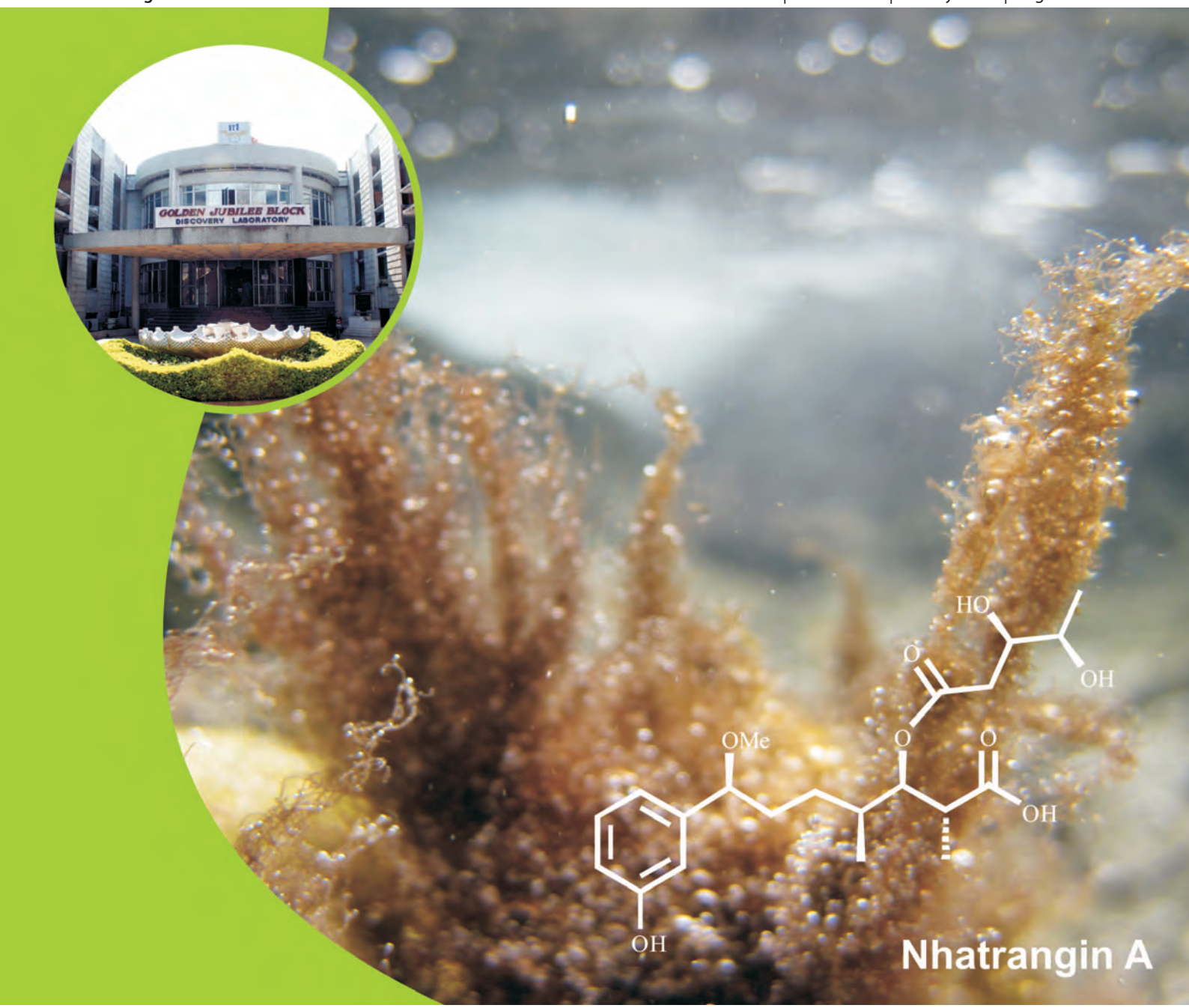
Organic & Biomolecular Chemistry

www.rsc.org/obc

Volume 11 | Number 27 | 21 July 2013 | Pages 4421–4560



ISSN 1477-0520

RSC Publishing

PAPER

Ahmed Kamal and Saidi Reddy Vangala

The first total synthesis of nhatrangin A

1477-0520(2013)11:27;1-6

Organic & Biomolecular Chemistry

RSC Publishing

PAPER

View Article Online
View Journal | View Issue

The first total synthesis of nhatrangin A†

Cite this: *Org. Biomol. Chem.*, 2013, **11**, 4442

Received 4th February 2013,
Accepted 26th March 2013

DOI: 10.1039/c3ob40252e

www.rsc.org/obc

Ahmed Kamal* and Saidi Reddy Vangala

The first total synthesis of nhatrangin A has been achieved. Pivotal bond forming events in the synthesis include Brown crotylboration, olefin cross-metathesis, Sharpless asymmetric dihydroxylation and Yamaguchi esterification.

Introduction

Structurally infringing natural products, with a variety of biological activities, has been a useful starting point for drug discovery over the years.[1] Among the various sources of natural products, marine cyanobacteria, especially *Lyngbya majuscula*, have proven to be a versatile starting point from which a number of secondary metabolites in excellent biological activities have been isolated.[2] A series of toxins, *viz.*, the aplysiatoxins, isolated from *L. majuscula*, are especially noteworthy. Many of the aplysiatoxins exhibit tumour-promoting activity through the activation of protein kinase C and anti-proliferative activity against the alymphocytic urine leukaemia (P-388) cell line.[3,4] The two polyketide metabolites, nhatrangin A (**1**) and nhatrangin B (Fig. 1), were isolated from a Vietnamese collection of *L. majuscula* in 2009.[5] The structures and relative configuration of these two new compounds were elucidated by extensive NMR spectroscopic techniques.

As a part of our research program aimed at developing stereoselective total syntheses of biologically active natural products[6] for advanced biological screening, we undertook investigations aimed at developing a concise and asymmetric total synthesis of nhatrangin A (**1**). Herein, we report our successful endeavor which culminated in the first total synthesis of nhatrangin A (**1**). Pinane mediated crotylboration, Sharpless asymmetric dihydroxylation (SAD) and lipase-mediated resolution were employed as key transformations to install the various asymmetric centers that are present in **1**.

The retrosynthetic analysis for nhatrangin A **1** is depicted in Scheme 1. We envisioned constructing the target natural product from compound **2**, which in turn could be accessed by a Yamaguchi esterification of fragments **3** and **4**. The β-hydroxy ester component **3** could be generated by a cross-metathesis reaction between the alkenes **5** and **6**, which can be assembled from 3-hydroxybenzaldehyde **7** and methyl (*S*)-3-hydroxy-2-methyl propionate **8**, respectively. The acid intermediate **4** could be constructed from propanediol **9**.

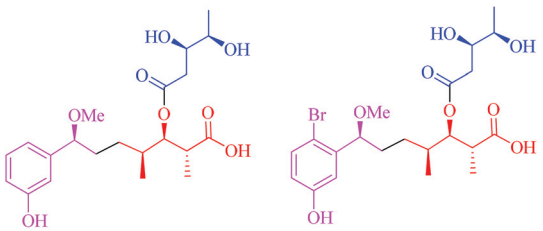


Fig. 1 Structures of nhatrangin A and nhatrangin B.

Results and discussion

Preparation of fragment 5

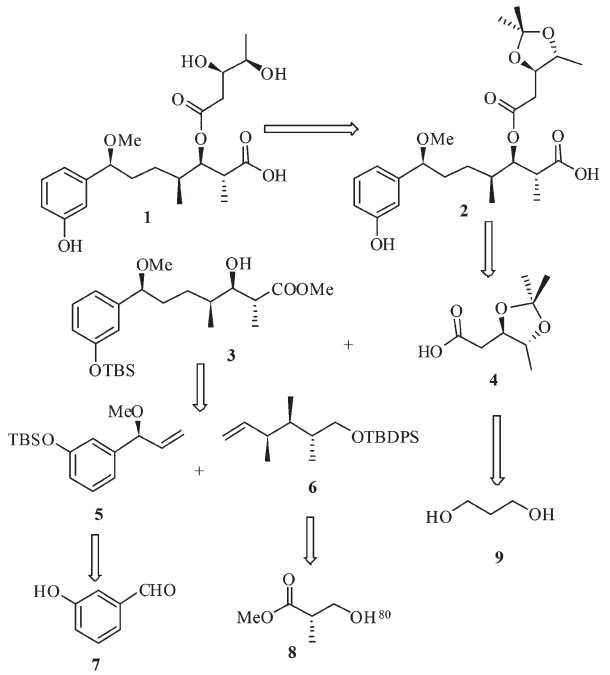
Our journey for the synthesis of nhatrangin A (**1**) began with the preparation of **5** as depicted in Scheme 2. Commercially available 3-hydroxybenzaldehyde (**7**) was treated with TBS-Cl in the presence of imidazole to afford the TBS ether **10**, followed by the addition of vinyl Grignard reagent to furnish the racemic allyl alcohol **11** in excellent yield. Lipase mediated resolution[7] of (±)-**11** produced the desired (*S*)-enantiomer **12** in 98.2% ee (41% yield and the absolute configuration was determined by using the refined Mosher method) along with the acetate of the (*R*)-enantiomer (**12a**, 53%, 91% ee). Methylation of **12** using MeI and NaH furnished the methyl ether **5** in 85% yield.

Preparation of fragment 3

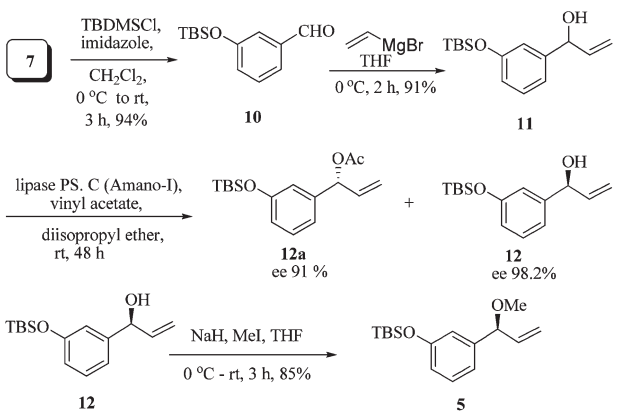
The other chiral alkene fragment **6** was prepared (Scheme 3) from commercially available methyl (*S*)-3-hydroxyl-2-methyl-propionate **8** (Roche ester). It was converted to the aldehyde **13** in three steps by following a known protocol[8] to initiate the

Medicinal Chemistry and Pharmacology, CSIR-Indian Institute of Chemical Technology, Hyderabad, 500007, India. E-mail: ahmedkamal@iict.res.in; Fax: +91-40-27193189; Tel: +91-40-27193157

†Electronic supplementary information (ESI) available. See DOI: 10.1039/c3ob40252e

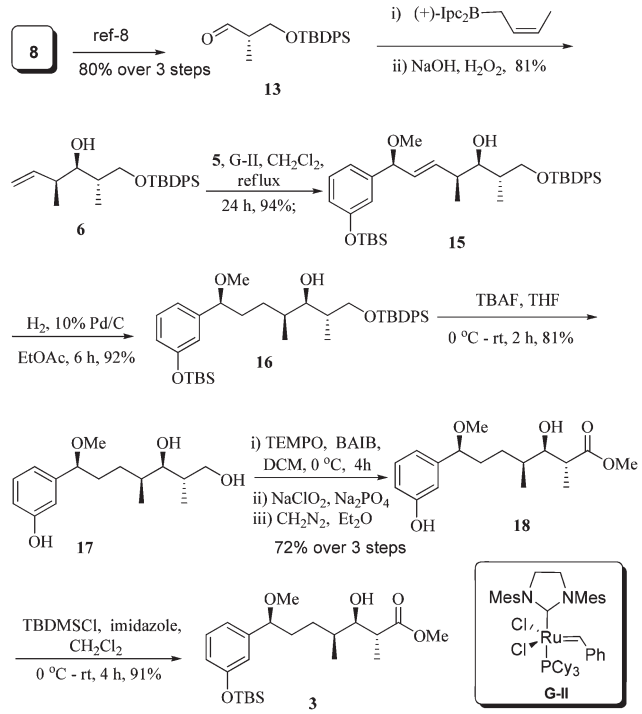


Scheme 1 Retrosynthetic approach for nhatrangin A (**1**).

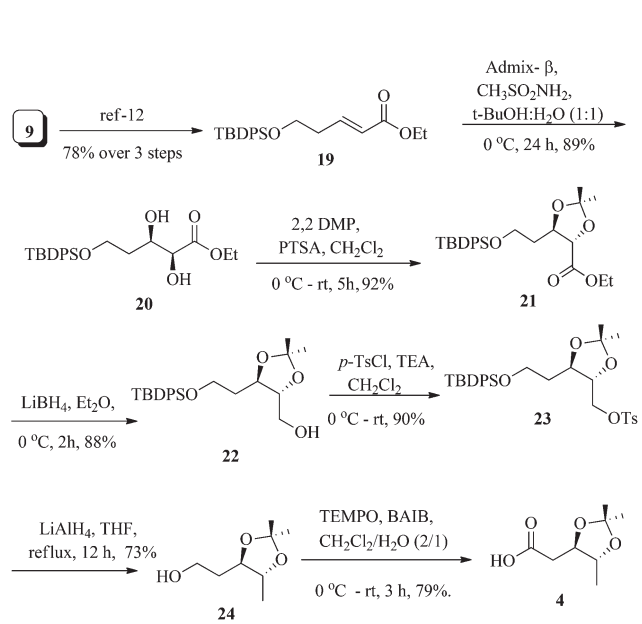


Scheme 2 Preparation of fragment **5**.

preparation of fragment **3**. Crotylboration with (+)-*B*-(*Z*)-crotyl diisopinocampheylborane[8] was carried out next to provide the homoallylic alcohol **6** as a single diastereomer. The coupling of two alkene fragments **5** and **6** was carried out by subjecting them to cross-metathesis[9] conditions using Grubbs 2nd generation catalyst afforded **15** in 94% yield. The product of the metathesis **15** was hydrogenated with Pd–C/H_2 to provide **16** in 92% yield. Double desilylation of the latter by treatment with TBAF, selective sequential oxidations of the primary alcohol in **17** by TEMPO/BAIB[10] and under Pinnick[11] conditions and subsequent esterification with diazomethane generated the β-hydroxy ester **18** in 72% yield over three steps. Treatment of **18** with TBS-Cl in the presence of imidazole reintroduced the silyl protecting group selectively onto the phenolic functionality and furnished the secondary alcohol **3**.



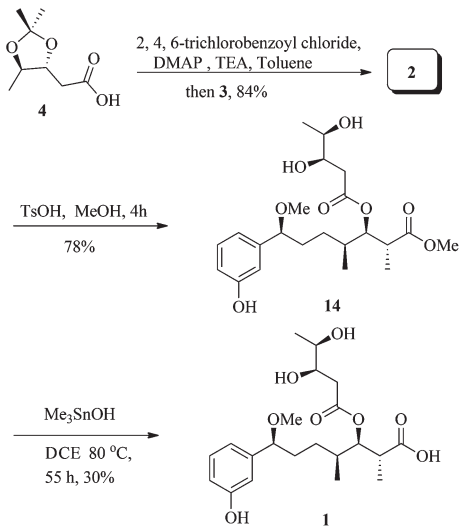
Scheme 3 Preparation of fragment **3**.



Scheme 4 Preparation of fragment **4**.

Preparation of fragment 4

After the preparation of **3**, we focused our attention on the synthesis of the chiral carboxylic acid fragment **4** from commercially available 1,3-propanediol **9** as illustrated in Scheme 4. α,β-Unsaturated ester **19** was synthesized from **9** as previously described (78% for 3 steps).[12] **19** then underwent Sharpless asymmetric dihydroxylation[12] (Admix-β) to afford the diol **20** in 89% yield and in 98% ee. It was protected as the acetonide by



Scheme 5 Complete synthesis of nhatrangin A (**1**).

using 2,2-dimethoxypropane in the presence of a catalytic amount of *p*-toluenesulphonic acid to give **21** in 92% yield. A simple $LiBH_4$ reduction furnished the primary alcohol **22** in 88% yield, which was then converted to the corresponding tosylate **23** by using *p*-toluenesulphonyl chloride in the presence of triethyl amine in 90% yield. This was then treated with $LiAlH_4$ under reflux to obtain **24** in 73% yield. The oxidation of the primary alcohol was carried out by using TEMPO[13] combined with BAIB in CH_2Cl_2–H_2O (2/1) to afford the desired carboxylic acid **4** in 79% yield (Scheme 5).

Completion of the synthesis of nhatrangin A

After synthesizing the fragments **3** and **4**, assembly of these two fragments was carried out by subjecting them to the Yamaguchi esterification conditions,[14] and the diester **2** was produced in 84% yield. The methyl ester of nhatrangin A (**14**) was obtained in 78% yield from **2** by treating it with PTSA in methanol. Finally, methyl ester (**14**) was converted to nhatrangin A (**1**) by following a protocol developed by Nicolaou[15] in which the ester was exposed to Me_3SnOH. Gratifyingly the natural product nhatrangin A (**1**) was obtained after work-up, albeit in 30% yield with $[\alpha]_D^{25}$ = +0.2 (*c* 0.05, MeOH).[16] The ^1H and ^{13}C NMR spectra of the synthetic material were in complete agreement with that reported for the natural product.

Conclusion

In conclusion, the first total synthesis of nhatrangin A (**1**) has been achieved and thus the structure assigned to the natural product has also been confirmed. The overall yield for the 14-step longest sequence, starting from methyl (2*S*)-3-hydroxy-2-methylpropionate (Roche ester), is 5.8%. The convergent approach employed herein is suitable for the synthesis of other isomers/congeners/analogues of this natural product. Efforts in this direction are being pursued presently in our laboratory and will be reported in due course.

Experimental section

General experimental

All ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ solvent on a Varian Bruker 300, a Varian Unity 400, and an Innova 500 MHz spectrometer at ambient temperature, chemical shifts δ were given in ppm on a scale downfield from TMS, and the coupling constants *J* are in Hz. The signal patterns are indicated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad peak. FTIR spectra were recorded as neat. Optical rotations were measured on a JASCO DIP-370 digital polarimeter using a 2 mL cell with a 1 dm path length, and the concentration *c* is given in g per 100 mL. Mass spectra were obtained on a Finnegan Mat1020B, a micromass VG 70-70H or an Agilent Technologies LC/MSD treapSL spectrometer operating at 70 eV using the direct inlet system and high-resolution mass spectra (HRMS) were recorded on a QSTAR XL Hybrid MS/MS mass spectrometer. HPLC was recorded on a SHIMADZU HPLC using Chiralcel OD-H, *n*-hexane and isopropanol as eluents. All the reagents and solvents were used without further purification unless specified otherwise. Technical grade ethyl acetate and petroleum ether used for column chromatography were distilled prior to use. Tetrahydrofuran (THF) and diethyl ether, when used as a solvent for reactions, were freshly distilled from sodium-benzophenone ketyl. Column chromatography was carried out using silica gel (60–120 mesh and 100–200 mesh) packed in glass columns. All reactions were performed under a nitrogen atmosphere and in flame-dried or oven-dried glassware with magnetic stirring.

Experimental procedures

(1*S*)-1-(3-[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxyphenyl)-2-propen-1-ol (12). To a 250 mL Erlenmeyer flask were added HPLC grade diisopropyl ether (100 mL), vinyl acetate (10 mL), lipase Amino-I (5 g), and the appropriate alcohol **11** (5 g, 18.93 mmol). The Erlenmeyer flask was sealed using a rubber stopper, and the reaction mixture was stirred in an orbital shaker at 32 °C with 180 rpm. The reaction progress was monitored by collecting samples and analyzing gas chromatography with the chiral stationary phase. After 48 h the reaction was complete, and the immobilized lipase was filtered off. The filtrate was evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, 10% EtOAc in hexane eluant), yielding the enantiomerically enriched *S*-alcohol **12** (2.4 g, 45%, ee 98%) as a colorless oil; $[\alpha]_D^{25}$ = +12.6 (*c* 0.3, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$): δ 0.19 (6H, s), 0.98 (9H, s), 5.13 (1H, d, *J* = 5.86 Hz), 5.17 (1H, dd, *J* = 10.19, 1.32 Hz), 5.32 (1H, dd, *J* = 16.99, 1.32 Hz), 6.01 (1H, m), 6.74 (1H, d, *J* = 8.12 Hz), 6.85 (1H, s), 6.92 (1H, d, *J* = 7.74 Hz), 7.19 (1H, t, *J* = 7.93 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.4, 18.2,

25.7, 75.1, 115.0, 117.9, 119.2, 119.3, 129.5, 140.2, 144.2, 155.8; IR ($CHCl_3$, cm^{-1}): ν_{max} 3400, 2930, 1586, 1484, 1473, 1277, 1259, 1003, 982, 840, 782 cm^{-1}; MS (ESI): (M^+ + Na) 287; HRMS (ESI): calcd for $C_{15}H_{24}O_2NaSi$: 287.1457, found: 287.1465.

***tert*-Butyl 3-[(1*S*)-1-methoxy-2-propenyl]phenoxydimethylsilane (5).** To a solution of the above alcohol **12** (2 g, 7.57 mmol) in THF (15 mL) was added NaH (181 mg, 7.57 mmol) at 0 °C and stirred for 10 min at the same temperature; to the reaction mixture was added MeI (1.2 g, 7.69 mmol). After stirring for 3 h at the same temperature, the reaction mixture was quenched with a saturated solution of aqueous NH_4Cl. After removing THF under reduced pressure the reaction mixture was extracted with EtOAc, washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 5 to 7% EtOAc in hexane eluant) afforded **5** (1.77 g, 85%) as a pale yellow color oil; $[\alpha]_D^{25}$ = +8.5 (*c* 0.5, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.12 (6H, s), 0.92 (9H, s), 3.24 (3H, s), 4.47 (1H, d, *J* = 6.86 Hz), 5.05–5.20 (2H, m), 5.78–5.89 (1H, m), 6.67 (1H, d, *J* = 7.89 Hz), 6.74 (1H, s), 6.82 (1H, d, *J* = 6.86 Hz), 7.12 (1H, t, *J* = 7.89 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.5, 18.1, 25.6, 56.3, 84.4, 116.1, 118.4, 119.2, 119.8, 129.3, 138.6, 142.3, 155.7; IR ($CHCl_3$, cm^{-1}): ν_{max} 2952, 2930, 1601, 1483, 1443, 1276, 1154, 1095, 839, 781 cm^{-1}; MS (ESI) *m*/*z*: (M^+ + Na) 301; HRMS (ESI): calcd for $C_{16}H_{26}O_2NaSi$: 301.1562, found: 301.1556.

(2*S*,3*R*,4*S*,5*E*,7*S*)-7-(3-[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxyphenyl)-1-(2,2-dimethyl-1,1-diphenylpropoxy)-7-methoxy-2,4-dimethyl-5-hepten-3-ol (15). To a stirred solution of olefin **6** (100 mg, 0.261 mmol) and olefin **5** (376 mg, 1.31 mmol) in dry CH_2Cl_2 (5 mL) was added the second generation Grubbs catalyst (G-II) (22 mg, 0.026 mmol). The solution was allowed to reflux under nitrogen. After 24 hours, the solution was allowed to remain exposed to air at room temperature, and was subsequently concentrated *in vacuo*, and purification by column chromatography (SiO_2, 5 to 8% EtOAc in hexane eluant) afforded **15** (150 mg, 94%) as a brown colored liquid; $[\alpha]_D^{27}$ = +16.5 (*c* 0.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.12 (6H, s), 0.89 (3H, d, *J* = 6.79 Hz), 0.98 (9H, s), 1.06 (9H, s), 1.11 (3H, d, *J* = 7.55 Hz), 1.78 (1H, m), 2.35 (1H, m), 3.29 (3H, s), 3.41 (1H, q, *J* = 6.89, 3.81 Hz), 3.62 (1H, dd, *J* = 9.55, 5.81 Hz), 3.78 (1H, m), 4.52 (1H, d, *J* = 7.78 Hz), 5.51 (1H, dd, *J* = 15.55, 6.81 Hz), 5.73 (1H, dd, *J* = 14.65, 7.78 Hz), 6.73 (1H, d, *J* = 7.78 Hz), 6.79 (1H, s), 6.87 (1H, d, *J* = 7.78 Hz), 7.17 (1H, t, *J* = 7.78 Hz), 7.34–7.48 (6H, m), 7.65–7.69 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.5, 14.2, 18.1, 19.1, 25.6, 26.7, 29.6, 36.8, 40.2, 56.1, 68.3, 79.2, 84.0, 118.3, 119.1, 119.7, 127.7, 129.2, 129.7, 130.2, 132.7, 135.6, 136.7, 143.1, 155.6; IR ($CHCl_3$, cm^{-1}): ν_{max} 3352, 2987, 2950, 1682, 1474, 1457, 1203, 1182, 1132, 1035 cm^{-1}; MS (ESI) *m*/*z*: (M^+ + Na) 655; HRMS (ESI): *m*/*z* calcd for $C_{38}H_{56}O_4NaSi_2$: 655.3614, found: 655.3634.

(2*S*,3*R*,4*S*,7*S*)-7-(3-[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxyphenyl)-1-(2,2-dimethyl-1,1-diphenylpropoxy)-7-methoxy-2,4-dimethylheptan-3-ol (16). To a solution of **15** (0.2 g, 0.316 mmol) in EtOAc (10 mL) was added 20 mg of 10% Pd/C and the mixture was stirred under a hydrogen atmosphere for 6 h. After the completion of the reaction, the solution was filtered through a celite pad and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2, 5% EtOAc in hexane eluant) to give **16** (0.18 g, 92%) as a colorless liquid; $[\alpha]_D^{25}$ = −9.1 (*c* 0.5, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.12 (6H, s), 0.71 (3H, d, *J* = 6.79 Hz), 0.86 (3H, d, *J* = 7.55 Hz), 0.97 (9H, s), 1.06 (9H, s), 1.21–1.94 (6H, m), 3.18 (3H, s), 3.45 (1H, dd, *J* = 8.31, 2.33 Hz), 3.45–3.71 (2H, m), 3.98 (1H, t, *J* = 7.36 Hz), 6.71–6.92 (3H, m), 7.21 (1H, m), 7.32–7.48 (6H, m), 7.61–7.73 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.4, 12.4, 13.3, 18.2, 19.1, 25.7, 26.8, 30.2, 35.3, 36.3, 37.4, 56.6, 69.7, 78.6, 84.2, 118.3, 119.2, 119.8, 127.7, 129.2, 129.8, 132.8, 135.6, 144.3, 155.7; IR ($CHCl_3$, cm^{-1}): ν_{max} 3491, 2961, 2930, 2851, 1483, 1427, 1275, 1096 cm^{-1}; MS (ESI) *m*/*z*: (M^+ + H) 635; HRMS (ESI): calcd for $C_{38}H_{59}O_4Si_2$: 635.3867, found: 635.3880.

(2*S*,3*R*,4*S*,7*S*)-7-(3-Hydroxyphenyl)-7-methoxy-2,4-dimethylheptane-1,3-diol (17). A solution of **16** (0.5 g, 0.788 mmol) in THF (10 mL) was cooled to 0 °C and TBAF (2.0 mL, 2.03 mmol, 1.0 M solution in THF) was added dropwise. The resulting brown solution was stirred at the same temperature for 2 h. Then, a mixture of Et_2O–H_2O 1 : 1 (20 mL) was added. The resulting layers were separated and washed with brine, dried over Na_2SO_4 and the solvents were evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, 25 to 30% EtOAc in hexane eluant) to obtain 203 mg (81%) of triol **17** as a colorless gummy product; $[\alpha]_D^{25}$ = −14.8 (*c* 0.2, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.73 (3H, d, *J* = 6.79 Hz), 0.82 (3H, d, *J* = 6.79 Hz), 1.25–1.91 (6H, m), 3.21 (3H, s), 3.42 (1H, dd, *J* = 9.06, 3.02 Hz), 3.61 (1H, dd, *J* = 10.57, 7.55 Hz), 3.69 (1H, dd, *J* = 1.57, 3.77 Hz), 4.04 (1H, t, *J* = 6.04 Hz), 6.74–6.79 (3H, m), 7.17 (1H, t, *J* = 7.55 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.3, 13.4, 29.7, 35.1, 35.5, 37.1, 56.6, 68.5, 79.6, 84.2, 113.3, 114.8, 118.6, 129.6, 143.6, 156.5; IR ($CHCl_3$, cm^{-1}): ν_{max} 3434, 2941, 1282, 1052, 669 cm^{-1}; MS (ESI) *m*/*z*: (M^+ + Na) 305; HRMS (ESI): calcd for $C_{16}H_{26}O_4Na$: 305.17233, found: 305.17212.

(2*R*,3*R*,4*S*,7*S*)-Methyl 3-hydroxy-7-(3-hydroxyphenyl)-7-methoxy-2,4-dimethylheptanoate (18). To a solution of compound **17** (0.25 g, 0.86 mmol) in dry CH_2Cl_2 (20 mL) were added TEMPO (15 mg, 0.085 mmol) and BAIB (0.42 g, 1.33 mmol) at 0 °C and it was stirred for 4 h at room temperature. CH_2Cl_2 was concentrated and directly transferred to a silica gel column and purified to obtain aldehyde, which was again dissolved in THF–H_2O–^{t}BuOH (6 mL/6 mL/1.2 mL) and to this solution were added $NaClO_2$ (0.175 g, 1.99 mmol) and NaH_2PO_4 (0.44 g, 3.695 mmol) in 3 mL H_2O at 0 °C and the reaction mixture was stirred for 12 h at room temperature. THF was removed under reduced pressure and 25 mL 1 M HCl was added and then extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to obtain the residue, which was dissolved in 20 mL sat. $NaHCO_3$ and extracted with Et_2O. The aqueous layer was acidified with 10 mL 3 M HCl and then extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to obtain carboxylic acid as a

colourless liquid; without purification, this was taken up for the next step.

The intermediate acid was dissolved in dry ether and treated with ethereal solution of diazomethane at 0 °C. After stirring for 0.5 h, an aqueous NH_4Cl solution was added and extracted with EtOAc. The combined organic layers, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (SiO_2, 10 to 15% EtOAc in hexane eluant) to obtain **18** (195 mg, 72%) as a colorless oil; $[\alpha]_D^{25}$ = −28.2 (*c* 0.25, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.84 (3H, d, *J* = 6.59 Hz), 1.09 (3H, d, *J* = 7.55 Hz), 1.35–1.45 (1H, m), 1.49–1.57 (1H, m), 1.61–1.69 (1H, m), 1.77–1.85 (1H, m), 2.56–2.63 (2H, m), 3.21 (3H, s), 3.57 (1H, m), 3.68 (3H, s), 4.02 (1H, t, *J* = 6.59 Hz), 5.88 (1H, s) 6.74 (1H, d, *J* = 7.69 Hz), 6.79 (1H, s), 6.81 (1H, d, *J* = 7.69 Hz) 7.18 (1H, t, *J* = 7.69 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.6, 14.3, 29.8, 34.8, 35.6, 43.1, 51.8, 56.6, 75.6, 84.1, 113.1, 114.6, 118.8, 129.5, 143.8, 156.3, 177.2; IR ($CHCl_3$, cm^{-1}): ν_{max} 3430, 2925, 1717, 1628, 1261, 1098, 791 cm^{-1}; MS (ESI) *m*/*z*: (M^+ + H) 311; HRMS (ESI): calcd for $C_{17}H_{26}O_5Na$: 333.16788, found: 333.16676.

(2*R*,3*R*,4*S*,7*S*)-Methyl 7-(3-(*tert*-butyldimethylsilyloxy)phenyl)-3-hydroxy-7-methoxy-2,4-dimethylheptanoate (3). To a solution of the alcohol **18** (0.2 g, 0.645 mmol) in dry DCM (5 mL) were added imidazole (0.08 g, 1.29 mmol) and TBDMSCl (0.11 g, 0.71 mmol). The resulting mixture was stirred at room temperature for 4 h. Progress of the reaction was monitored by TLC and after completion of the reaction, it was poured into water (25 mL) and extracted with diethyl ether (3 × 30 mL). The combined ethereal layer was washed with brine (30 mL) and dried over anhydrous Na_2SO_4. The residue obtained after the evaporation of the solvent was purified by column chromatography (SiO_2, 7 to 10% EtOAc in hexane eluant) to afford **3** (0.24 g, 91%) as a colorless oil; $[\alpha]_D^{25}$ = −23.4 (*c* 0.25, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.19 (6H, s), 0.84 (3H, d, *J* = 6.79 Hz), 0.98 (9H, s), 1.11 (3H, d, *J* = 7.55 Hz), 1.32–1.44 (1H, m), 1.47–1.71 (2H, m), 1.73–1.86 (1H, m), 2.45 (1H, d, *J* = 6.78 Hz), 2.61 (1H, m), 3.20 (3H, s), 3.56 (1H, m), 3.69 (3H, s), 4.01 (1H, q, *J* = 6.04, 1.57 Hz), 6.74 (1H, d, *J* = 7.55 Hz), 6.77 (1H, s), 6.86 (1H, d, *J* = 7.55 Hz), 7.19 (1H, t, *J* = 7.55 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.4, 12.6, 14.4, 18.2, 25.6, 29.9, 34.9, 35.8, 42.9, 51.7, 56.5, 75.7, 83.9, 118.1, 119.2, 119.7, 129.2, 143.9, 155.7, 176.8; IR ($CHCl_3$, cm^{-1}): ν_{max} 3432, 1726, 1638, 1281, 1124, 771 cm^{-1}; MS (ESI) *m*/*z*: (M^+ + Na) 447; HRMS (ESI): calcd for $C_{23}H_{40}O_5NaSi$: 447.25416, found: 447.25435.

Ethyl (2*S*,3*R*)-5-[1-(*tert*-butyl)-1,1-diphenylsilyl]oxy-2,3-dihydroxypentanoate (20). The solution of AD-mix-β (18.3 g) and $CH_3SO_2NH_2$ (1.24 g, 13.08 mmol) in ^{t}BuOH–H_2O 1 : 1 (200 mL) was stirred for 10 min at room temperature and then cooled to 0 °C and alkene **19** (5 g, 13.08 mmol) was added and stirred at 0 °C. After 24 h, the reaction mixture was quenched with sodium sulphite; it was diluted with EtOAc (20 mL), filtered through celite and the filtrate was concentrated under reduced pressure to give a diol, which was purified by column chromatography (SiO_2, 20% EtOAc in hexane eluant) to give pure diol **20** (4.84 g, 89%) as a colorless oil; $[\alpha]_D^{25}$ = +4.8 (*c* 0.2, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.05 (9H, s), 1.32 (3H, t, *J* = 6.79 Hz), 1.71–2.06 (2H, m), 3.01 (1H, d, *J* = 6.14 Hz), 3.31 (1H, d, *J* = 6.74 Hz), 3.81–3.94 (2H, m), 4.05 (1H, dd, *J* = 6.79, 2.27 Hz), 4.29 (2H, q, *J* = 7.55, 6.79 Hz), 7.33–7.46 (6H, m), 7.66–7.69 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 18.9, 26.7, 35.3, 61.7, 62.1, 71.4, 73.5, 127.7, 129.7, 132.8, 133.1, 135.4, 173.2; IR ($CHCl_3$, cm^{-1}): ν_{max} 3441, 2923, 2853, 1737, 1693, 1386, 1089, 1021, 703 cm^{-1}; MS (ESI) *m*/*z*: (M^+ + Na) 439; HRMS (ESI): calcd for $C_{23}H_{32}O_5NaSi$: 439.1916, found: 439.1921.

Ethyl (4*S*,5*R*)-5-(2-[1-(*tert*-butyl)-1,1-diphenylsilyl]oxyethyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (21). To a solution of the diol **20** (5 g, 12.01 mmol) in 20 mL of dry CH_2Cl_2 at 0 °C were added 2,2-dimethoxypropane (4.4 mL, 36.05 mmol) and TsOH (108 mg, 0.47 mmol) and the reaction mixture was stirred at ambient temperature for 3 h. The organic layer was evaporated under reduced pressure to afford the crude acetonide, which was purified by column chromatography (SiO_2, 5 to 7% EtOAc in hexane eluant) to yield **21** (5.04 g, 92%) as a colorless oil; $[\alpha]_D^{25}$ = +12.8 (*c* 0.2, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.05 (9H, s), 1.28 (3H, t, *J* = 7.17 Hz), 1.46 (6H, s), 1.82–2.14 (2H, m), 3.84 (2H, t, *J* = 6.42 Hz), 4.16–4.31 (3H, m), 4.35–4.43 (1H, m), 7.35–7.46 (6H, m), 7.66–7.69 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 19.2, 25.6, 26.7, 27.2, 36.3, 60.2, 61.2, 75.9, 78.9, 110.6, 127.5, 129.5, 133.6, 135.5, 170.6; IR ($CHCl_3$, cm^{-1}): ν_{max} 2932, 2858, 1756, 1598, 1367, 1177, 986, 740 cm^{-1}; MS (ESI) *m*/*z*: (M^+ + Na) 479; HRMS (ESI): calcd for $C_{26}H_{36}O_5NaSi$: 479.2229, found: 479.2241.

[(4*R*,5*R*)-5-(2-[1-(*tert*-Butyl)-1,1-diphenylsilyl]oxyethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]methanol (22). A solution of **21** (5 g, 10.09 mmol), in Et_2O (50 mL) and catalytic amount of water (1 mL), was treated with $LiBH_4$ (0.48 g, 21.92 mmol) at 0 °C. After stirring for 2 h at ambient temperature the reaction mixture was quenched with a saturated solution of aqueous NH_4Cl. After removing Et_2O under reduced pressure the reaction mixture was extracted with EtOAc, washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 10 to 12% EtOAc in hexane eluant) afforded **22** (3.99 g, 88%) as a colorless oil; $[\alpha]_D^{25}$ = +13.4 (*c* 0.3, $CHCl_3$), ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.05 (9H, s), 1.36 (3H, s), 1.37 (3H, s), 1.79 (2H, m), 3.56 (1H, dd, *J* = 11.86, 2.96 Hz), 3.72–3.76 (2H, m), 3.79–3.82 (2H, m), 4.03 (1H, q, *J* = 7.94, 4.94 Hz), 7.33–7.41 (6H, m), 7.63–7.65 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.3, 26.9, 27.1, 27.4, 35.9, 60.7, 61.8, 74.1, 81.4, 108.5, 127.7, 129.7, 133.7, 135.6; IR ($CHCl_3$, cm^{-1}): ν_{max} 3441, 2923, 2853, 1737, 1693, 1386, 1089, 1021, 703 cm^{-1}; MS (ESI) *m*/*z*: (M^+ + Na) 437; HRMS (ESI): calcd for $C_{24}H_{34}O_4NaSi$: 437.2124, found: 437.2114.

[(4*R*,5*R*)-5-(2-[1-(*tert*-Butyl)-1,1-diphenylsilyl]oxyethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl 4-methyl-1-benzenesulfonate (23). To a stirred solution of compound **22** (3 g, 7.24 mmol) in dry CH_2Cl_2 (25 mL) was added TEA (23 mL, 21.74 mmol) at room temperature and cooled to 0 °C; then *p*-toluenesulfonyl chloride (1.52 g, 7.97 mmol) was added and the reaction mixture was stirred for 4 h at room temperature. After the removal of the solvent under reduced pressure a residue was obtained, which was purified by column

chromatography (SiO_2, 4 to 6% EtOAc in hexane eluant) to obtain the tosylate compound **23** (3.7 g, 90%) as a colorless oil; $[\alpha]_D^{25}$ = +16.3 (*c* 0.3, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.03 (9H, s), 1.29 (3H, s), 1.33 (3H, s), 1.69–1.87 (2H, m), 2.42 (3H, s), 3.74–3.80 (2H, m), 3.86–3.92 (1H, m), 4.02 (1H, dt, *J* = 7.36, 4.41 Hz), 4.12 (2H, m), 7.21 (2H, d, *J* = 8.09 Hz), 7.35–7.44 (6H, m), 7.64–7.67 (4H, m), 7.78 (2H, d, *J* = 8.09 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.1, 21.6, 26.6, 26.8, 27.2, 35.7, 60.3, 68.9, 74.6, 78.1, 109.3, 127.6, 127.9, 129.6, 129.8, 132.7, 133.5, 135.5, 144.8; IR ($CHCl_3$, cm^{-1}): ν_{max} cm^{-1}; MS (ESI) *m*/*z*: (M^+ + Na) 591; HRMS (ESI): calcd for $C_{31}H_{40}O_6NaSiS$: 591.2212, found: 591.2187.

2-[(4*R*,5*R*)-2,2,5-Trimethyl-1,3-dioxolan-4-yl]-1-ethanol (24). To a stirred solution of tosylate **23** (5 g, 8.80 mmol) in THF (50 mL) at 0 °C was added $LiAlH_4$ (0.6 g, 17.60 mmol). The suspended mixture was stirred at reflux temperature for 12 h, cooled to 0 °C, diluted with 2 mL of THF, and then carefully treated successively with water and 10% aq. NaOH. The resulting mixture was stirred for 1 h and filtered through a celite pad; the filtrate was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was then purified by column chromatography (SiO_2, 12 to 15% EtOAc in hexane eluant) to obtain the alcohol **24** (1.02 g, 73%) as a colorless oil; $[\alpha]_D^{25}$ = +14.8 (*c* 0.4, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24 (3H, d, *J* = 6.04 Hz), 1.37 (3H, s), 1.38 (3H, s), 1.61–1.84 (2H, m), 3.57–3.66 (1H, td, *J* = 8.31, 3.02 Hz), 3.71–3.78 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.9, 27.1, 27.2, 33.9, 60.6, 76.7, 81.3, 108.2; IR ($CHCl_3$, cm^{-1}): ν_{max} 3444, 2983, 2360, 1635, 1372, 1220, 1090, 1002, 771 cm^{-1}; MS (ESI) *m*/*z*: (M^+ + Na) 183; HRMS (ESI): calcd for $C_8H_{16}O_3Na$: 183.0992, found: 183.0995.

2-[(4*R*,5*R*)-2,2,5-Trimethyl-1,3-dioxolan-4-yl]acetic acid (4). To a solution of the above alcohol **24** (1 g, 6.25 mmol) in CH_2Cl_2–H_2O (1 : 1) (10 mL) were added TEMPO (270 mg, 1.57 mmol) and BAIB (6.03 g, 18.75 mmol). After stirring at 0 °C for 3 h, the reaction mixture was diluted with CH_2Cl_2 and then washed with saturated aqueous $Na_2S_2O_3$. The organic layer was dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure to give the crude carboxylic acid. The crude product was purified by filter chromatography (SiO_2, 23 to 25% EtOAc in hexane eluant) to yield **4** (0.85 g, 79%) as a colorless gum; $[\alpha]_D^{25}$ = +4.8 (*c* 0.2, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.29 (3H, d, *J* = 6.44 Hz), 1.38 (3H, s), 1.41 (3H, s), 2.48–2.68 (2H, m), 3.79 (1H, m), 3.91 (1H, q, *J* = 7.36, 4.44 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.2, 26.9, 27.2, 37.4, 76.4, 78.0, 108.6, 173.3; IR ($CHCl_3$, cm^{-1}): ν_{max} 3443, 2957, 2932, 1786, 1639, 1242, 1174, 1056, 944 cm^{-1}; MS (ESI) *m*/*z*: 197 (M^+ + Na); HRMS (ESI): *m*/*z* calcd for $C_8H_{14}O_4Na$: 197.0942, found: 197.0952.

(2*R*,3*R*,4*S*,7*S*)-Methyl 7-(3-(*tert*-butyldimethylsilyloxy)phenyl)-7-methoxy-2,4-dimethyl-3-(2-((4*R*,5*R*)-2,2,5-trimethyl-1,3-dioxolan-4-yl)acetoxy)heptanoate (2). To a stirred solution of acid **4** (54 mg, 0.22 mmol) in toluene (2 mL) were added triethylamine (0.06 mL, 0.43 mmol), 2,4,6-trichlorobenzoyl chloride (0.0 mL, 0.32 mmol), and DMAP (39.3 mg, 0.32 mmol). Alcohol **3** (50 mg, 0.14 mmol) was then added in toluene (3 mL). The resulting solution was stirred for 10 h and to it toluene (10 mL) and saturated aqueous $NaHCO_3$ solution (10 mL) were added. The layers were separated, and the aqueous phase was extracted with toluene (3 × 5 mL). The combined organic phases were dried over Na_2SO_4, and the solvent was removed under vacuum. The crude product was purified by flash column chromatography (SiO_2, 8% EtOAc in hexane eluant) to furnish diester **2** (58 mg, 84% yield) as a colorless liquid; $[\alpha]_D^{25}$ = −1.9 (*c* 0.45, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.19 (6H, s), 0.88 (3H, d, *J* = 6.04 Hz), 0.98 (9H, s), 1.11 (3H, d, *J* = 6.79 Hz), 1.28 (3H, d, *J* = 6.04 Hz), 1.37 (3H, s), 1.41 (3H, s) 1.35–1.45 (2H, m), 1.58–1.82 (3H, m), 2.41 (2H, m), 2.76 (1H, m), 3.18 (3H, s), 3.63 (3H, s), 3.74–3.81 (1H, m), 3.87–3.99 (2H, m), 5.08 (1H, dd, *J* = 9.66, 3.77 Hz) 6.72 (1H, d, *J* = 7.55 Hz), 6.76 (1H, s), 6.86 (1H, d, *J* = 7.55 Hz), 7.18 (1H, t, *J* = 7.55 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.4, 13.5, 13.7, 17.4, 18.2, 25.6, 27.2, 27.3, 29.8, 33.8, 35.9, 37.8, 41.9, 51.7, 56.6, 76.8, 77.2, 78.3, 83.8, 108.3, 117.9, 119.2, 119.7, 129.3, 144.1, 155.7, 169.7, 174.2; IR ($CHCl_3$, cm^{-1}): ν_{max} 2965, 2938, 1743, 1702, 1266, 755 cm^{-1}; MS (ESI) *m*/*z*: (M^+ + Na) 603; HRMS (ESI): calcd for $C_{31}H_{52}O_8NaSi$: 603.33237, found: 603.33184.

(2*R*,3*R*,4*S*,7*S*)-Methyl 3-((3*R*,4*R*)-3,4-dihydroxy pentanoyloxy)-7-(3-hydroxyphenyl)-7-methoxy-2,4-dimethylheptanoate (14). To a stirred solution of diester **2** (50 mg, 0.344 mmol) in MeOH (5 mL) was added PTSA. The resulting solution was stirred for 4 h. The organic layer was evaporated under reduced pressure to afford the crude product, which was purified by column chromatography (SiO_2, 30% EtOAc in hexane eluant) to yield **14** (29 mg, 78% yield) as a colourless gummy product; $[\alpha]_D^{25}$ = −2.8 (*c* 0.25, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.82 (3H, d, *J* = 6.79 Hz), 1.11 (3H, d, *J* = 6.79 Hz), 1.21 (3H, d, *J* = 6.79 Hz), 1.25–1.38 (2H, m), 1.61–1.88 (3H, m), 2.43 (2H, d, *J* = 6.04 Hz), 2.68–2.79 (1H, m), 3.18 (3H, s), 3.63 (3H, s), 3.79 (1H, q, *J* = 6.79, 6.03 Hz), 4.01 (1H, t, *J* = 6.79 Hz), 4.11 (1H, q, *J* = 6.79, 6.03 Hz), 5.15 (1H, dd, *J* = 9.06, 3.02 Hz), 6.72 (1H, d, *J* = 7.55 Hz), 6.76 (1H, s), 6.79 (1H, d, *J* = 7.55 Hz), 7.18 (1H, t, *J* = 7.55 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.4, 13.7, 18.9, 29.6, 33.8, 34.7, 37.8, 41.8, 52.1, 56.5, 69.8, 72.2, 76.5, 83.8, 112.9, 115.2, 119.6, 129.5, 143.1, 156.4, 171.9, 174.9; IR ($CHCl_3$, cm^{-1}): ν_{max} 3432, 2956, 2926, 1734, 1708, 1633, 1262, 1100, 791 cm^{-1}; MS (ESI) *m*/*z*: (M^+ + Na) 449; HRMS (ESI): calcd for $C_{22}H_{34}O_8Na$: 449.21459, found: 449.21420.

(2*R*,3*R*,4*S*,7*S*)-3-((3*R*,4*R*)-3,4-Dihydroxypentanoyloxy)-7-(3-hydroxyphenyl)-7-methoxy-2,4-dimethylheptanoic acid (nhatrangin A (1)). To a solution of diester **5** (20 mg, 0.044 mmol) in anhydrous dichloroethane (2 mL) was added Me_3SnOH (60 mg, 0.464 mmol). The reaction mixture was stirred at 80 °C for 55 hours. The flask was then cooled to room temperature and DCE was removed under reduced pressure and dissolved in 1 mL sat. $NaHCO_3$ and extracted with Et_2O. The aqueous layer was acidified with 2 mL 3 M HCl and then extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to obtain the target molecule nhatrangin A **1** (5.6 mg, 30% yield and 55% starting material was recovered) as a brown colored oil; $[\alpha]_D^{25}$ = +0.2 (*c* 0.05, MeOH), ^{1}H NMR (500 MHz, DMSO-d_6):

δ 0.72 (3H, d, J = 6.8 Hz), 0.82 (3H, d, J = 7.4 Hz), 0.93 (3H, d, J = 6.8 Hz), 1.23 (2H, m) 1.62 (2H, m), 1.67 (1H, m), 2.17 (1H, dd, J = 15.4, 5.4 Hz), 2.25 (1H, d, J = 7.8 Hz), 2.36 (1H, dd, J = 15.4, 4.4 Hz), 3.08 (3H, s), 3.50 (1H, qd, J = 6.5, 6.03, 4.2 Hz), 3.74 (1H, m), 3.94 (1H, dd, J = 7.6, 4.4 Hz), 4.79 (1H, dd, J = 7.8, 4.4 Hz), 6.63 (1H, m), 6.65 (1H, m), 6.66 (1H, m), 7.11 (1H, t, J = 7.55 Hz), 9.31 (1H, s); ^{13}C NMR (125 MHz, DMSO-d_6): δ 13.9, 15.2, 18.0, 29.9, 33.3, 35.3, 38.3, 40.6, 55.9, 68.4, 70.9, 78.0, 83.2, 113.0, 114.2, 116.9, 129.1, 144.0, 157.4, 171.0, 176.5; IR ($CHCl_3$, cm^{-1}): ν_{max} 3473, 2956, 2928, 1726, 1623, 1465, 1275, 1096 cm^{-1}; MS (ESI) m/z: $(M - H)^-$: 411; HRMS (ESI): calcd for $C_{21}H_{31}O_8$: 411.20258, found: 411.20317.

Notes and references

1 (*a*) H. Reichenbach, *J. Ind. Microbiol. Biotechnol.*, 2001, **27**, 149; (*b*) H. Reichenbach and G. Höfle, in *Drug Discovery from Nature*, ed. S. Grabley and R. Thiericke, Springer, Berlin, Germany, 1999, pp. 149–179.

2 (*a*) S. P. Gunasekera, R. Ritson-Williams and V. J. Paul, *J. Nat. Prod.*, 2008, **71**, 2060; (*b*) L. T. Tan, Y. Y. Chang and T. Ashootosh, *Phytochemistry*, 2008, **69**, 2067; (*c*) A. Tripathi, J. Puddick, M. R. Prinsep, P. P. F. Lee and L. T. Tan, *J. Nat. Prod.*, 2009, **72**, 29.

3 (*a*) J. P. Arcoleo and I. B. Weinstein, *Proc. Am. Assoc. Cancer Res.*, 1984, **25**, 142; (*b*) Y. Kishi and R. R. Rando, *Acc. Chem. Res.*, 1998, **31**, 163.

4 J. S. Mynderse, R. E. Moore, M. Kashiwagi and T. R. Norton, *Science*, 1977, **196**, 538.

5 G. E. George, E. Chlipala, P. H. Tri, N. V. Hung, K. Krunic, S. H. Shim, D. D. Soejarto and J. Orjala, *J. Nat. Prod.*, 2010, **73**, 784.

6 (*a*) A. Kamal and S. R. Vangala, *Tetrahedron*, 2011, **67**, 1341; (*b*) A. Kamal, S. R. Vangala, N. V. S. Reddy and V. S. Reddy, *Tetrahedron: Asymmetry*, 2009, **20**, 2589; (*c*) A. Kamal, P. V. Reddy and S. Prabhakar, *Tetrahedron: Asymmetry*, 2009, **20**, 1120; (*d*) A. Kamal, T. Krishnaji and P. V. Reddy, *Tetrahedron: Asymmetry*, 2007, **18**, 1775; (*e*) A. Kamal, T. Krishnaji and P. V. Reddy, *Tetrahedron Lett.*, 2007, **48**, 7232; (*f*) A. Kamal, T. Krishnaji and G. B. R. Khanna, *Tetrahedron Lett.*, 2006, **47**, 8657.

7 (*a*) A. Kamal, A. A. Shaik, M. Sandbhor and M. S. Malik, *Tetrahedron: Asymmetry*, 2004, **15**, 935; (*b*) A. Kamal, M. S. Malik, A. A. Shaik and S. Azeeza, *Tetrahedron: Asymmetry*, 2008, **19**, 1078; (*c*) P. Chen and P. Xiang, *Tetrahedron Lett.*, 2011, **52**, 5758.

8 (*a*) H. C. Brown and K. S. Bhat, *J. Am. Chem. Soc.*, 1986, **108**, 293; (*b*) B. G. Lawhorn, S. B. Boga, S. E. Wolkenberg, D. A. Colby, C. Gauss, M. R. Swingle, L. Amable, R. E. Honkanen and D. L. Boger, *J. Am. Chem. Soc.*, 2006, **128**, 16720; (*c*) P. V. Ramachandran, A. Srivastava and D. Hazra, *Org. Lett.*, 2007, **9**, 157.

9 (*a*) A. K. Chatterjee, T. L. Choi, D. P. Sanders and R. H. Grubbs, *J. Am. Chem. Soc.*, 2003, **125**, 11360; (*b*) S. BouzBouz, R. Simmons and J. Cossy, *Org. Lett.*, 2004, **6**, 3465; (*c*) M. Scholl, S. Ding, C. W. Lee and R. H. Grubbs, *Org. Lett.*, 1999, **1**, 953.

10 A. De Mico, R. Margarita, L. Parlanti, A. Vescovi and G. Piancatelli, *J. Org. Chem.*, 1997, **62**, 6974.

11 B. S. Pinnick Bal, W. E. Childers and H. W. Pinnick, *Tetrahedron*, 2011, **67**, 1341.

12 (*a*) H. C. Kolb, M. S. V. Nieuwenhze and K. B. Sharpless, *Chem. Rev.*, 1994, **94**, 2483; (*b*) A. M. Heapy and M. A. Brimble, *Tetrahedron*, 2010, **66**, 5424.

13 (*a*) H. Miyaoka, M. Yamanishi, A. Hoshino and A. Kinbara, *Tetrahedron*, 2006, **62**, 4103; (*b*) C. R. Reddy, G. Dharmapuri and N. N. Rao, *Org. Lett.*, 2009, **11**, 5730.

14 J. Inanaga, K. Hirata, H. Saeki, T. Katsuki and M. Yamaguchi, *Bull. Chem. Soc. Jpn.*, 1979, **52**, 1989.

15 K. C. Nicolaou, A. A. Estrada, M. Zak, S. H. Lee and B. S. Safina, *Angew. Chem., Int. Ed.*, 2005, **44**, 1378.

16 Note: The optical rotations were measured at 0.05 *c* and 0.5 *c*. In the former, the rotation value obtained was +0.2 and in the latter the instrument showed an error message. It seems that the solution of the brown colored compound nhatrangin A (**1**) is not transparent enough at higher concentration to make a measurement possible. The low rotation value at 0.05 *c* may be due to the low magnitude of the optical rotation of the natural product itself.

