FULL PAPER

Stereoselective Synthesis of the C(1) – C(28) Fragment of Amphidinol 3

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A stereoselective synthesis of the polyol side chain (C(1) – C(28)) of amphidinol 3 has been accomplished following *Sharpless* epoxidation, *Crimmins* aldol reaction, *Jacobsen* kinetic resolution, *Sharpless* asymmetric dihydroxylation, and our own reaction for the synthesis of a chiral allylic alcohol from an epoxy alcohol. The olefin functionality was introduced by a cross metathesis and *Julia–Kocienski* olefination.

Keywords: Amphidinol 3, Stereoselective synthesis, *Sharpless* epoxidation, *Crimmins* aldol, Kinetic resolution, Cross metathesis, *Julia-Kocienski* olefination.

Introduction

Marine dinoflagellate-derived polyketides, such as brevetoxins, ciguatoxin, maitotoxin, amphidinolides, okadaic acid, and amphidinols, possess promising biological properties [1]. In particular, amphidinol 3 (AM 3) was isolated from the cultured cells (440 l) of the dinoflagellate *Amphidinium klebsi*, which is known to be hemolytic and antifungal in nature [2]. It is the first molecule in amphidinol's family and its complete structure was established by a newly developed configurational analysis [3]. Amphidinol 3 contains a skipped polyene chain with two highly oxygenated pyran rings and a polyol side chain with a total of 25 stereogenic centers on a contiguous 67 C-skeleton. Recently, *Oishi et al.* [4], proposed the revised structure of amphidinol 3 and its absolute configuration was found to be (*R*) at C(2). Owing to its complex structure and inherent biological activity, the synthesis of amphidinol 3 (**1**) has received special attention [5]. In continuation of our efforts toward the synthesis of complex natural products [6], we herein report a stereoselective approach for the synthesis of the C(1) – C(28) side chain of amphidinol 3 (**1**; *Fig.*).

The present approach for the synthesis of the polyol fragment **2** involves *Jacobsen* hydrolytic kinetic resolution [7], *Sharpless* asymmetric epoxidation [8], *Sharpless* asymmetric dihydroxylation [9], *Yadav*'s approach [10], *Crimmins* aldol reaction [11], *Grubbs* cross metathesis [12], and *Julia–Kocienski* olefination [13]. Our retrosynthetic analysis of the polyol side chain of AM3, **2**, is shown in *Scheme 1*. Retrosynthetically, the AM3 fragment **2** can be divided into two segments **3** and **4** by disconnecting the backbone at C(8)=C(9). The fragment **4** could be prepared by combining two fragments **7** (C(9) – C(21)) and **8** (C(20) – C(28)). Another fragment **3** was proposed to be obtained from segments **5** and **6**.

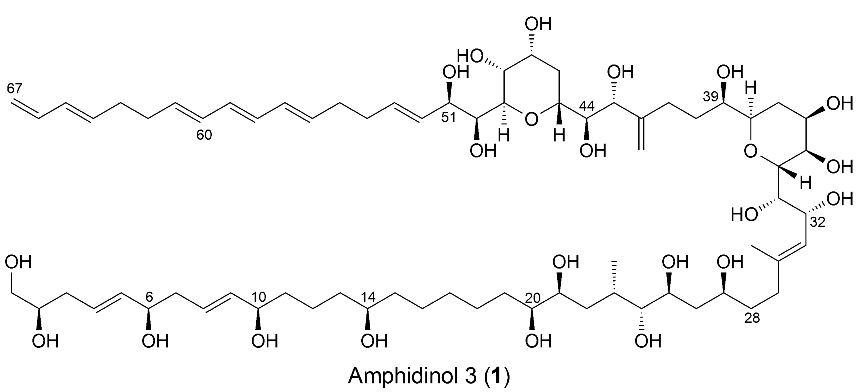

Figure. Structure of amphidinol 3 (**1**).

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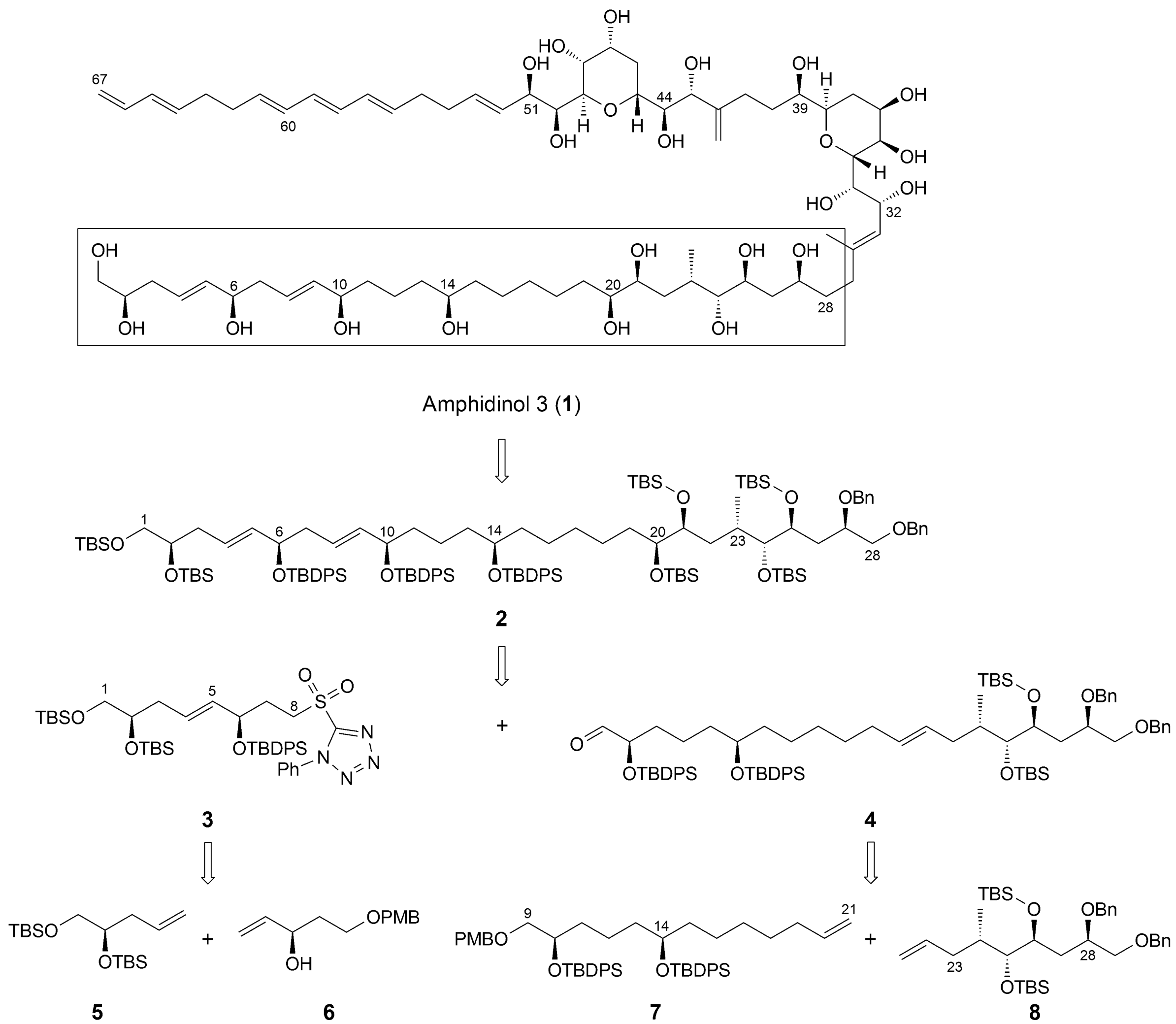
Scheme 1. Retrosynthesis of polyol side chain (C(1) – C(28)) of Amphidinol 3 (**1**).

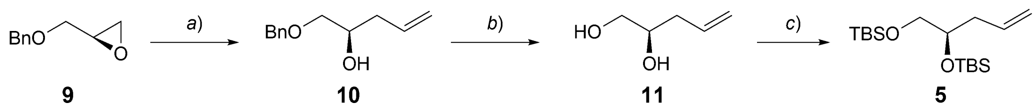


Results and Discussion

Accordingly, the synthesis of intermediate **5** began from (*R*)-benzylglycidyl ether **9**. Ring opening of the epoxide **9** with vinyl magnesium bromide in the presence of a catalytic amount of CuCN gave the homoallylic alcohol **10**. Debenzylation of **10** with Li in liquid NH_3 [14] afforded the diol **11**, which was protected as its di(*tert*-butyldimethylsilyl) ether **5** using *tert*-butyldimethylsilyl chloride (TBSCl) [15], imidazole, and a catalytic amount of 4-dimethylaminopyridine (DMAP) in anhydrous CH_2Cl_2 (*Scheme 2*).

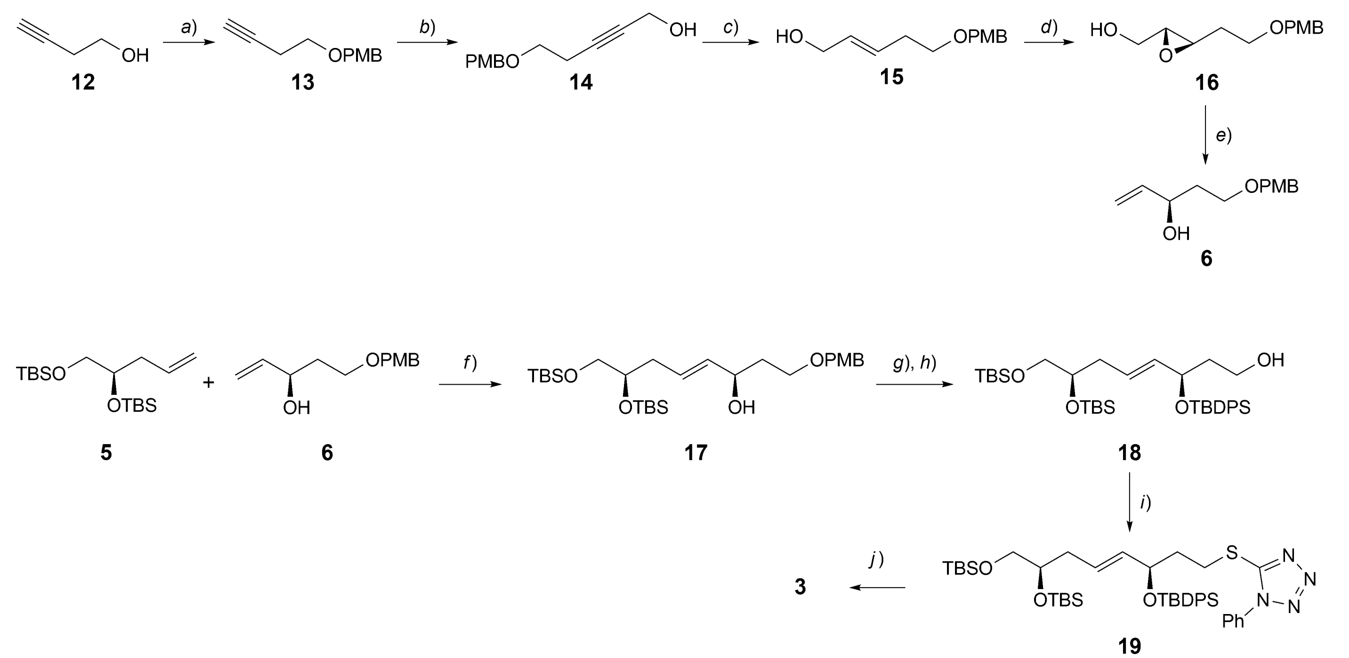
Another key intermediate **6** was prepared from a commercially available 3-butyn-1-ol (**12**). Protection of **12** with *p*-methoxybenzyl bromide in the presence of NaH in anhydrous THF at 0 °C gave the PMB ether **13**. Reaction of **13** with ethyl magnesium bromide followed by treatment with paraformaldehyde in anhydrous THF afforded the propargyl alcohol **14**. Reduction of **14** with $LiAlH_4$ in anhydrous THF at room temperature gave the desired *trans*-allylic alcohol **15**. *Sharpless* asymmetric epoxidation of **15** using $Ti(O^iPr)_4$, diisopropyl tartrate ((−)-DIPT), and *tert*-butyl hydroperoxide (TBHP) furnished the epoxy alcohol **16** [16]

Scheme 2



a) Vinyl magnesium bromide, CuCN, dry THF, −78 °C to 0 °C, 75%; *b*) Li, liq. NH_3, THF, −30 °C, 20 min, 75%; *c*) TBSCl, imidazole, CH_2Cl_2, 0 °C – r.t., 92%.

Scheme 3



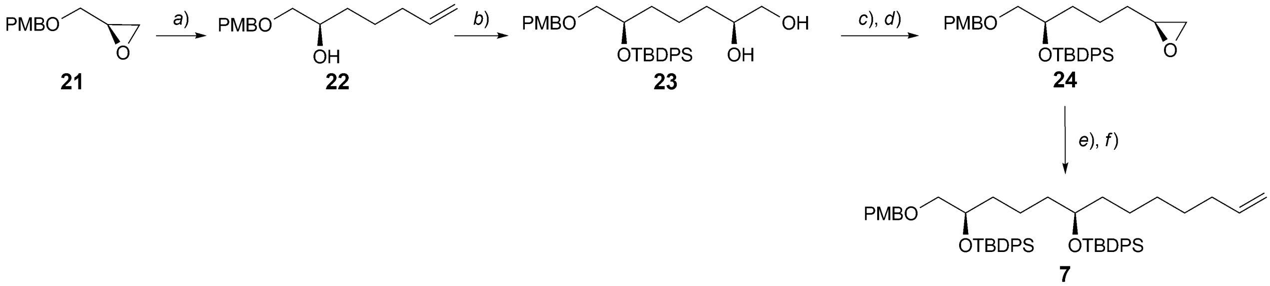
a) PMBBr, NaH, dry THF, 0 °C, 88%; *b*) Mg, EtBr, dry THF, 0 °C – r.t., $(CH_2O)_n$, 80%; *c*) $LiAlH_4$, dry THF, 0 °C – r.t., 80%; *d*) $Ti(OiPr)_4$, (–)-DIPT, TBHP, –20 °C, dry CH_2Cl_2, 85% yield, 90% d.e.; *e*) $(C_5H_5)_2TiCl_2$, Zn, $ZnCl_2$, dry THF, r.t., 85%, > 95% ee; *f*) *Grubbs*' *II* catalyst, CH_2Cl_2, 72%; *g*) TBDPSCl, DMAP, imidazole, CH_2Cl_2, 0 °C – r.t., 90%; *h*) DDQ, CH_2Cl_2, pH 7 buffer (9:1), 85%; *i*) *p*-TSH, TPP, DIAD, THF, 0 °C – r.t., 90%; *j*) $Mo_7O_{24}(NH_4)_6 \cdot 4\ H_2O$, H_2O_2, EtOH, 0 °C – r.t., 88%.

with 9:1 ratio of diastereoisomers, which are separable by column chromatography. Compound **16** was converted into allylic alcohol **6** using our own protocol [10] (*Scheme 3*). In order to get the advanced intermediate **3**, we adopted the cross metathesis strategy. Thus the cross-coupling of fragments **5** and **6** using *Grubbs*' *II* generation catalyst [12] (10 mol-%) in CH_2Cl_2 gave the *trans*-alkenol **17** exclusively. Protection of **17** with TBDPSCl in the presence of imidazole in CH_2Cl_2 afforded the TBDPS ether and deprotection of 4-methoxybenzyl (PMB) ether using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in CH_2Cl_2/H_2O (9:1) at pH 7 afforded the primary alcohol **18**. *Mitsunobu* reaction [17] of **18** with 1-phenyl-1*H*-tetrazole-5-thiol using diisopropyl azodicarboxylate (DIAD) and triphenylphosphine (TPP) in THF gave the sulfide **19**. Oxidation of sulfide **19** using a catalytic amount of ammonium molybdate [18] in the presence of H_2O_2 in EtOH furnished the sulfone **3** in good yield.

We next attempted the synthesis of intermediate **7**. Accordingly, the exposure of a racemic epoxide to *Jacobsen* hydrolytic kinetic resolution (HKR) conditions gave the *p*-methoxy benzyl glycidyl ether **21** [19] (*Scheme 4*). Regioselective ring opening of **21** with homoallyl $MgBr_2$, formed *in situ* from 4-bromo-1-butene and Mg in THF in the presence of CuBr gave the alkenol **22**. Protection of **22** as its silyl ether followed by *Sharpless* asymmetric dihydroxylation using AD-mix-α in ^{t}BuOH and H_2O (1:1) at 0 °C afforded the diol **23** as a mixture of diastereoisomers in the ratio of 8:2. Selective tosylation of the primary OH group of **23** under *Martinelli*'s conditions [20] using TsCl, Bu_2SnO, and Et_3N in CH_2Cl_2 afforded the *mono*-tosylate, which was used in the next step without further purification. Treatment of *mono*-tosylate with K_2CO_3 in MeOH afforded the epoxide **24**, which was then subjected to ring opening with *Grignard* reagent generated *in situ* from 6-bromo-1-hexene and magnesium [21] at 0 °C in the presence of 10 mol-% CuBr to afford the secondary alcohol, which was subsequently protected as its TBDPS ether using TBDPSCl, imidazole, and DMAP in CH_2Cl_2 to give the silyl ether **7**.

Another key intermediate **8** was prepared from a chiral epoxide **9** [22]. Ring opening of epoxide **9** with alkynyl ether under *Yamaguchi* conditions [23] afforded the secondary alcohol **25**, which was then protected as its benzyl ether **26** using benzyl bromide in the presence of NaH and a catalytic amount of TBAI in anhydrous THF (*Scheme 5*). Treatment of **26** with a catalytic amount of *p*-TSA in MeOH gave the propargyl alcohol **27**, which was then converted into *trans*-allylic alcohol **28** using $LiAlH_4$ under reflux conditions. Asymmetric epoxidation of allylic alcohol **28** under *Sharpless* conditions [(+)-diisopropyl tartrate, titanium(IV)isopropoxide, and *tert*-butyl hydroperoxide] in CH_2Cl_2 at –23 °C afforded the epoxy alcohol **29** in 9:1 diastereoisomeric ratio [8]. The epoxy alcohol **29** was further converted into allylic alcohol **30** using our own methodology [10], involving the reaction of epoxy alcohol with $(Et)_2TiCl$ and granulated Zn containing $ZnCl_2$ in THF under inert atmosphere. Protection of allylic alcohol **30** as its silyl ether **31** with TBDMSCl in

Scheme 4

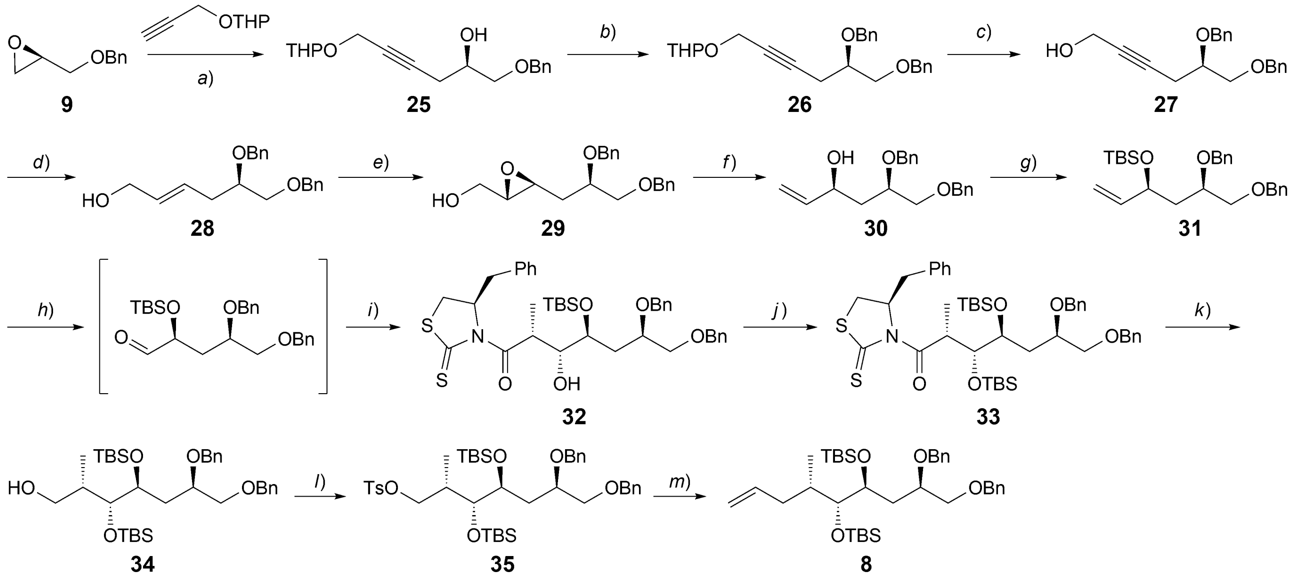


a) 4-Bromo-1-butene, Mg, CuBr, THF, −40 °C – r.t., 90%; *b*) TBDPSCl, DMAP, imidazole, CH_2Cl_2, 0 °C – r.t., 92%; *c*) AD-mix-α, ^{t}BuOH/H_2O, 90%; *d*) TsCl, Et_3N, Bu_2SnO, CH_2Cl_2, 0 °C – r.t., 95%; *e*) K_2CO_3, MeOH, 80%; *f*) 6-bromo-1-hexene, Mg, CuBr, THF, 0 °C, 85%; *g*) TBDPSCl, DMAP, imidazole, CH_2Cl_2, reflux, 95%.

the presence of imidazole and DMAP in CH_2Cl_2 at 0 °C followed by ozonolysis of the olefin gave the aldehyde. *Crimmins syn* aldol reaction [11] of the above aldehyde with (*S*)-1-(5-benzyl-2-thioxothiazolidin-3-yl)-propan-1-one using titanium tetrachloride and (−)-sparteine in CH_2Cl_2 under anhydrous conditions at 0 °C furnished the *syn*-aldol product **32** as a single diastereoisomer. The OH group of **32** was then protected with TBS-triflate and 2,6-lutidine in CH_2Cl_2 at 0 °C to afford the TBS ether **33**. Removal of the chiral auxiliary from **33** with $LiBH_4$ in THF/MeOH (9:1) at 0 °C gave the primary alcohol **34**. Protection of the OH group of **35** with TsCl in the presence of Et_3N and DMAP in CH_2Cl_2 followed by treatment with vinyl magnesium bromide in the presence of 10 mol-% Li_2CuCl_4 in Et_2O at −78 °C provided the desired product **8** in good yield [24].

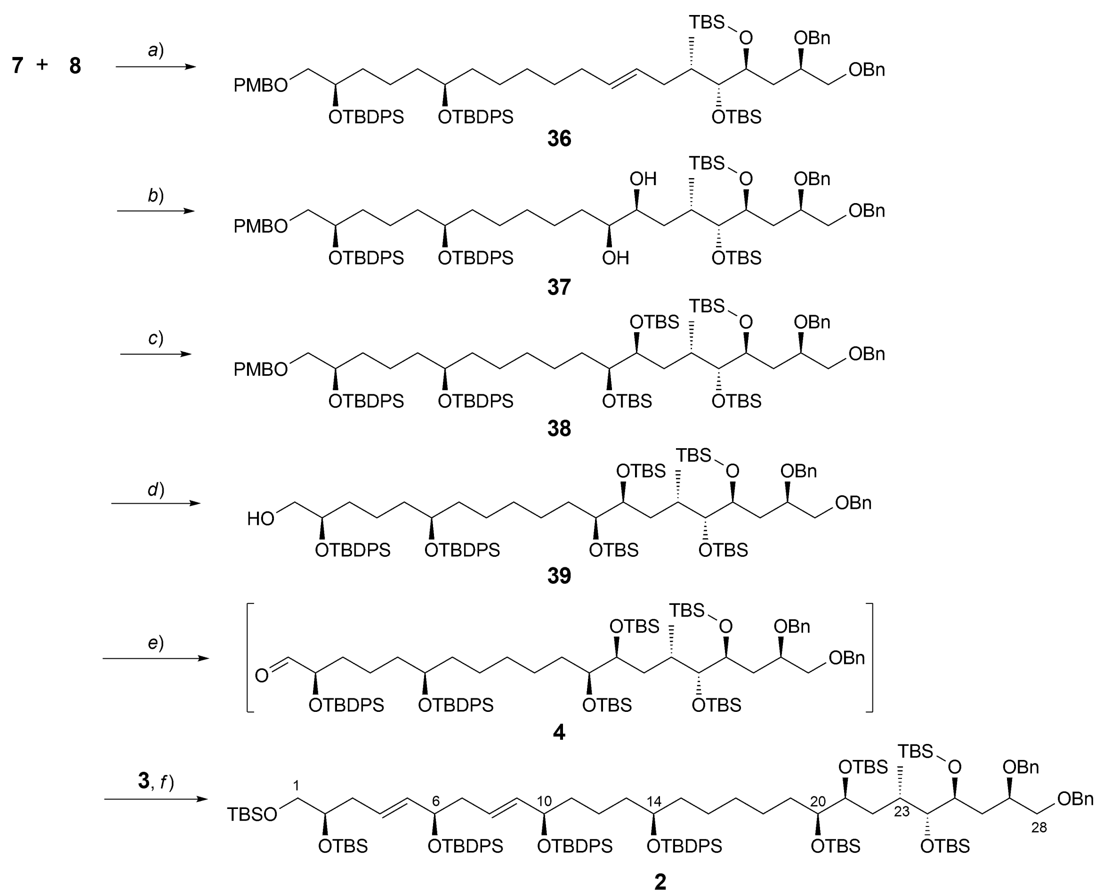
Having success in achieving key intermediates with required stereochemistry, we attempted the coupling of segments **7** and **8** by cross metathesis. Thus the cross-coupling of olefins **7** and **8** in 1:3 ratio in the presence of *Grubbs*' *II* generation catalyst (10 mol-%) in CH_2Cl_2 afforded the compound **36** (*Scheme 6*). Asymmetric dihydroxylation [9] of **36** under *Sharpless* conditions gave the diol **37** as a mixture of diastereoisomers in the ratio of 9:1. Protection of the diol using TBSOTf and 2,6-lutidine in CH_2Cl_2 gave the bis-silyl ether **38** in good yield. Treatment of **38** with DDQ in CH_2Cl_2/H_2O (9:1) at pH 7 buffer gave the primary alcohol **39**. Oxidation of the primary alcohol **39** with *Dess–Martin* periodinane [25] afforded the aldehyde **4**. Finally, the coupling of aldehyde **4** with C(1) – C(8) fragment **3** through a *Julia–Kocienski* olefination [13] using KHMDS at −78 °C afforded the fully protected C(1) – C(28) polyol fragment **2**

Scheme 5



a) BuLi, $BF_3·OEt_2$, THF, −78 °C, 80%; *b*) NaH, BnBr, TBAI, THF, 95%; *c*) *p*-TSA, MeOH, 95%; *d*) $LiAlH_4$, THF, reflux, 80%; *e*) L-(+)-DIPT, $Ti(O^iPr)_4$, TBHP, CH_2Cl_2, −20 °C, 90%; *f*) $(Et)_2TiCl_2$, Zn, $ZnCl_2$, Dry THF, r.t., 85%; *g*) TBSCl, imidazole, CH_2Cl_2, 0 °C – r.t., 92%; *h*) O_3, Ph_3P, 90%; *i*) (*S*)-1-(5-benzyl-2-thioxothiazolidin-3-yl-propan-1-one, $TiCl_4$, (–)-sparteine, CH_2Cl_2, 0 °C, 85%; *j*) 2,6,-lutidine, TBSOTf, CH_2Cl_2, 0 °C, 95%; *k*) $LiBH_4$, THF/MeOH, 91%; *l*) TsCl, DMAP, Et_3N, CH_2Cl_2, 92%; *m*) Li_2CuCl_4, vinyl magnesium bromide, dry Et_2O, −78 to 0 °C, 75%.

Scheme 6



a) *Grubbs*' *II*, CH_2Cl_2, 70% (9:1 *E*/*Z*); *b*) AD-mix-α, $MeSO_2NH_2$, *t*-BuOH/H_2O, 80%; *c*) 2,6-lutidine, TBSOTf, CH_2Cl_2, 95 %; *d*) DDQ, CH_2Cl_2/H_2O (pH 7 buffer) (9:1), 87%; *e*) DMP, $NaHCO_3$, CH_2Cl_2; *f*) KHMDS, THF, 18-crown-6 ether, −78 °C – r.t., 80%.

of amphidinol 3 (**1**) in 9:1 ratio of (*E/Z*)-isomers (C(9)=C(10)).

Conclusions

In conclusion, we have accomplished a highly stereoselective synthesis of the C(1) – C(28) fragment of amphidinol 3. This approach establishes ten stereogenic centers of amphidinol 3. Our approach successfully utilizes the *Jacobsen* hydrolytic kinetic resolution, *Sharpless* asymmetric epoxidation, *Sharpless* asymmetric dihydroxylation, *Yadav*'s protocol, *Crimmins* aldol reaction, cross metathesis, and *Julia–Kocienski* olefination protocols. It is a modular approach to produce other diastereoisomers of amphidinol 3; therefore, it would serve as a better option for new analogues.

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Experimental Part

General

All reagents were reagent grade and used without further purification unless specified otherwise. Solvents were distilled prior to use: THF, toluene, and Et_2O were distilled from Na and benzophenone ketyl, MeOH from Mg and I_2, CH_2Cl_2 from CaH_2. All air- or moisture-sensitive reactions were conducted under N_2 or Ar atmosphere in flame-dried or oven-dried glassware. Column chromatography (CC) was carried out using silica gel (SiO_2; 60 – 120 mesh or 100 – 200 mesh) packed in glass columns. Technical grade AcOEt and petroleum ether (PE) used for CC were distilled prior to use. Optical rotations were measured on digital polarimeter using a 1 ml cell with a 1 dm path length, *Horiba* (Japan) high-sensitive polarimeter *SEPA-300* at 25 °C. IR Spectra: *PerkinElmer IR-683* spectrophotometer (Shelton, USA) with NaCl optics. ^1H-NMR (200 and 300 MHz) and ^{13}C-NMR (50 and 75 MHz) spectra: *Varian Gemini FT-200* (Paloalto, USA) and *Bruker Avance 300* (Switzerland) instruments with TMS as internal standard in $CDCl_3$; the coupling constant *J* is given in Hz. The chemical shifts are reported in ppm downfield from TMS (Me_4Si) as internal standard and signal patterns are indicated as follows: *s*, *singlet*; *d*, *doublet*; *t*, *triplet*; *q*, *quartet*; *sext.*, *sextet*; *m*, *multiplet*; br., broad. MS: *Agilent Technologies 1100 Series* (Agilent ChemStation software; Waldbronn, Germany). Mass analysis was done in the ESI mode.

(5*R*)-2,2,3,3,8,8,9,9-Octamethyl-5-(prop-2-en-1-yl)-4,7-dioxa-3,8-disiladecane (**5**). To a soln. of alcohol **11** [14] (1.5 g, 14.70 mmol) in CH_2Cl_2 (30 ml) at 0 °C were added imidazole (4.23 g, 58.8 mmol); *tert*-butyl(chloro)dimethylsilane (6.61 g, 44.1 mmol) and a cat. amount of DMAP. The mixture was stirred at 0 °C for 1 h followed by warming it to r.t., and then poured into H_2O followed by separation of the org. layer. The aq. layer was extracted with CH_2Cl_2 and the combined org. extracts were dried ($MgSO_4$) and concentrated. The crude product was purified by flash CC (SiO_2; 5% AcOEt in hexanes) to yield **5** (4.46 g, 92% yield) as a colorless liquid. $[\alpha]_D^{20} = -1.72$ (c = 1.0, $CHCl_3$). IR (neat): 3070, 2958, 1452, 1125, 906. ^{1}H-NMR (300 MHz, $CDCl_3$): 5.86 – 5.71 (*m*, 1 H); 5.10 – 4.96 (*m*, 2 H); 3.70 – 3.63 (*m*, 1 H); 3.50 – 3.36 (*m*, 2 H); 2.36 – 2.25 (*m*, 1 H); 2.18 – 2.07 (*m*, 1 H); 0.88 (*s*, 9 H); 0.86 (*s*, 9 H); 0.03 (*s*, 12 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 135.2; 116.7; 72.8; 66.8; 39.0; 25.9; 25.8; 18.3; 18.1; −2.9; −4.3; −4.6; −5.3. ESI-MS: 353 ([*M* + Na]$^+$). HR-ESI-MS: 353.2300 ($C_{17}H_{38}NaO_2Si_2^+$, [*M* + Na]$^+$; calc. 353.2308).

(3*R*)-5-[(4-Methoxybenzyl)oxy]pent-1-en-3-ol (**6**). To a red soln. of titanocene (7.85 g, 31.5 mmol) in dry THF (80 ml) containing freshly fused $ZnCl_2$ (1.39 g, 10.5 mmol) was added Zn powder (1.39 g, 10.5 mmol) and the mixture stirred for 1 h. The resulting green soln. was added to **16** (2.5 g, 10.5 mmol) in dry THF (20 ml) through a cannula. After 5 min, the mixture was treated with 5% HCl (20 ml) and extracted thoroughly with Et_2O. The Et_2O layer was washed with H_2O, 10% aq. $NaHCO_3$, H_2O, and brine, and dried (Na_2SO_4). Evaporation of the solvent and purification by CC afforded pure alcohol **6** (1.98 g, 85% yield) as a colorless liquid. $[\alpha]_D^{20} = -9.8$ (c = 1, $CHCl_3$). IR (neat): 3443, 2934, 2861, 1612, 1512, 1246, 1092, 819. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.20 (*d*, *J* = 8.4, 2 H); 6.82 (*d*, *J* = 8.4, 2 H); 5.89 – 5.76 (*m*, 1 H); 5.24 (*d*, *J* = 17.1, 1 H); 5.07 (*d*, *J* = 10.5, 1 H); 4.42 (*s*, 2 H); 4.28 (br. *s*, 1 H); 3.79 (*s*, 3 H); 3.70 – 3.52 (*m*, 2 H); 2.80 – 2.68 (*m*, 1 H); 1.88 – 1.67 (*m*, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 159.1; 140.4; 129.9; 129.2; 114.2; 113.7; 72.8; 71.7; 67.9; 55.1; 36.1. ESI-MS: 245 ([*M* + Na]$^+$).

(3*R*,4*E*,7*R*)-7,8-bis{[*tert*-butyl(dimethyl)silyl]oxy}-1-[(4-methoxybenzyl)oxy]oct-4-en-3-ol (**17**). *Grubbs*' *II* generation catalyst (0.85 g, 0.1 mmol, 10 mol-%) was dissolved in 2 ml of degassed CH_2Cl_2 and it was added drop wise to a soln. of **6** (0.22 g, 1 mmol) and **5** (0.490 g, 1.5 mmol) in 3 ml of CH_2Cl_2 degassed by Ar. After completion of addition, the mixture was allowed to stir for 12 h under reflux conditions. The solvent was removed under reduced pressure and the crude product was purified by SiO_2 CC (AcOEt/hexane) to afford the pure product **17** (0.374 g, 72% yield based on **6**) as a colorless liquid. $[\alpha]_D^{20} = -2.83$ (c = 1.0, $CHCl_3$). IR (neat): 3390, 2940, 1428, 1642, 1034. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.25 – 7.16 (*m*, 2 H); 6.88 – 6.78 (*m*, 2 H); 5.72 – 5.61 (*m*, 1 H); 5.54 – 5.44 (*m*, 1 H); 4.43 (*s*, 2 H); 4.29 – 4.21 (*m*, 1 H); 3.79 (*s*, 3 H); 3.71 – 3.53 (*m*, 2 H); 3.50 – 3.35 (*m*, 2 H); 2.66 – 2.54 (*m*, 2 H); 2.35 – 2.22 (*m*, 1 H); 2.18 – 2.06 (*m*, 1 H); 1.83 – 1.71 (*m*, 1 H); 1.58 (br. *s*, 1 H); 0.88 (*s*, 9 H); 0.86 (*s*, 9 H); 0.04 (*s*, 6 H); 0.03 (*s*, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 159.1; 134.7; 134.6; 130.0; 129.2; 127.5; 113.7; 72.8; 71.6; 68.0; 66.7; 55.2; 37.2; 36.6; 25.9; 25.8; 18.2; 18.0; −4.4; −4.6; −5.3; −5.4. ESI-MS: 547 ([*M* + Na]$^+$). HR-ESI-MS: 547.3247 ($C_{28}H_{52}NaO_5Si_2^+$, [*M* + Na]$^+$; calc. 547.3251).

(3*R*,4*E*,7*R*)-7,8-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-3-{[*tert*-butyl(diphenyl)silyl]oxy}oct-4-en-1-ol (**18**). To a stirred biphasic soln. of ether **17** (300 mg, 0.4 mmol) in CH_2Cl_2 (10 ml) and pH 7 buffer (1 ml) at 0 °C was added DDQ (133 mg, 0.59 mmol). The mixture was stirred at 0 °C for 2 h and the reaction quenched with sat. $NaHCO_3$ soln. The separated aq. phase was extracted with CH_2Cl_2 (3 × 10 ml). The combined org. layers were washed with sat. $NaHCO_3$ soln. and brine, dried (Na_2SO_4), and evaporated under vacuum. The residue was purified by CC (AcOEt/hexane) to deliver 213 mg (85%) of **18** as colorless oil. $[\alpha]_D^{20} = +9.0$ (c = 1.0, $CHCl_3$). IR (neat): 3452, 3030, 1612, 1241, 1152. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.92 – 7.80 (*m*, 4 H); 7.65 – 7.48 (*m*, 6 H); 5.72 – 5.44 (*m*, 2 H); 4.60 – 4.49 (*m*, 1 H); 3.92 (br. *s*, 1 H); 3.80 – 3.70 (*m*, 2 H); 3.63 – 3.46 (*m*, 2 H); 2.37 – 2.07 (*m*, 3 H); 2.03 – 1.73 (*m*, 2 H); 1.24 (*s*, 9 H); 1.06 (*s*, 9 H); 1.03 (*s*, 9 H); 0.20 (*s*, 12 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 135.9; 135.8; 135.0; 133.8; 133.6; 129.7; 129.5; 127.5; 127.3; 126.2; 74.9; 73.2; 72.8; 68.7; 59.5; 39.8; 36.3; 27.0; 25.9; 25.8; 19.2; 18.2; 18.0; −4.4; −4.7; −5.3. ESI-MS: 661 ([*M* + NH_4]$^+$). HR-ESI-MS: 665.3866 ($C_{36}H_{62}NaO_4Si_3^+$, [*M* + Na]$^+$; calc. 665.3853).

5-{[(3*R*,4*E*,7*R*)-7,8-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-3-{[*tert*-butyl(diphenyl)silyl]oxy}oct-4-en-1-yl]sulfanyl}-1-phenyl-1*H*-tetrazole (**19**). DIAD (94.3 mg, 0.466 mmol) was added to a soln. of alcohol **18** (0.2 g, 0.311 mmol), 1-phenyl-1*H*-tetrazole-5-thiol (72 mg, 0.404 mmol), and TPP (106 mg, 0.404 mmol) in THF (10 ml) at 0 °C. The mixture was stirred at r.t. for 3 h and quenched with sat. NaCl (10 ml) soln. The org. layer was separated and the aq. layer was extracted with AcOEt. The combined org. layers were dried ($MgSO_4$) and concentrated. The purification of the crude product by flash CC (AcOEt in hexane) provided **19** (225 mg, 90%) as an oil. $[\alpha]_D^{20} = -2.20$ (c = 1.05, $CHCl_3$). IR (neat):1662, 1590, 1563, 1512. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.70 – 7.49 (*m*, 9 H); 7.42 – 7.26 (*m*, 6 H); 5.51 – 5.41 (*m*, 2 H); 4.35 – 4.21 (*m*, 1 H); 3.66 – 3.56 (*m*, 1 H); 3.46 – 3.26 (*m*, 4 H); 2.27 – 1.87 (*m*, 4 H); 1.08 (*s*, 9 H); 0.90 (*s*, 9 H); 0.86 (*s*, 9 H); 0.03 (*s*, 12 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 154.2; 135.9; 135.8;133.9; 133.7; 133.5; 129.9; 129.6; 129.4; 128.3; 127.5; 127.3; 123.6; 72.7; 72.5; 66.5; 37.0; 36.7; 28.9; 27.0; 25.9; 25.8; 19.2; 18.2; 18.0; −4.4; −4.7; −5.32; −5.39. ESI-MS: 825 ([*M* + Na]$^+$). HR-ESI-MS: 825.4044 ($C_{43}H_{66}N_4NaO_3SSi_3^+$, [*M* + Na]$^+$; calc. 825.4061).

5-{[(3*R*,4*E*,7*R*)-7,8-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-3-{[*tert*-butyl(diphenyl)silyl]oxy}oct-4-en-1-yl]sulfonyl}-1-phenyl-1*H*-tetrazole (**3**). To a soln. of **19** (200 mg, 0.25 mmol) in 3 ml of EtOH at 0 °C was added 0.1 ml of a soln. of the oxidant (made from 62 mg of Mo_7O_{24} $(NH_4)_6 \cdot 4$ H_2O in 0.1 ml of

30% *w*/*v* aq. H_2O_2). The mixture was stirred at r.t. for 48 h, quenched with H_2O, filtered through a *Celite* pad, and the filtrate extracted with AcOEt. The combined org. layers were dried and concentrated to leave a residue that was purified by CC over SiO_2 (hexane/AcOEt) to provide 183 mg (88%) of **3** as a colorless viscous oil. $[\alpha]_D^{20}$ = +3.0 (*c* = 1.8, $CHCl_3$). IR (neat): 2928, 1597, 1497, 1466, 1107. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.70 – 7.54 (*m*, 9 H); 7.42 – 7.29 (*m*, 6 H); 5.65 – 5.54 (*m*, 1 H); 5.47 – 5.39 (*m*, 1 H); 4.40 – 4.33 (*m*, 1 H); 3.72 – 3.58 (*m*, 3 H); 3.45 – 3.32 (*m*, 2 H); 2.25 – 2.07 (*m*, 2 H); 2.06 – 1.95 (*m*, 2 H); 1.08 (*s*, 9 H); 0.88 (*s*, 9 H); 0.85 (*s*, 9 H); 0.02 (*s*, 12 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 153.3; 135.8; 135.7; 135.7; 133.4; 133.2; 132.5; 131.3; 129.8; 129.6; 129.6; 129.0; 128.9; 127.7; 127.5; 125.0; 72.5; 71.2; 66.3; 52.1; 36.8; 29.6; 27.0; 25.9; 25.8; 19.2; 18.2; 18.0; –4.45; –4.80; –5.35; –5.41. ESI-MS: 858 ([*M* + Na]$^+$). HR-ESI-MS: 857.3959 ($C_{43}H_{66}N_4NaO_5SSi_3^+$, [*M* + Na]$^+$; calc. 857.3959).

(2*R*)-1-[(4-Methoxybenzyl)oxy]hept-6-en-2-ol (**22**). A 50 ml three-necked flask containing Mg turnings (310 mg, 12.88 mmol) and a stirring bar were dried in an oven at 100 °C for 2 h and cooled to r.t. under a stream of dry N_2. A portion of 4-bromo 1-butene (1.04 g, 7.73 mmol) in anh. THF (20 ml) was introduced and the reaction was initiated with a small crystal of I_2 and the remaining soln. was added over 10 min at r.t. under a cool H_2O circulation. The stirring was continued for another 2 h at r.t. and the mixture was cooled to –40 °C. Then CuI (49 mg, 0.258 mmol) was added and the mixture was allowed to stir for 30 min and then a soln. of epoxide **21** (0.5 g, 2.58 mmol) in dry THF was added drop wise over 10 min. The resulting mixture was stirred at –40 °C for 1 h and then allowed to stir at r.t. over 2 h. After completion, the reaction was quenched by sat. aq. NH_4Cl and extracted by Et_2O, washed with H_2O, and brine and dried (Na_2SO_4). Removal of the solvent followed by purification on SiO_2 gave the pure product **22** (0.58 g, 90%) as a colorless liquid. $[\alpha]_D^{20}$ = –2.6 (*c* = 2.5, $CHCl_3$). IR (neat): 3454, 2999, 1640, 1612, 1460, 1248, 1035. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.20 (*d*, *J* = 8.4, 2 H); 6.83 (*d*, *J* = 8.6, 2 H); 5.83 – 5.67 (*m*, 1 H); 5.02 – 4.88 (*m*, 2 H); 4.45 (*s*, 2 H); 3.79 (*s*, 3 H); 3.77 – 3.68 (*m*, 1 H); 3.41 (*dd*, *J* = 3.0, 9.2, 1 H); 3.26 – 3.18 (*m*, 1 H); 2.10 – 2.01 (*m*, 2 H); 1.60 – 1.32 (*m*, 4 H); 1.25 (br. *s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 159.2; 138.5; 129.9; 129.3; 127.0; 114.5; 113.7; 74.2; 72.9; 70.1; 55.1; 33.6; 32.4; 24.6. ESI-MS: 273 ([*M* + Na]$^+$). HR-ESI-MS: 273.1476 ($C_{15}H_{22}NaO_3^+$, [*M* + Na]$^+$; calc. 273.1467).

(2*S*,6*R*)-6-{[*tert*-Butyl(diphenyl)silyl]oxy}-7-[(4-methoxybenzyl)oxy]heptane-1,2-diol (**23**). The mixture of 10 ml of ^{t}BuOH, 10 ml of H_2O, and 2.29 g of AD-mix-α was stirred at r.t. until both phases are clear and then the soln. was cooled to 0 °C. The olefin **22** (0.8 g, 1.63 mmol) dissolved in 2 ml of ^{t}BuOH was added at once and the heterogeneous slurry is stirred vigorously at 0 °C for about 8 h, until TLC revealed the absence of the starting material. The reaction was quenched at 0 °C by addition of sodium sulfite, then warmed to r.t., and stirred for 30 min. The mixture was extracted with AcOEt (3 × 10 ml). The org. layer was washed with 2N KOH soln. and then dried (anh. Na_2SO_4). Removal of solvent and purification by SiO_2 CC afforded the diol **23** (0.77 g, 90 %) as a gummy liquid. $[\alpha]_D^{20}$ = +9.45 (*c* = 1.85, $CHCl_3$). IR (neat): 3400, 2858, 1612, 1302, 1109, 1037. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.63 (*d*, *J* = 6.7, 4 H); 7.42 – 7.27 (*m*, 6 H); 7.05 (*d*, *J* = 8.4, 2 H); 6.76 (*d*, *J* = 8.4, 2 H); 4.24 (*s*, 2 H); 3.85 – 3.76 (*m*, 1 H); 3.78 (*s*, 3 H); 3.55 – 3.44 (*m*, 2 H); 3.37 – 3.23 (*m*, 3 H); 1.57 – 1.12 (*m*, 8 H); 1.03 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 159.0; 135.9; 135.8; 134.3; 134.1; 130.4; 129.5; 129.4; 129.2; 127.4; 127.3; 113.6; 73.4; 72.7; 72.0; 71.9; 66.6; 55.2; 34.1; 33.0; 27.0; 20.6; 19.3. ESI-MS: 545 ([*M* + Na]$^+$). HR-ESI-MS: 545.2683 ($C_{31}H_{42}NaO_5Si^+$, [*M* + Na]$^+$; calc. 545.2699).

***tert*-Butyl({(2*R*)-1-[(4-methoxybenzyl)oxy]-5-[(2*S*)-oxiran-2-yl]pentan-2-yl}oxy)diphenylsilane** (**24**). To a stirred soln. of diol **23** (0.7 g, 1.34 mmol) in dry CH_2Cl_2 (10 ml), Bu_2SnO (6.6 mg, 0.026 mmol), TsCl (0.254 g, 1.34 mmol), and Et_3N (0.28 ml, 2.0 mmol) were added at 0 °C and allowed to stirred at r.t. for 6 h. Later, the reaction was quenched with sat. $NaHCO_3$ (5 ml), then extracted with CH_2Cl_2 (2 × 10 ml), dried with anh. Na_2SO_4, and concentrated under vacuum to afford the *mono*-tosylate. This was used for the next step without purification. To a stirred soln. of the above monotosylate in dry MeOH (10 ml) was added solid K_2CO_3 (0.346 g, 2.54 mmol) at 0 °C and stirred at the same temp. for 1 h. After completion of the reaction, K_2CO_3 was filtered through a *Celite* pad. MeOH was evaporated and extracted with $CHCl_3$ (2 × 10 ml). The combined org. layers were dried (anh. Na_2SO_4) and concentrated under vacuum. The residue was purified by SiO_2 CC (60 – 120 mesh, AcOEt/hexane) to afford the compound **24** (0.54 g, 80%, over two steps) as a liquid. $[\alpha]_D^{20}$ = +10.74 (*c* = 1.35, $CHCl_3$). IR (neat): 3010, 1622, 1250, 910. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.66 – 7.60 (*m*, 4 H); 7.41 – 7.26 (*m*, 6 H); 7.03 (*d*, *J* = 8.3, 2 H); 6.75 (*d*, *J* = 9.0, 2 H); 4.22 (*s*, 2 H); 3.86 – 3.79 (*m*, 1 H); 3.78 (*s*, 3 H); 3.35 – 3.25 (*m*, 2 H); 2.75 – 2.68 (*m*, 1 H); 2.64 – 2.60 (*m*, 1 H); 2.33 – 2.28 (*m*, 1 H); 1.58 – 1.23 (*m*, 6 H); 1.03 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 158.9; 135.9; 135.8; 134.4; 134.0; 130.4; 129.5; 129.4; 129.1; 127.4; 127.3; 113.5; 73.4; 72.6; 71.8; 52.2; 52.1; 47.0; 33.9; 32.4; 27.0; 21.0; 19.3. ESI-MS: 527 ([*M* + Na]$^+$).

(5*R*,9*R*)-5-(Hept-6-en-1-yl)-9-{[(4-methoxybenzyl)oxy]methyl}-2,2,12,12-tetramethyl-3,3,11,11-tetraphenyl-4,10-dioxa-3,11-disilatridecane (**7**). To a stirred soln. of **24** (0.4 g, 0.68 mmol) in CH_2Cl_2 (10 ml), imidazole (47.6 mg, 1.36 mmol) was added. After 5 min, TBSCl (0.28 g, 1.02 mmol) and cat. DMAP were added and stirred at r.t. for 2 h. The reaction was quenched by adding H_2O (5 ml) and extracted with CH_2Cl_2 (3 × 10 ml). The org. extracts were washed with brine (5 ml), dried (anh. Na_2SO_4) and concentrated under vacuum to remove the solvent and the crude was purified by CC to afford the pure product **7** (0.53 g, 95%) as a colorless liquid.

$[\alpha]_D^{20}$ = −7.6 (*c* = 1.35, $CHCl_3$). IR (neat): 2930, 1641, 1248, 1039, 702. ^{1}H-NMR (300 MHz, $CDCl_3$):7.64 – 7.54 (*m*, 8 H); 7.39 – 7.23 (*m*, 12 H); 7.03 – 6.96 (*m*, 2 H); 6.77 – 6.70 (*m*, 2 H); 5.81 – 5.63 (*m*, 1 H); 4.97 – 4.85 (*m*, 2 H); 4.17 (*s*, 2 H); 3.78 (*s*, 3 H); 3.74 – 3.69 (*m*, 1 H); 3.63 – 3.55 (*m*, 1 H); 3.25 – 3.15 (*m*, 2 H); 2.00 – 1.88 (*m*, 2 H); 1.33 – 1.17 (*m*, 14 H); 1.01 (*s*, 9 H); 1.00 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 159.4; 139.1; 135.9; 135.8; 134.6; 134.5; 129.4; 129.3; 129.1; 127.3; 127.3; 127.2; 114.0; 113.5; 73.6; 72.9; 72.5; 72.1; 55.2; 36.4; 36.3; 35.9; 34.3; 33.6; 29.1; 28.8; 27.0; 26.9; 24.5; 20.1; 19.3. ESI-MS: 844 ([*M* + NH_4]$^+$). HR-ESI-MS: 827.4925 ($C_{53}H_{70}O_4Si_2^+$, [*M* + H]$^+$; calc. 827.4890).

(2*R*)-1-(Benzyloxy)-6-(tetrahydro-2*H*-pyran-2-yloxy)hex-4-yn-2-ol (**25**). A soln. of BuLi in hexane (28.5 ml, 45.7 mmol, 1.6M soln.) was added to a soln. of 2-(prop-2-yn-1-yloxy)tetrahydro-2*H*-pyran (6.40 g, 45.7 mmol) in THF (40 ml) at −78 °C under N_2 atmosphere, and the mixture was stirred for 15 min. Then $BF_3 \cdot OEt_2$ (6.0 ml, 48.8 mmol) was added to the soln. and stirring was continued for 15 min at −78 °C. Finally, a soln. of epoxide **9** (5.0 g, 30.5 mmol) in dry THF (20 ml) was added, and after stirring the mixture for 3 h at −78 °C, the reaction was quenched by adding sat. aq. NH_4Cl soln. (20 ml). The mixture was extracted with AcOEt and dried (anh. Na_2SO_4). Evaporation of the solvent resulted in crude alcohol which was purified by CC to afford pure **25** (8.34 g, 90% yield) as a viscous liquid. $[\alpha]_D^{20}$ = −5.6 (*c* = 1.5, $CHCl_3$). IR (neat): 3431, 2943, 2868, 2233, 1728, 1446, 1367, 1248, 1109. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.36 – 7.22 (*m*, 5 H); 4.77 – 4.73 (*m*, 1 H); 4.55 (*s*, 2 H); 4.24 – 4.12 (*m*, 2 H); 3.94 – 3.87 (*m*, 1 H); 3.79 (*ddd*, *J* = 2.6, 8.9, 11.5, 1 H); 3.59 – 3.54 (*m*, 1 H); 3.53 – 3.42 (*m*, 2 H); 2.53 – 2.33 (*m*, 2 H); 1.88 – 1.77 (*m*, 1 H); 1.74 – 1.38 (*m*, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 137.7; 128.3; 127.6; 96.7; 84.2; 82.0; 78.1; 73.3; 72.8; 68.8; 61.9; 54.4; 30.1; 25.2; 23.4; 18.9. ESI-MS: 322 ([*M* + Na]$^+$), 305 ([*M* + H]$^+$).

{(2*S*,3*S*)-3-[(2*R*)-2,3-Bis(benzyloxy)propyl]oxiran-2-yl}methanol (**29**). To a freshly flame-dried double-necked round-bottom flask equipped with activated molecular sieves (4 Å, *ca.* 5 g) and dry CH_2Cl_2 (60 ml) at −20 °C were added $Ti(O^iPr)_4$ (0.83 ml, 2.76 mmol), L-(+)-diisopropyl tartrate (0.5 ml, 2.41 mmol), and the mixture was stirred for 20 min. To this mixture, allyl alcohol **28** (6.0 g, 19.5 mmol), followed by an interval of 20 min, TBHP (7.8 ml, 42.8 mmol, 5.5M soln. in decane) were added and stirring was continued till completion of the reaction 14 h). The mixture was warmed to 0 °C and quenched with H_2O (17 ml) and stirred vigorously for 30 min. The mixture was filtered through a sintered funnel and the filtrate was again stirred along with 20% aq. NaOH soln. (5 ml) sat. with solid NaCl. The biphasic soln. was separated and aq. layer was extracted with CH_2Cl_2 (2 × 30 ml). The combined org. extracts were dried (anh. Na_2SO_4) and concentrated under vacuum. The crude residue was purified by CC to afford the pure epoxide **29** as colorless oil (5.40 g, 85.0% yield). $[\alpha]_D^{20}$ = −10.3 (*c* = 1.65, $CHCl_3$). IR (neat): 3408, 2916, 2866, 1718, 1494, 1454, 1271, 1093, 904. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.36 – 7.21 (*m*, 10 H); 4.70 – 4.50 (*m*, 4 H); 3.83 – 3.66 (*m*, 2 H); 3.65 – 3.44 (*m*, 3 H); 3.05 – 2.96 (*m*, 1 H); 2.85 – 2.79 (*m*, 1 H); 1.87 – 1.78 (*m*, 2 H); 1.43 (br. *s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 138.3; 138.2; 128.3; 127.7; 127.6; 127.5; 75.5; 73.3; 71.9; 71.6; 61.5; 58.1; 53.0; 34.0. ESI-MS: 351 ([*M* + Na]$^+$). HR-ESI-MS: 351.1586 ($C_{20}H_{24}NaO_4^+$, [*M* + Na]$^+$; calc. 351.1572).

{[(3*S*,5*R*)-5,6-Bis(benzyloxy)hex-1-en-3-yl]oxy}(*tert*-butyl)dimethylsilane (**31**). To a stirred soln. of alcohol **30** (4.0 g, 12.8 mmol) in dry CH_2Cl_2 30 ml) at 0 °C, imidazole (1.85 g, 25.64 mmol), TBSCl (2.30 g, 15.38 mmol), and cat. amount of DMAP were added under N_2 atmosphere and stirred for 6 h. The mixture was warmed to r.t., diluted with H_2O (10 ml), and extracted with CH_2Cl_2 (2 × 15 ml). The combined org. layers were washed with brine (1 × 10 ml), dried (anh. Na_2SO_4), filtered, and concentrated under vacuum to afford the crude product. CC of the crude product afforded **31** as a colorless liquid (5.02 g, 92%). $[\alpha]_D^{20}$ = +6.4 (*c* = 0.85, $CHCl_3$). IR (neat): 3065, 2949, 1643, 1496, 1361, 1253, 1207, 1093, 923, 837, 777. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.56 – 7.38 (*m*, 10 H); 6.0 – 5.84 (*m*, 1 H); 5.24 – 5.13 (*m*, 2 H); 4.89 – 4.68 (*m*, 4 H); 4.45 – 4.36 (*m*, 1 H); 3.88 – 3.78 (*m*, 1 H); 3.71 (*d*, *J* = 3.1, 2 H); 2.08 – 1.95 (*m*, 1 H); 1.91 – 1.78 (*m*, 1 H); 1.06 (*s*, 9 H); 0.20 (*s*, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 141.1; 138.8; 138.3; 128.2; 128.1; 127.7; 127.5; 127.4; 127.3; 114.2; 74.9; 73.2; 72.9; 71.6; 71.1; 40.4; 25.8; 25.8; 18.1; −4.3; −4.9. ESI-MS: 449 ([*M* + Na]$^+$). HR-ESI-MS 449.2486 ($C_{26}H_{38}NaO_3Si^+$, [*M* + Na]$^+$; calc. 449.2488).

(2*S*,3*S*,4*S*,6*R*)-6,7-Bis(benzyloxy)-1-[(4*S*)-4-benzyl-2-thioxo-1,3-thiazolidin-3-yl]-4-{[*tert*-butyl(dimethyl)silyl]oxy}-3-hydroxy-2-methylheptan-1-one (**32**). A soln. of **31** (4.0, 9.45 mmol) in CH_2Cl_2 (40 ml) was cooled to −78 °C and ozone was bubbled though it until the soln. turned to light blue. To this cold soln., TPP (3.7 g, 14.17 mmol) was added and stirring was maintained at r.t. for 5 h. The solvent was evaporated and the residue was purified by CC on SiO_2 (hexane/AcOEt) afford aldehyde (3.38 g; 85%) as a colorless oil; this was used for the next step. Titanium tetrachloride (0.88 ml, 7.97 mmol) was added slowly to a soln. of 1-[(5*S*)-5-benzyl-2-thioxo-1,3-thiazolidin-3-yl] propan-1-one (2.10 g, 7.97 mmol) in CH_2Cl_2 (50 ml) at 0 °C and stirred for 5 min. To this yellow suspension, (–)-sparteine (4.5 ml, 19.92 mmol) was added. After stirring for 20 min, to the dark red enolate, freshly prepared above aldehyde (3.38 g, 7.97 mmol, 1.0 equiv.) dissolved in CH_2Cl_2 (8 ml) was added slowly to the above mixture at 0 °C. After 4 h, the reaction was quenched with the addition of half-sat. NH_4Cl. The org. layer was separated and the aq. layer was extracted (2 × 40 ml) with CH_2Cl_2. The combined org. layers were dried (Na_2SO_4), filtered, concentrated, and the crude product was purified by CC to provide the title compound **32** (4.68 g, 85%) as an oil: $[\alpha]_D^{20}$ = −36.5 (*c* = 2.0, $CHCl_3$). IR (neat): 3492, 2930, 2858, 1707, 1454, 1342, 1257, 1099, 837. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.34 – 7.10 (*m*, 15 H); 5.08 – 4.97 (*m*, 1 H); 4.78 – 4.54 (*m*, 3 H); 4.50 (*s*, 2 H); 3.99 – 3.89 (*m*, 2 H); 3.87 – 3.78 (*m*, 1 H); 3.49 (*d*, *J* = 4.9, 2 H); 3.23 (*dd*, *J* = 3.2, 13.0, 1 H); 3.02 – 2.91 (*m*, 2 H); 2.76 (*dd*, *J* = 6.9, 11.3, 1 H); 2.59 (*d*, *J* = 11.3, 1 H); 2.01 – 1.93 (*m*, 1 H); 1.76 – 1.65 (*m*, 1 H); 1.22 (*d*, *J* = 6.7, 3 H); 0.89 (*s*, 9 H); 0.08 (*s*, 3 H); 0.04 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 200.1; 177.5; 138.4; 138.0; 136.5; 129.3; 128.7; 128.2; 127.5; 127.3; 127.0; 126.8; 74.3; 73.3; 73.2; 72.4; 71.4; 69.8; 69.3; 40.7; 36.4; 35.8; 31.5; 29.6; 25.8; 17.8; 10.0; –4.2; –4.6. ESI-MS: 716 ([*M* + Na]$^+$). HR-ESI-MS: 694.3046 ($C_{38}H_{52}NO_5S_2Si^+$, [*M* + H]$^+$; calc. 694.3051).

(2*S*,3*R*,4*S*,6*R*)-6,7-Bis(benzyloxy)-3,4-bis{[*tert*-butyl(dimethyl)silyl]oxy}-2-methylheptan-1-ol (34). To a soln. of compound **33** (2.2 g, 2.27 mmol) in a solvent mixture of (THF/MeOH 9:1) 20 ml at 0 °C was $LiBH_4$ (79 mg, 3.40 mmol). The mixture was stirred for 1 h at 0 °C followed by an additional 1 h at r.t., then it was cooled to 0 °C, quenched with sat. aq. sodium potassium tartrate soln. (5 ml), diluted with AcOEt (15 ml), and sat. aq. sodium potassium tartrate soln. (10 ml). The mixture was stirred for 30 min at r.t. followed by separation of layers. The aq. layer was extracted with AcOEt, the combined org. layers were dried ($MgSO_4$), and concentrated. The crude product was purified by flash CC (AcOEt/hexanes) to provide the title compound **34** (1.5 g, 91%) as an oil. $[\alpha]_D^{20}$ = –5.0 (*c* = 1.2, $CHCl_3$). IR (neat): 3468, 3032, 2930, 1591, 1469, 1361, 1253, 1209, 1049, 835. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.40 – 7.20 (*m*, 10 H); 4.71 – 4.53 (*m*, 4 H); 3.97 – 3.88 (*m*, 1 H); 3.83 – 3.70 (*m*, 2 H); 3.64 – 3.49 (*m*, 2 H); 3.48 – 3.39 (*m*, 2 H); 1.94 – 1.66 (*m*, 3 H); 1.35 – 1.25 (*m*, 1 H); 0.98 – 0.87 (*m*, 21 H); 0.06 (*s*, 6 H); 0.02 (*s*, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 138.8; 128.2; 128.2; 127.7; 127.5; 127.5; 127.3; 77.5; 75.7; 73.3; 73.1; 72.5; 71.3; 65.4; 39.3; 35.8; 26.0; 25.9; 18.2; 18.0; 12.9; –3.5; –3.8; –4.7; –5.0. ESI-MS: 625 ([*M* + Na]$^+$). HR-ESI-MS: 625.3697 ($C_{34}H_{58}NaO_5Si_2^+$, [*M* + Na]$^+$; calc. 625.3720).

(5*S*,6*R*)-5-[(2*R*)-2,3-Bis(benzyloxy)propyl]-2,2,3,3,8,8,9,9-octamethyl-6-[(2*S*)-pent-4-en-2-yl]-4,7-dioxa-3,8-disiladecane (8). To a stirred soln. of alcohol **34** (1.0 g, 1.65 mmol) in dry CH_2Cl_2 (10 ml), TsCl (347 mg, 1.82 mmol), and Et_3N (0.35 ml, 2.47 mmol) were added at 0 °C and allowed to stirred at r.t. for 5 h. Later, the mixture was extracted with CH_2Cl_2 (2 × 25 ml), dried (anh. Na_2SO_4), and concentrated under vacuum. The residue was purified by CC (60 – 120 mesh, AcOEt/hexane) to afford monotosylated product **35** (1.2 g, 95%) as a liquid. This was used for the next step. To the stirred soln. of the monotosylated compound **35** (1.2 g, 1.58 mmol) in dry Et_2O (20 ml) was added Li_2CuCl_4 (0.16 ml, 0.16 mmol, 1.0 molar soln. in Et_2O) at –78 °C and stirred at the same temp. for 1 h. Vinyl magnesium bromide (6.32 ml, 6.32 mmol, 1.0M soln. in Et_2O) was added slowly at –40 °C under N_2 atmosphere and then the mixture was stirred for 3 h at the same temp. After 2 h, the reaction was quenched with sat. aq. NH_4Cl soln. (20 ml) at 0 °C, Et_2O was evaporated, and the mixture was extracted with AcOEt (2 × 20 ml). The combined org. layers were dried (anh. Na_2SO_4), and concentrated under vacuum. The residue was purified by CC SiO_2 (60 – 120 mesh, AcOEt/hexane) to afford compound **8** (0.73 mg, 75%) as a liquid. $[\alpha]_D^{20}$ = –19.6 (*c* = 1.45, $CHCl_3$). IR (neat): 2930, 2856, 1639, 1462, 1379, 1253, 1097, 835. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.57 – 7.37 (*m*, 10 H); 5.94 – 5.77 (*m*, 1 H); 5.08 – 4.97 (*m*, 2 H); 4.86 – 4.68 (*m*, 4 H); 4.00 – 3.86 (*m*, 2 H); 3.77 – 3.66 (*m*, 3 H); 2.39 – 2.25 (*m*, 1 H); 2.13 – 1.71 (*m*, 4 H); 1.11 – 1.00 (*m*, 21 H); 0.30 – 0.12 (*m*, 12 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 138.9; 138.3; 137.6; 128.2; 128.1; 127.6; 127.5; 127.4; 127.2; 115.8; 80.0; 75.9; 73.3; 72.7; 72.6; 71.2; 38.9; 36.5; 35.1; 29.6; 26.1; 26.0; 18.4; 18.0; 15.1; –3.3; –3.6; –4.5; –4.7. ESI-MS: 631 ([*M* + NH_4]$^+$). HR-ESI-MS: 635.3942 ($C_{36}H_{60}NaO_4Si_2^+$, [*M* + Na]$^+$; calc. 635.3928).

(5*S*,6*R*,7*S*,9*E*,16*R*,20*R*)-5-[(2*R*)-2,3-Bis(benzyloxy)propyl]-6-{[*tert*-butyl(dimethyl)silyl]oxy}-16-{[*tert*-butyl(diphenyl)silyl]oxy}-20-{[(4-methoxybenzyl)oxy]methyl}-2,2,3,3,7,23,23-heptamethyl-22,22-diphenyl-4,21-dioxa-3,22-disilatetracos-9-ene (36). *Grubbs*' *II* catalyst (13.83 mg, 0.01632 mmol) was dissolved in CH_2Cl_2 (1.0 ml) and added drop wise to a soln. of the compound **8** (100 mg, 0.1631 mmol) and compound **7** (404 mg, 0.4893 mmol) in CH_2Cl_2 (3 ml) at r.t. After completion of addition, the mixture was allowed to reflux for 0.25 h. The solvent was removed under reduced pressure and the crude product was purified by SiO_2 CC (PE/AcOEt) to afford the pure product **36** (161 mg, 70%) as an oil. $[\alpha]_D^{20}$ = –3.39 (*c* = 1.0, $CHCl_3$). IR (neat): 2976, 2854, 1647, 1458, 1361, 1251, 1109, 1030, 910, 767. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.71 – 7.60 (*m*, 8 H); 7.47 – 7.20 (*m*, 22 H); 7.09 – 7.01 (*m*, 2 H); 6.82 – 6.75 (*m*, 2 H); 5.43 – 5.18 (*m*, 2 H); 4.71 – 4.54 (*m*, 4 H); 4.22 (*s*, 2 H); 3.86 – 3.72 (*m*, 4 H); 3.70 – 3.43 (*m*, 3 H); 3.33 – 3.20 (*m*, 2 H); 2.18 – 1.50 (*m*, 5 H); 1.46 – 1.12 (*m*, 19 H); 1.10 – 1.03 (*m*, 21 H); 0.96 (*s*, 9 H); 0.90 (*s*, 9 H); 0.15 – 0.02 (*m*, 12 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 158.9; 139.0; 138.4; 135.9; 135.9; 135.8; 134.7; 134.2; 130.5; 129.4; 129.3; 129.1; 128.2; 128.2; 127.6; 127.5; 127.5; 127.48; 127.42; 127.37; 127.31; 127.2; 113.5; 76.0; 73.6; 73.4; 72.8; 72.6; 72.2; 71.2; 55.2; 37.7; 37.1; 36.5; 36.4; 35.1; 34.5; 32.7; 29.7; 29.6; 27.1; 27.0; 26.18; 26.11; 26.0; 19.4; 19.3; 18.5; 18.0; 15.2; 14.1; –3.2; –3.6; –4.5; –4.7. ESI-MS: 1430 ([*M* + NH_4]$^+$). HR-ESI-MS: 1433.8413 ($C_{87}H_{126}NaO_8Si_4^+$, [*M* + Na]$^+$; calc. 1433.8427).

(5*S*,6*R*,7*S*,9*S*,10*S*,16*R*,20*R*)-5-[(2*R*)-2,3-Bis(benzyloxy)propyl]-6-{[*tert*-butyl(dimethyl)silyl]oxy}-16-{[*tert*-butyl(diphenyl)silyl]oxy}-20-{[(4-methoxybenzyl)oxy]methyl}-2,2,3,3,7,23,23-heptamethyl-22,22-diphenyl-4,21-dioxa-3,22-disilatetracosane-9,10-diol (37). AD-mix-α (148 mg, 1.4 g/mmol) and methane sulfonamide (10 mg, 0.1062 mmol) were added to a 1:1 soln. of ^{t}BuOH/H_2O (2 ml total). The soln. was stirred for 20 min at r.t., and then cooled in an ice bath until a bright orange precipitate was formed. The reaction was stirred vigorously and a soln. of the compound **36** (150 mg, 0.1062 mmol) in 0.5 ml of ^{t}BuOH was added drop wise to the oxidant soln. and stirred for 32 h in an ice bath. The reaction was quenched with sodium sulfite (150 mg), and the mixture was stirred for 30 min. The mixture was diluted with AcOEt and washed with 4 ml of $NaHCO_3$. The aq. layer was washed with AcOEt (2 × 10 ml). The combined org. layers were dried (Na_2SO_4) and concentrated. The crude oil was purified by CC (hexanes/AcOEt) to yield **37** (122 mg; 80%) of a 14:1 mixture of diastereoisomers which were inseparable by HPLC. $[\alpha]_D^{20} = -6.38$ (*c* = 1.0, $CHCl_3$). IR (neat): 3437, 3070, 2932, 1587, 1464, 1249, 1109, 704. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.70 – 7.57 (*m*, 9 H); 7.43 – 7.19 (*m*, 21 H); 7.08 – 7.01 (*m*, 2 H); 6.81 – 6.74 (*m*, 2 H); 4.68 – 4.52 (*m*, 4 H); 4.28 – 4.19 (*m*, 2 H); 3.90 – 3.84 (*m*, 1 H); 3.83 – 3.73 (*m*, 4 H); 3.68 – 3.49 (*m*, 3 H); 3.34 – 3.09 (*m*, 3 H); 2.38 – 2.26 (*m*, 1 H); 2.10 – 1.96 (*m*, 1 H); 1.86 (br. *s*, 2 H); 1.68 – 1.57 (*m*, 1 H); 1.47 – 1.10 (*m*, 21 H); 1.05 (*s*, 21 H); 0.96 (*s*, 9 H); 0.92 (*s*, 9 H); 0.14 – 0.01 (*m*, 12 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 158.9; 138.9; 138.3; 135.9; 134.7; 134.1; 130.5; 129.4; 129.3; 129.1; 128.1; 128.3; 128.2; 127.7; 127.6; 127.45; 127.41; 113.6; 81.2; 76.0; 75.2; 73.6; 73.4; 73.0; 72.6; 72.29; 71.24; 55.2; 38.7; 36.4; 36.1; 35.3; 34.3; 33.6; 31.9; 29.7; 29.3; 27.1; 27.0; 26.1; 26.0; 22.7; 20.2; 19.4; 18.4; 14.1; −3.3; −3.6; −4.4; −4.6. ESI-MS: 1462 ($[M + NH_4]^+$). HR-ESI-MS: 1467.8510 ($C_{87}H_{128}NaO_{10}Si_4^+$, $[M + Na]^+$; calc. 1467.8482).

(5*S*,6*R*,7*S*,9*S*,10*S*,16*R*,20*R*)-5-[(2*R*)-2,3-Bis(benzyloxy)propyl]-6,9,10-tris{[*tert*-butyl(dimethyl)silyl]oxy}-16-{[*tert*-butyl(diphenyl)silyl]oxy}-20-{[(4-methoxybenzyl)oxy]methyl}-2,2,3,3,7,23,23-heptamethyl-22,22-diphenyl-4,21-dioxa-3,22-disilatetracosane (**38**). To a soln. of diol **37** (100 mg, 0.0690 mmol) in CH_2Cl_2 (4 ml) was added 2,6-lutidine (0.05 ml, 0.414 mmol), and the mixture was cooled to 0 °C. To this mixture was added drop wise TBSOTf (0.04 ml, 0.01656 mmol) and the mixture was maintained for 1 h. The reaction was quenched with sat. aq. $NaHCO_3$. The mixture was diluted with H_2O and the layers were separated. The aq. layer was extracted with CH_2Cl_2 (2 × 10 ml), the combined org. phases were washed with H_2O and with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by CC (Et_2O/hexane) furnished (110 mg, 95%) **38** as oil. $[\alpha]_D^{20} = -9.1$ (*c* = 1.2, $CHCl_3$). IR (neat): 2926, 2854, 1732, 1462, 1255, 1082, 968, 771. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.68 – 7.50 (*m*, 9 H); 7.41 – 7.15 (*m*, 21 H); 7.09 – 7.01 (*m*, 2 H); 6.83 – 6.76 (*m*, 2 H); 4.63 (*s*, 2 H); 4.57 – 4.51 (*m*, 2 H); 4.26 – 4.16 (*m*, 2 H); 3.82 – 3.71 (*m*, 4 H); 3.69 – 3.59 (*m*, 1 H); 3.59 – 3.47 (*m*, 3 H); 3.32 – 3.19 (*m*, 2 H); 1.98 – 1.87 (*m*, 1 H); 1.81 – 1.64 (*m*, 1 H); 1.64 – 1.49 (*m*, 3 H); 1.40 – 1.12 (*m*, 20 H); 1.07 – 1.00 (*m*, 21 H); 0.95 – 0.81 (*m*, 36 H); 0.17 – 0.03 (*m*, 24 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 158.9; 139.1; 138.5; 135.9; 135.8; 134.7; 134.1; 129.4; 129.3; 129.1; 128.3; 128.2; 127.6; 127.5; 127.4; 127.3; 127.2; 113.5; 81.3; 77.2; 76.2; 73.7; 73.3; 72.6; 71.2; 55.2; 38.7; 36.4; 35.8; 35.3; 34.5; 32.5; 31.9; 30.2; 29.7; 29.6; 29.3; 27.1; 27.2; 27.0; 26.1; 25.9; 25.8; 19.4; 19.3; 18.5; 18.4; 18.0; 17.9; 17.9; 14.1; −3.3; −3.5; −3.9; −4.4; −4.5; −4.0; −5.2. ESI-MS: 1348 ($[M$ + Na-*t*-butyl groups$]^+$). HR-ESI-MS: 1696.0221 ($C_{99}H_{156}NaO_{10}Si_6^+$, $[M + Na]^+$; calc. 1696.0211).

(2*R*,6*R*,12*S*,13*S*,15*S*,16*R*,17*S*,19*R*)-19,20-Bis(benzyloxy)-12,13,16,17-tetrakis{[*tert*-butyl(dimethyl)silyl]oxy}-2,6-bis{[*tert*-butyl(diphenyl)silyl]oxy}-15-methylicosan-1-ol (**39**). To a 0 °C soln. of PMB ether **38** (100 mg, 0.06 mmol) in CH_2Cl_2 (5 ml) was added pH 7 buffer (0.5 ml) and DDQ (20.4 mg, 0.09 mmol) in three portions over 30 min. Upon addition of DDQ the mixture became orange and as DDQ was consumed the reaction soln. became dark green. The reaction was monitored by TLC analysis (*ca.* 1.5 h) and then diluted with CH_2Cl_2 (5 ml) and sat. $NaHCO_3$ (5 ml). The mixture was then stirred vigorously for 10 min. The phases were separated and the aq. layer was washed with CH_2Cl_2 (3 × 5 ml). The org. phases were combined, dried (Na_2SO_4), and concentrated. The crude residue was purified by CC (hexane/AcOEt) to give **39** (81 mg, 87%) as oil: $[\alpha]_D^{20} = +8.3$ (*c* = 0.3, $CHCl_3$). IR (neat): 3412, 2926, 2854, 1464, 1255, 1109, 775. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.66 – 7.50 (*m*, 9 H); 7.43 – 7.17 (*m*, 21 H); 4.66 – 4.50 (*m*, 4 H); 3.84 – 3.70 (*m*, 1 H); 3.68 – 3.47 (*m*, 4 H); 3.43 – 3.26 (*m*, 1 H); 2.12 – 1.95 (*m*, 2 H); 1.93 – 1.76 (*m*, 1 H); 1.73 – 1.48 (*m*, 2 H); 1.44 – 1.14 (*m*, 21 H); 1.09 – 1.01 (*m*, 22 H); 0.96 – 0.82 (*m*, 36 H); 0.12 – 0.02 (*m*, 24 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 139.0; 138.4; 135.9; 135.8; 134.0; 129.9; 129.7; 129.5; 129.3; 128.28; 128.20; 127.7; 127.5; 127.4; 127.3; 81.4; 77.4; 76.1; 75.0; 73.9; 73.5; 73.3; 72.2; 71.2; 68.0; 38.8; 36.4; 35.7; 33.7; 32.5; 31.9; 30.1; 29.9; 29.7; 29.3; 27.2; 27.0; 27.0; 26.4; 26.1; 26.0; 25.9; 25.8; 25.1; 22.7; 19.7; 19.39; 19.33; 18.5; 18.4; 18.2; 17.98; 17.94; 14.1; −3.2; −3.4; −3.5; −3.9; −4.0; −4.3; −4.4; −4.5; −4.7; −4.8. HR-ESI-MS: 1575.9575 ($C_{91}H_{148}NaO_9Si_6^+$, $[M + Na]^+$; calc. 1575.9636).

(6*R*,8*E*,10*R*,12*E*,14*R*,18*R*,24*S*,25*S*,27*S*,28*R*,29*S*)-29-[(2*R*)-2,3-Bis(benzyloxy)propyl]-6,24,25,28-tetrakis{[*tert*-butyl(dimethyl)silyl]oxy}-10,14,18-tris{[*tert*-butyl(diphenyl)silyl]oxy}-2,2,3,3,27,31,31,32,32-nonamethyl-4,30-dioxa-3,31-disilatritriaconta-8,12-diene (**2**). To a 0 °C soln. of alcohol **39** (10 mg, 0.01 mmol) and $NaHCO_3$ (2.5 mg, 0.03 mmol) in CH_2Cl_2 (2 ml) was added *Dess–Martin* periodinane (6 mg, 0.0135 mmol). The mixture was stirred for 3 h in an ice bath and then poured into Et_2O (5 ml). The Et_2O mixture was stirred vigorously for 20 min and the mixture was filtered over *Celite* pad and washed with Et_2O (2 × 5 ml) and dried (Na_2SO_4), and filtered. The solvent was removed *in vacuo* and the crude oil was purified by CC afford the aldehyde **4** (9 mg, 90%) and it was subjected to *Julia* olefination reaction directly. To a stirred soln. of sulfone **3** (10 mg, 0.01 mmol) in dry THF (2 ml) was added a soln. of aldehyde **4** (9 mg) in THF (2 ml) and the mixture was cooled to −78 °C. A 0.5M soln. of KHMDS in toluene (0.03 ml, 0.01 mmol) was added drop wise to the sulfone/aldehyde mixture over a period of 5 min. The mixture was maintained for 4 h and then allowed to warm to r.t. over a 2 h period. The reaction was quenched with sat. aq. NH_4Cl, and the mixture was diluted with Et_2O and H_2O. The layers were separated; the combined org. phases were washed with brine and dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification by CC (AcOEt/hexane) furnished 10 mg (80%) of alkene **2** as colorless oil: $[\alpha]_D^{20} = -41.6$ ($c = 0.3$, $CHCl_3$). IR (neat): 2926, 2856, 1464, 1366, 1252, 1106. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.80 – 7.57 (*m*, 12 H); 7.51 – 7.27 (*m*, 28 H); 5.50 – 5.35 (*m*, 2 H); 5.33 – 5.10 (*m*, 2 H); 4.74 – 4.56 (*m*, 4 H); 4.11 – 3.91 (*m*, 1 H); 3.89 – 3.76 (*m*, 1 H); 3.75 – 3.52 (*m*, 7 H); 3.52 – 3.39 (*m*, 2 H); 2.16 – 1.91 (*m*, 2 H); 1.85 – 1.55 (*m*, 4 H); 1.49 – 1.26 (*m*, 30 H); 1.15 – 1.03 (*m*, 21 H); 1.02 – 0.86 (*m*, 54 H); 0.23 – 0.02 (*m*, 36 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 138.5; 138.3; 135.8; 134.8; 134.5; 134.5; 134.2; 133.5; 129.3; 128.27; 128.20; 127.5; 127.3; 127.2; 126.5; 126.0; 82.9; 81.9; 78.9; 74.5; 73.7; 73.3; 71.2; 66.7; 41.3; 38.1; 37.7; 37.2; 32.7; 31.9; 31.4; 30.1; 29.7; 29.3; 27.0; 26.1; 26.04; 26.0; 25.9; 25.8; 24.4; 22.7; 19.4; 19.2; 18.3; 18.2; 18.1; 17.9; 14.1; −3.2; −3.4; −3.6; −4.0; −4.3; −4.5; −4.8; −5.3.

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