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

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Abstract - Stereoselective synthesis of 2-epi-penaresidin A and its (15R, 16R)-
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 2S,3R,4S-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 studies23 in 1995. Recently, the absolute configurations at C-15 in 1 and 2 were finally determined to be S on the basis of 1H 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.,3

Penaresidin A 1 R₁ = R₂ = H
3 R₁ = R₂ = Ac
5 R₁ = MTPA, R₂ = Ac

Penaresidin B 2 R₁ = R₂ = H
4 R₁ = R₂ = Ac
6 R₁ = MTPA, R₂ = 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 (15R, 16R)-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, 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.

![Diagram of Scheme 2](image)

As shown in Scheme 3, compound (9) was readily prepared from 8 with high diastereomeric and enantiomeric excess. 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 LiAlH4 and the subsequent tosylation with TsCl in CH2Cl2 afforded 12 in 81.5% yield. Sharpless asymmetric dihydroxylation 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 is an exceptionally useful and general method in organic synthesis. For example, pyrrolidine and piperidine were readily constructed by the cyclization of sulfonamide alcohol. However, to the best of our knowledge, few examples have been applied to the formation of azetidine. Fortunately, when we treated compound (14) with DEAD and PPh3 in THF, the expected reaction occurred to afford the azetidine (15) in 92% yield.
Treatment of 15 with MgBr₂ in Et₂O 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) 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) was obtained while treating 17 with the Roush reagent (Z)-(R,R)-30. Conversion of 18' to (15R,16R)-7 was completed by the same...
procedure as before and the product was acetylated to give the tetraacetyl derivative \( (21') \) (Scheme 4).

\[
\begin{align*}
\text{OCH}_2\text{Ts} & \quad \text{TBSO} \quad \text{N} \quad \text{Ts} \\
\text{O} & \quad \text{H} \quad \text{O} \quad \text{H} \quad \text{O} \\
\text{17} & \quad \text{18'} \\
\text{1 steps} & \quad \text{2 steps} \\
\text{HO} & \quad \text{AcO} \\
\text{NH} & \quad \text{Ac} \quad \text{Ac} \\
\text{9'} & \quad \text{21'}
\end{align*}
\]

Reagents and Conditions: a) \( (Z)-(R,R) -30°C, \text{tetrahydrofuran,} \text{-78°C, 77%} \), n) \( \text{Ac}_2\text{O, py, CH}_2\text{Cl}_2, 33\% \) (from \( 20' \)).

Thus, we have provided a facile stereoselective synthesis of 2-\( \text{epi} \)-penaresidin A and its \((15R,16R)\)-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 \( \text{cm}^{-1} \). \( ^1\text{H} \) NMR spectra were recorded at Bruker AM 300 (300 MHz) or AMX 600 (600 MHz) spectrometer using TMS as internal standard. \( ^13\text{C} \) NMR spectra were recorded at Bruker AM 300 (75 MHz) spectrometer with the solvent peak (\( \text{CDCl}_3, \delta = 77.0 \text{ ppm} \)) 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).

\((2R,3S)-3-\text{Benzyloxy}-1,2-\text{epoxy}-4\)-pentene (9):

This compound was prepared according to the known procedure\(^6\) All the spectroscopic data were in agreement with those reported in the literature.

\((3S,4R)-3-\text{Benzyloxy}-15\)-tetrahydropyranoyloxypentadec-1-en-4-ol (10):

To a suspension of CuI (50 mg, 0.26 mmol) in THF (10 mL), 10-tetrahydropyranoyloxymagnesium bromide (10 mL, 3 mmol, 1 M in THF) was added at -50 °C under \( \text{N}_2 \) 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. \( \text{NH}_4\text{Cl} \) was added to the mixture, which was extracted with \( \text{EtOAc (3 x 10 mL)} \). The combined extract was washed with brine and dried over anhydrous \( \text{Na}_2\text{SO}_4 \). Evaporation followed by purification through flash column chromatography (eluent:
petroleum ether/ethyl acetate, 10:1) afforded 10 (722 mg, 76%) as a colorless oil. \([\alpha]_D +21.4^\circ \text{ (c 0.99, CHCl}_3)\). IR(film): 3480, 2926, 2855, 1460, 1120 cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 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\(_2\)Ph), 4.57 (dd, 1 H, J = 17.3, 1.4 Hz, 1-H), 5.38 (dd, 1 H, J = 10.5, 14 Hz, 3'-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\(_1\): C, 74.95; H, 10.25 Found: C, 74.76; H, 10.72

\((3S,4S)-3\)-Benzyloxy-4-azido-15-tetrahydropyrylloxypentadec-1-ene (11): To a solution of 10 (700 mg, 1.62 mmol) in CH\(_2\)Cl\(_2\) (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\(_2\)Cl\(_2\) 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\(_2\)O (3 x 10 mL), and the combined extract was washed with water and brine. Drying over anhydrous Na\(_2\)SO\(_4\) was followed by evaporation, and purification by flash column chromatography (eluent: petroleum ether/ethyl acetate, 10:1) to afford 11 (564 mg, 76%) as a colorless oil \([\alpha]_D +20.7^\circ \text{ (c 1.00, CHCl}_3)\). IR(film): 2928, 2855, 2104, 1454, 1260, 1034 cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 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\(_2\)Ph), 4.57 (m, 1 H, 2'-H), 5.31 (dd, 1 H, J = 17.8, 10 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).

\((3S,4S)-3\)-Benzyloxy-4-p-tolylsulfonylamino-15-tetrahydropyrylloxypentadec-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\(_2\)SO\(_4\) + 10H\(_2\)O was added to the mixture, which was filtered. The filtrate was concentrated to give a colorless oil, which was then dissolved in CH\(_2\)Cl\(_2\) (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\(_2\)Cl\(_2\) was added to dilute the mixture, which was washed with 1N HCl, sat. aq. NaHCO\(_3\) and brine. Drying over anhydrous Na\(_2\)SO\(_4\) 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. \([\alpha]_D +32.9^\circ \text{ (c 0.56, CHCl}_3)\) IR(film) 3280,
2928, 2855, 1455, 1162 cm⁻¹. ¹H NMR (CDCl₃) 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, ArCH₃), 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-OCH₂Ph), 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 C₃₄H₃₁NO₁₅S: C, 69.71; H, 8.77; N, 2.39. Found C, 69.69; H, 8.88; N, 2.29.

(2S,3R,4S)-3-Benzylxoy-4-p-tolylsulfonylamoio-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-H₂O (20 mL), K₃Fe(CN)₆ (6.58 g, 20 mmol), K₂CO₃ (2.76 g, 20 mmol) and OsO₄ (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, Na₂SO₃ (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 Na₂SO₄ 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. [α]D -6.3° (c 1.20, CHCl₃). IR(film) 3500, 3300, 2928, 2855, 1455, 1157 cm⁻¹. ¹H NMR (CDCl₃) δ: 0.03-1.82 (m, 26 H, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 3', 4', 5'-H), 2.41 (s, 3 H, ArCH₃), 2.36-3.88 (m, 9 H, 1, 2, 3, 4, 15, 6'-H), 4.48, 4.55 (AB, 2 H, J_AB = 11.2 Hz, 3-OCH₂Ph), 4.57 (m, 1 H, 2'-H), 5.24 (d, 1 H, 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 C₃₄H₃₁NO₁₅S: C, 65.88, H, 8.62; N, 2.26. Found C, 65.50; H, 8.82; N, 2.16.

(2S,3R,4S)-1-t-Butyldimethylsilyloxy-3-benzyloxylo-15-tetrahydropyranyloxypentadecan-2-01 (14):
To a solution of 13 (700 mg, 1.13 mmol) in dry DMF (5 mL), TBDMS (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 Na₂SO₄ 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. [α]D -13.7° (c 1.05, CHCl₃). IR(film): 3520, 3300, 2928, 2855, 1460, 1160 cm⁻¹. ¹H NMR (CDCl₃) δ: 0.03 (s, 3 H, SiCH₃), 0.04 (s, 3 H, SiCH₃), 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, ArCH₃), 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-OCH₂Ph),
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 (9.1), 354 (23.73), 277 (12.66), 155 (15.59), 91 (Bn, base), 85 (THP, 41.96). Anal. Calcd for C₄₀H₆₇NO₇SSi: C, 65.44; H, 9.20, N, 1.91. Found: C, 65.64, H, 9.39; N, 1.86.

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

To a solution of PPh₃ (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 (eluents: petroleum ether/ethyl acetate, 10:1) to give 15 (2.49 g, 92%) as a colorless oil. [α]D +21.3° (c 1.56, CHCl₃). IR(film): 2928, 2855, 1460, 1350, 1169 cm⁻¹. ¹H NMR (CDCl₃) δ: 0.05 (s, 3 H, SiCH₃), 0.08 (s, 3 H, SiCH₃), 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, ArCH₃), 3.38-4.13 (m, 9 H, 2, 3, 4, 11', 6''-H and 2-CH₂), 4.37, 4.72 (AB, 2 H, Jₐᵦ = 12.0 Hz, 3-OCH₂Ph), 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⁺-CH₂), 556 (4.42), 270 (33.94), 121 (50.49), 91 (Bn, base), 85 (THP, 34.93). Anal. Calcd for C₄₀H₆₇NO₇SSi: C, 65.44; H, 9.20, N, 1.91. Found: C, 65.64, H, 9.39; N, 1.86.

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

To a solution of MgBr₂ (2.39 g, 13 mmol) in dry Et₂O (80 mL), 15 (2.24 g, 3.13 mmol) was added under N₂ atmosphere. The mixture was stirred for 3 h at rt, and then water was added to the mixture, which was extracted with Et₂O (3 x 15 mL). The combined extract was washed with brine. Drying over anhydrous Na₂SO₄ was followed by evaporation, and purification by flash column chromatography (eluents: petroleum ether/ethyl acetate, 4:1) to yield 16 (1.14 g, 81%) as a colorless oil and the recovered 15 (638 mg). [α]D + 15 4° (c 1.16, CHCl₃). IR(film): 3400, 2928, 2855, 1470, 1340, 1258, 1163 cm⁻¹. ¹H NMR (CDCl₃) δ: 0.06 (s, 3 H, SiCH₃), 0.08 (s, 3 H, SiCH₃), 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, ArCH₃), 3.66 (t, 2 H, J = 6.7 Hz, 11'-H), 3.73-4.00 (m, 4 H, 2', 4'-H and 2-CH₂), 4.14 (t, 1 H, J = 9.8 Hz, 3-H), 4.39, 4.73 (AB, 2 H, Jₐᵦ = 12.0 Hz, 3-OCH₂Ph), 7.33 (m, 5 H, Ar-H), 7.36, 7.72 (AB, 4 H, Jₐᵦ = 8.2 Hz, Ar-H) ppm. MS (m/z, %): 616 (M⁺-CH₃), 574 (M⁺-Bu, 1.58), 270 (23.37), 149 (771), 91 (Bn, base). Anal. Calcd for C₃₅H₅₇NO₇SSi: C, 66.52; H, 9.09, N, 2.22. Found C, 66.53, H, 9.15, N, 2.24.
(2R,3R,4S)-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 CH₂Cl₂ (4 mL), DMSO (0.24 mL, 3.4 mmol, dissolved in 1 mL of CH₂Cl₂) was added at -78 °C under N₂ atmosphere. The mixture was stirred for 10 min, and then 16 (0.54 mL, 0.86 mmol, dissolved in 1 mL of CH₂Cl₂) was added. After the completion of the reaction, Et₃N (2 mL) was added to the mixture, which was warmed to rt. The stirring was continued for an additional 10 min, and CH₂Cl₂ was added to dilute the mixture, which was washed with water and brine. Drying over anhydrous Na₂SO₄ was followed by evaporation, and filtration over silica gel column to yield crude 17 (0.482 g, 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 (0.482 g, 0.77 mmol, dissolved in 1 mL of toluene), which was precooled to -78 °C, was added at -78 °C under N₂ 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 Na₂SO₄ was followed by evaporation, and purification by flash column chromatography (eluent: petroleum ether/ethyl acetate, 12:1) to afford 18 (0.460 g, 88%) as a colorless oil. [α]D + 8.5° (c 1.70, CHCl₃). IR(film): 3560, 2928, 2857, 1464, 1350, 1258, 1163 cm⁻¹. ¹H NMR (CDCl₃): δ: 0.06 (s, 3 H, SiCH₃), 0.09 (s, 3 H, SiCH₃), 0.93 (s, 9 H, t-Bu), 1.04 (d, 3 H, J = 6.9 Hz, 12'-CH₃), 1.26-1.49 (m, 20 H, I', 2, 3', 4', 5', 6', 7', 8', 9', 10'-H), 2.29 (m, 1 H, 12'-H), 2.46 (s, 3 H, ArCH₃), 3.50 (m, 1 H, 11'-H), 3.74-3.99 (m, 4 H, 2-H and 4-H), 4.14 (t, 1 H, J = 9.8 Hz, 3-H), 4.39, 4.73 (AB, 2 H, JAB = 12.0 Hz, 3-OCH₂Ph), 5.08 (dd, 1 H, 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-CH₃), 390 (6.00), 271 (11.9), 270 (31.21), 149 (10.19), 91 (Bn, base). Anal. Calcd for C₉₉H₇₅NO₃SSi. 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 (0.466 g, 0.74 mmol, dissolved in 1 mL of toluene), which was precooled to -78 °C, was added at -78 °C under N₂ 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 Na₂SO₄ was followed by evaporation, and purification by flash column chromatography (eluent: petroleum ether/ethyl acetate, 12:1) to afford 18' (0.388 g, 77%) as a colorless oil. [α]D + 22.7° (c 1.60, CHCl₃). IR(film): 3560, 2927.9, 2856.6, 1464 0, 1350 2, 1257.6, 1163.1 cm⁻¹. ¹H NMR (CDCl₃): δ: 0.06 (s, 3 H, SiCH₃), 0.09 (s, 3 H, SiCH₃), 0.93 (s, 9 H, t-Bu), 1.04 (d, 3 H, J = 6.9 Hz, 12'-CH₃), 1.26-1.49 (m, 20 H, 12'-H).
(11'S,12'S)-Isomer (19) To a solution of 18 (374 mg, 0.54 mmol) in THF (4 mL), n-Bu₄NF (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. NH₄Cl 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 Na₂SO₄ 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. [α]D + 20.3 ° (c 1.22, CHCl₃). IR(KBr) 3502, 2926, 2854, 1599, 1456, 1344, 1160, 1093 cm⁻¹. ¹H NMR (CDCl₃) δ: 1.02 (d, 3 H, J = 6.9 Hz, 12'-CH₃), 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, ArCH₃), 3.50 (m, 1 H, 11'-H), 3.77-4.05 (m, 5 H, 2, 3, 4-H and 2-CH₂), 4.40 (t, 1 H, 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-H₂O, 6.58), 390 (11.69), 214 (10.58), 155 (11.92), 91 (Bn, base). Anal. Calcd for C₃₅H₆₉NO₅SSi: C, 68.58; H, 9.66, N, 2.47.

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

(11'S,12'S)-Isomer (19) To a suspension of 18 (374 mg, 0.54 mmol) in THF (4 mL), n-Bu₄NF (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. NH₄Cl 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 Na₂SO₄ 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. [α]D + 20.3 ° (c 1.22, CHCl₃). IR(KBr) 3502, 2926, 2854, 1599, 1456, 1344, 1160, 1093 cm⁻¹. ¹H NMR (CDCl₃) δ: 1.02 (d, 3 H, J = 6.9 Hz, 12'-CH₃), 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, ArCH₃), 3.50 (m, 1 H, 11'-H), 3.77-4.05 (m, 5 H, 2, 3, 4-H and 2-CH₂), 4.40 (t, 1 H, 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-H₂O, 6.58), 390 (11.69), 214 (10.58), 155 (11.92), 91 (Bn, base). Anal. Calcd for C₃₅H₆₉NO₅SSi: C, 68.58; H, 9.66, N, 2.47.
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. [α]_D + 41.8° (c 0.56, CHCl₃). IR(KBr): 3500, 2927, 2855, 1459, 1340, 1159, 1093 cm⁻¹. ¹H NMR (CDCl₃) δ: 0.84 (d, J=6.7 Hz, 12'-CH₃), 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, ArCH₃), 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-CHI), 4.27 (t, 1 H, J=7.2 Hz, 3-H), 7.39, 7.71 (AB, 4 H, JAB = 7.8 Hz, Ar-H) ppm. MS (m/z, %): 466 (M⁺-H₂O, 5.05), 392 (40.64), 310 (26.36), 214 (69.38), 155 (base), 91 (Bn, 98.20) Anal. Calcd for C₂₀H₁₄N₂O₄S: C, 64.56; H, 9.38; N, 2.89. Found: C, 64.61; H, 9.79, N, 2.86.

(II'R,12'R)-Isomer (20'): In a manner similar to that described above, (II'R,12'R)-19' (60 mg, 0.1 mmol) was converted into (II'R,12'R)-20' (42 mg, 83%) mp 84-85 °C. [α]_D +59.7° (c 0.40, CHCl₃). IR(KBr): 3500, 2927, 2855, 1459, 1340, 1159, 1093 cm⁻¹. ¹H NMR (CDCl₃) δ: 0.84 (d, J=6.7 Hz, 12'-CH₃), 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, ArCH₃), 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-CHI), 4.27 (t, 1 H, J=7.2 Hz, 3-H), 7.39, 7.71 (AB, 4 H, JAB = 7.8 Hz, Ar-H) ppm. MS (m/z, %): 466 (M⁺-H₂O, 5.05), 392 (40.64), 310 (26.36), 214 (69.38), 155 (base), 91 (Bn, 98.20) HRMS: Calcd for C₂₀H₁₄N₂O₄S: 465.6884. Found: 465.2803.

(II'R,12'R)-Isomer (20'): In a manner similar to that described above, (II'R,12'R)-19' (60 mg, 0.1 mmol) was converted into (II'R,12'R)-20' (42 mg, 83%) mp 84-85 °C. [α]_D + 41.8° (c 0.56, CHCl₃). IR(KBr): 3500, 2927, 2855, 1459, 1340, 1159, 1093 cm⁻¹. ¹H NMR (CDCl₃) δ: 0.84 (d, J=6.7 Hz, 12'-CH₃), 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, ArCH₃), 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-CHI), 4.27 (t, 1 H, J=7.2 Hz, 3-H), 7.39, 7.71 (AB, 4 H, JAB = 7.8 Hz, Ar-H) ppm. MS (m/z, %): 466 (M⁺-H₂O, 5.05), 392 (40.64), 310 (26.36), 214 (69.38), 155 (base), 91 (Bn, 98.20) HRMS: Calcd for C₂₀H₁₄N₂O₄S: 465.6884. Found: 465.2803.

(2R,3R,4S)-2-Acetoxymethyl-3-acetoxy-4-(11'-acetoxy-12'-methyltetradecyl)-N-acetylanilidine (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 NaNaphthalene in DME (0.5 mL, 0.5 mmol) was added at -60 °C under N₂ 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 CHCl₃. The combined extract was washed with brine. Drying over anhydrous Na₂SO₄ 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 [α]_D + 11.3° (c 0.85, CHCl₃). IR(film): 2926, 2855, 1747, 1666, 1463, 1374, 1244, 1045 cm⁻¹. ¹H NMR (600 MHz, CDCl₃) δ: 0.88 (d, 3 H, J=6.7 Hz, 12'-CH₃), 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, 3 H), 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. ¹³C NMR (75
MHz, CDCl₃ 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}NO₅: 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%). [α]D +11° (c 0.27, CHCl₃). IR (film) 2926, 2855, 1747, 1666, 1463, 1374, 1244, 1045 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ: 0.88 (d, 3 H, J = 6.7 Hz, 12'-CH₃), 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), 1.45-1.56 (m, 3 H), 1.61 (m, 2 H), 1.97 (m, 4 H), 2.04 (s, 3 H), 2.07 (s, 3 H), 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. ¹³C NMR (75 MHz, CDCl₃) 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}NO₅: 497.3352. Found: 497 3336.

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REFERENCES


11. As determined by $^{19}$F NMR (282 MHz) spectrum of its Mosher ester derivative.

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