Organic & Biomolecular Chemistry

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A stereoselective synthesis of the C9–C19 subunit of (+)-peloruside A†

Cite this: *Org. Biomol. Chem.*, 2013, **11**, 2847

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Received 28th December 2012,
Accepted 18th February 2013

DOI: 10.1039/c3ob27508f

www.rsc.org/obc

The stereoselective synthesis of a C9–C19 fragment of the potent antitumor agent peloruside A is disclosed. The C11 stereogenic centre was created by a vinylogous Mukaiyama aldol reaction following Carreira's protocol, with excellent stereocontrol. The C13 stereogenic centre was introduced by a substrate controlled reduction. The C15 stereocentre was fashioned using Noyori's asymmetric transfer hydrogenation while the *Z*-trisubstituted double bond was formed by a regioselective hydrostannation of an alkyne followed by methylation of the resultant vinyl stannane using Lipshutz's protocol. The C18 chiral centre was introduced by a chemoenzymatic route.

Introduction

Peloruside A (**1**), a 16-membered macrolide, was isolated from the marine sponge *Mycale hentscheli* collected in Pelorus Sound of New Zealand by Northcote and co-workers.[1] Peloruside A displays potent antitumor activity against P388 murine leukemia cells with an IC_{50} value of 10 ng mL^{-1}.[2] It is a microtubule stabilizing agent and arrests cells in the G2-M phase of the cell cycle.[3] The clinical potential of peloruside A is highlighted by its activity against Taxol® resistant cells, being less susceptible than paclitaxel to MDR-cell lines.[4] Elucidation of its structure by NMR studies revealed a polyoxygenated macrolide containing a pyranose ring with a *Z*-configured trisubstituted alkene.

The significant biological activity of peloruside A combined with its scarcity in nature and densely functionalized structure have prompted numerous studies directed toward its synthesis. To date, a number of total syntheses[3,5–9] as well as synthetic studies of peloruside A have been reported.[10,11] Our retrosynthesis of peloruside A involved the scission of the C8–C9 bond and in the forward direction it was envisioned to create this bond by addition of the acetylide derived from alkyne **3**[12] (C1–C8 subunit) to the aldehyde **2** (C9–C19 subunit), Scheme 1. Herein, we report a stereoselective synthesis of the C9–C19 fragment of (+)-peloruside A adopting a strategy wherein two of the four stereocentres were introduced using metal complex-promoted catalytic asymmetric reactions; the remaining two by a substrate controlled reduction and enzymatic resolution. The *Z*-trisubstituted alkene is created by hydrostannation of an alkyne followed by reaction of the ensuing vinylstannane with dimethyl cuprate. Aldehyde **2** was envisioned to be obtained from alkenone **4** by a stereoselective reduction followed sequentially by protection of the resulting carbinol, selective deprotection to reveal the C9 hydroxy group and further oxidation. Alkenone **4** can be obtained from Weinreb amide **5** and the alkenyl lithium prepared from **6**. Compound **5** can be obtained from δ-lactone **7** which in turn was envisaged to be obtained by an asymmetric vinylogous Mukaiyama reaction of silyl ketene acetal **8** and aldehyde **9**.

Results and discussion

The synthesis began with the selective monoprotection of 2,2-dimethyl-1,3-propanediol **10** as its TBDPS ether **11**. Oxidation with IBX[13] cleanly afforded aldehyde **9** (P = TBDPS). The C11 stereocentre was created while extending the carbon chain by utilizing the vinylogous Mukaiyama aldol reaction pioneered by Carreira and co-workers.[14] Thus exposure of aldehyde **9** to ketene acetal **8**[15] in the presence of copper(II) fluoride/(*R*)-Tolbinap furnished the alcohol **12** (93 : 7 er, 52% yield).[16] It is noteworthy that the reaction proceeds cleanly, though in modest yield, on a sterically demanding aliphatic aldehyde as **9**. To the best of our knowledge this is the first report on a vinylogous Mukaiyama aldol reaction of **8** with an α-quaternary carbon-containing aldehyde. Heating of **12** with methanol in toluene at reflux[14] provided a chromatographically separable mixture of β-keto ester **13** and keto lactone **14** in a roughly 3 : 1 ratio. β-Keto ester **13** on *anti*-selective reduction following Evans' protocol[17] furnished diol **15** (>95% dr, 78% yield).[18] Lactonization of diol **15** promoted by anhydrous $ZnCl_2$[19]

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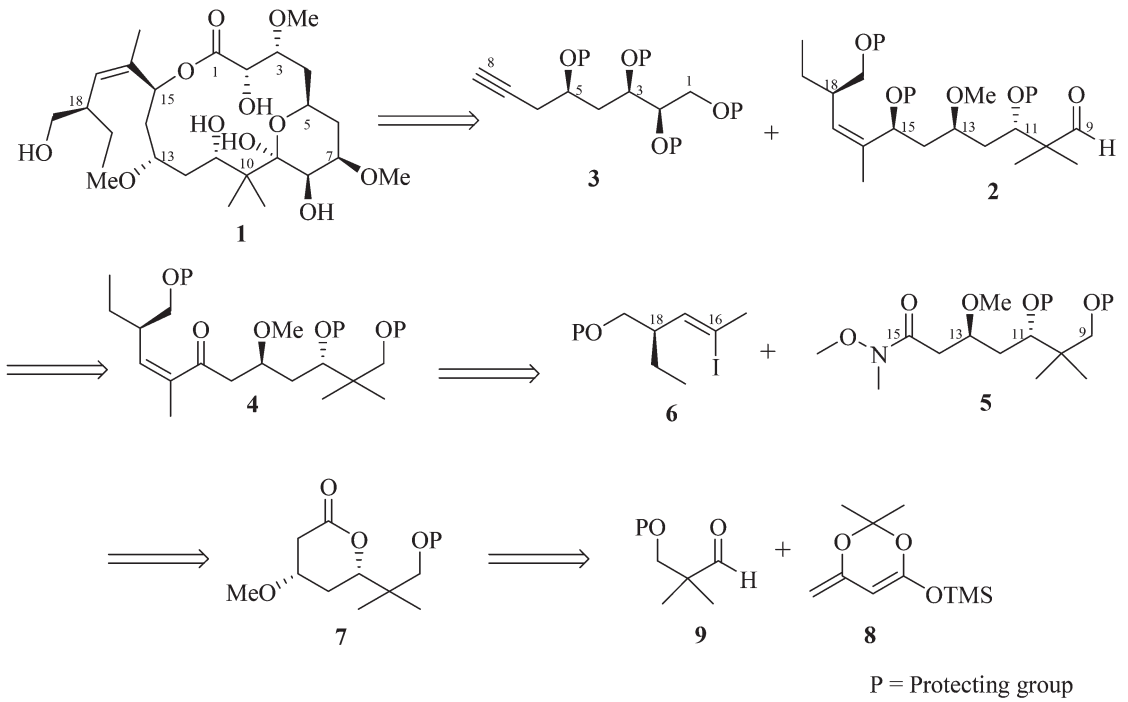
†Electronic supplementary information (ESI) available: Experimental procedures for the preparation of known compounds **11**, **9**, **8**, *anti*-1,3-acetonide of compounds **15**, **23**, **24**, **25**, **26**, **33** and *epi*-**33**. Copies of ^1H and ^{13}C NMR spectra for the compounds. See DOI: 10.1039/c3ob27508f



Scheme 1 Retrosynthetic analysis of (+)-peloruside A.

followed by treatment of the resulting hydroxy lactone **16** with MeI in the presence of Ag_2O furnished compound **7** (P = TBDPS), Scheme 2. The small quantity of keto lactone **14** was initially transformed into ene carbonate **17** by exposure to dimethyl sulfate in the presence of K_2CO_3 and further reduced with RANEY®-nickel[20] under an atmosphere of hydrogen to afford compound **7** diastereoselectively (>95% dr, 76% yield).

The introduction of a C16–C19 carbon chain and the creation of the C15 stereocentre were the next task. We initially explored the reaction of alkenyl lithium **20**, derived from iodo alkene **19**, with the Weinreb amide **18**, prepared from lactone **7**, as a means to secure α,β-unsaturated ketone **21**, expecting to reduce the keto group in **21** selectively *via* substrate control, Scheme 3.

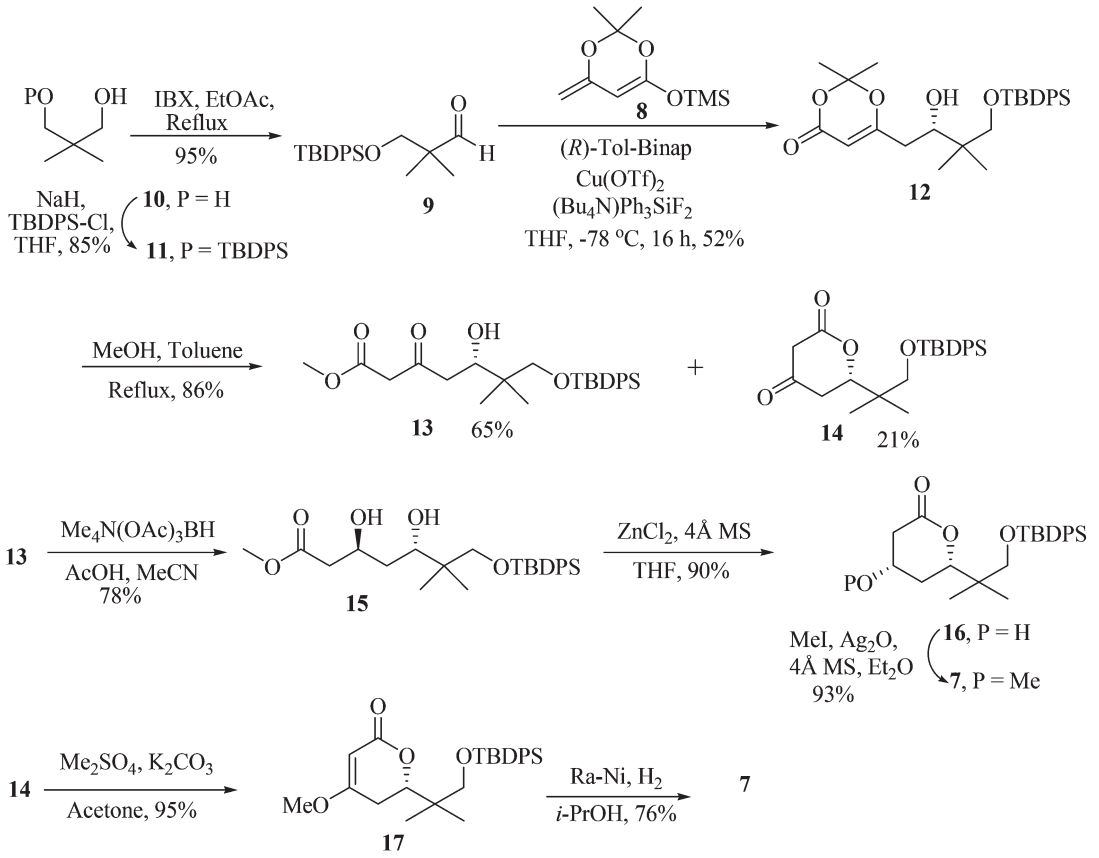
The iodo alkene **19** was prepared from diethyl 2-ethyl propanedioate **22** following a reported chemoenzymatic route.[21] Reduction of the diester **22** to diol **23** followed by selective monoprotection with TBS-Cl furnished silyl ether **24**. Resolution of **24** by lipase catalyzed transesterification using vinyl-acetate yielded optically pure alcohol **25** and acetate **26**. Hydrolysis of the acetate **26** by treatment with a catalytic quantity of anhydrous K_2CO_3 in methanol yielded alcohol *epi*-**25** that on oxidation employing Swern conditions[22] furnished aldehyde **27**. Wittig olefination following Zhao's protocol with the ylide derived from the iodo compound[23] **28** yielded iodo alkene **19** in modest yield, Scheme 4.

Lactone **7** was converted *via* Weinreb amide formation[24] to compound **29** that on treatment with TBS-OTf and 2,6-lutidine furnished amide **18**. Addition of alkenyl lithium **20**, prepared from **19** *via* lithium iodine exchange, to amide **18** afforded none of the expected ketone **21**, but the unsaturated amide **30**. The vinyl lithium reagent **20** functioned competitively as a base rather than as a nucleophile.[25] Since sp-hybridized nucleophiles are less basic than sp^2 nucleophiles, we attempted the reaction between alkynyl lithium prepared from **31** and amide **18**. The alkynyl ketone **32** was indeed obtained though in poor yield (10%) along with amide **30** as the major product (60–70),[26] Scheme 5.

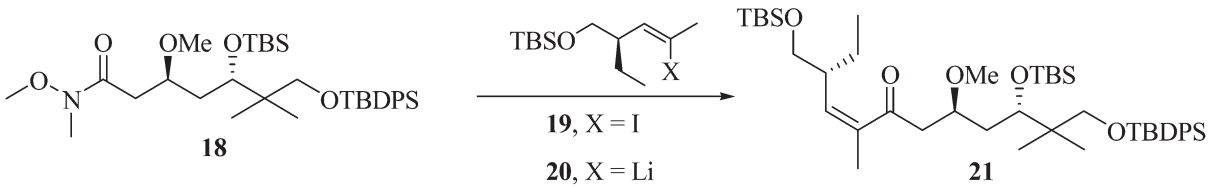
The preparation of alkyne **31** commenced with the alkynation of aldehyde **34**, obtained from **22** by the same sequence of reactions detailed in Scheme 4 except using TBDPS-Cl for monosilylation of diol **23**, using Ohira–Bestmann's protocol[27] to furnish alkyne **35**. TBAF mediated deprotection followed by protection of the resulting carbinol **36** using benzyl trichloroacetimidate in the presence of catalytic triflic acid yielded alkyne **31**, Scheme 6.

Alcohol *epi*-**33** was also converted to alkyne **31** by an initial benzyl ether formation to yield compound **37** that on TBAF mediated deprotection yielded alcohol **38**. Oxidation of **38** under Swern conditions followed by alkynation of the ensuing aldehyde yielded alkyne **31**.[28,29]

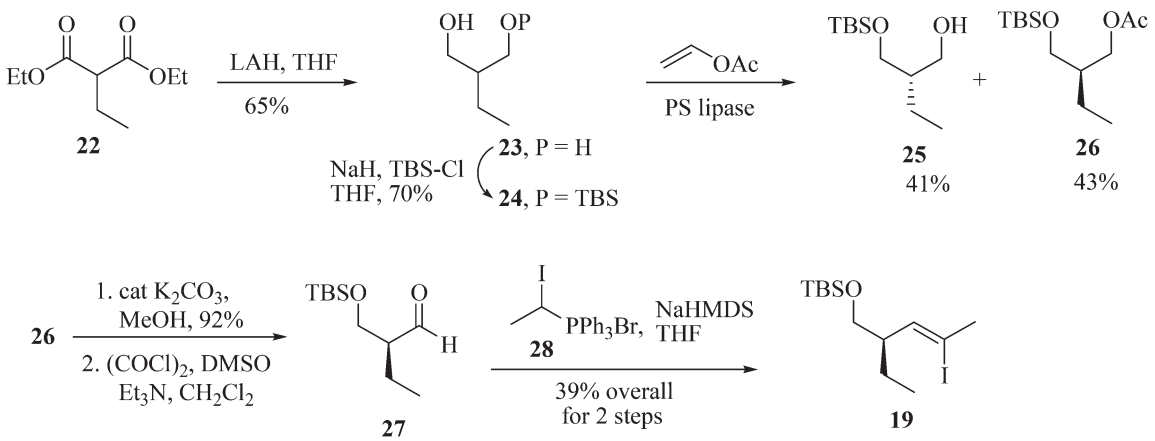
Having been unsuccessful in introducing the C16–C19 subunit by reaction of Weinreb amide **18** with alkenyl or alkynyl nucleophilic partners, we explored its introduction using Fukuyama's methodology. Lactone **7** was transformed under mild reaction conditions into thioester **39** by treatment with decanethiol[30] and trimethylaluminum.[31] Protection of the carbinol under standard conditions furnished TBS ether **40**. The alkyne **31** was coupled to thioester **40** under the conditions reported by Fukuyama[32] to furnish alkynone **32** in good yield, Scheme 7. Stereoselective reduction of alkynone **32** using Noyori's transfer-hydrogenation[33] methodology afforded the (*S*)-propargylic alcohol **41**[34,35] (8 : 2 dr, 85% yield).



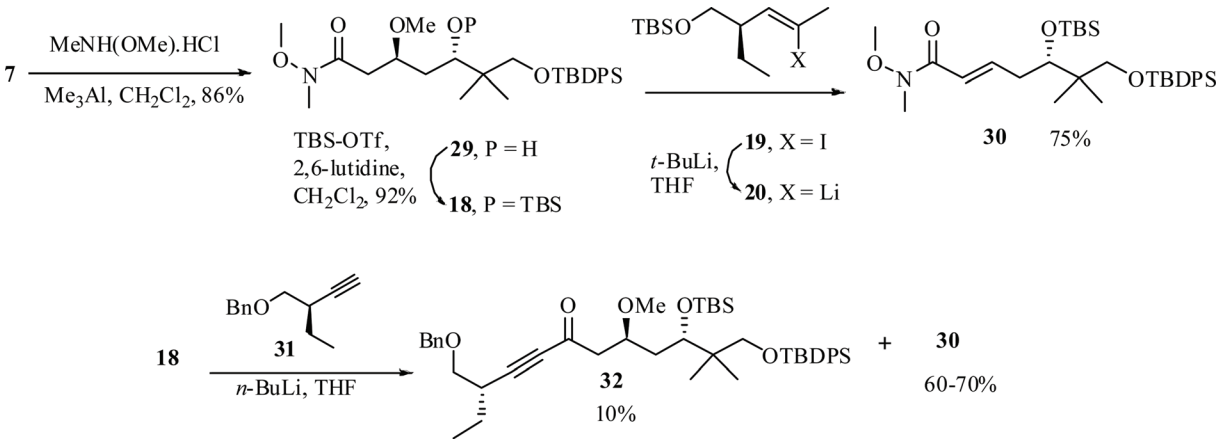
Scheme 2 Preparation of δ-lactone **7**.



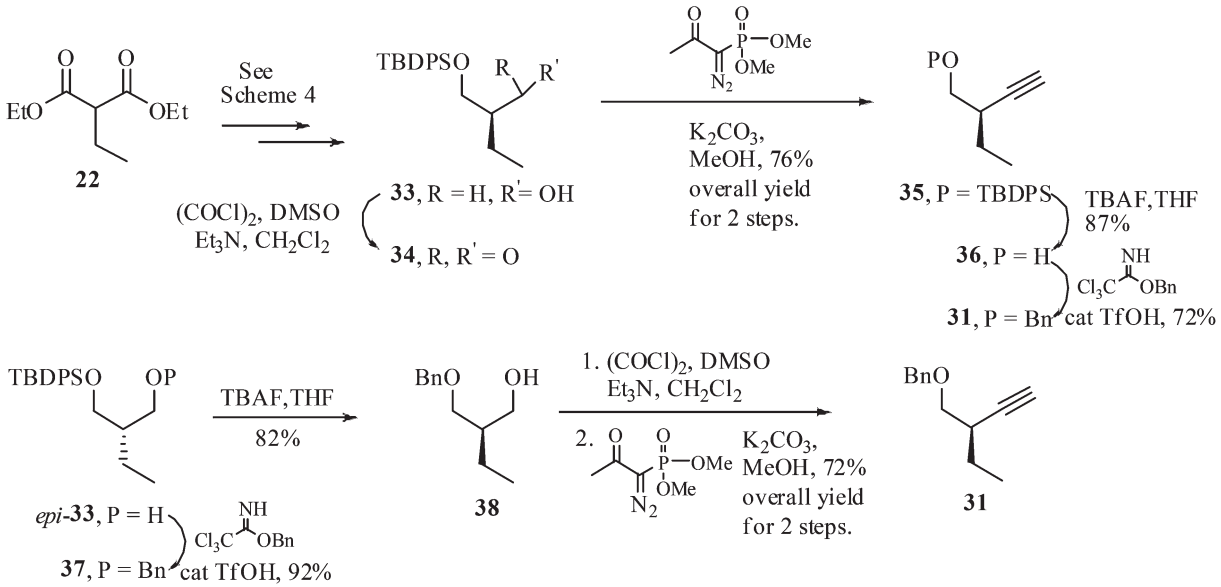
Scheme 3 Proposed route to unsaturated ketone **21**.



Scheme 4 Synthesis of iodo alkene **19**.



Scheme 5 Attempted preparation of unsaturated ketones **21** and **32**.

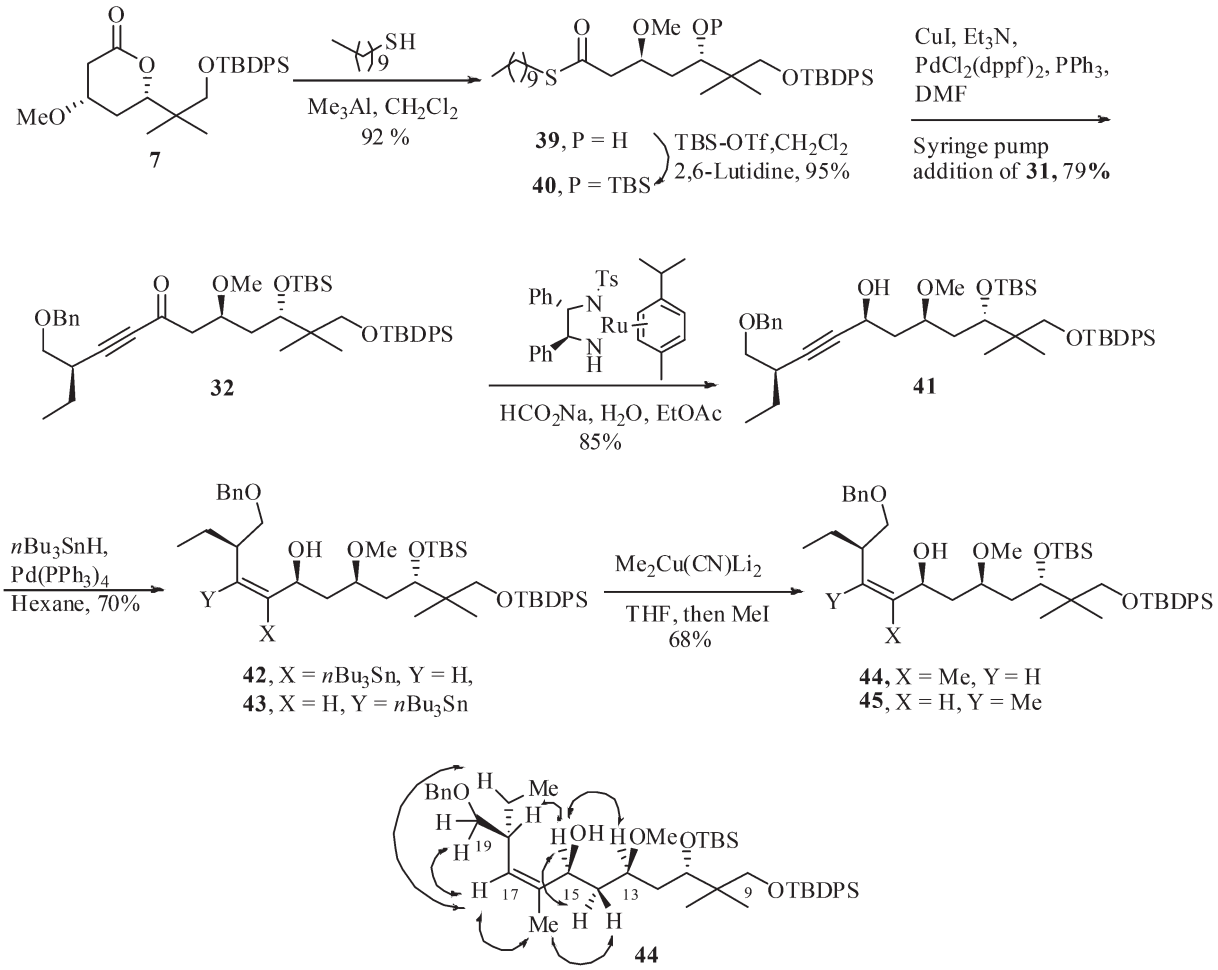


Scheme 6 Synthesis of alkyne **31**.

The major isomer **41** was separated and subjected to hydrostannation with nBu$_3$SnH in the presence of $PdCl_2(PPh_3)_2$[36] hoping to obtain the desired regioisomeric vinyl stannane **42** stereoselectively as the major isomer *via* hydroxy directed hydrostannation and also due to steric effects.[37] In the event hydrostannation of **41** in hexane afforded a 4 : 1 ratio of an inseparable mixture of vinyl stannanes **42** and **43** respectively.[38] The regioisomeric mixtures of stannanes were subjected to reaction with dimethylcopper cyanide following Lipshutz' protocol[39] to furnish a separable mixture of allyl alcohols **44** and **45**.[40] The structure of major product **44** was confirmed by ^{1}H NMR and characteristic NOE signals.[41] The C15 methine proton shows strong NOE with the C18 methine proton thus unambiguously establishing the *Z*-geometry of the trisubstituted alkene. It also reveals NOE with one of the C14 methylene protons and C13 methine proton. The olefinic proton shows NOE with the methyl group on the double bond, one of the methylene protons of the ethyl residue and the C19 methylene protons thus confirming its C17 location. The methyl group on the double bond shows NOE with the olefinic proton and one of the methylene protons at C14 proving its C16 location.

Conclusion

In summary, we have synthesized the C9–C19 fragment of peloruside A exploiting the vinylogous Mukaiyama aldol reaction, Noyori transfer-hydrogenation, *anti*-selective reduction and alkyne hydrostannation followed by cuprate addition as key steps. The fragment has been prepared in 13 steps (longest linear sequence) in 4.34% overall yield.



Scheme 7 Synthesis of the C9–C19 fragment.

Experimental section

Compound 12

A mixture of copper(II) trifluoromethanesulfonate (36 mg, 0.1 mmol) and (*R*)-Tol-BINAP (75 mg, 0.11 mmol) in THF (20 mL) was stirred at rt for 10 minutes to yield a clear yellow solution. A solution of tetrabutylammonium triphenyldifluorosilicate (TBAT) (110 mg, 0.2 mmol) in THF (2 mL) was added and stirring was continued for 10 minutes. After cooling the reaction mixture to −78 °C the ketene acetal **8** (1.6 mL, 7.5 mmol) was added dropwise followed by a solution of the aldehyde **9** (1.7 g, 5 mmol) in THF (5 mL). The color of the reaction mixture slowly changed to dark red color; the progress of the reaction was monitored by TLC. After 16 h, trifluoroacetic acid (2 mL) was added at −78 °C and the solution was allowed to warm to rt. Stirring was continued for an additional hour. The reaction mixture was diluted with ether (50 mL) and a saturated aqueous solution of $NaHCO_3$ was added dropwise until the evolution of gas ceased. The layers were separated and the aqueous layer was extracted with ether (3 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification of the residue by column chromatography using hexanes–EtOAc (8 : 2, v/v) as the eluent afforded pure aldol **12** (1.25 g, 2.6 mmol) in 52% yield as a viscous oil. TLC R_f = 0.22 (25% EtOAc–hexanes). $[\alpha]_D^{35}$ = −11.5 (*c* 1, $CHCl_3$). IR (KBr): 3474, 2959, 2933, 2859, 1752, 1635, 1391, 1274, 1108, 704, 505 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.68–7.58 (m, 4H), 7.48–7.32 (m, 6H), 5.28 (s, 1H), 3.83 (dd, *J* = 11.1, 1.5 Hz, 1H), 3.51–3.42 (m, 2H), 2.35 (dd, *J* = 14.2, 2.4 Hz, 1H), 2.18 (dd, *J* = 14.2, 10.6 Hz, 1H), 1.70 (s, 6H), 1.07 (s, 9H), 0.89 (s, 3H), 0.87 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4, 161.1, 135.4, 134.6, 132.3, 129.8, 127.9, 94.9, 74.3, 72.1, 38.8, 36.5, 26.6, 25.5, 24.1, 21.5, 19.2, 19.0. MS (ESI) 500 $[M + NH_4]^+$. HRMS (ESI) *m*/*z* calcd for $C_{28}H_{38}O_5NaSi$ 505.23807; found 505.23918.

Compounds 13 and 14

A solution of aldol adduct **12** (4.82 g, 10 mmol) in anhydrous methanol (8 mL, 200 mmol) and anhydrous toluene (20 mL) was heated to 110 °C in a sealed vessel for 1 h. The solvent was evaporated and the residue was purified by column chromatography using hexanes–EtOAc (8 : 2, v/v) to provide ketoester **13** (2.96 g, 6.5 mmol) in 65% yield as a viscous oil along with ketolactone **14** (890 mg, 2.1 mmol) in 21% yield as a viscous

oil. Ketoester **13**: TLC R_f = 0.35 (30% EtOAc–hexanes). $[\alpha]_D^{35}$ = −17.5 (*c* 1, $CHCl_3$). IR (KBr): 3490, 3069, 2933, 2858, 1744, 1716, 1428, 1262, 1108, 822, 704, 505 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.90–7.72 (m, 4H), 7.48–7.36 (m, 6H), 4.11 (dd, *J* = 9.2, 3.0 Hz, 1H), 3.73 (s, 3H), 3.55 (s, 2H), 3.49–3.44 (m, 2H), 2.73–2.59 (m, 2H), 1.06 (s, 9H), 0.90 (s, 3H), 0.83 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.2, 167.5, 135.5, 132.8, 132.7, 129.7, 127.7, 73.4, 71.8, 52.1, 49.7, 45.3, 38.7, 26.8, 23.3, 21.5, 19.1. MS (ESI) 479 $[M + Na]^+$. HRMS (ESI) *m*/*z* calcd for $C_{26}H_{36}O_5NaSi$ 479.22242; found 479.22133. Ketolactone **14**: TLC R_f = 0.15 (30% EtOAc–hexanes). $[\alpha]_D^{35}$ = −15.3 (*c* 1, $CHCl_3$). IR (KBr): 2931, 1717, 1466, 1393, 1219, 1102, 822, 765, 700, 503 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.64–7.61 (m, 4H), 7.46–7.36 (m, 6H), 4.71 (dd, *J* = 12.1 Hz, 3.1 Hz, 1H), 3.70 (d, *J* = 10.6 Hz, 1H), 3.52 (d, *J* = 18.9 Hz, 1H), 3.40 (d, *J* = 10.6 Hz, 1H), 3.38 (d, *J* = 18.9 Hz, 1H), 2.63 (dd, *J* = 18.1, 3.1 Hz, 1H), 2.50 (dd, *J* = 18.1, 12.1 Hz, 1H), 1.06 (s, 9H), 0.99 (s, 3H), 0.97 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.7, 167.2, 135.5, 132.9, 129.8, 127.7, 78.3, 68.9, 60.3, 46.9, 38.7, 26.8, 20.4, 19.3, 19.2. MS (ESI) 447 $[M + Na]^+$. HRMS (ESI) *m*/*z* calcd for $C_{25}H_{32}O_4NaSi$ 447.1967; found 447.1974.

Compound 15

To a solution of $Me_4NBH(OAc)_3$ (7.9 g, 30 mmol) in anhydrous acetonitrile (15 mL) was added acetic acid (15 mL) dropwise. The mixture was stirred at rt for 30 min. The mixture was cooled to −35 °C and a solution of keto ester **13** (2.28 g, 5 mmol) in anhydrous acetonitrile (5 mL) was added and stirring was continued for 18 h at −35 °C. The reaction mixture was quenched with aqueous sodium potassium tartrate and the mixture was allowed to warm to rt. The mixture was diluted with DCM and washed with aqueous $NaHCO_3$ solution. The layers were separated and the aqueous layer was re-extracted with DCM (4 × 40 mL). The combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4, concentrated and the residue purified by column chromatography using hexanes–EtOAc (7 : 3, v/v) to provide diol **15** (1.66 g, 3.9 mmol) in 78% yield as a highly viscous oil. TLC R_f = 0.15 (30% EtOAc–hexanes). $[\alpha]_D^{35}$ = −2.6 (*c* 1, $CHCl_3$). IR (KBr): 3488, 3047, 2951, 2882, 1727, 1349, 833, 703, 502 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.74–7.62 (m, 4H), 7.52–7.37 (m, 6H), 4.42–4.37 (m, 1H), 3.92 (dd, *J* = 9.3, 2.8 Hz, 1H), 3.75–3.71 (m, 4H), 3.52 (d, *J* = 5.6 Hz, 1H), 2.58 (d, *J* = 6.5 Hz, 2H), 1.63–1.57 (m, 2H), 1.07 (s, 9H), 0.90 (s, 3H), 0.81 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.1, 135.6, 133.2, 129.7, 127.7, 75.2, 73.6, 65.8, 51.7, 41.4, 37.2, 30.9, 26.8, 19.3, 19.1, 18.7. MS (ESI) 481 $[M + Na]^+$. HRMS (ESI) *m*/*z* calcd for $C_{26}H_{38}O_5NaSi$ 481.23807; found 481.23625.

Compound 16

To a mixture of flame dried $ZnCl_2$ (810 mg, 6 mmol) and activated 4 Å molecular sieves (1.5 g) in anhydrous THF (12 mL) was added a solution of diol **15** (1.35 g, 3 mmol) in anhydrous THF (6 mL) and the mixture was heated to reflux for 3 h. The mixture was filtered through a pad of Celite and the filter cake washed with ethyl acetate (2 × 10 mL). The combined filtrates were evaporated and the crude residue was purified by column chromatography using hexanes–EtOAc (7 : 3, v/v) to yield pure hydroxy lactone **16** (1.16 g, 2.7 mmol) in 90% yield as a viscous oil. TLC R_f = 0.10 (30% EtOAc–hexanes). $[\alpha]_D^{35}$ = +5.1 (*c* 1, $CHCl_3$). IR (KBr): 3423, 2923, 2853, 1731, 1462, 1108, 704, 504 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.70–7.61 (m, 4H), 7.48–7.32 (m, 6H), 4.29 (dd, *J* = 12.1, 2.3 Hz, 1H), 4.26–4.17 (m, 1H), 3.64 (d, *J* = 9.8 Hz, 1H), 3.38 (d, *J* = 9.8 Hz, 1H), 2.87 (dd, *J* = 16.6, 5.2 Hz, 1H), 2.42 (dd, *J* = 16.6, 7.5 Hz, 1H), 2.19–2.08 (m, 1H), 1.63–1.50 (m, 1H), 1.05 (s, 9H), 0.96 (s, 3H), 0.92 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.0, 135.5, 133.4, 133.2, 129.7, 127.7, 80.1, 69.3, 64.1, 39.4, 39.1, 32.4, 26.9, 20.4, 19.6, 19.3. MS (ESI) 444 $[M + NH_4]^+$. HRMS (ESI) *m*/*z* calcd for $C_{25}H_{34}O_4NaSi$ 449.21186; found 449.21125.

Lactone 7

A solution of **16** (4.26 g, 10 mmol) in anhydrous Et_2O (10 mL) was added to a slurry of activated 4 Å MS (4 g) and silver oxide (3.48 g, 15 mmol) in dry Et_2O (20 mL). To this slurry freshly distilled MeI (3.1 mL, 50 mmol) was added, heated to reflux for 1 h, filtered through a pad of Celite and the filter cake washed with Et_2O (3 × 20 mL). The filtrate was concentrated and the crude compound purified by column chromatography using hexanes–EtOAc (9 : 1, v/v) to provide **7** (4.1 g, 9.3 mmol) in 93% yield as a viscous oil. TLC R_f = 0.45 (25% EtOAc–hexanes). $[\alpha]_D^{35}$ = +4.7 (*c* 1, $CHCl_3$). IR (KBr): 2927, 2859, 1744, 1468, 1247, 1102, 821, 702, 502 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.72–7.68 (m, 4H), 7.49–7.38 (m, 6H), 4.33 (dd, *J* = 12.3, 2.0 Hz, 1H), 3.81–3.75 (m, 1H), 3.69 (d, *J* = 9.6 Hz, 1H), 3.43 (d, *J* = 9.6 Hz, 1H), 3.39 (s, 3H), 2.88 (dd, *J* = 17.1, 5.5 Hz, 1H), 2.53 (dd, *J* = 17.1, 6.8 Hz, 1H), 2.32–2.26 (m, 1H), 1.57–1.54 (m, 1H), 1.11 (s, 9H), 1.02 (s, 3H), 0.98 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.5, 135.5, 133.2, 133.1, 129.6, 127.6, 79.7, 72.7, 69.3, 55.8, 39.1, 36.1, 29.4, 26.8, 20.3, 19.6, 19.2. MS (ESI) 458 $[M + NH_4]^+$. HRMS (ESI) *m*/*z* calcd for $C_{26}H_{36}O_4NaSi$ 463.22751; found 463.22851.

Compound 17

To a solution of keto lactone **14** (848 mg, 2 mmol) in anhydrous acetone (10 mL) was added freshly purified $(MeO)_2SO_2$ (227 mL, 2.4 mmol), and solid K_2CO_3 (332 mg, 2.4 mmol) portionwise over 2 h. After further stirring at rt for 3 h, TLC examination revealed complete consumption of keto lactone. The reaction mixture was diluted with ether (50 mL) and washed with water (2 × 20 mL). The aqueous layer was extracted with ether (2 × 25 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. Purification of the residue by column chromatography using hexanes–EtOAc (8 : 2, v/v) afforded enol ether **17** (850 mg, 1.94 mmol) in 95% yield. TLC R_f = 0.3 (25% EtOAc–hexanes). $[\alpha]_D^{36}$ = −1.8 (*c* 1, $CHCl_3$). IR (KBr): 2956, 2802, 1761, 1441, 1114, 887, 724, 512 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.68–7.61 (m, 4H), 7.44–7.36 (m, 6H), 5.15 (s, 1H), 4.46 (dd, *J* = 13.4, 3.3 Hz, 1H), 3.75 (s, 3H), 3.66 (d, *J* = 10.0 Hz, 1H), 3.40 (d, *J* = 10.0 Hz, 1H), 2.69–2.55 (m, 1H), 2.24 (dd, *J* = 16.9, 3.5 Hz, 1H), 1.04 (s, 9H), 0.99 (s, 3H), 0.94 (s, 3H). ^{13}C NMR (75 MHz,

$CDCl_3$): δ 173.5, 167.4, 135.4, 133.2, 133.0, 129.5, 127.6, 90.0, 79.0, 68.9, 55.9, 38.7, 28.1, 26.7, 20.5, 19.7, 19.2. MS (ESI) 456 $[M + NH_4]^+$. HRMS (ESI) *m/z* calcd for $C_{26}H_{34}O_4NaSi$ 461.21186; found 461.21228.

Lactone 7

To a solution of compound **17** (219 mg, 0.5 mmol) in iso-propanol (5 mL) was added a slurry of catalytic amount of RANEY®-nickel. The reaction mixture was stirred for 6 h under an atmosphere of hydrogen at rt. The mixture was filtered through Celite, and the filter cake washed with EtOAc (3 × 10 mL). The combined filtrate was concentrated and the residue purified by column chromatography using hexanes–EtOAc (8 : 2, v/v) to furnish compound **7** (172 mg, 0.39 mmol) in 78% yield as a viscous oil.

Weinreb amide 29

To an ice cooled solution of *N*,*O*-dimethylhydroxylamine·HCl (588 mg, 6 mmol) in anhydrous CH_2Cl_2 (15 mL) was added Me_3Al (3 mL, 6 mmol, 2 M in toluene) slowly at 0 °C. After 20 minutes compound **7** (2.2 g, 5 mmol) in anhydrous CH_2Cl_2 (10 mL) was added slowly and the mixture stirred at the same temperature for 30 minutes. The reaction mixture was diluted with CH_2Cl_2 (30 mL) and quenched with ice pieces carefully followed by aq. 1 N HCl (12 mL). The layers were separated and the aqueous layer was extracted with DCM (3 × 25 mL). The combined organic layers were washed with aqueous $NaHCO_3$, water, brine, dried over Na_2SO_4 and concentrated. Purification of the residue by column chromatography using hexanes–EtOAc (7 : 3, v/v) afforded amide **29** (2.15 g, 4.3 mmol) in 86% yield as a viscous oil. TLC R_f = 0.15 (30% EtOAc–hexanes). $[\alpha]_D^{36}$ = −13.1 (*c* 1, $CHCl_3$). IR (KBr): 3485, 3070, 3049, 2961, 2933, 2859, 1724, 1469, 1427, 1254, 1189, 1107, 1002, 822, 744, 505 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.68–7.6 (m, 4H), 7.44–7.32 (m, 6H), 4.08–3.96 (m, 1H), 3.80 (dd, *J* = 7.9, 3.9 Hz, 1H), 3.68 (s, 3H), 3.53 (d, *J* = 9.8 Hz, 1H), 3.43–3.4 (m, 4H), 3.17 (s, 3H), 2.86 (dd, *J* = 15.8, 4.9 Hz, 1H), 2.48 (dd, *J* = 15.8, 5.9 Hz, 1H), 1.72–1.60 (m, 2H), 1.06 (s, 9H), 0.87 (s, 3H), 0.86 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.3, 135.5, 132.9, 129.6, 127.6, 75.9, 73.7, 71.9, 61.1, 57.6, 38.9, 36.8, 35.9, 31.9, 26.7, 21.8, 19.2, 19.1. MS (ESI) 524 $[M + Na]^+$. HRMS (ESI) *m/z* calcd for $C_{28}H_{44}NO_5Si$ 502.2988; found 502.3002.

Compound 18

To a solution of amide **29** (2 g, 4 mmol) in anhydrous CH_2Cl_2 (20 mL) cooled at 0 °C was added anhydrous 2,6-lutidine (0.72 mL, 6 mmol) followed by TBS-OTf (1.1 mL, 4.8 mmol). After 15 min the reaction was quenched by the addition of water. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, concentrated and the resulting residue was purified by column chromatography using hexanes–EtOAc (9 : 1, v/v) to afford **18** (2.26 g, 3.68 mmol) in 92% yield as a viscous oil. TLC R_f = 0.25 (20% EtOAc–hexanes). $[\alpha]_D^{34}$ = −13.9 (*c* 1, $CHCl_3$). IR (KBr): 3069, 2933, 1667, 1467, 1106, 833, 704 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.68–7.60 (m, 4H), 7.42–7.28 (m, 6H), 3.95–3.88 (m, 1H), 3.76 (d, *J* = 7.3 Hz, 1H), 3.69 (s, 3H), 3.49 (d, *J* = 9.6 Hz, 1H), 3.38–3.28 (m, 4H), 3.15 (s, 3H), 2.78 (dd, *J* = 14.7, 5.8 Hz, 1H), 2.29 (dd, *J* = 14.9, 5.6 Hz, 1H), 1.87–1.74 (m, 1H), 1.49–1.38 (m, 1H), 1.07 (s, 9H), 0.93 (s, 3H), 0.82 (m, 12H), 0.01 (s, 3H), −0.07 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.2, 135.7, 133.8, 129.4, 127.5, 74.4, 74.1, 70.1, 61.1, 56.2, 41.00, 39.6, 37.5, 32.1, 26.9, 26.2, 21.6, 20.4, 19.3, 18.4, −3.4, −4.0. MS (ESI) 638 $[M + Na]^+$. HRMS (ESI) *m/z* calcd for $C_{34}H_{57}O_5NNaSi_2$ 638.36675; found 638.36774.

Compound 19

To a cooled (−78 °C) solution of oxalyl chloride (1.75 mL, 20 mmol) in anhydrous DCM (30 mL) was added dimethylsulfoxide (4.7 mL, 40 mmol) dropwise. After 30 min a solution of alcohol, *epi*-**25** (2.18 g, 10 mmol) in DCM (30 mL) was added dropwise. The reaction mixture was stirred for 1.5 h before adding triethylamine (9 mL, 60 mmol). The resulting suspension was warmed slowly to rt, diluted with H_2O (30 mL) and extracted with DCM (3 × 50 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude aldehyde **27** as a light yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ 9.67 (d, *J* = 1.9 Hz, 1H), 3.86 (d, *J* = 5.4 Hz, 2H), 2.35–2.26 (m, 1H), 1.79–1.65 (m, 1H), 1.59–1.46 (m, 1H), 0.95 (t, *J* = 7.5 Hz, 3H), 0.87 (s, 9H), 0.04 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 180.5, 63.5, 50.0, 25.7, 21.3, 18.1, 11.6, −5.6. The crude aldehyde was taken ahead to the next step without further purification for fear of epimerization. To a suspension of $EtPh_3PBr$ (10.1 g, 22 mmol) in anhydrous THF (80 mL) cooled at −23 °C was added *n*-BuLi (8 mL, 20 mmol, 2.5 M in hexane) dropwise over 10 minutes to form a dark red solution. After an additional 30 minutes, the ylide was added *via* cannula over 20 minutes to a cooled (−78 °C) solution of iodine (5.4 g, 21 mmol) in anhydrous THF (80 mL). The resulting yellow slurry was stirred for 15 minutes and warmed to −23 °C. NaHMDS (18 mL, 18 mmol, 1 M in THF) was added dropwise over 10 minutes, and the resulting orange suspension was stirred for 20 minutes and cooled to −78 °C. A solution of crude aldehyde **27** (2.2 g, 10 mmol) in THF (20 mL) was added dropwise over 10 minutes and stirred for 2 h at the same temperature. The reaction mixture was quenched with MeOH (2.5 mL). The reaction mixture was filtered through a pad of Celite and the filter cake washed with ether (4 × 50 mL). The combined filtrates were washed with aqueous $Na_2S_2O_3$, brine, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography using hexanes–EtOAc (95 : 5, v/v) to furnish vinyl iodide **19** (1.33 g, 3.9 mmol) in 39% overall yield as an oil. TLC R_f = 0.15 (5% EtOAc–hexanes). $[\alpha]_D^{35}$ = +1.9 (*c* 1, $CHCl_3$). IR (KBr): 2956, 2929, 2857, 1465, 1253, 1105, 1059, 835, 775 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 5.20 (dd, *J* = 9.0, 1.1 Hz, 1H), 3.58–3.52 (m, 1H), 3.50–3.42 (m, 1H), 2.52 (s, 3H), 2.38–2.28 (m, 1H), 1.66–1.52 (m, 1H), 1.40–1.32 (m, 1H), 0.94–0.86 (m, 12H), 0.03 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.2, 101.4, 64.9, 50.9, 33.8, 25.9, 23.6, 18.3, 11.5, −5.3.

Compound 35

Aldehyde **34** was prepared in much the same way from **33** as disclosed earlier for the preparation of aldehyde **27** from *epi*-**25**. TLC R_f = 0.40 (10% EtOAc–hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.73 (d, J = 2.26 Hz, 1H), 7.70–7.61 (m, 4H), 7.43–7.36 (m, 6H), 3.88 (d, J = 6.0 Hz, 2H), 2.39–2.32 (m, 1H), 1.77–1.65 (m, 1H), 1.56–1.47 (m, 1H), 1.03 (s, 9H), 0.87 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.6, 135.5, 134.7, 129.5, 127.7, 62.2, 55.8, 26.7, 19.2, 18.4, 11.4. Aldehyde **34** without purification was employed in the next step. To the solution of the crude aldehyde **34** (1.5 g, 4.4 mmol) in anhydrous MeOH (22 mL) was added the Ohira–Bestmann reagent (1.02 g, 5.28 mmol) and solid K_2CO_3 (1.8 g, 13.2 mmol) at rt. The reaction mixture was stirred for 8 h at the same temperature. The reaction was quenched by addition of 10% aqueous HCl, and the mixture was extracted with ether (4 × 50 mL). The combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated. Purification of the residue by column chromatography using hexanes–EtOAc (95 : 5, v/v) afforded alkyne **35** (1.12 g, 3.3 mmol) in 76% overall yield for two steps as a colorless oil. TLC R_f = 0.44 (5% EtOAc–hexanes). $[\alpha]_D^{37}$ = +2.1 (c 1.1, $CHCl_3$). IR (KBr): 2961, 2931, 2860, 1427, 1110, 703 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68–7.60 (m, 4H), 7.40–7.28 (m, 6H), 3.72 (dd, J = 9.8, 5.2 Hz, 1H), 3.58 (dd, J = 9.8, 7.5 Hz, 1H), 2.53–2.40 (m, 1H), 1.95 (d, J = 2.2 Hz, 1H), 1.77–1.67 (m, 1H), 1.52–1.41 (m, 1H), 1.05 (s, 9H), 0.99 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.6, 133.6, 129.6, 127.6, 85.3, 70.0, 65.8, 36.1, 26.8, 24.0, 19.3, 11.3. MS (ESI) 359 $[M + Na]^+$. HRMS (ESI) m/z calcd for $C_{22}H_{28}ONaSi$ 359.18016; found 359.18121.

Compound 36

To a solution of alkyne **35** (1 g, 3 mmol) in anhydrous THF (9 mL) cooled at 0 °C was added TBAF (3.6 mL, 3.6 mmol, 1 M in THF). After 1 h the reaction mixture was concentrated and the crude compound was purified by column chromatography using EtOAc–hexanes (1 : 9 to 2 : 8, v/v) to afford pure hydroxyalkyne **36** (255 mg, 2.6 mmol) in 87% yield as a colorless oil. TLC R_f = 0.1 (10% EtOAc–hexanes). $[\alpha]_D^{37}$ = +2.8 (c 1, $CHCl_3$). IR (KBr): 3428, 2972, 2965, 2902, 1397, 1214, 703 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.71–3.53 (m, 2H), 2.57–2.47 (m, 1H), 2.15 (d, J = 2.3, 1H), 1.62–1.45 (m, 2H), 0.88 (t, J = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 82.6, 73.0, 69.9, 33.7, 24.4, 11.2.

Compound 31

To a solution of hydroxy alkyne **36** (196 mg, 2 mmol) and freshly prepared benzyl imidate (582 mg, 3 mmol) in a mixture of anhydrous CH_2Cl_2 (5 mL) and cyclohexane (5 mL) cooled at 0 °C was added a catalytic amount of triflic acid (2 drops). After 16 h, the reaction mixture was quenched with aqueous $NaHCO_3$. The mixture was filtered through a pad of Celite and the filter cake washed with a mixture of CH_2Cl_2 and cyclohexane. The combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated to provide the crude product which was purified by column chromatography using hexanes–EtOAc (95 : 5, v/v) to afford pure product **31** (270 mg, 1.44 mmol) in 72% yield as a colorless oil. TLC R_f = 0.4 (5% EtOAc–hexanes). $[\alpha]_D^{37}$ = +1.9 (c 1, $CHCl_3$). IR (KBr): 2961, 2928, 2873, 1456, 1097, 739 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38–7.26 (m, 5H), 4.56 (s, 2H), 3.54 (dd, J = 9.0, 6.7 Hz, 1H), 3.45 (dd, J = 9.0, 6.7 Hz, 1H), 2.68–2.56 (m, 1H), 2.09 (d, J = 2.2 Hz, 1H), 1.73–1.63 (m, 1H), 1.56–1.42 (m, 1H), 1.02 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.0, 128.2, 127.4, 126.4, 84.9, 72.9, 72.1, 69.9, 33.7, 24.3, 11.1.

Compound 37

Compound **37** was prepared from *epi*-**33** (2.72 g, 8 mmol) following the same procedure described for the preparation of compound **31** from alcohol **36**, in 92% yield (3.2 g, 7.36) after column chromatography using hexanes–EtOAc (97 : 3, v/v) as the eluent. TLC R_f = 0.6 (5% EtOAc–hexanes). $[\alpha]_D^{37}$ = +0.8 (c 1, $CHCl_3$). IR (KBr): 2931, 2908, 1792, 1767, 1214, 1110, 908, 702 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77–7.58 (m, 4H), 7.43–7.22 (m, 11H), 4.48 (s, 2H), 3.75–3.46 (m, 4H), 1.77–1.68 (m, 1H), 1.48–1.38 (m, 2H), 1.03 (s, 9H), 0.86 (t, J = 7.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.9, 135.5, 133.8, 129.4, 128.2, 127.7, 127.5, 127.3, 127.2, 72.9, 70.3, 63.3, 43.0, 26.9, 20.9, 19.3, 11.6. MS (ESI) 455 $[M + Na]^+$. HRMS (ESI) m/z calcd for $C_{28}H_{36}O_2NaSi$ 455.23768; found 455.23761.

Compound 38

Compound **38** was prepared following the same procedure disclosed for preparation of **36**. Compound **37** (2.6 g, 6 mmol) provided product **38** (950 mg, 4.9 mmol) in 82% yield after column chromatography using hexanes–EtOAc (95 : 5, v/v) as the eluent. TLC R_f = 0.2 (10% EtOAc–hexanes). $[\alpha]_D^{37}$ = +3.2 (c 1.1, $CHCl_3$). IR (KBr): 3302, 2964, 2930, 1455, 1097, 698 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34–7.22 (m, 5H), 4.49 (s, 2H), 3.67 (dd, J = 10.7, 3.4 Hz, 1H), 3.62–3.54 (m, 2H), 3.43 (d, J = 8.8, 1.7 Hz, 1H), 1.80–1.68 (m, 1H), 1.38–1.23 (m, 2H), 0.92 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.9, 127.9, 127.1, 72.8, 72.1, 63.9, 42.0, 20.5, 11.2. MS (ESI) 217 $[M + Na]^+$. HRMS (ESI) m/z calcd for $C_{12}H_{18}O_2Na$ 217.11990; found 217.11976.

Compound 31

Compound 31 was prepared from alcohol **38** following the same two step sequence disclosed for the preparation of alkyne **35** from alcohol **33**. Compound **38** (776 mg, 4 mmol) yielded alkyne **31** (540 mg, 2.9 mmol) in 72% overall yield after column chromatography using hexanes–EtOAc (98 : 2, v/v) as the eluent. The physical characteristics were identical to those obtained from alcohol **36**.

Compound 30

To a solution of iodo alkene **19** (57 mg, 0.3 mmol) in anhydrous THF (1 mL) cooled at 0 °C was added *t*-BuLi (0.19 mL, 0.3 mmol, 1.6 M in hexane) slowly. After 1 h the reaction mixture was cooled to −78 °C and the solution of amide **18** (154 mg, 0.25 mmol) in anhydrous THF (1 mL) was added slowly. After 3 h of stirring at the same temperature the

reaction mixture was quenched by the addition of aq. NH_4Cl. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated to provide the crude material. Purification by column chromatography using hexanes–EtOAc (85 : 15, v/v) provided compound **30** (118 mg, 0.2 mmol) in 80% yield as a viscous oil. TLC R_f = 0.28 (30% EtOAc–hexanes). $[\alpha]_D^{35}$ = −8.1 (*c* 1, $CHCl_3$). IR (KBr) 3052, 2948, 1672, 1552, 1153, 956, 833, 706 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.68–7.60 (m, 4H), 7.44–7.32 (m, 6H), 6.97 (ddd, *J* = 14.8, 8.3, 6.4 Hz, 1H), 6.32 (d, *J* = 14.8 Hz, 1H), 3.75 (dd, *J* = 6.4, 4.6 Hz, 1H), 3.66 (s, 3H), 3.49 (d, *J* = 9.2 Hz, 1H), 3.34 (d, *J* = 9.2 Hz, 1H), 3.29 (s, 3H), 2.58–2.50 (m, 1H), 2.38–2.30 (m, 1H), 1.09 (s, 9H), 0.97 (s, 3H), 0.85 (s, 9H), 0.83 (s, 3H), 0.02 (s, 3H), −0.06 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.7, 146.6, 135.6, 133.6, 129.5, 127.5, 119.6, 76.0, 70.2, 61.5, 41.3, 36.7, 32.2, 26.9, 26.0, 21.3, 21.0, 19.3, 18.2, −3.5, −4.3. MS (ESI) 606 $[M + Na]^+$. HRMS (ESI) *m*/*z* calcd for $C_{33}H_{53}O_4NNaSi_2$ 606.34053; found 606.34089.

Compound 39

To a solution of decanethiol (2.1 g, 12 mmol) in anhydrous CH_2Cl_2 (24 mL) cooled at 0 °C was added Me_3Al (4.5 mL, 9 mmol, 2 M in toluene) dropwise over 5 minutes and the mixture was stirred for another 30 minutes. A solution of lactone **7** (2.64 g, 6 mmol) in anhydrous CH_2Cl_2 (12 mL) was added slowly over a period of 10 min. After 1 h the reaction mixture was diluted with CH_2Cl_2 (20 mL) and poured slowly into a 250 mL beaker containing ice cooled water (20 mL) with stirring. Aq. 1 N HCl (10 mL) was added and layers were separated. The aqueous layer was extracted with DCM (3 × 20 mL). The combined organic layers were washed with aqueous $NaHCO_3$, water, brine, dried over Na_2SO_4 and concentrated. Purification of the residue by column chromatography using hexanes–EtOAc (9 : 1, v/v) furnished **39** (3.4 g, 5.5 mmol) in 92% yield as a viscous oil. TLC R_f = 0.10 (20% EtOAc–hexanes). $[\alpha]_D^{34}$ = −8.6 (*c* 1, $CHCl_3$). IR (KBr): 3446, 3070, 2863, 1697, 1086, 803, 616 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.69–7.62 (m, 4H), 7.45–7.36 (m, 6H), 4.29 (dd, *J* = 12.2, 2.6 Hz, 1H), 3.79–3.72 (m, 1H), 3.65 (d, *J* = 9.8 Hz, 1H), 3.39 (d, *J* = 9.8 Hz, 1H), 3.33 (s, 3H), 2.83 (dd, *J* = 16.8, 5.8 Hz, 1H), 2.54–2.44 (m, 2H), 2.30–2.20 (m, 1H), 1.64–1.46 (m, 3H) 1.41–1.24 (m, 15H), 1.07 (s, 9H), 0.98 (s, 3H), 0.95 (s, 3H), 0.94 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4, 135.4, 133.2, 133.0, 129.6, 127.6, 79.6, 72.7, 69.3, 55.8, 39.1, 36.1, 33.9, 31.7, 29.4, 29.2, 28.9, 28.2, 26.8, 24.5, 22.5, 20.3, 19.6, 19.2, 14.0. MS (ESI) 637 $[M + Na]^+$. HRMS (ESI) *m*/*z* calcd for $C_{36}H_{58}O_5NaSi_2$ 637.37173; found 637.37226.

Compound 40

To a solution of **39** (2.4 g, 4 mmol) in anhydrous CH_2Cl_2 (12 mL) cooled at 0 °C was added anhydrous 2,6-lutidine (0.71 mL, 6 mmol) followed by TBS-OTf (1.1 mL, 4.8 mmol). After 15 minutes the reaction mixture was quenched by addition of water. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated and the residue was purified by column chromatography using hexanes–EtOAc (95 : 5, v/v) to afford silyl ether **40** (2.77 g, 3.8 mmol) in 95% yield as a viscous oil. TLC R_f = 0.24 (10% EtOAc–hexanes). $[\alpha]_D^{35}$ = −9.8 (*c* 1, $CHCl_3$). IR (KBr): 2927, 2856, 1689, 1466, 1086, 772, 702 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.69–7.64 (m, 4H), 7.44–7.32 (m, 6H), 3.91–3.82 (m, 1H), 3.74 (d, *J* = 7.5 Hz, 1H), 3.49 (d, *J* = 9.8 Hz, 1H), 3.32–3.30 (m, 4H), 2.90–2.83 (m, 2H), 2.53 (dd, *J* = 14.3, 6.0 Hz, 1H), 1.82 (dd, *J* = 14.3, 10.5 Hz, 1H), 1.59–1.20 (m, 18H), 1.05 (s, 9H), 0.92 (s, 3H), 0.88 (t, *J* = 6.8 Hz, 3H), 0.82 (s, 9H), 0.80 (s, 3H), 0.08 (s, 3H), −0.08 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.9, 135.7, 133.7, 129.4, 127.5, 74.6, 73.8, 70.1, 55.9, 48.9, 40.9, 39.2, 31.8, 29.5, 29.4, 29.3, 29.1, 29.0, 28.8, 26.9, 26.2, 22.6, 21.5, 20.7, 19.3, 18.4, 14.1, −3.4, −3.8. MS (ESI) 751 $[M + Na]^+$. HRMS (ESI) *m*/*z* calcd for $C_{42}H_{72}O_4NaSSi_2$ 751.45821; found 751.45922.

Compound 32

To the mixture of thio ester **40** (1.57 g, 2 mmol), $PdCl_2(dppf)_2$ (163 mg, 0.2 mmol), CuI (950 mg, 5 mmol) triphenylphosphine (262 mg, 1 mmol) and Et_3N (0.8 mL) in anhydrous DMF (4 mL) was added a solution of alkyne **31** (940 mg, 5 mmol) in anhydrous DMF (6 mL) slowly over 6 h using a syringe pump at 60 °C. The reaction mixture was stirred for an additional 3 h at the same temperature. The reaction mixture was then diluted with ether (20 mL), quenched with water (10 mL) and the solids filtered through a pad of Celite. The filter cake was washed with ether (5 × 20 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography using hexanes–EtOAc (95 : 5, v/v) to afford alkynone **32** (1.17 g, 1.58 mmol) in 79% yield as a viscous oil. TLC R_f = 0.15 (10% EtOAc–hexanes). $[\alpha]_D^{35}$ = −11.0 (*c* 1, $CHCl_3$). IR (KBr): 2958, 2931, 2211, 1672, 1085, 769, 702 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.69–7.60 (m, 4H), 7.44–7.28 (m, 11H), 4.53 (s, 2H), 4.04–3.92 (m, 1H), 3.76 (d, *J* = 7.1 Hz, 1H), 3.58–3.48 (m, 3H), 3.35–3.30 (m, 4H), 2.86 (dd, *J* = 15.2, 6.6 Hz, 1H), 2.81–2.72 (m, 1H), 2.57 (dd, *J* = 15.2, 5.4 Hz, 1H), 1.90–1.64 (m, 2H), 1.60–1.36 (m, 2H), 1.06 (s, 9H), 0.92 (s, 3H), 0.88–0.81 (m, 15H), 0.08 (s, 3H), −0.07 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 185.4, 137.7, 135.6, 133.7, 129.4, 128.3, 127.6, 127.5, 94.6, 82.6, 73.7, 73.5, 73.0, 71.1, 70.0, 55.7, 50.6, 40.8, 39.1, 34.3, 26.2, 25.9, 23.9, 21.4, 20.6, 19.3, 18.3, 11.4, −3.4, −3.9. MS (ESI) 765 $[M + Na]^+$. HRMS (ESI) *m*/*z* calcd for $C_{45}H_{66}O_5NaSi_2$ 765.43410; found 765.43494.

Compound 41

A solution of compound **32** (185 mg, 0.25 mmol) in ethyl acetate (5 mL) was added to a suspension of [(*S*,*S*)-TsDPEN]Ru(*p*-cymene)Cl (15.9 mg, 0.025 mmol), sodium formate (272 mg, 4 mmol) and 1-butyl-3-methylimidazolium tetrafluoroborate (23 mg, 0.1 mmol) in water (5 mL). The reaction mixture was stirred for 7 h at rt. The phases were separated and the aqueous phase was extracted with ethyl acetate (2 ×

10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The crude product obtained was purified by column chromatography using hexanes–DCM–acetone (50 : 48 : 2, v/v) to furnish alcohol **41** (126 mg, 0.17 mmol) in 68% yield as a viscous oil along with a minor isomer (31.5 mg, 0.042 mmol) in 17% yield as a viscous oil. Major isomer: TLC R_f = 0.45 (25% EtOAc–hexanes). $[\alpha]_D^{35}$ = −16.3 (*c* 1, $CHCl_3$). IR (KBr): 3431, 3067, 2957, 2928, 2857, 1464, 1085, 830, 701 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.78–7.68 (m, 4H), 7.57–7.26 (m, 11H), 4.70–4.52 (m, 3H), 3.78 (dd, *J* = 6.8, 2.8 Hz, 1H), 3.76–3.33 (m, 8H), 2.76–2.64 (m, 1H), 2.16–1.90 (m, 2H), 1.88–1.60 (m, 2H), 1.56–1.28 (m, 2H), 1.08 (s, 9H), 0.98 (t, *J* = 7.4 Hz, 3H), 0.93 (s, 3H), 0.86–0.78 (m, 12H), 0.06 (s, 3H), −0.06 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.2, 135.4, 133.8, 129.5, 128.3, 127.6, 127.5, 85.6, 83.0, 75.9, 74.0, 73.0, 72.3, 70.1, 60.8, 55.0, 42.2, 41.1, 38.6, 33.9, 26.9, 26.2, 24.5, 21.6, 20.5, 19.3, 18.4, 11.4, −3.2, −4.0. MS (ESI) 762 $[M + NH_4]^+$. HRMS (ESI) *m*/*z* calcd $C_{45}H_{68}O_5NaSi_2$ 767.44975; found 767.45017. Minor isomer: ^1H NMR (500 MHz, $CDCl_3$): δ 7.71–7.61 (m, 4H), 7.48–7.22 (m, 11H), 4.55–4.43 (m, 3H), 3.77–3.61 (m, 2H), 3.56–3.47 (m, 3H), 3.38–3.32 (m, 4H), 2.83–2.75 (m, 1H), 1.97–1.87 (m, 2H), 1.63–1.53 (m, 2H), 1.42–1.31 (m, 2H), 1.07 (s, 9H), 0.93 (t, *J* = 7.0 Hz, 3H), 0.86–0.78 (m, 15H), 0.06 (s, 3H), −0.07 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.2, 135.7, 133.8, 129.5, 128.3, 127.6, 127.5, 85.4, 83.3, 76.0, 74.2, 72.9, 72.3, 70.4, 60.2, 55.8, 41.0, 40.7, 38.5, 33.9, 26.9, 26.1, 23.8, 21.6, 21.0, 19.3, 18.4, 11.4, −3.4, −4.0.

Compounds 42 and 43

To a solution of alkyne **41** (74 mg, 0.1 mmol) and $Pd(PPh_3)_4$ (7 mg, 0.01 mmol) in anhydrous hexane (1 mL) was added $n$$Bu_3SnH$ (0.06 mL, 0.2 mmol) in anhydrous hexane (1 mL) dropwise over a period of 1 h using a syringe pump. Removal of the solvent afforded the crude product which was purified by column chromatography using hexanes–EtOAc (95 : 5, v/v) to yield an inseparable mixture of regioisomers (72 mg, 0.07 mmol) as a viscous oil. TLC R_f = 0.45 (5% EtOAc–hexanes), $[\alpha]_D^{33}$ = −12.6 (*c* 0.5, $CHCl_3$). IR (KBr): 3411, 2896, 2975, 2953, 2857, 1465, 1136, 1068, 1011, 839, 705 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 7.83–7.70 (m, 8H), 7.56–7.30 (m, 22H), 5.32–5.24 (m, 1H), 4.88–4.76 (m, 1H), 4.62–4.50 (m, 5H), 3.88–3.74 (m, 4H), 3.68–3.58 (m, 2H), 3.52–3.28 (m, 12H), 2.78–2.60 (m, 2H), 2.20–1.82 (m, 4H), 1.76–1.32 (m, 30H), 1.16 (s, 18H), 1.06–0.84 (m, 68H), 0.16 (s, 6H), 0.00 (s, 6H). MS (ESI) 1037 $[M + H]^+$. HRMS (ESI) *m*/*z* calcd for $C_{57}H_{96}O_5NaSi_2Sn$ 1059.57105; found 1059.57064.

Compounds 44 and 45

To a suspension of copper cyanide (27 mg, 0.3 mmol) in anhydrous THF (1 mL) cooled at 0 °C was added methyl lithium (0.4 mL, 0.6 mmol, 1.5 M in ether), stirring was continued for 30 minutes before adding the inseparable mixture of vinylstannane **42** and **43** (104 mg, 0.1 mmol) in anhydrous THF (1 mL). After 1 h the reaction mixture was cooled to −78 °C. It was quenched with methyl iodide (0.2 mL), slowly warmed to rt, and aqueous NH_4Cl added. The mixture diluted with ether filtered through a pad of Celite to remove the insolubles and the filter cake washed with ether. The layers were separated, the aqueous layer was extracted with ether (2 × 10 mL) and the combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent afforded the crude product which was purified by column chromatography using hexanes–EtOAc (9 : 1, v/v) to furnish *Z*-trisubstituted alkene **44** (42.5 mg, 0.056 mmol) and alkene **45** (9.1 mg, 0.012 mmol) in 68% combined yield. *Compound* **44**: TLC R_f = 0.15 (10% EtOAc–hexanes). $[\alpha]_D^{35}$ = −15.0 (*c* 1, $CHCl_3$). IR (KBr): 3453, 2957, 2931, 2857, 1465, 1156, 831, 701 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.74–7.68 (m, 4H), 7.47–7.27 (m, 11H), 4.95 (d, *J* = 10.3 Hz, 1H), 4.55–4.40 (m, 3H), 3.71 (dd, *J* = 5.7, 2.3 Hz, 1H), 3.66–3.59 (m, 1H), 3.51 (d, *J* = 9.1 Hz, 1H), 3.39–3.21 (m, 6H), 2.75–2.69 (m, 1H), 1.97–1.82 (m, 2H), 1.72 (s, 3H), 1.58–1.21 (m, 4H), 1.06 (s, 9H), 0.92 (s, 3H), 0.88–0.77 (m, 15H), 0.06 (s, 3H), −0.07 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.1, 138.4, 135.7, 133.8, 129.4, 128.7, 128.4, 128.2, 127.5, 127.4, 76.3, 74.2, 73.8, 73.0, 70.2, 69.2, 54.2, 41.1, 39.5, 39.2, 38.5, 27.0, 26.2, 25.1, 21.6, 20.4, 19.4, 19.2, 18.4, 11.7, −3.3, −3.9. MS (ESI) 783 $[M + Na]^+$. HRMS (ESI) *m*/*z* calcd for $C_{46}H_{72}O_5NaSi_2$ 783.48105; found 783.48105. *Compound* **45**: TLC R_f = 0.14 (10% EtOAc–hexanes). $[\alpha]_D^{36}$ = −13.8 (*c* 1, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 7.74–7.64 (m, 4H), 7.45–7.24 (m, 11H), 4.92 (d, *J* = 10.3 Hz, 1H), 4.71 (d, *J* = 10.3 Hz, 1H), 4.49–4.41 (m, 2H), 3.77 (d, *J* = 6.9 Hz, 1H), 3.74–3.70 (m, 1H), 3.51 (d, *J* = 9.2 Hz, 1H), 3.39–3.19 (m, 6H), 2.71–2.63 (m, 1H), 2.00–1.86 (m, 2H), 1.75 (s, 3H), 1.53–1.20 (m, 4H), 1.07 (s, 9H), 0.93 (s, 3H), 0.87–0.80 (m, 15H), 0.06 (s, 3H), −0.05 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.2, 135.7, 133.8, 129.4, 128.4, 128.2, 127.5, 127.4, 75.8, 74.4, 73.8, 72.9, 70.2, 67.7, 55.3, 41.0, 39.5, 38.0, 37.9, 29.7, 26.9, 26.2, 25.1, 21.4, 20.5, 19.3, 19.0, 11.7, −3.3, −3.9. MS (ESI) 783 $[M + Na]^+$. HRMS (ESI) *m*/*z* calcd for $C_{46}H_{72}O_5NaSi_2$ 783.4816; found 783.4828.

Acknowledgements

V. V. K. is thankful to the UGC, New Delhi, for a fellowship. We thank the Ministry of Science and Technology for funding under the ORIGIN program. We thank Dr B. Jagadeesh, Head NMR center, for acquiring the NMR spectra and Dr R. Srinivas, Head NCMS division, for acquiring the mass spectra.

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41 The ^{1}H NMR and NOE confirmed the structure assigned to regioisomeric alkene **45**, see ESI.†

