Organic & Biomolecular Chemistry

ROYAL SOCIETY OF CHEMISTRY

PAPER

View Article Online
View Journal

Cite this: DOI: 10.1039/d1ob00661d

A concise/catalytic approach for the construction of the C14–C28 fragment of eribulin†

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Received 6th April 2021,
Accepted 26th April 2021

DOI: 10.1039/d1ob00661d

rsc.li/obc

A simple approach for the synthesis of the C14–C28 fragment of eribulin has been developed by employing a one-pot gold-catalyzed alkynol cyclization/Kishi reduction to construct the 1,5-*cis*-tetrahydropyran unit and a cross-metathesis/Sharpless asymmetric dihydroxylation–cycloetherification to install the 1,4-*trans*-tetrahydrofuran ring. Use of easily accessible building blocks, ease of operation and catalytic transformations as key reactions for the construction of THF/THP units highlight the current approach.

Introduction

Halaven® is the trade name of eribulin mesylate, which is one of the advanced anti-cancer drugs approved for the treatment of metastatic breast cancer.[1] Eribulin is the simplified structural analogue that was developed as a part of the total synthesis of the natural product halichondrin B.[2] Yet, eribulin is a sufficiently complex macrocyclic polyether skeleton bearing 35 linear carbon atoms embedded with 19 stereocenters. Thus, the synthesis of eribulin is a challenging task that has been attempted across several academic and industrial research labs.[3] The commercial synthesis of eribulin by Kishi's group took close to 62 steps, comprising the synthesis of three different fragments, C1–C13, C14–C26 and C27–C35, and the Nozaki–Hiyama–Kishi (NHK) reaction as the key coupling tools in the construction of C13–C14 and C26–C27 bonds.[4] During the last two decades, several reports have appeared, mainly on the construction of these fragments, the majority of which rely on the proven/powerful NHK coupling reaction.[3a,5] Yet, in the pursuit of finding alternative/non-infringing approaches, attempts were made to avoid NHK coupling, especially in the late stages, to synthesize advanced C1–C26 and C14–C35 building blocks.[6] In this manuscript, we describe a short and stereoselective approach for the synthesis of the C14–C28 fragment of the eribulin core that comprises tetrahydrofuran and tetrahydropyran rings that are separated by two carbons and bear respectively the 1,4-*trans*/1,5-*cis*-configuration and an internal *exo*-methylene group on each. The key reactions that we employed to construct the *C*-glycosidic linkage between these two rings are founded upon our recent report on *C*-glycoside synthesis *via* a one-pot gold-catalyzed alkynol cyclization and Kishi reduction.[7]

Results and discussion

As shown in Fig. 1, in our retrosynthetic strategy for the orthogonally protected C14–C28 fragment **1**, we intended to use the Wittig olefination to introduce both *exo*-methylene

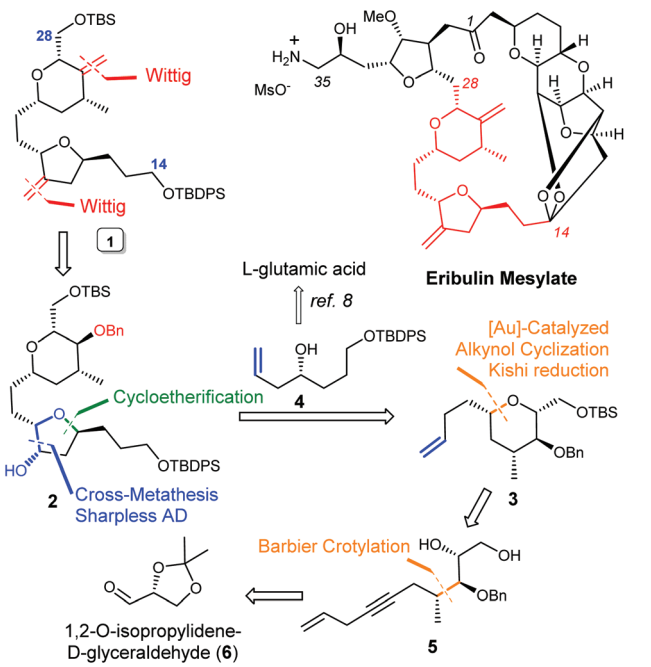

Fig. 1 Structure of eribulin mesylate and the targeted C14–C28 fragment and the planned retrosynthetic strategy.

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† Electronic supplementary information (ESI) available: NMR and HRMS spectra of all new compounds. See DOI: 10.1039/d1ob00661d

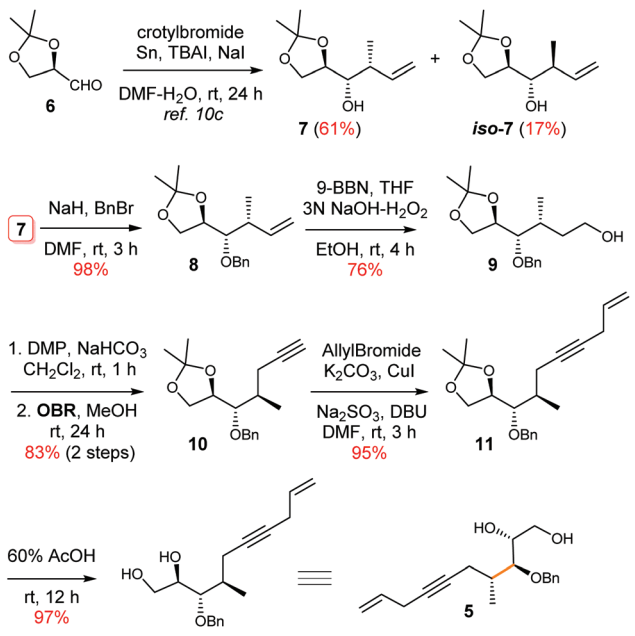
units in one go. For the construction of the 1,5-*cis*-THP unit **3**, a regioselective gold catalysed cyclization of alkynol **5** and subsequent stereoselective ketal reduction in the same pot should result in the but-3-enyl *C*-glycoside **3**. The terminal olefin in **3** was opted as a handle to construct the 1,4-*trans*-THF ring *via* cross-metathesis with the known olefin **4**[8] having a suitably positioned –OH that will undergo cycloetherification after Sharpless asymmetric dihydroxylation of the internal olefin resulting from the cross metathesis (Scheme 1).[9] The requisite stereocenters on the alkynol fragment **5** could be availed from the crotylated D-glyceraldehyde, while the stereocenter of olefin **4** could be availed by a Keck allylation[8a] strategy starting from 1,4-butane-diol or from L-(+)-glutamic acid[8b] following a chiral pool approach.

The proposed plan to secure the C14–C28 fragment of eribulin was started with the synthesis of the key alkynol **5** and its conversion to the *C*-glycoside **3** (Scheme 1). Following the procedure reported by Loh's group, the crotylation of acetonide protected D-glyceraldehyde **6** using crotyl bromide and tin in DMF–H_2O gave the homoallylic alcohol **7** as a major diastereomer in 61% yield.[10] The free –OH in compound **7** was protected as its benzyl ether **8** and it was converted to alkyne **10** by following a three-step protocol – hydroboration, oxidation and the Ohira–Bestmann reaction – with an overall yield of 63%.[11] Next, the *C*-allylation of the terminal alkyne unit in compound **10** was attempted initially by using *n*-BuLi and allylbromide, which gave the requisite product **11** in 90% yield.[12] However, when conducted on gram scales, the yield of the product was reduced drastically due to the decomposition of the starting alkyne. After a number of trials, the modified alkyne allylation strategy using CuI, K_2CO_3 and allyl bromide afforded the allyl homologated product **11** in excellent yields, even on gram scales.[13] Initially, the gold-catalyzed cyclization of compound **11** was attempted considering the ready deprotection of the acetonide group during the gold-catalyzed alkynol cycloisomerization.[14] As the yields were found to be moderate, compound **11** was subjected to acetonide hydrolysis employing 60% acetic acid in water to obtain the key intermediate **5**.

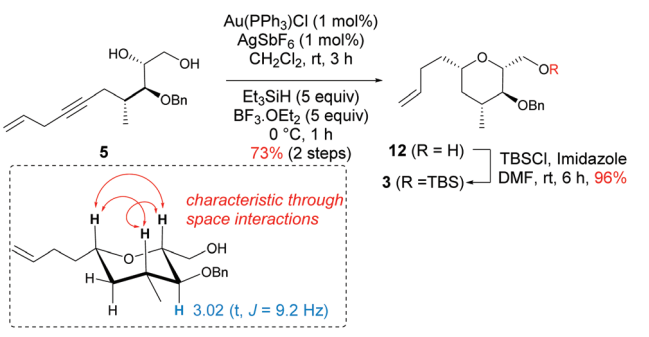
Alkynol **5** was subjected to gold-catalysed cyclization using $Au(PPh_3)Cl$ and $AgSbF_6$, followed by lactol reduction with Et_3SiH and $BF_3{\cdot}Et_2O$ to afford exclusively the key 1,5-*cis*-*C*-glycoside **12** in 73% yield over 2 steps (Scheme 2).[7] The stereochemistry of the newly formed anomeric centre in compound **12** was established with the help of characteristic through-space interactions and ^1H NMR coupling constants.[15] The free hydroxyl group in compound **12** was protected as its TBS ether to complete the synthesis of the key fragment **3**.

Coming to the synthesis of the alkene fragment **4**, the Keck allylation resulted only with 83% ee.[8a] To achieve a quick access to enantiopure **4** and validate our approach, it was synthesized from L-glutamic acid following the route developed by Shibuya's group.[8b] After a good amount of experimentation (Scheme 3), the cross-metathesis of fragments **3** and **4** was carried out in excellent yields by following Lipshutz's procedure using the Grubbs 2nd generation catalyst in the presence of CuI in ether under reflux to afford the inseparable diastereomeric mixture **13** (E/Z = 7/1).[16] The next task was to construct the 1,4-*trans*-THF ring with the requisite absolute configuration. As planned, the free hydroxyl group in compound **13** was converted to its mesylate and subjected to Sharpless asymmetric dihydroxylation using AD-mix-α.[9,17] The asymmetric dihydroxylation and the cycloetherification proceeded smoothly to provide the key disaccharide intermediate **2** with an inseparable diastereomeric ratio 7 : 1.[9c] Gratifyingly, the corresponding acetates **2-Ac** and **2′-Ac**, prepared for the purpose of characterization, were found to be separable by simple column chromatography and the relative stereochemistry of the newly constructed THF ring was established with the help of ^{13}C NMR chemical shift comparison with similar compounds (Fig. S1, ESI†) and also by 2D NMR analysis.[18]

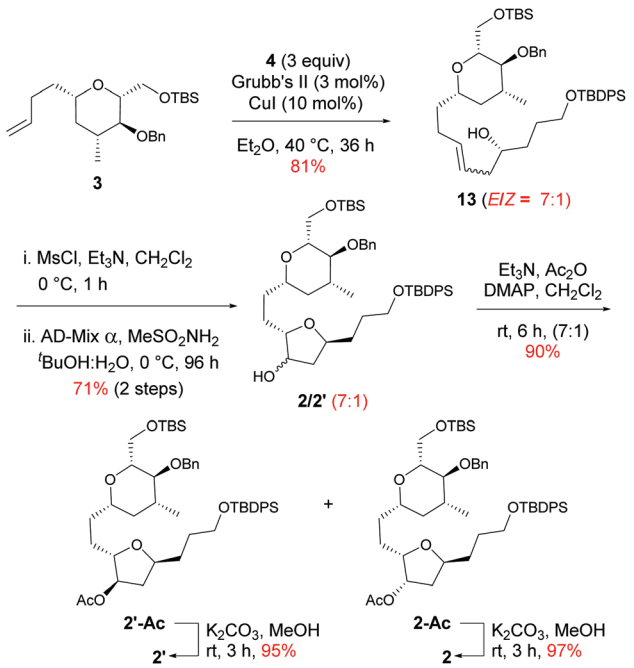
Having the key intermediates **2** and **2′** in our hand, the next task was the hydrogenolysis of the –OBn group and sub-



Scheme 1 Synthesis of the key alkynol **5**.



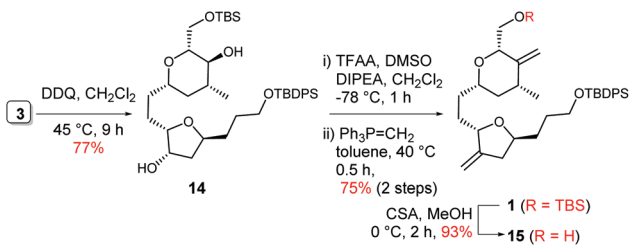
Scheme 2 Synthesis of the tetrahydropyran fragment **3**.



Scheme 3 Synthesis of the key disaccharide **2**.

sequent oxidation of both the ring –OH groups to the corresponding ketones followed by one-carbon Wittig homologation. In this pursuit, the hydrogenolysis of the major diastereomer **2** using 10% Pd/C and H_2 was found to be incomplete when conducted under atmospheric pressure and increasing the pressure resulted in the partial deprotection of the TBS group. At this juncture, the use of DDQ for oxidative debenzylation was found to be promising and provided the corresponding diol in a good yield (Scheme 4).[19]

The resulting diol **14** was subjected to the Swern oxidation followed by the Wittig olefination (with freshly prepared $Ph_3P{=}CH_2$ in toluene at 40 °C) to obtain the targeted fragment **1** in 75% yield over two steps.[20] The resulting compound **1** was fully characterized with the help of extensive 2D NMR analysis and compared with the previous data reported for similar derivatives (Table S1, ESI†). To this end, to check the possibility of selective chain extension, compound **1** was subjected to controlled desilylation with camphorsulfonic acid to afford the selective TBS deprotected derivative **15** in an excellent yield.



Scheme 4 Synthesis of the eribulin **C14–C28** fragment.

Conclusions

In conclusion, a simple approach for the synthesis of the C14–C28 fragment of eribulin has been established starting with the easily accessible building blocks that comprises a 14-step linear sequence with an overall yield of 7.2%. The central THF and THP rings were constructed with complete control over the stereoselectivity employing catalytic transformations such as gold-catalyzed alkynol cyclization, cross metathesis and Sharpless asymmetric dihydroxylation. This synthesis provided an important stepping stone in terms of finding novel alternatives for the synthesis of the eribulin core. Work in the direction of extending the key *C*-gold-catalyzed alkynol cyclization/Kishi reduction in constructing the *cis*-THF ring (C29–C32 being the triple bond placed between the C28–C29 carbons) for the synthesis of larger fragments, in general, and for the total synthesis of eribulin, in particular, is currently in progress.

Experimental section

General information

Air and/or moisture sensitive reactions were carried out in anhydrous solvents under an argon atmosphere in oven-dried glassware. All anhydrous solvents were distilled prior to use: dichloromethane and DMF from CaH_2; methanol from Mg cake; and benzene and THF on Na/benzophenone. Commercial reagents were used without purification. Column chromatography was carried out by using silica gel (60–120, 100–200, 230–400 mesh). ^1H and ^{13}C NMR chemical shifts are reported in ppm relative to chloroform-D (δ = 7.27) or TMS and coupling constants (J) are reported in hertz (Hz). The following abbreviations are used to designate signal multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, sxt = sextet, hept = septet, m = multiplet, b = broad. High Resolution Mass Spectra (HRMS) were recorded on a Q Exactive Hybrid Quadrupole Orbitrap Mass Spectrometer, where the mass analyser used for analysis is orbitrap.

(2*R*,3*S*,4*R*)-1,2-*O*-Isopropylidine-4-methylhex-5-ene-1,2,3-triol (7)[4]

At 0 °C, a solution of crotyl bromide (8.54 g, 6.5 mL, 53.8 mmol) in DMF–H_2O (DMF = 50 ml & H_2O = 1 ml) was treated with tin (5.02 g, 42.3 mmol), tetrabutylammonium iodide (710 mg, 1.9 mmol) and sodium iodide (5.76 g, 38.4 mmol) and stirred for five minutes at 0 °C followed by the addition of a solution of acetonide protected D-glyceraldehyde (5 g, 38.4 mmol) in DMF (10 mL). The reaction mixture was stirred at room temperature for 24 h and filtered through a Celite pad. The filtrate was passed through a short plug of 100–200 mesh silica gel column (petroleum ether : EtOAc, 50 : 50) to afford the crude product, which was further purified by silica gel column chromatography (petroleum ether : THF, 96 : 4) to afford compound **7** (4.36 g, 61% yield) and compound **iso-7** (1.24 g, 17% yield) as colourless liquids.

Compound 7

R_f = 0.4 (10% EtOAc in petroleum ether); $[\alpha]_D^{25}$: +41.3 (c = 5.0, $CHCl_3$); ^{1}H NMR (500 MHz): δ 1.10 (d, J = 6.9 Hz, 3H), 1.35 (s, 3H), 1.42 (s, 3H), 2.16 (br. s., 1H), 2.25 (m, 1H), 3.64 (dd, J = 5.0, 6.5 Hz, 1H), 3.90 (dd, J = 8.0, 7.3 Hz, 1H), 3.97 (dd, J = 6.5, 8.0 Hz, 1H), 4.11 (td, J = 4.6, 6.5 Hz, 1H), 5.74 (ddd, J = 8.0, 10.3, 17.2 Hz, 1H), 5.06 (m, 2H) ppm; ^{13}C NMR (125 MHz): δ 15.3 (q), 25.3 (q), 26.5 (q), 40.6 (d), 64.5 (t), 73.6 (d), 7 6.7 (d), 108.7 (s), 115.4 (t), 140.1 (d) ppm; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{10}H_{19}O_3$ 187.1329, found 187.1327.

Compound iso-7

R_f = 0.4 (10% EtOAc in petroleum ether); $[\alpha]_D^{25}$: +9.2 (c = 1.9, $CHCl_3$); ^{1}H NMR (400 MHz): δ 1.09 (d, J = 6.9 Hz, 3H), 1.37 (s, 3H), 1.42 (s, 3H), 1.92 (br. s., 1H), 2.36–2.46 (m, 1H), 3.61 (dd, J = 4.6, 7.6 Hz, 1H), 3.93 (t, J = 7.6 Hz, 1H), 4.0 (t, J = 7.6 Hz, 1H), 4.07 (q, J = 6.1 Hz, 1H), 5.10–5.16 (m, 2H), 5.86 (ddt, J = 7.6, 9.2, 17.6 Hz, 1H) ppm; ^{13}C NMR (100 MHz): δ 16.5 (q), 25.4 (q), 26.6 (q), 40.2 (d), 65.4 (t), 74.7 (d), 77.1 (d), 108.7 (s), 116.3 (t), 139.2 (d) ppm; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{10}H_{18}O_3Na$ 209.1148, found 209.1150.

(2*R*,3*S*,4*R*)-1,2-*O*-Isopropylidine-3-*O*-benzyl-4-methylhex-5-ene-1,2,3-triol (8)

At 0 °C, a suspension of sodium hydride (560 mg, 14 mmol, 60 wt%) in dry DMF (15 mL) was treated with a solution of compound **7** (2.0 g, 10.7 mmol) in DMF (5 mL) and stirred for 5 min, followed by the addition of benzyl bromide (1.40 mL, 11.8 mmol) dropwise. The cooling bath was removed and the reaction mixture was stirred at room temperature for 3 h. After complete consumption of the starting material as indicated by TLC, the reaction was quenched with cold water, the reaction mixture was diluted with EtOAc (30 mL) and the organic layer was separated. The aqueous layer was extracted with EtOAc (3 × 25 mL) and the combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude product was purified by silica gel chromatography (5% EtOAc in petroleum) to afford the benzyl protected compound **8** as a colourless liquid (2.91 g, 98% yield). R_f = 0.8 (10% EtOAc in petroleum ether); $[\alpha]_D^{25}$: +23.6 (c = 5.2, $CHCl_3$); ^{1}H NMR (400 MHz): δ 1.13 (d, J = 6.9 Hz, 3H), 1.40 (s, 3H), 1.47 (s, 3H), 2.44 (ddd, J = 6.9, 12.9, 13.7 Hz, 1H), 3.58 (t, J = 5.3 Hz, 1H), 3.95–4.05 (m, 2H), 4.22 (ddd, J = 4.6, 6.1, 6.9 Hz, 1H), 4.64 (d, J = 11.4 Hz, 1H), 4.74 (d, J = 11.4 Hz, 1H), 5.07 (dt, J = 1.2, 10.7 Hz, 1H), 5.11 (dt, J = 1.5, 17.5 Hz, 1H), 5.90 (ddt, J = 7.6, 10.7, 17.5 Hz, 1H), 7.31–7.38 (m, 5H) ppm; ^{13}C NMR (100 MHz): δ 15.3 (q), 25.4 (q), 26.5 (q), 40.3 (d), 65.5 (t), 74.5 (t), 76.8 (d), 82.4 (d), 108.6 (s), 114.6 (t), 127.5 (d), 127.7 (d, 2C), 128.2 (d), 128.3 (d), 138.6 (s), 141.1 (d) ppm; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{17}H_{24}O_3Na$ 299.1618, found 299.1620.

(2*R*,3*S*,4*R*)-1,2-*O*-Isopropylidine-3-*O*-benzyl-4-methylhexane-1,2,3,6-tetraol (9)

At 0 °C, a stirred solution of compound **8** (2.80 g, 10.1 mmol) in dry THF (20 mL) was treated with a solution of 0.5 M 9-BBN (30.4 ml, 15.2 mmol) over a period of 10 min. The reaction mixture was warmed to rt and stirring was continued for an additional 4 h. After complete consumption of the starting compound as indicated by TLC, the reaction mixture was cooled to 0 °C and treated with ethanol (25 ml) followed by 3 N NaOH (30 mL) and H_2O_2 (30% w/w, 30 mL). The contents were refluxed for 1 h and diluted with 10 mL of water. The organic layer was separated, washed with brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and purification of the crude product by silica gel column chromatography (50% EtOAc in petroleum ether) gave compound **9** (2.27 g, 76% yield) as a colorless oil. R_f = 0.35 (40% EtOAc in petroleum ether); $[\alpha]_D^{25}$: +20.1 (c = 0.4, $CHCl_3$); ^{1}H NMR (400 MHz): δ 0.98 (d, J = 6.9 Hz, 3H), 1.35 (s, 3H), 1.42 (s, 3H), 1.53 (ddd, J = 1.5, 6.1, 13.7 Hz, 1H), 1.76 (dt, J = 6.1, 13.7 Hz, 1H), 1.96–2.10 (m, 2H), 3.53 (dd, J = 3.1, 5.5 Hz, 1H), 3.64 (ddd, J = 6.6, 10.6, 13.6 Hz, 1H), 3.73 (ddd, J = 6.1, 10.9, 12.3 Hz, 1H), 3.92 (t, J = 7.6 Hz, 1H), 4.05 (dd, J = 6.9, 7.6 Hz, 1H), 4.18 (q, J = 6.1 Hz, 1H), 4.63 (d, J = 11.4 Hz, 1H), 4.69 (d, J = 11.4 Hz, 1H), 7.27–7.37 (m, 5H) ppm; ^{13}C NMR (100 MHz): δ 15.0 (q), 25.2 (q), 26.6 (q), 32.4 (d), 36.5 (t), 61.0 (t), 66.6 (t), 74.0 (d), 76.7 (d), 82.9 (d), 108.5 (s), 127.6 (d, 2C), 128.3 (d, 3C), 138.4 (s) ppm; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{17}H_{26}O_4Na$ 317.1723, found 317.1727.

(2*R*,3*S*,4*R*)-1,2-*O*-Isopropylidine-3-*O*-benzyl-4-methylhept-6-yne-1,2,3-triol (10)

At 0 °C, to a stirred solution of compound **9** (2.30 g, 7.8 mmol) in dry dichloromethane (25 mL) were added the Dess–Martin periodinane reagent (4.31 g, 10.2 mmol) and sodium bicarbonate (1.97 g, 23.4 mmol) and stirring was continued for 1 h at room temperature. After completion of the reaction, the reaction mixture was treated with sat. $NaHCO_3$ (15 mL) and diluted with dichloromethane (20 mL). The organic layer was separated and washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude aldehyde was forwarded for the next step without any purification.

The above crude aldehyde (2.28 g, 7.8 mmol) was dissolved in methanol (40 mL) and treated with potassium carbonate (3.23 g, 23.4 mmol) and the Ohira–Bestmann reagent (2.23 g, 10.14 mmol) and stirred for 24 h at room temperature. The reaction mass was filtered through a Celite pad and the filtrate was concentrated under reduced pressure. Purification of the crude product by silica gel column chromatography (5% EtOAc in petroleum ether) gave alkyne **10** as a colourless liquid (1.87 g, 83% yield). R_f = 0.6 (10% EtOAc in petroleum ether); $[\alpha]_D^{25}$: +10.1 (c = 3.0, $CHCl_3$); ^{1}H NMR (400 MHz): δ 1.04 (d, J = 7.0 Hz, 3H), 1.38 (s, 3H), 1.46 (s, 3H), 2.04–2.13 (m, 2H), 2.22 (ddd, J = 2.3, 6.1, 16.8 Hz, 1H), 2.34 (ddd, J = 2.3, 7.6, 16.8 Hz, 1H), 3.80 (dd, J = 3.1, 6.1 Hz, 1H), 3.94 (dd, J = 6.1, 7.9 Hz, 1H), 4.07 (dd, J = 6.5, 7.9 Hz, 1H), 4.16 (q, J = 6.1 Hz, 1H), 4.67 (d, J = 11.4 Hz, 1H), 4.74 (dd, J = 11.4 Hz, 1H), 7.28–7.34 (m, 1H), 7.34–7.38 (m, 4H) ppm; ^{13}C NMR (100 MHz): δ 14.3 (q), 23.2 (t), 25.2 (d), 26.7 (d), 35.1 (d), 66.3 (t), 69.7 (d), 74.6 (t), 76.8 (d), 80.8 (d), 83.1 (s), 108.6 (s), 127.6 (d, 3C), 128.3 (d, 2C), 138.5 (s)

ppm; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{18}H_{24}O_3Na$, 311.1618, found 311.1619.

(2*R*,3*S*,4*R*)-1,2-*O*-Isopropylidine-3-*O*-benzyl-4-methyl dec-9-en-6-yne-1,2,3-triol (11)

At 0 °C, a stirred solution of alkyne **10** (1.0 g, 3.5 mmol) in dry DMF (10 mL) was treated in sequence with allyl bromide (0.33 mL, 3.8 mmol), copper iodide (66 mg, 0.35 mmol), potassium carbonate (527 mg, 3.8 mmol), sodium sulphite (218 mg, 1.7 mmol) and DBU (0.26 mL, 1.7 mmol). The reaction mixture was warmed to rt and stirred for 3 h. The reaction mixture was diluted with EtOAc (50 mL) and water (50 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 25 mL). The combined organic layer was washed with water and brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the resulting crude product by silica gel column chromatography (5% EtOAc in petroleum ether) afforded the allylated compound **11** (1.08 g, 95% yield) as a colourless liquid. R_f = 0.6 (10% EtOAc in petroleum ether); $[\alpha]_D^{25}$: +11.6 (c = 4.8, $CHCl_3$); ^{1}H NMR (500 MHz): δ 1.02 (d, J = 6.9 Hz, 3H), 1.37 (s, 3H), 1.44 (s, 3H), 2.03 (ddd, J = 3.4, 6.9, 14.9 Hz, 1H), 2.23 (ddt, J = 2.3, 6.5, 14.5 Hz, 1H), 2.35 (ddt, J = 2.3, 8.0, 16.4 Hz, 1H), 2.97 (ddd, J = 2.1, 4.1, 6.7 Hz, 2H), 3.79 (dd, J = 3.4, 5.7 Hz, 1H), 3.92 (dd, J = 6.5, 8.0 Hz, 1H), 4.05 (dd, J = 6.1, 8.0 Hz, 1H), 4.16 (q, J = 6.1 Hz, 1H), 4.66 (d, J = 11.1 Hz, 1H), 4.74 (d, J = 11.1 Hz, 1H), 5.12 (ddt, J = 1.9, 3.4, 9.9 Hz, 1H), 5.33 (ddt, J = 1.5, 3.4, 16.8 Hz, 1H), 5.83 (ddt, J = 5.3, 10.3, 16.8 Hz, 1H), 7.30 (dd, J = 4.6, 8.8 Hz, 1H), 7.34–7.36 (m, 4H) ppm; ^{13}C NMR (125 MHz): δ 14.4 (q), 23.1 (t), 23.7 (t), 25.3 (q), 26.7 (q), 35.6 (d), 66.5 (t), 74.7 (t), 77.0 (d), 78.1 (s), 81.0 (d), 81.2 (s), 108.6 (s), 115.7 (t), 127.6 (d, 3C), 128.3 (d, 2C), 133.2 (d), 138.7 (s) ppm; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{21}H_{28}O_3Na$ 351.1931, found 351.1933.

(2*R*,3*S*,4*R*)-3-*O*-Benzyl-4-methyl dec-9-en-6-yne-1,2,3-triol (5)

A solution of compound **11** (1.07 g, 3.26 mmol) in 60% acetic acid in water (20 mL) was stirred at room temperature for 12 h. The reaction mixture was concentrated under reduced pressure and the resulting crude product was purified by column chromatography (40% EtOAc in petroleum ether) to afford diol **5** (910 mg, 97% yield) as a colourless liquid. R_f = 0.5 (50% EtOAc in petroleum ether); $[\alpha]_D^{25}$: +7.1 (c = 3.2, $CHCl_3$); ^{1}H NMR (500 MHz): δ 1.07 (d, J = 6.9 Hz, 3H), 2.00–2.08 (m, 1H), 2.20–2.35 (m, 2H), 2.93–2.97 (m, 2H), 3.67 (dd, J = 3.9, 6.3 Hz, 1H), 3.71–3.77 (m, 2H), 3.80 (ddd, J = 3.1, 5.3, 8.4 Hz, 1H), 4.64 (d, J = 11.4 Hz, 1H), 4.69 (d, J = 11.4 Hz, 1H), 5.10 (ddt, J = 1.5, 3.8, 9.9 Hz, 1H), 5.31 (ddt, J = 2.3, 3.8, 16.8 Hz, 1H), 5.83 (ddt, J = 4.6, 9.9, 16.8 Hz, 1H), 7.26–7.37 (m, 5H) ppm; ^{13}C NMR (125 MHz): δ 14.8 (q), 23.1 (t), 23.7 (t), 34.8 (d), 63.8 (t), 71.8 (d), 74.7 (t), 78.3 (s), 81.0 (s), 82.0 (d), 115.7 (t), 127.8 (d, 3C), 128.5 (d, 2C), 133.2 (d), 138.2 (s) ppm; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{18}H_{25}O_3$ 289.1798, found 289.1801.

((2*R*,3*S*,4*R*,6*S*)-3-(Benzyloxy)-6-(but-3-en-1-yl)-4-methyltetrahydro-2*H*-pyran-2-yl)methanol (12)

At room temperature, to a solution of alkynol **5** (900 mg, 3.12 mmol) in dry dichloromethane (10 mL) in a round bottom flask covered with silver foil was added $Au(PPh_3)Cl$ (15 mg, 31.2 μmol, 1 mol%) followed by $AgSbF_6$ (11 mg, 31.2 μmol, 1 mol%) and stirred for 3 h. After complete consumption of the starting material, triethyl silane (2.50 mL, 15.6 mmol) was added to the reaction mixture and cooled to 0 °C and treated slowly with $BF_3{\cdot}Et_2O$ (1.9 mL, 15.6 mmol). Stirring was continued at 0 °C for 1 h. After complete consumption of the starting material, 5 mL of saturated ammonium chloride was added and the reaction mixture was extracted with dichloromethane (2 × 25 mL). The combined organic layer was washed with brine, dried and concentrated under reduced pressure. The resulting crude product was purified by silica gel chromatography (10% EtOAc in petroleum ether) to afford compound **12** (660 mg, 73% yield) as a colourless liquid. R_f = 0.4 (10% EtOAc in petroleum ether); $[\alpha]_D^{25}$: +1.02 (c = 5.0, $CHCl_3$); ^{1}H NMR (400 MHz): δ 1.09 (d, J = 6.3 Hz, 3H), 1.10–1.17 (m, 1H), 1.52 (ddd, J = 6.7, 9.8, 14.0 Hz, 1H), 1.62 (td, J = 7.9, 14.0 Hz, 1H), 1.68–1.80 (m, 2H), 2.06–2.26 (m, 3H), 3.02 (t, 1H, J = 9.2 Hz, 1H), 3.29 (ddd, J = 2.5, 4.9, 9.2 Hz, 1H), 3.42 (dt, J = 5.5, 11.0 Hz, 1H), 3.74 (dt, J = 5.5, 11.0 Hz, 1H), 3.89 (ddd, J = 2.4, 5.5, 11.6 Hz, 1H), 4.63 (s, 2H), 4.97 (d, J = 9.8 Hz, 1H), 5.03 (dd, J = 1.2, 17.1 Hz, 1H), 5.83 (ddt, J = 6.7, 9.8, 17.1 Hz, 1H), 7.27–7.42 (m, 5H) ppm; ^{13}C NMR (100 MHz): δ 18.6 (q), 29.9 (t), 34.7 (t), 36.9 (d), 39.7 (t), 62.8 (t), 74.7 (t), 76.4 (d), 80.3 (d), 80.7 (d), 114.5 (t), 127.8 (d), 127.9 (d, 2C), 128.4 (d, 2C), 138.1 (s), 138.4 (d) ppm; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{18}H_{27}O_3$ 291.1955, found 291.1957.

(((2*R*,3*S*,4*R*,6*S*)-3-(Benzyloxy)-6-(but-3-en-1-yl)-4-methyltetrahydro-2*H*-pyran-2-yl)methoxy)(*tert*-butyl) dimethylsilane (3)

To a stirred solution of compound **12** (620 mg, 2.13 mmol) in dry DMF (10 mL) was added imidazole (436 mg, 6.40 mmol) followed by TBSCl (354 mg, 2.35 mmol) at 0 °C. After stirring for 6 h at room temperature, the reaction was quenched with water (10 mL) and the reaction mixture was diluted with EtOAc (25 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by silica gel chromatography (5% EtOAc in petroleum ether) to afford compound **3** (830 mg, 96% yield) as a colourless liquid. R_f = 0.8 (10% EtOAc in petroleum ether); $[\alpha]_D^{25}$: +5.8 (c = 2.2, $CHCl_3$); ^{1}H NMR (400 MHz): δ 0.10 (s, 3H), 0.11 (s, 3H), 0.94 (s, 9H), 1.05 (d, J = 6.6 Hz, 3H), 1.07–1.13 (m, 1H), 1.49 (ddd, J = 6.1, 11.0, 14.0 Hz, 1H), 1.55–1.78 (m, 3H), 2.13 (dt, J = 7.9, 14.6 Hz, 1H), 2.21 (dt, J = 7.9, 14.6 Hz, 1H), 3.09 (t, J = 9.5 Hz, 1H), 3.17 (dt, J = 2.3, 9.2 Hz, 1H), 3.35 (dt, J = 4.9, 10.4 Hz, 1H), 3.89 (dd, J = 3.0, 11.6 Hz, 2H), 4.60 (d, J = 11.0 Hz, 1H), 4.72 (d, J = 11.0 Hz, 1H), 4.96 (d, J = 10.4 Hz, 1H), 5.03 (d, J = 17.1 Hz, 1H), 5.84 (ddt, J = 6.7, 10.4, 17.1 Hz, 1H), 7.31 (dd, J = 2.4, 6.1 Hz,

1H), 7.33–7.40 (m, 4H) ppm; ^{13}C NMR (100 MHz); δ −5.3 (q), −4.8 (q), 18.4 (s), 18.8 (q), 26.0 (q, 3C), 30.0 (t), 35.0 (t), 36.9 (d), 39.9 (t), 63.2 (t), 74.5 (t), 76.0 (d), 80.2 (d), 81.2 (d), 114.4 (t), 127.6 (d), 128.1 (d, 2C), 128.4 (d, 2C), 138.7 (s), 138.8 (d) ppm; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{24}H_{41}O_3Si$ 405.2819, found 405.2828.

Synthesis of 7-((*tert*-butyldiphenylsilyl)oxy)hept-1-en-4-ol (4)[8b]

Compound **4** was prepared following the literature procedure reported by Shibuya and co-workers.[8b]

R_f = 0.3 (10% EtOAc in petroleum ether); $[\alpha]_D^{25}$: +4.1 (c = 2.2, $CHCl_3$); ^{1}H NMR (400 MHz): δ 1.07 (s, 9H), 1.48–1.57 (m, 1H), 1.63–1.74 (m, 3H), 2.16 (br. s., 1H), 2.20 (ddt, J = 1.0, 6.5, 14.0 Hz, 1H), 2.30 (dddt, J = 1.1, 5.1, 6.5, 11.4 Hz, 1H), 3.65–3.69 (m, 1H), 3.71 (t, J = 6.0 Hz, 2H), 5.11–5.17 (m, 2H), 5.85 (ddt, J = 7.0, 9.3, 16.8 Hz, 1H), 7.37–7.47 (m, 6H), 7.67–7.70 (m, 4H) ppm; ^{13}C NMR (100 MHz); δ 19.2 (s), 26.8 (q, 3C), 28.8 (t), 33.5 (t), 41.9 (t), 64.1 (t), 70.5 (d), 117.8 (t), 127.6 (d, 4C), 129.6 (d, 3C), 133.7 (s, 2C), 135.0 (d), 135.6 (d, 3C) ppm; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{23}H_{33}O_2Si$ 369.2244, found 369.2249.

Synthesis of compound 13 *via* cross metathesis of 3 with 4

Under argon, to a solution of compounds **3** (340 mg, 840 μmol) and **4** (929 mg, 2.52 mmol) in dry diethyl ether (20 mL) were added sequentially CuI (16 mg, 84 μmol) and Grubb's 2nd generation catalyst (21 mg, 25.2 μmol) at room temperature. The reaction mixture was kept at 40 °C for 36 h. The solvent was evaporated under reduced pressure and the crude product was purified by silica gel column chromatography (5% EtOAc in petroleum ether) to afford compound **13** (507 mg, 81% yield) as a colourless liquid. R_f = 0.3 (10% EtOAc in petroleum ether); $[\alpha]_D^{25}$: +1.04 (c = 1.1, $CHCl_3$); ^{1}H NMR (400 MHz); δ 0.09 (s, 3H), 0.10 (s, 3H), 0.93 (s, 9H), 1.02–1.05 (m, 3H), 1.06 (s, 9H), 1.44–1.55 (m, 2H), 1.60–1.72 (m, 7H), 2.07–2.25 (m, 5H), 3.08 (t, J = 9.5 Hz, 1H), 3.15 (ddd, J = 1.9, 3.5, 9.3 Hz, 1H), 3.28–3.39 (m, 1H), 3.61 (ddd, J = 4.1, 7.7, 11.9 Hz, 1H), 3.70 (d, J = 5.8 Hz, 2H), 3.83–3.93 (m, 2H), 4.59 (d, J = 10.9 Hz, 1H), 4.71 (d, J = 10.9 Hz, 1H), 5.44 (dt, J = 7.1, 15.1 Hz, 1H), 5.54 (dt, J = 6.6, 15.1 Hz, 1H), 7.29–7.45 (m, 10H), 7.65–7.70 (m, 5H) ppm; ^{13}C NMR (100 MHz): δ −5.2 (q), −4.8 (q), 18.4 (s), 18.7(q), 19.2 (s), 26.0 (q, 3C), 26.8 (q, 3C), 28.8 (t), 28.9 (t), 33.4 (t), 35.5 (t), 36.9 (d), 39.9 (t), 40.7 (t), 63.2 (t), 64.1 (t), 70.8 (d), 74.5 (t), 76.0 (d), 80.2 (d), 81.2 (d), 126.1 (d), 127.6 (d, 5C), 128.1 (d, 2C), 128.4 (d, 2C), 129.6 (d, 2C), 133.8 (s), 134.0 (d), 134.2 (s) 135.6 (d, 4C), 138.7 (s) ppm; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{45}H_{69}O_5Si_2$ 745.4678, found 745.4684.

Synthesis of disaccharide 2

At 0 °C, a solution of compound **13** (300 mg, 0.4 mmol) and triethyl amine (0.17 mL, 1.21 mmol) in dry dichloromethane (10 mL) was treated with methane sulfonyl chloride (0.047 mL, 0.6 mmol) and stirred at the same temperature for 1 h. The reaction was quenched with water and the reaction mixture was diluted with dichloromethane (10 mL). The organic layer was separated, washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude product was used for the next step without purification.

The above crude mesylate (330 mg, 0.4 mmol) was dissolved in ^{t}BuOH : H_2O (10 mL, 1 : 1, v/v) and cooled to 0 °C in a cryostat and treated with methane sulphonamide (114 mg, 1.2 mmol) and AD-mix-α (800 mg, 2.0 g mmol^{-1}). Stirring was continued for 96 h at 0 °C. After complete consumption of the starting compound as indicated by TLC, the reaction was quenched with saturated sodium sulfite solution (5 mL) and the reaction mixture was diluted with EtOAc (25 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 15 mL). The combined organic layer washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude product was purified by silica gel column chromatography (15% EtOAc in petroleum ether) to afford compounds **2** and **2′** in a diastereomeric mixture (217 mg, 71% yield) as a colourless liquid. R_f = 0.4 (20% EtOAc in petroleum ether).

To the stirred solution of the diastereomeric mixture of compounds **2** and **2′** (217 mg, 285 μmol) in dry dichloromethane (5 mL) were added triethylamine (0.2 mL, 1.43 mmol), acetic anhydride (81 μL, 855 μmol), and DMAP (7 mg, 57 μmol) at 0 °C and stirred at room temperature for 6 h. The reaction mixture was concentrated and the residue was dissolved in EtOAc (25 mL), washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the crude product by silica gel chromatography gave compounds **2-Ac** (180 mg, 79% yield) and **2′-Ac** (26 mg, 11% yield) as colourless liquids.

Compound 2-Ac. R_f = 0.3 (10% EtOAc in petroleum ether); $[\alpha]_D^{25}$: −0.3 (c = 4.9, $CHCl_3$); ^{1}H NMR (400 MHz): δ 0.08 (s, 3H), 0.09 (s, 3H), 0.92 (s, 9H), 1.03 (d, J = 6.4 Hz, 1H), 1.05 (s, 9H), 1.35–1.43 (m, 1H), 1.51–1.75 (m, 10H), 1.80 (ddd, J = 5.1, 9.1, 14.1 Hz, 1H), 2.05–2.07 (m, 1H), 2.09 (s, 3H), 3.08 (t, J = 9.5 Hz, 1H), 3.15 (ddd, J = 1.6, 3.4, 9.3 Hz, 1H), 3.69 (td, J = 2.3, 5.8 Hz, 2H), 3.29–3.37 (m, 1H), 3.84 (dd, J = 1.6, 11.5 Hz, 1H), 3.70 (td, J = 2.5, 5.9 Hz, 2H), 3.90 (dd, J = 3.5, 11.6 Hz, 1H), 3.95 (ddd, J = 3.6, 5.8, 9.1 Hz, 1H), 4.13 (ddd, J = 5.9, 9.3, 11.8 Hz, 1H), 4.58 (d, J = 10.9 Hz, 1H), 4.71 (d, J = 10.9 Hz, 1H), 5.29 (t, J = 3.9 Hz, 1H), 7.29–7.45 (m, 11H), 7.67 (dd, J = 1.5, 7.8 Hz, 4H) ppm; ^{13}C NMR (100 MHz): δ −5.3 (q), −4.8 (q), 18.4 (s), 18.7 (q), 19.2 (s), 21.1 (q), 25.4 (t), 26.0 (q, 3C), 26.9 (q, 3C), 29.1 (t), 32.1 (t), 32.3 (t), 36.9 (d), 39.3 (t), 39.9 (t), 63.2 (t), 63.8 (t), 74.5 (t), 75.5 (d), 76.4 (d), 76.9 (t), 80.1 (d, 2C), 81.3 (d), 127.6 (q, 4C), 127.6 (d), 128.1 (d, 2C), 128.4 (q, 2C), 129.5 (q, 2C), 134.0 (s, 2C), 135.6 (q, 4C), 138.7 (s), 17.05 (s) ppm; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{47}H_{71}O_7Si_2$ 803.4733, found 803.4734.

Compound 2′-Ac. R_f = 0.3 (10% EtOAc in petroleum ether); $[\alpha]_D^{25}$: −0.4 (c = 1.7, $CHCl_3$); ^{1}H NMR (400 MHz): δ 0.08 (s, 3H), 0.09 (s, 3H), 0.92 (s, 9H), 1.04 (d, J = 6.4 Hz, 3H), 1.06 (s, 9H), 1.51–1.74 (m, 12H), 2.05 (s, 3H), 2.43 (dt, J = 7.1, 14.0 Hz, 1H), 3.09 (t, J = 9.5 Hz, 1H), 3.16 (ddd, J = 1.6, 3.3, 9.3 Hz, 1H), 3.30–3.40 (m, 1H), 3.70 (t, J = 5.8 Hz, 2H), 3.85 (dd, J = 1.4, 11.4 Hz, 1H), 3.91 (dd, J = 3.3, 11.5 Hz, 1H), 3.94–4.03 (m, 2H), 4.60 (d, J = 10.9 Hz, 1H), 4.71 (d, J = 10.9 Hz, 1H), 4.93 (dt, J = 3.3,

6.8 Hz, 1H), 7.28–7.45 (m, 11H), 7.67 (dd, J = 1.5, 7.8 Hz, 4H) ppm; ^{13}C NMR (100 MHz): δ −5.3 (q), −4.8 (q), 18.4 (s), 18.7 (q), 19.2 (s), 21.2 (q), 25.9 (q, 3C), 26.9 (q, 3C), 28.6 (t), 29.2 (t), 31.6 (t), 32.4 (t), 36.9 (d), 37.5 (t), 39.9 (t), 63.2 (t), 63.7 (t), 74.5 (t), 76.2 (d), 77.0 (d), 78.7 (d), 80.1 (d), 81.2 (d), 82.6 (d), 127.6 (d, 4C), 127.6 (d), 128.1 (d, 2C), 128.4 (d, 2C), 129.5 (d, 2C), 134.0 (s, 2C), 135.5 (d, 4C), 138.7 (s), 170.8 (s) ppm; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{47}H_{70}O_7NaSi_2$ 825.4552, found 825.4542.

Compound 2

To a stirred solution of compound **2-Ac** (150 mg, 187 μmol) in methanol (5 mL) was added potassium carbonate (77 mg, 560 μmol) at room temperature. The reaction mixture was kept at room temperature for 3 h. After consumption of the starting material, methanol was removed under reduced pressure. The crude reaction mixture was diluted with ethyl acetate (5 mL) and partitioned with water (5 mL). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the reaction mixture by silica gel column chromatography gave compound **2** (138 mg, 97% yield) as a colourless liquid. R_f = 0.4 (20% EtOAc in petroleum ether); $[\alpha]_D^{25}$: +2.5 (c = 1.5, $CHCl_3$); ^{1}H NMR (400 MHz): δ 0.09 (s, 3H), 0.10 (s, 3H), 0.92 (s, 9H), 1.05 (s, 12H), 1.08–1.16 (m, 1H), 1.52–1.72 (m, 10H), 2.08 (dd, J = 6.3, 13.3 Hz, 1H), 2.35 (d, J = 3.8 Hz, 1H), 3.08 (t, J = 9.6 Hz, 1H), 3.22 (ddd, J = 2.1, 3.6, 9.3 Hz, 1H), 3.38–3.45 (m, 1H), 3.69 (td, J = 2.0, 6.1 Hz, 2H), 3.78 (ddd, J = 2.7, 6.0, 8.6 Hz, 1H), 3.84–3.91 (m, 2H), 4.15–4.25 (m, 2H), 4.60 (d, J = 11.0 Hz, 1H), 4.69 (d, J = 11.0 Hz, 1H), 7.28–7.45 (m, 11H), 7.67 (dd, J = 1.5, 7.6 Hz, 4H) ppm; ^{13}C NMR (100 MHz); δ −5.3 (q), −4.9 (q), 18.4 (s), 18.7 (q), 19.2 (s), 24.1 (t), 26.0 (q, 3C), 26.8 (q, 3C), 29.1 (t), 31.6 (t), 32.5 (t), 36.8 (d), 39.8 (t), 41.4 (t), 63.1 (t), 63.8 (t), 73.1 (d), 74.5 (t), 75.9 (d), 76.7 (d), 80.0 (d), 81.3 (d), 82.1 (d), 127.6 (d, 4C), 127.7 (s), 128.0 (d, 2C), 128.4 (d, 2C), 129.5 (d, 3C), 134.0 (s), 135.5 (d, 4C), 138.5 (s) ppm; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{45}H_{69}O_6Si_2$ 761.4627, found 761.4617.

Compound 2′

To a stirred solution of compound **2′-Ac** (20 mg, 25 μmol) in methanol (2 mL) was added potassium carbonate (10 mg, 75 μmol) at room temperature and stirred for 3 h. The reaction mixture was concentrated and dissolved in EtOAc (5 mL). The organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the reaction mixture by silica gel column chromatography gave compound **2′** (18 mg, 95% yield) as a colourless liquid. R_f = 0.4 (20% EtOAc in petroleum ether). $[\alpha]_D^{25}$: −0.2 (c = 0.34, $CHCl_3$); ^{1}H NMR (400 MHz): δ 0.08 (s, 3H), 0.09 (s, 3H), 0.91 (s, 9H), 1.05 (s, 12H), 1.11 (q, J = 12.0 Hz, 1H), 1.48–1.77 (m, 11H), 2.31 (dd, J = 6.9, 13.3 Hz, 1H), 3.03 (t, J = 9.5 Hz, 1H), 3.20 (ddd, J = 2.1, 4.1, 9.4 Hz, 1H), 3.31–3.43 (m, 1H), 3.68 (t, J = 5.9 Hz, 2H), 3.80–3.90 (m, 3H), 3.96 (dt, J = 6.8, 12.8 Hz, 1H), 4.01–4.11 (m, 1H), 4.59 (d, J = 10.8 Hz, 1H), 4.66 (d, J = 10.8 Hz, 1H), 7.27–7.25 (m, 11H), 7.67 (dd, J = 1.6, 7.8 Hz, 4H) ppm; ^{13}C NMR (100 MHz): δ −5.3 (q), −4.9 (q), 18.4 (s), 18.7 (q), 19.2 (s), 26.0 (q, 3C), 26.9 (q, 3C), 29.2 (t), 29.3 (t), 31.2 (t), 32.9 (t), 37.0 (d), 40.1 (t), 40.6 (t), 63.2 (t), 63.8 (t), 74.6 (t), 76.0 (d), 76.8 (d, 2C), 80.3 (d), 81.4 (d), 84.2 (d), 127.6 (d, 4C), 127.7 (d), 128.0 (d, 2C), 128.4 (d, 2C), 129.5 (d, 2C), 134.0 (s, 2C), 135.6 (d, 4C), 138.5 (s) ppm; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{45}H_{69}O_6Si_2$ 761.4627, found 761.4623.

Synthesis of compound 14

To a stirred solution of compound **2** (118 mg, 0.15 mmol) in dry dichloromethane (5 mL) and water (1 mL) was added DDQ (106 mg, 0.46 mmol) at room temperature. The reaction mixture was purged with nitrogen gas and stirred under reflux under an inert atmosphere for 9 h. After completion of the reaction, the reaction was quenched with saturated $NaHCO_3$ solution (5 mL), the organic layer was separated, and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the reaction mixture by silica gel column chromatography gave the diol **14** (80 mg, 77% yield) as a colourless liquid. R_f = 0.5 (30% EtOAc in petroleum ether); $[\alpha]_D^{25}$: −0.15 (c = 0.3, $CHCl_3$); ^{1}H NMR (400 MHz): δ 0.11 (s, 3H), 0.11 (s, 3H), 0.91 (s, 9H), 1.05 (s, 9H), 1.06 (d, J = 6.3 Hz, 3H), 1.47–1.80 (m, 10H), 1.96 (d, J = 4.9 Hz, 1H), 2.07 (dd, J = 6.3, 13.1 Hz, 1H), 3.15 (t, J = 8.6 Hz, 1H), 3.25 (td, J = 4.6, 8.6 Hz, 1H), 3.39–3.48 (m, 1H), 3.66–3.72 (m, 3H), 3.74 (d, J = 0.9 Hz, 1H), 3.76 (ddd, J = 2.8, 6.1, 7.1 Hz, 1H), 3.91 (dd, J = 4.5, 9.9 Hz, 1H), 4.18 (dd, J = 6.1, 9.3 Hz, 1H), 4.22 (d, J = 3.0 Hz, 1H), 7.36–7.45 (m, 6H), 7.65–7.69 (m, 4H) ppm; ^{13}C NMR (100 MHz): δ −5.7 (q), −5.6 (q), 17.9 (q), 18.1 (s), 19.2 (s), 24.3 (t), 25.8 (q, 3C), 26.9 (q, 3C), 29.1 (t), 31.7 (t), 32.5 (t), 36.9 (d), 38.6 (t), 41.5 (t), 63.8 (t), 66.8 (t), 73.2 (d), 76.4 (d), 76.8 (d), 77.2 (d), 78.1 (d), 81.8 (d), 127.6 (d, 4C), 129.5 (d, 2C), 134.0 (s, 2C), 135.6 (d, 4C) ppm; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{38}H_{63}O_6Si_2$ 671.4158, found 671.4158.

Synthesis of the eribulin fragment C14–C28 (1)

At −78 °C, to a solution of trifluoroacetic anhydride (77 μL, 551 μmol) in dry dichloromethane (0.5 mL) was added DMSO (78 μL, 1.10 mmol) in dichloromethane (0.5 mL) and stirred for 15 minutes. To this mixture, a solution of diol **14** (74 mg, 110 μmol) in dichloromethane (0.5 mL) was added dropwise and the mixture was stirred for another 30 min prior to the addition of diisopropylethylamine (0.3 mL, 1.65 mmol). Then, the reaction mixture was warmed to −20 °C and stirred for 1 h. After complete consumption of the starting material, as indicated by TLC, the reaction mixture was warmed to room temperature and treated with cold water (2 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 × 5 mL). The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude product was used for the next step without any purification.

To a stirred solution of methyltriphenylphosphonium bromide (187 mg, 525 μmol) in dry toluene (5 mL) was added

potassium *tert*-butoxide (59 mg, 525 μmol) at 0 °C. The solution was refluxed for 1 h and then cooled to 40 °C. The yellow supernatant solution was transferred to a 40 °C pre-heated solution of crude diketone (70 mg, 105 μmol) in toluene (1 mL) and kept for 30 minutes at the same temperature. The reaction mixture was cooled to room temperature and diluted with water (10 mL) and ethyl acetate (20 mL). The organic layer was separated, washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the crude product by column chromatography (10% EtOAc in petroleum ether) gave diene **1** (55 mg, 75% yield) as a colourless liquid. R_f = 0.5 (10% EtOAc in petroleum ether); $[\alpha]_D^{25}$: −5.8 (*c* = 1.1, $CHCl_3$); ^{1}H NMR (400 MHz): δ 0.08 (s, 3H), 0.09 (s, 3H), 0.90 (s, 9H), 1.05 (s, 9H), 1.08 (d, *J* = 6.1 Hz, 3H), 1.10–1.14 (m, 1H), 1.47–1.57 (m, 3H), 1.61–1.71 (m, 5H), 1.77 (ddd, *J* = 2.0, 4.4, 12.9 Hz, 1H), 2.19–2.30 (m, 2H), 2.63 (ddd, *J* = 1.6, 6.4, 15.4 Hz, 1H), 3.55–3.62 (m, 1H), 3.68 (td, *J* = 1.5, 6.0 Hz, 2H), 3.75 (t, *J* = 6.0 Hz, 1H), 3.80 (dd, *J* = 5.9, 10.1 Hz, 1H), 3.95 (dd, *J* = 5.4, 10.1 Hz, 1H), 3.98 (t, *J* = 6.5 Hz, 1H), 4.39 (d, *J* = 6.4 Hz, 1H), 4.83 (d, *J* = 1.5 Hz, 1H), 4.84 (d, *J* = 2.0 Hz, 1H), 4.90 (s, 1H), 4.96 (d, *J* = 1.9 Hz, 1H), 7.36–7.43 (m, 6H), 7.66–7.68 (m, 4H) ppm; ^{13}C NMR (100 MHz): δ −5.3 (q), −5.1 (q), 17.8 (q), 18.3 (s), 19.2 (s), 25.9 (q, 3C), 26.8 (q, 3C), 29.1 (t), 31.2 (t), 31.6 (t, 2C), 35.7 (d), 38.9 (t), 42.9 (t), 63.8 (t), 63.8 (t), 77.0 (d), 77.2 (d), 79.0 (d), 79.4 (d), 104.6 (t), 104.7 (t), 127.6 (d, 4C), 129.5 (d, 2C), 134.0 (s, 2C), 135.6 (d, 4C), 149.4 (s), 151.8 (s) ppm; HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{40}H_{63}O_4Si_2$ 663.4259, found 663.4263.

Compound 15

To a stirred solution of diene **1** (13 mg, 19.6 μmol) in methanol (2 mL) was added camphorsulfonic acid (1 mg, 3.9 μmol) at 0 °C. After stirring the reaction mixture for 2 h at the same temperature, triethylamine was added and concentrated under reduced pressure. Purification of the crude product by column chromatography gave the TBS deprotected compound **15** (10 mg, 93% yield) as a colourless liquid. R_f = 0.2 (20% EtOAc in petroleum ether); ^{1}H NMR (400 MHz): δ 1.05 (s, 9H), 1.09 (d, *J* = 6.5 Hz, 3H), 1.52–1.71 (m, 10H), 1.79 (ddd, *J* = 2.0, 4.6, 12.9 Hz, 1H), 2.22–2.30 (m, 2H), 2.64 (ddd, *J* = 1.8, 6.4, 15.4 Hz, 1H), 3.58–3.65 (m, 1H), 3.68 (td, *J* = 1.3, 5.9 Hz, 1H), 3.80–3.92 (m, 3H), 4.0 (dt, *J* = 6.4, 12.3 Hz, 1H), 4.40 (d, *J* = 5.4 Hz, 1H), 4.74 (s,1H), 4.81–4.85 (m, 2H), 4.98 (dd, *J* = 2.0, 4.1 Hz, 1H), 7.36–7.44 (m, 6H), 7.66 (dd, *J* = 1.5, 7.8 Hz, 4H) ppm; ^{13}C NMR (100 MHz): δ 17.6 (q), 19.2 (s), 26.8 (q, 3C), 29.1 (t), 31.4 (t), 31.5 (t), 31.7 (t), 35.4 (d), 38.9 (t), 42.5 (t), 63.1 (t), 63.8 (t), 77.1 (d), 77.2 (d), 78.2 (d), 79.4 (d), 104.7 (t, 2C), 127.6 (d, 4C), 129.5 (d, 2C), 134.0 (s, 2C), 135.6 (d, 4C), 148.5 (s), 151.8 (s) ppm; HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{34}H_{49}O_4Si$ 549.3395, found 549.3378.

Conflicts of interest

The authors declare no competing financial interest.

Acknowledgements

The authors acknowledge the CSIR (India) for funding this project and for a research fellowship to S. S.

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