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Total synthesis of 5-*epi*-Torrubiellutin C and its biological evaluation†

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The total synthesis of 5-*epi*-Torrubiellutin C is described in a fully stereocontrolled manner and linear sequence involving high yielding steps. The synthetic strategy involves the dicyclohexylboron chloride mediated Paterson's aldol protocol, Horner–Emmons olefination, $TiCl_4$ mediated *syn*-aldol reaction and ring closing metathesis (RCM) as the key steps. Furthermore, the resultant epimer was evaluated for cytotoxicity against DU145 (prostate), MCF-7 (breast) and A549 (lung) cancer cell lines, and the results showed that the 5-*epi*-Torrubiellutin C is as good as the natural product in bioassays.

Introduction

Torrubiellutins are 15-membered macrocyclic amides grafted on L-phenylalanine through ester–amide linkages. These compounds were recently isolated by Pittayakhajonwut *et al.* from the crude extract of the insect fungus; *Torrubiella luteorostrata* BCC 12904.[1] The crude extract exhibited low micromolar inhibition of MCF-7 and human epidermoid carcinoma (KB) cell lines. The further purification of this extract resulted in isolation of three macrolides, *viz.*, Torrubiellutins A–C (**1–3**, Fig. 1) along with the known pyrone diterpene. While Torrubiellutin C (**3**) showed very good cytotoxic activity, the pyrone exhibited good antimalarial properties.

Besides their 15-membered macrocyclic feature, torrubiellutins are enriched with seven asymmetric carbons, having an α, β-unsaturated amide and *tri*-substituted olefin functionalities. These challenging functionalities and our interest in the total synthesis of bioactive compounds[2] prompted us to embark on the endeavour of synthesizing this natural product.

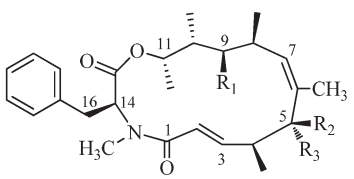
To the best of our knowledge, to date no synthetic effort has been reported towards the synthesis of torrubiellutins.

Results and discussion

The asymmetric centres present in this macrocycle are tailor made for 'aldol chemistry'. Thus, we relied heavily on utilizing asymmetric aldol reactions towards the target envisioned.

The local disconnections based on this background allowed us to initiate the synthesis starting from commercially available (*S*)-Roche ester through the diol **8**, aldehyde **7**, which could be further converted to the RCM precursor **4** *via* **6**. This may eventually be converted to the target molecule (Scheme 1).

In the next steps, (*S*)-Roche ester was silylated to **10**,[3] which was converted to ethyl ketone **9**[4] *via* Weinreb amide **11**, resulting in 87% yields over two steps. The asymmetric aldol (Paterson's aldol) reaction[5] of **9** with acetaldehyde in the presence of dicyclohexylboron chloride, followed by $LiBH_4$ reduction, provided the diol **8** with perfect stereocontrol (>98% dr ratio, the minor isomer was separated by column chromatography). The resultant major diol **8** was correlated with the data of reported compound **12** by replacing its silyl ether with benzyl ether.[6,7] The protective group manipulations, *viz.*, monobenzylation of **8**, followed by silylation to **13** and selective 1° desilylation to **14** were highly predictable with good yields. The compound **15** was oxidized using IBX and in turn was subjected to (*Z*)-controlled olefination conditions (Horner–Emmons olefination)[8] to realize **16** in yields of over 83%. No trace of other *trans*-diastereomer was observed during this transformation. The reduction of ester functionality in **16**



Torrubiellutin A (**1**), $R_1 = R_2 = OH$, $R_3 = H$
B (**2**), $R_1 = R_2 = OAc$, $R_3 = H$
C (**3**), $R_1 = OAc$, $R_2 = OH$, $R_3 = H$
5-*epi*-Torrubiellutin C (**3a**), $R_1 = OAc$, $R_2 = H$, $R_3 = OH$

Fig. 1 Structures of torrubiellutins.

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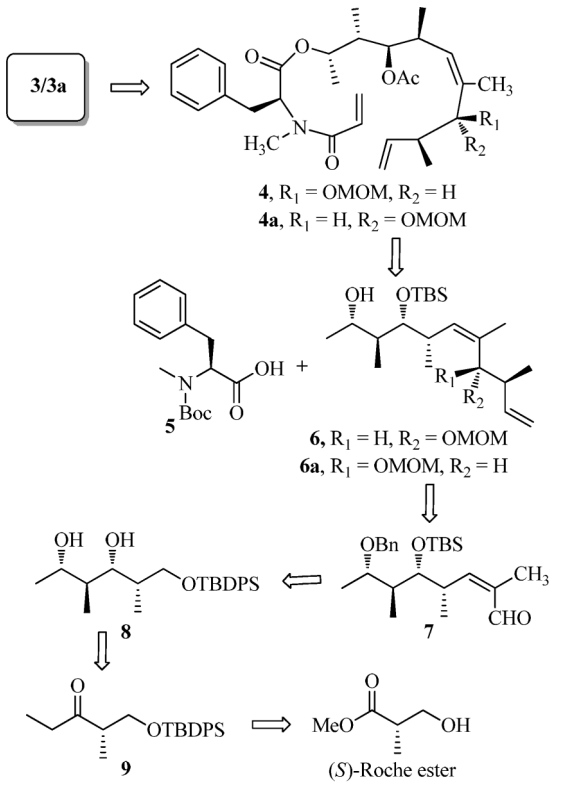
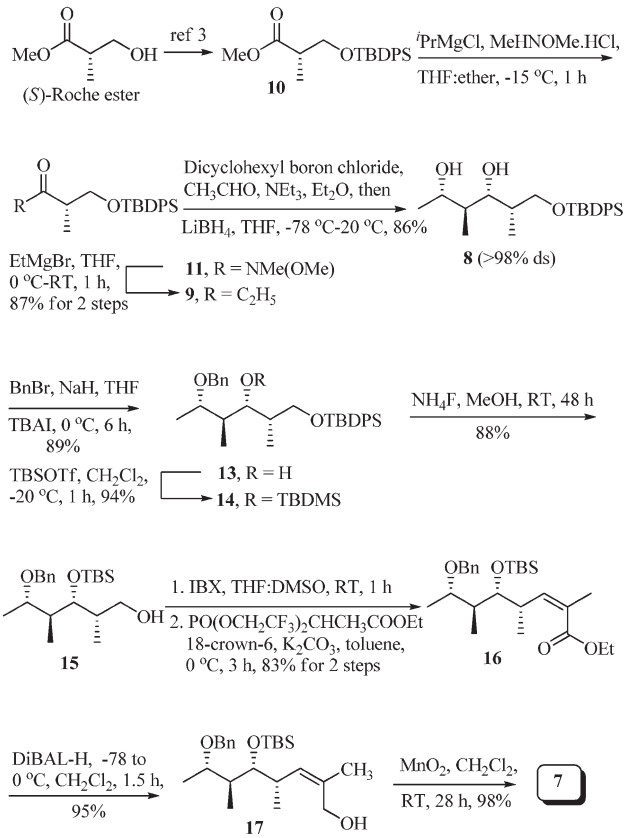
† Electronic supplementary information (ESI) available: Copies of ^1H NMR and ^{13}C NMR spectra of all the new compounds. See DOI: 10.1039/c3ra42127a



Scheme 1 Retrosynthetic analysis of Torrubiellutin C.



Scheme 2 Stereoselective synthesis of aldehyde **7**.

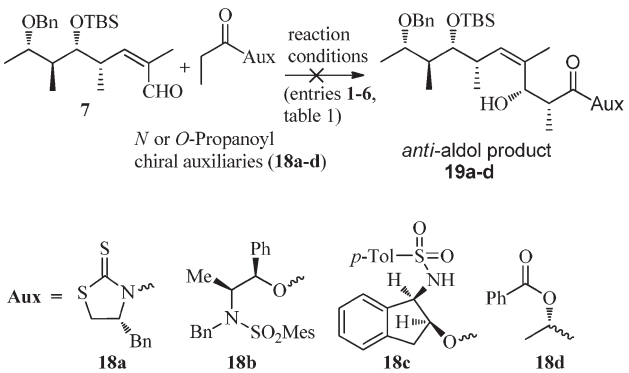
was achieved using DIBAL-H to produce the alcohol **17**, which was oxidized using MnO_2 to aldehyde **7** in a 98% yield (Scheme 2).

The real challenge of *anti*-aldol addition of the propionic amide (using auxiliaries **18a–d**) under various reaction conditions[5f,9–12] on to aldehyde **7** was futile. Unfortunately, no reaction was observed even after prolonged reaction times (see Scheme 3 and Table 1).

As we achieved an advanced stage of synthesis, not looking back, we attempted to form a *syn*-aldol[13] product with the known auxiliary **18e**[13a] using $TiCl_4$ and (−)-sparteine. Interestingly, the reaction was very smooth with good '*syn*' control (97 : 3 diastereomeric ratio) to give **19e** in 84% yield, after the minor isomer was separated by column chromatography (Scheme 4). The reason for the failure to obtain an *anti*-aldol may be due to steric congestion during the transition state (Fig. 2).

Further attempts to invert the C-5 hydroxyl of the target molecule in **19e** were again not successful. Therefore, we anticipated that this could be achieved after accomplishing the macrocycle. Thus, we proceeded further by protecting the free hydroxyl group in **19e** as MOM ether **20**, which was followed by the removal of the auxiliary with $LiBH_4$ to furnish the primary alcohol **21** in 90% yield. One carbon homologation of **21** to olefin **22** was achieved *via* IBX oxidation, followed by a Wittig reaction with $P^+Ph_3MeI^-$ in the presence of KO^tBu. The benzyl group in **22** was removed using Li/naphthalene to provide **6a** in 94% yield (Scheme 5).

After successful construction of the aliphatic propionate part **6a**, it was esterified with *N*-methyl-*N*-Boc phenylalanine **5**[14] using DCC and DMAP to realize the ester **23** in 88% yield (Scheme 6). The desilylation of **23** to alcohol **24**, which was then acetylated to **25**, were rather easy transformations and were achieved in quantitative yields. The Boc group in **25** was deprotected with TFA followed by immediate treatment with acryloyl chloride and Et_3N to produce acrylamide **4a** in 90% yield. The macrocyclization *via* RCM was accomplished rather efficiently using HG-II catalyst[15] (only 10% reaction conversion

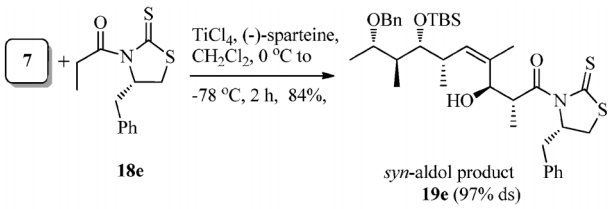


Scheme 3 Trials attempted in favour of key fragment **6**.

Table 1 *Anti*-aldol reactions of aldehyde **7** with auxiliaries (**18a–d**) under various reaction conditions

Entry	Reaction conditions	Reaction progress[a]
1	**18a**,[9] $MgBr_2{\cdot}OEt_2$ (10 mol%), aldehyde **7** (1.1 equiv.), Et_3N (2 equiv.), TMSCl (1.5 equiv.), 0.4 M in EtOAc, 24 h; then 5 : 1 THF/1.0 N HCl.	no reaction
2	**18a**,[9] $MgCl_2$ (10 mol%), aldehyde **7** (1.1 equiv.), Et_3N (2 equiv.), TMSCl (1.1 equiv.), 0.4 M in EtOAc, 24 h; then 5 : 1 THF/1.0 N HCl.	no reaction
3	**18b**,[10] *c*-Hex_2BOTf (2.0 equiv.), Et_3N (2.4 equiv.), −78 °C for 2 h; then aldehyde **7**, −78 °C for 1 h, 0 °C–RT for 15 h.	<2% product
4	**18c**,[11] $TiCl_4$, $^iPr_2NEt$, then aldehyde **7**, Bu_2BOTf, CH_2Cl_2, −78 °C–RT, 12 h.	mixture of products
5	**18d**,[5f,12] *c*-Hex_2BCl, NMe_2Et, 0 °C, 2 h; then aldehyde **7**, −78 °C–RT, 10 h.	no reaction
6	**18d**,[5f,12] *c*-Hex_2BCl, Et_3N, 0 °C, 1.5 h; then aldehyde **7**, −78 °C–RT, 12–15 h.	no reaction

[a] All reactions were performed according to known procedures.



Scheme 4 *Syn*-aldol reaction of aldehyde **7**.

was observed when Grubbs'-II catalyst is used) in 95% yield after several parameter corrections to realize the exclusive *trans*-macrolactam **26**. The MOM ether **26** was hydrolyzed under $LiBF_4$ conditions[16] to generate 5-*epi*-Torrubiellutin C (**3a**) (~213 mg), which has been thoroughly characterized (see experimental).

Furthermore, several attempts to epimerize the C-5 hydroxyl group in **3a** under Mitsunobu or oxidation–reduction conditions were not successful. This was rather disappointing taking into account the efforts that had gone into achieving the target molecule synthesis. Then, we anticipated that the resultant 5-*epi*-Torrubiellutin C (**3a**), having the entire functionality of the natural product, would be biologically useful. Thus, the epimer **3a** was subjected to screening for cytotoxic effects as reported.[17,18] Interestingly, the results from cytotoxic assays clearly showed its anti-cancer properties against the tested cell lines. The IC_{50} values showed that the cytotoxic effect of the tested compound on prostate cancer (DU145) and breast cancer (MCF-7) cell lines is comparable to that of the control drug doxorubicin, whereas it was less effective in lung cancer (A549) cells compared to the control. Previously, Pittayakhajonwut *et al.* reported cytotoxicity for the natural product. However, in their reported assays,[1] the determined efficacy of the natural product (**3**) was 5 fold less compared to the standard drug doxorubicin against MCF-7 (strong cytotoxicity compared to other cell types tested) cells. Thus, in our currently reported assays, the 5-*epi*-Torrubiellutin C (**3a**) showed better efficacy than the control drug doxorubicin on the same cell line, MCF-7 (breast cancer cells), suggesting that **3a** is more effective than **3**. Taken together, the present cytotoxic results clearly showed that the 'C-5 epimer' synthesized as an alternative to the original natural product is equally potent or more cytotoxic in selected cell types (see Table 2).

Conclusions

In summary, the total synthesis of the C-5 epimer of a cytotoxic natural product, Torrubiellutin C, has been achieved with

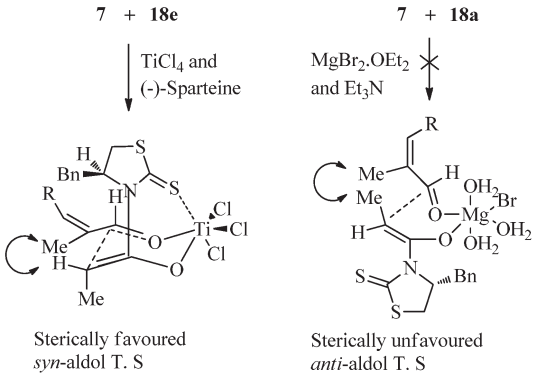
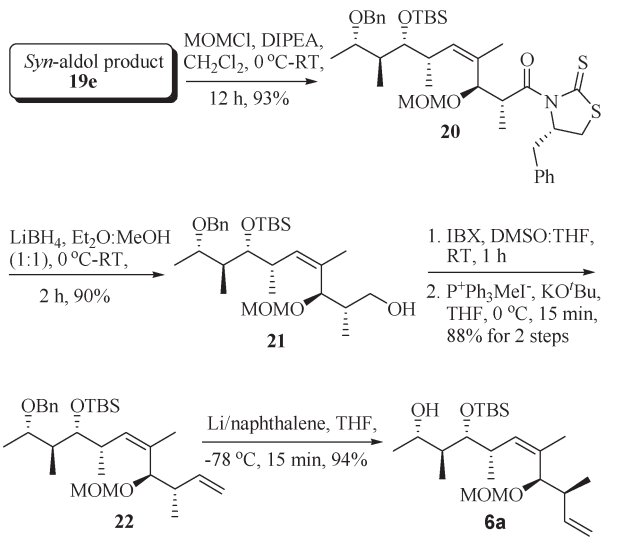
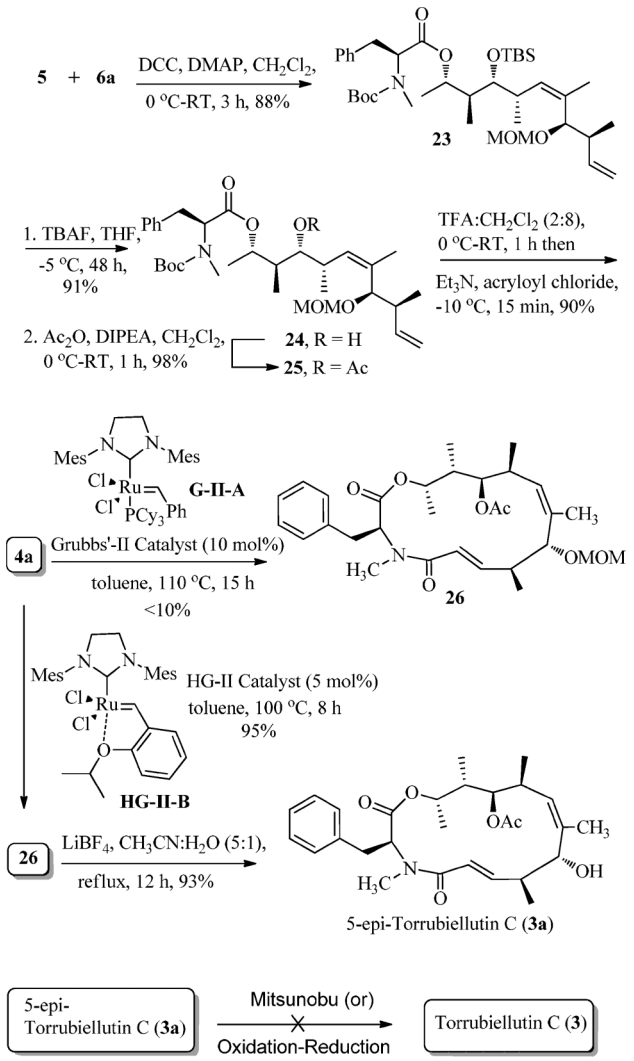


Fig. 2 Transition states during *syn*- and *anti*-aldol additions.



Scheme 5 Synthesis of fragment **6a** from *syn*-aldol adduct **19e**.



Scheme 6 Construction of 5-*epi*-torrubiellutin C (**3a**).

excellent stereocontrol, and it has also been proved that this isomer is as good as the natural product in bioassays.

Experimental

General

Reactions were monitored by thin-layer chromatography carried out on silica plates (silica gel 60 F254, Merck) using UV-light and anisaldehyde or potassium permanganate or β-naphthol for visualization. Column chromatography was performed on silica gel (60–120 or 100–200 mesh) using *n*-hexane and ethyl acetate as eluent. Evaporation of solvents was conducted under reduced pressure at temperatures below 50 °C. IR spectra were recorded on Perkin–Elmer 683, Nicolet Nexus 670 spectrometers. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solvent on 300 MHz, 400 MHz and 500 MHz NMR spectrometers. Chemical shifts δ and coupling constants J are given in ppm (parts per million) and Hz (hertz), respectively. Chemical shifts are reported relative to residual solvent as an internal standard for ^{1}H and ^{13}C ($CDCl_3$: δ 7.26 ppm for ^{1}H and 77.0 ppm for ^{13}C). Mass spectra were obtained on Finnigan MAT1020B, micromass VG 70–70H or LC/MSD trapSL spectrometers operating at 70 eV using direct inlet system.

Table 2 IC_{50} values of 5-*epi*-Torrubiellutin C (**3a**)

S. No	Compounds	IC_{50} value in μM		
		DU 145	MCF 7	A549
1	5-*epi*-Torrubiellutin C (**3a**)	8.88 ± 0.05	5.58 ± 0.86	23.08 ± 2.28
2	Doxorubucin	6.30 ± 0.12	7.39 ± 0.41	6.54 ± 0.14

Cytotoxicity evaluation against different cancer cell lines

Cellular viability was determined by MTT-microcultured tetrazolium assay using the reported protocol with minor modifications. Briefly, all three types of cell line were seeded to a flat bottom 96 (10 000 cells/100 μL) well plate and cultured in a medium containing 10% serum followed by incubation of these cells for 24 h with a constant supply of 5% CO_2 in a humid incubator so that they adhered to the surface of the plate. The synthesized epimer was resuspended in DMSO to prepare stock concentrations. Different concentrations of test compound and doxorubicin (as a standard control anti cancer drug) were prepared in DMSO and added to achieve final concentrations of 0 to 100 μM of compound to cells. Cells were further allowed to grow for 48 h with a constant supply of 5% CO_2 in a humid incubator. 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) was dissolved in PBS at 5 mg mL^{-1} and filter sterilized MTT solution was added for assay. After 48 h, MTT solution (10 μL per well) was added to the culture plate. Cells were further incubated in the CO_2 chamber for 2 h. Subsequently, the medium was removed and 100 μL of DMSO was added to cells. The absorbance of purple colour obtained was measured at 562 nm in a multimode microplate reader (Tecan GENios) is proportional to cell growth. From the observed %age of growth with and without test compound IC_{50} values were calculated. In this study, three types of cancer cell lines, *i.e.* human lung cancer (A549); human breast cancer (MCF-7) and prostate cancer (DU145) cell lines were tested for the cytotoxic effect of the epimer synthesized. The results presented are from three independent experiments, each in triplicates. The calculated IC_{50} values ± standard deviation are presented in Table 2.

Experimental details and analytical data for all the new compounds and comparison data for the known compounds are described below.

1-(*tert*-Butyldiphenylsilyloxy)-2-methylpentan-3-one (9). (a) To a stirred solution of the silylated ester **10** (ref. 3) (17.0 g, 47.7 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (13.9 g, 143.2 mmol) in dry THF (200 mL) at −15 °C, was slowly added *iso*-propylmagnesium chloride (12.2 g, 59.6 mL, 119.2 mmol, 2.0 M in Et_2O). The reaction mixture was stirred for 1 h at the same temperature. After completion of the reaction (monitored by TLC), it was quenched with saturated NH_4Cl solution (80 mL) at 0 °C and diluted with EtOAc (180 mL). The

organic layer was separated, washed with brine solution (120 mL), dried over anhydrous Na_2SO_4 and concentrated on a rotary evaporator. The resultant amide **11** (16.9 g, 92%) was used for the next step without purification.

(b) To the above crude Weinreb amide **11** (16.0 g, 41.5 mmol) dissolved in dry THF (160 mL), was slowly added EtMgBr (16.7 g, 99.5 mL, 124.6 mmol, 2.0 M in Et_2O) at 0 °C under N_2 atmosphere. The reaction mixture was stirred under the same conditions for 1 h (reaction progress was monitored by TLC). Then, it was quenched with aq. saturated NH_4Cl solution (70 mL), diluted with EtOAc (150 mL), the organic layer was separated and the aqueous layer was washed with EtOAc (2 × 80 mL). The combined organic layers were washed with brine (90 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography (2% EtOAc in hexanes) to afford the ethyl ketone **9** (13.9 g, 95%) as a colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66–7.58 (m, 4H), 7.45–7.33 (m, 6H), 3.79 (dd, J = 7.3, 9.5 Hz, 1H), 3.62 (dd, J = 5.9, 9.5 Hz, 1H), 2.85–2.75 (m, 1H), 2.61–2.43 (m, 2H), 1.01 (t, J = 7.3 Hz, 3H), 1.03 (s, 9H), 1.01 (d, J = 6.6, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 214.0, 135.5, 133.3, 133.1, 129.6, 127.6, 66.3, 48.1, 35.7, 26.6, 19.1, 13.0, 7.4; IR (KBr): ν 2934, 2860, 1715, 1466, 1428, 1386, 1110, 1087, 821, 740, 704 cm^{-1}; MS (ESI): m/z 377 (100) $[M + Na]^+$; HRMS (ESI): $[M + Na]^+$ $C_{22}H_{30}NNaO_2Si$: calcd. 377.1907; found, 377.1928; $[\alpha]_D^{30}$: +31.3 (c 1.0, $CHCl_3$).

(2*S*,3*S*,4*R*,5*S*)-6-(*tert*-Butyldiphenylsilyloxy)-3,5-dimethylhexane-2,4-diol (8). To a stirred solution of dicyclohexylboron chloride (11.5 g, 54.1 mL, 54.2 mmol, 1.0 M in diethyl ether) in anhydrous Et_2O (80 mL) at 0 °C under inert conditions, was added Et_3N (6.1 g, 8.8 mL, 61.0 mmol) followed by ethyl ketone **9** (12.0 g, 33.8 mmol) in diethyl ether (80 mL). After stirring for 2 h at 0 °C, the reaction mixture was cooled to −78 °C and acetaldehyde (5.4 mL, 84.7 mmol) was added. The reaction was maintained for 3 h at the same temperature. The reaction mass was kept at −20 °C for 20 h. Then, the reaction temperature was re-cooled to −78 °C, $LiBH_4$ (3.7 g, 169.4 mmol, 84.5 mL, 2.0 M in THF) was added and the mixture was stirred for 3 h. The temperature was raised to 0 °C and quenched with aq. saturated NH_4Cl solution (70 mL). The mixture was diluted with diethyl ether (100 mL), and the organic layer was separated and concentrated on a rotary evaporator. The resultant residue was dissolved in MeOH (140 mL) and cooled to 0 °C. NaOH (90 mL, 10%) and followed by H_2O_2 (31 mL, 30%) were added dropwise. After stirring for 3 h at room temperature, the reaction mixture was diluted with dichloromethane (200 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 × 100 mL). The combined organic layers were washed with brine (120 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude compound in a 98 : 2 diasteriomeric ratio. This was chromatographed (the minor isomer was separated) over silica gel (25% EtOAc/petroleum ether) to provide the pure diol **8** (11.6 g, 86%) as a colourless liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.73–7.60 (m, 4H), 7.53–7.33 (m, 6H), 3.92–3.71 (m, 3H), 3.69 (dd, J = 4.6, 9.8 Hz, 1H), 1.85–1.74 (m, 1H), 1.67–1.52 (m, 1H), 1.19 (d, J = 6.0 Hz, 3H), 1.07 (s, 9H), 0.98 (d, J = 6.9 Hz, 3H), 0.71 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.5, 135.4, 132.8, 132.5, 129.86, 129.80, 127.7, 79.9, 72.4, 69.4, 42.2, 36.0, 26.7, 20.9, 19.0, 12.6, 8.8; IR (KBr): ν 3403, 2963, 2931, 2859, 1467, 1427, 1109, 822, 740, 703, 611, 504 cm^{-1}; MS (ESI): m/z 401 (100) $[M + H]^+$; HRMS (ESI): $[M + Na]^+$ $C_{24}H_{36}NaO_3Si$: calcd. 423.2326; found, 423.2330; $[\alpha]_D^{30}$: −73.0 (c 0.5, $CHCl_3$).

(2*S*,3*R*,4*R*,5*S*)-5-(Benzyloxy-1-(*tert*-butyldiphenylsilyloxy)-2,4-dimethylhexan-3-ol (13). Diol **8** (11.0 g, 27.5 mmol) in dry THF (50 mL) was slowly added to a stirred suspension of NaH (1.6 g, 41.2 mmol, 60% w/v in dispersion mineral oil) in dry THF (120 mL) at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred at the same temperature for 20 min and benzyl bromide (5.6 g, 33.0 mmol) followed by TBAI (50 mg) were added. The reaction was maintained at 0 °C for 6 h. After completion of the reaction (monitored by TLC), it was quenched with saturated NH_4Cl solution (50 mL). The reaction mass was diluted with EtOAc (120 mL) and stirred for 10 min. The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 60 mL). The combined organic layers were washed with brine (80 mL), dried over Na_2SO_4 and concentrated on a rotary evaporator. The crude product was chromatographed over silica gel (8–10% EtOAc/petroleum ether) to provide the monobenzylated compound **13** (11.9 g, 89%) as a colourless liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70–7.59 (m, 4H), 7.43–7.17 (m, 11H), 4.57 (d, J = 11.7 Hz, 1H), 4.47 (d, J = 11.4 Hz, 1H), 3.83–3.74 (m, 1H), 3.72–3.63 (m, 3H), 3.34 (bs, 1H), 1.95–1.83 (m, 1H), 1.80–1.70 (m, 1H), 1.18 (d, J = 6.2 Hz, 3H), 1.06 (s, 9H), 0.88 (d, J = 6.7 Hz, 3H), 0.76 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.6, 135.5, 134.7, 129.6, 128.3, 127.6, 127.5, 127.4, 77.8, 75.3, 70.5, 68.5, 40.1, 36.6, 26.8, 19.1, 15.2, 10.9, 8.7; IR (KBr): ν 3484, 2961, 2930, 2857, 1467, 1427, 1383, 1109, 822, 739, 702, 610, 504 cm^{-1}; MS (ESI): m/z 513 (100) $[M + H]^+$; HRMS (ESI): $[M + Na]^+$ $C_{31}H_{42}NaO_3Si$: calcd. 513.2795; found, 513.2813; $[\alpha]_D^{31}$: −20.5 (c 1.0, $CHCl_3$).

(5*R*,6*S*)-5-((2*S*,3*S*)-3-(Benzyloxy)butan-2-yl)-2,2,3,3,6,10,10-heptamethyl-9,9-diphenyl-4,8-dioxa-3,9-disilaundecane (14). To a stirred solution of compound **13** (10.0 g, 20.4 mmol) in CH_2Cl_2 (90 mL), was added 2,6-lutidine (5.4 g, 51.0 mmol) at −78 °C under N_2 atmosphere. After stirring for 5 min, TBSOTf (8.0 g, 30.6 mmol) was added to the above reaction mixture at −78 °C. The reaction temperature was raised to −20 °C and stirred for 1 h. After completion of the reaction monitored by TLC, it was diluted with water (60 mL), the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with brine (80 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by column chromatography (2% EtOAc/petroleum ether) to afford disilylated compound **14** (11.2 g, 94%) as a colourless oily liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80–7.71 (m, 4H), 7.55–7.42 (m, 6H), 7.41–7.30 (m, 5H), 4.55 (dd, J = 11.9, 25.8 Hz, 2H), 3.90 (d, J = 7.7 Hz, 1H), 3.82–3.72 (m, 1H), 3.65 (t, J = 9.8 Hz, 1H), 3.52 (t, J = 7.1 Hz, 1H), 2.14–2.04 (m, 1H), 2.01–1.90 (m, 1H), 1.26–1.12 (m, 12H), 1.03–0.86 (m, 15H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.2, 135.5, 133.9, 129.4, 128.2, 127.5, 127.3, 127.1, 75.0, 72.4, 70.0, 66.9, 41.5, 38.2, 26.8, 26.1, 19.1, 18.4, 14.9, 10.4, 10.1, −3.9, −4.1; IR (KBr): ν 3067, 2956, 2932,

2859, 1465, 1383, 1254, 1107, 832, 773, 737, 701, 613, 502 cm^{-1}; MS (ESI): *m/z* 627 (100) $[M + Na]^+$; HRMS (ESI): $[M + Na]^+$ $C_{38}H_{56}NaO_4Si$: calcd. 627.3840; found, 627.3830; $[\alpha]_D^{30}$: −10.5 (*c* 1.0, $CHCl_3$).

(2*S*,3*R*,4*R*,5*S*)-5-(Benzyloxy-3-(*tert*-butyldimethylsilyloxy)-2,4-dimethylhexan-1-ol (15). NH_4F (11.0 g, 297.0 mmol) was added to disilylated compound **14** (9.0 g, 14.8 mmol) dissolved in methanol (120 mL). The reaction mixture was stirred at room temperature for 48 h. After completion of the reaction (reaction progress was monitored by TLC), it was quenched with saturated NH_4Cl solution (20 mL). The solvent was removed under reduced pressure. The resultant crude product was dissolved in EtOAc (120 mL). The organic layer was washed with water (80 mL), brine (80 mL), dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The resultant crude was chromatographed over silica gel (7–8% EtOAc/petroleum ether) to give the alcohol **15** (4.9 g, 88%) as a colourless gummy liquid.

^1H NMR (300 MHz, $CDCl_3$): δ 7.37–7.24 (m, 5H), 4.56 (d, *J* = 11.8 Hz, 1H), 4.43 (d, *J* = 11.7 Hz, 1H), 3.87 (dd, *J* = 2.1, 6.6 Hz, 1H), 3.70–3.61 (m, 1H), 3.52–3.39 (m, 2H), 2.07–1.95 (m, 1H), 1.88–1.76 (m, 1H), 1.15 (d, *J* = 6.0 Hz, 3H), 0.92–0.83 (m, 15H), 0.06 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.9, 128.2, 127.4, 127.3, 75.6, 72.8, 69.9, 66.4, 42.5, 38.2, 26.0, 18.2, 15.7, 11.3, 11.0, −4.0, −4.3; IR (KBr): *v* 3448, 2956, 2931, 2886, 2858, 1625, 1458, 1377, 1255, 1131, 1091, 1028, 836, 773, 697 cm^{-1}; MS (ESI): *m/z* 367 (100) $[M + H]^+$; HRMS (ESI): $[M + H]^+$ $C_{21}H_{39}O_3Si$: calcd. 367.2663; found, 367.2662; $[\alpha]_D^{31}$: +18.5 (*c* 1.0, $CHCl_3$).

(4*S*,5*R*,6*S*,7*S*,*Z*)-Ethyl-7-(benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-2,4,6-tri-methyloct-2-enoate (16). (a) To a stirred solution of IBX (4.6 g, 16.3 mmol) in DMSO (7.0 mL) under N_2 atmosphere, was added alcohol **15** (4.0 g, 10.9 mmol) in anhydrous THF (35 mL) at room temperature. The reaction mixture was stirred for 1 h and diluted with Et_2O (70 mL). The solids were removed through a pad of Celite®. The filtrate was washed with saturated aq. $NaHCO_3$ (3 × 50 mL) and dried over anhydrous Na_2SO_4. The solvent was reduced *in vacuo* to obtain the crude aldehyde (3.85 g, 97%) which was used directly for the next reaction without further purification.

(b) K_2CO_3 (8.7 g, 62.6 mmol) and 18-crown-6 (33.0 g, 125.2 mmol) were charged into a 250 mL flask containing 75 mL of anhydrous toluene under N_2 atmosphere. The reaction mixture was stirred at room temperature for 3 h before cooling to 0 °C. Ethyl-2-(bis(perfluoroethoxy)-phosphoryl)propanoate (4.3 g, 12.5 mmol) in toluene (20 mL) and the above aldehyde (3.8 g, 10.4 mmol) in toluene (20 mL) were then slowly added to the reaction mixture at 0 °C. The reaction was maintained at the same temperature for 3 h. After complete consumption of the starting material (the reaction progress was monitored by TLC), it was quenched with saturated NH_4Cl solution (30 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 40 mL). The combined organic layers were washed with brine (60 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The compound was purified by column chromatography (3% EtOAc/petroleum ether) to afford an α,β-unsaturated *cis*-ester **16** (4.0 g, 86%, no other isomer detected) as a colourless liquid.

^1H NMR (300 MHz, $CDCl_3$): δ 7.33–7.18 (m, 5H), 5.76 (d, *J* = 10.1 Hz, 1H), 4.53 (d, *J* = 11.8 Hz, 1H), 4.36 (d, *J* = 11.9, 1H), 4.19–4.09 (m, 2H), 3.73 (dd, *J* = 4.7, 6.1 Hz, 1H), 3.62–3.54 (m, 1H), 1.97–1.86 (m, 1H), 1.84 (s, 3H), 1.29 (t, *J* = 6.9 Hz, 3H), 1.10 (d, *J* = 6.0 Hz, 3H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.92–0.86 (m, 12H), 0.02 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.9, 147.0, 146.0, 139.3, 128.2, 127.1, 125.1, 76.1, 75.3, 69.8, 60.0, 43.0, 35.7, 26.1, 20.8, 18.3, 15.7, 14.2, 10.0, −3.9, −4.1; IR (KBr): *v* 3448, 2957, 2930, 2858, 1713, 1626, 1452, 1376, 1256, 1216, 1172, 1133, 1086, 1029, 835, 772, 697 cm^{-1}; MS (ESI): *m/z* 449 (100) $[M + H]^+$; HRMS (ESI): $[M + Na]^+$ $C_{26}H_{44}NaO_4Si$: calcd. 471.2901; found, 471.2896. $[\alpha]_D^{30}$: +10.5 (*c* 1.0, $CHCl_3$).

(4*S*,5*R*,6*S*,7*S*,*Z*)-7-(Benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-2,4,6-trimethyl-oct-2-en-1-ol (17). DIBAL-H (2.21 g, 11.0 mL, 15.6 mmol, 20% in hexanes) was slowly added to a stirred solution of α,β-unsaturated *cis*-ester **16** (3.5 g, 7.8 mmol) in anhydrous dichloromethane (30 mL) at −78 °C under N_2 atmosphere. The reaction temperature was slowly raised to 0 °C and stirred for 1.5 h and then 20% aq. solution of sodium potassium tartarate (5 mL) was added. Then, it was diluted with CH_2Cl_2 (60 mL) and allowed to stir at room temperature for clear separation of the layers. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude material was chromatographed over silica gel (8% EtOAc/petroleum ether) to give the allyl alcohol **17** (3.0 g, 95%) as a pale yellow liquid.

^1H NMR (300 MHz, $CDCl_3$): δ 7.39–7.20 (m, 5H), 5.02 (d, *J* = 10.1 Hz, 1H), 4.56 (d, *J* = 11.3 Hz, 1H), 4.41 (d, *J* = 11.3 Hz, 1H), 3.89 (d, *J* = 11.8 Hz, 1H), 3.73–3.62 (m, 2H), 3.50–3.43 (m, 1H), 2.88–2.76 (m, 1H), 2.00–1.85 (m, 1H), 1.73 (s, 3H), 1.11 (d, *J* = 6.0 Hz, 3H), 0.98–0.82 (m, 15H), 0.07 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.6, 133.2, 132.8, 128.2, 127.9, 127.4, 79.4, 76.4, 70.6, 61.2, 42.3, 36.3, 26.2, 21.8, 18.5, 17.9, 16.9, 13.6, −3.5, −3.9; IR (KBr): *v* 3426, 2959, 2932, 2858, 1457, 1379, 1254, 1083, 1059, 1030, 835, 773, 736 cm^{-1}; MS (ESI): *m/z* 429 (100) $[M + Na]^+$; HRMS (ESI) : $[M + Na]^+$ $C_{24}H_{42}NaO_3Si$: calcd. 429.2795; found, 429.2817; $[\alpha]_D^{30}$: −15.3 (*c* 0.75, $CHCl_3$).

(4*S*,5*R*,6*S*,7*S*,*Z*)-7-(Benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-2,4,6-trimethyloct-2-enal (7). To a solution of allyl alcohol **17** (2.8 g, 6.8 mmol) in anhydrous dichloromethane (40 mL), was charged a half-portion of freshly prepared MnO_2 (2.96 g, 34.0 mmol) under N_2 atmosphere. The reaction mixture was stirred for 15 h at room temperature. At this time, another half-portion of MnO_2 (2.96 g, 34.0 mmol) was charged and the stirring was continued for 13 h. After completion of the reaction (monitored by TLC), the solids were filtered through a pad of Celite® and washed with CH_2Cl_2 (100 mL). The filtrate was reduced on a rotary evaporator and the crude material was chromatographed over silica gel (5% EtOAc/petroleum ether) to afford an α,β-unsaturated *cis*-aldehyde **7** (2.73 g, 98%) as a pale yellow liquid.

^1H NMR (500 MHz, $CDCl_3$): δ 10.02 (s, 1H), 7.35–7.27 (m, 5H), 6.26 (d, *J* = 9.6 Hz, 1H), 4.58 (d, *J* = 11.5 Hz, 1H), 4.30 (d, *J* = 11.5 Hz, 1H), 3.77 (t, *J* = 5.7 Hz, 1H), 3.51–3.40 (m, 2H), 1.94–1.88 (m, 1H), 1.70 (s, 3H), 1.12 (d, *J* = 5.7 Hz, 3H), 1.04 (d, *J* = 6.7 Hz, 3H), 0.94–0.86 (m, 12H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C

NMR (75 MHz, $CDCl_3$): δ 191.3, 153.6, 139.0, 133.7, 128.3, 127.3, 127.2, 76.3, 75.6, 69.8, 44.2, 33.9, 29.6, 26.0, 22.6, 16.4, 14.0, 11.1, −3.9, −4.2; IR (KBr): *v* 2927, 2856, 1741, 1681, 1459, 1378, 1255, 1084, 1030, 835, 774, 735 cm^{-1}; MS (ESI): *m*/*z* 427 (100) $[M + Na]^+$; HRMS (ESI): $[M + Na]^+$ $C_{24}H_{40}NaO_3Si$: calcd. 427.2639; found, 427.2658; $[\alpha]_D^{30}$: +16.5 (*c* 1.0, $CHCl_3$).

(2*R*,3*R*,6*S*,7*R*,8*S*,9*S*,*Z*)-1-((*S*)-4-Benzyl-2-thioxothiazolidin-3-yl)-9-(benzyloxy)-(7-*tert*-butyldimethylsilyloxy-3-hydroxy-2,4,6,8-tetramethyldec-4-en-1-one (19e). In a 50 mL round-bottom flask was dissolved *N*-propanoyl thiazolidinethione [(*S*)-1-(4-benzyl-2-thioxothiazolidin-3-yl)-propan-1-one] **18e** (1.63g, 6.1 mmol) in 30 mL of anhydrous dichloromethane (CH_2Cl_2). $TiCl_4$ (1.17 g, 3.0 mL, 6.1 mmol, 2.0 M in CH_2Cl_2) was added to the above bright yellow solution which had been previously cooled down to 0 °C and the suspension was stirred at the same temperature for 15 min. To this resulting homogeneous orange solution was added (−)-sparteine (1.44 g, 6.1 mmol) at 0 °C. The brick-red solution was stirred at the same temperature for 30 min. This titanium enolate solution was re-cooled to −78 °C and aldehyde **7** (2.5 g, 6.1 mmol) in CH_2Cl_2 (15 mL) was added dropwise with rapid stirring. After stirring for 2 h, the reaction mixture was quenched by pouring into 15 mL of saturated aq. NH_4Cl solution. The organic layer was separated and aqueous portion was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were washed with brine solution (30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The diastereomeric ratio (97 : 3) was determined by HPLC (using a Waters HR C18 column and acetonitrile–water as eluent). The mixture of the two diastereomers were slowly separated by column chromatography (10% EtOAc/hexanes) and the major isomer **19e** (3.4 g, 84%) was afforded in pure form as a yellow gummy liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43–7.15 (m, 10H), 5.36–5.23 (m, 1H), 4.97–4.82 (m, 1H), 4.60–4.36 (m, 3H), 3.77–3.64 (m, 1H), 3.45–3.39 (m, 1H), 3.28 (dd, *J* = 7.3, 11.3 Hz, 1H), 3.13–2.88 (m, 3H), 2.78 (d, *J* = 11.3 Hz, 1H), 2.06–1.88 (m, 1H), 1.62 (s, 3H), 1.14 (d, *J* = 6.0 Hz, 3H), 1.05–0.81 (m, 18H), 0.10 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.7, 176.3, 138.5, 136.5, 133.7, 133.4, 129,3, 128.8, 128.3, 128.2, 127.5, 127.1, 80.7, 71.0, 70.0, 68.5, 42.2, 42.1, 36.89, 36.80, 30.9, 29.6, 26.3, 19.2, 18.5, 17.9, 17.4, 15.0, 14.4, −3.3, −3.8; IR (KBr): *v* 3449, 3307, 2929, 2855, 1694, 1626, 1580, 1451, 1375, 1354, 1258, 1171, 1133, 836, 772, 700 cm^{-1}; MS (ESI): *m*/*z* 692 (100) $[M + Na]^+$; HRMS (ESI): $[M + Na]^+$ $C_{37}H_{55}NNaO_4S_2Si$: calcd. 692.3234; found, 692.3261; $[\alpha]_D^{30}$: −2.5 (*c* 0.5, $CHCl_3$).

(2*R*,3*R*,6*S*,7*R*,8*S*,9*S*,*Z*)-1-((*S*)-4-Benzyl-2-thioxothiazolidin-3-yl)-9-(benzyloxy)-(7-*tert*-butyldimethylsilyloxy-3-(methoxymethoxy)-2,4,6,8-tetramethyldec-4-en-1-one (20). To a stirred solution of *syn*-aldol compound **19e** (3.0 g, 4.47 mmol) in CH_2Cl_2 (40 mL), was added di-isopropylethylamine (DIPEA) (1.73 g, 2.4 mL, 13.4 mmol) at 0 °C. After stirring for 15 min, it was treated with methoxymethyl chloride (MOMCl) (0.7 g, 8.9 mmol) at the same temperature. The reaction suspension was stirred at room temperature under N_2 atmosphere for 12 h. After complete consumption of the starting material (reaction progress was monitored by TLC), it was quenched with saturated aq. $NaHCO_3$ solution (20 mL). The organic layer was layer separated and aqueous layer was extracted with dichloromethane (2 × 40 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by column chromatography (7% EtOAc/petroleum ether) to afford the MOM ether **20** (2.97 g, 93%) as a yellowish gummy liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37–7.16 (m, 10H), 5.50–5.25 (m, 3H), 4.75 (d, *J* = 9.8 Hz, 1H), 4.58 (d, *J* = 6.7 Hz, 1H), 4.51–4.47 (m, 2H), 4.42 (d, *J* = 6.2 Hz, 1H), 3.82–3.77 (m, 1H), 3.48–3.43 (m, 1H), 3.36 (s, 3H), 3.34–3.25 (m, 1H), 3.03–2.95 (m, 3H), 2.79 (d, *J* = 11.3 Hz, 1H), 2.11–1.98 (m, 1H), 1.63 (s, 3H), 1.34 (d, *J* = 6.7 Hz, 3H), 1.05 (d, *J* = 6.0 Hz, 3H), 0.96 (d, *J* = 6.7 Hz, 3H), 0.92 (d, *J* = 6.0 Hz, 3H), 0.84 (s, 9H), −0.03 (s, 3H), −0.13 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.0, 175.0, 139.5, 139.4, 136.4, 129.3, 128.9, 128.8, 128.2, 127.3, 127.2, 127.1, 92.4, 74.3, 73.4, 69.9, 68.5, 55.2, 41.4, 40.4, 37.1, 33.3, 30.6, 29.6, 26.2, 18.5, 18.2, 15.7, 13.9, 12.1, 9.5, −3.2, −3.7; IR (KBr): *v* 2928, 2855, 1694, 1455, 1346, 1254, 1135, 1097, 1062, 1030, 834, 771, 741, 701 cm^{-1}; MS (ESI): *m*/*z* 736 (100) $[M + Na]^+$; HRMS (ESI): $[M + Na]^+$ $C_{39}H_{59}NO_5S_2SiNa$: calcd. 736.3496; found, 736.3435; $[\alpha]_D^{30}$: −14.5 (*c* 0.5, $CHCl_3$).

(2*R*,3*R*,6*S*,7*R*,8*S*,9*S*,*Z*)-9-(Benzyloxy)-7-(*tert*-butyldimethylsilyloxy)-3-(methoxymethoxy)-2,4,6,8-tetramethyldec-4-en-1-ol (21). To a stirred solution of MOM protected aldol adduct **20** (2.8 g, 3.92 mmol) in a 30 mL mixture of Et_2O : MeOH (1 : 1 ratio), was added lithium borohydride (172 mg, 7.84 mmol) in portions at 0 °C. The reaction mixture was allowed to stir for 2 h at room temperature. After completion of the reaction (monitored by TLC), it was acidified with saturated aq. $NaHSO_4$ solution (pH ~ 5). The reaction mixture was extracted with CH_2Cl_2 (60 mL), the combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude residue was chromatographed over silica gel (12% EtOAc/petroleum ether) to give the alcohol **21** (1.8 g, 90%) as a colourless gummy liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–7.18 (m, 5H), 5.45 (d, *J* = 9.8 Hz, 1H), 4.55–4.39 (m, 4H), 4.31 (d, *J* = 8.3 Hz, 1H), 3.77–3.67 (m, 1H), 3.53–3.44 (m, 2H), 3.40–3.31 (m, 4H), 2.78–2.66 (m, 1H), 2.00–1.82 (m, 1H), 1.62 (s, 3H), 1.05 (d, *J* = 5.3 Hz, 3H), 1.03 (d, *J* = 6.0 Hz, 3H), 0.92–0.88 (m, 12H), 0.86 (d, *J* = 6.7 Hz, 3H), 0.02 (s, 3H), −0.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.51, 137.50, 131.0, 128.2, 127.3, 127.2, 93.0, 77.4, 75.0, 74.7, 69.9, 65.5, 55.3, 41.3, 38.6, 33.4, 26.2, 18.5, 14.5, 13.7, 10.11, 10.10, −3.5, −3.7; IR (KBr): *v* 3449, 3307, 2930, 2856, 1625, 1581, 1450, 1375, 1259, 1170, 1134, 1030, 836, 770, 698 cm^{-1}; MS (ESI): *m*/*z* 531 (100) $[M + Na]^+$; HRMS (ESI): $[M + Na]^+$ $C_{29}H_{52}O_5SiNa$: calcd. 531.3476; found, 531.3412; $[\alpha]_D^{30}$: +45.0 (*c* 1.0, $CHCl_3$).

(5*R*,8*S*,9*R*,*Z*)-9-((2*S*,3*S*)-3-(Benzyloxy)butan-2-yl)-5-((*S*)-but-3-en-2-yl)-6,8,11,11,12,12-hexamethyl-2,4,10-trioxa-11-silatridec-6-ene (22). (a) To a stirred solution of IBX (1.41 g, 5.01 mmol) in DMSO (2.5 mL) under N_2 atmosphere was added alcohol **21** (1.7 g, 3.3 mmol) in anhydrous THF (10 mL) at room temperature. The reaction mixture was stirred for 45 min at the same temperature and diluted with Et_2O (20 mL). The solids were filtered through a Celite® pad, the filtrate was washed with saturated aq. $NaHCO_3$ solution (2 × 20 mL) and dried over anhydrous Na_2SO_4. The solvent was reduced *in*

vacuo to obtain the aldehyde (1.62 g, 96%), which was directly used for the next reaction without purification.

(b) To a 50 mL, two necked round-bottom flask, PPh_3MeI (3.56 g, 8.89 mmol) and KO^{t}Bu (0.83 g, 7.41 mmol) followed by 20 mL of anhydrous THF were charged and cooled to 0 °C under nitrogen atmosphere. After stirring for 1 h at the same temperature, the above aldehyde (1.5 g, 2.96 mmol) in 10 mL of dry THF was added dropwise. The reaction mixture was left at 0 °C for 15 min. Then, it was quenched by adding saturated aq. NH_4Cl solution (10 mL) and diluted with EtOAc (30 mL). The organic layer was separated and the aqueous portion was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine solution (30 mL), dried over Na_2SO_4 and concentrated on a rotary evaporator. The crude residue was chromatographed over silica gel (3% EtOAc/petroleum ether) to give the olefin **22** (1.31 g, 92%) as a colourless liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43–7.26 (m, 5H), 5.72–5.58 (m, 1H), 5.49 (d, J = 10.9 Hz, 1H), 5.12–4.97 (m, 2H), 4.63 (d, J = 6.6 Hz, 1H), 4.56 (q, J = 12.2, 17.7 Hz, 2H), 4.48 (d, J = 6.6 Hz, 1H), 4.15 (d, J = 9.6 Hz, 1H), 3.86–3.78 (m, 1H), 3.55 (dd, J = 2.7, 8.3 Hz, 1H), 3.42 (s, 3H), 2.79–2.66 (m, 1H), 2.54–2.40 (m, 1H), 2.12–1.97 (m, 1H), 1.66 (s, 3H), 1.22 (d, J = 6.6 Hz, 3H), 1.13 (d, J = 6.4 Hz, 3H), 1.02–0.88 (m, 15H), 0.10 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.0, 137.2, 128.9, 128.2, 128.1, 127.3, 127.1, 114.0, 92.7, 82.3, 74.5, 72.2, 69.9, 55.1, 41.1, 40.3, 33.2, 26.2, 17.8, 16.8, 14.3, 13.2, 10.3, 9.9, −3.4, −3.7; IR (KBr): ν 3429, 2931, 1640, 1458, 1376, 1253, 1095, 1033, 835, 771, 735 cm^{-1}; MS (ESI): m/z 527 (100) $[M + Na]^+$; HRMS (ESI): $[M + Na]^+$ $C_{30}H_{52}NaO_4Si$: calcd. 527.3527; found, 527.3484; $[\alpha]_D^{30}$: +49.1 (c 1.0, $CHCl_3$).

(2*S*,3*S*,4*R*,5*S*,8*R*,9*S*,*Z*)-4-(*tert*-Butyldimethylsilyloxy)-8-(methoxymethoxy)-3,5,7,9-tetramethylundeca-6, 10-dien-2-ol (6a). Lithium metal (166 mg, 23.8 mmol) was added in portions to a solution of naphthalene (3.65 g, 28.5 mmol) suspended in anhydrous THF (20 mL) under N_2 atmosphere. The mixture was stirred at room temperature for 2 h and the resulting dark green mixture was cooled to −20 °C. Then, benzylated compound **22** (1.2 g, 2.38 mmol) in dry THF (10 mL) was added dropwise to the above generated naphthalide solution at −20 °C. The reaction mixture was stirred at the same temperature for 15 min. Then, it was quenched with saturated aq. NH_4Cl solution (10 mL) and diluted with Et_2O (40 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (2 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and removed under reduced pressure. The crude was purified by column chromatography (6% EtOAc/petroleum ether) to afford the key alcohol **6a** (0.926 g, 94%) as a colourless gummy liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.65–5.50 (m, 1H), 5.43 (d, J = 9.8 Hz, 1H), 5.06–4.91 (m, 2H), 4.61 (d, J = 6.8 Hz, 1H), 4.44 (d, J = 6.8 Hz, 1H), 4.09 (d, J = 9.8 Hz, 1H), 3.71–3.49 (m, 2H), 3.38 (s, 3H), 2.71–2.57 (m, 1H), 2.50–2.36 (m, 1H), 1.59 (s, 3H), 1.17 (d, J = 6.0 Hz, 3H), 1.13 (d, J = 6.0 Hz, 3H), 0.94 (s, 9H), 0.90 (d, J = 6.8 Hz, 3H), 0.85 (d, J = 7.5 Hz, 3H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.0, 137.0, 129.6, 114.2, 92.5, 79.0, 76.5, 69.0, 55.3, 45.6, 40.2, 34.8, 29.6, 26.1, 20.9, 17.8, 16.8, 15.3, 14.1, −3.7, −4.2; IR (KBr): ν 3681, 2959, 2931, 1464, 1378, 1253, 1095, 1034, 950, 914, 834, 773 cm^{-1}; MS (ESI): m/z 437 (100) $[M + Na]^+$; HRMS (ESI): $[M + Na]^+$ $C_{23}H_{46}NaO_4Si$: calcd.437.3058; found, 437.3038; $[\alpha]_D^{30}$: +51.5 (c 1.0, $CHCl_3$).

(*S*)-(2*S*,3*S*,4*R*,5*S*,8*R*,9*S*,*Z*)-4-(*tert*-Butyldimethylsilyloxy)-8-(methoxymethoxy)-3,5,7,9-tetramethylundeca-6,10-dien-2-yl)-2-(*tert*-butoxycarbonyl(methyl)amino)-3-phenylpropanoate (23). To a suspension of Boc-*N*-Me-L-phenylalanine **5** (1.0 g, 3.86 mmol) and DCC (0.73 g, 3.86 mmol) in anhydrous dichloromethane (7 mL) was added DMAP (43 mg, 0.386 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min and alcohol **6a** (0.8 g, 1.93 mmol) in CH_2Cl_2 (3.0 mL) was added slowly to the above reaction mixture. The reaction was maintained for 1 h at 0 °C and another 2 h at room temperature. Upon completion of the reaction (monitored by TLC), H_2O (5 mL) was added and stirred for 10 min. The reaction mixture was diluted with a 20 mL mixture of CH_2Cl_2/hexanes (1 : 2 ratio) and cooled to 0 °C. The resulting white precipitate was filtered off and washed with CH_2Cl_2/hexanes (1 : 2 ratio, 20 mL). The filtrate was washed with saturated aq. $NaHCO_3$ solution (20 mL), washed with brine solution (20 mL), dried over Na_2SO_4 and concentrated on a rotary evaporator. The crude product was chromatographed over silica gel (6% EtOAc/petroleum ether) to afford the desired ester **23** (1.14 g, 88%) as a colourless gummy liquid. The NMR spectra of this compound showed a mixture of rotamers (60 : 40 ratio).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33–7.13 (m, 5H), 5.68–5.53 (m, 1H), 5.39 (d, J = 10.5 Hz, 1H), 5.29–5.13 (m, 1H), 5.07–4.91 (m, 2H), 4.59 (d, J = 6.8 Hz, 1H), 4.45 (d, J = 6.8 Hz, 1H), 4.08 (d, J = 9.8 Hz, 1H), 3.48–3.39 (m, 1H), 3.34 (s, 3H), 3.28 (dd, J = 6.0, 15.8 Hz, 1H), 3.09–2.93 (m, 2H), 2.78–2.68 (m, (**NMe**) 3H), 2.66–2.52 (m, 1H), 2.48–2.35 (m, 1H), 1.92–1.78 (m, 1H), 1.60 (s, 3H), 1.40–1.30 (m, (**Boc protons**) 9H), 1.19–1.07 (m, 6H), 0.93 (s, 9H), 0.88–0.81 (m, 6H), 0.09 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): ''M'' for major rotamer and ''m'' for minor rotamer, δ 170.4 (m), 170.1 (M), 155.6 (m), 155.1 (M), 140.0, 137.8 (M), 137.7 (m), 136.0, 130.7, 128.9, 128.4 (M), 128.3 (m), 126.5 (M), 126.3 (m), 114.1, 92.7, 80.1, 79.6, 77.1, 72.5, 61.4 (M), 59.9 (m), 55.1, 42.1 (M), 41.9 (m), 40.3, 35.2 (M), 35.0 (m), 33.1, 32.1 (m), 31.9 (M), 29.6, 28.2, 26.2, 18.5 (m), 17.8 (M), 16.8, 14.6 (m), 14.4 (M), 14.09 (M), 14.00 (m), 10.0, −3.5, −3.8; IR (KBr): ν 2958, 2928, 1732, 1701, 1457, 1388, 1368, 1263, 1141, 1035, 837, 772, 745 cm^{-1}; MS (ESI): m/z 698 (100) $[M + Na]^+$; HRMS (ESI): $[M + Na]^+$ $C_{38}H_{65}NNaO_7Si$: calcd. 698.4423; found, 698.4392; $[\alpha]_D^{30}$: +10.5 (c 1.0, $CHCl_3$).

(*S*)-(2*S*,3*R*,4*R*,5*S*,8*R*,9*S*,*Z*)-4-Hydroxy-8-(methoxymethoxy)-3,5,7,9-tetramethyl-undeca-6,10-dien-2-yl)-2-(*tert*-butoxycarbonyl(methyl)amino)-3-phenylpropanoate (24). Tetra-*n*-butylammonium fluoride (TBAF) (0.77 g, 3.0 mL, 1 M in THF, 2.96 mmol) was slowly added to the silylated ester **23** (1.0 g, 1.48 mmol) dissolved in anhydrous THF (10 mL) at −5 °C. The reaction mixture was allowed to stir for 48 h at the same temperature (−5 °C). Upon completion of the reaction (monitored by TLC), it was quenched with saturated aq. NH_4Cl solution (5 mL). The reaction mixture was charged with EtOAc (10 mL), the organic layer was separated and aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude compound was subjected to silica gel column chromatography (12%

EtOAc/hexanes) to afford the alcoholic ester **24** (0.756 g, 91%) as a colourless liquid. The NMR spectra of this compound showed a mixture of rotamers (55 : 45 ratio).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36–7.10 (m, 5H), 5.70–5.46 (m, 2H), 5.42–5.26 (m, 1H), 5.10–4.90 (m, 2H), 4.59 (d, J = 6.8 Hz, 1H), 4.45 (d, J = 6.8 Hz, 1H), 4.25–3.90 (m, 2H), 3.42–3.20 (m, 5H), 3.12–2.91 (m, 1H), 2.75 and 2.70 (s,s, equal to 3H of rotamers), 2.53–2.35 (m, 1H), 1.99–1.76 (m, 2H), 1.63 (s, 3H), 1.38 and 1.35 (s,s, equal to 9H of rotamers, **Boc protons**), 1.21–1.10 (m, 6H), 0.93–0.78 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): ''M'' for major rotamer and ''m'' for minor rotamer, δ 170.6 (m), 170.3 (M), 155.7 (m), 155.1 (M), 139.7, 137.6, 134.5 (m), 134.3 (M), 132.0 (M), 131.8 (m), 128.9, 128.4 (M), 128.3 (m), 126.5 (M), 126.4 (m), 114.2, 92.8, 80.1 (M), 79.8 (m), 77.1, 72.9, 68.1 (m), 67.6 (M), 61.3, 60.0, 55.1, 39.9, 35.2 (M), 34.9 (m), 33.4, 32.1 (m), 31.8 (M), 28.2, 17.9, 16.8, 13.9 (m), 13.7 (M), 12.9, 10.4 (m), 10.0 (M); IR (KBr): ν 3455, 2951, 2931, 1710, 1698, 1453, 1390, 1325, 1227, 1148, 1032, 949, 751, 698 cm^{-1}; MS (ESI): m/z 584 (100) $[M + Na]^+$; HRMS (ESI): $[M + Na]^+$ $C_{32}H_{51}NNaO_7$: calcd. 584.3558; found, 584.3584; $[\alpha]_D^{32}$: +56.0 (c 0.25, $CHCl_3$).

(*S*)-(2*S*,3*S*,4*R*,5*S*,8*R*,9*S*,*Z*)-4-Acetoxy-8-(methoxymethoxy)-3,5,7,9-tetramethylundeca-6,10-dien-2-yl)-2-(*tert*-butoxycarbonyl(methyl)amino)-3-phenylpropanoate (25). Diisopropyl-ethylamine (DIPEA) (230 mg, 0.3 mL, 1.78 mmol) and DMAP (5.4 mg, 0.04 mmol) were added to alcoholic ester **24** (0.5g, 0.89 mmol) dissolved in anhydrous dichloromethane (8 mL) at 0 °C. The reaction mixture was stirred for 10 min and Ac_2O (136 mg, 1.33 mmol) was added dropwise at 0 °C. The reaction mixture was left at room temperature for 1 h. Upon completion of the reaction (monitored by TLC), H_2O (4 mL) was added. The organic layer was separated and aqueous layer extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (9% EtOAc/petroleum ether) to afford acetylated product **25** (526 mg, 98%) as a colourless liquid. The NMR spectra of this compound showed a mixture of rotamers (55 : 45 ratio).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36–7.11 (m, 5H), 5.66–5.49 (m, 1H), 5.17 (d, J = 9.8 Hz, 1H), 5.10–4.87 (m, 3H), 4.86–4.55 (m, 3H), 4.42 (d, J = 6.8 Hz, 1H), 4.05 (d, J = 9.8 Hz, 1H), 3.35 (s, 3H), 3.32–3.21 (m, 1H), 3.08–2.92 (m, 1H), 2.83–2.66 (m, 4H), 2.50–2.35 (m, 1H), 2.10 (s, 3H), 2.07–1.95 (m, 1H), 1.57 (s, 3H), 1.38 and 1.34 (s,s, equal to 9H of rotamers, **Boc protons**), 1.20–1.07 (m, 6H), 0.96–0.81 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): ''M'' for major rotamer and ''m'' for minor rotamer, δ 170.6 (M), 170.2 (m), 155.7 (m), 155.0 (M), 139.8, 137.6 (M), 137.5 (m), 133.5, 132.2 (M), 132.1 (m), 128.9, 128.4, 128.3, 126.5 (M), 126.4 (m), 114.2, 92.5, 80.1 (M), 79.7 (m), 77.0, 75.9, 71.8 (M), 71.6 (m), 61.3, 59.9, 55.1, 39.8, 38.4 (M), 38.2 (m), 35.2 (M), 35.0 (m), 32.0 (m), 31.8 (M), 28.2, 20.9, 17.9, 16.8, 13.79 (m), 13.70 (M), 13.4, 9.9; IR (KBr): ν 2973, 2931, 1739, 1700, 1452, 1389, 1370, 1237, 1148, 1098, 1031, 964, 700 cm^{-1}; MS (ESI): m/z 626 (100) $[M + Na]^+$; HRMS (ESI): $[M + Na]^+$ $C_{34}H_{53}NNaO_8$: calcd. 626.3663; found, 626.3687; $[\alpha]_D^{30}$: +51.3 (c 0.25, $CHCl_3$).

(*S*)-(2*S*,3*S*,4*R*,5*S*,8*R*,9*S*,*Z*)-4-Acetoxy-8-(methoxymethoxy)-3,5,7,9-tetramethylundeca-6,10-dien-2-yl)-2-(*N*-methylacrylamido)-3-phenyl propanoate (4a). The stirred solution of Boc-protected ester **25** (0.5g, 0.82 mmol) in anhydrous CH_2Cl_2 (8 mL) at 0 °C under N_2 atmosphere, was treated with CF_3COOH (2 mL). The reaction temperature was raised to 25–30 °C and maintained for 1 h. The solvent and TFA were removed under reduced pressure. The resultant salt was dissolved in anhydrous dichloromethane (6 mL) and treated with triethylamine (167 mg, 0.24 mL, 1.65 mmol) at −10 °C. After stirring for 5 min, acryloyl chloride (110 mg, 0.11 mL, 1.24 mmol) was added dropwise at −10 °C. The reaction was maintained at the same temperature for 15 min. After completion of the reaction, it was diluted with H_2O (4 mL). The compound was extracted in dichloromethane (2 × 10 mL), the separated organic layer was dried over anhydrous Na_2SO_4 and concentrated on a rotary evaporator. The crude compound was purified by column chromatography (30% EtOAc/petroleum ether) to afford the *N*-acroylated product **4a** (415 mg, 90%) as a colourless liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33–7.09 (m, 5H), 6.53–6.37 (m, 1H), 6.30–6.06 (m, 1H), 5.71–5.40 (m, 2H), 5.36–5.22 (m, 1H), 5.16 (d, J = 9.8 Hz, 1H), 5.09–4.86 (m, 3H), 4.75 (dd, J = 2.6, 9.8 Hz, 1H), 4.68 (d, J = 6.8 Hz, 1H), 4.42 (d, J = 6.8 Hz, 1H), 4.05 (d, J = 9.8 Hz, 1H), 3.43–3.27 (m, 4H), 3.12–2.98 (m, 1H), 2.92 (s, 3H), 2.80–2.66 (m, 1H), 2.50–2.34 (m, 1H), 2.12–1.94 (m, 4H), 1.57(s, 3H), 1.19–1.06 (m, 6H), 0.95–0.76 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6, 169.9, 166.9, 139.8, 137.1, 133.5, 132.2, 128.7, 128.4, 127.5, 126.9, 126.6, 114.2, 92.6, 76.9, 76.0, 71.9, 58.7, 55.1, 39.9, 38.2, 34.7, 31.8, 29.6, 20.9, 17.9, 16.8, 13.8, 13.5, 10.1; IR (KBr): ν 2929, 1736, 1654, 1616, 1452, 1414, 1375, 1237, 1132, 1098, 1032, 957, 914, 700 cm^{-1}; MS (ESI): m/z 580 (100) $[M + Na]^+$; HRMS (ESI): $[M + Na]^+$ $C_{32}H_{47}NNaO_7$: calcd. 580.3245; found, 580.3236; $[\alpha]_D^{30}$: +12.1 (c 0.25, $CHCl_3$).

(3*S*,6*E*,8*S*,9*R*,10*Z*,12*S*,13*R*,14*S*,15*S*)-3-Benzyl-9-(methoxymethoxy)-4,8,10,12,14,15-hexa-methyl-2,5-dioxo-1-oxa-4-azacyclopentadeca-6,10-dien-13-yl acetate (26). Hoveyda–Grubbs second generation catalyst HG II (20 mg, 5 mol%) was added to a stirred solution of amide **4a** (0.35 g, 0.628 mmol) in anhydrous toluene (650 mL) in which air had been previously replaced by passing N_2 gas. The reaction mixture was heated to 100 °C and maintained for 8 h at the same temperature until TLC analysis indicated complete consumption of the starting material. The solvent was removed on a rotary evaporator and the resulting dark green residue was subjected to silica gel column chromatography (25% EtOAc/petroleum ether) to afford the exclusive ring closed *trans*-macrolactam **26** (315 mg, 95%) as a colourless semi-solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24–7.07 (m, 5H), 5.92–5.74 (m, 3H), 4.98 (d, J = 11.0 Hz, 1H), 4.82–4.70 (m, 1H), 4.48–4.33 (m, 3H), 4.20–4.08 (m, 1H), 3.46 (dd, J = 5.1, 14.4 Hz, 1H), 3.33–3.21 (m, 4H), 2.97–2.83 (m, 2H), 2.79 (s, 3H), 1.93–1.82 (m, 4H), 1.65 (s, 3H), 1.16 (d, J = 6.0 Hz, 3H), 0.98 (d, J = 6.0 Hz, 3H), 0.86 (d, J = 7.6 Hz, 3H), 0.77 (d, J = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2, 170.1, 168.0, 145.6, 137.0, 131.2, 130.8, 128.7, 128.3, 126.5, 121.9, 94.9, 80.4, 80.1, 73.6, 68.0, 55.7, 55.4, 39.2, 36.2, 34.4, 31.2, 29.6, 20.6, 18.8, 18.1, 16.9, 13.0; IR (KBr): ν 2923, 2851, 1734, 1640, 1453, 1371, 1236, 1102, 1029, 771 cm^{-1}; MS (ESI): m/z 552 (100) $[M + Na]^+$; HRMS (ESI): $[M + Na]^+$ $C_{30}H_{43}NNaO_7$: calcd. 552.2932; found, 552.2917; $[\alpha]_D^{32}$: −21.5 (c 1.0, $CHCl_3$).

(3*S*,6*E*,8*S*,9*R*,10*Z*,12*S*,13*R*,14*S*,15*S*)-3-Benzyl-9-hydroxy-4,8,10,12,14,15-hexamethyl-2,5-dioxo-1-oxa-4-azacyclopentadeca-6,10-dien-13-yl acetate (3a). A solution of MOM-protected compound **26** (0.25 g, 0.472 mmol) in a 5 mL mixture of CH_3CN : H_2O (5 : 1 ratio) was treated with $LiBF_4$ (0.44 g, 4.72 mmol). The reaction mixture was heated to reflux and maintained for 12 h. Upon completion of the reaction (monitored by TLC), the mixture was cooled to room temperature, then it was poured into 3 mL of water and the organic solvent (CH_3CN) was removed under reduced pressure. Aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with water (15 mL), brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was chromatographed over silica gel (25% EtOAc in PE) to afford the 5-*epi*-torrubiellution C (**3a**) (213 mg, 93% yield, 99.8% purity in HPLC) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25–7.07 (m, 5H), 5.87 (dd, J = 5.4, 10.3 Hz, 1H), 5.81–5.76 (m, 2H), 4.88 (d, J = 10.9 Hz, 1H), 4.82–4.71 (m, 1H), 4.47–4.35 (m, 2H), 3.47 (dd, J = 5.2, 14.9 Hz, 1H), 3.30–3.17 (m, 1H), 2.94–2.80 (m, 2H), 2.77 (s, 3H), 2.02–1.93 (m, 1H), 1.92–1.79 (m, 4H), 1.72 (s, 3H), 1.14 (d, J = 6.0 Hz, 3H), 0.95 (d, J = 6.8 Hz, 3H), 0.87 (d, J = 6.9 Hz, 3H), 0.77 (d, J = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2, 170.1, 168.0, 144.4, 137.6, 136.8, 128.8, 128.6, 128.3, 126.5, 123.1, 80.3, 76.5, 73.5, 55.4, 39.4, 38.1, 36.3, 34.4, 31.6, 29.6, 20.6, 19.5, 18.1, 16.8, 11.9; IR (KBr): ν 3448, 2923, 1734, 1626, 1581, 1452, 1376, 1259, 1172, 1133, 1020, 991, 771, 700 cm^{-1}; MS (ESI): m/z 508 (100) $[M + Na]^+$; HRMS (ESI): $[M + H]^+$ $C_{28}H_{40}NO_6$: calcd. 486.2826; found, 486.2846; Mp: 82–83 °C. $[\alpha]_D^{30}$: −36.1 (*c* 1.0, $CHCl_3$).

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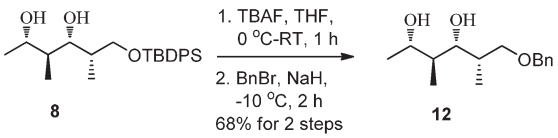
7



8 12

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