Stereoselective Synthesis of the C10–C18 Fragment of Iriomoteolide-3a

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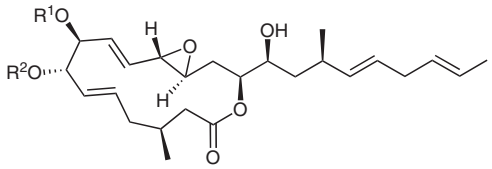
Abstract: An efficient synthesis of the highly stereogenic centered C10–C18 fragment of iriomoteolide-3a has been accomplished. Key steps include Sharpless asymmetric dihydroxylation and epoxidation for generation of the desired stereocenters.

Key words: macrolide, total synthesis, iriomoteolide-3a, *ortho*-Claisen rearrangement, Sharpless dihydroxylation

In 2008, Tsuda and co-workers isolated a potent cytotoxic macrolide, iriomoteolide-3a (**1**, Figure 1), from a marine benthic dinoflagellate *Amphidinium* sp. (strain HYA024), which was monoclonally separated from sea sand collected off Iriomote Island, Japan.[1] Iriomoteolide-3a (**1**) is a 15-membered macrolide having a novel carbon framework comprising eight stereogenic centers including an allyl epoxide, four hydroxy groups and two methyl branches. Compound **1** represents a unique and novel 15-membered macrolide class compared to the other known 15-membered macrolides. Further, the initial *in vitro* screening showed that iriomoteolide-3a (**1**) and its 7,8-*O*-isopropylidene derivative **2** (Figure 1) exhibit potent cytotoxicity against human B lymphocyte DG-75 and Raji cells in the low nanomolar range. The unique structural features of iriomoteolide-3a coupled with its potent cytotoxicity have attracted the attention of synthetic organic chemists. In 2009, Nevado and co-workers reported the first total synthesis of **1** along with biological evaluation of its analogues.[2] At the same time, we demonstrated the synthesis of the macrocyclic core of iriomoteolide-3a.[3] Later, the total synthesis of 7,8-*O*-isopropylidene iriomoteolide-3a was accomplished by Zhao and co-workers,[4] while synthesis of the C1–C9 fragment of **2** has been reported by Chang.[5]



$R^1 = R^2 = H$, iriomoteolide-3a (**1**)

$R^1–R^2 = CMe_2$, 7,8-*O*-isopropylidene derivative **2**

Figure 1 Structure of iriomoteolide-3a and its 7,8-*O*-isopropylidene derivative

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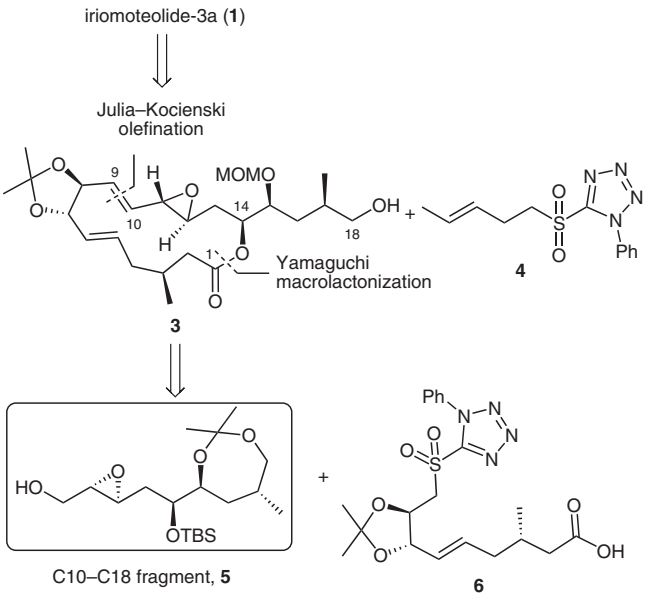
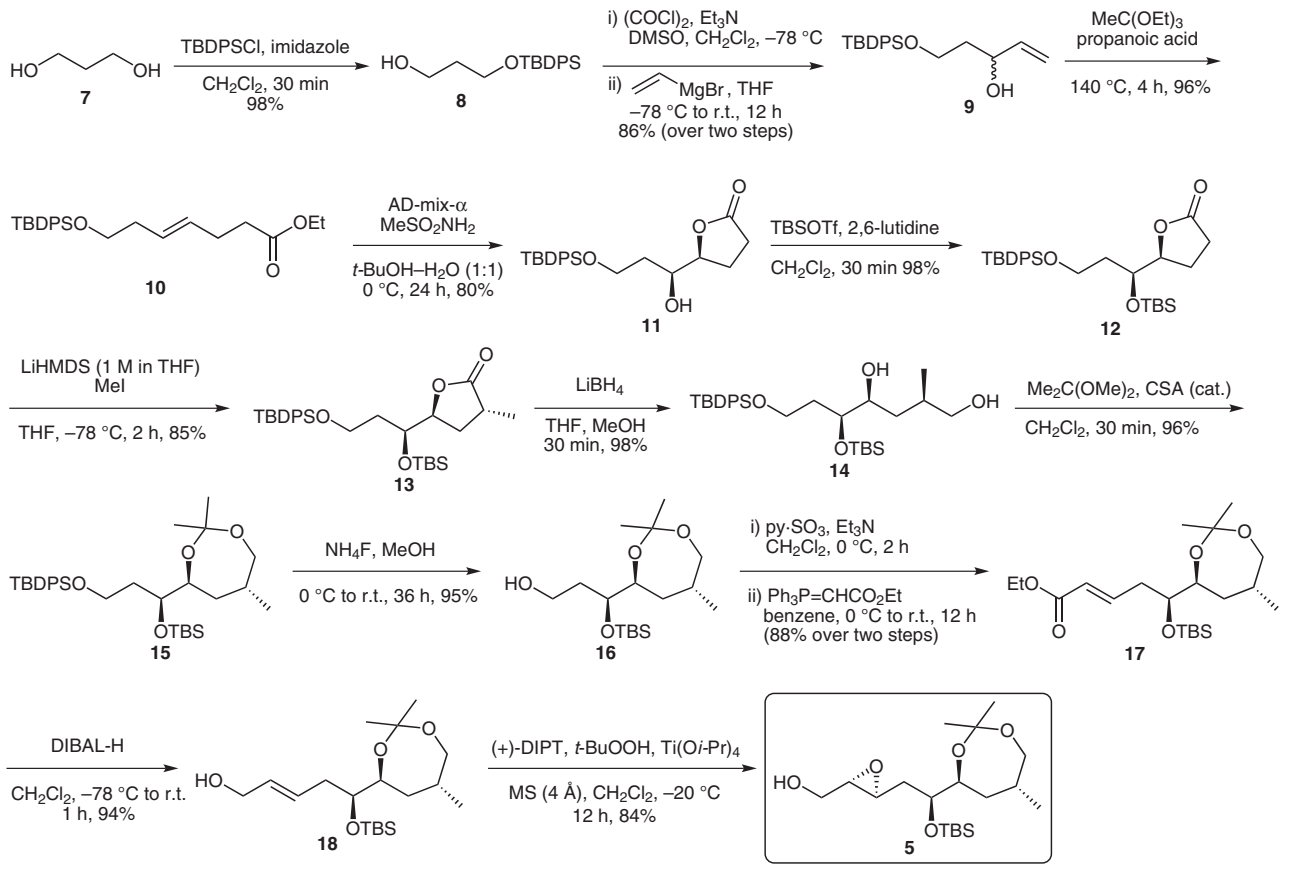
In continuation of our work on the synthesis of macrolides, including iriomoteolide-3a,[3,6] we initiated an alternative strategy towards various analogues of **1** for biological evaluation. In this paper, we report the synthesis of the C10–C18 fragment, a key subunit of iriomoteolide-3a (**1**) having five stereocenters.

As shown in Scheme 1, our synthetic strategy for iriomoteolide-3a is convergent and involves a late-stage assembly of macrocyclic core **3** and side chain **4**. The macrocycle **3** can be obtained from epoxy subunit **5** and sulfone **6** through a Julia–Kocienski olefination (C9–C10 bond formation) followed by Yamaguchi macrolactonization. The formation of the C9–C10 bond in all earlier approaches was accomplished using ring-closing metathesis.



Scheme 1 Retrosynthetic analysis of iriomoteolide-3a

The synthesis of epoxy segment **5** (C10–C18 fragment) was carried out as shown in Scheme 2, starting from propane-1,3-diol (**7**). Monoprotection of diol **7** as the *tert*-butyldiphenylsilyl ether provided compound **8** in 98% yield. Swern oxidation of alcohol to aldehyde followed by Grignard reaction with vinylmagnesium bromide afforded the allyl alcohol **9** in 86% yield over two steps.[7] Treatment of **9** with triethyl orthoacetate in the presence of propanoic acid at 140 °C for four hours gave the γ,δ-unsaturated ester **10** via *ortho*-Claisen rearrangement.[8] At this stage, the requisite chiral dihydroxy functionality on C14–C15 was achieved using Sharpless asymmetric dihydroxylation.



Scheme 2 Synthesis of the C10–C18 fragment **5**

Thus, exposure of **10** to AD-mix-α in the presence of methanesulfonamide provided the hydroxy γ-lactone **11** through a one-pot dihydroxylation followed by in situ lactonization.[9] The enantiomeric purity of this lactone **11** was confirmed at a later stage (intermediate **13**).[10] The free secondary alcohol of **11** was protected as the *tert*-butyldimethylsilyl ether **12**. Then, the introduction of the C17-methyl group was accomplished through a stereoselective methylation of lactone **12** under lithium hexamethyldisilazide/iodomethane conditions at –78 °C to afford exclusively **13** in 85% yield,[11] which was confirmed by NOE studies.[10,12]

Reduction of lactone **13** using lithium borohydride provided the 1,4-diol **14** in 98% yield, which was protected as the seven-membered acetonide **15** under 2,2-dimethoxypropane/10-camphorsulfonic acid reaction conditions.[13] Next, the *tert*-butyldiphenylsilyl group of **15** was selectively deprotected to alcohol **16** using ammonium fluoride in methanol (95% yield).[14] The next step involved the two-carbon extension by employing Parikh–Doering oxidation (py·SO_3, CH_2Cl_2)[15] to the corresponding aldehyde followed by a Wittig homologation with $Ph_3P{=}CHCO_2Et$ to obtain the α,β-unsaturated ester **17** in 88% yield over two steps as the *E*-isomer (>98%). Reduction of the ester **17** using diisobutylaluminum hydride at –78 °C afforded the allylic alcohol **18** in 94% yield. The desired chiral epoxide was introduced under Sharpless asymmetric epoxidation reaction conditions [(+)-DIPT, Ti(O*i*-Pr)$_4$, *t*-BuOOH, CH_2Cl_2, –20 °C][16] to produce fragment **5** in 84% yield with good stereoselectivity. Epoxide fragment **5** was fully characterized by mass spectrometry and ^{1}H NMR, ^{13}C NMR and IR spectroscopy.

In summary, asymmetric synthesis of the protected C10–C18 fragment having five stereogenic carbons of iriomoteolide-3a has been accomplished. Sharpless asymmetric dihydroxylation, stereoselective methylation and Sharpless asymmetric epoxidation reactions are the key steps to obtain the requisite stereocenters of the fragment.

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solvent at 300 and 75 MHz, respectively, on a Bruker Avance spectrometer at r.t. The chemical shifts (δ) are reported in ppm on a scale downfield from TMS as internal standard. Coupling constants *J* are in hertz (Hz). FTIR spectra were recorded as KBr thin films on a Perkin-Elmer 683 spectrophotometer. High resolution mass spectra (HRMS) were recorded on a quadrupole time-of-flight (Q-TOF) mass spectrometer (Agilent Technologies, classic G6510A) equipped with an ESI source [voltage: 80 V; capillary at 3000–3500 V; skimmer at 60 V; nitrogen as drying (300 °C; 9 L/min) and nebulizing (45 psi) gas]; *m*/*z* ratios are reported as values in atomic mass units. All the reagents and solvents were reagent grade and used without further purification, unless specified otherwise. Technical grade EtOAc and hexanes used for column chromatography were distilled prior to use. Column chromatography was carried out using silica gel (60–120 mesh) packed in glass columns. All reactions were performed under an atmosphere of nitrogen in flame-dried or oven-dried glassware with magnetic stirring.

5-(*tert*-Butyldiphenylsilyloxy)pent-1-en-3-ol (9)
A soln of DMSO (9.0 mL, 127.3 mmol) in CH_2Cl_2 (50 mL) was added to a soln of oxalyl chloride (5.51 mL, 63.6 mmol) in CH_2Cl_2 (50 mL) cooled at –78 °C. After 5 min, a soln of **8** (10.0 g, 31.8 mmol) in CH_2Cl_2 (83 mL) was added dropwise to the cold mixture over 5 min. After 20 min, Et_3N (17.7 mL, 127.3 mmol) was added, and the mixture was allowed to reach r.t. and poured into H_2O (125 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL). The collected organic phases were washed with brine (50 mL), dried (Na_2SO_4) and concentrated to give the crude aldehyde as a yellow oil, which was used in the next step without further purification.

To a soln of the crude aldehyde in distilled THF (150 mL) at –78 °C was added 1 M vinylmagnesium bromide in THF (38.1 mL, 38.1 mmol), and the mixture was stirred at that same temperature for 1 h. The mixture was further stirred overnight while the solution was allowed to warm to r.t. Sat. aq NH_4Cl (150 mL) was added into the white turbid solution chilled in an ice bath. The aqueous phase was extracted with EtOAc (3 × 100 mL) and the combined organic extracts were washed with H_2O (50 mL) and brine (2 × 50 mL), dried (Na_2SO_4) and concentrated under reduced pressure to give a yellow syrup. Purification by flash column chromatography (hexanes–EtOAc, 15:1) afforded **9** (9.30 g, 86%) as a slightly yellow oil.

IR (KBr): 3444, 2930, 2857, 1427, 1390, 1111, 923, 822 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.69–7.63 (m, 4 H), 7.44–7.33 (m, 6 H), 5.91–5.80 (m, 1 H), 5.30 (dt, *J* = 11.3, 17.1 Hz, 1 H), 5.12 (dt, *J* = 1.8, 10.3 Hz, 1 H), 4.42 (dd, *J* = 5.4, 11.3 Hz, 1 H), 3.94–3.78 (m, 2 H), 3.05 (br s, 1 H), 1.83–1.73 (m, 2 H), 1.07 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.5, 135.4, 132.9, 129.7, 127.7, 114.2, 72.0, 62.5, 38.2, 26.7, 18.9.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{21}H_{28}O_2SiNa$: 363.1751; found: 363.1738.

Ethyl (*E*)-7-(*tert*-Butyldiphenylsilyloxy)hept-4-enoate (10)
A mixture of **9** (5.0 g, 14.7 mmol), triethyl orthoacetate (24.3 mL, 132.3 mmol) and a catalytic amount of propanoic acid (1.0 mL, 13.5 mmol) was refluxed for 4 h, followed by the removal of triethyl orthoacetate. The residues were dissolved in EtOAc (80 mL) and the mixture was washed with brine (2 × 30 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexanes–EtOAc, 25:1) to afford **10** (5.78 g, 96%) as a yellow syrup.

IR (KBr): 2930, 2857, 1737, 1427, 1159, 1111, 1040, 823 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.69–7.59 (m, 4 H), 7.43–7.30 (m, 6 H), 5.47–5.40 (m, 2 H), 4.09 (q, *J* = 7.5 Hz, 2 H), 3.63 (t, *J* = 6.7 Hz, 2 H), 2.36–2.16 (m, 6 H), 1.23 (t, *J* = 7.5 Hz, 3 H), 1.03 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.1, 135.5, 133.9, 130.1, 129.4, 127.8, 127.5, 63.7, 60.1, 35.9, 34.2, 27.9, 26.8, 19.1, 14.2.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{25}H_{34}O_3SiNa$: 433.2561; found: 433.2560.

(*S*)-5-[(*S*)-3-(*tert*-Butyldiphenylsilyloxy)-1-hydroxypropyl]dihydrofuran-2(3*H*)-one (11)
Into a 250-mL round-bottom flask were added *t*-BuOH (29 mL), H_2O (29 mL), AD-mix-α (8.19 g, 1.4 g/mmol) and methanesulfonamide (556 mg, 5.8 mmol). The mixture was stirred at r.t. for 5 min and then cooled to 0 °C. To this cooled solution was added compound **10** (2.4 g, 5.8 mmol), and the mixture was stirred for 24 h at 0 °C. The reaction was quenched with sat. aq Na_2SO_3 soln at r.t. The mixture was diluted with EtOAc (50 mL) and, after separation of the layers, the aqueous layer was further extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine (40 mL) and dried (Na_2SO_4). The crude mixture was purified by flash column chromatography (20→30% EtOAc in hexanes) to give **11** (1.87 g, 80%) as a colorless oil.

$[\alpha]_D^{25}$ +20.1 (*c* 1.0, $CHCl_3$).

IR (KBr): 3458, 1773, 1219, 1111, 918, 772 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.69–7.60 (m, 4 H), 7.45–7.32 (m, 6 H), 4.38 (dt, *J* = 6.7, 3.0 Hz, 1 H), 3.95–3.77 (m, 3 H), 3.10 (br s, 1 H), 2.70–2.56 (m, 1 H), 2.50–2.35 (m, 1 H), 2.27–2.15 (m, 2 H), 1.98–1.82 (m, 1 H), 1.74–1.61 (m, 1 H), 1.05 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.6, 135.5, 133.0, 129.9, 127.8, 82.7, 72.6, 62.1, 34.6, 28.5, 26.8, 23.9, 19.0.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{23}H_{30}O_4SiNa$: 421.2078; found: 421.2101.

(*S*)-5-[(*S*)-2,2,3,3,10,10-Hexamethyl-9,9-diphenyl-4,8-dioxa-3,9-disilaundecan-5-yl]dihydrofuran-2(3*H*)-one (12)
To a cooled (0 °C) soln of hydroxy lactone **11** (3.0 g, 7.6 mmol) in CH_2Cl_2 (25 mL) were added TBSOTf (2.11 mL, 9.20 mmol) and 2,6-lutidine (2.22 mL, 19.2 mmol). The mixture was stirred at r.t. for 30 min and was then diluted with CH_2Cl_2 (15 mL). The organic phase was washed with sat. aq $NaHCO_3$ (20 mL) and brine (15 mL), dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (2→5% EtOAc in hexanes) to give the silylated lactone **12** (3.85 g, 98%) as a colorless oil.

$[\alpha]_D^{25}$ +10.2 (*c* 2.0, $CHCl_3$).

IR (KBr): 2956, 2889, 1782, 1470, 1255, 1110, 704 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.60–7.50 (m, 4 H), 7.39–7.21 (m, 6 H), 4.35 (dt, *J* = 6.7, 2.2 Hz, 1 H), 3.85 (q, *J* = 6.0 Hz, 1 H), 3.71 (t, *J* = 6.7 Hz, 2 H), 2.49–2.24 (m, 2 H), 2.16–2.01 (m, 1 H), 1.92–1.53 (m, 3 H), 1.00 (s, 9 H), 0.81 (s, 9 H), 0.05 (s, 3 H), 0.00 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.1, 135.4, 133.4, 129.6, 127.6, 81.7, 71.4, 59.9, 35.3, 28.5, 26.8, 25.7, 23.8, 19.1, 17.9, –4.5, –4.6.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{29}H_{44}O_4Si_2Na$: 535.2800; found: 535.2805.

(3*R*,5*S*)-5-[(*S*)-2,2,3,3,10,10-Hexamethyl-9,9-diphenyl-4,8-dioxa-3,9-disilaundecan-5-yl]-3-methyldihydrofuran-2(3*H*)-one (13)
To a stirred soln of lactone **12** (2.0 g, 3.90 mmol) in THF (20 mL) at –78 °C was added 1 M LiHMDS in THF (4.6 mL, 4.60 mmol). After 1 h, MeI (0.79 mL, 15.6 mmol) was added and the reaction mixture was stirred for an additional 1 h at –78 °C. The reaction was quenched with sat. aq NH_4Cl (20 mL) and the mixture was extracted with EtOAc (2 × 20 mL). The organic layer was dried (Na_2SO_4) and concentrated, and the crude product was purified by flash column chromatography (2→5% EtOAc in hexanes) to afford **13** (1.77 g, 85%) as a colorless liquid.

$[\alpha]_D^{25}$ +8.5 (*c* 1.0, $CHCl_3$).

IR (KBr): 2956, 2858, 1778, 1467, 1180, 838, 704 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.66–7.60 (m, 4 H), 7.45–7.32 (m, 6 H), 4.42–4.34 (m, 1 H), 3.91 (q, *J* = 6.0 Hz, 1 H), 3.76 (t, *J* = 6.0 Hz, 2 H), 2.72–2.56 (m, 1 H), 2.24–2.12 (m, 1 H), 1.90–1.60 (m, 3 H), 1.24 (d, *J* = 7.5 Hz, 3 H), 1.06 (s, 9 H), 0.87 (s, 9 H), 0.10 (s, 3 H), 0.06 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 180.2, 135.5, 133.5, 129.7, 127.6, 79.0, 71.5, 60.0, 35.5, 34.2, 32.1, 26.8, 25.7, 19.1, 17.9, 16.4, –4.5, –4.6.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{30}H_{46}O_4Si_2Na$: 549.2827; found: 549.2809.

(2*R*,4*S*,5*S*)-5-(*tert*-Butyldimethylsilyloxy)-7-(*tert*-butyldiphenylsilyloxy)-2-methylheptane-1,4-diol (14)
To a stirred soln of lactone **13** (4.6 g, 8.7 mmol) in THF (42 mL) at 0 °C were sequentially added MeOH (0.35 mL) and $LiBH_4$ (230 mg, 10.4 mmol). After 30 min, the reaction was quenched with sat. aq NH_4Cl (50 mL), and the mixture was extracted with Et_2O (2 × 40 mL). The extracts were dried (Na_2SO_4) and concentrated under reduced pressure, and the crude product was purified by column chro-

matography (10→20% EtOAc in hexanes) to afford **14** (4.54 g, 98%) as a colorless oil.

$[\alpha]_D^{25}$ +1.2 (*c* 2.0, $CHCl_3$).

IR (KBr): 3299, 2954, 2931, 2858, 1466, 1249, 1086, 835, 775 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.69–7.57 (m, 4 H), 7.46–7.32 (m, 6 H), 3.81–3.65 (m, 3 H), 3.65–3.57 (m, 1 H), 3.55–3.38 (m, 2 H), 2.66 (br s, 1 H), 2.46 (br s, 1 H), 1.98–1.76 (m, 2 H), 1.71–1.60 (m, 1 H), 1.57–1.36 (m, 2 H), 1.06 (s, 9 H), 0.94 (d, *J* = 6.5 Hz, 3 H), 0.88 (s, 9 H), 0.09 (s, 3 H), 0.05 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.4, 133.4, 129.6, 127.6, 72.7, 70.2, 67.4, 60.3, 37.4, 36.3, 32.4, 26.7, 25.8, 19.0, 18.0, 17.0, –4.3, –4.6.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{30}H_{51}O_4Si_2$: 531.3320; found: 531.3342.

(*S*)-2,2,3,3,10,10-Hexamethyl-9,9-diphenyl-5-[(4*S*,6*R*)-2,2,6-trimethyl-1,3-dioxepan-4-yl]-4,8-dioxa-3,9-disilaundecane (15)

To a soln of diol **14** (2.2 g, 4.15 mmol) in CH_2Cl_2 (20 mL) at 0 °C were added 2,2-dimethoxypropane (1.01 mL, 8.29 mmol) and CSA (48 mg, 0.20 mmol), and the mixture was stirred at r.t. for 30 min. Then, the reaction was quenched by adding sat. aq NH_4Cl soln and the resulting mixture was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated, and the residue was purified by column chromatography (2→5% EtOAc in hexanes) to afford acetonide **15** (2.28 g, 96%) as a colorless oil.

$[\alpha]_D^{25}$ –25.2 (*c* 2.0, $CHCl_3$).

IR (KBr): 2931, 2858, 1465, 1251, 1103, 999, 833, 703 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.68–7.60 (m, 4 H), 7.42–7.29 (m, 6 H), 3.91–3.63 (m, 5 H), 3.36–3.27 (m, 1 H), 1.93–1.72 (m, 2 H), 1.57–1.33 (m, 3 H), 1.32–1.22 (m, 6 H), 1.05 (s, 9 H), 1.03 (d, *J* = 6.0 Hz, 3 H), 0.85 (s, 9 H), 0.07 (s, 3 H), 0.00 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.5, 133.9, 129.4, 127.5, 100.3, 70.2, 69.6, 66.1, 60.9, 34.2, 33.6, 30.7, 26.8, 25.8, 25.0, 24.9, 19.2, 17.8, 16.8, –4.2, –4.8.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{33}H_{54}O_4Si_2Na$: 593.3453; found: 593.3480.

(*S*)-3-(*tert*-Butyldimethylsilyloxy)-3-[(4*S*,6*R*)-2,2,6-trimethyl-1,3-dioxepan-4-yl]propan-1-ol (16)

To a cooled (0 °C) stirred soln of **15** (2.45 g, 4.29 mmol) in MeOH (15 mL) was added NH_4F (1.5 g, 42.1 mmol), and the mixture was stirred for 36 h. The reaction was quenched with sat. aq $NaHCO_3$, and the mixture was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (5→10% EtOAc in hexanes) to provide **16** (1.32 g, 95%) as a colorless oil; **15** (50 mg) was recovered.

$[\alpha]_D^{25}$ –25.0 (*c* 1.0, $CHCl_3$).

IR (KBr): 3415, 2935, 1466, 1381, 1219, 1165, 1071, 835, 775 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.90–3.54 (m, 5 H), 3.42–3.30 (m, 1 H), 2.43 (br s, 1 H), 1.95–1.77 (m, 2 H), 1.68–1.37 (m, 3 H), 1.31 (s, 6 H), 1.03 (d, *J* = 6.0 Hz, 3 H), 0.90 (s, 9 H), 0.09 (s, 3 H), 0.08 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 100.6, 72.9, 69.8, 66.2, 60.3, 34.6, 33.7, 30.6, 25.7, 25.0, 24.6, 17.8, 16.7, –4.4, –4.9.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{36}O_4SiNa$: 355.2275; found: 355.2290.

Ethyl (*E*,*S*)-5-(*tert*-Butyldimethylsilyloxy)-5-[(4*S*,6*R*)-2,2,6-trimethyl-1,3-dioxepan-4-yl]pent-2-enoate (17)

To a soln of alcohol **16** (1.5 g, 4.51 mmol) in CH_2Cl_2–DMSO (3:1 v/v, 30 mL) at 0 °C were added Et_3N (3.16 mL, 22.5 mmol) and py·SO_3 (3.59 g, 22.5 mmol). After being stirred at 0 °C for 2 h, the reaction mixture was diluted with Et_2O (30 mL), washed with H_2O (20 mL) and brine (20 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residual crude aldehyde was used in the next step without further purification.

To a soln of the crude aldehyde in benzene (10 mL) at 0 °C was added $Ph_3P{=}CHCO_2Et$ (3.10 g, 9.03 mmol) and the reaction mixture was allowed to warm to r.t. After being stirred at r.t. for 12 h, the reaction mixture was concentrated under reduced pressure. Purification by flash chromatography (2→3% EtOAc in hexanes) afforded α,β-unsaturated ester **17** (1.59 g, 88%) as a colorless oil.

$[\alpha]_D^{25}$ –60.2 (*c* 0.5, $CHCl_3$).

IR (KBr): 2928, 2857, 1718, 1654, 1167, 1042, 774 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.01–6.86 (m, 1 H), 5.80 (d, *J* = 15.4 Hz, 1 H), 4.16 (q, *J* = 7.1 Hz, 2 H), 3.88–3.73 (m, 2 H), 3.71–3.59 (m, 1 H), 3.40–3.27 (m, 1 H), 2.54–2.34 (m, 1 H), 2.28–2.10 (m, 1 H), 1.92–1.76 (m, 1 H), 1.63–1.20 (m, 11 H), 1.01 (d, *J* = 6.0 Hz, 3 H), 0.88 (s, 9 H), 0.06 (s, 3 H), 0.02 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.6, 146.8, 123.3, 100.5, 73.5, 69.7, 65.9, 59.7, 34.6, 34.0, 30.9, 26.0, 25.2, 25.0, 18.1, 17.0, 14.5, –4.1, –4.4.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{21}H_{40}O_5SiNa$: 423.2537; found: 423.2543.

(*E*,*S*)-5-(*tert*-Butyldimethylsilyloxy)-5-[(4*S*,6*R*)-2,2,6-trimethyl-1,3-dioxepan-4-yl]pent-2-en-1-ol (18)

To a stirred soln of conjugated ester **17** (1.2 g, 3.0 mmol) in CH_2Cl_2 (15 mL) cooled to –78 °C was added a 20% soln of DIBAL-H in toluene (4.26 mL, 6.0 mmol) dropwise. The solution was stirred at –78 °C for 1 h, and the reaction was quenched by the addition of sat. aq potassium sodium tartrate soln (20 mL). Then, the mixture was warmed to r.t. and filtered through a pad of Celite®, and the residue was washed with sat. aq NaCl. The resulting mixture was extracted with CH_2Cl_2 (25 mL). The organic extract was concentrated to obtain the crude product, which was purified by column chromatography (5→10% EtOAc in hexanes) to give **18** (1.0 g, 94%) as a colorless oil.

$[\alpha]_D^{25}$ –34.0 (*c* 1.0, $CHCl_3$).

IR (KBr): 3464, 2930, 2854, 1218, 1075, 970, 834, 772 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.78–5.58 (m, 2 H), 4.05 (q, *J* = 4.5 Hz, 2 H), 3.89–3.69 (m, 2 H), 3.63–3.52 (m, 1 H), 3.37–3.27 (m, 1 H), 2.36–2.24 (m, 1 H), 2.13–1.98 (m, 1 H), 1.90–1.75 (m, 1 H), 1.60–1.35 (m, 2 H), 1.29 (s, 6 H), 1.01 (d, *J* = 6.7 Hz, 3 H), 0.89 (s, 9 H), 0.06 (s, 3 H), 0.02 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 131.0, 130.4, 100.4, 74.0, 69.9, 66.0, 63.7, 34.8, 34.2, 30.7, 25.8, 25.0, 24.9, 17.9, 16.8, –4.2, –4.5.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{38}O_4SiNa$: 381.2432; found: 381.2439.

[(2*S*,3*S*)-3-{(*S*)-2-(*tert*-Butyldimethylsilyloxy)-2-[(4*S*,6*R*)-2,2,6-trimethyl-1,3-dioxepan-4-yl]ethyl}oxiran-2-yl]methanol (5)

To a stirred mixture of powdered molecular sieves (4 Å, 4.0 g) and $Ti(O\textit{i}\text{-}Pr)_4$ (0.083 mL, 0.27 mmol) in CH_2Cl_2 (10 mL) cooled at –20 °C was added (+)-DIPT (0.22 mL, 0.94 mmol). The mixture was stirred at –20 °C for 10 min and a soln of allylic alcohol **18** (1.4 g, 3.9 mmol) in CH_2Cl_2 (12 mL) and 4 M *t*-BuOOH in toluene (3.8 mL, 15.6 mmol) were added successively. The resulting mixture was stirred at –20 °C for 12 h, then the reaction was quenched with H_2O (0.02 mL) and 20% aq NaOH (0.015 mL). The mixture was stirred at r.t. for 45 min, then the organic layer was separated and the reaction mixture was filtered. The aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL). The organic layer and the extracts were

combined, washed with brine (25 mL), dried (Na_2SO_4) and concentrated. The residual oil was purified by column chromatography (10→15% EtOAc in hexanes) to give **5** (1.22 g, 84%) as a colorless oil.

$[\alpha]_D^{25}$ –55.5 (*c* 1.0, $CHCl_3$).

IR (KBr): 3230, 2930, 2858, 1378, 1219, 1083, 836, 774 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.92–3.69 (m, 4 H), 3.60–3.46 (m, 1 H), 3.36–3.22 (m, 1 H), 3.05–2.98 (m, 1 H), 2.90–2.85 (m, 1 H), 1.89–1.73 (m, 1 H), 1.67–1.51 (m, 2 H), 1.44–1.19 (m, 8 H), 1.00 (d, *J* = 7.5 Hz, 3 H), 0.88 (s, 9 H), 0.09 (s, 3 H), 0.07 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 100.4, 71.2, 69.3, 66.0, 61.6, 59.2, 53.7, 33.5, 30.6, 25.7, 25.0, 24.7, 21.6, 17.8, 16.7, –4.2, –4.9.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{38}O_5SiNa$: 397.2381; found: 397.2378.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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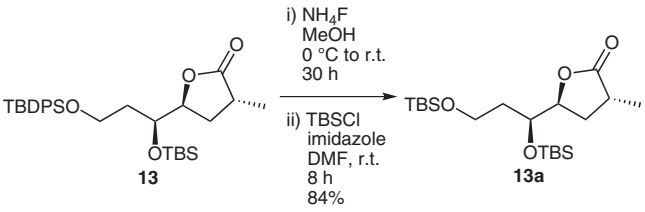
(10) Compound **13** was converted into a known compound **13a** (Scheme 3). A comparison of specific rotations {observed for **13a**: $[\alpha]_D^{30}$ +16.3 (*c* 1.0, $CHCl_3$), Lit.[3]: $[\alpha]_D^{30}$ +16.6 (*c* 1.0, $CHCl_3$)} showed that the enantiomeric excess in the Sharpless dihydroxylation was >95%, and also confirmed the exclusive formation of **13** from **12** (by NOE studies on **13a**[12]).



Scheme 3

(11) Mohapatra, D. K.; Sahoo, G.; Sankar, K.; Gurjar, M. K. *Tetrahedron: Asymmetry* **2008**, *19*, 2123.
(12) NOE experiments were carried out on compound **13a** and the enhancements are shown in Figure 2.

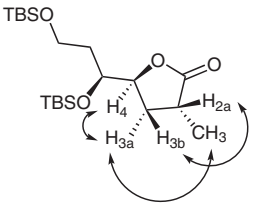


Figure 2

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