* = 14.3, 7.2 Hz, 1 H), 5.98 (d, *J* = 14.3 Hz, 1 H), 4.95–4.83 (m, 1 H), 3.84–3.72 (m, 1 H), 3.20–3.08 (m, 1 H), 3.00–2.92 (m, 2 H), 2.27–1.99 (m, 4 H), 1.90–1.70 (m, 4 H), 1.58–1.49 (m, 4 H), 1.33–1.25 (m, 8 H), 0.89 (t, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 174.2, 146.3, 75.2, 74.6, 59.7, 46.7, 35.9, 33.8, 30.4, 29.7, 28.7, 28.2, 27.4, 25.2, 25.0, 22.5, 14.0 ppm. $C_{17}H_{30}INO_2$ (407.33): calcd. C 50.13, H 7.42, N 3.44; found C 50.29, H 7.21, N 3.32.

To a solution of acid **8** (1.17 g, 2.4 mmol), HOBt (320 mg, 2.4 mmol), and EDC (600 mg, 3.1 mmol) in CH_2Cl_2 (15 mL) was added free amine **4** (1.19 g, 2.9 mmol) at 0 °C. After 12 h at room temperature, the reaction mixture was quenched with water, and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layer was washed with water and brine, dried with anhydrous Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (light petroleum/ethyl acetate, 4:1) to afford **3** (2.0 g, 96%) as a yellow oil. $[\alpha]_D^{25}$ = –19.4 (*c* = 1.3, $CHCl_3$). IR (liquid film, $CHCl_3$): $\tilde{\nu}$ = 2930, 2206, 2104, 1734, 1659, 1501, 1431, 1215, 1081 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 6.49 (dt, *J* = 14.3, 7.1 Hz, 1 H), 5.98 (d, *J* = 14.3 Hz, 1 H), 4.94–4.81 (m, 1 H), 4.56–4.44 (m, 1 H), 4.40 (dd, *J* = 5.6, 2.2 Hz, 1 H), 4.02 (dt, *J* = 7.6, 3.1 Hz, 1 H), 3.71 (dd, *J* = 7.2, 5.6 Hz, 1 H), 3.65–3.44 (m, 2 H), 2.45 (d, *J* = 2.2 Hz, 1 H), 2.29 (dt, *J* = 7.3, 1.6 Hz, 2 H), 2.14–2.00 (m, 6 H), 1.77–1.46 (m, 10 H), 1.41 (s, 3 H), 1.39 (s, 3 H), 1.36–1.26 (m, 26 H), 0.92 (m, 9 H), 0.91 (t, *J* = 6.7 Hz, 3 H), 0.17 (s, 3 H), 0.13 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.2 and 172.2 (rotamers), 171.7, 146.5 and 146.3 (rotamers), 108.9, 83.1 and 83.1 (rotamers), 78.4, 74.8 and 74.6 (rotamers), 74.5 and 74.4 (rotamers), 73.9, 63.9, 59.7 and 58.9 (rotamers), 47.0 and 46.3 (rotamers), 36.0 and 35.9 (rotamers), 34.1 and 33.9 (rotamers), 34.0 and 33.8 (rotamers), 32.0, 31.7, 29.7, 29.6, 29.5, 29.4, 28.8 and 28.7 (rotamers), 28.4 and 28.3 (rotamers), 27.9 and 27.7 (rotamers), 27.3, 27.2, 26.2, 25.8, 25.0, 24.8 (2 C), 22.6 and 22.5 (rotamers), 18.2, 14.1 and 14.0 (rotamers), –4.6, –4.9 ppm. $C_{44}H_{78}INO_6Si$ (872.08): calcd. C 60.60, H 9.02, N 1.61; found C 60.39, H 9.22, N 1.47.

28: Tetrakis(triphenylphosphane)palladium(0) (253 mg, 0. 2 mmol) and CuI (83 mg, 0.4 mmol) were added successively to a stirred solution of **3** (1.91 g, 2.2 mmol) in anhydrous Et_2NH (10 mL) at room temperature, and the reaction mixture was degassed (4×) gently with argon under fringe throng process. After 30 min, the reaction was quenched by the addition of water and extracted with diethyl ether (3 × 50 mL). The combined organic fraction was washed with brine, dried with anhydrous Na_2SO_4, and concentrated. The residue was purified on silica gel (230–400 mesh; light petroleum/ethyl acetate, 7:3) to afford **28** (572 mg, 35%) as a yellow oil. $[\alpha]_D^{25}$ = +1.9 (*c* = 1.7, $CHCl_3$). IR (liquid film, $CHCl_3$): $\tilde{\nu}$ = 2927, 1733, 1646, 1463, 1252, 1161, 1069 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.09 (dt, *J* = 15.8, 7.2 Hz, 1 H), 5.45 (d, *J* = 15.8 Hz, 1 H), 4.92–4.85 (m, 1 H), 4.72–4.71 (m, 1 H), 4.51 (dd, *J* = 9.1, 3.5 Hz, 1 H), 4.23 (dt, *J* = 7.8, 3.1 Hz, 1 H), 3.71 (dd, *J* = 8.0, 2.8 Hz, 1 H), 3.67–3.49 (m, 2 H), 2.35–2.18 (m, 4 H), 2.11 (t, *J* = 6.6 Hz, 2 H), 2.02–1.87 (m, 4 H), 1.58–1.46 (m, 10 H) 1.40 (s, 3 H), 1.39 (s, 3 H), 1.27 (m, 24 H), 0.94 (m, 9 H), 0.90 (t, *J* = 6.7 Hz, 3 H), 0.16 (s, 3 H), 0.13 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.0 and 171.9 (rotamers), 171.8, 145.2 and 144.7 (rotamers), 109.1 and 108.9 (rotamers), 108.2, 86.3 and 86.1 (rotamers), 85.1 and 85.0 (rotamers), 83.1 and 83.0 (rotamers), 76.0 and 75.5 (rotamers), 74.7, 62.2, 60.2 and 59.4 (rotamers), 47.0 and 46.3 (rotamers), 34.6 and 34.5 (rotamers), 34.0, 33.9 and 33.9 (rotamers), 33.7 and 33.6 (rotamers), 33.2 and 33.0 (rotamers), 32.0 and 31.7 (rotamers), 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 29.0, 28.9, 28.7, 28.6, 27.9 and 27.7 (rotamers), 27.5, 27.1 and 27.0 (rotamers), 25.9, 25.5, 25.3 and 25.2 (rotamers), 24.9, 24.8, 24.7 and 24.7 (rotamers), 22.7 and 22.7 (rotamers), 22.6 and 22.5 (rotamers), 18.4, 14.2 and 14.1 (rotamers), –4.8 ppm. $C_{44}H_{77}NO_6Si$ (744.17): calcd. C 71.01, H 10.43, N 1.88; found C 71.23, H 10.62, N 1.67.

(3a*R*,4*S*,14*S*,16a*S*,33a*S*)-14-Butyl-4-(*tert*-butyldimethylsilyloxy)-2,2-dimethylhexacosahydro-3a*H*-[1,3]dioxolo[4,5-*r*]pyrrolo[2,1-*c*][1,4]-oxaazacyclotriacontine-16,21(4*H*,22*H*)-dione (29): A suspension of **28** (450 mg, 0.6 mmol) and Raney Ni (75 mg) in ethanol (5 mL) was stirred under a hydrogen atmosphere at normal pressure and temperature. After 12 h, the reaction mixture was filtered through a pad of Celite and concentrated. The residue was purified by silica gel column chromatography (light petroleum/ethyl acetate, 7:3) to provide **29** (420 mg, 92%) as a colorless oil. $[\alpha]_D^{25}$ = –19.8 (*c* = 0.9, $CHCl_3$). IR (liquid film, $CHCl_3$): $\tilde{\nu}$ = 2929, 1730, 1638, 1463, 1380, 1215 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.92–4.86 (m, 1 H), 4.51 (dd, *J* = 9.1, 3.5 Hz, 1 H), 4.00–3.96 (m, 1 H), 3.84–3.79 (m, 1 H), 3.74–3.65 (m, 1 H), 3.62–3.47 (m, 2 H), 2.29–2.12 (m, 4 H), 2.05–1.86 (m, 4 H), 1.66–1.58 (m, 4 H), 1.54–1.49 (m, 8 H), 1.37 (s, 6 H), 1.25 (m, 32 H), 0.90 (m, 9 H), 0.89 (t, *J* = 6.7 Hz, 3 H), 0.07 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.0 and 171.9 (rotamers), 171.8, 107.8, 81.8 and 81.7 (rotamers), 76.1, 75.0 and 74.8 (rotamers), 72.0 and 71.8 (rotamers), 60.1 and 59.3 (rota-

mers), 47.0 and 46.2 (rotamers), 34.9 and 34.5 (rotamers), 34.1 and 33.9 (rotamers), 33.7, 33.6, 33.5, 33.4, 31.9 and 31.8 (rotamers), 31.6 and 31.6 (rotamers), 30.0, 29.6 (2 C), 29.5, 29.3, 29.2, 29.0 and 28.9 (rotamers), 28.6, 27.4 and 27.3 (rotamers), 27.2, 25.9, 25.6 and 25.3 (rotamers), 25.0 (2 C), 24.8 and 24.7 (rotamers), 24.6, 24.4, 22.6 and 22.6 (rotamers), 22.5 and 22.4 (rotamers), 18.1, 14.1 and 13.9 (rotamers), –4.3, –4.5 ppm. $C_{44}H_{83}NO_6Si$ (750.22): calcd. C 70.44, H 11.15, N 1.87; found C 70.23, H 11.27, N 1.77.

(3*S*,13*S*,15*S*,32a*S*)-3-Butyl-13,14,15-trihydroxyoctacosahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxaazacyclotriacontine-1,28(3*H*)-dione (30): A solution of **29** (336 mg, 0.45 mmol) and *p*TSA (50 mg) in methanol (5 mL) was stirred at room temperature for 4 h. The reaction mixture was neutralized (pH 6) by the addition of Et_3N (0.5 mL) and concentrated. The residue was purified by silica gel column chromatography (light petroleum/ethyl acetate, 2:3) to afford **30** (217 mg, 82%) as a light-yellow oil. $[\alpha]_D^{25}$ = –19.4 (*c* = 1.0, $CHCl_3$). IR (liquid film, $CHCl_3$): $\tilde{\nu}$ = 3413, 2924, 1737, 1631, 1463, 1277, 1193 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.92–4.84 (m, 1 H), 4.50 (dd, *J* = 9.1, 3.5 Hz, 1 H), 3.92–3.80 (m, 2 H), 3.63–3.57 (m, 2 H), 3.52–3.44 (m, 1 H), 2.31–2.09 (m, 8 H), 2.03–1.89 (m, 4 H), 1.66–1.49 (m, 10 H), 1.27 (m, 30 H), 0.89 (t, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.3 and 172.1 (rotamers), 172.0, 76.2, 75.0 and 74.9 (rotamers), 70.3, 60.2 and 59.3 (rotamers), 47.0 and 46.3 (rotamers), 34.6, 34.5, 34.0 and 33.8 (rotamers), 33.6 and 33.5 (rotamers), 32.7 and 32.7 (rotamers), 32.6 and 32.6 (rotamers), 31.9 and 31.6 (rotamers), 29.7, 29.6 (2 C), 29.5, 29.4, 29.3, 29.2, 28.8 and 28.8 (rotamers), 28.4 and 28.3 (rotamers), 27.4 and 27.4 (rotamers), 25.5 and 25.5 (rotamers), 24.8 and 24.7 (rotamers), 22.7 and 22.7 (rotamers), 22.5 and 22.4 (rotamers), 14.1 and 14.0 (rotamers) ppm. $C_{35}H_{65}NO_6$ (595.89): calcd. C 70.55, H 10.99, N 2.35; found C 70.41, H 11.17, N 2.18.

Penarolide Sulfate A_1 (1): Sulfur trioxide/pyridine complex (296 mg, 1.86 mmol) was added to a solution of triol **30** (37 mg, 0.06 mmol) in dry DMF (3 mL) under a nitrogen atmosphere, and the mixture was stirred at room temperature for 36 h. Water (4 mL) was added at 0 °C, and the reaction mixture was stirred for 30 min and then basified (pH 9) at 0 °C by adding saturated $NaHCO_3$ solution (6 mL). After stirring for 30 min, the resulting solution was concentrated in vacuo. The residue was triturated with ethyl acetate and filtered. The residue was purified by silica gel column chromatography (methanol/ethyl acetate, 3:7) to afford penarolide sulfate A_1 (**1**; 47 mg, 84%) as an amorphous solid. $[\alpha]_D^{25}$ = –24.6 (*c* = 0.5, CH_3OH). IR (nujol): $\tilde{\nu}$ = 2927, 1734, 1636, 1248, 1184 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ = 5.04 (d, *J* = 5.8 Hz, 1 H), 4.66 (d, *J* = 9.4 Hz, 1 H), 4.63–4.61 (m, 1 H), 4.40 (dd, *J* = 8.7, 4.6 Hz, 1 H), 3.63 (t, *J* = 7.5 Hz, 2 H), 2.43 (dt, *J* = 15.1, 7.5 Hz, 2 H), 2.30–2.23 (m, 2 H), 2.14–1.92 (m, 4 H), 1.85–1.77 (m, 2 H), 1.58–1.45 (m, 14 H), 1.30 (m, 28 H), 0.90 (t, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 174.2, 173.8, 80.7, 79.4, 78.9, 76.2, 61.0, 48.8, 35.2, 34.7, 31.7, 31.3, 30.9, 30.8, 30.6, 30.4, 28.5, 26.4, 26.0, 25.8, 23.5, 14.3 ppm. MS (ESI): *m*/*z* = 924.69 $[M + Na]^+$.

(3a*S*,4*S*,14*S*,16a*S*,33a*S*)-14-Butyl-4-hydroxy-2,2-dimethylhexacosahydro-3a*H*-[1,3]dioxolo[4,5-*γ*]pyrrolo[2,1-*c*][1,4]oxaazacyclotriacontine-16,21(4*H*,22*H*)-dione (31): To a stirred solution of compound **29** (94 mg, 0.13 mmol) in THF (3 mL) was added TBAF (1.0 M in THF, 0.19 mL) dropwise. The reaction mixture was then stirred for 1 h, by which time the reaction was complete (as monitored by TLC). The reaction was then quenched by the addition of water, and the reaction mixture was concentrated under reduced pressure. The crude mass was taken up in water and extracted with ethyl acetate (3 × 10 mL), washed with brine, dried with anhydrous Na_2SO_4, and concentrated. The crude residue was then purified by silica gel column chromatography (light petroleum/ethyl acetate, 3:2) to furnish **31** (75 mg, 94%) as a light-yellow oil. $[\alpha]_D^{25}$ = –25.5 (*c* = 0.3, $CHCl_3$). IR (liquid film, $CHCl_3$): $\tilde{\nu}$ = 3205, 2854, 1735, 1638, 1404, 1246 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.91–4.85 (m, 1 H), 4.50 (dd, *J* = 8.7, 3.3 Hz, 1 H), 4.03–4.00 (m, 2 H), 3.82 (m, 1 H), 3.73–3.67 (m, 1 H), 3.64–3.50 (m, 2 H), 2.32–2.13 (m, 4 H), 2.06–1.91 (m, 4 H), 1.67–1.61 (m, 4 H), 1.52–1.43 (m, 8 H), 1.40 (s, 3 H), 1.39 (s, 3 H), 1.26 (m, 32 H), 0.89 (t, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.0 and 171.9 (rotamers), 171.7, 108.0, 82.9 and 82.8 (rotamers), 76.0 and 75.4 (rotamers), 75.2 and 74.8 (rotamers), 70.2 and 70.0 (rotamers), 60.2 and 59.3 (rotamers), 47.0 and 46.3 (rotamers), 34.6 and 34.5 (rotamers), 34.0, 33.8 and 33.7 (rotamers), 33.6, 32.1, 32.0, 31.7, 29.7, 29.5, 29.4, 29.3 (2 C), 29.1 and 29.0 (rotamers), 28.8 and 28.7 (rotamers), 28.6, 27.5 (2 C), 27.4 (2 C), 27.1, 25.9 and 25.8 (rotamers), 25.4, 25.3, 25.2, 24.9 and 24.8 (rotamers), 22.7 and 22.6 (rotamers), 22.6 and 22.5 (rotamers), 14.2 and 14.1 (rotamers) ppm. $C_{38}H_{69}NO_6$ (635.96): calcd. C 71.77, H 10.94, N 2.20; found C 71.64, H 11.03, N 2.37.

General Procedure for Enzyme Inhibition Assay: Inhibition assay for the inhibitory potencies of the desulfated penarolide sulfate A_1 (**30**) was determined by measuring the residual hydrolytic activities of the glycosidases of the corresponding *p*-nitrophenyl glycosides in the presence of desulfated penarolide sulfate A_1 (**30**) spectrophotometrically.

In the case of α-glucosidase (yeast), the assay was performed in a citrate phosphate buffer (50 mM, pH 6.8) with *p*-nitrophenyl α-D-glucopyranoside as the substrate. The enzyme was incubated with the inhibitor at various concentrations for 30 min, and the substrate was then added. The reaction was carried out at 37 °C for 30 min and then quenched with a Na_2CO_3 solution.

In the case of β-glucosidase (almond), the assay was performed in a citrate phosphate buffer (50 mM, pH 5.5) with *p*-nitrophenyl β-D-glucopyranoside as the substrate. The reaction was carried out at 37 °C for 30 min and then quenched with a Na_2CO_3 solution.

In the case of α-galactosidase (green coffee beans), the assay was performed in a citrate phosphate buffer (50 mM, pH 6.5) with *p*-nitrophenyl α-D-galactopyranoside as the substrate. The reaction was carried out at 25 °C for 20 min and then quenched with a Na_2CO_3 solution.

In the case of β-galactosidase, each assay was performed in citrate buffer (50 mM, pH 4.5) with *p*-nitrophenyl β-D-galactosidase as the substrate. The reaction was carried out at 25 °C for 20 min and then quenched with a Na_2CO_3 solution.

In the case of α-mannosidase (jack bean), the assay was performed in an acetate buffer (50 mM, pH 4.5) with *p*-nitrophenyl α-D-mannopyranoside as the substrate. The reaction was carried out at 25 °C for 20 min and then quenched with a Na_2CO_3 solution.

In the case of β-mannosidase (snail acetone), the assay was performed in an acetate buffer (50 mM, pH 4.0) with *p*-nitrophenyl β-D-mannopyranoside as the substrate. The reaction was carried out at 25 °C for 20 min and then quenched with a Na_2CO_3 solution.

Supporting Information (see footnote on the first page of this article): Representative ^1H and ^{13}C NMR spectra of all compounds outlined in the Experimental Section.

Acknowledgments

D. B. and K. S. S. thank the Council of Scientific and Industrial Research (CSIR), New Delhi, for financial assistance in the form

of a research fellowship. We thank Dr. Ganesh Pandey, HOD, Organic Chemistry Division, for his constant support and encouragement.

[1] Y. Nakao, T. Maki, S. Matsunaga, R. W. M. Van Soest, N. Fusetani, *Tetrahedron* **2000**, *56*, 8977–8987.

[2] a) W. Wang, F. Nan, *J. Org. Chem.* **2003**, *68*, 1636–1639; b) R. Beugelmans, A. Bigot, M. Bios-Chousy, J. Zhu, *J. Org. Chem.* **1996**, *61*, 771–774.

[3] K. Sonogashira, Y. Tohada, N. Hagihara, *Tetrahedron Lett.* **1975**, *16*, 4467–4470.

[4] a) R. B. Greenwald, H. Zhao, P. Reddy, *J. Org. Chem.* **2003**, *68*, 4894–4896; b) T. Kawaguchi, N. Funamori, Y. Matsuya, H. Nemoto, *J. Org. Chem.* **2004**, *69*, 505–509.

[5] a) K. Nakayama, H. C. Kawato, H. Inagaki, R. Nakajima, A. Kitamura, K. Someya, T. Ohta, *Org. Lett.* **2000**, *2*, 977–980; b) K. B. Sharpless, W. Amberg, Y. L. Bennani, G. A. Crispino, J. Hartung, K.-S. Jeong, H. L. Kwong, K. Morikawa, Z. M. Wang, D. Xu, X. L. Zhang, *J. Org. Chem.* **1992**, *57*, 2768–2771; c) H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483–2547.

[6] a) Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune, K. B. Sharpless, *J. Am. Chem. Soc.* **1987**, *109*, 5765–5780; b) T. Katsuki, K. B. Sharpless, *J. Am. Chem. Soc.* **1980**, *102*, 5974–5976; c) T. Katsuki, V. S. Martin, *Org. React.* **1996**, *48*, 1–300.

[7] a) W. S. Wadsworth, W. D. Emmons, *J. Am. Chem. Soc.* **1961**, *83*, 1733–1738; b) M. A. Blanchette, W. Choy, J. T. Davis, A. P. Essenfeld, S. Masamune, W. R. Rousch, T. Sakai, *Tetrahedron Lett.* **1984**, *25*, 2183–2186.

[8] Enantiomeric purity of **13** was estimated (98.4% *ee*) by HPLC analysis by using a chiracel OJ-H column (6.0% *i*PrOH/*n*-hexane, flow rate 0.5 mL min^{-1}, λ = 220 nm).

[9] S. Takano, K. Samizu, T. Sugihara, K. Ogasawara, *J. Chem. Soc., Chem. Commun.* **1989**, 1344–1345 and references cited therein.

[10] Y. Oikawa, T. Yoshioka, O. Yonemitsu, *Tetrahedron Lett.* **1982**, *23*, 885–888.

[11] M. K. Gurjar, C. Pramanik, D. Bhattasali, C. V. Ramana, D. K. Mohapatra, *J. Org. Chem.* **2007**, *72*, 6591–6594.

[12] a) D. A. Franklin, Z. Junyi, L. Yingxin, X. He, D. B. Charles, *J. Org. Chem.* **2005**, *70*, 5413–5419; b) M. Bessodes, C. Boukarim, *Synlett* **1996**, 1119–1120.

[13] a) E. J. Corey, M. Chaykovsky, *J. Am. Chem. Soc.* **1965**, *87*, 1353–1364; b) H. Nozaki, H. Itô, D. Tunemoto, K. Kondô, *Tetrahedron* **1966**, *22*, 441–446; c) T. Sakakibara, R. J. Sudoh, *J. Chem. Soc., Chem. Commun.* **1977**, 7–8.

[14] a) M. Tokunaga, J. F. Larrow, E. N. Jacobsen, *Science* **1997**, *277*, 936–938; b) E. Furrow, S. E. Schaus, E. N. Jacobsen, *J. Org. Chem.* **1998**, *63*, 6776–6777.

[15] Enantiomeric purity of **23** was estimated (98.8% *ee*) by HPLC analysis by using a chiracel OD-H column (100% *n*-Hexane, flow rate 1 mL min^{-1}, λ = 214 nm).

[16] Enantiomeric purity of **24** was estimated (93.3% *ee*) by HPLC analysis by using a chiracel OJ-H column (7.0% *i*PrOH/*n*-hexane, flow rate 0.7 mL min^{-1}, λ = 220 nm).

[17] a) A. P. Rauter, J. Figueiredo, M. Ismael, T. Canda, J. Font, M. Figueredo, *Tetrahedron: Asymmetry* **2001**, *12*, 1131–1146; b) G. Just, C. Luthe, *Can. J. Chem.* **1980**, *58*, 1799–1805.

[18] L. Poppe, K. Recseg, L. Novak, *Synth. Commun.* **1995**, *25*, 3993–4000.

[19] a) C. H. Heathcock, R. Ratcliffe, *J. Am. Chem. Soc.* **1971**, *93*, 1746–1757; b) W. H. Hartung, C. Simonoff, *Org. React.* **1953**, *7*, 263–326.

[20] K. Takai, K. Nitta, K. Utimoto, *J. Am. Chem. Soc.* **1986**, *108*, 7408–7410.

[21] G. L. Stahl, R. Walter, C. W. Smith, *J. Org. Chem.* **1978**, *43*, 2285–2286.

[22] a) R. B. Woodward, W. E. Doering, *J. Am. Chem. Soc.* **1945**, *67*, 860–874; b) N. Chida, T. Tobe, M. Suwama, M. Ohtsuka, S. Ogawa, *J. Chem. Soc., Chem. Commun.* **1990**, 994–995.

[23] a) A. Ichihara, M. Ubukata, S. Sakamura, *Tetrahedron Lett.* **1977**, *18*, 3473–3476; b) P. Yakambaram, V. G. Puranik, M. K. Gurjar, *Tetrahedron Lett.* **2006**, *47*, 3781–3783.

[24] a) L. Lazar, M. Csavas, A. Borbas, G. Gyemant, A. Liptap, *Arkivoc* **2004**, *7*, 196–207; b) L. D. Lu, C. R. Shie, S. S. Kulkarni, G. R. Pan, X. A. Lu, S. C. Hung, *Org. Lett.* **2006**, *8*, 5995–5998; c) L. G. Lange III, C. A. Spilburg, US Patent Application No. 07/429398, **1991**.

[25] G. Legler, S. Pohl, *Carbohydr. Res.* **1986**, *155*, 119–129.

[26] M. Dixon, *Biochem. J.* **1953**, *55*, 170–171.

[27] S. Vijayasaradhi, J. Singh, I. S. Aidhen, *Synlett* **2000**, 110–112.

[28] M. Iwata, H. Ohrui, *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2837.

[29] K. S. Kim, Y. H. Song, B. H. Lee, C. S. Hahn, *J. Org. Chem.* **1986**, *51*, 404–407.

[30] K. W. C. Poon, K. M. Lovell, K. N. Dresner, A. Datta, *J. Org. Chem.* **2008**, *73*, 752–755.

Received: July 9, 2008
Published Online: November 14, 2008

