Tetrahedron: *Asymmetry* 23 (2012) 252–263

Contents lists available at SciVerse ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Formal total synthesis of aspergillides A and B

Gangavaram V.M. Sharma *, Vennampalli Manohar

Organic and Biomolecular Chemistry Division, CSIR-Indian Institute of Chemical Technology, Hyderabad 500 007, India

ARTICLE INFO

Article history:
Received 19 January 2012
Accepted 14 February 2012
Available online 14 March 2012

ABSTRACT

The formal total synthesis of the cytotoxic 14-membered macrolides, aspergillides A and B is described. A combination of a chiron approach and an asymmetric synthesis is adopted for the synthesis of the target macrolides. The required 2,6-*syn* and 2,6-*anti* tetrahydropyrans were constructed via a tandem Sharpless asymmetric epoxidation and 6-*exo* cyclization on δ-hydroxy allylic alcohols, as the key steps. The requisite chiral synthon was prepared from L-ascorbic acid.

1. Introduction

Aspergillides A, B and C (**1**, **2** and **3**, Fig. 1), the first examples of 14-membered macrolactones embedded with a 2,3,6-trisubstituted tetrahydropyran (THP) moiety, were isolated from the marine fungus *Aspergillus ostianus* strain 01F313 by Kusumi et al.[1] in 2008. Aspergillides **1**–**3** possess good cytotoxic properties against mouse lymphocytic leukemia cells (L1210).[1] Initially, the stereochemistry of aspergillides A and B was reported as (3*S*,4*S*,7*R*,13*S*) and (3*S*,4*S*,7*R*,13*R*), respectively,[1] which upon their total synthesis by Uenishi et al.[2] in 2009, proved to be incorrect. Later, the structures of aspergillides A and B were revised by X-ray crystallographic studies of their *m*-bromo benzoate derivatives.[3] Only two examples were found in the recent literature,[4] where the tetrahydropyran (THP) was not part of a hemiacetal or acetal moiety. Aspergillide A **1** contains four stereocenters (3*R*,4*S*,7*R*,13*S*) with a 3,7-*cis*-bridged THP, while aspergillide B **2** contains four stereocenters (3*S*,4*S*,7*R*,13*S*) with a 3,7-*trans*-bridged THP. The structural complexity and biological activity of **1** and **2** have attracted the attention of synthetic chemists.[5–7] The main synthetic challenge in these molecules is the construction of the *cis*- and *trans*- bridged THP in a stereoselective fashion. In previous reports, Uenishi et al.[2] applied the Pd(II)-catalyzed cyclization of a 6-hydroxy allylic alcohol. Marco et al.[5b,c,6a] and She et al.[7a] employed *C*-glycosidation, while Kuwahara et al.[5a,6b] used a Ferrier-type reaction on a cyclic acetal and a silyl ketene acetal. Fuwa et al.[5d,e] used intramolecular oxa-conjugate cyclization, while Sabitha et al.[5f] and Takahashi et al.[5h] used SmI_2-induced intramolecular cyclization. Likewise, Shishido et al.[5g] used a transannular oxy-Michael reaction, whereas, Jennings et al.[7b] utilized a diastereoselective oxocarbenium allylation for the construction of the desired *trans*- or *cis*-THPs in a stereoselective manner.

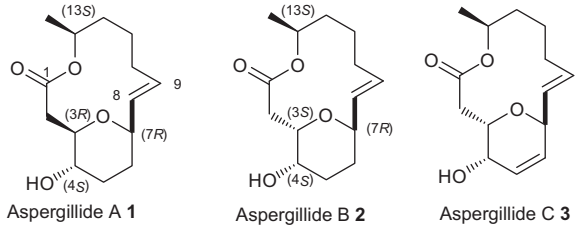


Figure 1. Corrected and revised structures.

In continuation of our program on the synthesis of lactone-containing biologically active natural products,[8] we herein report the formal total synthesis of aspergillides A **1** and B **2** by the combination of a chiron approach and the stereoselective construction of the tetrahydropyran via a tandem Sharpless asymmetric epoxidation (SAE)/6-*exo* cyclization.

2. Results and discussion

The retrosynthetic analysis (Scheme 1) of macrolide **2** revealed that it could be realized via macrolactonization from the seco-acid **4**, which in turn could be obtained from alcohol **5** and acid **6** via cross metathesis. Acid **6** was obtained from tetrahydropyran diol **7**, which could be formed stereoselectively using a tandem SAE/6-*exo* cyclization from δ-hydroxy allylic alcohol **8**. The required diol **8** in turn could be obtained from epoxide **9**, an L-ascorbic acid derivative.

2.1. Synthesis of the acid (C1–C8) segment 6

The known[8i,9] epoxide **9** (Scheme 2), derived from L-ascorbic acid, upon regioselective opening with vinylmagnesium bromide

* Corresponding author. Tel.: +91 40 2719 3154; fax: +91 40 2716 0387x0757.
E-mail address: esmvee@iict.res.in (G.V.M. Sharma).

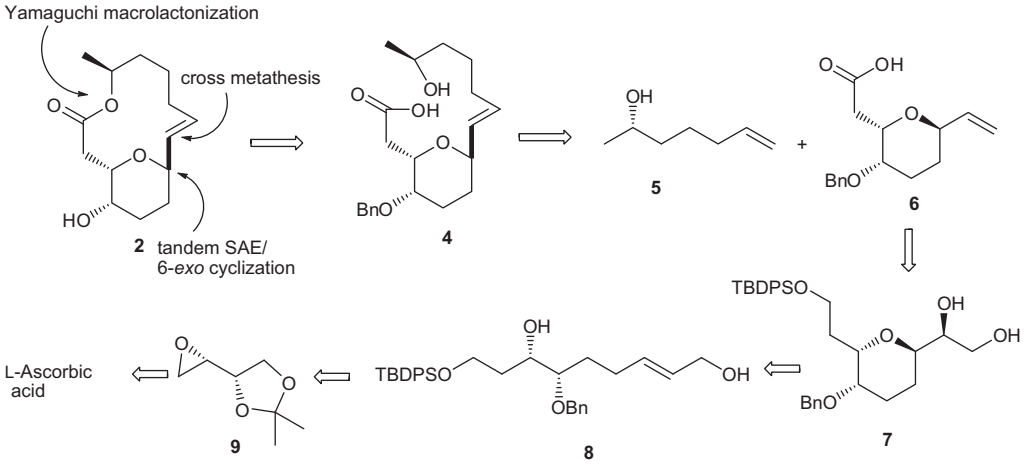
0957-4166/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2012.02.009

in THF in the presence of CuI[10] gave **10** in 84% yield. Alcohol **10** on subsequent reaction with PMBBr in the presence of NaH in THF gave ether **11** (75%). Ozonolysis of olefin **11** in CH_2Cl_2 at −78 °C followed by reduction of the resultant aldehyde with $NaBH_4$ at room temperature in MeOH gave alcohol **12** (74%).

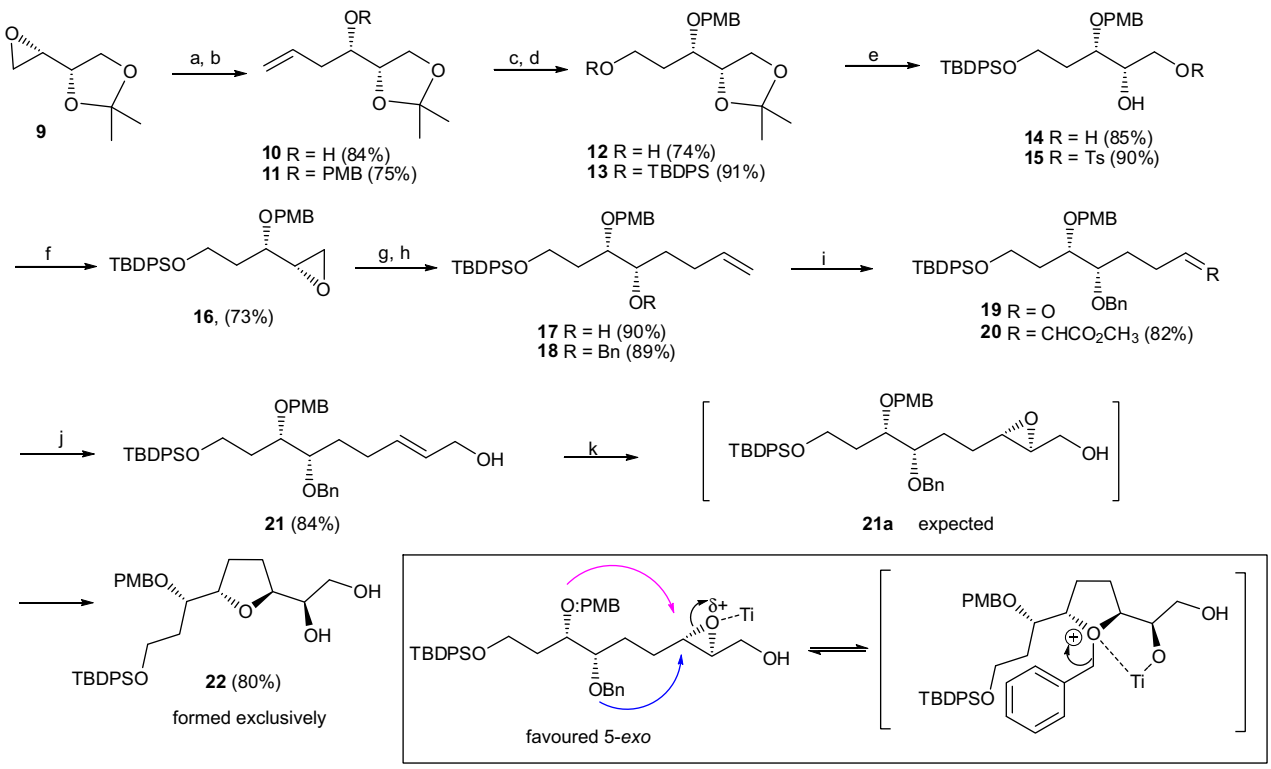
Treatment of alcohol **12** with TBDPSCl and imidazole in CH_2Cl_2 gave **13** in 91% yield. Deprotection of the acetonide in **13** with $CuCl_2{\cdot}2H_2O$ in CH_3CN afforded diol **14** (85%), which upon further chemoselective tosylation in the presence of Bu_2SnO[11] and Et_3N in CH_2Cl_2 furnished monotosylate **15** in 90% yield. Nucleophilic cyclization of tosylate **15** in the presence of K_2CO_3 in MeOH at room temperature afforded epoxide **16** in 73% yield.

Regioselective opening of epoxide **16** upon reaction with allylmagnesium chloride in dry ether in the presence of CuI[10] gave alcohol **17** (90%), which upon subsequent masking of the hydroxy group in **17** with BnBr in THF in the presence of NaH gave ether **18** in 89% yield. Ozonolysis of olefin **18** (Scheme 2) in CH_2Cl_2 gave aldehyde **19**, which upon subsequent Wittig olefination with (methoxycarbonylmethylene)triphenyl phosphorane in benzene at reflux gave α,β-unsaturated ester **20** (82%). Selective reduction of the ester in **20** with DIBAL-H in CH_2Cl_2 furnished allylic alcohol **21** in 84% yield.

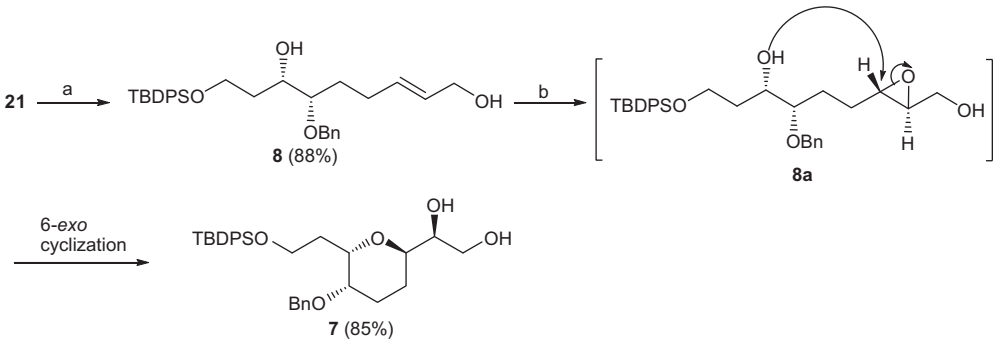
At this stage, we planned to synthesize the required tetrahydropyran via a Sharpless asymmetric epoxidation followed by



Scheme 1. Retrosynthesis of aspergillide B (**2**).



Scheme 2. Reagents and conditions: (a) vinylmagnesium bromide, dry THF, CuI, −40 °C to rt, 4 h; (b) PMBBr, NaH, dry THF, 0 °C to rt, 6 h; (c) (i) O_3, CH_2Cl_2, dimethylsulfide, −78 °C, 15 min; (ii) $NaBH_4$, MeOH, 0 °C to rt, 1 h; (d) TBDPSCl, imidazole, CH_2Cl_2, 0 °C to rt, 2 h; (e) (i) $CuCl_2{\cdot}2H_2O$, CH_3CN, 0 °C to rt, 45 min; (ii) Bu_2SnO, TsCl, Et_3N, rt, 30 min; (f) K_2CO_3, MeOH, rt, 1 h; (g) allylmagnesium chloride, CuI, dry ether, −40 °C to rt, 2 h; (h) BnBr, NaH, dry THF, 0 °C to rt, 5 h; (i) (i) O_3, CH_2Cl_2, dimethylsulphide, −78 °C, 15 min; (ii) $Ph_3P{=}CHCO_2Me$, benzene, reflux, 2 h; (j) DIBAL-H, CH_2Cl_2, 0 °C, 1 h; (k) (+)-DIPT, Ti(O*i*-Pr)$_4$, cumene hydroperoxide, 4 Å MS, CH_2Cl_2, −20 °C to rt, 8 h.



Scheme 3. Reagents and conditions: (a) DDQ, CH_2Cl_2:H_2O (19:1), 0 °C to rt, 1 h; (b) Sharpless asymmetric epoxidation, Table 1.

deprotection of the PMB ether and acid mediated 6-*exo* cyclization.[12,13] Accordingly, **21** was subjected to a Sharpless asymmetric epoxidation with (+)-DIPT, cumene hydroperoxide and Ti(O*i*-Pr)$_4$ in CH_2Cl_2. The epoxidation reaction resulted in the 5-*exo* cyclized furan derivative **22** (80%) as the only distinguishable product, instead of giving **21a**. It was assumed that due to chelation of the titanium, the thermodynamically more stable and more favoured 5-*exo* cyclization resulted in the cleavage of the benzyl ether after formation of the epoxide, wherein the epoxide opening protocol was governed by Baldwin rules.[14] The Ti(O*i*-Pr)$_4$ was believed to be acting as an internal acid in activating the epoxide for cyclization. Similar observations were reported by Takahashi et al.,[15] in which the MOM group migrated from the δ-position to the furan diol.

Due to this unexpected result, we decided to investigate the tandem Sharpless asymmetric epoxidation and 6-*exo* cyclization on the δ-hydroxy allylic alcohol **8** rather than allylic alcohol **21**. Accordingly, **21** (Scheme 3) upon selective cleavage of the PMB ether with DDQ in aq CH_2Cl_2 gave allylic alcohol **8** in 88% yield. The tandem Sharpless asymmetric epoxidation (SAE)/6-*exo* cyclization[16] of **8** gave the desired tetrahydropyran **7**. As can be seen from Table 1, the use of *tert*-butyl hydroperoxide (TBHP), and catalytic (entry 1) and stoichiometric amounts (entry 2) of Ti(O*i*-Pr)$_4$ and (−)-DIPT gave **7** in poor yields.

The use of cumene hydroperoxide (CHP) gave better results, although low yields were observed with catalytic amounts of reagents. Better results were achieved when stoichiometric amounts of reagents (Table 1, entries 4, 5, and 6) were used. Work-up under basic, neutral, and acidic conditions gave similar results and entry 5 was found to be the best reaction condition to give **7** in 85% yield. We believed that due to the ready availability of the nucleophile (free hydroxy) for the cyclization, the kinetically controlled 6-*exo* cyclization was favoured to result in **7** where Ti(O*i*-Pr)$_4$ acted as an internal acid.

Diol **7** (Scheme 4) upon olefination under Masayoshi conditions[16a] as well as under PPh_3, imidazole and I_2 conditions[16b] gave olefin **24** in poor yields. However, in a two-step procedure, diol **7** was subjected to oxidative cleavage with $NaIO_4$ in aq acetone to give aldehyde **23**, which upon further treatment with (methylene)triphenylphosphonium iodide and *t*-BuOK gave olefin **24** in 76% yield. Deprotection of the silyl group in the olefin with TBAF in THF at room temperature gave alcohol **25** (74%), which upon oxidation with TEMPO and BIAB[17] in aq CH_2Cl_2 afforded acid **6** in 70% yield.

2.2. Synthesis of macrolactone

Acid **6** (0.36 mmol) and alcohol **5**[18] (1.8 mmol) were subjected to cross metathesis[19,6a] in the presence of Grubbs second generation catalyst **G-II** (0.07 mmol) in CH_2Cl_2 at 40 °C to give hydroxy acid **4** (Scheme 5) in 48% yield, along with **4a** in 25% yield, a homodimer of **5**. Macrolactonization of the resulting hydroxy acid **4** under the Yamaguchi protocol[20] by using 2,4,6-trichlorobenzoyl chloride, followed by cyclization in the presence of DMAP under high dilution conditions in toluene afforded the *E*-macrolactone **26** in 52% yield. Finally, since the conversion of **26** into aspergillide B **2** has already been reported in the literature,[6a] the synthesis of **26** formally constitutes the synthesis of **2**. The spectroscopic data of **26** and the specific rotation value, $[\alpha]_D^{25} = -54.5$ (*c* 0.6, $CHCl_3$); Lit.[6a] $[\alpha]_D = -56.3$ (*c* 1.5, $CHCl_3$) are in good agreement with the data reported by Marco et al.[6a]

2.3. Formal total synthesis of aspergillide A 1

Aspergillide A **1** is the C3-epimer of aspergillide B **2**, which possesses a 2,3,6-trisubstituted tetrahydropyran with a *cis*-ring junction. The retrosynthetic analysis of **1** (Scheme 6) revealed that *bis*-olefin **27** could be a late stage intermediate, which, upon RCM reaction[19] would generate the macrolide ring structure. The *bis*-olefin **27** in turn could be realized by the esterification of acid **28** with alcohol **5**, while acid **28** could be obtained from pyran diol **29**.

The *cis*-2,3,6-trisubtituted tetrahydropyran moiety was envisaged to come from δ-hydroxy allylic alcohol **30** by tandem asymmetric epoxidation and stereo- and regioselective openings through a 6-*exo* cyclization under Sharpless asymmetric epoxidation conditions. The δ-hydroxy allylic alcohol **30** could be realized from olefin **18**, a synthetic intermediate of aspergillide B **2**, by inverting the C-3 stereocenter under Mitsunobu[21] reaction conditions.

2.4. Synthesis of macrolactone 1

The PMB ether **18** (Scheme 7) was treated with DDQ in aq CH_2Cl_2 to give the hydroxy olefin **31** (93%). The Mitsunobu[21] reaction of alcohol **31** upon treatment with *p*-nitrobenzoic acid, PPh_3 and DIAD in THF at room temperature afforded **32** (81%), which upon base mediated hydrolysis in the presence of K_2CO_3 in MeOH gave **33** in 84% yield. The reaction of alcohol **33** with PMBBr in the presence of NaH in THF furnished ether **34** in 86% yield.

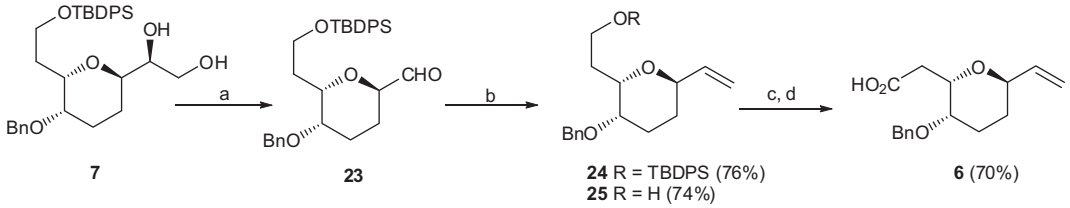
Olefin **34** was subjected to ozonolysis in CH_2Cl_2 and Wittig olefination of aldehyde **34a** with (methoxycarbonylmethylene)triphenylphosphorane in benzene at reflux gave the α,β-unsaturated ester **35** (87%). Reduction of the ester **35** with DIBAL-H in CH_2Cl_2 afforded the alcohol **36** (86%), which upon oxidative cleavage with DDQ in aq CH_2Cl_2 gave δ-hydroxy allylic alcohol **37** in 80% yield. Alcohol **37** underwent an SAE/6-*exo* cyclization under standard reaction conditions without adding an external acid to furnish tetrahydropyran diol **29** (83%), with epoxidation and concomitant opening of the epoxide.

Diol **29** upon oxidative cleavage with $NaIO_4$ in aq acetone gave aldehyde **38**, which upon Wittig olefination with (methylene)triphenylphosphonium iodide and *t*-BuOK in THF afforded olefin **39**

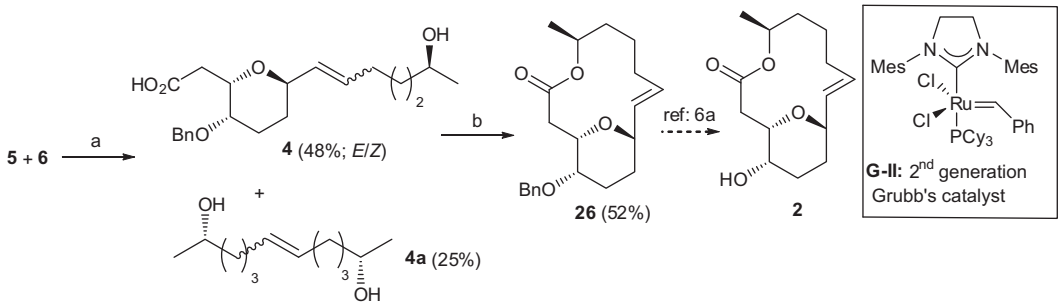
Table 1
Tandem SAE/6-*exo* cyclization

Entry	Reagents and conditions[a]	Time	Work-up	Yield (%)
1	(+)-DIPT (0.2 equiv), Ti(O*i*-Pr)$_4$ (0.1 equiv), TBHP (1.2 equiv), −20 °C	2 h at −20 °C then −10 °C for 48 h	1 g NaOH in 1 mL brine/1 g of **8**	15
2	(+)-DIPT (1.0 equiv), Ti(O*i*-Pr)$_4$ (1.0 equiv), TBHP (2.0 equiv), −20 °C	2 h at −20 °C then −10 °C for 12 h	1 g NaOH in 1 mL brine/1 g of **8**	55
3	(+)-DIPT (0.2 equiv), Ti(O*i*-Pr)$_4$ (0.1 equiv), CHP (1.5 equiv), −20 °C	1 h at −20 °C then −10 °C for 12 h	1 g NaOH in 1 mL brine/1 g of **8**	60
4	(+)-DIPT (1.2 equiv), Ti(O*i*-Pr)$_4$ (1.2 equiv), CHP (2.0 equiv), −20 °C	1 h at −20 °C then −10 °C for 5 h	1 g NaOH in 1 mL brine/1 g of 8	85
5	(+)-DIPT (1.2 equiv), Ti(O*i*-Pr)$_4$ (1.2 equiv), CHP (2.0 equiv), −20 °C	1 h at −20 °C then −10 °C for 5 h	Aq sat. Na_2SO_4	85
6	(+)-DIPT (1.2 equiv), Ti(O*i*-Pr)$_4$ (1.2 equiv), CHP (2.0 equiv), −20 °C	1 h at −20 °C then −10 °C for 5 h	4 M HCl, aq sat. Na_2SO_4	80

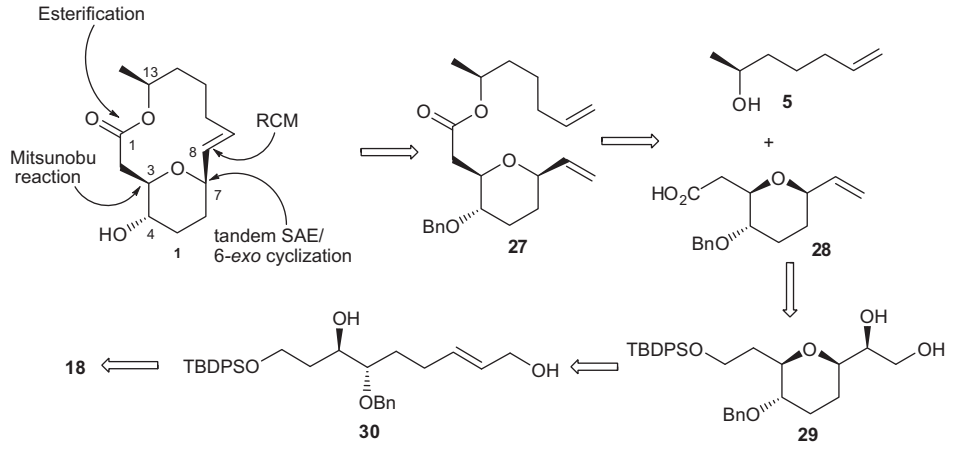
[a] All reactions were performed under pre-dried 4 Å molecular sieves in dry CH_2Cl_2.



Scheme 4. Reagents and conditions: (a) $NaIO_4$, acetone:H_2O (9:1), rt, 30 min; (b) PPh_3CH_3I, *t*-BuOK, dry THF, −10 °C to rt, 6 h; (c) TBAF, dry THF, rt, 1 h; (d) TEMPO, BIAB, H_2O:CH_2Cl_2, (1:1), 0 °C, 1 h.



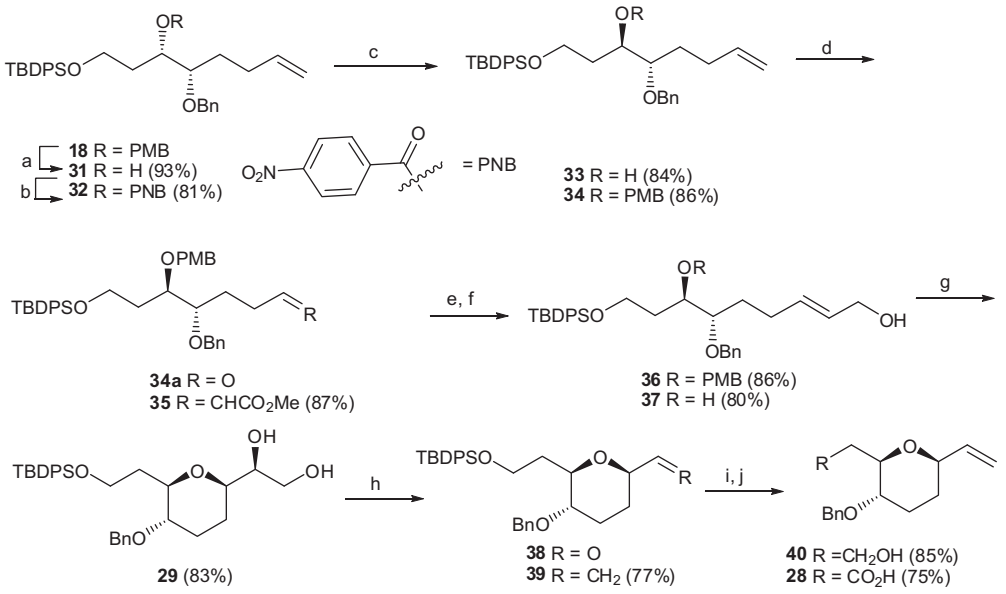
Scheme 5. Reagents and conditions: (a) **G-II**, CH_2Cl_2, reflux, 2 h; (b) (i) 2,4,6-trichlorobenzoyl chloride, Et_3N, 0 °C to rt, THF, 2 h; (ii) DMAP, dry toluene, 60 °C, 6 h.



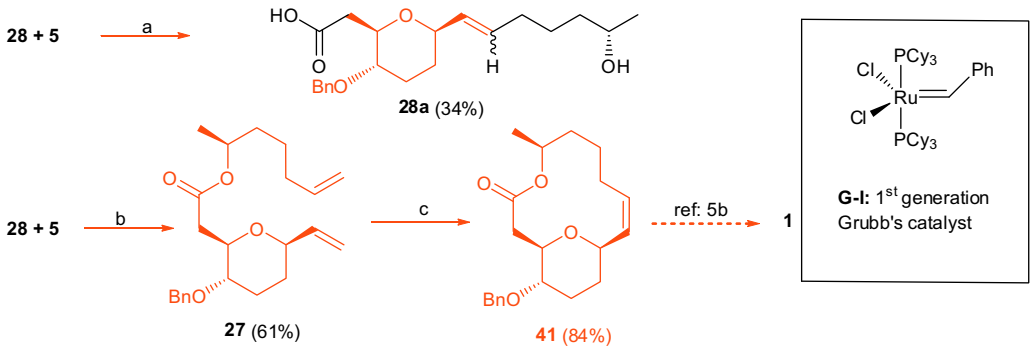
Scheme 6. Retrosynthetic analysis of aspergillide A (**1**).

(77%). Treatment of **39** with TBAF in THF at room temperature furnished alcohol **40** (85%), which upon subsequent oxidation with TEMPO and BIAB[17] in aq CH_2Cl_2 gave acid **28** in 75% yield.

In a further study on the synthesis of **1**, both fragments **28** and **5** (Scheme 8) were subjected to cross metathesis to give very low yield of the expected product. In order to increase the yield, instead of a cross metathesis/macrolactonization protocol, we decided to use an esterification/RCM protocol. Accordingly, esterification of acid **28** with alcohol **5** in the presence of EDCI and DMAP gave *bis*-olefin **27** in 61% yield.[22] The *bis*-olefin upon RCM in the presence of Grubbs first generation catalyst **G-I** gave macrolactone **41** in 84% yield. The observed ^1H, ^{13}C NMR and specific rotation data, $[\alpha]_D^{25} = +68.1$ (*c* 0.27, $CHCl_3$), Lit:[5b] $[\alpha]_D^{25} = +67.5$ (*c* 1.13, $CHCl_3$) for *Z*-olefin **41**, were in accordance with the reported data by Marco et al.[5b] Since, the conversion of **41** into **1** has already been reported, the synthesis of **41** constitutes the formal total synthesis of **1**.



Scheme 7. Reagents and conditions: (a) DDQ, CH_2Cl_2:H_2O (19:1), 0 °C to rt, 1 h; (b) *p*-NO_2PhCO_2H, PPh_3, DIAD, dry THF, 0 °C to rt, 2 h; (c) (i) K_2CO_3, MeOH, rt, 2 h; (ii) PMBBr, NaH, dry THF, 0 °C to rt, 5 h; (d) (i) O_3, CH_2Cl_2, dimethylsulphide, −78 °C, 15 min; (ii) Ph_3P=CHCOOMe, benzene, reflux, 2 h; (e) DIBALH, CH_2Cl_2, 0 °C, 1 h; (f) DDQ, CH_2Cl_2:H_2O (19:1), 0 °C to rt, 1 h; g) (+)-DIPT, Ti(*Oi*-Pr)$_4$, CHP, 4 Å MS, CH_2Cl_2, −20 °C, 5 h; (h) (i) $NaIO_4$, acetone:H_2O (5:1), rt, 30 min; (ii) PPh_3CH_3I, *t*-BuOK, dry THF, −10 °C to rt, 6 h; (i) TBAF, dry THF, rt, 1 h; (j) TEMPO, BIAB, CH_2Cl_2, 0 °C, 1 h.



Scheme 8. Reagents and conditions: (a) 20 mol % **G-II**, dry CH_2Cl_2, reflux, 6 h; (b) EDCI, DMAP, CH_2Cl_2, 0 °C to rt, 5 h; (c) 10 mol % **G-I**, dry CH_2Cl_2, reflux, 5 h.

3. Conclusion

In conclusion, the formal total synthesis of two tetrahydropyran (THP) 14-membered macrolides, aspergillides A **1** and B **2** has been achieved by a combination of a chiron approach and asymmetric synthesis. The THP ring construction was achieved via a tandem SAE/6-*exo* cyclization of the epoxide. Thus, 2,3,6-trisubstituted THP was very efficiently formed in a one pot procedure without adding an external acid catalyst in good yields.

4. Experimental

4.1. General methods

Solvents were dried over standard drying agents and freshly distilled prior to use. Chemicals were purchased and used without further purification. All column chromatography separations were performed using silica gel (Acme's 60–120 mesh). Organic solutions were dried over anhydrous Na_2SO_4 and concentrated below 40 °C in vacuo. ^{1}H NMR (200 MHz, 300 MHz, and 500 MHz) and ^{13}C NMR (50 MHz, 75 MHz and 100 MHz) spectra were measured with a Varian Gemini FT-200 MHz spectrometer, Bruker Avance 300 MHz, Varian Inova 400 MHz, and Varian Unity Inova-500 MHz with tetramethylsilane as an internal standard for solutions in deuteriochloroform. *J* values are given in hertz. IR spectra were recorded on Perkin–Elmer IR-683 spectrophotometer with NaCl optics. Optical rotations were measured with JASCO DIP 300 digital polarimeter at 25 °C. Mass spectra were recorded on CEC-21–11013 or Fannigan Mat 1210 double focusing mass spectrometers operating at a direct inlet system or LC/MSD Trap SL (Agilent Technologies).

4.1.1. (*S*)-1-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)but-3-en-1-ol 10

To a stirred solution of **9** (12.0 g, 83.33 mmol) in dry THF (60 mL), copper (I) iodide (7.93 g, 41.67 mmol) was added and cooled to −40 °C. A solution of vinylmagnesium bromide (2.0 N solution in THF; 83.33 mL, 166.66 mmol) was added dropwise. After 4 h, the reaction mixture was treated with aq NH_4Cl solution (30 mL) dropwise. It was then filtered through Celite and the filtrate was extracted with ethyl acetate (2 × 50 mL). The organic layers were dried (Na_2SO_4), evaporated under reduced pressure and the residue was purified by column chromatography (Silica gel, 60–120 mesh, 20% EtOAc in pet. ether) to afford **10** (12.0 g,

84%) as a colorless liquid. $[\alpha]_D^{25} = -11.2$ (*c* 1.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.83 (m, 1H, olefinic), 5.10 (m, 2H, olefinic), 3.97 (dd, 2H, *J* = 6.0, 6.8 Hz, $-OCH_2$), 3.72 (ddd, 1H, *J* = 1.5, 4.5, 11.3 Hz, $-OCH_2$), 3.54 (m, 1H, $-OCH_2$), 2.22 (dt, 2H, *J* = 1.5, 6.8 Hz, $-CH_2$=$CHCH_2$), 2.07 (d, 1H, *J* = 5.3 Hz, –OH), 1.41 (s, 3H, $-CMe_2$), 1.34 (s, 3H, $-CMe_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.0, 117.9, 78.4, 71.5, 65.9, 38.1, 26.5, 25.2; IR (neat): 3452, 3076, 2985, 2929, 1640, 1375, 1213, 854 cm^{-1}; ESIMS: $(M+Na)^+$ 195.

4.1.2. (*S*)-4-((*S*)-1-(4-Methoxybenzyloxy)but-3-enyl)-2,2-dimethyl-1,3-dioxolane 11

A cooled (0 °C) solution of **10** (12.0 g, 69.77 mmol) in dry THF (120 mL), was treated with NaH 60% in wax (6.98 g, 174.42 mmol) and stirred for 30 min. A solution of PMBBr (16.74 g, 83.72 mmol) [prepared from *p*-methoxybenzyl alcohol (12.0 g, 86.96 mmol) and PBr_3 (4.09 mL, 43.48 mmol) in ether] in dry THF (40 mL) was added dropwise and stirred at room temperature for 6 h. The reaction mixture was treated with aq NH_4Cl solution (20 mL) and extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with water (2 × 30 mL), brine (50 mL) and dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the residue purified by column chromatography (silica gel, 60–120 mesh, 15% EtOAc in pet. ether) to furnish **11** (15.4 g, 75%) as a yellow liquid. $[\alpha]_D^{25} = -26.9$ (*c* 3.75, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 7.20 (d, 2H, *J* = 8.3 Hz, ArH-PMB), 6.81 (d, 2H, *J* = 8.3 Hz, ArH-PMB), 5.81 (dddd, 1H, *J* = 6.8, 9.8, 13.6, 16.2 Hz, olefinic), 5.10–5.01 (m, 2H, olefinic), 4.58 (d, 1H, *J* = 11.3 Hz, benzylic), 4.56 (d, 1H, *J* = 11.3 Hz, benzylic), 4.12 (q, 1H, *J* = 6.0 Hz, –OCH), 3.91 (dd, 1H, *J* = 6.8, 8.3 Hz, –OCH), 3.79 (s, 3H, $-OCH_3$), 3.65 (m, 1H, –OCH), 3.44 (m, 1H, –OCH), 2.19 (m, 2H, $-CH_2$), 1.40 (s, 3H, $-CH_3$), 1.33 (s, 3H, $-CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.0, 134.5, 130.6, 129.3, 117.1, 113.7, 109.2, 78.7, 77.8, 72.1, 71.3, 65.7, 55.1, 35.2, 26.4, 25.3; IR (neat): 3072, 2985, 2935, 1611, 1513, 1248, 1071 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{24}O_4Na$ $[M+Na]^+$ 315.1572; found 315.1573.

4.1.3. (*S*)-3-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-3-(4-methoxybenzyloxy)-propan-1-ol 12

A solution of **11** (15.0 g, 51.37 mmol) in CH_2Cl_2 (100 mL) was cooled to −78 °C and then bubbled with ozone gas for 15 min and quenched with $(CH_3)_2S$ (50 mL). The solvent was evaporated to give aldehyde **11a**, which was used for further reaction.

To a solution of the above aldehyde **11a** (14.1 g, 43.25 mmol) in MeOH (70 mL), $NaBH_4$ (0.5 g, 12.75 mmol) was added at 0 °C and stirred at room temperature for 1 h. Next, MeOH was evaporated under reduced pressure, the residue was diluted with water (50 mL) and extracted with ethyl acetate (2 × 50 mL). The organic layers were washed with brine (10 mL), dried (Na_2SO_4), evaporated and the residue purified by column chromatography (silica gel, 60–120 mesh, 20% EtOAc in pet. ether) to afford **12** (10.5 g, 74%) as a colorless liquid. $[\alpha]_D^{25} = -119.4$ (*c* 0.69, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.22 (d, 2H, *J* = 8.5 Hz, ArH-PMB), 6.82 (d, 2H, *J* = 8.5 Hz, ArH-PMB), 4.67 (d, 2H, *J* = 11.3 Hz, benzylic), 4.54 (d, 1H, *J* = 11.3 Hz, benzylic), 4.18 (dd, 1H, *J* = 6.6, 13.8 Hz, –OCH), 3.94 (dd, 1H, *J* = 6.6, 8.3 Hz, –OCH), 3.79 (s, 3H, $-OCH_3$), 3.63 (m, 4H, 2× $-OCH_2$), 2.03 (br s, 1H, –OH), 1.60 (m, 2H, $-CH_2$), 1.42 (s, 3 H, $-CH_3$), 1.36 (s, 3H, $-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.3, 130.4, 129.7, 113.8, 109.4, 78.4, 77.5, 72.5, 65.9, 59.7, 55.1, 33.0, 26.5, 25.5; IR (neat): 3431, 2985, 2934, 1611, 1512, 1374, 1246, 1037, 846, 819 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{24}O_5Na$ $[M+Na]^+$ 319.1521; found 319.1512.

4.1.4. *tert*-Butyl ((*S*)-3-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-(4-methoxybenzyloxy)pro- poxy) diphenyl silane 13

To a stirred solution of **12** (9.4 g, 31.76 mmol) in CH_2Cl_2 (100 mL), imidazole (5.40 g, 79.4 mmol) and TBDPSCl (10.48 g, 38.11 mmol) were added at 0 °C and stirred at room temperature for 2 h. The solvent was evaporated and the residue purified by column chromatography (silica gel, 60–120 mesh, 5% EtOAc in pet. ether) to give **13** (15.5 g, 91%) as a colorless oil. $[\alpha]_D^{25} = -33.3$ (*c* 0.64, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.60 (m, 4H, ArH-TBDPS), 7.42–7.29 (m, 6H, ArH-TBDPS), 7.12 (d, 2H, *J* = 8.7 Hz, ArH-PMB), 6.74 (d, 2H, *J* = 8.7 Hz, ArH-PMB), 4.61 (dd, 1H, *J* = 11.3 Hz, benzylic), 4.44 (d, 1H, *J* = 11.3 Hz, benzylic), 4.15 (dd, 1H, *J* = 6.8, 13.6 Hz, –OCH), 3.89 (dd, 1H, *J* = 6.8, 8.3 Hz, –OCH), 3.77 (s, 3H, $-OCH_3$), 3.80–3.70 (m, 4H, $-OCH_2$), 3.68–3.54 (m, 2H, $-OCH_2$), 1.58 (m, 2H, $-CH_2$), 1.40 (s, 3H, $-CH_3$), 1.33 (s, 3H, CH_3), 1.04 (s, 9H, *t*-butyl); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.2, 135.6, 133.8, 129.7, 129.5, 127.7, 113.7, 109.3, 96.2, 78.5, 76.3, 72.7, 66.0, 60.1, 55.1, 33.9, 26.9, 25.6, 19.3; IR (neat): 3455, 3069, 2931, 2858, 1612, 1512, 1427, 1373, 1246, 1104, 1076, 701 cm^{-1}; HRMS (ESI): calcd. for $C_{32}H_{42}O_5NaSi$ $[M+Na]^+$ 557.2699; found 557.2707.

4.1.5. (2*S*,3*S*)-5-(*tert*-Butyldiphenylsilyloxy)-3-(4-methoxybenzyloxy)pentane-1,2-diol 14

To a stirred solution of **13** (15.2 g, 28.43 mmol) in acetonitrile (75 mL) at 0 °C, $CuCl_2{\cdot}2H_2O$ (5.82 g. 34.12 mmol) was added and stirred at room temperature for 45 min. It was then neutralized with aq $NaHCO_3$ (20 mL) and the resulting greenish mixture was filtered through Celite. The filtrate was extracted with ethyl acetate (2 × 50 mL) and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue by column chromatography (silica gel, 60–120 mesh, 40% EtOAc in pet. ether) afforded **14** (12.01 g, 85%) as a colorless oil. $[\alpha]_D^{25} = +31.3$ (*c* 4.4, $CHCl_3$); IR (neat): 3450, 3069, 2932, 2859, 1612, 1513, 1465, 1247, 1079, 936, 701 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.62 (m, 4H, ArH-TBDPS), 7.38 (m, 6H, ArH-TBDPS), 7.12 (d, 2H, *J* = 8.7 Hz, ArH-PMB), 6.78 (d, 2H, *J* = 8.7 Hz, ArH-PMB), 4.52 (d, 1H, *J* = 11.0 Hz, benzylic), 4.33 (d, 1H, *J* = 11.0 Hz, benzylic), 3.78 (s, 3H, $-OCH_3$), 3.75 (d, *J* = 6.0 Hz, 2H, $-OCH_2$), 3.70–3.64 (m, 1H, –OCH), 3.63–3.50 (m, 3H, –OCH), 2.60 (br s, 2H, –OH), 1.83 (m, 2H, $-CH_2$), 1.05 (s, 9H, *t*-butyl); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.3, 135.5, 133.3, 130.0, 129.7, 129.6, 127.7, 113.8, 76.6, 73.0, 72.0, 64.0, 60.1, 55.2, 33.2, 26.8, 19.1; HRMS (ESI): calcd. for $C_{29}H_{38}O_5NaSi$ $[M+Na]^+$ 517.2386; found 517.2392.

4.1.6. (2*S*,3*S*)-5-(*tert*-Butyldiphenylsilyloxy)-2-hydroxy-3-(4-methoxybenzyloxy)pentyl 4-methoxy benzenesulfonate 15

To a stirred solution of **14** (12.0 g, 24.26 mmol) in CH_2Cl_2 (120 mL), Et_3N (6.57 mL, 48.52 mmol) and Bu_2SnO (94.0 mg, 0.49 mmol) were added. After 5 min, *p*-TsCl (5.12 g, 26.69 mmol) was added and stirred for 30 min. The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with water (2 × 50 mL), brine (50 mL) and dried (Na_2SO_4). The organic layer was evaporated under reduced pressure and the residue purifed by column chromatography (60–120 silica gel, 10% EtOAc in pet. ether) to give **15** (14.2 g, 90%) as a colorless liquid. ^1H NMR (300 MHz, $CDCl_3$): δ 7.78 (d, 4H, *J* = 8.3 Hz, ArH-tosyl), 7.62 (m, 4H, ArH-TBDPS), 7.43–7.28 (m, 6H, ArH-TBDPS), 7.10 (d, 2H, *J* = 8.7 Hz, ArH-PMB), 6.76 (d, 2H, *J* = 8.7 Hz, ArH-PMB), 4.45 (d, 1H, *J* = 11.0 Hz, benzylic), 4.29 (d, 1H, *J* = 11.0 Hz, benzylic), 3.96 (dd, 1H, *J* = 1.9, 5.7 Hz, –OCH), 3.80 (s, 3H, $-CH_3$), 3.80–3.69 (m, 3H, –OCH), 3.03 (br s, 1H, –OH), 2.50–2.40 (m, 2H, $-CH_2OTBDPS$), 2.44 (s, 3H, $-CH_3$), 1.78 (m, 2H, $-CH_2$), 1.04 (s, 9H, *t*-butyl); IR (neat): 3447, 2930, 2858, 1739, 1610, 1513, 1362, 1178, 1035, 819, 703 cm^{-1}; HRMS (ESI) calcd. for $C_{36}H_{44}O_7NaSiS$ $[M+Na]^+$ 671.2474; found 671.2469.

4.1.7. *tert*-Butyl ((*S*)-3-(4-methoxybenzyloxy)-3-((*S*)-oxiran-2-yl)propoxy)diphenylsilane 16

A solution of tosylate **15** (14.0 g, 21.53 mmol) in MeOH (70 mL) was treated with K_2CO_3 (7.42 g, 53.82 mmol) and stirred at room

temperature for 1 h. The reaction mixture was treated further with aq NH_4Cl solution (20 mL). Next, MeOH was evaporated under reduced pressure and the residue was extracted with solvent ether (3 × 75 mL). The organic layer was washed with water (75 mL), brine (75 mL), dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography (silica gel, 60–120 mesh, 10% EtOAc in pet. ether) to furnish **16** (7.52 g, 73%) as a colorless liquid. $[\alpha]_D^{25} = -23.2$ (*c* 3.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 (dd, 4H, *J* = 1.3, 7.7 Hz, ArH-TBDPS), 7.41–7.28 (m, 6H, ArH-TBDPS), 7.17 (d, 2H, *J* = 8.5 Hz, ArH-PMB), 6.76 (d, 2H, *J* = 8.5 Hz, ArH-PMB), 4.74 (d, 1H, *J* = 11.3 Hz, benzylic), 4.46 (d, 1H, *J* = 11.3 Hz, benzylic), 3.77 (s, 3H, $-OCH_3$), 3.80–3.64 (m, 2H, $-OCH_2$), 3.26 (td, 1H, *J* = 4.3, 9.3 Hz, –OCH), 2.98 (m, 1H, epoxy), 2.69 (t, 1H, *J* = 7.4 Hz, 1H, epoxy), 2.40 (dd, 1H, *J* = 2.6, 4.9 Hz, epoxy), 1.75 (m, 2H, $-CH_2$), 1.01 (s, 9H, *t*-butyl); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.0, 135.5, 133.7, 130.7, 129.6, 129.6, 129.3, 127.6, 113.7, 77.1, 71.6, 59.8, 55.1, 43.1, 35.2, 26.8, 19.1; IR (neat): 3451, 3068, 2932, 2858, 1735, 1612, 1512, 1464, 1247, 1106, 1036, 821, 703 cm^{-1}; HRMS *m/z* (M+Na)$^+$calculated for $C_{29}H_{36}O_4NaSi$ 499.2280, found 499.2259.

4.1.8. (3*S*,4*S*)-1-(*tert*-Butyldiphenylsilyloxy)-3-(4-methoxybenzyloxy)oct-7-en-4-ol 17

To a stirred solution of epoxide **16** (7.5 g, 15.76 mmol) in dry diethyl ether (100 mL), copper (I) iodide (1.50 g, 7.88 mmol) was added and the mixture was cooled to -40 °C. A solution of allylmagnesium chloride in ether (generated from Mg 1.13 g, 47.28 mmol and allyl chloride 3.87 mL, 47.28 mmol in 50 mL ether) was added. After 2 h, it was worked up as described for **10** and purified by column chromatography (silica gel, 60–120 mesh, 12% EtOAc in pet. ether) to afford **17** (7.41 g, 90%) as a colorless liquid. $[\alpha]_D^{25} = +8.4$ (*c* 3.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 (br m, 4H, ArH-TBDPS), 7.44–7.31 (br m, 6H, ArH-TBDPS), 7.12 (d, 2H, *J* = 8.7 Hz, ArH-PMB), 6.77 (d, 2H, *J* = 8.7 Hz, ArH-PMB), 5.76 (m, 1H, olefinic), 4.95 (m, 2H, olefinic), 4.49 (d, 1H, *J* = 11.0 Hz, benzylic), 4.36 (d, 1H, *J* = 11.0 Hz, benzylic), 3.78 (s, 3H, $-OCH_3$), 3.78–3.70 (m, 2H, $-OCH_2$), 3.46 (m, 2H, $-OCH_2$), 2.28–2.03 (m, 2H, $-CH_2$allylic), 1.89–1.67 (m, 2H, $-CH_2$), 1.52–1.37 (m, 2H, $-CH_2$), 1.05 (s, 9H, *t*-butyl); ^{13}C NMR^{13}C NMR (75 MHz, $CDCl_3$): δ 159.2, 138.5,135.5, 133.5, 130.4, 129.7, 129.5, 127.7, 114.7, 113.8, 78.9, 72.4, 60.3, 55.2, 33.6, 32.6, 30.0, 26.8, 19.1; IR (neat): 3450, 3070, 2932, 2858, 1611, 1513, 1427, 1248, 1107, 1083, 703 cm^{-1}; HRMS *m/z* (M+Na)$^+$calculated for $C_{32}H_{42}O_4NaSi$: 541.2750, found: 541.2736.

4.1.9. ((3*S*,4*S*)-4-(Benzyloxy)-3-(4-methoxybenzyloxy)oct-7-enyloxy)(*tert*-butyl) diphenylsilane 18

To a cooled (0 °C) solution of **17** (7.40 g, 14.29 mmol) in dry THF (45 mL), 60% NaH in paraffin wax (1.43 g, 35.72 mmol) was added and stirred for 30 min. The reaction mixture was treated with a solution of BnBr (2.05 mL, 17.15 mmol) in dry THF (40 mL), and stirred at room temperature for 5 h. It was then worked up as described for **11** and purified by column chromatography (silica gel, 60–120 mesh, 6% EtOAc in pet. ether) to furnish **18** (7.7 g, 89%) as a colorless oil. $[\alpha]_D^{25} = -39.9$ (*c* 1.65, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (m, 4H, ArH-TBDPS), 7.40–7.18 (m, 11H, ArH-TBDPS+Bn), 7.09 (d, 2H, *J* = 8.3 Hz, ArH-PMB), 6.74 (d, 2H, *J* = 8.3 Hz, ArH-PMB), 5.72 (m, 1H, olefinic), 4.93 (m, 2H, olefinic), 4.57 (d, 1H, *J* = 11.5 Hz, benzylic), 4.57–4.45 (m, 2H, benzylic), 4.40 (d, 1H, *J* = 11.5 Hz, benzylic), 3.84 (s, 3H, $-OCH_3$), 3.77 (s, 3H, $-OCH_3$), 3.73 (m, 2H, $-OCH_2$), 3.45 (m, 1H, –OCH), 2.07–1.80 (m, 2H, $-CH_2$), 1.74–1.45 (m, 2H, $-CH_2$), 1.37–1.21 (m, 2H, $-CH_2$), 1.05 (s, 9H, *t*-butyl); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.2, 138.8, 138.7, 135.6, 133.9, 131.0, 129.6, 129.4, 128.3, 128.3, 127.9, 127.7, 127.5, 114.8, 113.7, 96.2, 78.8, 75.5, 72.4, 72.3, 60.5, 55.1, 32.9, 30.2, 29.0, 27.1, 19.4; IR (neat): 3450, 3069, 2931, 2858, 1613, 1512, 1247, 1105, 1083, 765, 701 cm^{-1}; HRMS *m/z* calculated for $C_{39}H_{48}O_4NaSi$ (M+Na)$^+$ 631.3219, found 631.3240.

4.1.10. (6*S*,7*S*,*E*)-Methyl 6-(benzyloxy)-9-(*tert*-butyldiphenylsilyloxy)-7-(4-methoxybenzy- loxy)non-2-enoate 20

A solution of **18** (3.0 g, 4.93 mmol) in CH_2Cl_2 (30 mL) was cooled to −78 °C and bubbled with ozone gas for 15 min and treated with $(CH_3)_2S$ (5 mL). The solvent was evaporated to give aldehyde **19** as a colorless liquid, which was used for further reaction.

Aldehyde **19** (2.9 g, 4.76 mmol) was dissolved in benzene (30 mL) and treated with (methoxycarbonylmethylene)triphenylphosphorane (1.96 g, 5.72 mmol) at reflux. After 2 h, the solvent was evaporated and the residue was purified by column chromatography (silica gel, 60–120 mesh, 5% EtOAc in pet. ether) to furnish **20** (2.61 g, 82%) as a colorless oil. $[\alpha]_D^{25} = -55.1$ (*c* 3.75, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (m, 4H, ArH-TBDPS), 7.40–7.16 (m, 11H, ArH-TBDPS+Bn), 7.11 (d, 2H, *J* = 8.7 Hz, ArH-PMB), 6.87 (dt, 1H, *J* = 6.8, 15.7 Hz, olefinic), 6.77 (d, 2H, *J* = 8.7 Hz, ArH-PMB), 5.69 (d, 1H, *J* = 15.7 Hz, olefinic), 4.57 (d, 1H, *J* = 11.5 Hz, benzylic), 4.42 (br s, 2H, benzylic), 4.36 (d, 1H, *J* = 11.5 Hz, benzylic), 3.85 (m, 1H, –OCH), 3.78 (s, 3H, $-OCH_3$), 3.77–3.67 (m, 2H, $-OCH_2$), 3.70 (s, 3H, $-OCH_3$), 3.38 (m, 1H, –OCH), 2.37–2.03 (m, 2H, $-CH_2$), 1.93–1.62 (m, 2H, $-CH_2$), 1.53 (m, 2H, $-CH_2$), 1.05 (s, 9H, *t*-butyl); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.0, 159.1, 149.4, 138.3, 135.4, 133.8, 133.6, 130.7, 129.5, 129.4, 128.3, 127.9, 127.6, 120.9, 113.7, 78.6, 75.1, 72.5, 72.2, 60.3, 55.2, 51.3, 32.6, 28.6, 28.0, 26.8, 19.1; IR (neat): 3428, 3431, 2949, 2859, 1722, 1655, 1612, 1512, 1432, 12349, 1104, 821, 702 cm^{-1}; HRMS *m/z* calculated for $C_{41}H_{50}O_6NaSi$ (M+Na)$^+$ 689.3274, found 689.3299.

4.1.11. (6*S*,7*S*,*E*)-6-(Benzyloxy)-9-(*tert*-butyldiphenylsilyloxy)-7-(4-methoxybenzyloxy)non-2-en-1-ol 21

To a solution of **20** (2.51 g, 3.77 mmol) in CH_2Cl_2 (15 mL), DIBAL-H (1.0 M solution in hexanes, 7.54 mL, 7.54 mmol) was added at 0 °C. The resultant solution was stirred at 0 °C for 1 h and treated with MeOH (5 mL). The reaction mixture was diluted with EtOAc (20 mL), followed by aq potassium sodium tartrate (5 mL) and stirred vigorously at room temperature for an additional 1 h. It was then filtered through Celite, after which the filtrate was dried (Na_2SO_4), evaporated and the residue purified by column chromatography (silica gel, 60–120 mesh, 15% EtOAc in pet. ether) to give **21** (2.06 g, 84%) as a colorless oil. $[\alpha]_D^{25} = -41.3$ (*c* 3.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (m, 4H, ArH-TBDPS), 7.40–7.27 (m, 6H, ArH-TBDPS), 7.27–7.20 (m, 5H, ArH-Bn), 7.09 (d, 2H, *J* = 8.4 Hz, ArH-PMB), 6.78 (d, 2H, *J* = 8.7 Hz, ArH-PMB), 5.62–5.46 (m, 2H, olefinic), 4.56 (d, 1H, *J* = 11.7 Hz, benzylic), 4.47–4.38 (m, 3H, benzylic), 3.97 (d, 2H, *J* = 4.5 Hz, $-CH_2$allylic), 3.87–3.79 (m, 1H, –CHOPMB), 3.79–3.68 (m, 2H, $-CH_2$OTBDPS), 3.76 (s, 3H, $-OCH_3$), 3.41 (m, 1H, –CHOBn), 2.22–2.11 (m, 1H, $-CH_2$), 2.05–1.82 (m, 2H, $-CH_2$), 1.70–1.35 (m, 3H, $-CH_2$), 1.05 (s, 9H, *t*-butyl); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.2, 138.6, 135.5, 133,8, 133.8, 132.6, 130.9, 129.6, 129.4, 128.3, 127.9, 127.6, 127.5, 113.7, 78.8, 75.4, 72.4, 72.2, 63.6, 60.4, 55.5, 32.8, 29.1, 28.6, 26.9, 19.3; IR (neat): 3448, 3067, 2929, 2857, 1611, 1511, 1245, 1081, 699 cm^{-1}; HRMS *m/z* calculated for $C_{40}H_{50}O_5NaSi$ (M+Na)$^+$ 661.3325, found 661.3357.

4.1.12. (*R*)-1-((2*R*,5*R*)-5-((*S*)-3-(*tert*-Butyldiphenylsilyloxy)-1-(4-methoxybenzyloxy)propyl) tetrahydrofuran-2-yl)ethane-1,2-diol 22

To a slurry of 4 Å molecular sieves powder (1.50 g) in CH_2Cl_2 (10 mL), (+)-DIPT (0.22 g, 0.94 mmol) was added and cooled to −20 °C. Next, Ti(O*i*-Pr)$_4$ (0.22 mL, 0.78 mmol) was added and stirred at −20 °C for 30 min. To this mixture, cumene hydroperoxide (0.22 mL, 1.56 mmol) was added and stirred at the same

temperature for 30 min. A solution of **21** (0.50 g, 0.78 mmol) in CH_2Cl_2 (2 mL) was added to the reaction mixture and stirred at −20 °C for 1 h. The reaction mixture was stored at −10 °C for 8 h and treated with NaOH in brine (1 g in 1 mL brine/1 g of **21**) solution. It was then allowed to warm to room temperature with vigorous stirring for 3 h, diluted with ethyl acetate (10 mL) and filtered through Celite. The filtrate was extracted with EtOAc (3 × 15 mL) and the combined organic layers were washed with brine (15 mL), dried (Na_2SO_4) and evaporated under reduced pressure. Purification of the residue by column chromatography (silica gel, 60–120 mesh, 30% EtOAc in pet. ether) gave diol **22** (0.35 g, 80%) as a colorless oil. $[\alpha]_D^{25} = -3.8$ (*c* 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 (d, 4H, *J* = 6.8 Hz, ArH-TBDPS), 7.41–7.31 (m, 6H, ArH-TBDPS), 7.13 (d, 2H, *J* = 8.3 Hz, ArH-PMB), 6.76 (d, 2H, *J* = 8.3 Hz, ArH-PMB), 4.52 (d, 1H, *J* = 11.0 Hz, benzylic), 4.42 (d, 1H, *J* = 11.0 Hz, benzylic), 3.94–3.82 (m, 2H, –OCH_2), 3.78 (s, 3H, –OCH_3), 3.81–3.69 (m, 2H, –OCH_2), 3.58–3.46 (m, 3H, –OCH), 3.21 (m, 1H, –OCH), 2.12 (br, 1H, –OH), 1.94–1.67 (m, 6H, 3 × –CH_2), 1.05 (s, 9H, *t*-butyl); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.1, 135.5, 133.6, 130.1, 129.7, 129.6, 127.6, 113.7, 80.8, 80.6, 77.4, 73.4, 72.3, 63.6, 60.3, 55.1, 34.2, 28.0, 26.8, 26.1, 19.1; IR (neat): 3759, 3421, 3068, 2931, 2858, 1612, 1512, 1247, 1105, 1078, 702 cm^{-1}; HRMS *m/z* calculated for $C_{33}H_{44}O_6NaSi$ (M+Na)$^+$ 587.2804, found 587.2830.

4.1.13. (6*S*,7*S*,*E*)-6-(Benzyloxy)-9-(*tert*-butyldiphenylsilyloxy) non-2-ene-1,7-diol 8

To a solution of **21** (1.7 g, 2.66 mmol) in H_2O:CH_2Cl_2 (20 mL, 1:19), DDQ (0.72 g, 3.19 mmol) was added and stirred at room temperature for 1 h. The reaction mixture was treated with aq $NaHCO_3$ (5 mL), filtered and washed with CH_2Cl_2 (20 mL). The filtrate was washed with water (10 mL), brine (10 mL), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, 60–120 mesh, 30% EtOAc in pet. ether) to furnish **8** (1.21 g, 88%) as a colorless oil. $[\alpha]_D^{25} = -11.3$ (*c* 1.35, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (d, 4H, *J* = 7.0 Hz, ArH-TBDPS), 7.43–7.22 (m, 11H, ArH-TBDPS+Bn), 5.71–5.53 (m, 2H, olefinic), 4.57 (d, 1H, *J* = 11.7 Hz, benzylic), 4.54 (d, 1H, *J* = 11.7 Hz, benzylic), 4.03 (d, 2H, *J* = 4.5 Hz, –CH_2Oallylic), 3.94–3.74 (m, 3H, –OCH+–OCH_2), 3.79–3.68 (m, 2H, –CH_2OTBDPS), 3.76 (s, 3H, –OCH_3), 3.41 (m, 1H, –CHOBn), 3.32 (dt, *J* = 4.3, 7.4 Hz, 1H, –OCH), 2.75 (br s, 1H, –OH), 2.14 (td, 2H, *J* = 5.9, 14.5 Hz, –CH_2allylic), 1.82–1.50 (m, 4H, 2 × –CH_2), 1.05 (s, 9H, *t*-butyl); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.5, 135.6, 132.4, 129.8, 129.6, 128.4, 127.8, 127.8, 127.7, 96.2, 81.2, 72.4, 70.9, 63.6, 62.5, 34.7, 29.2, 28.2, 27.0, 19.2; IR (neat): 3421, 3067, 2928, 2857, 1656, 1460, 1421, 1105, 1002, 701 cm^{-1}; HRMS *m/z* calculated for $C_{32}H_{42}O_4NaSi$ (M+Na)$^+$ 541.2750, found 541.2727.

4.1.14. (*R*)-1-((2*R*,5*S*,6*S*)-5-(Benzyloxy)-6-(2-(*tert*-butyldiphenylsilyloxy)ethyl)-tetrahydro-2*H*-pyran-2-yl)ethane-1,2-diol 7

To a slurry of 4 Å molecular sieves powder (2.0 g) in CH_2Cl_2 (10 mL), (+)-DIPT (0.10 g, 0.43 mmol) was added and cooled to −20 °C. Next, Ti(O*i*-Pr)$_4$ (0.06 mL, 0.22 mmol) and cumene hydroperoxide (0.58 mL, 4.16 mmol) were added with an interval of 30 min. A solution of allylic alcohol **8** (1.12 g, 2.16 mmol) in CH_2Cl_2 was added and stirred at −20 °C for 1 h. The reaction mixture was then stored at -10 °C for 5 h. Work up as described for **22** and purification of the residue by column chromatography (silica gel, 60–120 mesh, 30% EtOAc in pet. ether) afforded diol **7** (0.98 g, 85%) as a colorless oil. $[\alpha]_D^{25} = -63.7$ (*c* 2.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (m, 4H, ArH-TBDPS), 7.43–7.33 (m, 6H, ArH-TBDPS), 7.33–7.22 (br m, 5H, ArH-Bn), 4.50 (m, 2H, benzylic), 4.29 (dt, 1H, *J* = 4.9, 14.4 Hz, –OCHpyran), 3.73 (m, 2H, –OCH), 3.56 (m, 1H, –OCH), 3.49–3.33 (br m, 4H, –OCH), 2.15 (br, 2H, –OH), 1.94–1.81 (m, 4H, 2 × –CH_2), 1.79–1.52 (m, 2H, –CH_2), 1.05 (s, 9H, *t*-butyl); ^{13}C NMR (50 MHz, $CDCl_3$): δ 135.6, 133.8, 129.6, 128.4, 127.7, 127.6, 127.5, 74.4, 72.8, 70.7, 70.4, 70.3, 63.5, 60.1, 27.2, 26.9, 25.6, 24.0, 19.2; IR (neat): 3422, 3067, 2932, 2859, 1631, 1428, 1105, 702 cm^{-1}; HRMS *m/z* calculated for $C_{32}H_{42}O_5NaSi$ (M+Na)$^+$ 557.2699, found 557.2672.

4.1.15. (2-((2*S*,3*S*,6*R*)-3-(Benzyloxy)-6-vinyl-tetrahydro-2*H*-pyran-2-yl)ethoxy) (*tert*-butyl) diphenylsilane 24

To a cooled (0 °C) solution of **7** (0.95 g, 1.78 mmol) in H_2O:acetone (1:9, 10 mL), $NaIO_4$ (0.46 g, 2.14 mmol) was added and stirred at room temperature for 30 min. Acetone was removed under reduced pressure below 30 °C and the residue extracted with CH_2Cl_2 (2 × 20 mL). The organic layer was washed with water (20 mL), brine (20 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give aldehyde **23** in quantitative yield.

To a solution of (methyl)triphenylphosphonium iodide (2.50 g, 6.20 mmol) in dry THF (30 mL), potassium *tert*-butoxide (0.50 g, 4.43 mmol) was added at -5 °C and stirred for 6 h below 0 °C. A solution of aldehyde **23** (0.89 g, 1.77 mmol) in dry THF (10 mL) was added to the reaction mixture and stirred at room temperature for 2 h. It was then treated with saturated aq NH_4Cl (15 mL) and extracted with EtOAc (3 × 20 mL). The organic layers were washed with water (25 mL), brine (25 mL) and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue by column chromatography (silica gel, 60–120 mesh, 5% EtOAc in pet. ether) furnished olefin **24** (0.68 g, 76%) as a colorless gummy oil. $[\alpha]_D^{25} = -45.75$ (*c* 1.10, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (m, 4H, ArH-TBDPS), 7.38–7.28 (m, 6H, ArH-TBDPS), 7.28–7.23 (m, 5H, ArH-Bn), 5.76 (ddd, 1H, *J* = 4.9, 10.8, 15.7 Hz, olefinic), 5.11 (dd, 2H, *J* = 10.8, 17.7 Hz, olefinic), 4.53 (d, 1H, *J* = 11.8 Hz, benzylic), 4.44 (d, 1H, *J* = 11.8 Hz, benzylic), 4.16 (m, 1H, –CHOpyran), 4.07 (m, 1H, –CHOpyran), 3.81 (td, 1H, *J* = 5.4, 8.8 Hz, –OCH_2), 3.69 (td, 1H, *J* = 5.4, 10.8 Hz, –OCH), 3.44 (m, 1H, –OCH), 2.01–1.88 (m, 2H, –CH_2), 1.81–1.68 (m, 3H, –CH_2 and –CH_2'), 1.47–1.38 (m, 1H, –CH_2), 1.04 (s, 9H, *t*-butyl); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.6, 135.7, 134.1, 133.9, 129.6, 128.3, 127.7, 127.6, 127.5, 115.4, 74.1, 70.6, 70.3, 69.9, 60.4, 30.2, 29.8, 27.1, 23.8, 19.4; IR (neat): 3449, 2926, 2856, 1637, 1463, 1213, 1107, 762 cm^{-1}; HRMS *m/z* calculated for $C_{32}H_{40}O_3NaSi$ (M+Na)$^+$ 523.2644, found 523.2656.

4.1.16. 2-((2*S*,3*S*,6*R*)-3-(Benzyloxy)-6-vinyl-tetrahydro-2*H*-pyran-2-yl)ethanol 25

To a cooled (0 °C) solution of **24** (0.66 g, 1.32 mmol) in dry THF (5 mL) under a nitrogen atmosphere, a 1.0 M solution of TBAF in THF (1.58 mL, 1.58 mmol) was added and stirred for 1 h. It was then diluted with water (5 mL) and extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with water (2 × 10 mL), brine (10 mL) and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue by column chromatography (silica gel, 60–120 mesh, 20% EtOAc in pet. ether) afforded **25** (0.25 g, 74%) as a colorless liquid. $[\alpha]_D^{25} = -39.8$ (*c* 0.55, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37–7.24 (m, 5H, ArH-Bn), 5.81 (ddd, 1H, *J* = 6.4, 10.6, 17.0 Hz, olefinic), 5.12 (dd, 2H, *J* = 10.6, 17.4 Hz, olefinic), 4.61 (d, 1H, *J* = 11.3 Hz, benzylic), 4.45 (d, 1H, *J* = 11.3 Hz, benzylic), 4.27 (dt, 1H, *J* = 5.3, 6.8 Hz, –CHOpyran), 4.04 (dt, 1H, *J* = 3.8, 7.6 Hz, –CHOpyran), 3.75 (t, 2H, *J* = 5.3 Hz, –OCH_2), 3.48–3.43 (dt, 1H, *J* = 3.8, 5.3 Hz, –OCH), 2.34–1.92 (m, 3H, –CH_2), 1.80 (m, 1H, –CH_2), 1.75–1.56 (m, 1H, –CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.8, 134.8, 128.4, 127.7, 127.6, 116.2, 73.9, 73.5, 71.1, 70.7, 61.4, 30.5, 26.5, 23.2; IR (neat): 3425, 2927, 2856, 1653, 1512, 1456, 1378, 1249, 1025, 699 cm^{-1}; HRMS *m/z* calculated for $C_{16}H_{22}O_3Na$ (M+Na)$^+$ 285.1466, found 285.1478.

4.1.17. 2-((2*S*,3*S*,6*R*)-3-(Benzyloxy)-6-vinyl-tetrahydro-2*H*-pyran-2-yl)acetic acid 6

To a stirred solution of **25** (0.22 g, 0.84 mmol) in CH_2Cl_2:H_2O (1:1, 1 mL), TEMPO (39.1 mg, 0.25 mmol) and BIAB (80.5 mg, 2.5 mmol) were added at 0 °C and stirred for 1 h. The reaction mixture was diluted with water (5 mL) and extracted with CH_2Cl_2 (2 × 20 mL). The organic layers were washed with brine (10 mL), dried (Na_2SO_4), evaporated and the residue purified by column chromatography (silica gel, 60–120 mesh, 20–25% EtOAc in pet. ether) to give acid **6** (0.16 g, 70%) as a colorless gummy oil. $[\alpha]_D^{25} = -31.0$ (*c* 0.25, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34–7.20 (m, 5H, ArH-Bn), 5.80 (dt, 1H, *J* = 4.6, 11.0 Hz, olefinic), 5.27–5.14 (m, 2H, olefinic), 4.60 (d, 1H, *J* = 11.9 Hz, benzylic), 4.47 (d, 1H, *J* = 11.9 Hz, benzylic), 4.35 (m, 1H, –CHOpyran), 4.27 (m, 1H, –CHOpyran), 3.50 (m, 1H, –CHOBn), 2.72 (dd, 1H, *J* = 8.5, 15.7 Hz, –CαH), 2.61 (dd, 1H, *J* = 5.1, 15.7 Hz, –CαH′), 2.04–1.94 (m, 1H, –CH_2), 1.79 (m, 1H, –CH_2'), 1.51–1.25 (m, 2H, –CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.7, 138.0, 137.4, 128.4, 127.6, 116.4, 72.9, 71.5, 70.7, 70.1, 34.4, 29.5, 25.7; IR (neat): 3450, 2928, 2855, 1737, 1639, 1438, 1363, 1277, 1075, 1040, 921, 699 cm^{-1}; HRMS *m*/*z* calculated for $C_{16}H_{20}O_4Na$ (M+Na)$^+$ 299.1259, found 299.1260.

4.1.18. 2-(2*R*,3*S*,6*R*)-3-(Benzyloxy)-6-[(6*S*)-hydroxyhept-1-*E*,*Z*-enyl]tetrahydropyran-2-yl} acetic acid 4

Grubbs second generation catalyst **G-II** (59 mg, ca. 0.07 mmol) and alcohol **5** (0.205 g, 1.8 mmol) were dissolved in dry, deoxygenated CH_2Cl_2 (30 mL) under an N_2 atmosphere. After heating the solution to reflux, acid **6** (0.10 g, 0.36 mmol) dissolved in dry deoxygenated CH_2Cl_2 (8 mL) was added. The mixture was then stirred at reflux for 2 h. After cooling to room temperature, it was quenched through the addition of DMSO (0.64 mL, 9.0 mmol) followed by stirring for 12 h. The volatiles were evaporated under reduced pressure and the residue purified by column chromatography (silica gel, 60–120 mesh). First eluted (25% EtOAc in pet. ether) was (2*S*,11*S*,*E*)-dodec-6-ene-2,11-diol **4a** (44.5 mg, 25%) as a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.74 (dddd, 1H, *J* = 6.8, 10.2, 13.2, 16.9 Hz, olefinic), 4.95 (m, 2H, olefinic), 3.76 (sextet, 1H, *J* = 6.0 Hz, –OCH), 2.06 (td, 2H, *J* = 6.4, 13.2 Hz, –CH_2), 1.61–1.31 (m, 4H, 2 × –CH_2), 1.51 (d, 6H, *J* = 6.0 Hz, –CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.6, 114.7, 68.0, 38.8, 33.8, 33.7, 25.2, 23.5; IR (neat): 3341, 2936, 2827, 1535, 1460, 1134, 1015 cm^{-1}.

The second eluted (40% EtoAc in pet. Ether) was **4** (62.2 mg, 48%) as an inseparable 4:1 *E*/*Z* mixture of olefins as a brown colored oil. ^{1}H NMR (500 MHz, $CDCl_3$): (signals from major isomer) δ 7.33 (m, 5H, ArH-Bn), 5.75–5.44 (m, 2H, olefinic), 4.62 (d, 1H, *J* = 11.7 Hz, benzylic), 4.44 (d, 1H, *J* = 11.7 Hz, benzylic), 4.33 (sextet, 2H, *J* = 6.0 Hz, –OCH), 3.50 (dd, 1H, *J* = 4.5, 8.3 Hz, –OCH), 2.79 (m, 1H, –CαH), 2.53 (dd, 1H, *J* = 4.2, 15.5 Hz, –CαH′), 2.14–1.97 (m, 4H, 2 × –CH_2), 1.81 (m, 2H, –CH_2), 1.53–1.38 (m, 4H, 2 × –CH_2), 1.18 (d, 3H, *J* = 6.0 Hz, –CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): (signals for major isomer) δ 175.2, 138.1, 133.5, 132.0, 129.1, 128.4, 127.7, 73.1, 71.6, 70.7, 70.1, 68.0, 38.4, 32.1, 29.7, 26.0, 25.0, 23.2, 22.9; IR (neat): 3450, 2928, 2855, 1737, 1639, 1438, 1363, 1277, 1075, 1040, 921, 699 cm^{-1}; HRMS (ESI): calcd. for $C_{21}H_{30}O_5Na$ [M+Na]$^+$ 385.1990; found 385.1974.

4.1.19. (1*S*,5*S*,11*R*,14*S*)-14-(Benzyloxy)-5-methyl-4,15 dioxabicyclo[9.3.1] pentadec-9*E*-en-3-one 26

A solution of hydroxy acid **4** (50 mg, 0.14 mmol, *E*/*Z* mixture) in dry THF (1 mL) at 0 °C under an N_2 atmosphere was treated with Et_3N (0.6 mL, 0.42 mmol) and 2,4,6-trichlorobenzoyl chloride (102.4 mg, 0.42 mmol) sequentially. After stirring at room temperature for 2 h, it was diluted with toluene (20 mL). Next, this mixture was added dropwise over 5 h to a solution of DMAP (0.171 g, 1.4 mmol) in dry toluene (150 mL) preheated at 60 °C. After completion of the addition, the reaction mixture was further stirred at 60 °C for 1 h. It was then cooled to room temperature and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 60–120 mesh, 8% EtOAc in pet. ether) furnished lactone **26** (24.5 mg, 52%) as a colorless oil. $[\alpha]_D^{25} = -54.5$ (*c* 0.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36–7.25 (br m, 5H, ArH-Bn), 6.18 (dddd, 1H, *J* = 1.8, 4.6, 10.9, 15.5 Hz, H-9), 5.64 (dd, 1H, *J* = 4.1, 15.5 Hz, H-8), 5.06 (m, 1H, H-13), 4.72 (d, 1H, *J* = 12.3 Hz, benzylic), 4.48 (m, 1H, H-7), 4.39 (d, 1H, *J* = 12.3 Hz, benzylic), 4.18 (br d, 1H, *J* = 10.9 Hz, H-3), 3.32 (br s, 1H, H-4), 2.64 (dd, 1H, *J* = 10.9, 14.1 Hz, H-2), 2.25–2.15 (m, 2H, H-6, H-10), 2.10 (dd, 1H, *J* = 1.4, 14.1 Hz, H-2′), 2.05–1.90 (m, 2H, H-5, H-10′), 1.85–1.75 (m, 2H, H-11, H-12), 1.70–1.55 (br m, 2H, H-5′, H-12′), 1.45–1.30 (br m, 2H, H-6′, H-11′), 1.17 (d, 3H, *J* = 6.5 Hz, Me–C13); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 138.5, 137.6, 128.6, 128.2, 127.8, 127.5, 73.0, 71.2, 70.4, 69.9, 68.9, 39.9, 31.7, 30.6, 24.8, 23.0, 22.9, 19.1; IR (neat): 3450, 2938, 1730, 1646, 1377, 1207, 1096, 1044, 869 cm^{-1}; HRMS *m*/*z* calculated for $C_{21}H_{28}O_4Na$ (M+Na)$^+$ 367.1885, found 367.1878.

4.1.20. (3*S*,4*S*)-4-(Benzyloxy)-1-(*tert*-butyldiphenylsilyloxy)oct-7-en-3-ol 31

To a solution of **18** (3.20 g, 5.26 mmol) in aq CH_2Cl_2 (30 mL, 19:1), DDQ (1.43 g, 6.31 mmol) was added and stirred at room temperature for 1 h. Work-up as described for **8** and purification of the residue by column chromatography (silica gel, 60–120 mesh, 30% EtOAc in pet. ether) furnished **31** (2.39 g, 93%) as a yellow liquid. $[\alpha]_D^{25} = -7.3$ (*c* 1.47, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63 (m, 4H, ArH-TBDPS), 7.39–7.32 (br m, 6H, ArH-TBDPS), 7.30–7.20 (m, 5H, ArH-Bn), 5.77 (m, 1H, olefinic), 4.96 (m, 2H, olefinic), 4.60 (d, 1H, *J* = 11.3 Hz, benzylic), 4.50 (d, 1H, *J* = 11.3 Hz, benzylic), 3.89 (m, 2H, –OCH_2), 3.77 (m, 1H, –OCH), 3.32 (dt, 1H, *J* = 4.9, 7.2 Hz, –CHOBn), 2.66 (d, 1H, *J* = 3.8 Hz, –OH), 2.15 (m, 2H, –CH_2 allylic), 1.81–1.54 (m, 4H, 2 × –CH_2), 1.05 (s, 9H, *t*-butyl); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.5, 135.5, 134.7, 133.3, 129.7, 129.5, 128.3, 127.8, 127.6, 114.7, 81.5, 72.5, 70.9, 62.3, 34.9, 29.7, 29.2, 26.9, 19.1; IR (neat): 3451, 2929, 2851, 1608, 1527, 1273, 1105, 918, 702 cm^{-1}; HRMS *m*/*z* calculated for $C_{31}H_{40}O_3NaSi$ (M+Na)$^+$ 511.2644, found 511.2618.

4.1.21. (3*R*,4*S*)-4-(Benzyloxy)-1-(*tert*-butyldiphenylsilyloxy)oct-7-en-3-yl-4-nitrobenzoate 32

To a solution of **31** (2.35 g, 4.82 mmol), Ph_3P (4.42 g, 16.87 mmol) and *p*-nitrobenzoic acid (3.38 g, 20.24 mmol) in dry THF (25 mL), DIAD (3.32 mL, 16.87 mmol) was added at 0 °C and stirred under an N_2 atmosphere for 2 h. The solvent was evaporated under reduced pressure and the residue purified by column chromatography (silica gel, 10% EtOAc in pet. ether) to afford **32** (2.49 g, 81%) as a colorless oil. $[\alpha]_D^{25} = -15.95$ (*c* 1.03, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.23 (d, 2H, *J* = 8.7 Hz, ArH-PNB), 8.07 (d, 2H, *J* = 8.7 Hz, ArH-PNB), 7.70–7.53 (m, 4H, ArH-TBDPS), 7.44–7.29 (m, 6H, ArH-TBDPS), 7.27–7.17 (m, 5H, ArH-Bn), 5.75 (m, 1H, olefinic), 5.60 (m, 1H, –OCHPNB), 4.98 (m, 2H, olefinic), 4.61 (d, 1H, *J* = 11.3 Hz, benzylic), 4.46 (d, 1H, *J* = 11.3 Hz, benzylic), 3.81–3.71 (m, 1H, –OCHBn), 3.77–3.62 (m, 2H, –OCH_2), 2.60 (m, 1H, –CH_2), 2.35–2.20 (m, 1H, –CH_2), 2.19–1.93 (m, 2H, –CH_2), 1.86–1.57 (m, 2H, –CH_2), 1.03 (s, 9H, *t*-butyl); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.1, 150.4, 138.2, 137.9, 135.7, 135.5, 130.7, 129.6, 128.3, 127.9, 127.6, 127.6, 123.4, 115.2, 79.5, 73.8, 72.4, 60.0, 32.0, 30.0, 30.0, 26.8, 19.1; IR (neat): 3416, 3068, 2932, 2859, 1722, 1608, 1527, 1462, 1427, 1273, 1105, 918, 702 cm^{-1}; HRMS *m*/*z* calculated for $C_{38}H_{43}NO_6NaSi$ (M+Na)$^+$ 660.2761, found 660.2718.

4.1.22. (3*R*,4*S*)-4-(Benzyloxy)-1-(*tert*-butyldiphenylsilyloxy)oct-7-en-3-ol 33

A solution of **32** (2.40 g, 3.77 mmol) in MeOH (25 mL) was treated with K_2CO_3 (1.56 g, 11.31 mmol) and stirred at room tempera-

ture for 2 h. Next, MeOH was evaporated under reduced pressure and the residue was extracted with solvent ether (3 × 50 mL). The organic layers were washed with water (75 mL), brine (75 mL), dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (silica gel, 60–120 mesh, 25% EtOAc in pet. ether) to afford **33** (1.55 g, 84%) as a colorless liquid. $[\alpha]_D^{25} = -15.2$ (*c* 1.88, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.64 (m, 4H, ArH-TBDPS), 7.44–7.31 (m, 6H, ArH-TBDPS), 7.29–7.17 (m, 5H, ArH-Bn), 5.77 (m, 1H, olefinic), 4.95 (m, 2H, olefinic), 4.58 (d, 1H, *J* = 11.7 Hz, benzylic), 4.56 (d, 1H, *J* = 11.7 Hz, benzylic), 3.97 (m, 1H, –CHOH), 3.90–3.77 (m, 2H, $-CH_2$OTBDPS), 3.38 (m, 1H, –OCHBn), 2.89 (br m, 1H, –OH), 2.36–2.02 (m, 2H, $-CH_2$allylic), 1.80–1.65 (m, 2H, $-CH_2$), 1.62–1.33 (m, 2H, $-CH_2$), 1.05 (s, 9H, *t*-butyl); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.6, 135.5, 135.5, 129.7, 128.3, 127.8, 127.7, 127.5, 123.5, 114.7, 81.5, 72.2, 71.7, 62.8, 34.0, 29.6, 28.9, 26.8, 19.0; IR (neat): 3451, 3072, 2928, 2859, 1600, 1512, 1427, 1248, 1108, 1083, 703 cm^{-1}; HRMS *m/z* calculated for $C_{31}H_{40}O_3NaSi$ $(M+Na)^+$ 511.2644, found 511.2619.

4.1.23. ((3*R*,4*S*)-4-(Benzyloxy)-3-(4-methoxybenzyloxy)oct-7-enyloxy)(*tert*-butyl)diphenyl- silane 34

To a cooled (0 °C) and stirred solution of **33** (1.50 g, 3.07 mmol) in dry THF (10 mL), NaH (0.307 g, 7.67 mmol) was added and stirred for 30 min. It was then treated with a solution of PMBBr (0.74 g, 3.68 mmol) in dry THF (5 mL). After 5 h, it was worked up as described for **11** and purified by column chromatography (silica gel, 60–120 mesh, 15% EtOAc in pet. ether) to furnish **34** (1.60 g, 86%) as a yellow liquid. $[\alpha]_D^{25} = +1.4$ (*c* 2.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61 (m, 4H, ArH-TBDPS), 7.39–7.18 (br m, 11H, ArH-TBDPS+Bn), 7.11 (d, 1H, *J* = 8.2 Hz, ArH-PMB), 6.74 (d, 2H, *J* = 8.2 Hz, ArH-PMB), 5.73 (m, 1H, olefinic), 4.93 (m, 2H, olefinic), 4.66 (d, 1H, *J* = 11.9 Hz, benzylic), 4.55 (d, 1H, *J* = 11.9 Hz, benzylic), 4.45 (d, 1H, *J* = 11.9 Hz, benzylic), 4.37 (d, 1H, *J* = 11.9 Hz, benzylic), 3.83–7.72 (m, 2H, $-OCH_2$), 3.76 (s, 3H, $-OCH_3$), 3.50 (m, 1H, –OCH), 3.46 (br m, 1H, –OCH), 2.26–2.02 (m, 2H, $-CH_2$), 1.78–1.66 (m, 3H, $-CH_2$), 1.51–1.41 (m, 1H, $-CH_2$), 1.04 (s, 9H, *t*-butyl); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.0, 138.8, 138.5, 135.5, 133.9, 130.9, 129.6, 129.3, 128.3, 127.8, 127.6, 127.4, 114.7, 113.7, 80.0, 77.0, 72.2, 72.0, 60.6, 55.2, 33.7, 30.2, 30.0, 26.9, 19.2; IR (neat): 3452, 3069, 2928, 2860, 1613, 1502, 1240, 1101, 1082, 701 cm^{-1}; HRMS *m/z* calculated for $C_{39}H_{48}O_4NaSi$ $(M+Na)^+$ 631.3219; found 631.3240.

4.1.24. (6*S*,7*S*,*E*)-Methyl-6-(benzyloxy)-9-(*tert*-butyldiphenylsilyloxy)-7-(4-methoxybenzy- loxy) non-2-enoate 35

A solution of **34** (1.60 g, 2.63 mmol) in CH_2Cl_2 (15 mL) was cooled to −78 °C and bubbled with ozone gas for 15 min. It was then quenched with $(CH_3)_2S$ (2 mL) and the solvent evaporated to give aldehyde **34a** as a colorless oil in quantitative yield.

The crude aldehyde **34a** was dissolved in benzene (30 mL) and treated with (methoxycarbonylmethylene)triphenylphosphorane (1.83 g, 5.33 mmol) at reflux. After 2 h, the solvent was evaporated and the residue purified by column chromatography (silica gel, 60–120 mesh, 5% EtOAc in pet. ether) to furnish **35** (1.52 g, 87%) as a colorless oil. $[\alpha]_D^{25} = -10.95$ (*c* 2.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61 (br m, 4H, ArH-TBDPS), 7.41–7.30 (m, 6H, ArH-TBDPS), 7.27–7.23 (m, 5H, ArH-Bn), 7.10 (d, 2H, *J* = 8.5 Hz, ArH-PMB), 6.88 (dd, 1H, *J* = 6.8, 13.8 Hz, -olefinic), 6.74 (d, 1H, *J* = 8.5 Hz, ArH-PMB), 5.71 (d, 1H, *J* = 15.7 Hz, olefinic), 4.68–4.55, 4.41, 4.38 (4 × d, 4H, benzylic), 3.84–3.73 (m, 2H, $-CH_2$OTBDPS), 3.77 (s, 3H, $-OCH_3$), 3.72–3.68 (m, 1H, –CHOPMB), 3.70 (s, 3H, $-OCH_3$), 3.45 (m,1H, –CHOBn), 3.39–2.11 (br m, 2H, $-CH_2$), 1.84–1.62 (m, 3H, $-CH_2$), 1.58–1.44 (m, 1H, CH_2), 1.05 (s, 9H, *t*-butyl); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.0, 159.0, 149.2, 136.4, 135.5, 133.8, 130.8, 129.6, 129.3, 128.3, 127.8, 127.6, 121.0, 113.7, 80.0, 76.7, 72.2, 60.5, 55.2, 51.3, 32.6, 28.6, 28.0, 26.9, 19.2; IR (neat): 3430, 3031, 2949, 2859, 1720, 1649, 1612, 1511, 1432, 1249, 1104, 821, 702 cm^{-1}; HRMS (ESI): calcd. for $C_{41}H_{50}O_6NaSi$ $[M+Na]^+$ 689.3274; found 689.3299.

4.1.25. (6*S*,7*R*,*E*)-6-(Benzyloxy)-9-(*tert*-butyldiphenylsilyloxy)-7-(4-methoxybenzyloxy)non-2-en-1-ol 36

To a solution of **35** (1.40 g, 2.1 mmol) in CH_2Cl_2 (10 mL), DIBAL-H (1.0 M solution in hexanes, 5.25 mL, 5.25 mmol) was added at 0 °C and stirred for 1 h. Work-up as described for **21** and purification of the residue by column chromatography (silica gel, 60–120 mesh, 10 to 15% EtOAc in pet. ether) gave allylic alcohol **36** (1.15 g, 86%) as a colorless oil. $[\alpha]_D^{25} = -2.8$ (*c* 4.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61 (m, 4H, ArH-TBDPS), 7.39–7.20 (m, 11H, ArH-TBDPS+Bn), 7.11 (d, 2H, *J* = 8.7 Hz, ArH-PMB), 6.75 (d, 2H, *J* = 8.7 Hz, ArH-PMB), 5.55 (m, 2H, olefinic), 4.67 (d, 1H, *J* = 11.9 Hz, benzylic), 4.55 (d, 1H, *J* = 11.4 Hz, benzylic), 4.45 (d, 1H, *J* = 11.9 Hz, benzylic), 4.39 (d, 1H, *J* = 11.4 Hz, benzylic), 4.09 (m, 1H, –CHO), 3.99 (m, 2H, $-OCH_2$), 3.83–3.73 (m, 2H, –OCH), 3.77 (s, 3H, $-OCH_3$), 3.47 (m, 1H, –OCHBn), 2.23–1.18 (m, 2H, $-CH_2$allylic), 1.77–1.64 (m, 3H, CH_2), 1.51–1.40 (m, 1H, $-CH_2$), 1.05 (s, 9H, *t*-butyl); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.0, 138.7, 136.8, 135.5, 133.8, 132.6, 130.9, 129.6, 129.3, 128.3, 127.8, 127.6, 127.5, 113.7, 80.0, 76.9, 72.9, 66.1, 63.6, 60.6, 55.2, 33.8, 29.7, 28.7, 26.9, 19.2; IR (neat): 3450, 2931, 2859, 1736, 1617, 1458, 1246, 1102, 970, 701 cm^{-1}; HRMS (ESI): calcd. for $C_{40}H_{50}O_5NaSi$ $[M+Na]^+$ 661.3325; found 661.3357.

4.1.26. (6*S*,7*R*,*E*)-6-(Benzyloxy)-9-(*tert*-butyldiphenylsilyloxy)-non-2-ene-1,7-diol 37

To a solution of **36** (1.1 g, 1.72 mmol) in H_2O:CH_2Cl_2 (10 mL, 1:19), DDQ (0.47 g, 2.06 mmol) was added and stirred at room temperature for 1 h. Work-up was as described for **8** and the residue purified by column chromatography (silica gel, 60–120 mesh, 30% EtOAc in pet. ether) to furnish **37** (0.71 g, 80%) as a colorless oil. $[\alpha]_D^{25} = -22.9$ (*c* 2.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (m, 4H, ArH-TBDPS), 7.41–7.34 (m, 6H, ArH-TBDPS), 7.30–7.22 (m, 5H, ArH-Bn), 5.73 (m, 1H, olefinic), 5.52 (m, 1H, olefinic), 4.58 (d, 1H, *J* = 11.4 Hz, benzylic), 4.52 (d, 1H, *J* = 11.4 Hz, benzylic), 4.46 (d, 2H, *J* = 6.4 Hz, $-CH_2$OH), 3.95 (m, 1H, –OCH), 3.90–3.80 (m, 2H, $-CH_2$OTBDPS), 3.35 (m, 1H, –CHOBn), 2.89 (br, 1H, –OH), 2.28–2.06 (m, 2H, $-CH_2$), 1.74–1.67 (m, 2H, $-CH_2$), 1.60–1.52 (m, 1H, –CH), 1.43–1.33 (m, 1H, –CH), 1.06 (s, 9H, *t*-butyl); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.5, 135.5, 133.1, 133.0, 132.8, 129.8, 129.3, 128.4, 127.7, 127.6, 81.4, 72.2, 71.8, 63.7, 62.9, 34.0, 29.1, 28.1, 26.8, 19.1; IR (neat): 3450, 3055, 2919, 2825, 1601, 1501, 1235, 1061, 702 cm^{-1}; HRMS (ESI): calcd. for $C_{32}H_{42}O_4NaSi$ $[M+Na]^+$ 541.2750; found 541.2727.

4.1.27. (*S*)-1-((2*R*,5*S*,6*R*)-5-(Benzyloxy)-6-(2-(*tert*-butyldiphenylsilyloxy)ethyl)-tetrahydro-2*H*-pyran-2-yl)ethane-1,2-diol 29

To a slurry of 4 Å molecular sieves powder (1.0 g) in CH_2Cl_2 (10 mL), (+)-DIPT (0.20 g, 0.97 mmol) was added and cooled to −20 °C. Next, Ti(O*i*-Pr)$_4$ (0.28 mL, 0.97 mmol), cumene hydroperoxide (0.27 mL, 1.94 mmol) and a solution of allylic alcohol **37** (0.50 g, 0.97 mmol) in CH_2Cl_2 (2 mL) were added sequentially with an interval of 30 min and stirred at −20 °C for 1 h. The reaction mixture was then kept at −20 °C for 5 h. Worked up as described for **7** and purified the residue by column chromatography (silica gel, 60–120 mesh, 30% EtOAc in pet. ether) to afford diol **29** (0.43 g, 83%) as a colorless oil. $[\alpha]_D^{25} = +80.6$ (*c* 2.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 (m, 4H, ArH-TBDPS), 7.40–7.29 (m, 6H, ArH-TBDPS), 7.30–7.22 (m, 5H, ArH-Bn), 4.60 (d, 1H, *J* = 11.6 Hz, benzylic), 4.40 (d, 1H, *J* = 11.6 Hz, benzylic), 3.75 (m, 2H, $-CH_2$OH), 3.54 (m, 2H, $-CH_2$OTBDPS), 3.45 (dd, 1H, *J* = 5.3, 10.1 Hz, –CHOpyran), 3.37 (td, 1H, *J* = 2.4, 9.2 Hz, –CHOpyran), 3.29 (m, 1H, –CHOH), 3.01 (td, 1H, *J* = 4.3, 10.1 Hz, –CHOBn),

2.27–2.19 (m, 2H, –CH), 1.79 (m, 1H, $-CH_2$), 1.49 (m, 1H, $-CH_2$), 1.38 (m, 2H, $-CH_2$), 1.05 (s, 9H, *t*-butyl); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.4, 135.5, 133.9, 129.5, 128.3, 127.7, 127.6, 127.6, 78.4, 77.6, 77.2, 73.5, 70.78, 63.6, 60.3, 35.3, 28.8, 26.8, 26.4, 19.2; IR (neat): 3566, 3448, 3064, 2922, 2829, 1612, 1502, 1264, 1081, 703 cm^{-1}; HRMS (ESI): calcd. for $C_{32}H_{42}O_5NaSi$ $(M+Na)^+$ 557.2699; found 557.2679.

4.1.28. (2-((2*R*,3*S*,6*R*)-3-(Benzyloxy)-6-vinyl-tetrahydro-2*H*-pyran-2-yl)ethoxy) (*tert*-butyl) diphenylsilane 39

The diol **29** (0.40 g, 0.75 mmol) was treated with $NaIO_4$ (0.19 g, 0.9 mmol) in acetone:H_2O (5:1, 6 mL) at room temperature for 30 min. Work-up as described for **23** gave (2*R*,5*S*,6*R*)-5-(benzyloxy)-6-(2-(*tert*-butyldiphenylsilyloxy)ethyl)-tetrahydro-2*H*-pyran-2-carba- ldehyde **38**, which was used for further reaction.

To a solution of (methyl)triphenylphosphonium iodide (1.05 g, 2.59 mmol) in dry THF (10 mL), potassium *tert*-butoxide (0.21 g, 1.85 mmol) was added at -10 °C and stirred for 6 h. A solution of **38** (0.37 g, 0.74 mmol) in THF (10 mL) was added dropwise to the above solution and stirred at room temperature for 1 h. Work-up as described for **24** and purification of the residue by column chromatography (silica gel, 60–120 mesh, 5% EtOAc in pet. ether) furnished **39** (0.28 g, 77%) as a colorless oil. $[\alpha]_D^{25} = +96.0$ (*c* 1.75, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.64 (m, 4H, ArH-TBDPS), 7.38–7.22 (m, 11H, ArH-TBDPS+Bn), 5.76 (ddd, 1H, *J* = 4.8, 10.6, 15.5 Hz, olefinic), 5.08 (dd, 2H, *J* = 10.6, 17.4 Hz, olefinic), 4.58 (d, 1H, *J* = 11.6 Hz, benzylic), 4.42 (d, 1H, *J* = 11.6 Hz, benzylic), 3.86 (m, 1H, –OCHpyran), 3.81–3.73 (m, 2H, $-OCH_2$), 3.46 (m, 1H, –OCHpyran), 3.06 (m, 1H, –OCHBn), 2.29–2.19 (m, 2H, $-CH_2$), 1.76 (m, 1H, $-CH_2$), 1.58 (m, 1H, $-CH_2$), 1.50–1.29 (m, 2H, $-CH_2$), 1.04 (s, 9H, *t*-butyl); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.6, 135.6, 134.1, 132.0, 129.4, 128.3, 127.6, 127.5, 127.5, 114.5, 77.3, 77.3, 77.0, 70.8, 60.2, 35.3, 30.7, 29.3, 26.8, 19.2; IR (neat): 3440, 2928, 2841, 1615, 1442, 1213, 1107 cm^{-1}; HRMS (ESI): calcd. for $C_{32}H_{40}O_3NaSi$ $[M+Na]^+$ 523.2644; found 523.2655.

4.1.29. 2-((2*R*,3*S*,6*R*)-3-(Benzyloxy)-6-vinyl-tetrahydro-2*H*-pyran-2-yl)ethanol 40

To a cooled (0 °C) solution of **39** (0.25 g, 0.5 mmol) in dry THF (15 mL) under a nitrogen atmosphere, TBAF (0.6 mL, 0.6 mmol) was added and stirred for 1 h. Work-up as described for **25** and purification of the residue by column chromatography (silica gel, 60–120 mesh, 25% EtOAc in pet. ether) gave **40** (0.11 g, 85%) as a liquid. $[\alpha]_D^{25} = +152.5$ (*c* 0.81, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–7.23 (m, 5H, ArH-Bn), 5.77 (ddd, 1H, *J* = 5.3, 10.6, 17.4 Hz, olefinic), 5.18 (td, 1H, *J* = 1.5, 17.4 Hz, olefinic), 5.06 (td, 1H, *J* = 1.5, 17.4 Hz, olefinic), 4.60 (d, 1H, *J* = 11.7 Hz, benzylic), 4.45 (d, 1H, *J* = 11.7 Hz, benzylic), 3.85, (m, 1H, –CHO), 3.74 (t, 2H, *J* = 5.3 Hz, $-OCH_2$), 3.47 (td, 1H, *J* = 3.0, 8.7 Hz, –CHO), 3.14 (td, 1H, *J* = 4.2, 9.8 Hz, –CHOBn), 2.63 (br s, 1H, –OH), 2.27 (m, 1H, –CH), 2.12 (m, 1H, –CH), 1.74 (m, 2H, $-CH_2$), 1.44 (m, 2H, $-CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.1, 134.8, 128.4, 127.8, 127.8, 115.2, 81.5, 77.9, 76.5, 70.8, 61.6, 34.3, 30.6, 28.9; IR (neat): 3420, 2929, 2850, 1655, 1512, 1456, 1378, 1249, 1025, 699 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{22}O_3Na$ $[M+Na]^+$ 285.1466; found 285.1478.

4.1.30. 2-((2*R*,3*S*,6*R*)-3-(Benzyloxy)-6-vinyl-tetrahydro-2*H*-pyran-2-yl)acetic acid 28

To a stirred solution of **40** (0.09 g, 0.34 mmol) in CH_2Cl_2:H_2O (1:1) (1 mL), TEMPO (16 mg, 0.1 mmol) and BIAB (0.33 g, 1.02 mmol) were added at 0 °C and stirred for 1 h. Work-up as described for **6** and purification by column chromatography (silica gel, 60–120 mesh, 25% EtOAc in pet. ether) gave **33** (70.5 mg, 75%) as a liquid. $[\alpha]_D^{25} = +153.2$ (*c* 1.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–7.23 (m, 5H, ArH-Bn), 5.81 (ddd, 1H, *J* = 5.0, 10.5, 16.6 Hz, olefinic), 5.23 (dd, 1H, *J* = 11.1, 17.7 Hz, olefinic), 4.63 (d, 1H, *J* = 11.6 Hz, benzylic), 4.43 (d, 1H, *J* = 11.6 Hz, benzylic), 3.91 (dd, 1H, *J* = 5.0, 10.5 Hz, –OCHpyran), 3.74 (td, 1H, *J* = 3.3, 7.7 Hz, –OCHpyran), 3.18 (td, 1H, *J* = 4.4, 10 Hz, –OCHBn), 2.90 (dd, 1H, *J* = 3.9, 15.5 Hz, –CαH), 2.51 (dd, 1H, *J* = 7.7, 15.5 Hz, –CαH), 2.31 (qd, 1H, *J* = 3.3, 7.2 Hz, $-CH_2$), 1.82 (qd, 1H, *J* = 3.3, 5.5 Hz, $-CH_2$), 1.49 (m, 2H, $-CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.5, 137.9, 137.8, 128.3, 127.7, 127.6, 115.2, 77.8, 77.0, 76.3, 70.8, 38.1, 30.5, 26.7 IR (neat): 3450, 2928, 2855, 1737, 1639, 1438, 1363, 1277, 1075, 1040, 921, 699 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{20}O_4Na$ $[M+Na]^+$ 299.1259; found 299.1260.

4.1.31. (*S*)-Hept-6-en-2-yl-2-((2*R*,3*S*,6*R*)-3-(benzyloxy)-6-vinyl-tetrahydro-2*H*-pyran-2-yl)- acetate 27

To a stirred solution of acid **28** (50.0 mg, 0.18 mmol) in dry CH_2Cl_2 (2 mL) at °C, under an N_2 atmosphere, EDCI (51.8 mg, 0.27 mmol) and DMAP (33.0 mg, 0.27 mmol) were added. After 10 min, alcohol **5** (25.0 mg, 0.22 mmol) in dry CH_2Cl_2 (2 mL) was added and stirred for 5 h. The reaction mixture was treated with an aq NH_4Cl solution (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was sequentially washed with 1 M HCl (10 mL), water (10 mL), brine (10 mL) and dried (Na_2SO_4). The solvent was evaporated and the residue purified by column chromatography (silica gel, 60–120 mesh, 5% EtOAc in pet. ether) to furnish **27** (41.0 mg, 61%) as a colorless oil. $[\alpha]_D^{25} = +100.8$ (*c* 0.49, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 -7.27 (m, 5H, ArH-Bn), 5.83–5.73 (m, 2H, olefinic), 5.22–4.93 (m, 4H, olefinic), 4.92 (m, 1H, –CHOester), 4.63 (d, 1H, *J* = 11.9 Hz, benzylic), 4.44 (d, 1H, *J* = 11.1 Hz, benzylic), 3.86 (m, 1H, –OCH), 3.76 (td, 1H, *J* = 4.0, 9.0 Hz, –OCH), 3.18 (td, 1H, *J* = 4.5, 9.5 Hz, –OCH), 2.86 (dd, 1H, *J* = 4.0, 14.9 Hz, –CαH), 2.41 (dd, 1H, *J* = 9.0, 14.9 Hz, –CαH), 2.28 (m, 1H, –CH), 2.02 (dd, 2H, *J* = 5.0, 11.9 Hz, $-CH_2$), 1.80 (m, 1H, –CH), 1.60–1.24 (br m, 6H, 3 × $-CH_2$), 1.17 (d, 3H, *J* = 6.0 Hz, $-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2, 138.5, 138.1, 128.3, 127.8, 127.7, 127.6, 114.8, 114.6, 77.6, 77.6, 76.5, 70.7, 70.5, 38.6, 35.4, 33.4, 30.6, 28.9, 24.6, 19.9; IR (neat): 3450, 2928, 2855, 1730, 1639, 1448, 1353, 1270, 1075, 1040 cm^{-1}; HRMS (ESI): calcd. for $C_{23}H_{32}O_4Na$ [M+Na] 395.3192; found 395.2197.

4.1.32. (1*R*,5*S*,11*R*,14*S*,*Z*)-14-(Benzyloxy)-5-methyl-4,15-dioxa-bicyclo[9.3.1]-pentadec-9-en-3-one 41

To a stirred solution of 10 mol % of Grubbs first generation ruthenium catalyst **G-I** in deoxygenated dry CH_2Cl_2 (100 mL) at reflux, a solution of diene **27** (20.0 mg, 0.05 mmol) in CH_2Cl_2 (20 mL) was added slowly over a period of 1 h and stirred for 3 h under an N_2 atmosphere at the same temperature. The reaction mixture was cooled to room temperature and stirring was continued for a further 2 h. Next, DMSO (0.20 mL, 2.5 mmol) was added and allowed to stir for an additional 10 h. The reaction mixture was concentrated to give a brown residue, which was purified by column chromatography (silica gel, 60–120 mesh, 4–5% EtOAc in pet. ether) to afford **41** (15.5 mg, 84%) as a colorless oil. $[\alpha]_D^{25} = +68.1$ (*c* 0.27, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33–7.23 (br m, 5H, ArH-Bn), 5.55 (tdd, 1H, *J* = 2.6, 5.6, 10.8 Hz, olefinic), 5.11 (dd, 1H, *J* = 2.0, 11.3 Hz, –CH–CHOester), 5.00 (m, 1H, olefinic), 4.61 (d, 1H, *J* = 11.8 Hz, benzylic), 4.41 (d, 1H, *J* = 11.8 Hz, benzylic), 4.06 (br d, 1H, *J* = 11.3 Hz, –CHOpyran), 3.67 (td, 1H, *J* = 2.6, 11.8 Hz, –CHOpyran), 3.11 (m, 1H, –CHOBn), 2.85 (dd, 1H, *J* = 2.6, 11.8 Hz, –CαH), 2.24 (m, 3H, –CαH and $-CH_2$allylic), 1.82–1.76 (m, 1H, $-CH_2$alkyl), 1.70–1.40 (br m, 7H, $-CH_2$alkyl), 1.22 (d, 3H, *J* = 6.2 Hz, $-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.3, 138.2, 135.4, 128.3, 128.1, 127.6, 127.6, 80.0, 76.5, 75.0, 70.4, 69.6, 39.2, 34.4, 31.7, 29.4, 28.0, 25.8, 20.9; IR (neat): 3450, 2926, 2851, 1720, 1431, 1366, 1277, 1075, 1040, 921 cm^{-1}; HRMS (ESI): calcd. for $C_{21}H_{28}O_4Na$ [M+Na] 367.1885; found 367.1884.

Acknowledgments

The authors are thankful to MLP-0010, for financial support. V. M. thanks the Council of Scientific and Industrial Research (CSIR), India, for financial support in the form of a fellowship.

References

1. Kito, K.; Ookura, R.; Yoshida, S.; Namikoshi, M.; Ooi, T.; Kusumi, T. *Org. Lett.* **2008**, *10*, 225–228.
2. Hande, S. M.; Uenishi, J. *Tetrahedron Lett.* **2009**, *50*, 189–192.
3. Ookura, R.; Kito, K.; Saito, Y.; Kusumi, T.; Ooi, T. *Chem. Lett.* **2009**, *38*, 384.
4. Neopeltolide (a 14-membered macrolide containing a *cis*-2,6-disubstituted tetrahydropyran ring): (a) Wright, A. E.; Botelho, J. C.; Guzman, E.; Harmody, D.; Linley, P.; McCarthy, P. J.; Pitts, T. P.; Pomponi, S. A.; Reed, J. K. *J. Nat. Prod.* **2007**, *70*, 412–416; (a benzofused 14-membered macrolide containing a *trans*-2,6- disubstituted tetrahydropyran ring): (b) Pochonin, J.; Shinonaga, H.; Kawamura, Y.; Ikeda, A.; Aoki, M.; Sakai, N.; Fujimoto, N.; Kawashima, A. *Tetrahedron Lett.* **2009**, *50*, 108–110.
5. For the synthesis of (−)-aspergillide A, see: (a) Nagasawa, T.; Kuwahara, S. *Tetrahedron Lett.* **2010**, *51*, 875–877; (b) Díaz-Oltra, S.; Angulo-Pachón, C. A.; Murga, J.; Carda, M.; Marco, J. A. *J. Org. Chem.* **2010**, *75*, 1775–1778; (c) Díaz-Olta, S.; Angulo-Pachón, C. A.; Murga, J.; Falomir, E.; Carda, M.; Marco, J. A. *Chem. Eur. J.* **2011**, *17*, 675–688; (d) Fuwa, H.; Yamaguchi, H.; Sasaki, M. *Org. Lett.* **2010**, *12*, 1848–1851; (e) Fuwa, H.; Yamaguchi, H.; Sasaki, M. *Tetrahedron* **2010**, *66*, 7492–7503; (f) Sabitha, G.; Reddy, D. V.; Rao, A. S.; Yadav, J. S. *Tetrahedron Lett.* **2010**, *51*, 4195–4198; (g) Kanematsu, M.; Yoshida, M.; Shishido, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 2618–2620; (h) Izuchi, Y.; Kanomata, N.; Koshino, H.; Hongo, Y.; Nakata, T.; Takahashi, S. *Tetrahedron: Asymmetry* **2011**, *22*, 246–251.
6. For the synthesis of (−)-aspergillide B, see: (a) Diaz-Oltra, S.; Angulo-Pachon, C. A.; Kneeteman, M. N.; Murga, J.; Carda, M.; Marco, J. A. *Tetrahedron Lett.* **2009**, *50*, 3783–3785; (b) Nagasawa, T.; Kuwahara, S. *Biosci. Biotechnol. Biochem.* **2009**, *73*, 1893–1894. and see also refs 2, 5c, 5d and 5g.
7. For the synthesis of (+)-aspergillide B, see: (a) Liu, J.; Xu, K.; He, J.; Zhang, L.; Pan, X.; She, X. *J. Org. Chem.* **2009**, *74*, 5063–5066; (b) Hendrix, A. J. M.; Jennings, M. P. *Tetrahedron Lett.* **2010**, *51*, 4260–4262.
8. (a) Sharma, G. V. M.; Mallesham, S. *Tetrahedron: Asymmetry* **2010**, *21*, 2646–2658; (b) Sharma, G. V. M.; Mallesham, S.; Chandramouli, Ch. *Tetrahedron: Asymmetry* **2009**, *20*, 2513–2529; (c) Sharma, G. V. M.; Babu, K. V. *Tetrahedron: Asymmetry* **2008**, *19*, 577–583; (d) Sharma, G. V. M.; Raman Kumar, K. *Lett. Org. Chem.* **2007**, *4*, 465–472; (e) Sharma, G. V. M.; Babu, K. V. *Tetrahedron: Asymmetry* **2007**, *18*, 2175–2184; (f) Sharma, G. V. M.; Reddy, K. L. *Tetrahedron: Asymmetry* **2006**, *17*, 3197–3202; (g) Sharma, G. V. M.; Reddy, K. L.; Reddy, J. J. *Tetrahedron Lett.* **2006**, *47*, 6537–6540; (h) Sharma, G. V. M.; Reddy, J. J.; Reddy, K. L. *Tetrahedron Lett.* **2006**, *47*, 6531–6535; (i) Sharma, G. V. M.; Reddy, Ch. G. *Tetrahedron: Asymmetry* **2006**, *17*, 1081–1088.
9. Abushnab, E.; Venishetti, P.; Leiby, R. W.; Singh, H. K.; Mikkilineni, A. B.; Wu, D. C. J.; Saibaba, R.; Panzica, P. *J. Org. Chem.* **1988**, *53*, 2598–2602.
10. (a) Felpin, F.-X.; Lebreton, J. *J. Org. Chem.* **2002**, *67*, 9192–9199; (b) Shyla, G.; Arumugam, S. *Tetrahedron Lett.* **2007**, *48*, 8544–8546.
11. Martinelli, M. J.; Nayyar, N. K.; Moher, E. D.; Dhokte, U. P.; Pawlak, J. M.; Vaidyanathan, R. *Org. Lett.* **1999**, *1*, 447–450.
12. (a) Sharpless, K. B.; Katsuki, T. *J. Am. Chem. Soc.* **1980**, *102*, 5974–5976; (b) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765–5780.
13. (a) Saito, T.; Fuwa, H.; Sasaki, M. *Tetrahedron* **2011**, *67*, 429–445; (b) Saito, T.; Fuwa, H.; Sasaki, M. *Org. Lett.* **2009**, *11*, 5274–5277.
14. (a) Baldwin, J. E. *J. Chem. Soc. Chem. Comm.* **1976**, 734–736; (b) Baldwin, J. E.; Cutting, J.; Dupont, W.; Cruse, L.; Silberman, L.; Thomas, R. C. *J. Chem. Soc. Chem. Comm.* **1976**, 736–738; (c) Baldwin, J. E.; Thomas, R. C.; Kruse, L. I.; Silberman, L. *J. Org. Chem.* **1997**, *42*, 3846–3852.
15. Takahashi, S.; Hongo, Y.; Ogawa, N.; Koshino, H.; Nakata, T. J. *Org. Chem.* **2006**, *71*, 6305–6308.
16. (a) Masayoshi, A.; Hiroshi, O.; Kahei, T. *Chem. Lett.* **1986**, *7*, 879–882; (b) Mereyala, H. B.; Pannala, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, *11*, 1755–1758.
17. (a) Huang, L.; Teumelsan, N.; Huang, X. *Chem. Eur. J.* **2006**, *12*, 5246–5252; (b) Epp, J. B.; Widlanski, T. S. J. *Org. Chem.* **1999**, *64*, 293–295.
18. Dixon, D. J.; Ley, S. V.; Tate, E. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2385–2394.
19. (a) Grubbs, R. H. *Handbook of Metathesis*; Wiley-VCH: Germany, 2003; (b) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900–1923; (c) Chatterjee, A. K.; Choi, T. L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.
20. (a) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993; (b) Parenty, A.; Moreau, X.; Campagne, J. M. *Chem. Rev.* **2006**, *106*, 911–939.
21. (a) Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380–2382; (b) Mitsunobu, O.; Eguchi, O. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 3427–3430.
22. (a) Chen, J. N.; Hsu, F. M.; Wang, H. C.; Wu, C. W.; Cheng, P. S.; Tsai, W. L. *J. Chin. Chem. Soc.* **2006**, *53*, 931–938; (b) Tapas, D.; Rajib, B.; Samik, N. *Tetrahedron: Asymmetry* **2010**, *21*, 2206–2211.