STEREOSELECTIVE SYNTHESIS OF 2-*EPI*-PENARESIDIN A AND ITS (15*R*,16*R*)-STEREOISOMER

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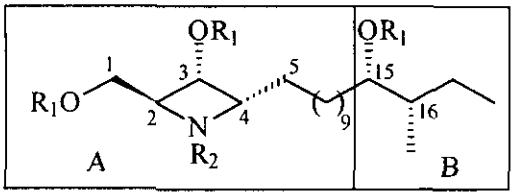
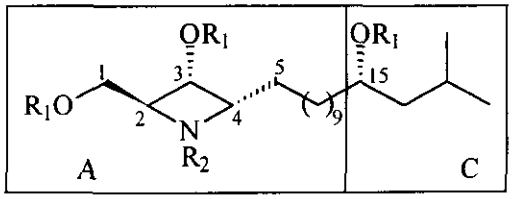
Abstract - Stereoselective synthesis of 2-*epi*-penaresidin A and its (15*R*, 16*R*)-stereoisomer was described.

In 1991, penaresidin A (**1**) and B (**2**), which are the first sphingosine-derived azetidine alkaloids possessing potent actomyosin ATPase-activating activity, have been isolated as a 1.5:1 inseparable mixture by Kobayashi *et al* from the Okinawan marine sponge *Penares* sp.[1] The 2*S*,3*R*,4*S*-configurations of the azetidine ring moiety in **1** and **2** (part A), and the *syn* configuration between C-15 and C-16 (part B) in **1** were established from the synthetic studies[2,3] in 1995. Recently, the absolute configurations at C-15 in **1** and **2** were finally determined to be *S* on the basis of ^{1}H NMR data of the tri-*O*-MTPA esters (**5** and **6**) of natural specimen.[4] The unique structures and the biological activity of **1** and **2** make them attractive to synthetic chemists. Almost at the same time in 1995, the first synthesis of a straight chain analog of penaresidins and the total synthesis of **1** were reported by Kamikawa *et al.*[2] and K. Mori *et al.*,[3a]





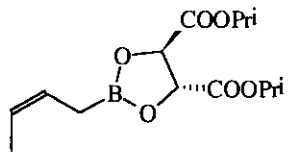
Penaresidin A **1** $R_1 = R_2 = H$
3 $R_1 = R_2 = Ac$
5 R_1 = MTPA, R_2 = Ac

Penaresidin B **2** $R_1 = R_2 = H$
4 $R_1 = R_2 = Ac$
6 R_1 = MTPA, R_2 = Ac

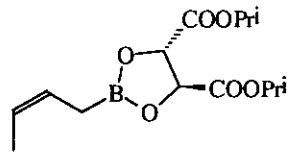
Scheme 1

respectively In this paper, we wish to describe a full account of our synthesis of 2-*epi*-penaresidin A(**7**) and its (15*R*, 16*R*)-stereoisomer(**7'**).

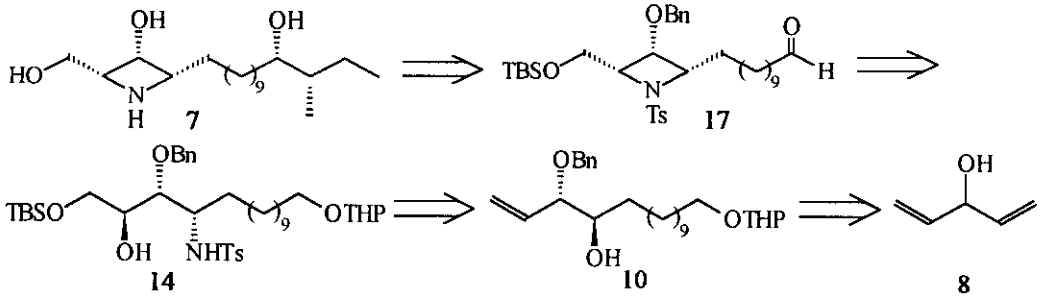
As shown in **Scheme 2**, the chiralities on C-15 and C-16 of **7** could be introduced at a late stage by means of Roush reaction,[5] so that both of the two stereoisomers with the *syn* configuration between C-15 and C-16 could be obtained by treatment of **17** with two different Roush reagents [(*Z*)-(*R,R*)-**30** and (*Z*)-(*S,S*)-**30**]. The azetidine ring in **17** could be considered as a ring closure product derived from sphingosine. Thus, the target compound (**7**) could be obtained from symmetric divinylcarbinol (**8**) *via* **10**,**14** and **17**



(*Z*)-(*R,R*)-30



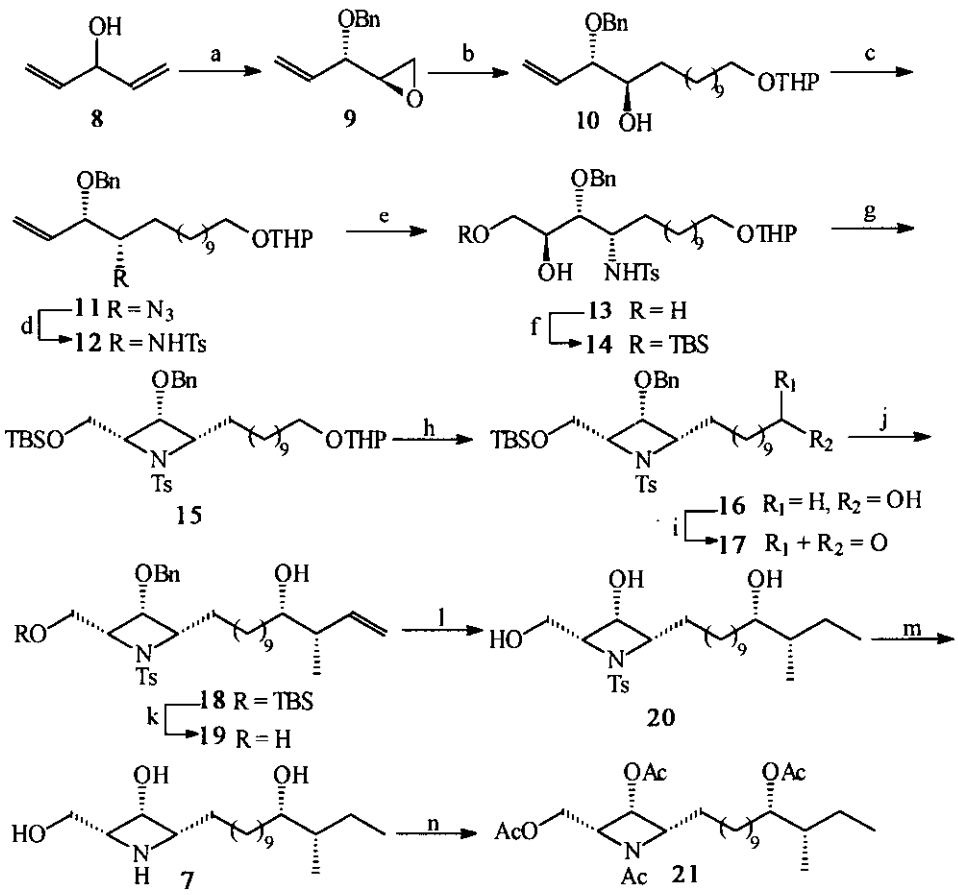
(*Z*)-(*S,S*)-30



Scheme 2

As shown in **Scheme 3**, compound (**9**) was readily prepared from **8** with high diastereomeric and enantiomeric excess [6] The ring opening reaction of the epoxide (**9**) with Grignard reagent in the presence of a catalytic amount of CuI was dependent on the reaction temperature. When the reaction was performed at -20 °C, the bromide was obtained as the major product; however, the satisfactory result was obtained at -50 °C to afford **10** in 76% yield Mesylation of the hydroxy group of **10** was followed by treatment of the product with sodium azide in DMF at 90 °C to give **11**. Reduction of **11** with $LiAlH_4$ and the subsequent tosylation with TsCl in CH_2Cl_2 afforded **12** in 81.5% yield Sharpless asymmetric dihydroxylation[7] of **12** with DHQD-CLB as ligand almost exclusively yielded **13**. Regioselective protection of the primary hydroxy group of **13** was completed by treatment of **13** with TBDMSCl in DMF at 0°C in the presence of imidazole to give **14**

It is well known that the Mitsunobu reaction[8] is an exceptionally useful and general method in organic synthesis. For example, pyrrolidine and piperidine were readily constructed by the cyclization of sulfonamide alcohol [9] However, to the best of our knowledge, few examples[10] have been applied to the formation of azetidine. Fortunately, when we treated compound (**14**) with DEAD and PPh_3 in THF, the expected reaction occurred to afford the azetidine (**15**) in 92% yield.



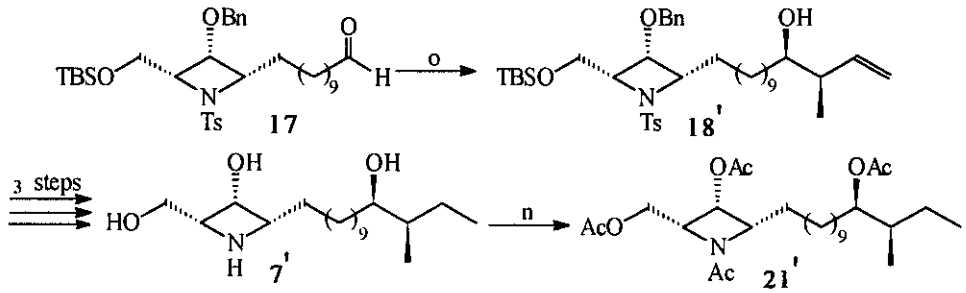
Reagents and Conditions a) i TBHP, L-(+)-DIPT, Ti(O-*iso*-Pr)$_4$, 4Å MS, CH_2Cl_2, -20°C,10 days, 65% ii BnBr, NaH, *n*-Bu_4NI, THF, -10°C, 80%, b) $BrMgCH_2(CH_2)_8OTHP$, CuI, -50°C, 76%, c) i MsCl, NEt_3, CH_2Cl_2 ii . NaN_3 DM, 90°C, 76% (2 steps), d) i $LiAlH_4$, THF ii TsCl, py, CH_2Cl_2, 81 5% (2 steps), e) DHQD-CLB, OsO_4, K_2CO_3, $K_3[Fe(CN)_6]$, *t*-BuOH/H_2O(1 1), 84%, f) TBDMSCl, imidazole, DMF, 0°C, 94%; g) PPh_3, DEAD, THF, 92 %, h) $MgBr_2$, Et_2O, 81%, i) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C, NEt_3, 89%, j) (*Z*) - (*S,S*) -30, 4Å MS, toluene, -78°C, 88%, k) *n*-Bu_4NF, THF, 92%, l) 10% Pd/C, H_2, EtOH, 85%, m) Na, naphthalene, DME, -60°C; n) Ac_2O, py, CH_2Cl_2, 40% (from 20)

Scheme 3

Treatment of **15** with $MgBr_2$ in Et_2O completed the selective removal of THP group to give **16**. Swern oxidation of **16** gave a somewhat unstable aldehyde (**17**) which was directly exposed to the Roush reagent (*Z*)-(*S,S*)-**30** to afford **18** (72% d.e, inseparable)[11] without purification. Removal of TBS group of **18** and the subsequent hydrogenation of the product yielded **20** Reduction of **20** with Na-naphthalene completed the removal of Ts group to afford the target compound (**7**), which was acetylated to give the tetraacetyl derivative (**21**)

In the similar manner as that of **7**, compound (**18'**) (72% d.e, inseparable)[11] was obtained while treating **17** with the Roush reagent (*Z*)-(*R,R*)-**30** Conversion of **18'** to (15*R*,16*R*)-**7** was completed by the same

procedure as before and the product was acetylated to give the tetraacetyl derivative (**21'**) (**Scheme 4**).



Reagents and Conditions: o) (*Z*) - (*R,R*) -30, 4Å MS, toluene, -78°C, 77%, n) Ac_2O, py, CH_2Cl_2, 33% (from 20').

Scheme 4

Thus, we have provided a facile stereoselective synthesis of 2-*epi*-penaresidin A and its (15*R*,16*R*)-stereoisomer from divinylcarbinol (**8**) and an efficient method to construct azetidine.

EXPERIMENTAL

Melting points were measured on MEL-TEMP and are uncorrected. IR spectra were recorded on a FTS-185 spectrophotometer and only the strongest / structurally most important peaks were listed in cm^{-1}, ^1H NMR spectra were recorded at Bruker AM 300 (300 MHz) or AMX 600 (600 MHz) spectrometer using TMS as internal standard. ^{13}C NMR spectra were recorded at Bruker AM 300 (75 MHz) spectrometer with the solvent peak ($CDCl_3$, δ = 77.0 ppm) as a reference. Routine MS were run on a Finnigan 4021 apparatus Optical rotations were measured on a Perkin-Elmer 241 polarimeter at the sodium D line and 22°C. Flash column chromatography were carried out using silica gel (200-300 mesh, made in Shanghai, China).

(2*R*,3*S*)-3-Benzyloxy-1,2-epoxy-4-pentene (9) :

This compound was prepared according to the known procedure [6b] All the spectroscopic data were in agreement with those reported in the literature.

(3*S*,4*R*)-3-Benzyloxy-15-tetrahydropyranyloxypentadec-1-en-4-ol (10) :

To a suspension of CuI (50 mg, 0 26 mmol) in THF (10 mL), 10-tetrahydropyranyloxydecylmagnesium bromide (10 mL, 3 mmol, 1 M in THF) was added at -50 °C under N_2 atmosphere. After the mixture was stirred at -50 °C for 10 min, a solution of 9 (500 mg, 2.6 mmol) in 1 mL of THF was added dropwise. After the completion of the reaction monitored by TLC, sat. aq. NH_4Cl was added to the mixture, which was extracted with EtOAc (3 x 10 mL). The combined extract was washed with brine and dried over anhydrous Na_2SO_4. Evaporation followed by purification through flash column chromatography (eluent:

petroleum ether/ethyl acetate, 10:1) afforded **10** (722 mg, 76%) as a colorless oil. $[\alpha]_D$ + 21.4 ° (c 0 99, $CHCl_3$). IR(film): 3480, 2926, 2855, 1460, 1120 cm^{-1}. ^1H NMR ($CDCl_3$) δ· 1 26-1.85 (m, 26 H, 5 , 6 , 7 , 8 , 9 , 10 , 11 , 12 , 13 , 14 , 3' , 4' , 5'-H), 3.34-3.90 (m, 6 H, 3 , 4 , 15 , 6'-H), 4.38, 4 63 (AB, 2 H, J_{AB} = 11 9 Hz, 3-OCH_2Ph), 4.57 (m, 1 H, 2'-H), 5.29 (dd, 1 H, J = 17.3, 1.4 Hz, 1-H), 5.38 (dd, 1 H, J = 10.5, 1 4 Hz, 1-H), 5 84 (m, 1 H, 2-H), 7.28 (m, 5 H, Ar-H) ppm MS (m/z, %): 433 (M^+ +1 ,0 52), 349 (84 89), 241 (65 69), 91 (Bn , 62.09), 85 (THP , base) Anal Calcd for $C_{27}H_{44}O_4$· C, 74 95 , H, 10 25 Found : C, 74 76; H , 10 72

(3*S*,4*S*)-3-Benzyloxy-4-azido-15-tetrahydropyranyloxypentadec-1-ene (11) :

To a solution of **10** (700 mg, 1.62 mmol) in CH_2Cl_2 (5 mL), MsCl (0.14 mL, 1.8 mmol) and NEt_3 (0.28 mL, 2.0 mmol) were added at 0 °C, and then the mixture was stirred at rt for 4 h. then CH_2Cl_2 was added to dilute the mixture, which was washed with 1N HCl, sat. aq. $NaHCO_3$ and brine. Removal of the solvent gave a yellow oil which was then dissolved in DMF (5 mL) without purification. Sodium azide (316 mg, 4.8 mmol) was added, and then the mixture was stirred at 90 °C for 5 h. After the completion of the reaction, water was added. The mixture was extracted with Et_2O (3 x 10 mL), and the combined extract was washed with water and brine. Drying over anhydrous Na_2SO_4 was followed by evaporation, and purification by flash column chromatography (eluent: petroleum ether/ethyl acetate, 50·1) to afford 11 (564 mg, 76%) as a colorless oil $[\alpha]_D$ -20 7 ° (c 1 00, $CHCl_3$). IR(film): 2928, 2855, 2104, 1454, 1260, 1034 cm^{-1} ^1H NMR ($CDCl_3$) δ· 1.25-1.85 (m, 26 H, 5 , 6 , 7 , 8 , 9 , 10 , 11 , 12 , 13 , 14 , 3' , 4' , 5'-H), 3.27 (m, 1 H), 3.30-3 53 (m, 2 H), 3 70-3 79 (m, 2 H), 3 86 (m, 1 H), 4.40, 4.64 (AB, 2 H, J_{AB} = 11.9 Hz, 3-OCH_2Ph), 4.57 (m, 1 H, 2'-H), 5.31 (dd, 1 H, J = 17 8, 1 0 Hz, 1-H), 5 36 (dd, 1 H, J = 10.9, 1.0 Hz, 1-H), 5 78 (m, 1 H, 2-H), 7.33 (m, 5 H, Ar-H) ppm MS (m/z, %) 346 (M^+ - OTHP, 54.28), 347 (13.17), 91 (Bn, 100), 85 (THP, 73.53).

(3*S*,4*S*)-3-Benzyloxy-4-*p*-tolylsulfonylamino-15-tetrahydropyranyloxypentadec-1-ene (12) ·

To a suspension of $LiAlH_4$ (3.2 g, 85 mmol) in dry THF (25 mL), a solution of **11** (3 9 g, 8 5 mmol) in 5 mL of THF was added at rt After the completion of the reaction, Na_2SO_4 •$10H_2O$ was added to the mixture, which was filtered. The filtrate was concentrated to give a colorless oil, which was then dissolved in CH_2Cl_2 (30 mL) without purification TsCl (8.1 g, 42 5 mmol) and NEt_3 (7.1 mL, 51 mmol) were added at rt. After the completion of the reaction monitored by TLC, CH_2Cl_2 was added to dilute the mixture, which was washed with 1N HCl, sat. aq. $NaHCO_3$ and brine. Drying over anhydrous Na_2SO_4 was followed by evaporation, and purification by flash column chromatography (eluent: petroleum ether/ethyl acetate, 10.1) to afford **12** (4.07 g, 81.5%) as a colorless oil. $[\alpha]_D$ + 32.9 ° (c 0.56, $CHCl_3$) IR(film) 3280,

2928, 2855, 1455, 1162 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.03-1.76 (m, 26 H, 5 , 6 , 7 , 8 , 9 , 10 , 11 , 12 , 13 , 14 , 3' , 4' , 5'-H), 2 33 (s, 3 H, $ArCH_3$), 3.21-3.81 (m, 6 H, 3 , 4 , 15 , 6'-H), 4.17, 4.46 (AB, 2 H, J_{AB} = 11.9 Hz, 3-OCH_2Ph), 4.50 (m, 1 H, 2'-H), 4.62 (d, 1 H, J = 8.7 Hz, NH), 5.09 (d, 1 H, J = 17 4 Hz, 1-H), 5.13(d, 1 H, J = 8 3 Hz, 1-H), 5.53 (m, 1 H, 2-H), 7.20 (m, 7 H, Ar-H), 7.63 (d, 2 H, J = 8.2 Hz, Ar-H) ppm. MS (m/z, %). 354 (96.42), 355 (24.83), 155 (38 09), 91 (Bn, base), 85 (THP, 97.04). Anal. Calcd for $C_{34}H_{51}NO_5S$: C, 69 71; H, 8.77; N, 2 39 Found . C , 69.69; H, 8 88; N, 2.29.

(2*S*,3*R*,4*S*)-3-Benzyloxy-4-*p*-tolylsulfonylamino-15-tetrahydropyranyloxypentadecan-1,2-diol (13) :
To a solution of DHQD-CLB (63 mg, 0.14 mmol) in a mixture of 1:1 *t*-BuOH-H_2O (20 mL), $K_3Fe(CN)_6$ (6.58 g, 20 mmol), K_2CO_3 (2.76 g, 20 mmol) and OsO_4 (4 mL, 0 2 mmol, 0.05 M in *t*-BuOH) were added. The mixture was stirred at rt for 10 min, and then **12** (3.9 g, 6 7 mmol) was added After the completion of the reaction, Na_2SO_3 (10 g) was added to the mixture, and the stirring was continued for another 20 min. The mixture was extracted with EtOAc (3 x 25 mL), and the combined extract was washed with brine. Drying over anhydrous Na_2SO_4 was followed by evaporation, and purification by flash column chromatography (eluent· petroleum ether/ethyl acetate, 1 1) to afford **13** (3.48 g, 84 %) as a colorless viscous oil. $[\alpha]_D$ -6.3 ° (c 1.20, $CHCl_3$). IR(film) 3500, 3300, 2928, 2855, 1455, 1157cm^{-1}. ^1H NMR ($CDCl_3$) δ· 0 86-1 82 (m, 26 H, 5 , 6 , 7 , 8 , 9 , 10 , 11 , 12 , 13 , 14 , 3' , 4' , 5'-H), 2.41 (s, 3 H, $ArCH_3$), 3.36-3.88 (m, 9 H, 1 , 2 , 3 , 4 , 15 , 6'-H), 4.48, 4 55 (AB, 2 H, J_{AB} = 11.2 Hz, 3-OCH_2Ph), 4.57 (m, 1 H, 2'-H), 5.24 (d, 1H, J = 10 0 Hz, NH), 7 32 (m, 7 H, Ar-H), 7.74 (d, 2 H, J = 8.2 Hz, Ar-H) ppm MS (m/z, %) 355 (18.98), 354 (75.80), 155 (25.56), 91 (Bn, base), 85 (THP, 58.53) Anal. Calcd for $C_{34}H_{53}NO_7S$ C, 65.88, H, 8.62; N, 2.26. Found C , 65 50; H, 8 82; N, 2 16.

(2*S*,3*R*,4*S*)-1-*tert*-Butyldimethylsilyloxy-3-benzyloxy-4-*p*-tolylsulfonylamino-15-tetrahydropyranyloxypentadecan-2-ol (14)
To a solution of **13** (700 mg ,1 13 mmol) in dry DMF (5 mL), TBDMSCl (190 mg, 1.25 mmol) and imidazole (170 mg, 2.5 mmol) were added at 0 °C. The mixture was stirred for 5 h, and then water was added to quench the reaction. The mixture was extracted with EtOAc (3 x 10 mL), and the combined extract was washed with water and brine. Drying over anhydrous Na_2SO_4 was followed by evaporation, and purification by flash column chromatography (eluent. petroleum ether/ethyl acetate, 6:1) to afford **14** (800 mg, 94 %) as a colorless oil $[\alpha]_D$ -13 7 ° (c 1 05, $CHCl_3$). IR(film): 3520, 3300, 2928, 2855, 1460, 1160 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.03 (s, 3 H, $SiCH_3$), 0.04 (s, 3 H, $SiCH_3$), 0.88 (s, 9 H, *t* -Bu), 1.10-1.84 (m, 26 H, 5 , 6 , 7 , 8 , 9 , 10 , 11 , 12 , 13 , 14 , 3' , 4' , 5'-H), 2.42 (s, 3 H, $ArCH_3$), 2.74 (m, 1 H, 2-OH), 3.27-3.87 (m, 9 H, 1 , 2 , 3 , 4 , 15 , 6'-H), 4.36, 4.48 (AB, 2 H, J_{AB} = 11.4 Hz, 3-OCH_2Ph),

4 58 (m, 1 H, 2'-H), 5 34 (d, 1 H, J = 9.8 Hz, NH), 7 26 (m, 7 H, Ar-H), 7 76 (d, 2 H, J = 7.8 Hz, Ar-H) ppm MS (m/z, %)· 650 (7.60), 410 (9.11), 354 (23 73), 277 (12 66), 155 (15 59), 91 (Bn, base), 85 (THP, 41.96). Anal. Calcd for $C_{40}H_{67}NO_7SSi$· C, 65 44; H, 9.20, N, 1.91. Found : C, 65.64, H, 9.39; N, 1.86

(2*R*,3*R*,4*S*)-2-*tert*-Butyldimethylsilyloxy-3-benzyloxy-4-(11'-tetrahydropyranyloxyundecyl)-*N*-*p*-tolylsulfonylazetidine (15) .

To a solution of PPh_3 (2 0 g, 7.6 mmol) in dry THF (10 mL), DEAD (1.2 mL, 7.6 mmol) was added dropwise at 0 °C The mixture was stirred for 0.5 h, and then **14** (2.8 g, 3.8 mmol) was added After the completion of the reaction, removal of solvent was followed by flash column chromatography (eluent· petroleum ether/ethyl acetate, 10:1) to give **15** (2.49 g, 92 %) as a colorless oil. $[\alpha]_D$ +21.3 ° (c 1 56, $CHCl_3$) IR(film)· 2928, 2855, 1460, 1350, 1169 cm^{-1} ^1H NMR ($CDCl_3$) δ· 0.05 (s, 3 H, $SiCH_3$), 0.08 (s, 3 H, $SiCH_3$), 0.88 (s, 9 H, *t*-Bu), 1 24-1 88 (m, 26 H, 1' , 2' , 3' , 4' , 5' , 6' , 7' , 8' , 9' , 10' , 3" , 4", 5"-H), 2.45 (s, 3 H, ArCH_3), 3 38 -4 13 (m, 9 H, 2 , 3 , 4 , 11' , 6"-H and 2-CH_2), 4.37, 4.72 (AB, 2 H, J_{AB} = 12 0 Hz, 3-OCH_2Ph), 4.58 (m, 1 H, 2"-H), 7 29 (m, 7 H, Ar-H), 7 70 (d, 2 H, J = 8.0 Hz, Ar-H) ppm MS (m/z, %): 700 (M^+-CH_3), 556 (4.42), 270 (33.94), 121 (50.49), 91 (Bn, base), 85 (THP, 34 93). Anal. Calcd for $C_{40}H_{65}NO_6SSi$: C, 67.09, H, 9.15; N, 1.96 Found : C, 67.11; H, 9.22; N, 1.99.

(2*R*,3*R*,4*S*)-2-*tert*-Butyldimethylsilyloxy-3-benzyloxy-4-(11'-hydroxyundecyl)-*N*-*p*-tolylsulfonylazetidine (16) .

To a solution of $MgBr_2$ (2.39 g ,13 mmol) in dry Et_2O (80 mL), **15** (2 24 g, 3.13 mmol) was added under N_2 atmosphere. The mixture was stirred for 3 h at rt , and then water was added to the mixture, which was extracted with Et_2O (3 x 15 mL) The combined extract was washed with brine. Drying over anhydrous Na_2SO_4 was followed by evaporation, and purification by flash column chromatography (eluent petroleum ether/ethyl acetate, 4·1) to yield **16** (1 14 g, 81 %) as a colorless oil and the recovered **15** (638 mg). $[\alpha]_D$ + 15 4 ° (c 1 16, $CHCl_3$). IR(film): 3400, 2928, 2855, 1470, 1340, 1258, 1163 cm^{-1}. ^1H NMR ($CDCl_3$) δ· 0 06 (s, 3 H, $SiCH_3$), 0 08 (s, 3 H, $SiCH_3$), 0.90 (s, 9 H, *t*-Bu), 1 26-1.72 (m, 20 H, 1' , 2' , 3' , 4' , 5' , 6' , 7' , 8' , 9' , 10'-H), 2 46 (s, 3 H, $ArCH_3$), 3 66 (t, 2 H, J = 6 7 Hz, 11'-H), 3.73- 4.00 (m, 4 H, 2 , 4-H and 2-CH_2), 4.14 (t, 1 H, J = 9.8 Hz, 3-H), 4 39, 4 73 (AB, 2 H, J_{AB} = 12 0 Hz, 3-OCH_2Ph), 7.33 (m, 5 H, Ar-H), 7 36, 7.72 (AB, 4 H, J_{AB} = 8.2 Hz, Ar-H) ppm MS (m/z, %)· 616 (M^+-CH_3), 574 (M^+-Bu, 1.58), 270 (23 37), 149 (7 71), 91 (Bn, base). Anal. Calcd for $C_{35}H_{57}NO_5SSi$ · C, 66.52; H, 9 09, N, 2.22 Found C, 66.53, H, 9 15, N, 2.24.

(2*R*,3*R*,4*S*)-2-*tert*-Butyldimethylsilyloxy-3-benzyloxy-4-(11'-hydroxy-12'-methyltetradec-13'-enyl)-*N*-*p*-tolylsulfonylazetidine

(11'*S*,12'*S*)-Isomer (18) : To a solution of oxalyl chloride (0.15 mL, 1 7 mmol) in CH_2Cl_2 (4 mL), DMSO (0.24 mL, 3.4 mmol, dissolved in 1 mL of CH_2Cl_2) was added at -78 °C under N_2 atmosphere. The mixture was stirred for 10 min, and then **16** (540 mg, 0.86mmol, dissolved in 1 mL of CH_2Cl_2) was added. After the completion of the reaction, Et_3N (2 mL) was added to the mixture, which was warmed to rt. The stirring was continued for an additional 10 min, and CH_2Cl_2 was added to dilute the mixture, which was washed with water and brine. Drying over anhydrous Na_2SO_4 was followed by evaporation, and filtration over silica gel column to yield crude **17** (482 mg, 89%) as a yellow oil.

To a mixture of (*Z*)-(*S*,*S*)-**30** (2.5 mL, 2.5 mmol, 1.0 M in toluene) and 4 Å MS (120 mg) in dry toluene (5 mL), crude **17** (482 mg, 0.77 mmol, dissolved in 1 mL of toluene), which was precooled to -78 °C, was added at -78 °C under N_2 atmosphere. The mixture was stirred for 3 h and then warmed to rt To the mixture, 10 mL of 2 N NaOH was added. The mixture was filtered, and the filtrate was extracted with EtOAc (3 x 10 mL) The combined extract was washed with brine. Drying over anhydrous Na_2SO_4 was followed by evaporation, and purification by flash column chromatography (eluent: petroleum ether/ethyl acetate, 12:1) to afford **18** (460 mg, 88 %) as a colorless oil $[\alpha]_D$ + 8.5 ° (c 1.70, $CHCl_3$) IR(film): 3560, 2928, 2857, 1464, 1350, 1258, 1163 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.06 (s, 3 H, $SiCH_3$), 0.09 (s, 3H, $SiCH_3$), 0.93 (s, 9 H, *t*-Bu), 1.04 (d, 3 H, J = 6 9 Hz, 12'-CH_3), 1.26-1.49 (m, 20 H, 1' , 2' , 3' , 4' , 5' , 6' , 7' , 8' , 9' , 10'-H), 2 29 (m, 1 H, 12'-H), 2 46 (s, 3 H, ArCH_3), 3.50 (m, 1 H, 11'-H), 3.74-3.99 (m, 4 H, 2 , 4-H and 2-CH_2), 4.14 (t, 1 H, J= 9.8 Hz, 3-H), 4 39, 4.73 (AB, 2 H, J_{AB} = 12.0 Hz, 3-OCH_2Ph), 5.08 (dd, 1H , J = 9.8, 1.0 Hz, 13'-H), 5 10 (dd, 1 H, J = 17.8, 1.0 Hz, 13'-H), 5 82 (ddd, 1 H, J = 17 8, 9.8, 7 2 Hz, 14'-H), 7.28 (m, 7 H, Ar-H), 7 72 (d, 2 H, J = 8.1 Hz, Ar-H) ppm MS (m/z, %): 669 (M^+-1-CH_3), 390 (6.00), 271 (11 9), 270 (31.21), 149 (10.19), 91 (Bn, base). Anal. Calcd for $C_{39}H_{63}NO_5SSi$. C, 68.28; H, 9.26; N, 2.04. Found C, 68.31; H, 9.50; N, 2.07.

(11'*R*,12'*R*)-Isomer (18'): To a mixture of (*Z*)-(*R*,*R*)-**30** (1 mL, 1 mmol, 1.0 M in toluene) and 4 Å MS (100 mg) in dry toluene (4 mL) , crude **17** (466 mg, 0 74 mmol, dissolved in 1 mL of toluene), which was precooled to -78 °C, was added at -78 °C under N_2 atmosphere. The mixture was stirred for 3 h and then warmed to rt. 10 mL of 2 N NaOH was added to the mixture, which was filtered. The filtrate was extracted with EtOAc (3 x 10 mL), and the organic layer was washed with brine Drying over anhydrous Na_2SO_4 was followed by evaporation, and purification by flash column chromatography (eluent: petroleum ether/ethyl acetate, 12:1) to afford **18'** (388 mg, 77 %) as a colorless oil. $[\alpha]_D$ + 22.7 ° (c 1.60, $CHCl_3$). IR(film): 3560, 2927.9, 2856.6, 1464 0, 1350 2, 1257.6, 1163.1 cm^{-1} ^1H NMR ($CDCl_3$) δ: 0.06 (s, 3 H, $SiCH_3$), 0.09 (s, 3H, $SiCH_3$), 0 93 (s, 9 H, *t*-Bu), 1.04 (d, 3 H, J = 6.9 Hz, 12'-CH_3), 1 26-1 49 (m, 20 H,

1' , 2' , 3' , 4' , 5' , 6' , 7' , 8' , 9' , 10'-H), 2.29 (m, 1 H, 12'-H), 2.46 (s, 3 H, $ArCH_3$), 3.50 (m, 1 H, 11'-H), 3 74-3.99 (m, 4 H, 2 , 4-H and 2-CH_2), 4.14 (t, 1 H, J = 9.8 Hz, 3-H), 4.39, 4.73 (AB, 2 H, J_{AB} = 12 0 Hz, 3-OCH_2Ph), 5.08 (dd, 1H, J = 9.8, 1.0 Hz, 13'-H), 5 10 (dd, 1 H, J = 17 8, 1.0 Hz, 13'-H), 5.82 (ddd, 1 H, J = 17.8, 9.8, 7.2 Hz, 14'-H), 7.28 (m, 7 H, Ar-H), 7.72 (d, 2 H, J = 8.1 Hz, Ar-H) ppm MS (m/z, %) 669 (M^+-1-CH_3), 390 (6 00), 271 (11.9), 270 (31.21), 149 (10.19), 91 (Bn, base). Anal Calcd for $C_{39}H_{63}NO_5SSi$: C, 68.28; H, 9.26; N, 2.04. Found : C, 68.58; H, 9.66, N, 1.94

(2*R*,3*R*,4*S*)-2-Hydroxymethyl-3-benzyloxy-4-(11'-hydroxy-12'-methyltetradec-13'-enyl)-*N*-*p*-tolylsulfonyl-azetidine

(11'*S*,12'*S*)-Isomer (19) To a solution of **18** (374mg, 0.54 mmol) in THF (4 mL), *n*-Bu_4NF (1 mL, 1 mmol, 1.0 M in THF) was added. The mixture was stirred for 2 h at rt After the completion of the reaction, sat aq. NH_4Cl was added to quench the reaction. The mixture was extracted with EtOAc (3 x 5 mL), and the organic layer was washed with brine. Drying over anhydrous Na_2SO_4 was followed by evaporation, and purification by flash column chromatography (eluent. petroleum ether/ethyl acetate, 2.1) to afford **19** (288 mg, 92 %) as a white solid. mp 46-49 °C. $[\alpha]_D$ + 20.3 ° (c 1 22, $CHCl_3$) IR(KBr) 3502, 2926, 2854, 1599, 1456, 1344, 1160, 1093 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.02 (d, 3 H, J = 6 9 Hz, 12'-CH_3), 1 26-1.93 (m, 20 H, 1' , 2' , 3' , 4' , 5' , 6' , 7' , 8' , 9' , 10'-H), 2.28 (m, 1H, 12'-H), 2 46 (s, 3 H, $ArCH_3$), 3 50 (m, 1 H, 11'-H), 3 77-4.05 (m, 5 H, 2 , 3 , 4-H and 2-CH_2), 4 40, 4.46 (AB, 2 H, J_{AB} = 11.8 Hz, 3-OCH_2Ph), 5.08 (d, 1H, J = 9.8 Hz, 13'-H), 5.09 (d, 1 H, J = 17.7 Hz, 13'-H), 5.81 (ddd, 1 H, J = 17.7, 9 8, 7.3 Hz, 14'-H), 7.28 (m, 7 H, Ar-H), 7 73 (d, 2 H, J = 8 1 Hz, Ar-H) ppm. MS (m/z, %) 554 (M^++1-H_2O, 6.58), 390 (11.69), 214 (10 58), 155 (11.92), 91 (Bn, base) Anal Calcd for $C_{33}H_{49}NO_5S$. C, 69 32, H, 8.64; N, 2.45 Found : C, 69 24; H, 8 84, N, 2 47.

(11'*R*,12'*R*)-Isomer (19') : In a manner similar to that described above, (11'*R*,12'*R*)-**18'** (86 mg, 0.13 mmol) was converted into (11'*R*,12'*R*)-**19'** (66 mg, 92%) mp 70-72 °C. $[\alpha]_D$ + 33 3 ° (c 0.61, $CHCl_3$). IR (KBr) 3502, 2926, 2854, 1599, 1456, 1344, 1160, 1093 cm^{-1}. ^1H NMR($CDCl_3$) δ: 1.02 (d, 3 H, J = 6.9 Hz, 12'-CH_3), 1 26-1 93 (m, 20 H, 1' , 2' , 3' , 4' , 5' , 6' , 7' , 8' , 9' , 10'-H), 2.28 (m, 1H, 12'-H), 2 46 (s, 3 H, $ArCH_3$), 3.50 (m, 1 H, 11'-H), 3.77-4 05 (m, 5 H, 2 , 3 , 4-H and 2-CH_2), 4.40, 4.46 (AB, 2 H, J_{AB} = 11.8 Hz, 3-OCH_2Ph), 5 08 (d, 1H, J = 9.8 Hz, 13'-H), 5.09 (d, 1 H, J = 17.7 Hz, 13'-H), 5.81 (ddd, 1 H, J = 17.7, 9 8, 7.3 Hz, 14'-H), 7.28 (m, 7 H, Ar-H), 7 73 (d, 2 H, J = 8.1 Hz, Ar-H) ppm. MS (m/z, %) 554 (M^++1-H_2O, 6.58), 390 (11.69), 214 (10.58), 155 (11.92), 91 (Bn, base)

(2*R*,3*R*,4*S*)-2-Hydroxymethyl-3-hydroxy-4-(11'-hydroxy-12'-methyltetradecyl)-*N*-*p*-tolylsulfonylazetidine

(11'*S*,12'*S*)-Isomer (20) To a suspension of 10 % Pd-C (50 mg) in 95 % EtOH (30 mL), 19 (240 mg,

0.42 mmol) was added. The mixture was stirred under hydrogen atmosphere at rt overnight. Filtration and removal of solvent afforded a residue, which was purified by flash column chromatography (eluent: petroleum ether/ethyl acetate, 1:1) to give **20** (170 mg, 85 %) as a white solid mp 82-84 °C. $[\alpha]_D$ + 41.8 ° (c 0 56, $CHCl_3$). IR(KBr): 3500, 2927, 2855, 1459, 1340, 1159, 1093 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0 84 (d, 3 H, J = 6.7 Hz, 12'-CH_3), 0.91 (t, 3 H, J = 7.0 Hz, 14'-H), 1.16-1.89 (m, 23 H, 1' , 2' , 3' , 4' , 5' , 6' , 7' , 8' , 9' , 10' , 12' , 13'-H), 2.47 (s, 3 H, ArCH_3), 2.61 (m, 3 H, OH), 3 54 (m, 1 H, 11'-H), 3.74-4.04 (m, 4 H, 2 , 4 -H and 2-CH_2), 4.27 (t, 1 H, J = 7.2 Hz, 3-H), 7 39, 7.71 (AB, 4 H, J_{AB} = 7 8 Hz, Ar-H) ppm. MS (m/z, %) 466 (M^+-H_2O, 5.05), 392 (40 64), 310 (26.36), 214 (69 38), 155 (base), 91 (Bn, 98.20) Anal. Calcd for $C_{26}H_{45}NO_5S$: C, 64.56; H, 9 38; N, 2.89. Found : C, 64. 61; H, 9 79, N, 2.86.

(*11'R,12'R*)-Isomer (20') : In a manner similar to that described above, (11'*R*,12'*R*)-**19'** (60 mg, 0.1 mmol) was converted into (11'*R*,12'*R*)-**20'** (42 mg, 83 %) mp 84-85°C. $[\alpha]_D$ +59.7 ° (c 0.40, $CHCl_3$). IR (KBr): 3500, 2927, 2855, 1459, 1340, 1159, 1093 cm^{-1} ^1H NMR ($CDCl_3$) δ: 0.84 (d, 3 H, J = 6.7 Hz, 12'-CH_3), 0.91 (t, 3 H, J = 7.0 Hz, 14'-H), 1.16-1.89 (m, 23 H, 1' , 2' , 3' , 4' , 5' , 6' , 7' , 8' , 9' , 10' , 12' , 13'-H), 2 47 (s, 3 H, ArCH_3), 2 61 (m, 3 H, OH), 3 54 (m, 1 H, 11'-H), 3 74 -4.04 (m, 4 H, 2 , 4 -H and 2-CH_2), 4.27 (t, 1 H, J = 7 2 Hz, 3-H), 7.39, 7 71 (AB, 4 H, J_{AB} = 7.8 Hz, Ar-H) ppm MS (m/z, %): 466 (M^+-H_2O, 5.05), 392 (40.64), 310 (26 36), 214 (69.38), 155 (base), 91 (Bn, 98.20) HRMS: Calcd for $C_{26}H_{43}NO_4S$: 465.6884. Found : 465 2903.

(2*R*,3*R*,4*S*)-2-Acetoxymethyl-3-acetoxy-4-(11'-acetoxy-12'-methyltetradecyl)-*N*-acetylazetidine

(11'*S*,12'*S*)-Isomer (21) : To a solution of **20** (62 mg, 0.13 mmol) in DME (2 mL), a 1 M solution of Na-naphthalene in DME (0 5 mL, 0.5 mmol) was added at -60 °C under N_2 atmosphere The mixture was stirred for 0.5 h. After the completion of the reaction, water was added to the mixture, which was extracted with $CHCl_3$ The combined extract was washed with brine. Drying over anhydrous Na_2SO_4 was followed by evaporation to give the crude product (7) which was directly dissolved in CH_2Cl_2 without purification. Acetic anhydride (0.05 mL, 0.53 mmol) and pyridine (0.1 mL) were added to the mixture, which was stirred for 5 h. After the completion of the reaction, EtOAc was added to dilute the mixture, which was washed with 1N HCl, sat. aq. $NaHCO_3$ and brine. Drying over anhydrous Na_2SO_4 was followed by evaporation, and purification by flash column chromatography (eluent: petroleum ether/ethyl acetate, 2:1) to afford **21** (25 mg, 40 %) as a colorless oil $[\alpha]_D$ + 11 3 ° (c 0.85, $CHCl_3$). IR(film): 2926, 2855, 1747, 1666, 1463, 1374, 1244, 1045 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ: 0 88 (d, 3 H, J = 6.7 Hz, 12'-CH_3), 0.89 (t, 3 H, J = 7.5 Hz, 14'-H), 1 14 (m, 1 H, 13'-H), 1 25 (m, 16 H, 2' , 3' , 4' , 5' , 6' , 7' , 8' , 9'-H), 1.40 (m, 1 H, 13'-H), 1 45-1.56 (m, 3 H), 1.61 (m, 2 H), 1.97 (m, 4 H), 2.04 (s, 3 H), 2 07 (s, 3H), 2 10 (s, 3 H), 4.36-4.50 (m, 3 H), 4 60-4.70 (m, 1 H), 4.86 (m, 1 H), 5.57 (m, 1 H) ppm ^{13}C NMR (75

MHz, $CDCl_3$) δ: 19 27, 20.38, 20.65, 20 88, 21.27, 24.99, 25.82, 26.78, 29.05, 29 62, 29.74, 29.77, 30 26, 31.48, 38.08, 60.85, 61.34, 62.53, 63 39, 64 24, 64.49, 66.21, 76.79, 170 11, 170.49, 171 12, 172 31 ppm MS (m/z, %): 498 (M^++1, 10.15), 438 (21 94), 398 (64 37), 378 (15 48), 292 (12.48), 238 (19 99), 84 (36.02), 43 (base). HRMS : Calcd for $C_{27}H_{47}NO_7$: 497.3352 Found: 497.3363.

(11'*R*,12'*R*)-Isomer (21') : In a manner similar to that described above, (11'*R*,12'*R*)-**20'** (25 mg, 0.05 mmol) was converted into (11'*R*,12'*R*)-**21'** (6 mg, 33%). $[\alpha]_D$ + 11 9 ° (c 0.27, $CHCl_3$). IR(film) 2926, 2855, 1747, 1666, 1463, 1374, 1244, 1045 cm^{-1} ^1H NMR (300 MHz, $CDCl_3$) δ: 0 88 (d, 3 H, J = 6.7 Hz, 12'-CH_3), 0 89 (t, 3 H, J = 7.5 Hz, 14'-H), 1.14 (m, 1 H, 13'-H), 1.25 (m, 16 H, 2', 3', 4', 5', 6', 7', 8', 9'-H), 1.40 (m, 1 H, 13'-H), 1.45-1.56 (m, 3 H), 1.61 (m, 2 H), 1.97 (m, 4 H), 2.04 (s, 3 H), 2 07 (s, 3H), 2.10 (s, 3 H), 4 36-4.50 (m, 3 H), 4 60-4.70 (m, 1 H), 4.86 (m, 1 H), 5.57 (m, 1 H) ppm ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.27, 20.38, 20 65, 20.88, 21.27, 24.99, 25 82, 26.78, 29 05, 29.62, 29 74, 29.77, 30.26, 31.48, 38 08, 60 85, 61 34, 62.53, 63.39, 64 24, 64.49, 66.21, 76.79, 170.11, 170.49, 171.12, 172 31 ppm MS (m/z, %): 498 (M^++1, 10.15), 438 (21.94), 398 (64.37), 378 (15 48), 292 (12 48), 238 (19.99), 84 (36 02), 43 (base). HRMS : Calcd for $C_{27}H_{47}NO_7$: 497.3352. Found: 497 3336.

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