Stereoselective Preparation of C1–C10 and C11–O14 Fragments of Narbonolide: Exploiting the Versatility of Thiazolidinethione Chiral Auxiliary[1]

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

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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

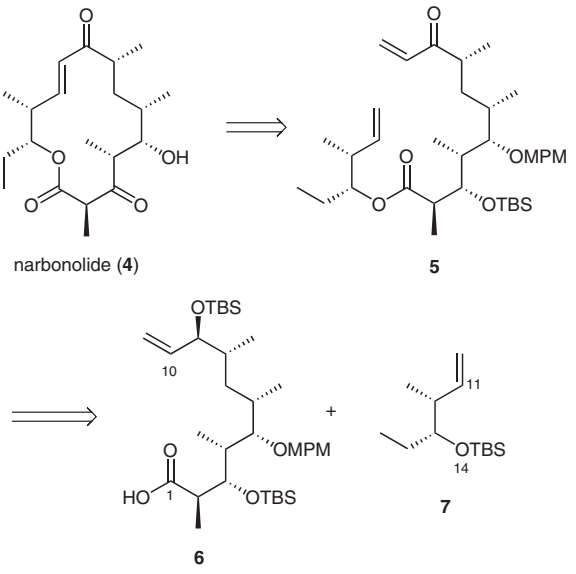
The macrolide antibiotic erythromycin A (**1**) has served as both a clinically useful agent for the treatment of Gram-positive bacterial infections as well as a starting point for the semisynthesis of derivatives with improved physiochemical and microbiological properties.[2] Several of these derivatives, 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 telithromycin[6a] (**2**) from Aventis Pharma and cethromycin[6b,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 macrocytes in telithromycin and cethromycin has resulted in total syntheses from the groups of Masamune[8a] 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 macrolides[9] 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–C10[10] and C11–O14 fragments of norbonolide.

Accordingly, our synthesis began with the condensation of 3-propanoylthiazolidinethione[11] **8** with acrolein by utilizing Crimmins' protocol[12] [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 **10** with lithium borohydride and subsequent iodination of the resulting alcohol **11**. The resulting iodide **12** was then subjected to Myers alkylation[13] conditions.



Scheme 1 Retrosynthesis of narbonolide **4**

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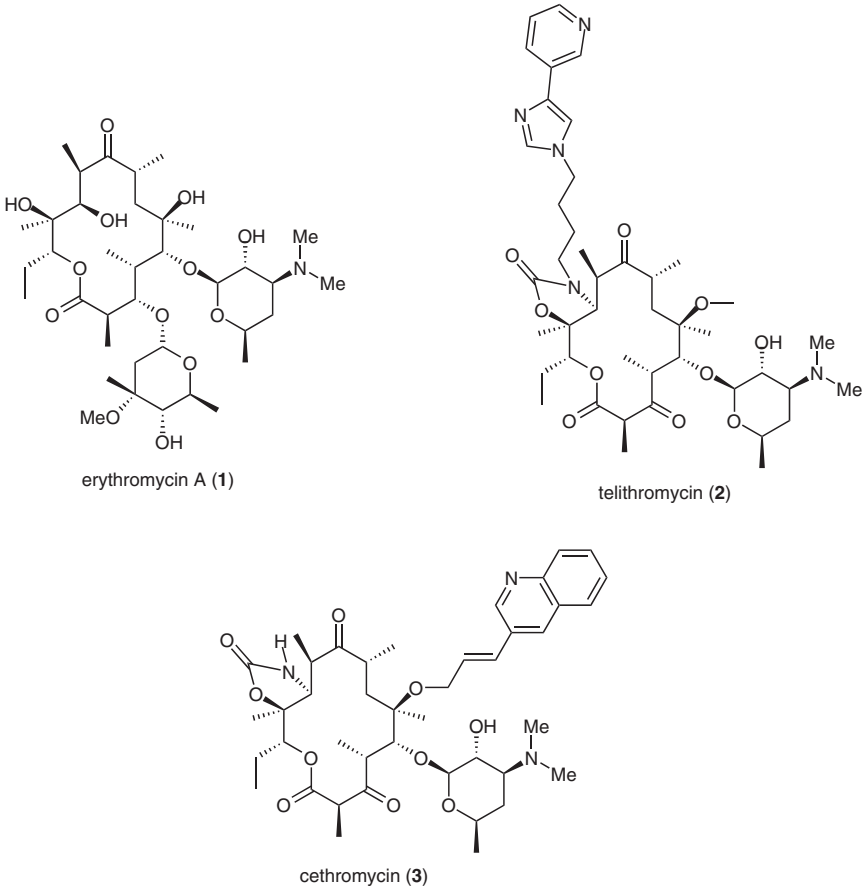


Figure 1

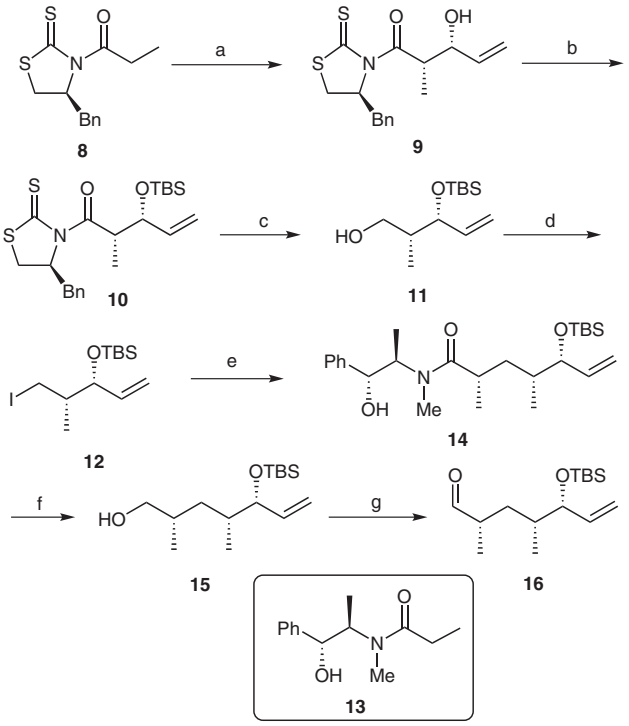
Treatment of the iodide **12** with (*R*,*R*)-*N*-propanoylpseudoephedrine (**13**) at 40 °C proceeded cleanly to furnish the amide **14** in 77% yield. Removal of chiral auxiliary was accomplished with lithium amidotrihydroborate[14] to produce alcohol **15**, which was further oxidized to aldehyde **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 *syn*-aldol product **17** by Crimmins protocol [Ti-mediated enolization using *i*-Pr_2NEt (1 equiv) as a base].[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 *syn*-aldol adduct **22**[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).

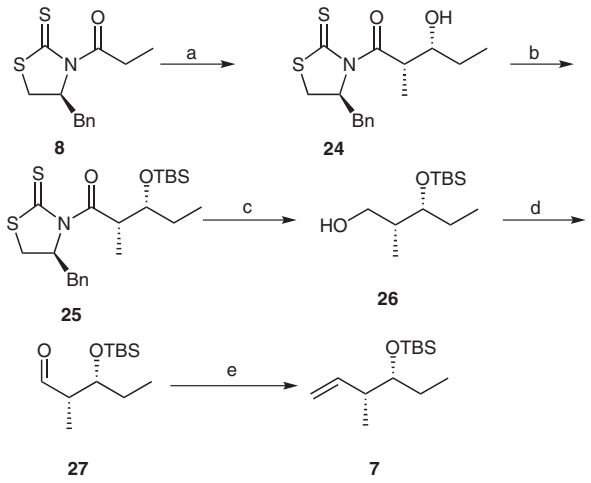
The synthesis of fragment **7** commenced with an Evans *syn*-aldol reaction between thiazolidinethione **8** and propanal to give aldol product **24**. The resulting aldol **24** was silylated with *tert*-butyldimethylsilyl triflate, followed by the reductive removal of the chiral auxiliary with lithium borohydride to afford the alcohol **26**.

Oxidation of the alcohol **26** with (diacetoxyiodo)benzene/2,2,6,6-tetramethyl-1-piperidinyloxyl 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[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.

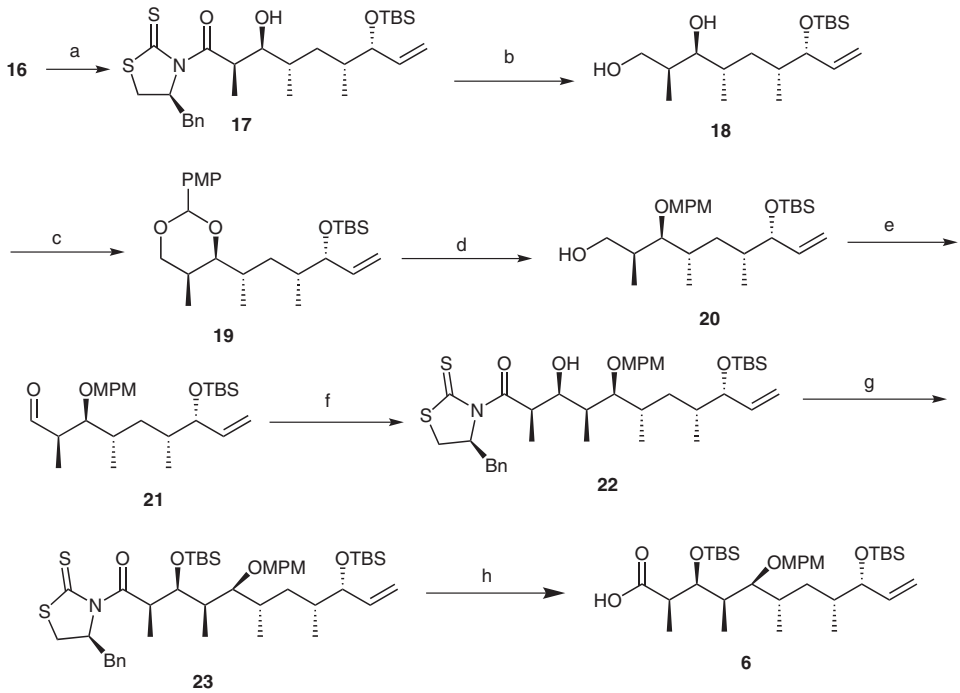


Scheme 2 *Reagents and conditions*: (a) $TiCl_4$, (–)-sparteine, NMP, acrolein, CH_2Cl_2, –78 °C to 0 °C, 80%; (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 85%; (c) $LiBH_4$, Et_2O, H_2O, 0 °C, 76%; (d) Ph_3P, I_2, imidazole, Et_2O–MeCN (4:1), r.t., 79%; (e) **13**, *i*-Pr_2NH, BuLi, LiCl, THF, 77%; (f) *i*-Pr_2NH, BuLi, $BH_3{\cdot}NH_3$, THF, 90%; (g) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, r.t., 95%.



Scheme 4 *Reagents and conditions*: (a) $TiCl_4$, (–)-sparteine, NMP, EtCHO, –78 °C to 0 °C, 85%; (b) TBSOTf, 2,6-lutidine, 0 °C, 91%; (c) $LiBH_4$, Et_2O, H_2O, 0 °C, 70%; (d) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, r.t., 90%; (e) Tebbe's reagent, THF, 0 °C, 46%.

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 ^{13}C NMR spectra are determined in $CDCl_3$ were determined on Varian Mercury Plus 400 MHz and Varian Gemini-2000 200 MHz spectrometers, respectively; ^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 $KMnO_4$ stain. Unless stated otherwise re-



Scheme 3 *Reagents and conditions*: (a) **8**, $TiCl_4$, *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 74%; (b) $NaBH_4$, EtOH, r.t., 81%; (c) 4-$MeOC_6H_4CH(OMe)_2$, CSA, CH_2Cl_2, r.t., 92%; (d) DIBAL-H, CH_2Cl_2, 0 °C, 79%; (e) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, r.t., 95%; (f) **8**, $TiCl_4$, *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 83%; (g) TBSOTf, *i*-Pr_2NEt, CH_2Cl_2, 0 °C to r.t., 81%; (h) LiOH, 30% H_2O_2, THF–H_2O, 0 °C, 65%.

actions were performed under N_2 atmosphere. All other reagents were purchased from Aldrich at the highest commercial quality and used without further purification.

(2*S*,3*R*)-1-[(*S*)-4-Benzyl-2-thioxothiazolidin-3-yl]-3-hydroxy-2-methylpent-4-en-1-one (9)

To a soln of **8** (10.0 g, 37.7 mmol) in CH_2Cl_2 (100 mL) at 0 °C was added $TiCl_4$ (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 then acrolein (3.0 mL, 45.2 mmol) was added dropwise; the mixture was stirred at –78 °C for 1 h and then at 0 °C for 1 h. Sat. aq NH_4Cl (50 mL) was added, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried (Na_2SO_4) and filtered and the filtrate was concentrated under vacuum. The crude product was purified by 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%); $[\alpha]_D^{25}$ +184.7 (*c* 1.00, $CHCl_3$).

IR (neat): 3481, 2980, 2935, 1695, 1166 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.26 (m, 5 H), 5.83 (ddd, *J* = 17.5, 10.5, 5.0 Hz, 1 H), 5.32 (d, *J* = 17.5 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).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 201.3, 177.3, 137.4, 136.3, 129.4, 128.9, 127.2, 116.3, 116.0, 73.6, 72.6, 43.8, 36.7, 32.2, 11.0.

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

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{19}NaNO_2S_2$: 344.0756; found: 344.0755.

(2*S*,3*R*)-1-[(*S*)-4-Benzyl-2-thioxothiazolidin-3-yl]-3-(*tert*-butyldimethylsilyloxy)-2-methylpent-4-en-1-one (10)

To a soln of **9** (9.0 g, 28.0 mmol) in CH_2Cl_2 (150 mL) at 0 °C was added 2,6-lutidine (4.9 mL, 42.0 mmol, 1.5 equiv) and TBSOTf (7.7 mL, 33.6 mmol, 1.2 equiv) sequentially and the mixture was stirred at 0 °C for 1 h. The reaction was quenched with sat. aq $NaHCO_3$ (100 mL), the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were washed with brine (100 mL), dried (Na_2SO_4), and filtered. The filtrate was concentrated under vacuum to give a crude product that was purified by column chromatography (silica gel, EtOAc–hexane, 7:93) to afford **10** as a bright yellow oil. Yield: 10.3 g (85%); $[\alpha]_D^{25}$ +197.4 (*c* 1.00, $CHCl_3$).

IR (neat): 2929, 2856, 1701, 1251, 837 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.26 (m, 5 H), 5.85 (ddd, *J* = 17.5, 10.5, 6.0 Hz, 1 H), 5.16–5.09 (m, 3 H), 4.59 (m, 1 H), 4.32 (t, *J* = 6.5 Hz, 1 H), 3.32–3.27 (m, 2 H), 3.04 (dd, *J* = 13.0, 11.0 Hz, 1 H), 2.87 (d, *J* = 11.0 Hz, 1 H), 1.23 (d, *J* = 6.5 Hz, 3 H), 0.88 (s, 9 H), 0.03 (s, 3 H), 0.01 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 201.1, 176.2, 139.2, 136.6, 129.4, 128.8, 127.1, 115.7, 76.4, 69.4, 45.8, 36.5, 32.2, 25.7, 18.1, 12.5, –4.3, –5.1.

MS (ESI): *m*/*z* (%) = 436 (100) $[M + H]^+$, 304 (80).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{34}NO_2S_2Si$: 436.1803; found: 436.1800.

(2*R*,3*R*)-3-(*tert*-Butyldimethylsilyloxy)-2-methylpent-4-en-1-ol (11)

To a soln of thione **10** (10.2 g, 23.4 mmol) in Et_2O (100 mL) at 0 °C was added, H_2O (0.94 mL, 58.6 mmol, 2.5 equiv) and $LiBH_4$ (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 NH_4Cl (100 mL) and extracted with Et_2O (3 × 100 mL). The combined organic layers were dried (Na_2SO_4) 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%); $[\alpha]_D^{25}$ +16.4 (*c* 0.50, $CHCl_3$).

IR (neat): 3369, 2956, 2858, 1028, 837, 775 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.87 (ddd, *J* = 17.5, 10.5, 6.0 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).

^{13}C NMR (50 MHz, $CDCl_3$): 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) $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{27}O_2Si$: 231.1780; found: 231.1780.

(2*S*,3*R*)-3-(*tert*-Butyldimethylsilyloxy)-1-iodo-2-methylpent-4-ene (12)

To a soln of alcohol **11** (4.0 g, 17.4 mmol) in Et_2O–MeCN (4:1, 80 mL) at r.t. was added Ph_3P (9.12 g, 34.8 mmol) and then imidazole (2.36 g, 34.8 mmol) sequentially and the mixture was stirred for 10 min; during this time the mixture became a clear soln. I_2 (8.82 g, 34.8 mmol) was added and the mixture was stirred for 15 min, washed with sat. aq $Na_2S_2O_3$ (100 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried (Na_2SO_4) and filtered and the filtrate was concentrated under vacuum. The crude product was purified by flash column chromatography (silica gel, EtOAc–hexane, 2:98) to afford **12** as a colorless oil. Yield: 4.67 g (79%); $[\alpha]_D^{25}$ +15.0 (*c* 1.00, $CHCl_3$).

IR (neat): 2927, 2856, 1251, 1074, 775 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.76 (ddd, *J* = 17.0, 10.5, 6.0 Hz, 1 H), 5.22 (dd, *J* = 17.0, 1.6 Hz, 1 H), 5.13 (dd, *J* = 10.5, 1.6 Hz, 1 H), 4.15–4.12 (m, 1 H), 3.33 (dd, *J* = 10.5, 6.0 Hz, 1 H), 3.01 (dd, *J* = 10.0, 7.0 Hz, 1 H), 1.76–1.70 (m, 1 H), 1.00 (d, *J* = 7.0 Hz, 3 H), 0.89 (s, 9 H), 0.08 (s, 3 H), 0.03 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 139.2, 115.6, 76.0, 42.5, 25.8, 15.4, 12.6, –4.2, –4.8.

MS (ESI): *m*/*z* (%) = 341 (100) $[M + H]^+$.

(2*S*,4*R*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)-*N*-[(1*R*,2*R*)-2-hydroxy-1-methyl-2-phenylethyl]-*N*,2,4-trimethylhept-6-enamide (14)

A stirrer bar and LiCl (6.53 g, 149.3 mmol, 12.7 equiv) were placed in a 250-mL round-bottomed flask and flame dried for 10 min under high vacuum, then allowed to cool to r.t. under N_2 atmosphere. THF (30 mL) was then added and cooled to –78 °C, whereupon *i*-Pr_2NH (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 at this temperature for 5 min. The mixture was then warmed to 0 °C for 10 min and then cooled to –78 °C. Pseudoephedrine amide **13** (5.45 g, 24.6 mmol, 2.1 equiv) in THF (30 mL) was added and the mixture was stirred at –78 °C for 1 h, 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

THF (10 mL) was added. Then the mixture was slowly warmed to 40 °C and stirred overnight. Sat. aq NH_4Cl (50 mL) was added to quench the reaction, the layers were separated, and the aqueous layer was extracted with EtOAc (3 × 75 mL). The combined organic layers were dried (Na_2SO_4) 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%); $[\alpha]_D^{25}$ –28.8 (*c* 1.00, $CHCl_3$).

IR (neat): 3365, 2956, 2927, 1620, 835, 775 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.26 (m, 5 H), 5.78 (ddd, *J* = 17.0, 10.5, 6.5 Hz, 1 H), 5.40 (s, 1 H), 5.09 (dd, *J* = 17.0, 1.6 Hz, 1 H), 5.07 (dd, *J* = 10.5, 1.6 Hz, 1 H), 4.61 (m, 1 H), 4.11 (br s, 1 H), 3.94 (dd, *J* = 5.5, 4.5 Hz, 1 H), 2.84 (s, 3 H), 2.78–2.73 (m, 1 H), 1.84–1.78 (m, 1 H), 1.53–1.42 (m, 2 H), 1.15 (d, *J* = 7.0 Hz, 3 H), 1.08 (d, *J* = 6.5 Hz, 3 H), 0.89 (s, 9 H), 0.76 (d, *J* = 7.0 Hz, 3 H), 0.04 (s, 3 H), 0.007 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 179.0, 142.6, 139.9, 128.2, 127.4, 126.1, 114.7, 78.1, 76.3, 59.5, 37.6, 36.8, 34.2, 25.8, 18.2, 18.0, –4.2, –4.9.

MS (ESI): *m*/*z* (%) = 434 (100) $[M + H]^+$, 302 (20).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{25}H_{44}NO_3Si$: 434.3099; found: 434.3090.

(2*S*,4*R*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)-2,4-dimethylhept-6-en-1-ol (15)

To a soln of *i*-Pr_2NH (4.39 mL, 31.2 mmol) in THF (20 mL) at –78 °C was added 1.6 M BuLi in hexanes (18.2 mL, 29.1 mmol) and the soln was stirred for 5 min at –78 °C. The resulting soln was then warmed to 0 °C for 10 min and then to r.t. for 5 min and it was then cooled to 0 °C. Solid $NH_3{\cdot}BH_3$ complex (0.96 g, 31.1 mmol) was then added; during the addition vigorous evolution of gas ensued. The mixture was stirred at 0 °C for 10 min and then it was warmed to r.t. and stirred for an additional 10 min. The mixture was cooled to 0 °C then the amide **14** (3.0 g, 6.9 mmol) in THF (20 mL) was added and the mixture was warmed to r.t. and stirred overnight. The soln was quenched with 10% aq HCl (50 mL) at 0 °C and stirred at this temperature for 30 min and then the layers were separated and the aqueous layer was extracted with Et_2O (3 × 75 mL). The combined organic layers were washed successively with 10% aq HCl (50 mL) and 5 M aq NaOH (50 mL), then dried (Na_2SO_4) and filtered and he filtrate was concentrated under vacuum. The crude product was purified by flash column chromatography (silica gel, EtOAc–hexane, 10:90) to afford **15** as a colorless oil. Yield: 1.69 g (90%); $[\alpha]_D^{25}$ +16.4 (*c* 0.50, $CHCl_3$).

IR (neat): 3334, 2956, 2927, 1251, 1028, 837, 775 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.78 (ddd, *J* = 17.0, 10.5, 6.5 Hz, 1 H), 5.12 (dd, *J* = 17.0, 1.5 Hz, 1 H), 5.08 (dd, *J* = 10.5, 1.5 Hz, 1 H), 3.96–3.93 (m, 1 H), 3.53 (dd, *J* = 10.5, 4.5 Hz, 1 H), 3.39 (dd, *J* = 10.5, 6.5 Hz, 1 H), 1.75–1.73 (m, 1 H), 1.72–1.60 (m, 2 H), 1.53–1.48 (m, 2 H), 0.95 (d, *J* = 7.0 Hz, 3 H), 0.89 (s, 9 H), 0.87 (d, *J* = 7.0 Hz, 3 H), 0.04 (s, 3 H), 0.01 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 139.7, 114.8, 77.5, 67.8, 37.0, 35.9, 33.1, 25.9, 18.2, 17.9, 15.7, –4.3, –4.9.

MS (ESI): *m*/*z* (%) = 273 (100) $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{32}NaO_2Si$: 295.2071; found: 295.2069.

(2*S*,4*R*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)-2,4-dimethylhept-6-enal (16)

To a soln of **15** (1.0 g, 3.6 mmol) in CH_2Cl_2 (20 mL) was added $PhI(OAc)_2$ (1.42 g, 4.4 mmol) followed by the addition of TEMPO (57 mg, 0.4 mmol) and the mixture was stirred for 2 h. The reaction was quenched by the addition sat. aq $Na_2S_2O_3$–sat. aq $NaHCO_3$ (5:1, 50 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried (Na_2SO_4) and filtered and the filtrate was concentrated under vacuum. The crude product was purified by flash column chromatography (silica gel, EtOAc–hexane, 2:98) to afford **16** as a colorless oil. Yield: 940 mg (95%); $[\alpha]_D^{25}$ +24.2 (*c* 0.50, $CHCl_3$).

IR (neat): 2958, 2929, 1732, 1251, 837, 775 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.52 (d, *J* = 3.0 Hz, 1 H), 5.76 (ddd, *J* = 17.0, 10.5, 6.0 Hz, 1 H), 5.13 (dd, *J* = 17.0, 2.0 Hz, 1 H), 5.08 (dd, *J* = 10.5, 2.0 Hz, 1 H), 3.96–3.93 (m, 1 H), 2.45–2.41 (m, 1 H), 1.93–1.86 (m, 1 H), 1.62–1.57 (m, 2 H), 1.07 (d, *J* = 7.0 Hz, 3 H), 0.87 (s, 9 H), 0.86 (d, *J* = 7.0 Hz, 3 H), 0.01 (s, 3 H), –0.01 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 205.4, 139.0, 115.2, 77.3, 44.1, 37.1, 33.6, 25.8, 18.2, 15.3, 14.4, –4.3, –4.9.

MS (ESI): *m*/*z* (%) = 271 (100) $[M + H]^+$, 155 (40).

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{30}NaO_2Si$: 293.1915; found: 293.1913.

(2*R*,3*S*,4*S*,6*R*,7*R*)-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 **8** (900 mg, 3.4 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added $TiCl_4$ (0.4 mL, 3.5 mmol). The resulting orange slurry was stirred for 5 min, *i*-Pr_2NEt (0.6 mL, 3.5 mmol) was added (deep red) and the mixture was stirred at 0 °C for 20 min. To this mixture, aldehyde **16** (916 mg, 3.4 mmol) in CH_2Cl_2 (2 mL) was added and the mixture was stirred at 0 °C for 1 h. The reaction was quenched by addition of sat. aq NH_4Cl (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried (Na_2SO_4) 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 **17** as a bright yellow oil. Yield: 1.35 g (74%); $[\alpha]_D^{25}$ +107.0 (*c* 0.50, $CHCl_3$).

IR (neat): 2956, 2927, 1678, 1255, 1163, 837, 775 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.26 (m, 5 H), 5.84 (ddd, *J* = 17.0, 10.5, 6.5 Hz, 1 H), 5.38–5.33 (m, 1 H), 5.13 (dd, *J* = 17.0, 2.0 Hz, 1 H), 5.07 (dd, *J* = 10.5, 2.0 Hz, 1 H), 4.90–4.88 (m, 1 H), 4.00–3.98 (m, 1 H), 3.71 (dd, *J* = 9.0, 2.0 Hz, 1 H), 3.35 (dd, *J* = 11.5, 7.0 Hz, 1 H), 3.25 (dd, *J* = 13.0, 4.0 Hz, 1 H), 3.02 (dd, *J* = 13.0, 10.5 Hz, 1 H), 2.87 (d, *J* = 11.5 Hz, 1 H), 1.98–1.91 (m, 2 H), 1.80–1.73 (m, 2 H), 1.17 (d, *J* = 7.5 Hz, 3 H), 0.90 (d, *J* = 8.0 Hz, 3 H), 0.89 (s, 9 H), 0.87 (d, *J* = 7.0 Hz, 3 H), 0.05 (s, 3 H), 0.007 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 201.2, 179.0, 140.2, 136.5, 129.4, 128.9, 127.2, 114.5, 77.6, 75.4, 69.0, 40.7, 37.4, 37.3, 36.9, 34.1, 31.7, 25.9, 18.2, 16.5, 16.4, 10.1, –4.2, –4.8.

MS (ESI): *m*/*z* (%) = 536 (100) $[M + H]^+$, 520 (60), 404 (60).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{28}H_{46}NO_3S_2Si$: 536.2675; found: 536.2688.

(2*S*,3*S*,4*S*,6*R*,7*R*)-7-(*tert*-Butyldimethylsilyloxy)-2,4,6-trimethylnon-8-ene-1,3-diol (18)

To a soln of thione **17** (1.2 g, 2.2 mmol) in EtOH (20 mL) was added $NaBH_4$ (340 mg, 9.0 mmol) and the mixture was stirred for 15 min; by this time yellow color of the reaction had faded. The reaction was then quenched by the addition of sat. aq NH_4Cl (25 mL) and then it was diluted with CH_2Cl_2 (50 mL), the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried (Na_2SO_4) and filtered and the filtrate was concentrated in vacuo. The crude product was purified by

flash column chromatography (silica gel, EtOAc–hexane, 25:75) to afford diol **18** as a colorless oil. Yield: 600 mg (81%); $[\alpha]_D^{25}$ +8.4 (*c* 0.50, $CHCl_3$).

IR (neat): 3485, 2958, 2929, 1415, 1334, 835, 775 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.80 (ddd, *J* = 17.0, 10.5, 6.5 Hz, 1 H), 5.14–5.02 (m, 2 H), 3.99–3.98 (m, 1 H), 3.73–3.42 (m, 3 H), 2.55 (br s, 1 H), 2.15 (br s, 1 H), 1.82–1.67 (m, 4 H), 0.92 (d, *J* = 7.0 Hz, 3 H), 0.87 (s, 9 H), 0.86 (d, *J* = 6.0 Hz, 3 H), 0.81 (d, *J* = 7.0 Hz, 3 H), 0.02 (s, 3 H), 0.001 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 139.3, 115.0, 114.5, 79.9, 77.7, 68.1, 37.8, 36.8, 36.0, 35.0, 25.9, 17.2, 17.0, 8.8, –4.2, –4.8.

MS (ESI): *m*/*z* (%) = 331 (100) $[M + H]^+$, 199 (60).

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{38}NaO_3Si$: 353.2489; found: 353.2488.

(3*R*,4*R*,6*S*)-3-(*tert*-Butyldimethylsilyloxy)-6-[(4*S*,5*S*)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl]-4-methylhept-1-ene (19)

To a soln of diol **18** (500 mg, 1.5 mmol) in CH_2Cl_2 (10 mL) was added 4-$MeOC_6H_4CH(OMe)_2$ (0.5 mL, 3.0 mmol) and CSA (18 mg, 0.07 mmol). The mixture was stirred overnight and then washed with 10% aq $NaHCO_3$ (20 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried (Na_2SO_4) 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%); $[\alpha]_D^{25}$ –7.2 (*c* 1.00, $CHCl_3$).

IR (neat): 2956, 1517, 1247, 829, 775 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.40 (d, *J* = 9.0 Hz, 2 H), 6.86 (d, *J* = 9.0 Hz, 2 H), 5.79 (ddd, *J* = 17.0, 10.5, 6.0 Hz, 1 H), 5.39 (s, 1 H), 5.07 (dd, *J* = 17.0, 2.0 Hz, 1 H), 5.02 (dd, *J* = 10.5, 2.0 Hz, 1 H), 4.02–3.93 (m, 3 H), 3.80 (s, 3 H), 3.41 (dd, *J* = 9.5, 2.0 Hz, 1 H), 1.97–1.83 (m, 2 H), 1.77–1.68 (m, 2 H), 1.67–1.62 (m, 1 H), 1.15 (d, *J* = 7.0 Hz, 3 H), 0.85 (d, *J* = 6.5 Hz, 3 H), 0.83 (s, 9 H), 0.83 (d, *J* = 6.5 Hz, 3 H), –0.03 (s, 3 H), –0.038 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 159.7, 140.5, 131.8, 127.4, 114.2, 113.4, 101.7, 85.1, 74.1, 55.3, 37.1, 37.0, 32.3, 30.2, 25.8, 18.1, 16.2, 15.0, 11.0, –4.2, –4.9.

MS (ESI): *m*/*z* (%) = 449 (100) $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{45}O_4Si$: 449.3102; found: 449.3087.

(2*S*,3*S*,4*S*,6*R*,7*R*)-7-(*tert*-Butyldimethylsilyloxy)-3-(4-methoxybenzyloxy)-2,4,6-trimethylnon-8-en-1-ol (20)

To a soln of **19** (550 mg, 1.2 mmol) in CH_2Cl_2 (10 mL) at 0 °C, was added 20% soln of DIBAL-H in toluene (2.2 mL, 3.1 mmol) and the mixture was stirred for 30 min. The mixture was gradually warmed to r.t. and stirred for 3 h and then it was cooled to 0 °C and quenched by dropwise addition of EtOH (1 mL) and followed by sat. aq potassium sodium tartrate (20 mL). The soln was warmed to r.t. and stirred until 2 clear layers were observed. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried (Na_2SO_4) and filtered and the filtrate was concentrated under vacuum. The crude product was purified by flash column chromatography (silica gel, EtOAc–hexane, 12:88) to afford **20** as a colorless oil. Yield: 436 mg (79%); $[\alpha]_D^{25}$ +22.2 (*c* 0.50, $CHCl_3$).

IR (neat): 3419, 2956, 2929, 1514, 1247 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.26 (d, *J* = 8.5 Hz, 2 H), 6.86 (d, *J* = 8.5 Hz, 2 H), 5.79 (ddd, *J* = 17.0, 10.5, 6.5 Hz, 1 H), 5.10 (dd, *J* = 17.0, 1.2 Hz, 1 H), 5.06 (dd, *J* = 10.5, 1.2 Hz, 1 H), 4.57 (d, *J* = 11.0 Hz, 1 H), 4.39 (d, *J* = 10.5 Hz, 1 H), 3.96–3.93 (m, 1 H), 3.80 (s, 3 H), 3.54 (br s, 2 H), 3.33 (dd, *J* = 6.5, 3.0 Hz, 1 H), 2.08–2.04 (m, 1 H), 1.93–1.90 (m, 1 H), 1.73–1.66 (m, 3 H), 0.95 (d, *J* = 5.5 Hz, 3 H), 0.94 (d, *J* = 5.0 Hz, 3 H), 0.88 (d, *J* = 6.5 Hz, 3 H), 0.87 (s, 9 H), 0.02 (s, 3 H), 0.01 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 159.0, 139.9, 131.1, 129.1, 114.7, 113.7, 83.7, 76.4, 72.7, 67.4, 55.2, 37.2, 36.8, 36.4, 33.0, 25.9, 18.2, 16.8, 16.3, 11.5, –4.2, –4.9.

MS (ESI): *m*/*z* (%) = 451 (100) $[M + H]^+$, 319 (20).

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{26}H_{46}NaO_4Si$: 473.3068; found: 473.3063.

(2*R*,3*S*,4*S*,6*R*,7*R*)-7-(*tert*-Butyldimethylsilyloxy)-3-(4-methoxybenzyloxy)-2,4,6-trimethylnon-8-enal (21)

To a soln of **20** (500 mg, 1.1 mmol) in CH_2Cl_2 (10 mL) was added $PhI(OAc)_2$ (429 mg, 1.3 mmol) followed by the addition of TEMPO (10 mg, 0.05 equiv). The mixture was stirred for 2 h and then the reaction was quenched by the addition of sat. aq $Na_2S_2O_3$–sat. aq $NaHCO_3$ (5:1, 20 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and filtered and the filtrate was concentrated under vacuum. The crude product was purified by flash column chromatography (silica gel, EtOAc–hexane, 3:97) to afford **21** as a colorless oil. Yield: 470 mg (95%); $[\alpha]_D^{25}$ –0.66 (*c* 1.00, $CHCl_3$).

IR (neat): 2956, 2929, 1726, 1514, 1249 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.70 (d, *J* = 1.0 Hz, 1 H), 7.20 (d, *J* = 9.0 Hz, 2 H), 6.85 (d, *J* = 9.0 Hz, 2 H), 5.77 (ddd, *J* = 17.0, 10.0, 6.5 Hz, 1 H), 5.13–5.05 (m, 2 H), 4.42 (d, *J* = 11.0 Hz, 1 H), 4.40 (d, *J* = 11.0 Hz, 1 H), 3.95–3.92 (m, 1 H), 3.80 (s, 3 H), 3.68 (dd, *J* = 6.0, 3.0 Hz, 1 H), 2.56–2.53 (m, 1 H), 2.08–2.05 (m, 1 H), 1.71–1.58 (m, 3 H), 1.17 (d, *J* = 7.0 Hz, 3 H), 0.95 (d, *J* = 7.0 Hz, 3 H), 0.87 (d, *J* = 7.0 Hz, 3 H), 0.80 (s, 9 H), 0.01 (s, 3 H), –0.003 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 204.8, 159.1, 139.7, 130.6, 129.1, 114.9, 113.7, 81.1, 77.4, 72.4, 55.2, 48.5, 37.2, 36.2, 33.6, 25.9, 18.2, 16.8, 16.3, 8.7, –4.2, –4.9.

MS (ESI): *m*/*z* (%) = 471 (100) $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{26}H_{44}NaO_4Si$: 471.2915; found: 471.2907.

(2*R*,3*S*,4*S*,5*S*,6*S*,8*R*,9*R*)-1-[(*S*)-4-Benzyl-2-thioxothiazolidin-3-yl]-9-(*tert*-butyldimethylsilyloxy)-3-hydroxy-5-(4-methoxybenzyloxy)-2,4,6,8-tetramethylundec-10-en-1-one (22)

To a soln of **8** (265 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added $TiCl_4$ (0.11 mL, 1.0 mmol). The resulting orange slurry was stirred for 5 min, *i*-Pr_2NEt (0.14 mL, 1.0 mmol) was added (deep red) and the mixture was stirred for 20 min. Aldehyde **21** (450 mg, 1.00 mmol) in CH_2Cl_2 (2 mL) was added and the mixture was stirred at 0 °C for 1 h. The reaction was quenched by the addition of sat. aq NH_4Cl (10 mL), the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried (Na_2SO_4) and filtered and the filtrate was concentrated under vacuum. The crude product was purified by flash column chromatography (silica gel, EtOAc–hexane, 7:93) to afford aldol **22** as a bright yellow oil. Yield: 591 mg (83%); $[\alpha]_D^{25}$ –85.4 (*c* 0.50, $CHCl_3$).

IR (neat): 3512, 2954, 2929, 1691, 1514, 1249 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.27 (m, 5 H), 7.24 (d, *J* = 9.0 Hz, 2 H), 6.85 (d, *J* = 9.0 Hz, 2 H), 5.82 (ddd, *J* = 17.0, 10.5, 6.5 Hz, 1 H), 5.24–5.15 (m, 1 H), 5.10–5.03 (m, 2 H), 4.61 (d, *J* = 11.0 Hz, 1 H), 4.52 (t, *J* = 7.0 Hz, 1 H), 4.34 (d, *J* = 11.0 Hz, 1 H), 3.96–3.91 (m, 2 H), 3.78 (s, 3 H), 3.31–3.26 (m, 2 H), 3.21–3.18 (m, 2 H), 3.03 (dd, *J* = 13.0, 10.5 Hz, 1 H), 2.88 (d, *J* = 11.0 Hz, 1 H), 2.16–2.14 (m, 1 H), 1.72–1.59 (m, 4 H), 1.32 (d, *J* = 6.5 Hz, 3

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).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 200.7, 177.7, 159.1, 140.2, 136.3, 130.5, 129.4, 129.0, 128.9, 127.2, 114.7, 113.7, 86.1, 77.6, 76.4, 72.3, 68.6, 55.2, 42.1, 37.0, 36.8, 36.8, 36.6, 32.8, 32.1, 25.9, 18.2, 16.2, 16.1, 13.4, 8.6, –4.1, –4.8.

MS (ESI): *m*/*z* (%) = 714 (20) $[M + H]^+$, 560 (100).

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{39}H_{59}NaO_5SiS_2$: 736.3526; found: 736.3502.

(2*R*,3*S*,4*R*,5*S*,6*S*,8*R*,9*R*)-1-[(*S*)-4-Benzyl-2-thioxothiazolidin-3-yl)-3,9-bis(*tert*-butyldimethylsilyloxy)-5-(4-methoxybenzyloxy)-2,4,6,8-tetramethylundec-10-en-1-one (23)

To a soln of **22** (300 mg, 0.4 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added *i*-Pr_2NEt (0.18 mL, 1.0 mmol) followed by the dropwise addition of TBSOTf (0.12 mL, 0.5 mmol). The mixture was stirred at this temperature for 30 min, brought to up r.t. and then stirred overnight. The mixture was cooled and quenched by the addition sat. aq $NaHCO_3$ (10 mL). It was then diluted with CH_2Cl_2 (10 mL), the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) 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 **23** as a bright yellow oil. Yield: 281 mg (81%); $[\alpha]_D^{25}$ –66.8 (*c* 0.35, $CHCl_3$).

IR (neat): 2954, 2927, 1691, 1249 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): 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 (ddd, *J* = 17.0, 10.5, 6.5 Hz, 1 H), 5.18–5.06 (m, 3 H), 4.55–4.53 (m, 1 H), 4.50 (d, *J* = 11.0 Hz, 1 H), 4.42 (d, *J* = 11.0 Hz, 1 H), 4.01 (dd, *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* = 6.5 Hz, 3 H), 0.99 (d, *J* = 7.0 Hz, 3 H), 0.95 (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).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 200.5, 177.3, 158.8, 140.3, 136.6, 131.6, 129.4, 128.8, 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) $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{45}H_{73}NNaO_5S_2Si_2$: 850.4359; found: 850.4366.

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

To a soln of thione **23** (220 mg, 0.265 mmol) in a mixture of THF and H_2O (4:1, 5 mL) at 0 °C was added 30% aq H_2O_2 (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%); $[\alpha]_D^{25}$ +1.6 (*c* 1.00, $CHCl_3$).

IR (neat): 2954, 2929, 1707, 1514, 1249, 835, 775 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26 (d, *J* = 8.5 Hz, 2 H), 6.79 (d, *J* = 8.5 Hz, 2 H), 5.74 (ddd, *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), 0.905 (s, 9 H), 0.88 (s, 9 H), 0.02 (s, 6 H), 0.001 (s, 6 H).

^{13}C NMR (50 MHz, $CDCl_3$): 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) $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{35}H_{65}O_6Si_2$: 637.0687; found: 637.0661.

(2*S*,3*R*)-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 CH_2Cl_2 (75 mL) at 0 °C was added $TiCl_4$ (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 NH_4Cl (75 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 75 mL). The combined organic layers were dried (Na_2SO_4) and filtered. The filtrate was concentrated under vacuum. The crude product was purified by flash column chromatography (silica gel, EtOAc–hexane, 10:90) to afford **24** as a bright yellow oil. Yield: 5.18 g (85%); $[\alpha]_D^{25}$ +78.0 (*c* 1.00, $CHCl_3$).

IR (neat): 3402, 2962, 1693, 1165 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.25 (m, 5 H), 5.37–5.32 (m, 1 H), 4.54–4.48 (m, 1 H), 3.86–3.82 (m 1 H), 3.42–3.37 (m, 1 H), 3.22 (dd, *J* = 13.0, 4.0 Hz, 1 H), 3.04 (dd, *J* = 13.0, 11.0 Hz, 1 H), 2.89 (d, *J* = 11.0 Hz, 1 H), 2.62 (br s, 1 H), 1.60–1.49 (m, 1 H), 1.48–1.41 (m, 1 H), 1.24 (d, *J* = 7.0 Hz, 3 H), 0.95 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 201.3, 178.4, 136.3, 129.4, 128.9, 127.3, 73.7, 68.8, 42.8, 36.7, 32.0, 27.2, 10.3, 10.2.

MS (ESI): *m*/*z* (%) = 324 (85) $[M + H]^+$, 209 (100).

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{21}NNaO_2S_2$: 346.0909; found: 346.0911.

(2*S*,3*R*)-1-[(*S*)-4-Benzyl-2-thioxothiazolidin-3-yl]-3-(*tert*-butyldimethylsilyloxy)-2-methylpentan-1-one (25)

To a soln of **24** (5.1 g, 15.8 mmol) in CH_2Cl_2 (75 mL) at 0 °C was added 2,6-lutidine (2.75 mL, 23.7 mmol) and TBSOTf (4.35 mL, 18.9 mmol) sequentially. The mixture was stirred for 1 h and then the reaction was quenched by the addition of sat. aq $NaHCO_3$ (50 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried (Na_2SO_4) 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 **25** as a bright yellow oil. Yield: 6.27 g (91%); $[\alpha]_D^{25}$ +23.4 (*c* 1.00, $CHCl_3$).

IR (neat): 1691, 1253, 1163, 835 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.27 (m, 5 H), 5.22–5.16 (m, 1 H), 4.61–4.55 (m, 1 H), 3.99–3.95 (m, 1 H), 3.34–3.26 (m, 2 H), 3.04 (dd, *J* = 13.0, 11.0 Hz, 1 H), 2.88 (d, *J* = 11.0 Hz, 1 H), 1.61–1.47 (m, 2 H), 1.22 (d, *J* = 7.0 Hz, 3 H), 0.88 (s, 9 H), 0.87 (t, *J* = 3.0 Hz, 3 H), 0.05 (s, 3 H), 0.02 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 200.9, 176.9, 136.7, 129.5, 128.9, 127.2, 74.9, 69.5, 43.7, 36.5, 31.9, 28.0, 25.8, 18.0, 12.0, 9.4, –4.1, –4.7.

MS (ESI): *m*/*z* (%) = 438 (100) $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{36}NO_2S_2Si$: 438.7438; found: 438.7392.

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

To a soln of thione **25** (6.0 g, 13.7 mmol) in Et_2O (50 mL) at 0 °C was added, H_2O (0.62 mL, 34.3 mmol, 2.5 equiv) and $LiBH_4$ (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 NH_4Cl (50 mL) and extracted with Et_2O (3 × 100 mL). The organic layer was dried (Na_2SO_4) 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%); $[\alpha]_D^{25}$ +1.4 (*c* 1.00, $CHCl_3$).

IR (neat): 3348, 2958, 2929, 1253 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): 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* = 4.0 Hz, 3 H), 0.81 (d, *J* = 7.5 Hz, 3 H), 0.09 (s, 3 H), 0.07 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): 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) $[M + H]^+$.

(2*S*,3*R*)-3-(*tert*-Butyldimethylsilyloxy)-2-methylpentanal (27)[16]

To a soln of **26** (300 mg, 1.3 mmol) in CH_2Cl_2 (5 mL) was added $PhI(OAc)_2$ (499 mg, 1.5 mmol) followed by the addition of TEMPO (10 mg, 0.05 equiv). The mixture was stirred for 2 h and then the reaction was quenched by the addition of sat. aq $Na_2S_2O_3$–sat. aq $NaHCO_3$ (5:1, 10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) 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%); $[\alpha]_D^{25}$ +54.2 (*c* 0.7, $CHCl_3$).

(3*R*,4*R*)-4-(*tert*-Butyldimethylsilyloxy)-3-methylhex-1-ene (7)

To a soln of aldehyde **27** (200 mg, 0.9 mmol) in THF (5 mL) at 0 °C was added 0.5 M Tebbe's reagent (1.7 mL, 1.0 mmol) dropwise. The resulting dark-brown mixture was allowed to warm to r.t. for 10 min, diluted with Et_2O (10 mL), and aq 0.1 M NaOH (5 drops) was added. Some bubbling was observed at this point, Na_2SO_4 added, and the slurry was filtered through a short pad of silica gel. The filtrate was concentrated under vacuum and purified by flash column chromatography (silica gel, EtOAc–hexane, 2:98) to afford **7** as a colorless oil. Yield: 90 mg (46%); $[\alpha]_D^{25}$ +24.4 (*c* 0.50, $CHCl_3$).

IR (neat): 2956, 2927, 1462, 1251, 771 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.81 (ddd, *J* = 18.0, 10.5, 7.5 Hz, 1 H), 4.98 (dd, *J* = 10.5, 1.6 Hz, 1 H), 4.95–4.93 (m, 1 H), 3.47–3.42 (m, 1 H), 2.31–2.26 (m, 1 H), 1.46–1.37 (m, 2 H), 0.94 (d, *J* = 7.0 Hz, 3 H), 0.87 (s, 9 H), 0.86 (t, *J* = 2.0 Hz, 3 H), 0.02 (s, 6 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 141.8, 113.6, 76.4, 42.3, 26.5, 25.9, 15.0, 9.5, –4.3, –4.4.

MS (ESI): *m*/*z* (%) = 229 (100) $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{29}OSi$: 229.4535; found: 229.4482.

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