Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 4518

www.rsc.org/obc

PAPER

A stereoselective total synthesis of 7,8-*O*-isopropylidene iriomoteolide-3a†

Yao Zhang, Lisheng Deng and Gang Zhao*

Received 26th December 2010, Accepted 30th March 2011
DOI: 10.1039/c0ob01253j

A stereoselective total synthesis of 7,8-*O*-isopropylidene iriomoteolide-3a has been achieved by using Yamaguchi esterification, Julia–Kocienski olefination, organocatalytic α-oxidation, and ring-closing metathesis reaction as key bond-forming steps.

A family of structurally diverse macrolides, iriomoteolides-1a–c[1] and iriomoteolide-3a[2] were isolated from a marine benthic dinoflagellate *Amphidinium sp*. (strain HYA024). Iriomoteolide-3a and its 7,8-*O*-isopropylidene derivative displayed a potent cytotoxicity against human B lymphocyte DG-75 cells (IC_{50} = 0.08 and 0.02 μg mL^{-1}, respectively) and Raji cells (IC_{50} = 0.05 and 0.02 μg mL^{-1}, respectively). Iriomoteolide-3a is a 15-membered macrolide bearing an allylic epoxide, three hydroxyl groups, and four *E*-double bonds. The first total synthesis of iriomoteolide-3a was accomplished by Nevado's group recently.[3] Considering better bioactivity, we chose 7,8-*O*-isopropylidene iriomoteolide-3a as a target molecule and described a full account of our efforts on total synthesis of 7,8-*O*-isopropylidene iriomoteolide-3a as a part of our ongoing studies directed toward the synthesis of amphidinolides.[4]

As shown in Scheme 1, Our retrosynthetic approach to **1** involved four major disconnections, which revealed key fragments **2–4**. Fragment **4** was planned to construct C18–19 at the end of our synthetic sequence by a Julia–Kocienski olefination. An esterification and RCM reaction was envisioned to assemble fragments **2** and **3**. Fragment **2** was constructed by a Julia–Kocienski olefination between **6** and **7**. Fragment **3** was made up by a lithium–iodine exchange of **9** and nucleophilic addition to Weinreb amide **8**. All the key fragments can be derived from commercially available materials. Finally, we also tried to obtain iriomoteolide-3a by deprotecting the 7,8-*O*-isopropylidene.

Preparation of C6–C9 fragment 6

As outlined in Scheme 2, segment **6** was prepared *via* a sequence of high-yielding steps. According to the known procedure, we prepared methyl ester **13** from starting material L-tartaric acid.[5] The reduction of **13** with LAH in THF provide diol **14**. After mono-protection by PMBCl, we provided the crude aldehyde **6** by Swern oxidation, which can be directly used in the next step without purification.

Key Laboratory of Synthetic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai, 200032, P. R. China. E-mail: zhaog@mail.sioc.ac.cn

† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra of all new compounds, and chiral HPLC chromatograms for **2–8**, **16–21** (±)-**23**, **26–35**. See DOI: 10.1039/c0ob01253j

Table 1 Base and solvent effect on Julia–Kocienski olefination[a]

Base	Solvent	Temp. (°C)/*t* (h)	Yield[b]	*E*/*Z*[c]
KHMDS	DME	−78 °C/2 h–r.t.	38	5 : 1
KHMDS	DME	−78 °C/6 h–r.t.	40	5 : 1
KHMDS	DME/HMPA(9 : 1)	−78 °C/6 h–r.t.	42	5 : 1
LiHMDS	DMF/DMPU(1 : 3)	−78 °C/2 h–r.t.	58	10 : 1
LiHMDS	DMF/DMPU(1 : 3)	−78 °C/6 h–r.t.	68	10 : 1

[a] Reaction conditions: **7** (1.0 equiv.), **6** (5.0 equiv.), base (1.5 equiv.). [b] Yield of the isolated product after column chromatography of **18**. [c] *E*/*Z* Determined by isolate yield after column chromatography of **19**.

Preparation of C1–C5 fragment 7

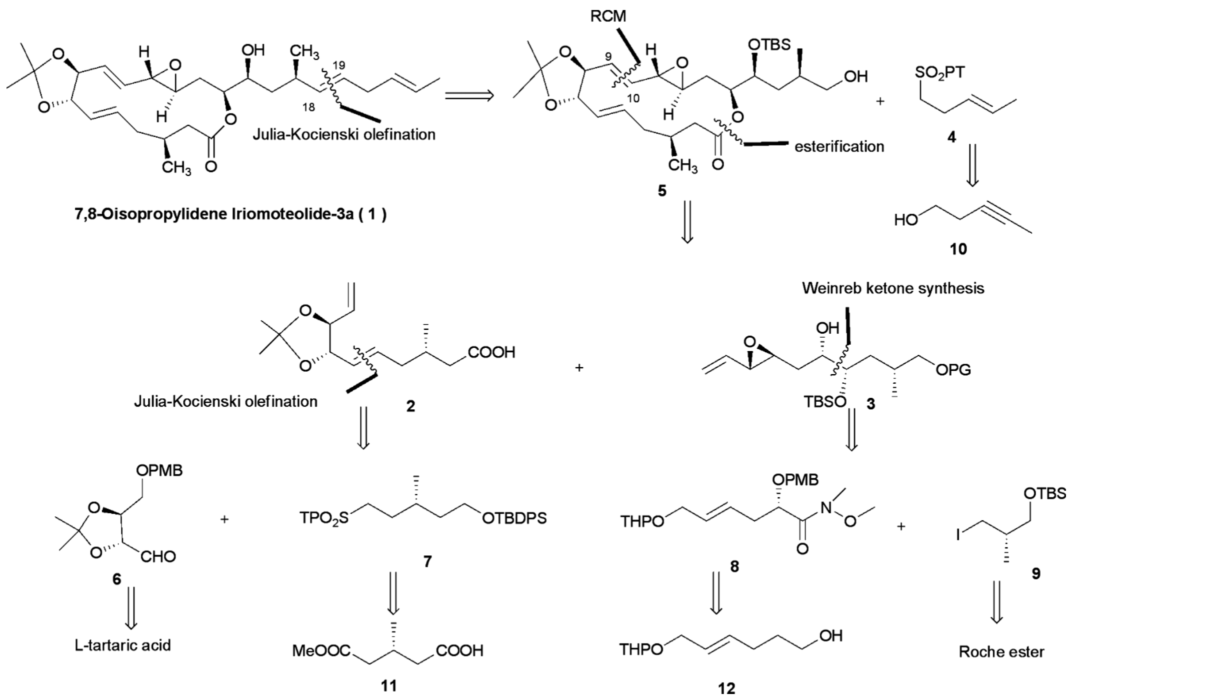
Fragment **7** (Scheme 3) was prepared by starting from commercially available mono-ester **11** (ee > 90%). According to a known procedure, we prepared **16** with mono-TBDPS protection.[6] Substitution of the hydroxyl group of **16** with 1-phenyl-1*H*-tetrazole-5-thiol *via* Mitsunobu reaction and H_2O_2 oxidation catalyzed by ammonium molybdate in EtOH afforded the sulfone **7** in 59% overall yield.

The required building block **18** was prepared by Julia–Kocienski olefination[7] between aldehyde **6** and sulfone **7**. Screening the bases and solvents (Table 1), deprotonation of sulfone **19** by LiHMDS in THF, then treatment by the aldehyde in DMF/DMPU (v/v = 1 : 3) gave a better yield and higher selectivity.

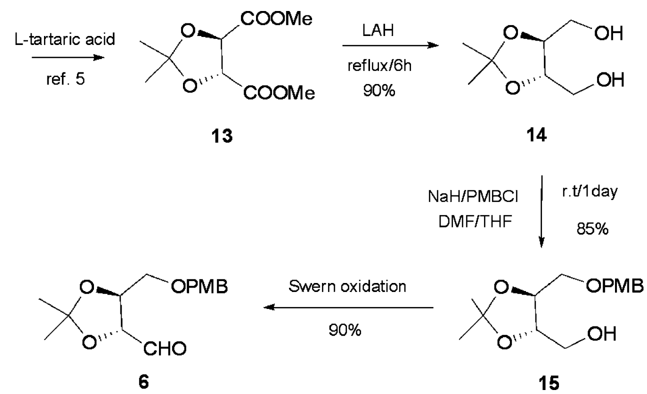
Removing the PMB group by DDQ afforded pure *E*-isomer of alkene **19** (Scheme 4) which can be separated from the *E*/*Z* mixture by flash column chromatography. Parikh–Doering oxidation of **19**, followed by Wittig methylenation of the resulting aldehyde, afforded the alkene **20**. The conversion of alkene **20** to the desired acid fragment **2** was successfully accomplished by the deprotection of the TBDPS group of **20** with TBAF in THF, followed by Parikh–Doering oxidation and $NaClO_2$ oxidation, to carboxylic acid **2** in 83% overall yield for three steps.

Preparation of C10–C18 fragment 3

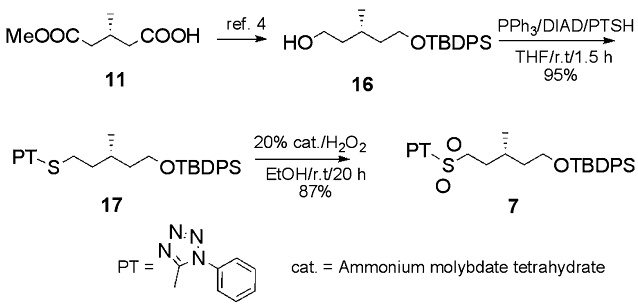
As shown in Scheme 5, the synthesis of the C10–15 fragment **8** was investigated using alcohol **12** as a starting material which can be conveniently prepared *via* several steps from 1,4-butanediol by a known procedure.[8] A proline catalyzed α-oxyamination of



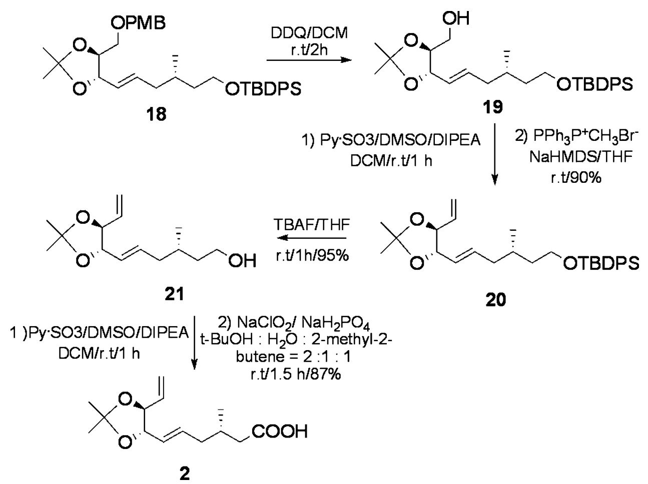
Scheme 1 Retrosynthetic analysis.



Scheme 2 Synthesis of aldehyde **6**.



Scheme 3 Synthesis of sulfone **7**.

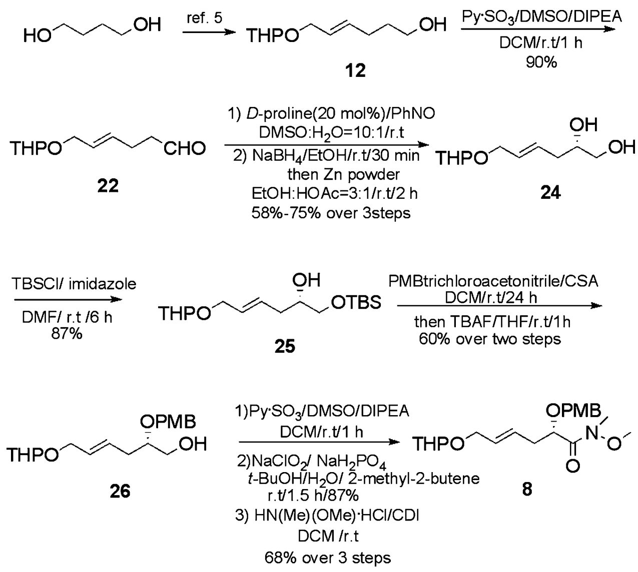


Scheme 4 Synthesis of acid **2**.

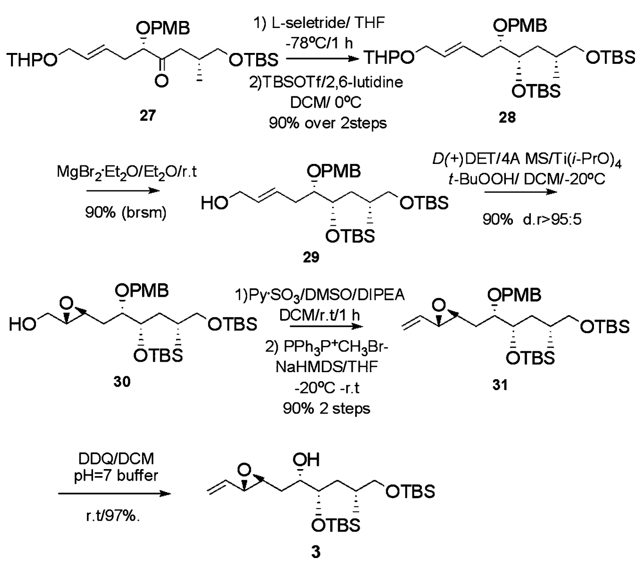
the aldehyde **22** can be accomplished with highly enantioselectivity using nitrosobenzene as an electrophilic source of oxygen (determined by chiral HPLC analysis).[9] Water content played a key role in this reaction: the yield raised notably with an addition of 10% H_2O ($v_{DMSO}/v_{H_2O} = 10:1$) in the reaction system, because of inhibition of self-aldol condensation of **22**. A three-step protection–deprotection sequence involving selective protection of the primary hydroxyl group with TBSCl, secondary hydroxyl as PMB ether under acid conditions, deprotection of primary TBS ether with TBAF produced the alcohol **27** in 52% yield over three steps. Alcohol **27** was oxidized by using Parikh–Doering oxidation to the corresponding aldehyde, followed by using $NaClO_2$ to carboxylic acid, then treatment with CDI and Weinreb amide gave the C10–15 fragment **8**.

The alkyl iodine **9** was prepared by the known method from Roche Ester in multigram scale.[10] Exchanging with *t*-BuLi in Et_2O, then treatment with Weinreb amide **8**, provided C10–C18 ketone **27**.

As shown in Scheme 6, the reduction of ketone **27** with L-selectride, followed by protection of the secondary hydroxyl group with TBSOTf provided **28** in a 90% yield (d.r. > 95 : 5). The THP



Scheme 5 Synthesis of fragment **8**.

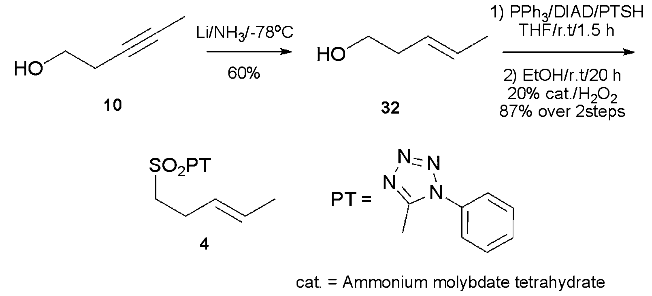


Scheme 6 Synthesis of fragment **3**.

group was removed by $MgBr_2 \cdot Et_2O$ to give allylic alcohol **29** in a 90% yield. The required chiral epoxide was introduced at this stage *via* a Sharpless asymmetric epoxidation reaction, using (+)-diethyl tartrate to yield epoxide **30** in 88% yield with good stereoselectivity (d.r. > 95 : 5). The conversion of the epoxy alcohol **30** to allylic epoxide **31** was accomplished by using Parikh–Doering oxidation followed by one-carbon Wittig methylenation. We have chosen DDQ at −15 °C to remove the PMB group of **31** to obtain the free hydroxyl group of **3** for the esterification reaction with fragment **2**.

Preparation of C19–C23 fragment

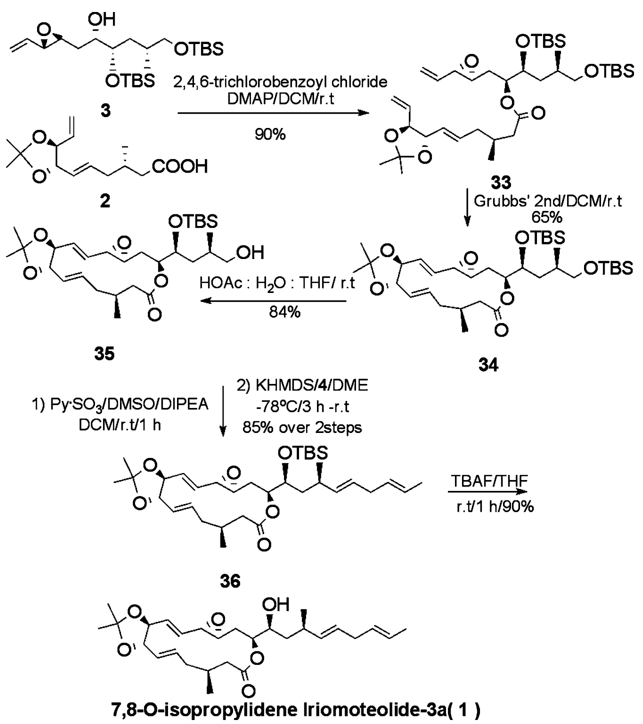
Sulfone **4** was prepared from **10** in three steps (Scheme 7) by Birch reduction, Mitsunobu displacement and oxidation by H_2O_2 catalyzed by ammonium molybdate in EtOH.



Scheme 7 Synthesis of sulfone **4**.

Completion of the total synthesis of 7,8-*O*-isopropylidene iriomoteolide-3a

With the above three fragments **2**, **3** and **4** in hand, our subsequent designed strategy called for the assembly of the acid **2** and alcohol **3** first (Scheme 8). Thus, the esterification of carboxylic acid **2** with alcohol **3** was carried out under Yamaguchi conditions[11] to produce compound **33** in a 90% yield. Reaction of **33** with second-generation Grubbs' catalyst in dichloromethane at room temperature provided single *E*-isomers **34** in a 65% yield.[12] We removed the primary TBS group in the presence of secondary OTBS groups in a mixed THF/H_2O/HOAc solvent. The free alcohol **35** was then oxidized by using Parikh–Doering oxidation to give the corresponding aldehyde, following by addition to an excess of sulfone **4** and KHMDS at −70 °C in DME solution, to give crude product **36** with high *E*-selectivity, which need not to be isolated. Finally, we afforded 7,8-*O*-isopropylidene iriomoteolide-3a by removing the silyl groups with TBAF at room temperature.



Scheme 8 Completion of the total synthesis of 7,8-*O*-isopropylidene iriomoteolide-3a.

Conclusion

In summary, we have achieved the total synthesis of 7,8-*O*-isopropylidene iriomoteolide-3a *via* a concise, and convergent strategy using readily available and inexpensive chiral building blocks. Fragment **2** was synthesized in 9 steps and 40% overall yield from the known compound **16**; Fragment **3** was prepared in 16 steps and 11% overall yield from the known compound **12**. We completed the synthesis of 7,8-*O*-isopropylidene iriomoteolide-3a in 21 steps for the longest linear sequence and 3.9% overall yield.

It is very disappointing that we failed to remove the 7,8-*O*-isopropylidene even by trying a great many acidic systems because the allylic epoxide is very unstable even in a weak acid.

Experimental

General

The ^{1}H NMR and ^{13}C NMR spectra were recorded at ambient temperature using a Varian Mercury 300 or a Bruker Avance 400 instrument. The FTIR spectra were scanned with a Nicolet Avatar 360 FTIR. ESIMS and ESIHRMS were recorded with a PE Mariner APITOF and an APEX III (7.0 Tesla) FTMS mass spectrometer. Dry THF was distilled from Na under N_2 and dry DCM, DMSO, DMF, DMPU and DME was distilled from CaH_2 under N_2 unless otherwise specified, all other solvents and reagents were commercially available and used as received without any further purification. PE (chromatography solvent) stands for petroleum ether (60–90 °C).

(*R*)-5-((5-((*tert*-Butyldiphenylsilyl)oxy)-3-methylpentyl)thio)-1-phenyl-1*H*-tetrazole (17)

PTSH (3.56 g, 20 mmol) and PPh_3 (5.24 g, 20 mmol) were added to a solution of **16** (2.85 g, 8.0 mmol) in 100 mL THF at 0 °C. Then DIAD (3.94 mL, 30 mmol) was added dropwise at this temperature. The reaction mixture was stirred for 1 h. Water was added to the mixture when TLC showed completion of the reaction, then diluted with EtOAc (100 mL). The organic layer was washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (25 : 1 PE/EtOAc) on silica gel gave compound **17** (4.0 g, 7.6 mmol, 95%) as a colorless oil: $[\alpha]_D^{20}$ −2.8 (*c* 1.00, $CHCl_3$); IR (neat): 3070, 3050, 2930, 2857, 1597, 1110 1106, 760, 739, 704, 613 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66–7.34(m, 15H), 3.73–3.69(m, 2H), 3.43–3.37(m, 2H), 1.83–1.80(m, 2H), 1.65–1.60(m, 2H), 1.43(m, 1H), 1.03(s, 9H), 0.92–0.90(d, J = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 135.6, 133.9, 130.1, 129.8, 129.7, 127.7, 123.9, 123.7, 61.7, 39.1, 36.0, 31.3, 28.9, 26.9, 19.2; ESIMS *m/z* 539.2 ([M + Na]$^+$); HRESIMS Calcd for $C_{29}H_{36}ON_4SSiNa$: ([M + Na]$^+$) 539.2285, found 539.2271.

(*R*)-5-((5-((*tert*-Butyldiphenylsilyl)oxy)-3-methylpentyl)sulfonyl)-1-phenyl-1*H*-tetrazole (7)

Ammonium molybdate tetrahydrate (2.56 g, 1.5 mmol) was added to a solution of **17** (4.0 g, 7.6 mmol) in 50 mL EtOH at 0 °C. Then H_2O_2 (8.50 mL, 30%, 80 mmol) was added dropwise at this temperature. The reaction mixture was stirred for 2.5 h. Saturated $Na_2S_2O_3$ solution was added to the mixture and stirred for another 2 h. The reaction mixture was diluted with EtOAc (100 mL), after the EtOH was evaporated. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (25 : 1 PE/Et_2O) on silica gel gave compound **7** (3.6 g, 6.6 mmol, 87%) as a colorless oil: $[\alpha]_D^{20}$ −2.2 (*c* 1.00, $CHCl_3$); IR (neat): 3070, 3050, 2930, 2931, 2858 1595, 1498, 1471, 1390, 1177, 824, 762, 708, 688 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71–7.57(m,9H), 7.44–7.35(m, 6H), 3.77–3.65(m, 4H), 1.97–1.77(m, 3H), 1.64–1.57(m, 1H), 1.44–1.38(m, 1H), 1.10(s, 9H), 0.94–0.92(d, J = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 136.1, 134.3, 133.6, 132.0, 130.2, 128.2, 125.6, 62.0, 54.5, 39.3, 29.3, 29.0, 27.4, 19.7; ESIMS *m/z* 571.2 ([M + Na]$^+$); HRESIMS Calcd for $C_{29}H_{36}O_3N_4SSiNa$: ([M + Na]$^+$) 571.2159, found 571.2170.

tert-Butyl(((*S*,*E*)-6-((4*S*,5*S*)-5-(((4-methoxybenzyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-methylhex-5-en-1-yl)oxy)diphenylsilane (18)

LiHMDS (2.4 mL, 1.0 M in THF, 2.4 mmol), was added to a solution of **7** (658 mg, 1.2 mmol) in 5.0 mL THF at −78 °C. Then aldehyde **6** which was prepared *via* standard Swern oxidation in DMF/THF solution (3 : 1, 20 mL) was added dropwise at this temperature for 15 min. The reaction mixture was stirred for another 6 h then was allowed to warm to room temperature over night. Water was added to the mixture when TLC showed completion of the reaction, then diluted with EtOAc (35 mL). The organic layer was washed with water and brine then dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (40 : 1 PE/EtOAc) on silica gel gave compound **18** (490 mg, 0.8 mmol, 63%) as a colorless oil: $[\alpha]_D^{20}$ = 2.6 (*c* 1.00, $CHCl_3$); IR (neat): 2955, 2930, 2858, 1605, 1513, 1248, 1095, 1089, 703, 613 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75–7.74(m, 4H), 7.50–7.44(m, 6H), 7.33(d, J = 7.6 Hz, 2H), 6.93(d, J = 7.6 Hz, 3H), 5.78–5.72(m, 1H), 5.52–5.47(dd, J = 15.2, 7.2 Hz, 1H), 4.59(s, 2H), 4.24(t, J = 8.2 Hz, 1H), 3.93(br s, 1H), 3.87(s, 3H), 3.76(br s, 2H), 3.65–3.57(m, 2H), 2.17–2.10(m, 1H), 1.97–1.85(m, 1H), 1.78–1.62(m, 1H), 1.62–1.52(m,1H) 1.47(s, 6H), 1.40–1.30(m, 1H), 1.13(s, 9H), 0.90–0.88(d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 135.6, 134.8, 134.0, 130.2, 129.6, 129.5, 128.4, 127.7, 113.8, 109.1, 80.3, 79.3, 73.2, 69.1, 62.1, 55.3, 39.7, 39.1, 29.5, 27.1, 27.0, 19.5, 19.3; ESIMS *m/z* 625.3 ([M + Na]$^+$); HRESIMS Calcd for $C_{37}H_{50}O_5SiNa$: ([M + Na]$^+$) 625.3329, found 625.3320.

((4*S*,5*S*)-5-((*S*,*E*)-6-((*tert*-Butyldiphenylsilyl)oxy)-4-methylhex-1-en-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (19)

DDQ (370 mg, 1.62 mmol) was added to a solution of **18** (490 mg, 0.81 mmol) in 10 mL DCM at room temperature. The reaction mixture was stirred for 1 h. Water was added to the mixture when TLC showed completion of the reaction, then diluted with EtOAc (25 mL). The organic layer was washed with saturated Na_2HCO_3 solution and brine then dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (10 : 1 PE/EtOAc) on silica gel gave compound **19** (385 mg, 0.81 mmol, 100%) as a colorless oil: $[\alpha]_D^{20}$ = 4.0 (*c* 1.00, $CHCl_3$); IR (neat): 3473, 3071, 2956, 2858, 1472 1379, 1242, 1111, 737, 688 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75–7.74(m, 4H), 7.52–7.45(m, 6H), 5.84(m, 1H), 5.53–5.47(dd, J = 15.2, 7.2 Hz, 1H), 4.37(t, J = 8.0 Hz, 1H), 3.90–3.78(m, 4H), 3.70–3.60(m, 1H), 2.15–2.09(m, 2H), 2.04–1.96(m, 1H), 1.83–1.77(m, 1H), 1.71–1.67(m, 1H) 1.52(s, 6H), 1.50–1.40(m, 1H), 1.13(s, 9H), 0.93(d, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.4, 133.9, 129.4, 127.9, 127.5, 108.8, 81.1, 78.1, 61.8, 60.7, 39.6, 38.9, 29.3, 27.0, 26.9, 26.8, 19.4, 19.1; ESIMS m/z 505.5 ([M + Na]$^+$); HRESIMS Calcd for $C_{29}H_{42}O_4SiNa$: ([M + Na]$^+$) 505.2745, found 505.2757.

tert-Butyl(((*S*,*E*)-6-((4*S*,5*S*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)-3-methylhex-5-en-1-yl)oxy)diphenylsilane (20)

DMSO (1.1 mL, 1.5 mmol) and DIPEA (0.85 mL, 2.3 mmol) were added to a solution of **19** (360 mg, 0.75 mmol) in 6 mL DCM at 0 °C. Then Py·SO_3 complex (750 mg, 3.75 mmol) was added at this temperature. The reaction mixture was stirred for 1 h. Water was added to the mixture when TLC showed completion of the reaction, then diluted with Et_2O (15 mL). The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed by rotary evaporation and the residue was used directly in the following step. NaHMDS (1.3 mL, 2.0 M in THF 2.6 mmol) was added to a solution of $PPh_3P^+CH_3Br^-$ (950 mg, 2.63 mmol) in 10 mL THF at 0 °C The reaction mixture was stirred for 30 min at 0 °C. Then a solution of above aldehyde in 3.0 mL THF was added to the mixture dropwise and stirred for 3 h. Water was added to the mixture when TLC showed completion of the reaction, then diluted with EtOAc (15 mL). The organic layer was washed with water and brine then dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (100 : 1 PE/EtOAc) on silica gel gave compound **20** (320 mg, 0.67 mmol, 89%) as a colorless oil: $[\alpha]_D^{20}$ = 20.8 (c 1.00, $CHCl_3$); IR (neat): 3120, 2985, 2931, 2859, 1473, 1428, 1370, 1239, 1111, 823, 688 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75–7.73(m, 4H), 7.52–7.44(m, 6H), 5.87–5.77(m, 2H), 5.60–5.21(m, 1H), 4.13(d, J = 4.0 Hz, 2H), 3.74–3.71(m, 2H), 2.12–1.85 (m, 2H), 1.80–1.70(m, 1H), 1.69–1.58(m, 1H) 1.52(s, 6H), 1.42–1.57(m, 1H), 1.13(s, 9H), 0.93(d, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.5, 134.8, 134.3, 134.0, 129.5, 127.5, 127.2, 118.3, 108.8, 82.2, 61.9, 39.7, 38.9, 29.4, 27.0, 26.9, 26.8, 19.5, 19.1; ESIMS m/z 501.3 ([M + Na]$^+$); HRESIMS Calcd for $C_{30}H_{42}O_3SiNa$: ([M + Na]$^+$) 501.2795, found 501.2810.

(*S*,*E*)-6-((4*S*,5*S*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-3-methylhex-5-en-1-ol (21)

TBAF (1.0 mL, 1 M in THF, 1.0 mmol) was added to a solution of **20** (320 mg, 0.67 mmol) in 10 mL THF at room temperature. The reaction mixture was stirred for 2 h. Water was added to the mixture when TLC showed completion of the reaction, then diluted with EtOAc (30 mL). The organic layer was washed with brine then dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (10 : 1 PE/EtOAc) on silica gel gave compound **21** (150 mg, 0.63 mmol, 95%) as a colorless oil: $[\alpha]_D^{20}$ = 36.0 (c 1.00, $CHCl_3$); IR (neat): 3442, 2986, 2956, 2874, 1457, 1372, 1239, 1050, 878 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85–5.70(m, 2H), 5.64–5.22(m, 3H), 4.09–4.03(br s, 2H), 3.71–3.65(m, 2H), 2.16–1.96(m, 2H), 1.71–1.56(m, 3H) 1.44(s, 6H), 1.42–1.30(m, 1H), 0.93(d, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.5, 134.2, 127.3, 118.5, 108.8, 82.2, 82.1, 60.7, 39.6, 39.1, 29.4, 27.0, 26.9, 19.39; ESIMS m/z 263.2 ([M + Na]$^+$); HRESIMS Calcd for $C_{14}H_{24}O_3SiNa$: ([M + Na]$^+$) 263.1618, found 263.1622.

(*S*,*E*)-6-((4*S*,5*S*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-3-methylhex-5-enoic acid (2)

DMSO (1.0 mL, 1.3 mmol) and DIPEA (0.75 mL, 2.0 mmol) were added to a solution of **19** (150 mg, 0.63 mmol) in 6 mL DCM at 0 °C. Then Py·SO_3 complex (630 mg, 3.0 mmol) was added at this temperature. The reaction mixture was stirred for 1 h. Water was added to the mixture when TLC showed completion of the reaction, then diluted with Et_2O (15 mL). The organic layer was washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation gave the aldehyde which was used directly in the following step. NaH_2PO_4 (270 mg, 1.96 mmol) was added to a solution of above aldehyde in 8 mL t-BuOH/H_2O/2-methyl-2-butene (V:V:V = 2 : 2 : 1) at 0 °C. Then $NaClO_2$ (170 mg, 1.96 mmol) was added at this temperature The reaction mixture was stirred for 30 min at 0 °C. Saturated $Na_2S_2O_3$ solution was added to the mixture and stirred for another 2 h when TLC showed completion of the reaction, then diluted with EtOAc (20 mL). The organic layer was washed with water and brine then dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (5 : 1 PE/EtOAc) on silica gel gave compound **2** (138 mg, 0.55 mmol, 82%) as a colorless oil: $[\alpha]_D^{20}$ = 26.2 (c 1.00, $CHCl_3$); IR (neat): 3100, 2987, 2932, 1703, 1380, 1239, 1055, 880, 813 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82–5.68(m, 2H), 5.50–5.23(m, 3H), 4.07–4.03(m, 2H), 2.38(dd, J = 8.4, 2.0 Hz, 1H), 2.33–1.96(m, 4H), 1.44(s, 6H), 0.93(d, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.4, 134.2, 133.6, 128.2, 118.8, 109.0, 82.4, 82.0, 40.6, 39.2, 29.9, 27.1, 27.0, 19.5; ESIMS m/z 277.2 ([M + Na]$^+$); HRESIMS Calcd for $C_{14}H_{21}O_4$: ([M − H]$^+$) 253.1445, found 253.1454.

(2*S*,*E*)-6-((Tetrahydro-2*H*-pyran-2-yl)oxy)hex-4-ene-1,2-diol (24)

Water (0.3 mL) and D-proline (22 mg, 0.2 mmol) was added to a solution of **22** (200, 1.0 mmol) in 3.0 mL DMSO at room temperature. Then PhNO (80 mg, 0.5 mmol) was added in one portion. The reaction mixture was stirred for 1 h. All the mixture was allowed to transfer into another solution of $NaBH_4$ (100 mg, 3 mmol) in EtOH (10.0 mL) and stirred for 30 min. Acetone was added to the mixture when TLC showed completion of the reaction, then diluted with EtOAc (25 mL). The organic layer was washed with water and brine then dried over anhydrous $MgSO_4$. Removal of the solvent by rotary evaporation and column chromatography (4 : 1 PE/EtOAc) on silica gel gave compound **23** as a dark brown oil. This compound was not very stable, so we determined the ee value as quickly as possible and directly it used in next step (for compound **23** see in the supporting information 95% e.e. (t_R (major) = 38.26 min, t_R (minor) = 27.73 min) as determined by HPLC on a CHIRALPAK AS-H column (0.46 cm × 25 cm) eluting with hexane/isopropanol = 9 : 1 at a flow rate of 0.7 mL min^{-1} with the UV detector set to 254 nm.) Compound **23** was dissolved by a mixed solution of EtOH/HOAc = 3 : 1. Zn powder (320 mg, 5 mmol) was added in one portion. Grey solid was filtered when TLC showed completion of the reaction, then diluted with EtOAc (30 mL), The organic layer was washed with saturated Na_2CO_3 and brine then dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (1 : 1 PE/EtOAc) on silica gel gave compound **24** (70 mg, 0.32 mmol, 64%) as a colorless oil $[\alpha]_D^{20}$ = 2.69 (*c* 1.00, $CHCl_3$); IR (neat): 3406, 2940, 2870, 1441, 1117, 1010, 903, 813 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.79–5.70(m, 2H), 4.64(t, *J* = 3.9 Hz, 1H), 4.20(m, 1H), 4.05–3.83(m, 2H), 3.76(br s, 1H), 3.64(m, 1H), 3.58–3.42(m, 2H), 3.07(br s, 1H), 2.87(br s, 1H), 2.34–2.17(m, 2H), 1.85–1.23(m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 129.8, 129.7, 129.4, 98.1, 98.0, 71.3, 67.8, 67.7, 66.1, 62.3, 36.3, 30.6, 25.3, 19.4; ESIMS *m*/*z* 239.1 ($[M + Na]^+$); HRESIMS Calcd for $C_{11}H_{20}O_4Na$: ($[M + Na]^+$) 239.1254, found 239.1257.

(2*S*,*E*)-2-((4-Methoxybenzyl)oxy)-6-((tetrahydro-2*H*-pyran-2-yl)oxy)hex-4-en-1-ol (26)

Newly prepared PMB-trichloroacetonitrile complex (3.0 mmol), CSA (10 mg, 5% mmol) was added to a solution of **25** (330 mg, 1.0 mmol) in 15 mL DCM at room temperature for 2 days. Water was added to the mixture when TLC showed completion of the reaction, then diluted with Et_2O (30 mL). The organic layer was washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation gave a residue which was directly used in the following step. TBAF (2.0 mL, 1.0 M in THF, 2.0 mmol) was added to a solution of the above mixture in 10 mL THF at room temperature. The reaction mixture was stirred for 2 h. Water was added to the mixture, then diluted with EtOAc (30 mL). The organic layer was washed with brine then dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (5 : 1 PE/EtOAc) on silica gel gave compound **26** (200 mg, 0.66 mmol, 60%) as a colorless oil: $[\alpha]_D^{20}$ = 13.8 (*c* 1.00, $CHCl_3$); IR (neat): 3456,2939, 2869, 1612, 1513, 1248, 1076, 975, 818 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27–7.24(d, *J* = 8.4 Hz, 2H), 6.89–6.86(d, *J* = 8.4 Hz, 2H), 5.72–5.68(m, 2H), 4.64–4.48(m, 3H), 4.20(m, 1H), 3.97–3.82(m, 2H), 3.80(s, 3H), 3.65–3.43(m, 4H), 2.38–2.30(m, 2H), 2.01(br s, 1H), 1.85–1.23(m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 130.3, 129.4, 129.1, 113.8, 97.8, 78.8, 71.2, 67.5, 64.0, 62.1, 55.2, 33.9, 30.6, 25.4, 19.4.; ESIMS *m*/*z* 359.2 ($[M + Na]^+$); HRESIMS Calcd for $C_{19}H_{28}O_5Na$: ($[M + Na]^+$) 359.1825, found 359.1829.

(2*S*,*E*)-*N*-Methoxy-2-((4-methoxybenzyl)oxy)-*N*-methyl-6-((tetrahydro-2*H*-pyran-2-yl)oxy)hex-4-enamide (8)

DMSO (5.2 mL, 6.3 mmol), DIPEA (3.2 mL, 9.0 mmol) was added to a solution of **26** (1.01 g, 3.0 mmol) in 30 mL DCM at 0 °C. Then Py·SO_3 complex (3.0 g, 15.0 mmol) was added at this temperature. The reaction mixture was stirred for 1 h. Water was added to the mixture when TLC showed completion of the reaction, then diluted with Et_2O (15 mL). The organic layer was washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation gave a residue which was directly used in the following step. NaH_2PO_4 (1.5 g, 9.0 mmol) was added to a solution of above aldehyde in 18 mL *t*-BuOH/H_2O/2-methyl-2-butene (V : V : V = 2 : 2 : 1) at 0 °C. Then $NaClO_2$ (0.9 g, 9.0 mmol) was added at this temperature The reaction mixture was stirred for 30 min at 0 °C. Saturated $Na_2S_2O_3$ solution was added to the mixture and stirred for another 2 h when TLC showed completion of the reaction, then diluted with EtOAc (50 mL). The organic layer was washed with water and brine then dried over anhydrous $MgSO_4$. Removal of the solvent by rotary evaporation gave a residue which was directly used in the following step. CDI (0.96 g, 6.0 mmol) was added to a solution of the above acid in 18 mL DCM at 0 °C. Then HN(Me)(OMe)·HCl (0.73 g, 7.5 mmol) was added at this temperature. The reaction mixture was stirred over night. Water was added to the mixture when TLC showed completion of the reaction, then diluted with EtOAc (30 mL). The organic layer was washed with brine then dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (4 : 1 PE/EtOAc) on silica gel gave compound **8** (825 mg, 2.1 mmol, 69%) as a colorless oil: $[\alpha]_D^{20}$ −33.0 (*c* 1.00, $CHCl_3$); IR (neat): 2940, 2869, 1672, 1613, 1513, 1464, 1201, 1078, 817 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26–7.25(d, *J* = 8.4 Hz, 2H), 6.85–6.82(d, *J* = 8.4 Hz, 2H), 5.79–5.59(m, 2H), 4.58(d, *J* = 5.7 Hz, 1H), 4.31(d, *J* = 6.0 Hz, 1H), 4.16(dd, *J* = 8.6, 2.0 Hz, 1H), 3.94–3.80(m, 2H), 3.77(s, 3H), 3.51(s, 3H), 3.46–3.41(m, 1H), 3.17(s, 3H), 2.58–2.38(m, 2H), 1.85–1.23(m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 159.3, 129.8, 129.5, 129.4, 128.8, 113.7, 97.7, 74.8, 71.0, 67.3, 62.1, 61.2, 55.1, 35.2, 30.6, 25.4, 19.4; ESIMS *m*/*z* 416.3 ($[M + Na]^+$); HRESIMS Calcd for $C_{21}H_{31}O_6NNa$: ($[M + Na]^+$) 416.2051, found 416.2044.

(2*R*,5*S*,*E*)-1-((*tert*-Butyldimethylsilyl)oxy)-5-((4-methoxybenzyl)oxy)-2-methyl-9-((tetrahydro-2*H*-pyran-2yl)oxy)non-7-en-4-one (27)

t-BuLi (2.5 mL, 1.6 M in pentane, 4.0 mmol) was added to a solution of **9** (630 mg, 2.0 mmol) in 6.0 mL Et_2O at −78 °C for 15 min. A solution of amide **8** (400 mg, 1.0 mmol) in 3.0 mL THF was added to the mixture at the same temperature then stirred for 1 h. Water was added when TLC showed completion of the reaction, then diluted with EtOAc (30 mL). The organic layer was washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (20 : 1 PE/EtOAc) on silica gel gave compound **27** (400 mg, 0.76 mmol, 76%) as a colorless oil: $[\alpha]_D^{20}$ −15.1 (*c* 1.00, $CHCl_3$); IR (neat): 2952, 2857, 1715, 1613, 1514, 1250, 1092, 1026, 837, 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29–7.27(d, *J* = 8.4 Hz, 2H), 6.91–6.89(d, *J* = 8.4 Hz, 2H), 5.71–5.69(m, 2H), 4.64(s, 1H), 4.48(AB q, *J* = 11.6 Hz, 2H), 4.20(dd, *J* = 8.0 Hz, 2.0 Hz, 1H), 3.97–3.83(m, 3H), 3.84(s, 3H), 3.54–3.49(m, 2H), 3.44–3.40(m, 1H), 2.73(dd, *J* = 8.0, 2.4 Hz, 1H), 2.46(t, *J* = 5.6 Hz, 2H), 2.42(dd, *J* = 8.4, 4.0 Hz, 1H), 2.31–2.40(m, 1H), 1.89–1.50(m, 6H), 0.93–0.88(m, 12H), 0.06(s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.4, 159.9, 130.2, 130.1, 128.8, 98.3, 84.6, 72.6, 67.9, 62.7, 55.8, 42.3, 35.8, 31.6, 31.1, 26.4, 26.0, 20.0, 18.8, 17.3, −4.9; ESIMS *m*/*z* 543.5 ($[M + Na]^+$); HRESIMS Calcd for $C_{29}H_{48}O_6SiNa$: ($[M + Na]^+$) 543.3112, found 543.3115.

(5*S*,7*R*)-5-((1*S*,*E*)-1-((4-Methoxybenzyl)oxy)-5-((tetrahydro-2*H*-pyran-2-yl)oxy)pent-3-en-1-yl)-2,2,3,3,7,10,10,11,11-nonamethyl-4,9-dioxa-3,10-disiladodecane (28)

L-selectride (1.6 mL, 1.0 M in THF, 1.6 mmol) was added to a solution of **27** (415 mg, 2.0 mmol) in 6.0 mL THF at −78 °C for 1 h. A solution of amide 8 (400 mg, 1.0 mmol) in 3.0 mL

THF was added to the mixture at the same temperature then stirred for 1 h. Acetone was added to the mixture when TLC showed completion of the reaction, then diluted with EtOAc (25 mL). The organic layer was washed with water and brine then dried over anhydrous $MgSO_4$. Removal of the solvent by rotary evaporation gave a residue which was directly used in next step. 2,6-Lutidine (0.35 mL, 2.0 mmol) was added to a solution of above residue in DCM (5.0 mL) at 0 °C, TBSOTf (0.4 mL, 1.6 mmol) was added at this temperature. The reaction mixture was stirred for 30 min at 0 °C Water was added to the mixture when TLC showed completion of the reaction, then diluted with EtOAc (15 mL). The organic layer was washed with brine then dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (50 : 1 PE/EtOAc) on silica gel gave compound **28** (460 mg, 0.72 mmol, 90%) as a colorless oil: $[\alpha]_D^{20}$ −19.7 (*c* 1.00, $CHCl_3$); IR (neat): 2930, 2857, 1613, 1513, 1464, 1250, 1079, 1024, 836, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29–7.26(d, J = 8.4 Hz, 2H), 6.90–6.88(d, J = 8.4 Hz, 2H), 5.82–5.74(m, 1H), 5.70–5.62(m, 1H), 4.67(t, J = 3.6 Hz, 1H), 4.55–4.46(m, 2H), 4.21(m, 1H), 3.99–3.87(m, 3H), 3.83(s, 3H), 3.55–3.50(m, 2H), 3.43–3.45(m, 2H), 2.44–2.40(m, 1H), 2.24–2.08(m, 1H), 1.89–1.50(m, 6H), 1.23–1.17(m, 1H), 0.96–0.88(m, 21H), 0.08–0.06(m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 132.1, 131.0, 129.3, 128.0, 113.6, 97.6, 81.4, 71.8, 70.6, 67.9, 67.7, 62.2, 55.3, 35.1, 32.2, 32.0, 30.7, 26.0, 25.5, 19.5, 18.3, 18.0, −4.2, −4.5, −5.3, −5.4; ESIMS m/z 659.6 ([M + Na]$^+$); HRESIMS Calcd for $C_{35}H_{64}O_6Si_2Na$: ([M + Na]$^+$) 659.4134, found 659.4137.

(5*S*,6*S*,8*R*,*E*)-6,9-Bis((*tert*-butyldimethylsilyl)oxy)-5-((4-methoxybenzyl)oxy)-8-methylnon-2-en-1-ol (29)

$MgBr_2 \cdot Et_2O$ (464 mg, 0.72 mmol) was added to a solution of **28** (460 mg, 072 mmol) in 10 mL Et_2O at room temperature. The reaction mixture was stirred for 2 h. Water was added to the mixture when TLC showed no extra product appeared, then diluted with EtOAc (10 mL). The organic layer was washed with brine then dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (50 : 1 to 15 : 1 PE/EtOAc) on silica gel gave compound **28** (204 mg, 0.32 mmol) and compound **29** (170 mg, 0.31 mmol) as a colorless oil: $[\alpha]_D^{20}$ −29.8 (*c* 1.00, $CHCl_3$); IR (neat): 3397, 2954, 2886, 2857, 1613, 1514, 1471, 1250, 1086, 836, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.30(d, J = 8.4 Hz, 2H), 6.95–6.93(d, J = 8.4 Hz, 2H), 5.77–5.74(m, 2H), 4.50(AB q, J = 11.6 Hz, 2H), 4.13(s, 2H), 3.98–3.96(m, 1H), 3.88(s, 3H), 3.57–3.40(m, 3H), 2.42–2.38(m, 1H), 2.29–2.21(m, 1H), 1.86–1.74(m, 2H), 1.34(br s, 1H), 1.28–1.25(m, 1H), 0.96–0.88(m, 21H), 0.08–0.06(m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 130.9, 130.7, 129.4, 113.6, 81.5, 71.7, 70.5, 67.8, 63.8, 55.3, 35.1, 32.2, 31.8, 26.0, 25.9, 18.4, 18.1, −4.2, −4.5, −5.4; ESIMS m/z 575.6 ([M + Na]$^+$); HRESIMS Calcd for $C_{30}H_{54}O_5Si_2Na$: ([M + Na]$^+$) 575.3559, found 575.3569

((2*S*,3*R*)-3-((2*S*,3*S*,5*R*)-3,6-Bis((*tert*-butyldimethylsilyl)oxy)-2-((4-methoxybenzyl)oxy)-5-methylhexyl)oxiran-2-yl)methanol (30)

Activated 4 Å MS (100 mg) and D-(+)DET (90 mg, 0.32 mmol) was added to a solution of Ti(*i*-PrO)$_4$ (0.1 mL, 0.39 mmol) in 5.0 mL DCM and stirred for 30 min at −20 °C. *t*-BuOOH (0.24 mL, 5.5 M in toluene, 1.3 mmol) was added at this temperature and stirred for another 40 min. Finally a solution of **29** (180 mg, 0.32 mmol) was added and stirred at −20 °C for 12 h. Saturated Na_2SO_3 solution was added to the mixture and stirred for another 2 h when TLC showed completion of the reaction, then diluted with EtOAc (15 mL). The organic layer was washed with water and brine then dried over anhydrous $MgSO_4$. Removal of the solvent by rotary evaporation and column chromatography (10 : 1 PE/EtOAc) on silica gel gave compound **30** (170 mg, 0.31 mmol) as a colorless oil: $[\alpha]_D^{20}$ −40.8 (*c* 1.00, $CHCl_3$); IR (neat): 3449, 2954, 2857, 1612, 1514, 1471, 1251, 1087, 836, 775, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26–7.23(d, J = 8.8 Hz, 2H), 6.89–6.86(d, J = 8.4 Hz, 2H), 4..49(AB q, J = 11.2 Hz, 2H), 3.97–3.84(m, 2H), 3.80(s, 3H), 3.62–3.54(m, 2H), 3.50(dd, J = 7.2, 2.4 Hz, 1H), 3.41–3.33(m, 1H), 3.06–3.02(m, 1H), 2.94(dd, J = 7.0, 2.0 Hz, 1H), 2.03(br s, 1H), 1.81–1.63(m, 4H), 1.20–1.12 (m, 1H), 0.96–0.88(m, 21H), 0.08–0.06(m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 130.7, 129.3, 113.8, 79.1, 72.0, 69.8, 67.8, 61.7, 59.4, 55.3, 54.1, 34.8, 32.2, 31.3, 26.0, 18.5, 18.4, 18.0, −4.2, −4.5, −5.4; ESIMS m/z 591.2 ([M + Na]$^+$); HRESIMS Calcd for $C_{30}H_{56}O_6Si_2Na$: ([M + Na]$^+$) 591.3508, found 591.3509.

(5*S*,7*R*)-5-((*S*)-1-((4-Methoxybenzyl)oxy)-2-((2*R*,3*S*)-3-vinyloxiran-2-yl)ethyl)-2,2,3,3,7,10,10,11,11-nonamethyl-4,9-dioxa-3,10-disiladodecane (31)

DMSO (0.5 mL, 0.67 mmol) and DIPEA (0.4 mL, 1.0 mmol) were added to a solution of **30** (192 mg, 0.34 mmol) in 6 mL DCM at 0 °C. Then Py·SO_3 complex (330 mg, 1.7 mmol) was added at this temperature. The reaction mixture was stirred for 1 h. Water was added to the mixture when TLC showed completion of the reaction, then diluted with Et_2O (15 mL). The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed by rotary evaporation and the residue was directly used in the following step. NaHMDS (0.85 mL, 2.0 M in THF 1.7 mmol) was added to a solution of $PPh_3P^+CH_3Br^-$ (627 mg, 1.7 mmol) in 10 mL THF at 0 °C The reaction mixture was stirred for 30 min at 0 °C. Then a solution of the above aldehyde in 3.0 mL THF was added to the mixture dropwise and stirred at −40 °C for 3 h. Water was added to the mixture when TLC showed completion of the reaction, then diluted with EtOAc (15 mL). The organic layer was washed with water and brine, then dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (100 : 1 PE/EtOAc) on silica gel gave compound **31** (183 mg, 0.34 mmol, 98%) as a colorless oil: $[\alpha]_D^{20}$ −26.2 (*c* 1.00, $CHCl_3$); IR (neat): 2955, 2930, 2857, 1605, 1514, 1471, 1250, 1084, 837, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26–7.21(d, J = 8.8 Hz, 2H), 6.88–6.82(d, J = 8.4 Hz, 2H), 5.63–5.27(m, 3H), 4.50(AB q, J = 11.2 Hz, 2H), 3.98–3.94(m, 1H), 3.80(s, 3H), 3.60–3.55(m, 1H), 3.43(dd, J = 7.2, 2.4 Hz, 1H), 3.36(dd, J = 7.8, 3.0 Hz, 1H), 3.15–3.12(dd, J = 7.0, 2.0 Hz, 1H), 2.94(t, J = 7.2 Hz, 1H), 1.86–1.63(m, 4H), 1.18–1.06(m, 1H), 0.96–0.88(m, 21H), 0.08–0.06(m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 136.0, 130.8, 129.4, 119.0, 113.8, 79.0, 72.0, 69.9, 67.8, 59.6, 58.6, 55.3, 34.8, 32.2, 31.7, 25.9, 18.5, 18.4. 18.0, −4.1, −4.6, −5.3; ESIMS m/z 587.2 ([M + Na]$^+$); HRESIMS Calcd for $C_{31}H_{56}O_5Si_2Na$: ([M + Na]$^+$) 587.3559, found 587.3563.

(2*S*,3*S*,5*R*)-3,6-Bis((*tert*-butyldimethylsilyl)oxy)-5-methyl-1-((2*R*,3*S*)-3-vinyloxiran-2-yl)hexan-2-ol (3)

DDQ (138 mg, 0.6 mmol) was added to a solution of **31** (180 mg, 0.34 mmol) in 10 mL DCM and pH = 7.0 buffer at −20 °C. The reaction mixture was stirred for 1 h. Water was added to the mixture when TLC showed completion of the reaction, then diluted with EtOAc (25 mL). The organic layer was washed with saturated Na_2HCO_3 solution and brine then dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (10 : 1 PE/EtOAc) on silica gel gave compound **19** (142 mg, 0.32 mmol, 96%) as a colorless oil: $[\alpha]_D^{20}$ −26.0 (*c* 1.00, $CHCl_3$); IR (neat): 3489, 2955, 2929, 2887, 1472, 1256, 1080, 790, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.63–5.30(m, 3H), 3.80–3.67(m, 2H), 3.50(dd, *J* = 7.0, 2.0 Hz, 1H), 3.40(dd, *J* = 7.8, 3.0 Hz, 1H), 3.17(dd, *J* = 7.0, 2.0 Hz, 1H), 3.10–3.06(m, 1H), 2.30(d, *J* = 8.0 Hz, 1H), 1.96–1.79(m, 2H), 1.76–1.65(m, 1H), 1.54–1.46(m, 1H), 1.25–1.16(m, 1H), 0.92–0.88(m, 21H), 0.08(s, 6H), 0.06(s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7, 119.2, 73.2, 70.0, 68.5, 58.9, 58.3, 37.3, 32.2, 25.9, 18.3, 18.0, 17.2, −4.1, −4.5, −5.4; ESIMS *m/z* 467.4 ([M + Na]$^+$); HRESIMS Calcd for $C_{23}H_{48}O_4Si_2Na$: ([M + Na]$^+$) 467.2983, found 467.3003.

(*S*,*E*)-(2*S*,3*S*,5*R*)-3,6-Bis((*tert*-butyldimethylsilyl)oxy)-5-methyl-1-((2*S*,3*S*)-3-vinyloxiran-2-yl)hexan-2-yl-6-((4*S*,5*S*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)-3-methylhex-5-enoate (33)

Compound **2** (30 mg, 0.12 mmol), compound **3** (45 mg, 0.1 mmol) and DMAP (65 mg, 0.5 mmol) were mixed together in 5 mL DCM at 0 °C. Then 2,4,6-trichlorobenzoyl chloride (50 mg, 0.21 mmol) was added. The reaction mixture was stirred for 24 h. Water was added to the mixture when TLC showed completion of the reaction, then diluted with Et_2O (20 mL). The organic layer was washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (35 : 1 PE/EtOAc) on silica gel gave compound **33** (65 mg, 0.1 mmol, 97%) as a colorless oil: $[\alpha]_D^{20}$ −25.0 (*c* 1.00, $CHCl_3$); IR (neat): 2956, 2930, 2857, 1737, 1480, 1370, 1257, 1085, 1057, 837, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.90–5.71(m, 2H), 5.60–5.44(m, 3H), 5.38–5.25(m, 3H), 5.04(dt, *J* = 10.0 Hz, 3.2 Hz, 1H), 4.11–4.07(m, 2H), 3.92–3.88(m, 1H), 3.42(dd, *J* = 7.2 Hz, 2.4 Hz, 1H), 3.37(dd, *J* = 7.8 Hz, 3.0 Hz, 1H), 3.10(dd, *J* = 7.0, 2.0 Hz, 1H), 2.87(dt, *J* = 5.6, 1.2 Hz, 1H), 2.40–2.30(m, 1H), 2.14–2.00(m, 5H), 1.80–1.72(m, 2H), 1.64–1.56(m, 1H), 1.47(s, 6H), 1.24–1.16(m, 1H), 0.98–0.90(m, 24H), 0.15(s, 3H), 0.09(s, 3H), 0.05(s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 135.6, 134.3, 133.5, 128.2, 119.3, 118.7, 109.0, 82.4, 82.1, 72.9, 70.2, 37.8, 59.0, 27.7, 41.1, 39.3, 35.7, 32.0, 31.6, 30.0, 27.1, 25.9, 19.5, 18.3, 18.0, 17.8, −4.3, −4.6, −5.4; ESIMS *m/z* 703.6 ([M + Na]$^+$); HRESIMS Calcd for $C_{37}H_{68}O_7Si_2Na$: ([M + Na]$^+$) 70.3.4396, found 703.4396.

(3a*S*,4*E*,7*S*,11*S*,12a*S*,13a*S*,14*E*,15a*S*)-2,2,7-Trimethyl-11-((5*S*,7*R*)-2,2,3,3,7,10,10,11,11-nonamethyl-4,9-dioxa-3,10-disiladodecan-5-yl)-6,7,8,11,12,12a,13a,15a-octahydro-[1,3]dioxolo[4,5-h]oxireno[2,3-d][1]oxacyclopentadecin-9(3a*H*)-one (34)

Grubbs' 2nd catalyst (9.6 mg, 0.012 mmol) was added to a solution of **33** (40 mg, 0.058 mmol) in 50 mL DCM without oxygen. The reaction mixture was stirred for 12 h. Removal of the solvent by rotary evaporation when TLC showed completion of the reaction and column chromatography (30 : 1 PE/EtOAc) on silica gel gave compound **34** (26 mg, 0.0377 mmol, 65%) as a colorless oil: $[\alpha]_D^{20}$ = 46.5 (*c* 1.00, $CHCl_3$); IR (neat): 2955, 2930, 2857, 1738, 1471, 1370, 1255, 1056, 870, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.92–5.82(m, 2H), 5.50(dd, *J* = 12.0, 4.0 Hz, 1H), 5.36(dd, *J* = 12.4, 4.8 Hz, 1H), 5.20(dt, *J* = 10.0, 3.2 Hz, 1H), 4.04(t, *J* = 8.4 Hz, 2H), 3.94(t, *J* = 8.8 Hz, 2H), 3.82(q, *J* = 5.4 Hz, 2H), 3.45–3.36(m, 2H), 3.05(d, *J* = 9.6 Hz, 1H), 2.85(d, *J* = 10.0 Hz, 1H), 2.44(d, *J* = 14.8 Hz, 1H), 2.30–2.20(m, 2H), 1.95–1.85(m, 2H), 1.81–1.70(m, 2H), 1.65–1.56(m, 1H), 1.49–1.41(m, 6H), 1.23–1.17(m, 1H), 1.05(d, *J* = 5.6 Hz, 3H), 0.98–0.90(m, 21H), 0.15(s, 3H), 0.09(s, 3H), 005(s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 135.6, 135.0, 132.6, 127.5, 109.5, 83.0, 81.4, 72.5, 70.9, 67.9, 59.2, 58.2, 37.3, 36.5, 36.3, 33.3, 32.4, 31.7, 27.1, 26.0, 25.8, 21.1, 18.3, 18.0, 17.9, −4.4, −5.4; ESIMS *m/z* 675.7 ([M + Na]$^+$); HRESIMS Calcd for $C_{35}H_{64}O_7Si_2Na$: ([M + Na]$^+$) 675.4083, found 675.4104.

(3a*S*,4*E*,7*S*,11*S*,12a*S*,13a*S*,14*E*,15a*S*)-11-((1*S*,3*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-4-hydroxy-3-methylbutyl)-2,2,7-trimethyl-6,7,8,11,12,12a,13a,15a-octahydro-[1,3]dioxolo[4,5-h]oxireno[2,3-d][1]oxacyclopentadecin-9(3a*H*)-one (35)

Compound **34** (40 mg, 0.061 mmol) was dissolved by a mixed solution of THF/H_2O/HOAc = 1 : 1 : 1, diluted with EtOAc (30 mL), when TLC showed completion of the reaction The organic layer was washed with saturated Na_2CO_3 and brine then dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (3 : 1 PE/EtOAc) on silica gel gave compound **35** (28 mg, 0.051 mmol, 84%) as a white solid. $[\alpha]_D^{20}$ = 56.4 (*c* 0.5, $CHCl_3$); IR (neat): 3406, 2940, 2870, 1441, 1117, 1010, 903, 813 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.93–5.85(m, 2H), 5.50(dd, *J* = 12.0, 4.0 Hz, 1H), 5.40–5.25(m, 2H), 4.04(t, *J* = 8.4 Hz, 2H), 3.94(t, *J* = 8.8 Hz, 2H), 3.82(q, *J* = 5.4 Hz, 2H), 3.45–3.36(m, 2H), 3.05(d, *J* = 9.6 Hz, 1H), 2.85(d, *J* = 10.0 Hz, 1H), 2.44(d, *J* = 14.8 Hz, 1H), 2.30–2.20(m, 2H), 1.95–1.85(m, 2H), 1.71–1.70(m, 2H), 1.64–1.57(m, 1H), 1.49–1.41(m, 6H), 1.20–1.12(m, 1H), 1.05(d, *J* = 5.6 Hz, 3H), 0.98–0.90(m, 12H), 0.13(s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 135.6, 134.9, 132.8, 127.5, 109.6, 83.0, 81.4, 72.1, 71.5, 68.0, 59.3, 27.9, 37.5, 37.3, 36.5, 33.4, 33.1, 32.0, 27.1, 25.8, 21.2, 18.1, 18.0, −4.4, −4.5; ESIMS *m/z* 538.3 ([M + Na]$^+$); HRESIMS Calcd for $C_{29}H_{50}O_7SiNa$: ([M + Na]$^+$) 538.3026, found 538.3022.

7,8-*O*-Isopropylidene iriomoteolide-3a (1)

DMSO (0.06 mL, 0.1 mmol), DIPEA (0.05 mL, 0.1 mmol) was added to a solution of **35** (25 mg, 0.046 mmol) in 4 mL DCM at 0 °C. Then Py·SO_3 complex (50 mg, 0.25 mmol) was added at this temperature. The reaction mixture was stirred for 1 h. Water was added to the mixture when TLC showed completion of the reaction, then diluted with Et_2O (15 mL). The organic layer was washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation gave a residue which was directly used in the following step. KHMDS (0.5 mL, 0.6 M in toluene, 0.3 mmol), was added to a solution of **4** (56 mg, 0.2 mmol) in 5.0 mL DME at −78 °C. Then the above aldehyde in DME solution (2.0 mL) was added dropwise at this temperature for 15 min. The reaction mixture was stirred for another 3 h then was allowed to warm to room temperature for another 2 h. Water was added to the mixture when TLC showed completion of the reaction, then diluted with EtOAc (20 mL). The organic layer was washed with water and brine then dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation gave a residue which was directly used in the following step. TBAF (0.1 mL, 1 M in THF, 0.1 mmol) was added to a solution of above mixture in 3.0 mL THF at room temperature. The reaction mixture was stirred for 2 h. Water was added to the mixture when TLC showed completion of the reaction, then diluted with EtOAc (15 mL). The organic layer was washed with brine then dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (8 : 1 PE/EtOAc) on silica gel gave compound **1** (13 mg, 0.027 mmol, 59%) as a white solid: $[\alpha]_D^{20}$ = 26.2 (*c* 0.5, $CHCl_3$); IR (neat): 3489, 2956, 2926, 2855, 1735, 1456, 1378, 1237, 1095, 970, 879 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.82–5.74(m, 2H), 5.42–5.34(m, 2H), 5.32–5.20(m, 1H), 5.16–5.09(m, 2H), 3.95(t, J = 8.4 Hz, 2H), 3.85(t, J = 8.8 Hz, 2H), 3.52(br s, 1H), 2.99 (d, J = 9.2 Hz, 1H) 2.80(d, J = 9.6 Hz, 1H), 2.60(s, 2H), 2.41(d, J = 16.8 Hz, 1H), 2.30(br s, 1H), 2.20–2.10(m, 2H), 1.91–1.75(m, 2H), 1.81–1.70(m, 2H), 1.64–1.55(m, 1H), 1.67–1.56(m, 4H), 1.37–1.35(m, 6H), 1.25–1.15(m, 2H), 0.98(d, J = 6.4 Hz, 3H), 0.94(d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 135.6, 135.3, 134.9, 132.7, 129.5, 128.8, 127.6, 125.7, 109.6, 83.0, 81.4, 73.3, 70.9, 40.8, 37.2, 36.6, 35.5, 34.1, 33.5, 33.3, 29.7, 27.1, 21.7, 21.2, 17.9; ESIMS *m/z* 497.3 ($[M + Na]^+$); HRESIMS Calcd for $C_{28}H_{42}O_6Na$: ($[M + Na]^+$) 497.2884, found 497.2878.

Acknowledgements

Research support from National Basic Research Program of China (973 Program, 2010CB833200), the National Natural Science Foundation of China (No.20172064, 203900502, 21032006), Shanghai Natural Science Council, and Excellent Young Scholars Foundation of National Natural Science Foundation of China (20525208) is gratefully acknowledged.

References

1 (*a*) M. Tsuda, K. Oguchi, R. Iwamoto, Y. Okamoto, E. Fukushi, J. Kawabata, T. Ozawa and A. Masuda, *J. Nat. Prod.*, 2007, **70**, 1661–1663; (*b*) M. Tsuda, K. Oguchi, R. Iwamoto, Y. Okamoto, J. Kobayashi, E. Fukushi, J. Kawabata, T. Ozawa, A. Masuda, Y. Kitaya and K. Omasa, *J. Org. Chem.*, 2007, **72**, 4469–4474.
2 K. Oguchi, M. Tsuda, R. Iwamoto, Y. Okamoto, J. Kobayashi, E. Fukushi, J. Kawabata, T. Ozawa, A. Masuda, Y. Kitaya and K. Omasa, *J. Org. Chem.*, 2008, **73**, 1567–1570.
3 R. Cribiú, C. Jäger and C. Nevado, *Angew. Chem., Int. Ed.*, 2009, **48**, 8780–8783.
4 (*a*) L.-S. Deng, X.-P. Huang and G. Zhao, *J. Org. Chem.*, 2006, **71**, 4625; (*b*) L.-S. Deng, Z.-X. Ma, Y.-Z. Zhang and G. Zhao, *Synlett*, 2007, 87–90; (*c*) L.-S. Deng, Z.-X. Ma and G. Zhao, *Synlett*, 2008, 728–730; (*d*) Z.-Q. Ye, L.-S. Deng, S. Qian and G. Zhao, *Synlett*, 2009, 2469–2472.
5 (*a*) A. Carpita, S. Braconi and R. Rossi, *Tetrahedron: Asymmetry*, 2005, **16**, 2501–2508; (*b*) M. Ono, K. Nishimura, H. Tsubouchi, Y. Nagaoka and K. Tomioka, *J. Org. Chem.*, 2001, **66**, 8199–8203.
6 B.-C. Hong, F.-L. Chen, S.-H. Chen, J.-H. Liao and J.-H. Lee, *Org. Lett.*, 2005, **7**, 557–560.
7 For Julia–Kocienski olefination, see: (*a*) C. H. Kim, H. J. An, W. K. Shin, W. Yu, S. K. Woo, S. K. Jung and E. Lee, *Angew. Chem., Int. Ed.*, 2006, **45**, 8019–8021; (*b*) K. Ishigami, H. Watanabe and T. Kitahara, *Tetrahedron*, 2005, **61**, 7546–7533.
8 (*a*) H. Nakamura, K. Aoyagi, J. G. Shim and Y. Yamamoto, *J. Am. Chem. Soc.*, 2001, **123**, 372–377; (*b*) S. Sasmal, A. Geyer and M. E. Maier, *J. Org. Chem.*, 2002, **67**, 6260–6263.
9 S. P. Brown, M. P. Brochu, C. J. Sinz and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2003, **125**, 10808–10809.
10 (*a*) Z. Tan and E. Negishi, *Angew. Chem., Int. Ed.*, 2004, **43**, 2911–2914; (*b*) M. Bogenstätter, A. Limberg, L. E. Overman and A. L. Tomasi, *J. Am. Chem. Soc.*, 1999, **121**, 12206–12207.
11 J. Inanaga, K. Hirata, H. Saeki, T. Katsuki and M. Yamaguchi, *Bull. Chem. Soc. Jpn.*, 1979, **52**, 1989–1993.
12 A. Fürstner, C. Nevado, M. Waser, M. Tremblay, C. Chevrier, F. Teplý, E. Moulin and O. Müller, *J. Am. Chem. Soc.*, 2007, **129**, 9150–9161.

