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PAPER

Diastereoselective synthesis of the C17–C30 fragment of amphidinol 3†

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The diastereoselective synthesis of the C17–C30 fragment of amphidinol 3 (AM3) **1** was achieved from the enantio-enriched aldehyde **20**, Weinreb amide **14** and 2-bromo-3-(trimethylsilyl)propene, which was used as a bifunctional conjunctive reagent. The absolute configuration of the stereogenic centers, in both aldehyde **20** and Weinreb amide **14**, were efficiently controlled by using (+)-(*R*)-methyl-*p*-tolylsulfoxide as the unique source of chirality.

Introduction

Amphidinols (AMs) are fascinating biologically active polyketide metabolites that exhibit potent hemolytic activity against human erythrocytes as well as antifungal activity.[1] Since the first isolation and identification of amphidinol 1 in 1991[2] from the marine dinoflagellates of the *Amphidinium* genus,[3] nearly 20 closely related toxins have been isolated from the dinoflagellates *Amphidinium klebsii* and *Amphidinium carterae*[1,4] along with similar structurally related compounds such as luteophanol A,[5] lingshuiol A,[6] and karatungiol.[7] More recently, a structurally closely related structure called karlotoxin, which possesses hemolytic activity, was not isolated from *Amphidinium* but from another source, *Karlodinium veneficum*.[8] Amphidinols, unlike polycyclic ethers isolated from other dinoflagellates, are mainly characterized by linear polyketides and polyolefins. Among those, amphidinol 3 (AM3) **1**, which was isolated in 1996 from *Amphidinium klebsii*,[3] has the most potent hemolytic and antifungal activities. It is worth noting that, among the known antifungal agents, amphidinol 3 and all AMs are unique as they possess neither nitrogenous polycycles present in synthetic drugs, nor macrocyclic structures commonly found in polyene-macrolide antibiotics. A hairpin conformation of amphidinols acting by a facial amphiphilic interaction with membrane lipids or by penetration of the hydrophobic chain in the membrane has been proposed to account for membrane permeabilizing activities.[9] A few years ago, two new homologues of amphidinols (AM14 and AM15) closely related to AM7, with a truncated polyhydroxyl chain and a modified polyene part, were extracted from the same organism,[4b] and the biological activities of these short-chained AMs have been investigated and compared with known homologues. This study has shown that the hydrophobicity of the polyene chain of AMs dramatically affects the membrane-disrupting activity and that the polyhydroxyl chain moderately modulates the potency of the biological activity.

The potent antifungal activity displayed by AM3 **1**, which exceeds that of commercial antifungal compounds such as amphotericin B, has prompted the interest of biologists in studying its mechanism of action which is believed to be different from that of amphotericin B.[10] Thus, amphidinols may provide an interesting model to gain a better understanding of the mechanism of antifungal activities, which eventually could help to develop better drugs for treatment of AIDS-related diseases and those upon transplantation.

Although the total synthesis of AM3 has not yet been realized, several creative approaches to polyol,[3b,11] pyranyl[11b–d,12] and polyene[12e,f,13] fragments have been reported by several teams including the contribution from Rychnovsky *et al.* toward the synthesis of the most advanced fragment C1–C52.[11b]

Presently, we expand on our successful approaches to the C53–C67 polyene fragment[13a,b] and the C18–C30 polyol fragment[11a] by defining a new strategy to the C17–C30 fragment **A** bearing a terminal olefin at the C30 position. Our previously designed Julia–Kocienski olefination strategy allowing the stereoselective construction of the C30–C31 double bond has been abandoned because Rychnovsky observed very low reactivity of the C31-aldehyde towards a large panel of nucleophiles.[11b] Consequently, we decided to disconnect AM3 **1** at the C31–C32 bond and use a Nozaki–Hiyama–Kishi coupling to form this bond.[14]

On the basis of the retrosynthetic plan illustrated in Scheme 1, the C17–C30 fragment **A** could be obtained from three subunits: (1) an optically active α-hydroxyaldehyde **E**; (2) a bifunctional

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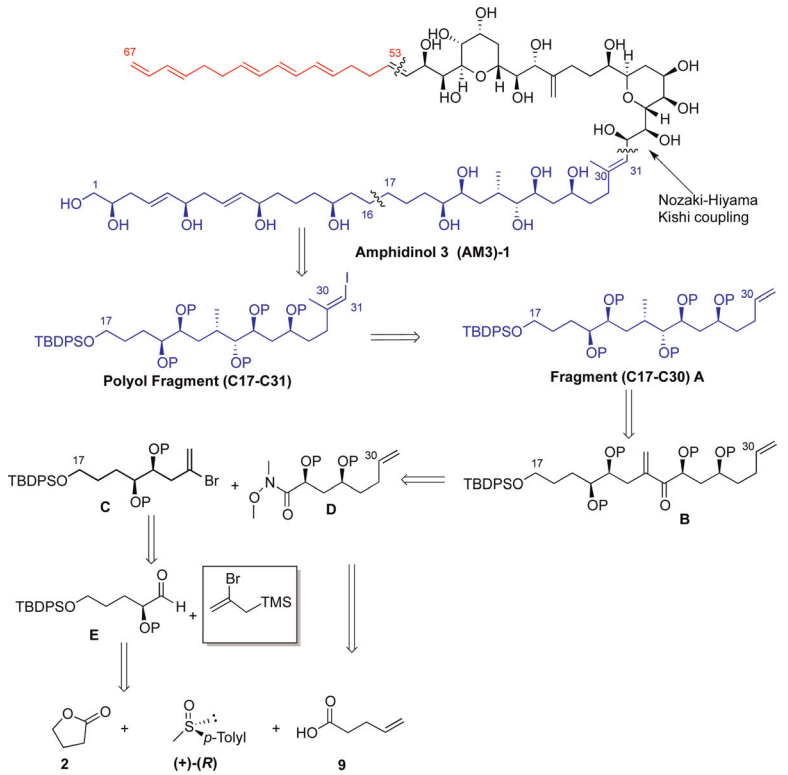
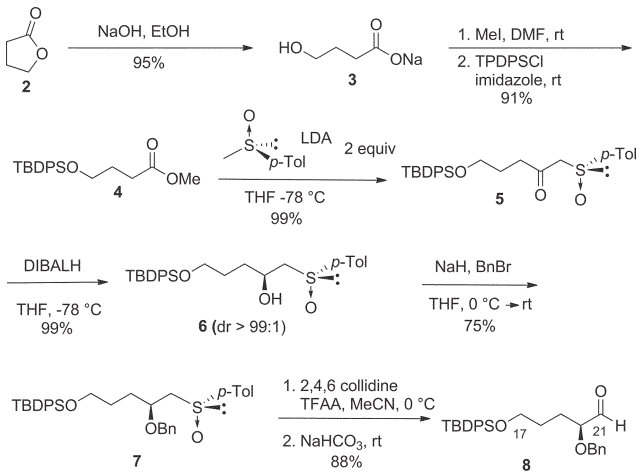


Scheme 1 Retrosynthetic analysis of the C17–C30 fragment **A** of AM3-**1**.

2-bromo-3-(trimethylsilyl)propene; (3) an optically active Weinreb amide **D** possessing a *syn* 1,3-diol. By combining the ability to metalate a vinyl bromide and the nucleophilicity of an allylsilane, the readily available 2-bromo-3-(trimethylsilyl)-propene could serve as a dianion equivalent.[15]

Our initial strategy focused on a diastereoselective addition of allylsilane to aldehyde **E** through the Cram-chelate transition state, followed by the addition of the resulting vinyl bromide **C** to Weinreb amide **D**. A chemo- and diastereoselective reduction of the *exo*-methylene group of the C23–C24 enone[16] in fragment **B** using L-selectride and subsequent diastereoselective reduction of the ketone by $Zn(BH_4)_2$ would control the stereogenic center at C23 and C24 present in compound **A**. Enantioselective preparation of aldehyde **E** and Weinreb amide **D** from γ-butyrolactone **2** and pentenoic acid **9** would be performed using (+)-(*R*)-methyl-*p*-tolylsulfoxide as the unique source of chirality (Scheme 1).

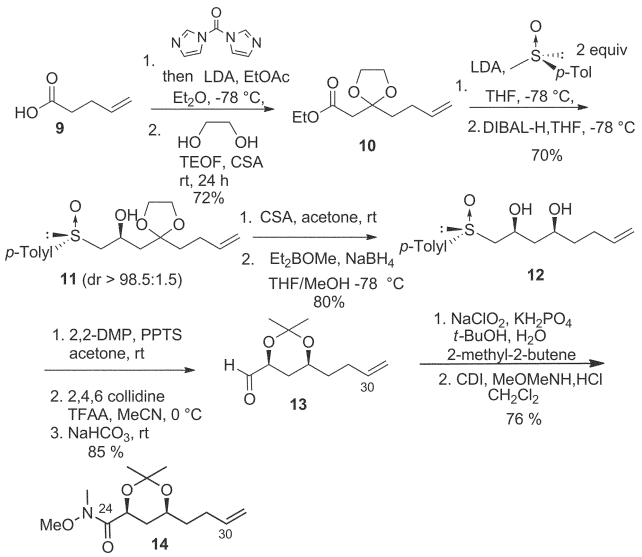


Scheme 2 Synthesis of aldehyde **8** (fragment C17–C21).

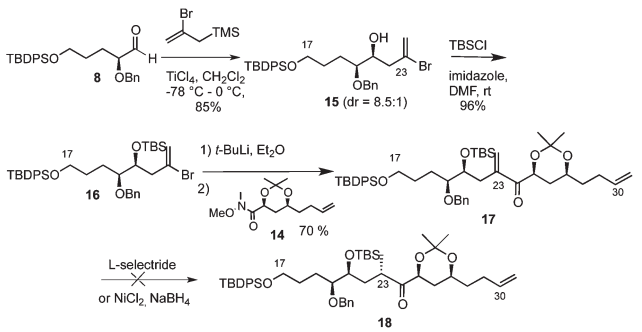
Results and discussion

The synthesis of aldehyde **8** started with the ring-opening of lactone **2** under basic conditions (NaOH, EtOH, 95%) to furnish ω-hydroxycarboxylate **3** which was subsequently transformed into the protected ester **4** (MeI, DMF then TPDPSCl, imid., 91%). This compound was treated with the lithiated anion of (+)-(*R*)-methyl-*p*-tolyl-sulfoxide (2 equiv.) to produce β-ketosulfoxide **5** (99%). It is worth noting that the direct condensation of the chiral sulfoxide on butyrolactone **2**[17] was possible, however, in lower yield in **5** (68% instead of 90%). From β-ketosulfoxide **5**, a sulfoxide-directed diastereoselective reduction of the ketone at C20 (DIBAL-H, 99%)[18] followed by protection of the obtained β-hydroxysulfoxide **6** with benzyl bromide and a subsequent Pummerer rearrangement of the resulting sulfoxide **7** (2,4,6-collidine, TFAA, then $NaHCO_3$, 88%) provided the enantiopure aldehyde **8**[19] in 53% overall yield (Scheme 2).

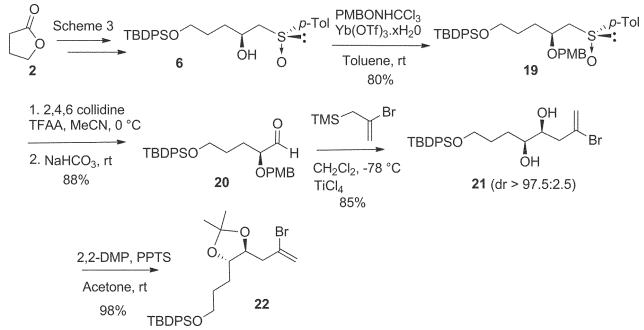
The second fragment, Weinreb amide **14**, was prepared from β,δ-dihydroxy-sulfoxide **12** in two steps (Scheme 3). The synthesis of **12** was realized from protected β-ketoester **10**, obtained in two steps from pentenoic acid **9** in 72% yield *via* the corresponding imidazolide derivative. Addition of two equivalents of (+)-(*R*)-lithio-methyl-*p*-tolyl-sulfoxide to **10**, followed by a



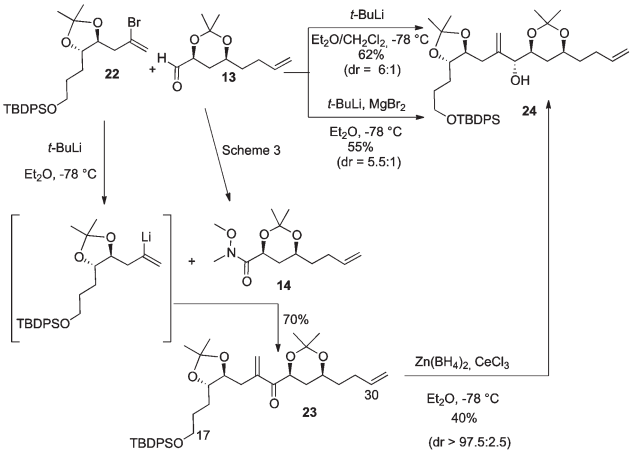
Scheme 3 Synthesis of Weinreb amide **14** (fragment C24–C30).



Scheme 4 Synthesis of enone **17** and reduction attempts of the methylene group at C23.



Scheme 5 Synthesis of vinyl bromide **22**.



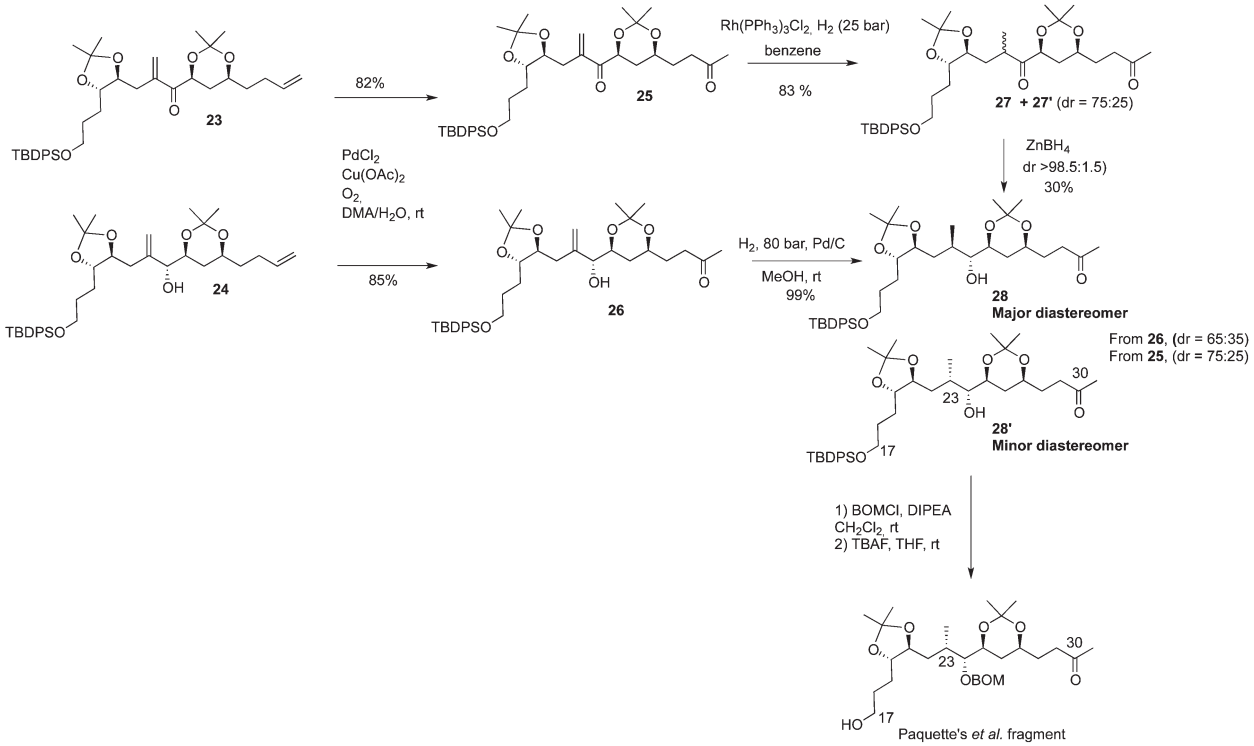
Scheme 6 Synthesis of allylic alcohol **24**.

diastereoselective reduction by DIBAL-H of the resulting β-ketosulfoxide, led to β-hydroxysulfoxide **11** (dr > 98.5 : 1.5). Subsequent deprotection of **11** under acidic conditions followed by a Prasad–Narasaka *syn*-diastereoselective reduction (Et_2BOMe/$NaBH_4$, THF/MeOH, −78 °C)[20] afforded dihydroxysulfoxide **12**[21] (40% overall yield from **9**). After acetonide protection of **12** followed by a TFAA-induced Pummerer rearrangement, aldehyde **13** was isolated in 85% yield. Oxidation of the latter under Pinnick conditions[22] followed by treatment with *N,O*-dimethylhydroxylamine hydrochloride delivered Weinreb amide **14** in 76% yield. Thus, compound **14** was obtained in 11 steps from **9** with an overall yield of 26% (Scheme 3).

With both compounds **8** and **14** in our hands, the synthesis of the C17–C30 fragment was undertaken. Treatment of commercially available 2-bromo-3-(trimethylsilyl)propene with $TiCl_4$ in CH_2Cl_2 at −78 °C[23] followed by the addition of aldehyde **8** provided compound **15** (C17–C23 fragment) with an 8.5/1 diastereomeric ratio in favor of *syn* 1,2-diol **15**, which was isolated in 85% yield. After protection of the hydroxyl group at C21 as a TBDPS-ether and treatment with *tert*-BuLi (Et_2O at −78 °C), the organolithium intermediate was added to Weinreb amide **14**, leading to enone **17** in 70% yield, this latter corresponds to the C17–C30 fragment (Scheme 4).

Having synthesized enone **17**, we turned our attention to the reduction of the *exo*-methylene group at C23 to obtain α-methyl ketone **18**. This transformation was troublesome due to a competing reduction of the terminal double bond. According to the literature, we anticipated that the use of L-selectride could afford the desired configuration at C23.[16] However, after examining an array of conditions, including $NiCl_2$/$NaBH_4$,[16] the recovery of the starting material and/or its decomposition was observed (Scheme 4).

Due to these difficulties, the transformation of the terminal double bond into a methyl ketone, prior to reduction of the *exo*-methylene group, was examined. This alternative presents several advantages: (1) the methyl ketone can be easily transformed to a vinyl iodide which will be a good candidate for a Nozaki–Hiyama–Kishi coupling;[24] (2) the chemoselective reduction of the *exo*-methylene group could be facilitated and (3) the stereochemical outcomes of this reduction should be easily assigned by chemical correlation to a fragment previously described by Paquette *et al.*[11d] To gain better access to this fragment, the protecting group of the secondary hydroxy in aldehyde **8** was modified (Scheme 5). A PMB-ether was selected instead of a benzyl ether in order to allow for selective removal of the protecting group. Interestingly, the PMB removal proceeded



Scheme 7 Access to Paquette *et al.*'s fragment.

quantitatively during the condensation of **20** with 2-bromo-3-(trimethylsilyl)propene in the presence of $TiCl_4$, producing diol **21** with excellent yield and diastereoselectivity (dr > 97.5 : 2.5; yield = 85%). After protection of the resulting *syn* 1,2-diol as an isopropylidene acetal, **22** was isolated in 98% yield (Scheme 5).

Access to allylic alcohol **24** (fragment C17–C30) was acquired according to two pathways (Scheme 6).

The first one was a direct condensation of the lithium derivative generated from vinyl bromide **22** (*t*-BuLi, Et_2O, −78 °C) with aldehyde **13** providing the desired allylic alcohol **24** in 62% yield with rather good diastereoselectivity (dr = 6 : 1). It is worth noting that the use of $MgBr_2$ as an additive did not give better yield and stereoselectivity in **24**. The second pathway, which allowed the confirmation of the relative configuration of the major diastereoisomer obtained previously, was achieved from enone **23** resulting from the condensation of the lithium derivative generated from vinylic bromide **22** with Weinreb amide **14**, followed by a stereoselective reduction of the obtained enone **23** with $Zn(BH_4)_2$ in the presence of cerium chloride,[25] producing **24** in 28% overall yield with a dr up to 97.5 : 2.5.

To transform enone **23** and alcohol **24** into fragment C17–C30, a Wacker oxidation of these compounds was achieved to furnish the corresponding methylketones **25** and **26** ($PdCl_2$, $Cu(OAc)_2$, O_2, DMA/H_2O) respectively in good 82 and 85% yields (Scheme 7). The stereoselective reduction of the *exo*-methylene group in **26** was performed under 80 bars of hydrogen in the presence of Pd/C in good yield (99%) however with poor diastereoselectivity as **28** and **28′** were obtained in a ratio of 65/35.[26] On the other hand, hydrogenation of **25** with Wilkinson's catalyst, $RhCl(P(C_6H_5)_3)_3$, provided ketone **27** and **27′** in 83% yield, as a mixture of diastereoisomers (dr = 75 : 25). A highly diastereoselective reduction (dr > 98.5 : 1.5) of ketone **27** and **27′**, as a 75/25 mixture of two diastereoisomers, took place when $Zn(BH_4)_2$ was used as the reductive agent as alcohols **28** and **28′** were obtained with the same ratio of 75/25, the major isomer being the major compound obtained by hydrogenation of **26**. Finally, the fragment previously reported by Paquette *et al.*[11d] was prepared from separated minor diastereoisomer **28′** in two steps (BOMCl, DIEPA then TBAF) showing unambiguously that compound **28′** possesses the desired absolute configuration[27] at C23 (Scheme 7).

Conclusion

In conclusion, we report herein an efficient coupling of the bifunctional 2-bromo-3-(trimethylsilyl)propene with aldehyde **20** and aldehyde **13** as well as the coupling of vinyl bromide **22** with Weinreb amide **14** to obtain the C17–C30 fragment of amphidinol **3**. Starting from butyrolactone **8** and pentenoic acid **10**, the absolute configuration of the stereocenters in aldehydes **20** and **13** has been highly controlled using (+)-(*R*)-methyl-*p*-tolylsulfoxide as the unique source of chirality. Either reduction of the *exo*-methylene group at C23 and then the ketone at C24 in the C17–C30 skeleton or the opposite gave the corresponding fragment C17–C30 of amphidinol **3**.

Experimental section

General

Reagents and solvents were purchased as reagent grade and used without further purification. THF was distilled over sodium

benzophenone ketyl. Dichloromethane was distilled over CaH_2 and acetonitrile over P_2O_5. Flash column chromatography (FC) was performed using silica gel 60 for preparative column chromatography (40–63 mm), unless specifically noted otherwise. Demetallated silica gel was prepared according to a published procedure.[28] Thin layer chromatography (TLC) was performed on glass sheets coated with silica gel 60 F_{254} (otherwise stated), visualization by UV light or through staining with phosphomolybdic acid, $KMnO_4$ or vanillin. Optical rotations were measured on a polarimeter with a sodium lamp and are reported as follows: α_D (c g per 100 mL, solvent). NMR spectra (^1H and ^{13}C) were recorded on a 300 MHz or 400 MHz spectrometer. Chemical shifts are reported in ppm with the solvent ($CDCl_3$) resonance as the δ 7.26 ppm (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, s ap = apparent singlet, mc = multiplet center, coupling constants Hz, integration). Carbon NMR (^{13}C NMR) spectra were also run at various field strengths as indicated. Spectra were recorded in $CDCl_3$ using residual undeuterated solvent (77 ppm) as an internal reference. Infra red (IR) spectra were recorded on a diamond ATR spectrometer using neat samples. Infra red frequencies are reported in wavenumbers (cm^{-1}), intensities were determined qualitatively and are reported as strong (s), medium (m) or weak (w). Solid Lewis acids were flame-dried in the reaction flask under vacuum and under argon before use.

Synthesis of (*R*)-5-(*tert*-butyldiphenylsilyloxy)-1-(*p*-tolylsulfinyl)-pentan-2-one 5. To a solution of diisopropylamine (1.59 mL, 11.35 mmol) in 15 mL of THF cooled at −78 °C was added dropwise *n*-BuLi (6.48 mL, 1.60 M in hexane, 10.37 mmol). The resulting solution was stirred for 1 h at −78 °C, prior to the addition of a solution of (+)-(*R*)-methyl-*p*-tolyl-sulfoxide (1.52 g, 9.87 mmol) in 12 mL of THF at −78 °C. After stirring for 1 h at −78 °C, the anion solution was transferred *via* a transfer syringe to a −78 °C cold solution of the ester **4** (1.76 g, 4.94 mmol) in 18 mL of THF and stirred for 1 h. The reaction mixture was then diluted with 20 mL of Et_2O, hydrolyzed with aqueous saturated NH_4Cl (20 mL) and washed with brine (20 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on demetallated silica gel (Et_2O) to furnish the β-ketosulfoxide **5** as a colorless oil (2.34 g, 4.89 mmol, 99%): $[\alpha]_D^{25}$ +90.6° (c = 1.43 in $CHCl_3$), R_f 0.63 (Et_2O); ^1H NMR (300 MHz, $CDCl_3$) δ 7.61–7.64 (m, 4H), 7.52 (B of A_2B_2, J_{AB} = 8.1 Hz, $\Delta\nu$ = 63.3 Hz, 2H), 7.35–7.45 (m, 6H), 7.31 (A of A_2B_2, J_{AB} = 8.1 Hz, $\Delta\nu$ = 63.3 Hz, 2H), 3.79 (AB, J_{AB} = 13.5 Hz, $\Delta\nu$ = 34.7 Hz, 2H), 3.63 (t, J = 6.1 Hz, 2H), 2.49–2.68 (m, 2H), 2.40 (s, 3H), 1.74–1.83 (m, 2H), 1.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.4, 142.1, 139.8, 135.5, 133.6, 130.0, 129.6, 127.7, 124.01, 68.2, 62.7, 41.5, 26.9, 26.1, 21.5, 19.2; IR:2931, 2858, 1712, 1590, 1494, 1472, 1428, 1390, 1362, 1110, 1056, 963, 823, 810, 741, 705, 688 cm^{-1}; HRMS ES m/z $(M + Li)^+$ calcd for $C_{28}H_{34}LiO_3SSi$ 485.2152, found 485.2100.

Synthesis of (*S*)-5-(*tert*-butyldiphenylsilyloxy)-1-((*R*)-*p*-tolylsulfinyl)pentan-2-ol 6. To a solution of β-ketosulfoxide **5** (614 mg, 1.28 mmol) in 10 mL of THF cooled at −78 °C was added dropwise DIBAL-H (1.60 mL, 1.0 M in toluene, 1.60 mmol). The resulting solution was stirred for 5 h at −78 °C, quenched with 2 mL of MeOH, diluted with 10 mL of EtOAc, hydrolyzed with an aqueous saturated solution of sodium-potassium tartrate (10 mL) and stirred overnight until a clear phase-separation occurred. The aqueous phase was extracted with EtOAc (3 × 20 mL) and the combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue by flash column chromatography on demetallated silica gel (EtOAc/cyclohexane: 1/1) gave the β-hydroxysulfoxide **6** as a colorless oil (611 mg, 1.27 mmol, 99%): $[\alpha]_D^{25}$ +120.0° (c = 1.15 in $CHCl_3$); R_f 0.37 (EtOAc/cyclohexane: 1/1); ^1H NMR (300 MHz, $CDCl_3$) δ 7.62–7.66 (m, 4H), 7.51–7.53 (m, 2H), 7.32–7.45 (m, 8H), 4.17–4.24 (m, 1H), 3.61–3.69 (m, 2H), 2.85 (AB of ABX, J_{AB} = 13.4 Hz, J_{AX} = 9.8 Hz, J_{BX} = 2.0 Hz, $\Delta\nu$ = 102.9 Hz, 2H), 2.42 (s, 3H), 1.54–1.68 (m, 4H), 1.03 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.5, 139.9, 135.55, 135.5, 133.65, 133.6, 130.1, 130.0, 129.6, 127.6, 124.0, 124.0, 66.6, 63.8, 61.7, 34.0, 28.3, 26.8, 21.4, 19.2; IR: 3365, 2930, 2858, 1472, 1428, 1390, 1110, 1085, 1027, 1010, 908, 823, 807, 729, 700, 687 cm^{-1}; HRMS ES m/z $(M + Li)^+$ calcd for $C_{28}H_{36}LiO_3SSi$ 487.2310, found 487.2274.

Synthesis of ((*S*)-4-(benzyloxy)-5-((*R*)-*p*-tolylsulfinyl)pentyloxy)(*tert*-butyl)diphenylsilane 7. A solution of alcohol **6** (958 mg, 1.99 mmol) in 5 mL of THF was added dropwise at 0 °C to a solution of oil-free sodium hydride (96 mg, 3.99 mmol) in 20 mL of THF. The reaction mixture was stirred for 30 min, prior to the addition of benzyl bromide (592 µL, 4.98 mmol). After 30 min at 0 °C and 3 h at room temperature the resulting solution was carefully hydrolyzed by adding 5 mL of an aqueous saturated solution of NH_4Cl. The aqueous layer was extracted with EtOAc (3 × 20 mL) and the combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (EtOAc/cyclohexane: 2/5) to give the benzyl ether **7** (854 mg, 1.49 mmol, 75%) as a colorless oil: $[\alpha]_D^{25}$ +91.2° (c = 1.43 in $CHCl_3$); R_f 0.60 (EtOAc/cyclohexane: 1/1); ^1H NMR (300 MHz, $CDCl_3$) δ 7.62–7.67 (m, 4H), 7.46–7.47 (m, 2H), 7.27–7.43 (m, 13H), 4.67 (AB, J_{AB} = 11.0 Hz, $\Delta\nu$ = 11.5 Hz, 2H), 4.07–4.14 (X of ABX, m, 1H), 3.65 (t, J = 6.1 Hz, 2H), 2.82–2.91 (AB of ABX, m, 2H), 2.42 (s, 3 H), 1.52–1.85 (m, 4 H), 1.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.6, 141.3, 138.0, 135.5, 133.8, 130.0, 129.6, 128.4, 128.1, 127.8, 127.6, 123.8, 73.2, 72.3, 64.6, 63.6, 30.2, 27.6, 26.9, 21.4, 19.2; IR 2930, 2857, 1494, 1472, 1455, 1428, 1105, 1086, 1045, 1016, 998, 938, 822, 807, 738, 699 cm^{-1}; HRMS ES m/z $(M + Na)^+$ calcd for $C_{35}H_{42}NaO_3SSi$ 593.2516, found 593.2472.

Synthesis of (*S*)-2-(benzyloxy)-5-(*tert*-butyldiphenylsilyloxy)-pentanal 8. To a solution of sulfoxide **7** (850 mg, 1.49 mmol) in 12 mL of MeCN cooled at 0 °C was added dropwise subsequently 2,4,6-collidine (595 µL, 4.47 mmol) and trifluoroacetic anhydride (1.56 g, 1.04 mL, 7.45 mmol). The reaction mixture was stirred for 30 min, prior to the addition of 12 mL of an aqueous saturated solution of $NaHCO_3$, warmed to room temperature and stirred for 1 h at this temperature. The aqueous layer was extracted with EtOAc (3 × 15 mL) and the combined

organic layers were washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (EtOAc/cyclohexane: 1/9) gave the aldehyde **8** (585 mg, 1.31 mmol, 88%) as a colorless oil: $[\alpha]_D^{25}$ −30.6° (*c* = 1.03 in $CHCl_3$); R_f 0.46 (EtOAc/cyclohexane: 1/10); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.65 (d, *J* = 2.0 Hz, 1H); 7.65–7.68 (m, 4H), 7.29–7.47 (m, 11H), 4.59 (AB, J_{AB} = 11.7 Hz, $\Delta\nu$ = 41.7 Hz, 2H), 3.78 (ddd, *J* = 7.4 Hz, *J* = 5.2 Hz, *J* = 2.0 Hz, 1H), 3.64 (t, *J* = 6.0 Hz, 2H), 1.57–1.93 (m, 4H), 1.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.5, 137.3, 135.5, 133.8, 129.6, 128.5, 128.0, 128.0, 127.6, 83.2, 72.4, 63.2, 27.7, 26.9, 26.419, 19.209; IR: 2858, 1733, 1472, 1455, 1428, 1106, 1090, 1028, 1007, 998, 937, 823, 794, 738, 699 cm^{-1}, Anal calcd for $C_{28}H_{34}O_3Si$: C, 75.29; H, 7.67; found C, 75.23; H, 7.598.

Synthesis of 1-(2-but-3-enyl-1,3-dioxolan-2-yl)-3-((*R*)-*p*-tolylsulfinyl)propan-2-one. To a solution of diisopropylamine (6.4 mL, 45.4 mmol) in 50 mL of THF cooled at −78 °C was added dropwise *n*-BuLi (28.4 mL, 1.60 M in hexane, 45.4 mmol). The resulting solution was stirred for 1 h at −78 °C, prior to the addition of a solution of (+)-(*R*)-methyl-*p*-tolyl-sulfoxide (7.0 g, 45.4 mmol) in 40 mL of THF at −78 °C. After stirring for 1 h at −78 °C, a solution of ester **10** (4.31 g, 20.17 mmol) in 40 mL of THF was added dropwise. The reaction mixture was stirred for 5 h at −78 °C, hydrolyzed with an aqueous saturated solution of NH_4Cl (150 mL) and warmed to room temperature. The aqueous layer was extracted with EtOAc (3 × 100 mL) and the combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the crude by flash column chromatography on silica gel (EtOAc/cyclohexane: 1/1 → 7/3) afforded the sulfoxide as a yellow oil (4.61 g, 14.25 mmol, 72%): $[\alpha]_D^{25}$ +135.7° (*c* = 0.79 in $CHCl_3$); R_f 0.25 (EtOAc/cyclohexane: 1/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 7.8 Hz, 2H), 5.65–5.82 (m, 1H), 4.97 (dq, *J* = 17.1 Hz, *J* = 2.4 Hz, 1H), 4.91 (dq, *J* = 10.2 Hz, *J* = 2.7 Hz, 1H), 3.90–3.98 (m, 6H), 2.84 (AB, J_{AB} = 13.5 Hz, $\Delta\nu$ = 29.7 Hz, 2H), 2.40 (s, 3 H), 2.00–2.12 (m, 2 H), 1.63–1.72 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.2, 142.0, 139.7, 137.8, 130.0, 124.1, 114.6, 109.1, 69.0, 64.9, 51.8, 37.0, 27.5, 21.4; IR 2922, 1708, 1641, 1494, 1359, 1306, 1085, 1035, 950, 911, 809 cm^{-1}; HRMS ES *m*/*z* (M + Li)$^+$ calcd for $C_{17}H_{22}LiO_4S$ 329.1394, found 329.1385.

Synthesis of (*S*)-1-(2-but-3-enyl-1,3-dioxolan-2-yl)-3-((*R*)-*p*-tolylsulfinyl)propan-2-ol 11. Dibal-H (17 mL, 1.0 M in toluene, 17 mmol) was added dropwise to β-ketosulfoxide (*vide supra*) (2.2 g, 6.83 mmol) dissolved in 100 mL of THF cooled at −78 °C. The resulting solution was stirred for 2 h at −78 °C, quenched with 20 mL of MeOH, diluted with 65 mL of EtOAc, hydrolyzed with a saturated sodium-potassium tartrate solution (65 mL) and stirred overnight. The aqueous phase was extracted with EtOAc (3 × 100 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/cyclohexane: 1/1 → 6/4) affording the β-hydroxysulfoxide **11** as a white solid (2.19 g, 6.75 mmol, 99%): $[\alpha]_D^{25}$ +206.7° (*c* = 1.00 in $CHCl_3$); R_f 0.46 (EtOAc/cyclohexane: 4/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.1 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 5.69–5.85 (m, 1H), 4.99 (d, *J* = 18.3, 1H), 4.94 (d, *J* = 10.2, 1H), 4.42–4.53 (m, 1H), 3.89–3.99 (m, 4H), 2.77–2.93 (m, 2 H), 2.41 (s, 3 H), 2.01–2.13 (m, 2 H), 1.82–1.89 (m, 2 H), 1.61–1.73 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.2, 140.5, 137.8, 129.8, 123.7, 114.4, 110.7, 64.6, 64.5, 62.7, 42.6, 36.3, 27.7, 21.2; IR 3359, 2927, 1710, 1641, 1492, 1398, 1305, 1085, 1030, 911, 810 cm^{-1}; HRMS ES *m*/*z* (M + Na)$^+$ calcd for $C_{17}H_{24}NaO_4S$ 347.1288, found 347.1247.

Synthesis of (2*S*)-2-hydroxy-1((*R*)-*p*-tolylsulfinyl)-oct-7-en-4-one. Acetal **11** (1.09 g, 3.36 mmol) in 35 mL of acetone was treated with (±)-10-camphorsulfonic acid (170 mg, 0.73 mmol). The reaction was stirred for 24 h and diluted with 20 mL of CH_2Cl_2. The organic phase was washed with a saturated $NaHCO_3$ solution (2 × 10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure affording hydroxyketone as a solid, which was directly used for the next step without further purification. For analysis, a sample was recrystallized in ether to give a white solid: m.p. 73–75 °C; $[\alpha]_D^{25}$ +228.6° (*c* = 0.61 in $CHCl_3$); R_f 0.45 (EtOAc/cyclohexane: 4/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.1 Hz, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 5.69–5.86 (m, 1H), 5.01 (d, *J* = 17.1, 1H), 4.98 (d, *J* = 10.2, 1H), 4.57–4.68 (m, 1H), 2.90 (AB of ABX, J_{AB} = 13.5, J_{AX} = 9.5 Hz, J_{BX} = 2.7 Hz, $\Delta\nu$ = 86.24 Hz, 2H), 2.64–2.70 (m, 2H), 2.45–2.56 (m, 2 H), 2.43 (s, 3 H), 2.26–2.36 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.0, 141.6, 136.6, 130.1, 123.9, 123.9, 115.5, 65.8, 63.4, 48.6, 42.6, 27.3, 21.4; IR 3361, 2907, 1710, 1641, 1494, 1376, 1049, 1038, 905, 808 cm^{-1}; HRMS ES *m*/*z* (M + Na)$^+$ calcd for $C_{15}H_{20}NaO_3S$ 303.1025, found 303.0989.

Synthesis of (2*S*,4*S*)-7-(4-methoxybenzyloxy)-1-((*R*)-*p*-tolylsulfinyl)octane-2,4-diol 12. Diethylmethoxy borane (4 mL, 1.0 M in THF, 4 mmol) was added dropwise to crude hydroxyketone (*vide supra*) (874 mg, 3.12 mmol) in 40 mL of THF/MeOH (4/1) at −78 °C. The resulting mixture was stirred for 20 min, prior to the addition of sodium borohydride (138 mg, 4.06 mmol). The reaction was stirred for 4 h at −78 °C and was quenched with 38 mL of acetic acid, warmed up to room temperature, diluted with EtOAc (50 mL) and treated with a saturated $NaHCO_3$ solution up to pH = 6. The aqueous phase was extracted with EtOAc (3 × 100 mL) and the combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was taken up in MeOH, heated and concentrated *in vacuo*. This procedure was repeated four times. The residue was purified by flash column chromatography on silica gel (EtOAc/cyclohexane: 6/4) affording the diol **12** as a white solid (704 mg, 2.49 mmol, 80% over two steps): m.p. 110–114 °C; $[\alpha]_D^{25}$ +230.3° (*c* = 1.00 in $CHCl_3$), R_f 0.33 (EtOAc/cyclohexane: 4/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 5.71–5.88 (m, 1H), 5.01 (dd, *J* = 17.3, *J* = 1.7, 1H), 4.95 (d, *J* = 10.7 Hz, 1H), 4.38–4.55 (m, 1H), 3.81–3.97 (m, 1H), 3.61 (s broad, 2 H), 2.87 (ABX, J_{AB} = 13.2 Hz, J_{AX} = 9.6 Hz, J_{BX} = 1.8 Hz, $\Delta\nu$ = 116.3 Hz, 2H), 2.42 (s, 3 H),

2.02–2.24 (m, 2 H), 1.41–1.75 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.7, 139.4, 138.3, 130.1, 124.0, 114.9, 71.3, 67.4, 62.2, 42.7, 36.9, 29.6, 21.4; IR 3284, 2907, 1641, 1494, 1450, 1318, 1105, 1084, 1034, 910, 810 cm^{-1}; HRMS ES *m/z* $(M + Li)^+$ calcd for $C_{15}H_{22}LiO_3S$ 289.1445, found 289.1407.

Synthesis of (4*S*,6*S*)-4-(3-(4-methoxybenzyloxy)butyl-2,2-dimethyl-6(*R*)-*p*-tolylsulfinylmethyl)-1,3-dioxane. 2,2-Dimethoxypropane (4.5 mL, 36.7 mmol) and PPTS (109 mg, 433 µmol) were added to diol **12** (608 mg, 1.45 mmol) in 14 mL of acetone at room temperature. The reaction was stirred for 16 h, hydrolyzed with 10 mL of a saturated $NaHCO_3$ solution and poured in 30 mL of EtOAc. The aqueous layer was extracted with EtOAc (3 × 20 mL) and the combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (EtOAc/cyclohexane: 2/1) gave the acetal as a solid (352 mg, 1.09 mmol, 95%): m. p. 59–61 °C; $[\alpha]_D^{25}$ +204.7° (*c* = 0.51 in $CHCl_3$); R_f 0.76 (EtOAc/cyclohexane: 4/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 5.72–5.87 (m, 1H), 4.93–5.06 (m, 2 H), 4.42–4.57 (m, 1H), 3.85–3.97 (m, 1H), 2.70–2.86 (m, 2 H), 2.41 (s, 3 H), 2.01–2.25 (m, 2 H), 1.52 (s, 3 H), 1.45–1.70 (m, 2 H), 1.44 (s, 3 H), 1.17–1.38 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.3, 138.0, 130.0, 123.8, 114.8, 99.2, 67.9, 65.0, 63.5, 36.4, 35.2, 30.0, 29.0, 21.3, 21.3, 19.8; IR 2993, 2937, 1638, 1494, 1436, 1376, 1263, 1195, 1170, 1053, 1033, 807 cm^{-1}; HRMS ES *m/z* $(M + Li)^+$ calcd for $C_{18}H_{16}LiO_3S$ 329.1758, found 329.1711.

Synthesis of (4*S*,6*S*)-6-(3-(4-methoxybenzyloxy)butyl)-2,2-dimethyl-1,3-dioxane-4-carbaldehyde 13. 2,4,6-Collidine (0.72 mL, 5.54 mmol) and trifluoroacetic anhydride (1.2 mL, 8.63 mmol) were added dropwise subsequently to a solution of sulfoxide (*vide supra*) (568 mg, 1.76 mmol) in 20 mL of MeCN cooled at 0 °C. The reaction mixture was stirred for 45 min, prior to the addition of 20 mL of a saturated $NaHCO_3$ solution, warmed to room temperature and stirred for 1 h 30 min. The aqueous layer was extracted with EtOAc (3 × 100 mL) and the combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (EtOAc/cyclohexane: 5/95 → 20/80) gave the aldehyde **13** as a colorless oil (325 mg, 1.58 mmol, 90%): $[\alpha]_D^{25}$ −37.9° (*c* = 0.33 in $CHCl_3$); R_f 0.37 (EtOAc/cyclohexane: 1/3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.59 (s, 1H), 5.72–5.88 (m, 1H), 4.93–5.09 (m, 2H), 4.28 (dd, *J* = 12.3 Hz, 3.0 Hz, 1H), 3.53–4.00 (m, 1H), 2.03–2.25 (m, 2H), 1.49–1.68 (m, 2H), 1.47 (s, 3H), 1.46 (s, 3H), 1.31 (q, *J* = 12.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.3, 137.9, 115.0, 99.1, 74.1, 67.5, 35.2, 31.0, 29.8, 28.9, 19.5; IR: 2993, 2927, 1739, 1641, 1435, 1380, 1267, 1201, 1111, 911 cm^{-1}; HRMS ES *m/z* $(M + Li)^+$ calcd for $C_{11}H_{18}LiO_3$ 205.1411, found 205.1395.

Synthesis of (4*S*,6*S*)-6-(but-3-enyl)-*N*-methoxy-*N*,2,2-trimethyl-1,3-dioxane-4-carboxamide 14. To aldehyde **13** (148 mg, 0.75 mmol) in 14 mL of *t*-BuOH and 14 mL of water was added subsequently KH_2PO_4 (605 mg, 4.45 mmol), 2-methyl-2-butene (3.92 g, 6.4 mL, 56 mmol) and $NaClO_2$ (227 mg, 2.51 mmol). The reaction mixture was stirred for 5 h 30 min and organic solvents were removed under reduced pressure. The aqueous layer was extracted 3 times with EtOAc and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude acid, which was used for the next step without purification. To a solution of the crude acid in 4 mL of CH_2Cl_2 was added portionwise carbonyldiimidazole (184 mg, 1.14 mmol). The reaction mixture was stirred for 1 h at room temperature, prior to the addition of *N*,*O*-dimethylhydroxylamine hydrochloride (110 mg, 1.13 mmol). The reaction mixture was stirred overnight at room temperature, filtered to remove insoluble materials and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (EtOAc/cyclohexane: 20/80) gave the amide **14** as a colorless oil (146.7 mg, 0.57 mmol, 76%): $[\alpha]_D^{25}$ −24.1° (*c* = 0.86 in $CHCl_3$); R_f 0.4 (EtOAc/cyclohexane: 1/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.71–5.88 (m, 1H), 4.91–5.07 (m, 2H), 4.82 (d, *J* = 10.2 Hz, 1 H), 3.84–3.97 (m, 1H), 3.73 (s, 3H), 3.19 (s, 3 H), 2.03–2.24 (m, 2 H), 1.49–1.87 (m, 4H), 1.47 (s, 3 H), 1.44 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 138.0, 114.8, 99.2, 67.8, 67.0, 61.6, 35.2, 32.3, 32.0, 30.0, 29.0, 19.4; IR 2992, 2937, 1671, 1642, 1440, 1380, 1258, 1199, 1165, 1115, 972, 912 cm^{-1}; HRMS ES *m/z* $(M + Li)^+$ calcd for $C_{13}H_{23}LiO_4$ 264.1782, found 264.1768.

Synthesis of (4*S*,5*S*)-5-(benzyloxy)-2–8-(*tert*-butyldiphenylsilyloxy)oct-1-en-4-ol 15. To a solution of aldehyde **8** (460 mg, 1.03 mmol) in 8 mL of CH_2Cl_2 was added dropwise at −78 °C a solution of $TiCl_4$ (1.03 mL, 1.0 M in CH_2Cl_2, 1.03 mmol), followed by the dropwise addition of 2-bromo-3-(trimethylsilyl) propene (199 mg, 1.03 mmol). The reaction mixture was stirred for 2 h 30 min at −78 °C, 30 min at 0 °C and hydrolyzed with an aqueous saturated solution of NH_4Cl (8 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by flash column chromatography on silica gel (EtOAc/cyclohexane: 1/6) to give the alcohol **15** (495 mg, 0.87 mmol, 85%) as a colourless oil as the favoured diastereomer (8.5/1): $[\alpha]_D^{25}$ +7.6° (*c* = 1.10 in $CHCl_3$); R_f 0.48 (EtOAc/cyclohexane: 1/5); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67–7.71 (m, 4H), 7.28–7.47 (m, 11H), 5.63 (d, *J* = 1.6 Hz, 1H), 5.50 (d, *J* = 1.6 Hz, 1H), 4.57 (AB, J_{AB} = 11.4 Hz, $\Delta\nu$ = 47.7 Hz, 2H), 3.93–3.98 (X of ABX, m, 1H), 3.71 (t, *J* = 5.9 Hz, 2H), 3.39 (dt as q, *J* = 5.2 Hz, 1H), 2.51–2.68 (AB of ABX, m, 2H), 2.09 (s, br., 1H), 1.59–1.87 (m, 4H), 1.08 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.1, 135.6, 133.9, 130.7, 129.6, 128.5, 127.9, 127.8, 127.6, 119.2, 80.2, 72.0, 70.1, 63.8, 45.5, 28.2, 26.9, 26.2, 19.2; IR 3461, 2931, 2858, 1472, 1455, 1428, 1390, 1207, 1105, 1088, 1070, 1028, 998, 938, 889, 797, 738, 699 cm^{-1}; HRMS ES *m/z* $(M + Li)^+$ calcd for $C_{31}H_{39}BrLiO_3Si$ 573.2007, found 573.1943.

Synthesis of (5*S*,6*S*)-6-(benzyloxy)-5-(2-bromoallyl)-2,2,3,312,12-hexamethyl-11,11-diphenyl-4,10-dioxa-3,11-disilatridecane 16. A solution of alcohol **15** (300 mg, 532 µmol) in 3 mL of DMF was treated subsequently with imidazole (72 mg, 1.06 mmol), *N*,*N*-dimethylaminopyridine (2 mg, 16.4 µmol) and TBSCl (120 mg, 798 mmol) at room temperature. After 16 h the

reaction mixture was poured on diethyl ether/H_2O (1/1) (20 mL). The organic layer was washed with distilled water (3 × 10 mL). The aqueous layer was extracted with Et_2O (3 × 20 mL) and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (EtOAc/cyclohexane: 1/40) afforded the silylether **16** (347 mg, 0.51, 96%) as a colorless oil: $[\alpha]_D^{25}$ −16.5° (c = 1.00 in $CHCl_3$); R_f: 0.46 (EtOAc/cyclohexane: 1/40); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67–7.70 (m, 4H), 7.67–7.70 (m, 4H), 7.27–7.46 (m, 11H), 5.61 (s, 1H), 5.45 (d, J = 1.2 Hz, 1H), 4.57 (AB, J_{AB} = 11.5 Hz, $\Delta\nu$ = 44.4 Hz, 2H), 4.18–4.23 (X of ABX, m, 1H), 3.62–3.76 (m, 2H), 3.34–3.39 (m, 1H), 2.29–2.75 (AB of ABX, m, 2H), 1.26–1.88 (m, 4H), 1.07 (s, 9H), 0.87 (s, 9H), 0.07 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5, 135.6, 134.1, 132.5, 129.5, 128.3, 128.0, 127.6, 127.6, 119.2, 81.3, 72.1, 69.3, 64.2, 43.7, 29.9, 26.9, 25.8, 25.1, 19.2, 18.0, −4.5, −4.5; IR 2954, 2929, 2893, 2857, 1472, 1463, 1428, 1389, 1361, 1251, 1091, 1028, 1006, 957, 936, 885, 826, 810, 776, 738, 699 cm^{-1}; HRMS ES m/z (M + Li)$^+$ calcd for $C_{37}H_{53}BrLiO_3Si_2$ 687.2871, found 687.2845.

Synthesis of (4*S*,5*S*)-5-(benzyloxy)-1-((4*S*,6*S*)-6-(but-3-en-1-yl)-2,2-dimethyl-1,3-dioxan-4-yl)-4-((*tert*-butyldimethylsilyl)oxy)-8-((*tert*-butyldiphenylsilyl)oxy)-2-methyleneoctan-1-one 17. To a solution of vinyl bromide **16** (243 mg, 0.36 mmol) in 3.5 mL of Et_2O cooled at −78 °C was added dropwise *t*-BuLi (0.46 mL, 1.7 M in pentane, 0.78 mmol). The reaction mixture was stirred for 40 min at −78 °C and a solution of amide **14** (50 mg, 0.19 mmol) in 2.5 mL of Et_2O was added *via* a cannula. The temperature was gradually increased until 0 °C during 3 h and the reaction mixture was quenched with an aqueous saturated solution of NH_4Cl. The mixture was extracted 3 times with Et_2O and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by flash column chromatography on silica gel (EtOAc/cyclohexane: 1/30) yielding the coupling compound **17** (106 mg, 0.13 mmol, 70%) as a colourless oil: $[\alpha]_D^{25}$ −21.6° (c = 1.0 in $CHCl_3$); R_f 0.65 (EtOAc/cyclohexane: 1/6); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64–7.69 (m, 5H), 7.28–7.44 (m, 10H), 6.25 (d, J = 0.6 Hz, 1H), 5.90 (s, 1H), 5.71–5.89 (m, 1H), 4.94–5.08 (m, 2H), 4.87 (dd, J = 10.8 Hz, J = 3.6 Hz, 1H), 4.59 (AB, J_{AB} = 11.4 Hz, $\Delta\nu$ = 79.6 Hz, 2H), 3.98–4.06 (m, 1H), 3.82–3.97. (m, 1H), 3.55–3.76 (m, 2H), 3.28–3.36 (m, 1H), 2.83 (dd, J = 12.9 Hz, J = 2.7 Hz, 1H), 2.05–2.24 (m, 3H), 1.75–1.87 (m, 2H), 1.50–1.71 (m, 6H), 1.49 (s, 3H), 1.45 (s, 3H), 1.05 (s, 9H), 0.83 (s, 9H), −0.07 (s, 3H), −0.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.1, 143.2, 138.8, 138.1, 135.6, 134.1, 129.6, 129.5, 128.3, 128.0, 127.55, 127.5, 114.9, 99.2, 81.5, 71.6, 71.5, 70.3, 67.9, 64.3, 35.3, 34.2, 33.1, 30.0, 29.99, 29.0, 26.9, 25.9, 24.7, 19.3, 19.2, 17.9, −4.4; IR 2929, 2856, 1683, 1641, 1380, 1255, 1201, 1106, 1085, 936, 826, 775, 738, 700 cm^{-1}; HRMS ES m/z (M + Li)$^+$ calcd for $C_{48}H_{70}LiO_6Si_2$ 805.4866, found 805.4823.

Synthesis of *tert*-butyl((*S*)-4-(4-methoxybenzyloxy)-5-((*R*)-*p*-tolylsulfinyl)pentyloxy)-diphenylsilane 19. To a solution of β-hydroxysulfoxide **6** (1.85 g, 3.83 mmol) in 20 mL of THF at room temperature was added methoxybenzyl-trichloracetimidate‡ (1.53 g, 5.745 mmol) and $Yb(OTf)_3{\cdot}H_2O$ (124 mg, 0.20 mmol). The resulting mixture was stirred for 16 h at room temperature and hydrolyzed with 15 mL of distilled water. The aqueous layer was extracted with EtOAc (3 × 15 mL) and the combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/cyclohexane: 1/1) to give the protected alcohol **22** as a yellow oil (2.01 g, 3.41 mmol, 80%): $[\alpha]_D^{25}$ +55.73° (c = 1.50 in $CHCl_3$); R_f 0.29 (EtOAc/cyclohexane: 1/2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.7–7.6 (m, 18H), 4.52 (AB, J_{AB} = 8.7 Hz, $\Delta\nu$ = 8.95 Hz, 2H), 3.97 (m, 1H), 3.71 (s, 3H), 3.56 (t, J = 6.3 Hz, 2H), 2.76 (m, 2H), 2.32 (s, 3H), 1.40–1.70 (m, 4H), 0.95 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 141.6, 141.3, 135.5, 133.9, 130.2, 130.0, 129.7, 129.6, 127.6, 123.8, 113.9, 72.9, 72.0, 64.6, 63.6, 55.3, 30.2, 27.7, 26.9, 21.4, 19.20; IR: 2931, 2857, 1726, 1612, 1587, 1513, 1494, 1463, 1427, 1390, 1359, 1302, 1246, 1174, 1109, 1085, 1033, 1013, 937, 821, 808, 741, 701, 687 cm^{-1}; HRMS ES m/z (M + Na)$^+$ calcd for $C_{36}H_{44}NaO_4SSi_2$ 623.262, found 623.262.

Synthesis of (*S*)-5-(*tert*-butyldiphenylsilyloxy)-2-(4-methoxybenzyloxy)-pentanal 20. To a solution of sulfoxide **19** (950 mg, 1.62 mmol) in 16 mL of MeCN cooled at 0 °C was added dropwise subsequently 2,4,6-collidine (537 mg, 0.6 mL, 4.88 mmol) and trifluoroacetic anhydride (1.2 mL, 8.1 mmol). The reaction mixture was stirred for 30 min, prior to the addition of 65 mL of a saturated solution of $NaHCO_3$, warmed to room temperature and stirred for 1 h. The aqueous layer was extracted with EtOAc (3 × 50 mL) and the combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/cyclohexane: 1/9) to give the aldehyde **20** (683 mg, 1.42 mmol, 88%) as a brown oil: $[\alpha]_D^{25}$ −19.6° (c = 1.00 in $CHCl_3$), R_f 0.21 (EtOAc/cyclohexane: 1/3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.65 (d, J = 2.1 Hz, 1H), 6.8–7.7 (m, 14H), 4.50 (AB, J_{AB} = 9 Hz; $\Delta\nu$ = 34.15 Hz, 2H), 3.80 (s, 3H), 3.70 (m, 1H), 3.64 (t, J = 6 Hz, 2H), 1.57–1.98 (m, 4H), 1.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.7, 159.5, 135.6, 133.8, 129.7, 129.6, 129.4, 127.5, 113.9, 82.9, 72.1, 63.2, 55.3, 27.7, 26.9, 26.4, 19.2; IR: 3071, 2931, 2857, 1732, 1612, 1587, 1513, 1471, 1463, 1427, 1389, 1373, 1361, 1302, 1246, 1173, 1106, 1088, 1034, 1007, 997, 937, 821, 741, 700, 687 cm^{-1}; HRMS ES m/z (M + Na)$^+$ calcd for $C_{29}H_{36}NaO_4Si$ 499.228, found 499.225.

Synthesis of (4*S*,5*S*)-2-bromo-8-(*tert*-butyldiphenylsilyloxy)oct-1-ene-4,5-diol 21. To a solution of aldehyde **20** (253 mg, 0.53 mmol) in 4 mL of CH_2Cl_2 was added dropwise at −78 °C a solution of $TiCl_4$ (0.5 mL, 1.0 M in CH_2Cl_2, 0.53 mmol), followed by the dropwise addition of 2-bromo-3-(trimethylsilyl) propene (100 mg, 0.53 mmol). The reaction mixture was stirred for 3 h at −78 °C and hydrolyzed with a saturated solution of NH_4Cl (4 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated

‡J. E. Audis, L. Boisvert, A. D. Patten, A. Villalobos, S. J. Danishefsky, *J. Org. Chem.*, 1989, **54**, 3738.

in vacuo. The crude material was purified by flash column chromatography on silica gel (EtOAc/cyclohexane: 1/6) giving the diol **21** as a colorless oil as the only *syn* diastereomer (215 mg, 0.45 mmol, 85%): $[\alpha]_D^{25}$ −3.23° (*c* = 1.07, $CHCl_3$); R_f 0.53 (EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 7.25–7.55 (m, 10H), 5.59 (d, *J* = 1.08 Hz, 1H), 5.40 (d, *J* = 1.59 Hz, 1H), 3.66 (m, 1H), 3.59 (t, *J* = 3.27 Hz, 2H), 3.40 (m, 1H), 2.87 (m, 1H), 2.51 (m, 2H), 2.25 (m, 1H, OH), 1.45–1.68 (m, 4H), 0.93 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.6, 133.5, 130.6, 129.8, 127.7, 119.6, 72.9, 71.7, 64.2, 46.0, 31.0, 28.7, 26.9, 19.2; IR: 3397, 2930, 2856, 1738, 1631, 1472, 1427, 1389, 1245, 1106, 889, 822, 739, 700, 687 cm^{-1}; HRMS ES *m/z* $(M + Na)^+$ calcd for $C_{24}H_{33}BrNaO_3Si$ 499.127, found 499.128.

Synthesis of (3-((4*S*,5*S*)-5-(2-bromoallyl)-2,2-dimethyl-1,3-dioxolan-4-yl)propoxy)(*tert*-butyl)diphenylsilane 22. To a solution of diol **21** (120 mg, 0.25 mmol) in 3 mL of acetone and 0.9 mL of 2,2-dimethoxypropane was added PPTS (22 mg, 0.093 mmol) at room temperature. The reaction mixture was stirred for 16 h, hydrolyzed with 2 mL of a saturated solution of $NaHCO_3$ and poured into 30 mL of EtOAc. The aqueous layer was extracted with EtOAc (3 × 6 mL) and the combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (EtOAc/cyclohexane: 2/98) gave the acetal **22** (127 mg, 0.25 mmol, 98%) as a colorless oil: $[\alpha]_D^{25}$ −12.37° (*c* = 1.03, $CHCl_3$); R_f 0.81 (EtOAc/cyclohexane: 1/4); ^1H NMR (300 MHz, $CDCl_3$) δ 7.26–7.68 (m, 10H), 5.72 (d, *J* = 0.9 Hz, 1H), 5.50 (d, *J* = 1.5 Hz, 1H), 3.95 (td, *J* = 7.68 Hz, *J* = 4.68 Hz, 1H), 3.7 (m, 3H), 2.65 (AB (ABX), J_{AB} = 15 Hz, J_{AX} = 7.5 Hz, J_{BX} = 4.5 Hz, $\Delta\nu$ = 43.88 Hz, 2H), 1.5–1.8 (m, 4H), 1.39 (s, 3H), 1.37 (s, 3H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.6, 134.0, 129.6, 129.4, 127.6, 119.1, 108.5, 80.4, 78.1, 63.6, 45.3, 29.3, 29.0, 27.3, 27.2, 26.9, 19.2; HRMS ES *m/z* $(M + Na)^+$ calcd for $C_{27}H_{37}BrNaO_3Si$ 539.159, found 539.159.

Synthesis of 1-((4*S*,6*S*)-6-(but-3-enyl)-2,2-dimethyl-1,3-dioxan-4-yl)-2-(((4*R*,5*R*)-5-(3-(*tert*-butyldiphenylsilyloxy)propyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)prop-2-en-1-one 23. To a solution of vinyl bromide **22** (600 mg, 1.16 mmol) in 15 mL of Et_2O cooled at −78 °C was added dropwise *t*-BuLi (1.36 mL, 1.7 M in pentane, 2.32 mmol). The reaction mixture was stirred for 40 min at −78 °C and a solution of amide **14** (150 mg, 0.58 mmol) in 15 mL of Et_2O was added *via* a cannula. The temperature was gradually increased until 0 °C during 3 h and the reaction mixture was quenched with an aqueous saturated solution of NH_4Cl. The mixture was extracted 3 times with Et_2O and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by flash column chromatography on silica gel (EtOAc/cyclohexane: 1/30) yielding the coupling compound **23** (246 mg, 0.40 mmol, 70%) as a colorless oil: $[\alpha]_D^{25}$ −9.41° (*c* = 0.505 in $CHCl_3$); R_f 0.65 (EtOAc/cyclohexane: 1/6); ^1H NMR (300 MHz, $CDCl_3$) δ 7.3–7.7 (m, 10H), 6.24 (s, 1H), 6.01 (s, 1H), 5.79 (ddt, J_{trans} = 16.86 Hz, J_{cis} = 10.05 Hz, ^3J = 6.6 Hz, 1H), 4.97 (m, 2H), 4.91 (dd, *J* = 11.64 Hz, *J* = 2.79 Hz, 1H), 3.75 (m, 1H), 3.45–3.7 (m, 4H), 2.45 (AB (ABX), J_{AB} = 22.5 Hz, J_{AX} = 2.7 Hz, J_{BX} = 8.1 Hz, $\Delta\nu$ = 88.95 Hz, 2H), 2.1 (m, 2H), 1.49 (s, 3H), 1.44 (s, 3H), 1.35 (s, 3H), 1.34 (s 3H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.1, 142.5, 138.1, 135.6, 134.0, 129.5, 128.4, 127.6, 115.0, 108.1, 99.2, 80.6, 78.9, 71.4, 67.9, 63.7, 35.3, 35.1, 32.9, 30.2, 30.0, 29.0, 27.3, 27.3, 26.9, 26.9, 19.4, 19.2; IR: 3072, 2986, 2931, 2858, 1731, 1684, 1641, 1589, 1428, 1378, 1252, 1200, 1164, 1109, 1088, 996, 962, 938, 912, 865, 822, 740 710, 687 cm^{-1}; HRMS ES *m/z* $(M + Na)^+$ calcd for $C_{38}H_{54}NaO_6Si$ 657.358, found 657.360.

Synthesis of (*R*)-1-((4*S*,6*S*)-6-(but-3-enyl)-2,2-dimethyl-1,3-dioxan-4-yl)-2-(((4*R*,5*R*)-5-(3-(*tert*-butyldiphenylsilyloxy)propyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)prop-2-en-1-ol 24

*Way A: stereoselective reduction of enone **23**.* To a solution of enone **23** (173 mg, 0.273 mmol) in 10 mL of Et_2O cooled at 0 °C was added $CeCl_3$ (20 mg, 0.082 mmol) and dropwise a freshly prepared solution of $Zn(BH_4)_2$ (1.15 mL. 0.183 M in Et_2O, 0.210 mmol). The mixture was stirred for 20 min at 0 °C and quenched with 10 mL of an NH_4Cl saturated solution. The mixture was extracted 3 times with Et_2O and the combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by flash column chromatography on silica gel (EtOAc/cyclohexane: 1/15 then 1/6) giving the alcohol (69 mg, 0.11 mmol, 40%) as a colorless oil as the *trans* diastereomer **24** only.

*Way B: stereoselective addition of vinyl bromide **22** to aldehyde **13** in the presence of magnesium bromide.* Dibromomethane (1.25 g, 6.65 mmol) in 1.7 mL of distillated toluene was added dropwise over 30 min in a solution of magnesium (173 mg, 7.11 mmol) in 5 mL of distillated Et_2O at RT. The reaction was stirred for 30 min at RT and was clarified for 1 h 30 min (solution supposed at 1 M).

t-BuLi (1.7 M in hexane, 270 µL, 0.457 mmol) was added dropwise in a solution of vinyl bromide **22** (107.5 mg, 0.21 mmol) in 3 mL of THF at −78 °C. The reaction was stirred for 30 min at −78 °C and turned to deep yellow. $MgBr_2$ solution (1 M, 210 µL, 0.210 mmol) was added at −78 °C, and the reaction was stirred for 30 min at −78 °C. Aldehyde **13** (33 mg, 0.166 mmol) in 2 mL of dichloromethane was added *via* a cannula. The reaction was stirred for 1 h 30 min at −78 °C and allowed to warm to RT.

The reaction was hydrolyzed with NH_4Cl solution, aqueous phase extracted three times with DCM. Organic phases were washed with brine, dried over Na_2SO_4, filtrated and evaporated. Diastereoisomers (5.5/1) were separated by flash chromatography (EtOAc/cyclohexane 1/6), giving the alcohol **24** (58 mg, 0.091 mmol, 55%) as a colorless oil.

*Way C: stereoselective addition of vinyl bromide **22** to aldehyde **13**.* *t*-BuLi (1.7 M in hexane, 173 µL, 0.295 mmol) was added dropwise in a solution of vinyl bromide **22** (70 mg, 0.136 mmol) in 2 mL of distillated Et_2O at −78 °C. The reaction was stirred for 45 min at −78 °C, the solution turned to deep yellow. Aldehyde **13** (14 mg, 0.067 mmol) in 2 mL of Et_2O was added *via* a cannula to the reaction, and the reaction was stirred for 2 h at −78 °C. The reaction was allowed to warm to RT and was hydrolyzed with NH_4Cl solution. The aqueous phase was extracted three times with Et_2O, organic phases were washed with brine, dried over Na_2SO_4, filtrated, evaporated. The two diastereoisomers (6/1) were separated by flash chromatography (EtOAc/

cyclohexane 1/6), giving the alcohol **26** (27 mg, 0.042 mmol, 62%) as a colorless oil.

Major diastereoisomer $[\alpha]_D^{25}$ −22.71° (c = 1.035 in $CHCl_3$), R_f 0.28 (EtOAc/cyclohexane: 1/6); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.70 (m, 10H), 5.79 (ddt, J_{trans} = 17.01 Hz, J_{cis} = 10.17 Hz, ^3J = 6.75 Hz, 1H), 5.21 (s, 1H), 5.07 (s, 1H), 4.97 (m, 2H), 4.05 (m, 1H), 3.95 (m, 1H), 3.80 (m, 1H), 3.6–3.75 (m, 4H), 3.15 (m, 1H), 2.27 (d, J = 5.7 Hz, 2H), 2.12 (m, 2H), 1.1–18 (m, 20H), 1.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.1, 138.3, 135.6, 134.0, 129.6, 127.6, 115.5, 114.7, 108.3, 98.6, 81.0, 80.7, 76.6, 70.64, 68.0, 63.6, 35.8, 35.5, 31.1, 30.1, 29.2, 29.0, 28.8, 27.7, 27.2, 26.9, 19.8, 19.2; IR: 3473, 3072, 2988, 2930, 2857, 1741, 1641, 1472, 1462, 1428, 1378, 1239, 1199, 1165, 1109, 1089, 1047, 990, 909, 823, 740, 701, 687 cm^{-1}; HRMS ES m/z $(M + Na)^+$ calcd for $C_{38}H_{56}NaO_6Si$ 659.374, found 659.378.

Minor diastereoisomer, R_f 0.24 (EtOAc/cyclohexane: 1/6); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.70 (m, 10H), 5.79 (m, 1H), 5.10 (s, 1H), 5.03 (s, 1H), 4.97 (m, 2H), 4.25 (m, 1H), 3.6–3.95 (m, 6H), 3.15 (m, 1H), 2.10–2.32 (m, 4H), 1.1–1.8 (m, 20H), 1.05 (s, 3H).

Synthesis of 4-((4*S*,6*S*)-6-((*R*)-2-(((4*R*,5*R*)-5-(3-(*tert*-butyldiphenylsilyloxy)propyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-1-hydroxyallyl)-2,2-dimethyl-1,3-dioxan-4-yl)butan-2-one 26. To a solution of alcohol **24** (20 mg, 0.030 mmol) in a mixture of 2 mL of dimethylacetamide and 0.7 mL of water was added $Cu(OAc)_2$ (13 mg, 0.065 mmol) and $PdCl_2$ (3 mg, 0.016 mmol). The flask was connected with a balloon of O_2 and the reaction mixture was stirred for 3 days at room temperature. The reaction mixture was extracted 3 times with ethyl acetate and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by flash column chromatography on silica gel (EtOAc/hexane 1/4), giving the methyl ketone **26** (16.6 mg, 0.025 mmol, 85%) as a colorless oil: $[\alpha]_D^{25}$ −21.03° (c = 0.98, $CHCl_3$); R_f 0.25 (EtOAc/cyclohexane 1/4); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26–7.68 (m, 10H), 5.21 (s, 1H, 17), 5.07 (s, 1H), 4.05 (d, J = 5.01 Hz, 1H), 3.95 (m, 1H), 3.80 (m, 1H), 3.6–3.75 (m, 4H), 2.52 (t, J = 2.47 Hz, 2H), 2.26 (d, J = 5.7 Hz, 2H), 2.13 (s, 3H), 1.5–1.9 (m, 6H), 1.2–1.45 (m, 14H), 1.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.6, 144.1, 135.6, 133.9, 129.6, 127.6, 115.6, 108.3, 98.6, 81.0, 80.7, 76.6, 70.6, 67.9, 63.6, 39.1, 35.8, 31.1, 30.3, 30.0, 29.9, 29.0, 28.8, 27.3, 27.2, 26.9, 19.8, 19.2; HRMS ES m/z $(M + Na)^+$ calcd for $C_{38}H_{56}NaO_6Si$ 659.374, found 659.378.

Synthesis of (*R*)-2-(((4*S*,5*S*)-5-(3-((*tert*-butyldiphenylsilyl)oxy)propyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-1-((4*S*,6*S*)-2,2-dimethyl-6-(3-oxobutyl)-1,3-dioxan-4-yl)allyl pivalate. To a solution of **26** (16 mg, 0.025 mmol) and DMAP (1 mg, 0.009 mmol) in pyridine (2 mL) was added pivaloyl chloride (5 µL, 0.038 mmol) at 0 °C. The reaction was stirred at 70 °C for 24 h, and then cooled down to RT and MeOH (200 µL) was added. The reaction was stirred for 1 h at RT and then concentrated under reduced pressure and diluted with EtOAc. The solution was washed respectively with 1 N HCl, a saturated solution of $NaHCO_3$, and water. The organic layer was dried over Na_2SO_4, filtrated and evaporated. The crude was purified by flash chromatography (EtOAc/hexane 1/6) affording the corresponding pivalate (16.5 mg, 0.022 mmol, 88%); $[\alpha]_D^{25}$ −14.72° (c = 1.03, $CHCl_3$); R_f 0.72 (EtOAc/cyclohexane 2/3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.61 (m, 10H), 5.10 (d, J = 4.8 Hz, 1H), 5.05 (d, J = 3.3 Hz, 2H), 4.01 (m, 1H), 3.55–3.76 (m, 5H), 2.41–2.47 (m, 2H), 2.15–2.25 (m, 2H), 2.07 (s, 3H), 1.4 (m, 8H), 1.05–1.35 (m, 21H), 0.97 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.6, 177.0, 141.9, 135.5, 133.9, 129.5, 127.6, 114.3, 108.1, 98.6, 80.8, 79.3, 76.9, 69.3, 67.7, 63.7, 39.0, 38.7, 36.4, 31.9, 30.0, 29.9, 29.7, 29.1, 27.4, 27.3, 27.2, 26.9, 19.6, 19.2; HRMS ES m/z $(M + Na)^+$ calcd for $C_{43}H_{64}NaO_8Si$ 759.424, found 759.426.

Synthesis of 4-((4*S*,6*S*)-6-((1*R*)-3-((4*R*,5*R*)-5-(3-((*tert*-butyldiphenylsilyl)oxy)propyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-1-hydroxy-2-methylpropyl)-2,2-dimethyl-1,3-dioxan-4-yl)butan-2-one 28. Pd/C (4 mg, 10% WT) was added to a solution of **26** (32 mg, 0.05 mmol) in 5 mL of MeOH in an autoclave. The autoclave was purged three times with H_2 and the reaction was stirred overnight over 80 bars of H_2 at RT. The reaction was filtrated over celite, concentrated and purified by flash chromatography (EtOAc/hexane 1/4) affording the hydrogenated compound as a mixture of two diastereoisomers **28** and **28′** (31 mg, 0.048 mmol, 99%): R_f 0.41–0.44 (EtOAc/cyclohexane 2/3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.68 (m, 10H), 3.5–3.95 (m), 3.31 (t, J = 6.16 Hz), 2.95 (m), 2.54 (m), 2.15 (s, 3H), 1.97 (m), 1.45–1.90 (m), 1.30–1.45 (m, 12H), 1.05 (s, 9H), 1.10 (d, J = 7.04 Hz, 3H), 0.91 (d, J = 6.76 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.6, 208.6, 135.5, 133.9, 129.5, 127.6, 108.1, 108.2, 98.4, 98.4, 81.0, 81.3, 78.3, 79.5, 77.2, 77.2, 69.1, 69.9, 67.9, 68.1, 63.5, 63.6, 39.1, 39.1, 34.8, 31.9, 32.3, 31.7, 30.3, 30.3, 30.1, 29.9, 29.0, 28.8, 28.9, 27.2, 27.3, 26.8, 19.6, 19.7, 19.2, 14.0, 16.2; HRMS ES m/z (M + Na) calcd for $C_{38}H_{58}NaO_7Si$ 677.391, found 677.384.

Compound **27** was really unstable and was consequently directly reduced to **28** and **28′**.

Synthesis of Paquette's fragment 4-((4*S*,6*S*)-6-((1*R*)-1-((benzyloxy)methoxy)-3-((4*S*,5*S*)-5-(3-hydroxypropyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-methylpropyl)-2,2-dimethyl-1,3-dioxan-4-yl)butan-2-one. BOMCl (75%, 25 µL, 0.132 mmol) was added to a solution of **32** (28 mg, 0.044 mmol), DIPEA (50 µL, 0.27 mmol) and Bn_4NI (2 mg, 4.4 µmol) in CH_2Cl_2 (2 mL). The reaction was stirred for four days at RT and then quenched with water (2 mL). The aqueous phase was extracted three times with CH_2Cl_2; the organic phases were washed with brine, dried over Na_2SO_4, and evaporated giving **33**, which was directly used for the next step without further purification. TBAF (40 µL, 1 M, 0.040 mmol) was added to a solution of **33** (14 mg, 0.019 mmol) in THF (1 mL). The reaction was stirred for 6 h at RT and quenched with brine. The aqueous phase was extracted three times with EtOAc, and the organic phases were dried over Na_2SO_4, filtrated, concentrated and purified by flash chromatography (EtOAc/hexane 1/6) affording Paquette *et al.*'s fragment (15.3 mg, 0.028 mmol, 65%).

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