Stereoselective Preparation of C1–C10 and C11–O14 Fragments of Narbonolide: Exploiting the Versatility of Thiazolidinethione Chiral Auxiliary

C. Prasad Narasimhulu, Parthasarathi Das*
Discovery Research, Dr. Reddy’s Laboratories Ltd., Bollaram Road, Miyapur, Hyderabad 500 049, India
Fax +91(40)23045438; E-mail: parthasarathi@drreddys.com; E-mail: parthads@yahoo.com
Received 13 August 2008

Abstract: An efficient stereoselective synthesis of the C1–C10 and C11–O14 fragments of narbonolide, have been accomplished by using a thiazolidinonethione as chiral auxiliary. The stereocenters at C2, C3, C4, C5, C8, and C9 in C1–C10 fragment and C12 and C13 in C11–C14 fragment were generated via asymmetric acyl-thiazolidinethione aldol reactions whereas the stereocenter at C6 was installed by means of Myers alkylation.

Key words: acyl-thiazolidinethione, aldol reaction, Crimmins protocol, Myers alkylation, Tebbe reaction

The macrolide antibiotic erythromycin A (1) has served as both a clinically useful agent for the treatment of Gram-positive bacterial infections as well as a starting point for the semisynthesis of derivatives with improved physicochemical and microbiological properties.2 Several of these derivatives, including clarithromycin, azithromycin, and roxithromycin, possess improved acid stability and oral bioavailability and have enjoyed significant commercial success. However, a serious problem, not adequately addressed by these agents, is the growing prevalence of erythromycin-resistant bacteria.3

The discovery of the ketolides,4 erythromycin derivatives incorporating a C3 ketone modification, revealed a class of compounds with excellent activity against some macrolide-resistant bacteria, especially the clinically important respiratory tract pathogen Streptococcus pneumoniae.5 The considerable promise shown by ketolides have catalyzed a resurgence in macrolide antibiotic research in the pharmaceutical industry.6 Ketolides like telithromycin6a (2) from Aventis Pharma and cethromycin6b,c (3) from Abbott Laboratories (Figure 1) have been successfully launched into the market.

Narbonolide (4) is a 14-membered polyketide macrolactone biosynthesized by the pikromycin polyketide synthase (PKS) system of Streptomyces venezuelae ATCC 15439.7 The macrolide 4 consists of seven stereocenters including the sensitive chiral center at C2. Its significant therapeutic potential, structural similarity to the macrocycles in telithromycin and cethromycin has resulted in total syntheses from the groups of Masamune8a and Fecik.8b,c However, these syntheses have one or more complicating factors such as a low yield of the key macrocyclization reaction, inability to differentiate the C3 and C5 positions for chemoselective reactions and highly optimized protecting group strategies that decrease the synthetic efficiency.

As part of our ongoing programme towards the total synthesis of macrolides9 we became particularly interested in the total synthesis of narbonolide (4). We envisaged that the core structure of narbonolide (4) could be constructed via ring-closing metathesis of the bis-alkene 5, which in turn could be made via esterification of C1–C10 fragment 6 and C11–O14 fragment 7 (Scheme 1). In this paper, we report the versatility of thiazolidinethione as a chiral auxiliary in the stereoselective preparation of C1–C1010 and C11–O14 fragments of norbonolide.

Accordingly, our synthesis began with the condensation of 3-propanoylthiazolidinethione11 8 with acrolein by utilizing Crimmins’ protocol12 [Ti-mediated enolization using (–)-sparteine (1 equiv) and NMP (1 equiv)] to yield the desired Evans syn-aldol product 9 in 80% with excellent diastereoselectivity (20:1). Silylation of the aldol product 9 with tert-butyldimethylsilyl triflate afforded 10 in good yield. The iodide 12 was obtained after the reductive removal of the chiral auxiliary from thione 11 with lithium borohydride and subsequent iodination of the resulting alcohol 11. The resulting iodide 12 was then subjected to Myers alkylation13 conditions.

Scheme 1 Retrosynthesis of narbonolide 4
Treatment of the iodide 12 with (R,R)-N-propanoylpsuedoephedrine (13) at 40 °C proceeded cleanly to furnish the amide 14 in 77% yield. Removal of chiral auxiliary was accomplished with lithium amidotrihydroborate\textsuperscript{14} to produce alcohol 15, which was further oxidized to aldehyde 16 by treatment with (diacetoxyiodo)benzene/2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) in excellent yield (Scheme 2).

The aldehyde 16 was condensed with 3-propanoylthiazolidinethione 8 to give the non-Evans \textit{syn}-aldol product 17 by Crimmins protocol [Ti-mediated enolization using i-Pr\textsubscript{2}NEt (1 equiv) as a base].\textsuperscript{12} The reaction was readily scalable, providing reproducible results in terms of both yield and diastereoselectivity (20:1). Reductive removal of thiazolidinethione of 17 with sodium borohydride produced diol 18. The 1,3-diol in 18 was then protected with 4-methoxybenzaldehyde dimethyl acetal affording the corresponding acetal 19, which after reductive hydrolysis with diisobutylaluminum hydride afforded primary alcohol 20 in good yield. The resulting alcohol was oxidized to the corresponding aldehyde 21 and subjected to aldol reaction with thiazolidinethione 8 to obtain non-Evans \textit{syn}-aldol adduct 22\textsuperscript{12} in 83% yield and excellent diastereoselectivity (≥96%). The aldol product was silylated to give 23, which on subsequent oxidative hydrolysis afforded C1–C10 fragment 6 with all the desired stereocenters (Scheme 3).

The synthesis of fragment 7 commenced with an Evans \textit{syn}-aldol reaction between thiazolidinethione 8 and propanal to give aldol product 24. The resulting aldol 24 was silylated with tert-butylidimethylsilyl triflate, followed by the reductive removal of the chiral auxiliary with lithium borohydride to afford the alcohol 26. Oxidation of the alcohol 26 with (diacetoxyiodo)benzene/2,2,6,6-tetramethyl-1-piperidinylxol produced aldehyde 27. At this stage terminal olefination of the aldehyde proved to be problematic. Various attempts at the olefination of aldehyde 23 with methyltriphenylphosphonium bromide with different bases (BuLi, NaHMDS) and direct/indirect addition of substrates, as well as varying the temperature (−78 °C to r.t.) were unsuccessful. However, terminal olefin of 27 was achieved by treatment with Tebbe’s reagent\textsuperscript{15} in 46% yield (Scheme 4).

In summary, an efficient and enantioselective synthesis of the C1–C10 and C11–O14 fragments of narbonolide have been completed, demonstrating the versatility of thiazolidinethione as chiral auxiliary. This successful approach will be directly applicable to the synthesis of narbonolide; progress toward this goal is currently underway in our laboratory.
Optical rotations were measured on a Jasco DIP-370 digital polarimeter at 25 °C; concentrations (c) are quoted in g/100 mL. IR spectra were recorded on a Schimadzu IR Prestige 21 FT-IR spectrophotometer. 1H NMR and 13C NMR spectra are determined in CDCl₃; 1H NMR used TMS as an internal reference. Coupling constants were corrected to the nearest value after decimal. ESI-MS spectra were obtained on a Perkin Elmer API 3000 spectrometer. Column chromatography used silica gel, grade 60–120, 100–200 mesh. Reactions were monitored by TLC (silica gel plates, 60 F254), visualized with UV light or alkaline KMnO₄ stain. Unless stated otherwise re-

Scheme 2 Reagents and conditions: (a) TiCl₄, (−)-sparteine, NMP, acrolein, CH₂Cl₂, –78 °C to 0 °C, 80%; (b) TBSOTf, 2,6-lutidine, CH₂Cl₂, 0 °C, 85%; (c) LiBH₄, Et₂O, H₂O, 0 °C, 76%; (d) Ph₃P, I₂,imidazole, Et₂O–MeCN (4:1), r.t., 79%; (e) i-Pr₂NH, BuLi, LiCl, THF, 77%; (f) i-Pr₂NH, BuLi, BH₃·NH₃, THF, 90%; (g) TEMPO, Ph(OAc)₂, CH₂Cl₂, r.t., 95%.

Scheme 3 Reagents and conditions: (a) 8, TiCl₄, i-Pr₂NEt, CH₂Cl₂, 0 °C, 74%; (b) NaBH₄, EtOH, r.t., 81%; (c) 4-MeOC₆H₄CH(OMe)₂, CSA, CH₂Cl₂, r.t., 92%; (d) DIBAL-H, CH₂Cl₂, 0 °C, 79%; (e) TEMPO, Ph(OAc)₂, CH₂Cl₂, r.t., 95%; (f) 8, TiCl₄, i-Pr₂NEt, CH₂Cl₂, 0 °C, 83%; (g) TBSOTf, i-Pr₂NEt, CH₂Cl₂, 0 °C to r.t., 81%; (h) LiOH, 30% H₂O₂, THF–H₂O, 0 °C, 65%.

Scheme 4 Reagents and conditions: (a) TiCl₄, (−)-sparteine, NMP, EtCHO, –78 °C to 0 °C, 85%; (b) TBSOTf, 2,6-lutidine, CH₂Cl₂, 0 °C, 91%; (c) LiBH₄, Et₂O, H₂O, 0 °C, 70%; (d) TEMPO, Ph(OAc)₂, CH₂Cl₂, r.t., 90%; (e) Tebbe’s reagent, THF, 0 °C, 46%.

Synthesis 2009, No. 3, 474–482  © Thieme Stuttgart · New York
actions were performed under N₂ atmosphere. All other reagents were purchased from Aldrich at the highest commercial quality and used without further purification.

(2S,3R)-1-[(S)-4-Benzyl-2-thioxothiazolidin-3-yl]-3-hydroxy-2-methylpent-4-en-1-ol (10)

To a soln of 8 (10.0 g, 37.7 mmol) in CH₂Cl₂ (100 mL) at 0 °C was added TiCl₄ (4.3 mL, 39.6 mmol). The resulting orange slurry was stirred for 5 min and then (~)-sparteine (8.7 mL, 37.7 mmol) was added; during the addition, the mixture became deep red in color (characteristic of the enolate). The mixture was stirred at 0 °C for 20 min and then it was cooled to –78 °C. NMP (3.63 mL, 37.7 mmol) was added. The mixture was stirred for a further 10 min at this temperature until acrolein (3.0 mL, 45.2 mmol) was added. The mixture was stirred at –78 °C for 1 h and then at 0 °C for 1 h. Sat. aq NH₄Cl (50 mL) was added, the layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (3 × 100 mL). The combined organic layers were dried (Na₂SO₄) and filtered and the filtrate was concentrated under vacuum. The crude product was purified by flash column chromatography (silica gel, EtOAc–hexane, 20:80) to afford 9 with excellent diastereoselectivity (20:1) as a bright yellow oil. Yield: 9.7 g (80%); [α]D²⁵ +184.7 (c 1.00, CHCl₃).

IR (neat): 3481, 2980, 2935, 1695, 1166 cm⁻¹.


1H NMR (400 MHz, CDCl₃): δ = 7.36–7.26 (m, 5 H), 5.83 (dd, J = 17.5, 10.5, 0.5 Hz, 1 H), 5.32 (d, J = 17.5, 1.0 Hz, 1 H), 5.33–5.22 (m, 1 H), 5.20 (d, J = 10.5 Hz, 1 H), 4.58 (m, 1 H), 4.46 (m, 1 H), 3.39 (dd, J = 12.4, 6.8 Hz, 1 H), 3.23 (dd, J = 13.5, 4.0 Hz, 1 H), 3.05 (dd, J = 13.5, 11.0 Hz, 1 H), 2.9 (d, J = 11.0 Hz, 1 H), 1.25 (d, J = 7.0 Hz, 3 H).

13C NMR (50 MHz, CDCl₃): δ = 201.3, 177.3, 137.4, 136.3, 129.4, 201.1, 176.2, 139.2, 136.6, 129.4, 125.7, 121.0, 73.6, 72.6, 43.8, 36.7, 36.7, 32.2, 11.0.

MS (ESI): m/z (%) = 322 (100) [M + H]+, 210 (80).


(2S,3R)-1-[(S)-4-Benzyl-2-thioxothiazolidin-3-yl]-3-hydroxy-2-methylpent-4-en-1-one (11)

To a soln of alcohol 11 (4.0 g, 17.4 mmol) in Et₂O–MeCN (4:1, 80 mL) at r.t. was added Ph₃P (9.12 g, 34.8 mmol) and then imidazole (7.14 mL, 50.7 mmol, 4.3 equiv) and 1.6 M BuLi in hexanes (29.4 mL, 46.8 mmol, 4 equiv) were added sequentially, and the resulting mixture was stirred for 10 min; during the addition, the mixture became deep red in color (characteristic of the enolate). The mixture was stirred at 0 °C for 20 min, then warmed to 0 °C for 15 min, then to r.t. for a further 10 min. The mixture was cooled to 0 °C and iodide 12 (4.0 g, 11.8 mmol, 1 equiv) in

(2R,3R,5R)-3-[(tert-Butylidimethylsilyloxy)-2-methylpent-4-en-1-ol (12)

To a soln of thione 10 (10.2 g, 23.4 mmol) in Et₂O (100 mL) at 0 °C was added. H₂O (0.94 mL, 58.6 mmol, 2.5 equiv) and LiBD₄ (1.28 g, 58.6 mmol, 2.5 equiv) sequentially. The resulting mixture was stirred at 0 °C for 1 h, by which time the yellow color of the reaction had faded, whereupon the reaction was quenched by careful addition of sat. aq NH₄Cl (100 mL) and extracted with Et₂O (3 × 100 mL). The combined organic layers were dried (Na₂SO₄) and filtered and the filtrate was concentrated under vacuum. The crude product was purified by flash column chromatography (silica gel, EtOAc–hexane, 5:95) to afford 11 as a colorless oil. Yield: 4.1 g (76%); [α]D²⁵ +16.4 (c 0.50, CHCl₃).

IR (neat): 3369, 2956, 2858, 1028, 837, 775 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 5.87 (dd, J = 17.5, 10.5, 0.5 Hz, 1 H), 5.23 (dd, J = 17.5, 2.0 Hz, 1 H), 5.18 (dd, J = 10.5, 2.0 Hz, 1 H), 4.25 (dd, J = 6.0, 4.5 Hz, 1 H), 3.65 (dd, J = 11.0, 8.0 Hz, 1 H), 3.48 (m, 1 H), 2.72 (br s, 1 H), 1.99–1.95 (m, 1 H), 0.90 (s, 9 H), 0.81 (d, J = 7.0 Hz, 3 H), 0.08 (s, 3 H), 0.05 (s, 3 H).

13C NMR (50 MHz, CDCl₃): δ = 137.8, 115.8, 65.6, 40.9, 25.8, 18.1, 12.2, –4.5, –5.2.

MS (ESI): m/z (%) = 231 (100) [M + H]+.

THF (10 mL) was added. Then the mixture was slowly warmed to 40 °C and stirred overnight. Sat. aq NH₄Cl (50 mL) was added to quench the reaction, the layers were separated, and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried (Na₂SO₄) and filtered and the filtrate was concentrated under vacuum. The crude product was purified by flash column chromatography (silica gel, EtOAc–hexane, 25:75) to afford 14 as a colorless viscous oil. Yield: 3.92 g (77%); [a]D₂⁰ +28.8 (c 1.00, CHCl₃).

IR (neat): 3365, 2956, 2927, 1620, 835, 775 cm⁻¹.

MS (ESI): m/z (%) = 139.7, 35.9, 33.1, 25.9, 18.2, 17.9, 15.7, –4.3, –4.9.

HRMS (ESI): [M + Na] + found: 302 (100) [M + H]+, 536 (60), 404 (60).

HRMS (ESI): [M + Na]⁺ calculated for C₁₃H₂₅NO₃Si: 356.2675; found: 356.2688.

(2R,3S,4S,6R,7R)-1-[(S)-4-Benzyl-2-thioxothiazolidin-3-yl]-7-(tert-butyldimethylsilyloxy)-3-hydroxy-2,4,6-trimethylnon-8-en-1-one (17)

To a soln of thione 17 (1.2 g, 2.2 mmol) in EtOH (20 mL) was added NaBH₄ (340 mg, 9.0 mmol) and the mixture was stirred for 9 min by this time yellow color of the reaction had faded. The reaction was then quenched by the addition of sat. aq NH₄Cl (25 mL) and then it was diluted with CH₂Cl₂ (3 × 50 mL). The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 × 50 mL). The combined organic layers were dried (Na₂SO₄) and filtered and the filtrate was concentrated under vacuum. The crude product was purified by flash column chromatography (silica gel, EtOAc–hexane, 25:75) to afford 18 as a colorless oil. Yield: 940 mg (95%); [a]D₂⁰ +42.4 (c 0.50, CHCl₃).

IR (neat): 2958, 2929, 1732, 1251, 837, 775 cm⁻¹.

HRMS (ESI): [M + Na]⁺ calculated for C₁₃H₂₅NO₃Si: 293.1915; found: 293.1913.

Synthesis 2009, No. 3, 474–482 © Thieme Stuttgart · New York
flash column chromatography (silica gel, EtOAc–hexane, 25:75) to afford diol 18 as a colorless oil. Yield: 600 mg (81%); [α]D2520 +8.4 (c 0.50, CHCl3).

IR (neat): 3485, 2958, 2929, 1415, 1334, 835, 775 cm−1.

1H NMR (400 MHz, CDCl3): δ = 2.88 (d, J = 10.5, 6.5 Hz, 2 H), 2.97 (d, J = 10.5, 6.5 Hz, 3 H), 3.58 (s, 1 H), 3.66 (dd, J = 6.0, 3.0 Hz, 1 H), 4.57 (d, J = 9.0 Hz, 2 H), 6.85 (d, J = 9.0 Hz, 2 H), 7.17 (d, J = 9.0 Hz, 3 H), 7.77 (d, J = 9.0 Hz, 3 H), 9.03 (br s, 1 H), 11.03 (br s, 1 H). MS (ESI): m/z (%) = 344 (100) [M + H]+.


(3R,4R,6S)-3-(4-tert-Butyldimethylsilyloxy)-1-(3S,5S)-2-(4-methoxy-phenyl)-5-methyl-3-dioxo-4-yl)-4-methylhept-1-one (19)

To a soln of diol 18 (500 mg, 1.5 mmol) in CHCl3 (10 mL) was added 1.0 M aq NaOH (10 mL) and CSA (18 mg, 0.07 mmol). The mixture was stirred overnight and then washed with 10% aq NaHCO3 (20 mL). The layers were separated and the aqueous layer was extracted with CH2Cl2 (3 × 25 mL). The combined organic layers were dried (Na2SO4) and filtered, and the filtrate was concentrated under vacuum. The crude product was purified by flash column chromatography (silica gel, EtOAc–hexane, 17:83) to afford 19 as a colorless oil. Yield: 624 mg (92%); [α]D2520 +7.2 (c 1.00, CHCl3).

IR (neat): 2956, 1517, 1247, 789, 775 cm−1.

1H NMR (400 MHz, CDCl3): δ = 3.37 (d, J = 10.5, 6.5 Hz, 2 H), 3.59 (s, 1 H), 3.74 (d, J = 6.0, 3.0 Hz, 1 H), 4.49 (d, J = 9.0 Hz, 2 H), 7.14 (d, J = 9.0 Hz, 3 H), 7.72 (d, J = 9.0 Hz, 3 H), 9.01 (br s, 1 H), 10.99 (br s, 1 H). MS (ESI): m/z (%) = 351 (100) [M + H]+.


(3S,4S,5S,6S,7R,8R)-7-(tert-Butyldimethylsilyloxy)-3-(4-methoxy-benzyl)-2,4,6,8-tetramethyl-10-en-1-ol (20)

To a soln of 19 (550 mg, 1.2 mmol) in CHCl3 (10 mL) at 0 °C, was added 3% aq NaHCO3 (10 mL) and followed by sat. aq potassium sodium tartrate (20 mL). The soln was warmed to r.t. and then the reaction was quenched by the addition of sat. aq Na2S2O3–sat. aq NaHCO3 (5:1, 20 mL). The layers were separated and the aqueous layer was extracted with CHCl3 (3 × 20 mL). The combined organic layers were dried (Na2SO4) and filtered, and the filtrate was concentrated under vacuum. The crude product was purified by flash column chromatography (silica gel, EtOAc–hexane, 3:7) to afford 21 as a colorless oil. Yield: 470 mg (95%); [α]D2520 +6.6 (c 1.00, CHCl3).

IR (neat): 2956, 1517, 1415, 1334, 835, 775 cm−1.

1H NMR (400 MHz, CDCl3): δ = 3.29 (d, J = 10.5, 6.5 Hz, 2 H), 3.70 (d, J = 9.0 Hz, 2 H), 6.52 (d, J = 9.0 Hz, 2 H), 6.70 (d, J = 9.0 Hz, 2 H), 7.09 (d, J = 9.0 Hz, 2 H), 7.76 (d, J = 9.0 Hz, 2 H), 9.02 (br s, 1 H), 10.89 (br s, 1 H). MS (ESI): m/z (%) = 351 (100) [M + H]+.

H), 0.98 (d, J = 6.5 Hz, 3 H), 0.93 (d, J = 7.0 Hz, 3 H), 0.89 (s, 9 H), 0.88 (d, J = 6.5 Hz, 3 H), 0.02 (s, 3 H), 0.005 (s, 3 H).

13C NMR (50 MHz, CDCl3): δ = 179.2, 159.0, 140.1, 131.1, 129.0, 114.7, 113.6, 83.6, 76.4, 74.9, 73.1, 55.2, 43.0, 39.5, 37.5, 36.2, 33.6, 26.1, 25.9, 23.8, 20.8, 18.3, 16.9, 16.8, 11.2, 10.9, −4.0, −4.1, −4.2, −4.8.

MS (ESI): m/z (%) = 659 (100) [M + Na]+, 637 (95) [M + H]+.


(2S,3R,5R,6S,8R,8R)-1-(S)-4-Benzyl-2-thioxothiazolidin-3-yl)-3-hydroxy-2-methylpentan-1-one (24)

To a soln of 8 (5 g, 18.8 mmol) in CH2Cl2 (75 mL) at 0 °C was added TiCl4 (2.17 mL, 19.8 mmol). The resultant orange slurry was stirred for 5 min, (−)-sparteine (4.33 mL, 18.8 mmol) was added forming the characteristic enolate color (deep red). The mixture was stirred at 0 °C for 20 min, then cooled to −78 °C and NMP (1.81 mL, 18.8 mmol) was added. The mixture was stirred for 10 min and then freshly distilled propanal (1.51 mL, 20.6 mmol) was added dropwise. The mixture was stirred at −78 °C for 1 h and then at 0 °C for 1 h. The reaction was quenched by the addition of sat. aq NH4Cl (75 mL). The layers were separated and the aqueous layer was extracted with CH2Cl2 (3 × 75 mL). The combined organic layers were dried (Na2SO4) and filtered and the filtrate was concentrated under vacuum.

The crude product was purified by flash column chromatography (silica gel, EtOAc–hexane, 4:96) to afford 23a as a bright yellow oil. Yield: 281 mg (81%); [α]D25 +78.0 (c 1.00, CHCl3).

IR (neat): 2954, 2929, 1701, 1163 cm−1.

1H NMR (400 MHz, CDCl3): δ = 7.33–7.26 (m, 5 H), 7.24 (d, J = 8.0 Hz, 2 H), 6.82 (d, J = 8.0 Hz, 2 H), 5.88 (d, J = 17.0, 6.5 Hz, 1 H), 5.18–5.06 (m, 3 H), 4.53–4.53 (m, 1 H), 4.50 (d, J = 11.0 Hz, 1 H), 4.42 (d, J = 11.0 Hz, 1 H), 4.01 (d, J = 6.5, 3.5 Hz, 1 H), 3.96–3.94 (m, 1 H), 3.77 (s, 3 H), 3.31–3.29 (m, 1 H), 3.23–3.20 (m, 2 H), 3.01 (dd, J = 13.0, 11.0 Hz, 1 H), 2.80 (d, J = 11.0 Hz, 1 H), 2.09–2.08 (m, 1 H), 1.77–1.69 (m, 2 H), 1.58–1.54 (m, 2 H), 1.27 (d, J = 6.0 Hz, 3 H), 0.99 (d, J = 7.0 Hz, 3 H), 0.93 (s, 9 H), 0.89 (s, 9 H), 0.88 (d, J = 6.0 Hz, 3 H), 0.10 (s, 3 H), 0.08 (s, 3 H), 0.04 (s, 3 H), 0.01 (s, 3 H).

13C NMR (50 MHz, CDCl3): δ = 202.3, 166.2, 140.3, 132.4, 129.4, 128.7, 128.7, 127.1, 114.8, 113.5, 83.5, 78.1, 75.7, 73.2, 69.3, 55.2, 43.3, 40.6, 37.3, 36.4, 35.1, 33.2, 32.0, 26.3, 26.0, 18.5, 18.3, 17.4, 17.1, 15.0, 11.1, −3.3, −3.8, −4.1, −4.7.

MS (ESI): m/z (%) = 828 (100) [M + H]+.


(2S,3R,5S,6R,8R,9R)-3-Bis((tert-butyldimethylsilyloxy)-5-(4-methoxybenzyloxy)-2,4,6,8-tetramethylundec-10-enoic Acid (6)

To a soln of thiochrome 23 (220 mg, 0.265 mmol) in a mixture of THF and H2O (4.1, 5 mL) at 0 °C was added 30% aq H2SO4 (0.3 mL, 2.7 mmol) followed by the addition of LiOH (33.5 mg, 0.8 mmol). The mixture was stirred for 1 h and then directly loaded on to a column (silica gel, EtOAc–hexane, 10:90) and eluted to afford 6. Yield: 109 mg (65%); [α]D25 +25.4 (c 1.00, CHCl3).

IR (neat): 2954, 2929, 1707, 1514, 1249, 835, 775 cm−1.

1H NMR (400 MHz, CDCl3): δ = 7.26 (d, J = 8.5 Hz, 2 H), 6.79 (d, J = 8.5 Hz, 2 H), 5.74 (dd, J = 17.0, 10.5, 6.5 Hz, 1 H), 5.05 (dd, J = 17.0, 2.0 Hz, 1 H), 5.00 (dd, J = 10.5, 1.2 Hz, 1 H), 4.47 (d, J = 11.0 Hz, 1 H), 4.36 (d, J = 11.0 Hz, 1 H), 4.02–3.99 (m, 1 H), 3.90–3.88 (m, 1 H), 3.73 (s, 3 H), 3.14 (dd, J = 5.5, 3.5 Hz, 1 H), 2.67 (dd, J = 7.0, 3.5 Hz, 1 H), 2.02–1.98 (m, 1 H), 1.83–1.80 (m, 1 H), 1.68–1.61 (m, 4 H), 1.13 (d, J = 7.0 Hz, 3 H), 0.97 (d, J = 6.5 Hz, 3 H), 0.94 (d, J = 6.5 Hz, 3 H), 0.90 (s, 3 H), 0.90 (s, 9 H), 0.88 (s, 9 H), 0.82 (s, 6 H), 0.001 (s, 6 H).

13C NMR (50 MHz, CDCl3): δ = 195.2, 159.3, 140.1, 131.1, 129.0, 114.7, 113.6, 83.6, 76.4, 74.9, 73.1, 55.2, 43.0, 39.5, 37.5, 36.2, 33.6, 26.1, 25.9, 23.8, 20.8, 18.3, 16.9, 16.8, 11.2, 11.0, −4.0, −4.1, −4.2, −4.8.

MS (ESI): m/z (%) = 645 (100) [M + Na]+, 623 (95) [M + H]+.

(2R,3R)-3-(tert-Butylidemethylsilyloxy)-2-methylpentan-1-ol (26)

To a solution of thione 25 (6.0 g, 13.7 mmol) in Et₂O (50 mL) at 0 °C was added, H₂O (0.62 mL, 34.3 mmol, 2.5 equiv) and LiBH₄ (720 mg, 58.6 mmol, 2.5 equiv) sequentially; the resulting mixture was stirred at 0 °C for 1 h. At this time yellow color of the reaction had faded, whereupon the reaction was quenched by careful addition of sat. aq NH₄Cl (50 mL) and extracted with Et₂O (3 × 100 mL). The organic layer was dried (Na₂SO₄) and filtered and the filtrate was concentrated under vacuum. The crude product was purified by flash column chromatography (silica gel, EtOAc–hexane, 15:85) to afford 26 as a colorless oil. Yield: 2.23 g (70%); [α]D²⁵ +1.4 (c 1.00, CHCl₃).

IR (neat): 3348, 2958, 2929, 1253 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 3.71–3.66 (m, 2 H), 3.51 (dd, J = 11.0, 5.5 Hz, 1 H), 2.53 (br s, 1 H), 1.97–1.94 (m, 1 H), 1.54–1.47 (m, 2 H), 0.90 (s, 9 H), 0.89 (t, J = 7.5 Hz, 3 H), 0.81 (d, J = 7.5 Hz, 3 H), 0.09 (s, 3 H), 0.07 (s, 3 H).

¹³C NMR (50 MHz, CDCl₃): δ = 76.4, 66.1, 39.2, 25.8, 25.1, 18.0, 11.8, 10.7, −4.4, −4.5.

MS (ESI): m/z (%) = 233 (100) [M + H]+.

(2S,3R)-3-(tert-Butylidemethylsilyloxy)-2-methylpentanal (27)(a)

To a solution of 26 (300 mg, 1.3 mmol) in CH₂Cl₂ (5 mL) was added Ph₂O (10 mg, 0.05 equiv). The mixture was stirred for 2 h and then the reaction was quenched by the addition of the reaction mixture and sat. aq Na₂SO₄–sat. aq NaHCO₃ (5:1, 10 mL). The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 × 20 mL). The combined organic layers were dried (Na₂SO₄) and filtered and the filtrate was concentrated under vacuum. The crude product was purified by flash column chromatography (silica gel, EtOAc–hexane, 4:96) to afford 27 as a colorless oil. Yield: 265 mg (90%); [α]D²⁵ +24.4 (c 0.50, CHCl₃).

HRMS (ESI): m/z (%) = 229 (100) [M + H]+.

Acknowledgment

We thank Dr. Reddy’s Laboratories Ltd. for financial support and encouragement. Help from the analytical department in recording spectral data is appreciated.

References

1. DRL Publication No. 670.
