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PAPER

Formal total synthesis of (−)-exiguolide†

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The formal total synthesis of (−)-exiguolide through the chiral-pool approach is described. The key reactions involved for formation of the macrocyclic core from two subunits are Julia–Kocienski olefination and Yamaguchi macrolactonization. The major methylene *bis*-tetrahydropyran fragment was achieved in a convergent manner from L-glutamic acid and L-aspartic acid involving the *oxa*-Michael reaction and an aldol-driven reductive etherification as key steps for the formation of a tetrahydropyran ring. The other sulfone subunit was prepared *via* an Evans aldol reaction.

Introduction

(−)-Exiguolide (**1**, Fig. 1) was isolated in 2006 by Ohta, Ikegami and co-workers from the marine sponge *Geodia exigua* Thiele (order Astrophorida, family Geodiidae).[1] The structure, along with relative stereochemistry, has been determined by a combination of wide NMR study, conformational analysis based on nuclear Overhauser effect spectroscopy (NOESY) correlations and *J*-based configuration analysis. Structurally, it is a 20-membered macrolide with a methylene *bis*-tetrahydropyran (THP) subunit, five carbon–carbon double bonds and seven asymmetric carbons. The presence of the bispyran framework and the exocyclic enoate attached to one of the THP-rings are common motifs that can be found in marine antineoplastic agents, bryostatins.[2] (−)-Exiguolide specifically inhibits the fertilization of sea urchin (*Hemicentrotus pulcherrimus*) gametes but not embryogenesis of the fertilized egg at higher concentrations. Based on these biological and structural features of (−)-**1**, an assumption has been made that (−)-exiguolide represents a structurally simplified analogue of the bryostatins.[2b] The limited supply and structural complexity of (−)-**1** renders this molecule and its analogues important targets for chemical synthesis towards further evaluation of biological activities.

In 2008, Lee and co-workers reported the total synthesis of (+)-exiguolide, an enantiomer of the natural product, using ring-closing metathesis, Prins cyclization, radical cyclization and Sonogashira coupling as the key steps.[3] From this synthesis, they have determined the absolute stereochemistry of (−)-exiguolide. Later, three total syntheses of (−)-**1** were published.[4] In the year 2010, Fuwa and Sasaki reported the total synthesis of (−)-**1** *via* Julia–Kocienski olefination, reductive etherification, intramolecular *oxa*-conjugate addition and Suzuki–Miyayura coupling as the key reactions.[4a] In the same year, Roulland and co-workers accomplished (−)-**1** using Yamaguchi macrolactonization, Trost's ruthenium-catalyzed ene–yne cross-coupling, reductive etherification and Sonogashira cross-coupling as steps.[4b] Recently, Scheidt and co-workers have described the enantioselective synthesis of (−)-exiguolide by dioxinone-directed Prins cyclizations to construct the THP-rings, as well as for macrocyclization and Leibeskind Cu^{I}-mediated coupling to stitch the side chain. Further, they have evaluated the ability of (−)-**1** to inhibit cell growth on nine cancer cell lines and found significant antiproliferative activity against A549 lung cancer cells compared to others.[4c] Prior to this work, Fuwa *et al.* also elucidated the assessment of the growth inhibitory activity of synthetic (−)-exiguolide and its analogues against a panel of human cancer cell lines and observed that (−)-**1** is an effective antiproliferative agent against the NCI-H460 human lung large carcinoma (log GI_{50} = −8.00) as well as the A549 human lung adenocarcinoma cell lines (log GI_{50} = −6.19).[5] Notably (−)-**1** has been found to have a 10 to 100-fold greater potency than bryostatin (log GI_{50} = −5.6 for NCI-H460, −5.4 for A549). They have also investigated the structure–activity relationships, which elucidated that the C5-methoxycarbonylmethylidene group and length of the side chain are important for biological activity.

Our interest in macrolides and THP-containing molecules[6] coupled with the distinctive structure of (−)-exiguolide has encouraged us to attempt the synthesis of (−)-**1**. In this paper, we provide the full details of our work on the formal total synthesis of (−)-exiguolide.[7] The retrosynthetic analysis of (−)-exiguolide

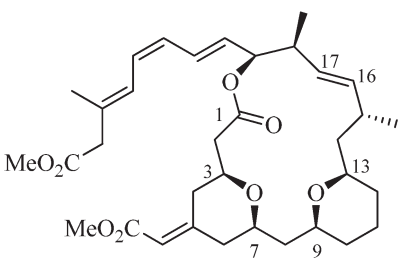

Fig. 1 Structure of (−)-exiguolide (**1**).

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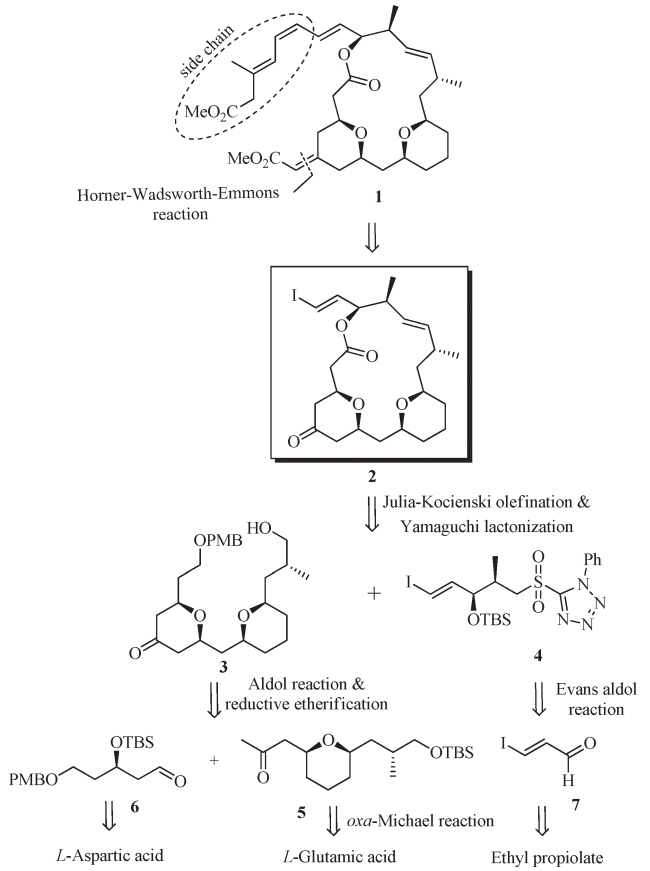
† Electronic supplementary information (ESI) available: Copies of ^{1}H NMR and ^{13}C NMR spectra of all the new compounds. See DOI: 10.1039/c2ra21161k.



Scheme 1 Retrosynthetic analysis of (−)-**1**.

is illustrated in Scheme 1. We envisioned that the side chain installation on iodo-macrocyclic core **2** would be at the final stage of the synthesis, which may be helpful for preparing new analogs. The macrocycle **2** could be realized from *bis*-THP subunit **3** and iodo-sulfone **4** through Julia–Kocienski olefination (C16–C17 double bond formation) followed by Yamaguchi macrolactonization. The synthesis of fragment **3** was planned in a convergent fashion from the THP-ketone **5** and aldehyde **6**, utilizing an aldol-reaction followed by reductive etherification. Notably, THP-ketone **5** may in turn be obtained from L-glutamic acid using the *oxa*-Michael reaction, and aldehyde **6** could be derived from L-aspartic acid. The iodo-sulfone precursor **4** was envisaged from ethyl propiolate *via* iodo acrolein **7** by the Evans aldol approach.

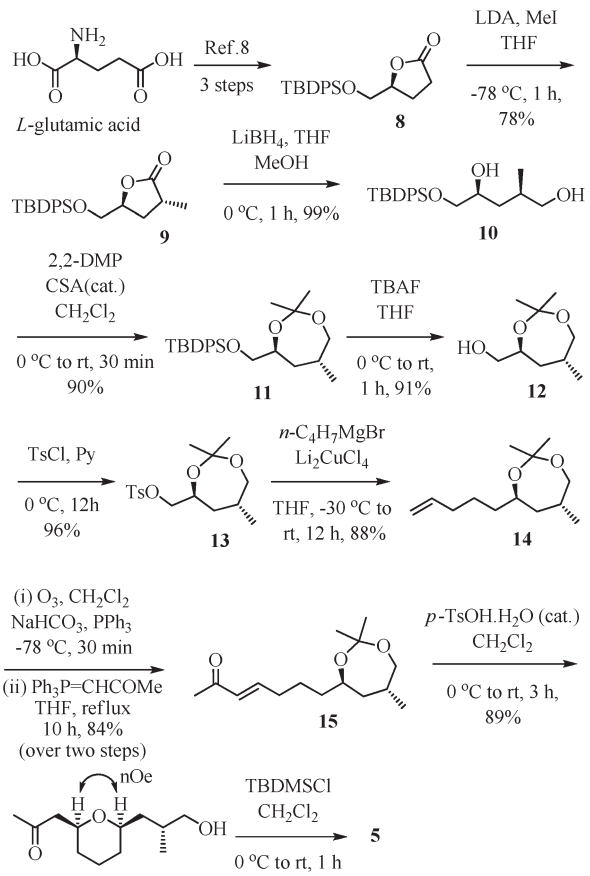
Results and discussion

Synthesis of THP-ketone, C6–C16 fragment (5)

The synthesis of THP-ketone **5** was initiated by carrying out the preparation of the known *tert*-butyldiphenyl silyl protected (4*S*)-hydroxymethyl-4-butanolide **8** from L-glutamic acid using the literature method.[8] In the first step, stereoselective methylation of **8** was carried out under LDA/MeI/−78 °C reaction conditions to get **9** in 78% yield. This reaction installed the C-15 methyl stereo center.[9] The reductive opening of lactone **9** using lithium borohydride provided the 1,4-diol **10** in 99% yield. Subsequent protection of 1,4-diol **10** under 2,2-DMP/CSA reaction conditions afforded a seven-membered acetonide **11** in 90% yield. Then, the deprotection of the *tert*-butyldiphenyl silyl group of **11** was accomplished using tetrabutyl ammonium fluoride to give the alcohol **12** in 91% yield. In order to substitute the primary hydroxyl group with a four-carbon chain, a two-step procedure was planned. Accordingly, the alcohol **12** was tosylated (TsCl/Py, 96% yield) to **13**, and subsequently tosylate **13** was subjected to a Schlosser copper-catalyzed Grignard coupling reaction with 3-butenyl magnesium bromide in the presence of dilithium tetrachloro cuprate, to give **14** in 88% yield.[10] Synthesis of precursor **15** for the *oxa*-Michael reaction towards the pyran-ring formation was initially accomplished from **14** using a cross-metathesis reaction with methyl vinyl ketone in 56% yield.[11] Alternatively, to get a better yield, olefin **14** was subjected to ozonolysis followed by a Wittig olefination (PPh_3=CHCOMe), to provide α,β-unsaturated ketone **15** in 84% yield (over two steps). Hydrolysis of acetonide **15** and consequent *oxa*-Michael addition were accomplished through a *p*-TSA-catalyzed one-pot reaction to get pyran **16** in 89% yield.[12] The NOE effect between H-9 and H-13 (2D NOESY) confirmed the relative *syn*-relationship of 2,6-disubstituted tetrahydropyran. The protection of the free-hydroxyl group of pyran **16** as *tert*-butyldimethyl silyl ether using TBSCl/imidazole gave the desired THP-ketone fragment **5** in 95% yield.

Synthesis of aldehyde, C1–C5 fragment (6)

Synthesis of the C1–C5 subunit (Scheme 3) commenced with the preparation of epoxide **17** from commercially available L-aspartic acid using a known procedure.[13] The conversion of



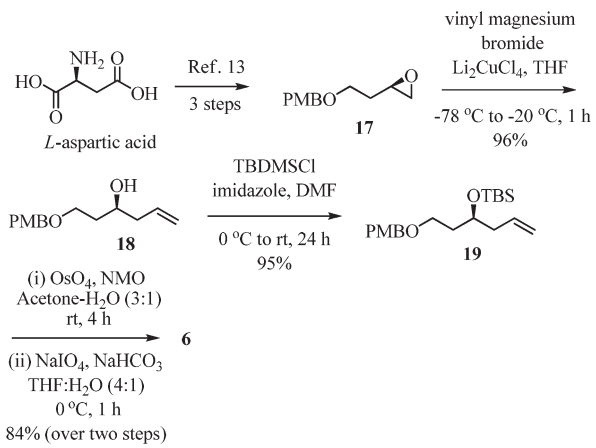
Scheme 2 Synthesis of THP-ketone fragment **5**.

the epoxide **17** to homoallylic alcohol **18** was accomplished through the copper(I)-catalyzed addition of vinyl magnesium bromide in 96% yield.[14] Alcohol **18** was protected as *tert*-butyldimethyl silyl ether **19** in 95% yield (TBSCl/imidazole/DMF). It was then subjected to osmium-catalyzed dihydroxylation of the olefin followed by cleavage of the diol using sodium periodate to furnish aldehyde **6** in 84% yield.[15]

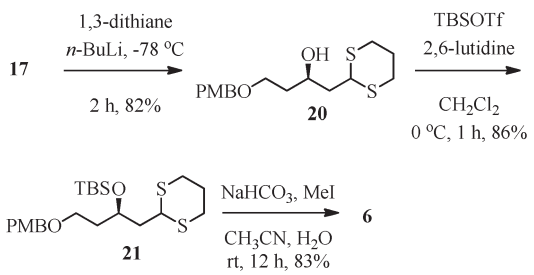
In an alternative approach to **6**, a route *via* the opening of epoxide **17** with 1,3-dithiane was explored (Scheme 4). Thus, the treatment of epoxide **17** with 1,3-dithiane in the presence of *n*-butyl lithium gave the alcohol **20** in 82% yield. Protection of the hydroxyl group in **20** as *tert*-butyldimethyl silyl ether gave compound **21** in 86% yield (TBSOTf/2,6-lutidine/CH_2Cl_2) and subsequent deprotection of thioacetal using MeI/$NaHCO_3$ in CH_3CN/H_2O afforded the aldehyde **6** in 83% yield.[16]

Synthesis of sulfone fragment 4

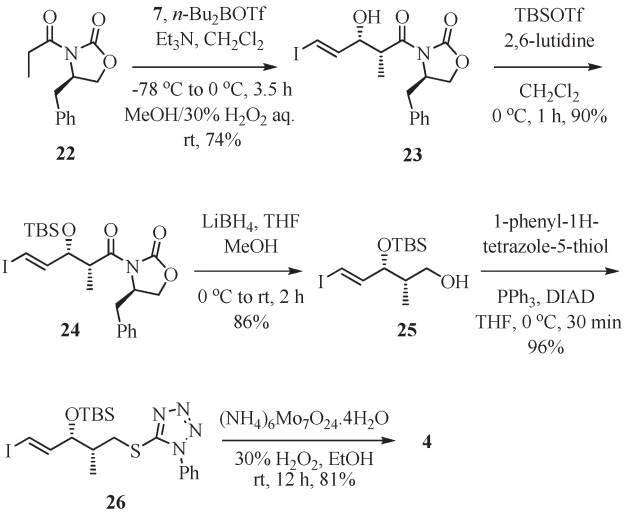
As shown in Scheme 5, synthesis of the sulfone fragment **4** was based on known iodo acrolein **7**, which was prepared from ethyl propiolate by a reported three-step sequence.[17] For the required *syn*-propionate homologation, an Evans aldol reaction[18] of **7** with the di-*n*-butylboron enolate of (*R*)-4-benzyl-3-propionyloxazolidin-2-one (**22**) was carried out to furnish the *syn*-product **23** in 74% yield. Exposure of **23** to TBSOTf/2,6-lutidine in CH_2Cl_2 gave the TBS-ether **24** in 90% yield. Compound **24** was treated with $LiBH_4$ in THF–MeOH for the reductive removal of the auxiliary, to furnish alcohol **25**. A Mitsunobu reaction[19] of alcohol **25** with 1-phenyl-1*H*-tetrazole-5-thiol to thio tetrazole **26** (96% yield), followed by ammonium molybdate catalyzed



Scheme 3 Synthesis of aldehyde fragment **6**.



Scheme 4 Alternative strategy for aldehyde **6**.



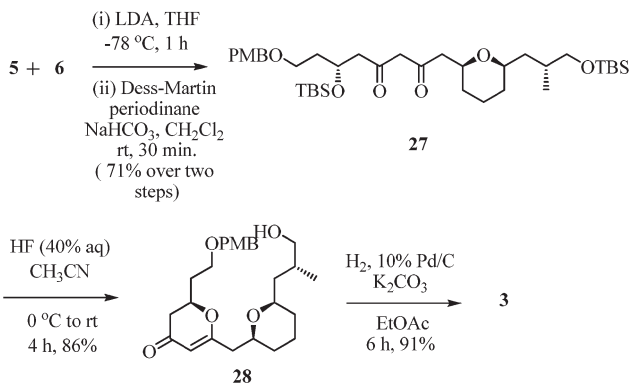
Scheme 5 Synthesis of sulfone fragment **4**.

oxidation[20] of **26**, completed the synthesis of sulfone **4** in 81% yield.

Coupling of fragments

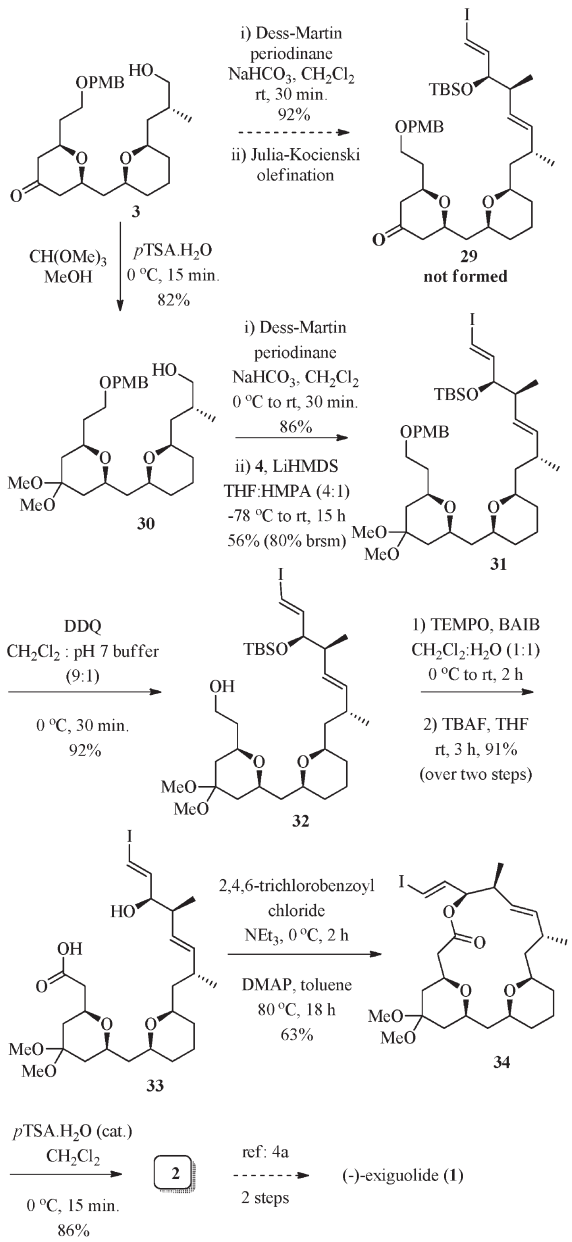
Having all the desired fragments **4**, **5** and **6** in hand, we next proceeded to the synthesis of methylene *bis*-tetrahydropyran subunit **3** through an aldol driven reductive etherification strategy (Scheme 6). Hence, an aldol reaction of aldehyde **6** with the lithiated enolate of **5**, derived using LDA, formed an aldol product as a inseparable mixture of diastereomers. This mixture was treated with Dess–Martin periodinane to give *β*-diketone **27** (71% yield over two steps), which entirely existed as the enol form (confirmed by ^{1}H NMR). Deprotection of the TBS groups and cyclization was achieved in a one-pot operation by the reaction of **27** with HF (40% aq. solution) in CH_3CN at room temperature, to furnish dihydropyranone **28** in 86% yield.[21] Hydrogenation of **28** proceeded with the exclusive formation of *cis*-tetrahydropyranone **3** in 91% yield.[22] The *syn*-relationship of both the THP rings was confirmed by 2D NOESY experiments.

Next, the task was to couple the *bis*-THP subunit **3** with sulfone **4** by Julia–Kocienski reaction.[23] Accordingly, oxidation of alcohol **3** with Dess–Martin periodinane gave the corresponding aldehyde (92% yield), but the following olefination of



Scheme 6 Synthesis of *bis*-THP subunit **3**.

aldehyde with sulfone **4** using KHMDS as a base failed to give the desired product **29**. Varying the reaction conditions (using different bases and solvent systems) also didn't help to get the desired product. These disappointing results prompted us to protect the keto-group present on the THP ring prior to the Julia–Kocienski reaction. Thus, exposure of **3** to trimethyl orthoformate/*p*-TSA·H_2O (cat.) in MeOH afforded the ketal **30** in 82% yield. Now, the primary alcohol in **30** was oxidized to an aldehyde followed by Julia–Kocienski olefination with sulfone **4** using LiHMDS in THF : HMPA (4 : 1), affording **31** in 56% yield (80% brsm) with *E*-selectivity (>20 : 1) at the newly formed C16–C17 double bond. Unmasking the *p*-methoxybenzyl ether of **31** was achieved using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in CH_2Cl_2 : pH 7 buffer (9 : 1) to provide **32** in 92% yield.[24] To advance **32** towards a substrate suitable for the intramolecular Yamaguchi macrolactonization, the primary hydroxyl of **32** was oxidized to carboxylic acid under BAIB–TEMPO reaction[25] conditions, followed by deprotection of the TBS-group with tetrabutylammonium fluoride (TBAF), to afford the hydroxy acid **33** in 91% yield (over two steps). Intramolecular macrolactonization of the hydroxy acid **33** under Yamaguchi reaction conditions[26] gave the ketal protected macrolactone **34** in 63% yield. Further, hydrolysis of the ketal group of macrolide **34** with *p*-TSA·H_2O (cat.) provided the desired macrocycle **2**, whose spectral data matched exactly to that of the same compound prepared by Fuwa *et al.* for the synthesis of (−)-exiguolide (Scheme 7).[4a]



Scheme 7 Synthesis of the macrocyclic core of (−)-exiguolide (**1**).

Conclusions

In summary, a flexible convergent synthesis of a macrocyclic precursor of (−)-exiguolide has been accomplished through a maximum-length linear sequence of 25 steps. The key reactions in the described route are the *oxa*-Michael reaction and an aldol driven reductive etherification for THP-ring formation, Julia–Kocienski olefination and Yamaguchi macrolactonization for macrocycle synthesis. We believe that the synthetic strategy developed is practical and scalable from inexpensive commercially available natural amino acids.

Experimental

General

Reactions were monitored by thin-layer chromatography carried out on silica plates (silica gel 60 F254, Merck) using UV-light and anisaldehyde or *β*-naphthol for visualization. Column chromatography was performed on silica gel (60–120 mesh) using hexanes, ethyl acetate, methanol and chloroform as the eluent. Evaporation of solvents was conducted under reduced pressure at temperatures less than 45 °C. IR spectra were recorded on a Perkin-Elmer 683, Nicolet Nexus 670 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ solvent on a 300 MHz, 400 MHz and 500 MHz NMR spectrometer. Chemical shifts δ and coupling constants J are given in ppm (parts per million) and Hz (Hertz) respectively. Chemical shifts are reported relative to the residual solvent as an internal standard for ^{1}H and ^{13}C ($CDCl_3$: δ 7.26 ppm for ^{1}H and 77.0 ppm for ^{13}C). Mass spectra were obtained on a Finnigan MAT1020B, micromass VG 70–70H or LC/MSD trapSL spectrometer operating at 70 eV using a direct inlet system.

(3*R*,5*S*)-5-((*tert*-Butyldiphenylsilyloxy)methyl)-3-methyldihydrofuran-2(3H)-one (9). To a solution of diisopropyl amine (1.97 mL, 14 mmol) in dry THF (60 mL) at 0 °C was added *n*-BuLi (2.5 M in hexane, 5.6 mL, 14 mmol). After 30 min, the solution was cooled to −78 °C and a solution of **8** (5.0 g, 14 mmol) in dry THF (20 mL) was added dropwise. After 45 min at −78 °C, iodo methane (1.5 mL, 21 mmol) was added, and the solution was stirred for a further 1 h. The reaction was quenched with saturated aqueous NH_4Cl (20 mL) and extracted with ether (2 × 50 mL). The combined organic layer was washed with brine (25 mL), dried over Na_2SO_4, filtered and evaporated to dryness under reduced pressure. The residue was purified by column chromatography (silica gel, hexanes : EtOAc = 81 : 15) to give **9**

(4.0 g, 78%) as a colorless oil. R_f 0.40 (20% EtOAc in hexanes); IR (KBr): ν_{max} 2931, 2858, 1760, 1191, 1109, 1024, 826, 703 cm^{-1}; $[\alpha]_D^{20}$ = +32.0 (c = 1.20, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 7.70–7.62 (m, 4H), 7.48–7.35 (m, 6H), 4.59–4.50 (m, 1H), 3.85 (dd, J = 11.3, 3.4 Hz, 1H), 3.66 (dd, J = 11.3, 3.2 Hz, 1H), 2.94–2.78 (m, 1H), 2.44 (ddd, J = 12.6, 9.6, 2.8 Hz, 1H), 2.07–1.89 (m, 1H), 1.29 (d, J = 7.3 Hz, 3H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 180.3, 135.4, 132.8, 132.3, 129.8, 127.8, 77.5, 65.4, 34.2, 32.1, 26.6, 19.1, 16.3; MS (ESI): m/z = 391 $[M + Na]^+$ HRMS: calcd. for $C_{22}H_{32}O_3SiN$ $(M + NH_4)^+$ 386.2146; found 386.2160.

(2*R*,4*S*)-5-(*tert*-Butyldiphenylsilyloxy)-2-methylpentane-1,4-diol (10). To a stirred solution of **9** (5.0 g, 13.6 mmol) in THF (65 mL) at 0 °C was sequentially added MeOH (0.65 mL, 16.32 mmol) and $LiBH_4$ (414 mg, 19.02 mmol). After 1 h, the reaction was quenched with saturated aqueous NH_4Cl (50 mL) and extracted with EtOAc (2 × 50 mL). The combined organic layer was dried over Na_2SO_4 and evaporated to dryness under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexanes : EtOAc = 70 : 30) to give **10** (5.0 g, 99%) as a colorless oil. R_f 0.40 (30% EtOAc in hexanes); IR (KBr): ν_{max} 3415, 2957, 2931, 2861, 1111, 758, 703 cm^{-1}; $[\alpha]_D^{27}$ = +3.0 (c = 1.10, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.67–7.60 (m, 4H), 7.46–7.33 (m, 6H), 3.87 (m, 1H), 3.58 (dd, J = 10.0, 3.6 Hz, 1H), 3.55–3.39 (m, 3H), 2.81 (br s, 2H), 1.93–1.77 (m, 1H), 1.52–1.31 (m, 2H), 1.07 (s, 9H), 0.90 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.4, 133.0, 129.8, 127.7, 69.2, 67.9, 67.5, 36.4, 32.2, 26.8, 19.1, 16.9; MS (ESI): m/z = 395 $[M + Na]^+$; HRMS: calcd. for $C_{22}H_{32}O_3SiNa$ $(M + Na)^+$ 395.2013; found 395.2029.

***tert*-Butyldiphenyl(((4*S*,6*R*)-2,2,6-trimethyl-1,3-dioxepan-4-yl)methoxy)silane (11).** To compound **10** (700 mg, 1.88 mmol) in CH_2C1_2 (10 ml) was added camphorsulfonic acid (44 mg, 0.19 mmol) followed by 2,2-dimethoxypropane (0.58 mL, 4.70 mmol). After completion of the reaction (monitored by TLC), saturated $NaHCO_3$ (10 mL) was added to the reaction mixture and extracted with CH_2C1_2 (2 × 25 ml). The combined organic layer was dried over Na_2SO_4 and evaporated to dryness under reduced pressure. The residue was purified by column chromatography (silica gel, hexanes : EtOAc = 95 : 5) to give **11** (700 mg, 90%) as a colorless oil. R_f 0.50 (10% EtOAc in hexanes); IR (KBr): ν_{max} 2934, 2861, 1760, 1219, 1110, 1080, 703 cm^{-1}; $[\alpha]_D^{20}$ = −14.5 (c = 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 7.70–7.60 (m, 4H), 7.42–7.30 (m, 6H), 3.93–3.81 (m, 2H), 3.59 (dd, J = 10.2, 6.6 Hz, 1H), 3.44 (dd, J = 10.2, 5.8 Hz, 1H), 3.36–3.28 (m, 1H), 1.86–1.74 (m, 1H), 1.54–1.36 (m, 2H), 1.28 (s, 3H), 1.22 (s, 3H), 1.04 (s, 9H), 1.02 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.7, 135.6, 129.6, 127.6, 100.7, 68.8, 67.2, 65.9, 37.5, 31.0, 26.8, 25.0, 19.2, 17.1; MS (ESI): m/z = 435.1 $[M + Na]^+$.

((4*S*,6*R*)-2,2,6-Trimethyl-1,3-dioxepan-4-yl)methanol (12). A solution of **11** (1.20 g, 2.91 mmol) in THF (15 mL) was cooled to 0 °C and TBAF (4.37 mL, 4.37 mmol, 1.0 M solution in THF) was added dropwise. The resulting brown solution was stirred at room temperature for 2 h. The reaction was quenched with saturated aqueous NH_4Cl (20 mL) and extracted with EtOAc (2 × 25 mL). The combined organic layer was washed with brine (15 mL), dried over Na_2SO_4 and evaporated to dryness under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexanes : EtOAc = 80 : 20) to give **12** (460 mg, 91%) as a colorless oil. R_f 0.40 (30% EtOAc in hexane); IR (KBr): ν_{max} 3367, 2927, 2873, 1375, 1219, 1045, 773 cm^{-1}; $[\alpha]_D^{27}$ = +11.8 (c = 0.80, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 4.00–3.90 (m, 1H), 3.87 (dd, J = 12.0, 1.5 Hz, 1H), 3.48–3.31 (m, 3H), 1.93–1.79 (m, 1H), 1.55–1.43 (m, 1H), 1.33 (s, 6H), 1.31–1.24 (m, 1H), 1.04 (d, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 108.8, 73.7, 69.6, 67.3, 36.9, 32.8, 26.8, 25.7, 16.7.

((4*S*,6*R*)-2,2,6-Trimethyl-1,3-dioxepan-4-yl)methyl 4-methylbenzenesulfonate (13). Tosyl chloride (2.18 g, 11.4 mmol) was added to an ice cooled solution of **12** (1.81 g, 10.4 mmol) in dry pyridine (10 mL). The mixture was left to stand overnight in a refrigerator. It was then diluted with ice-water, and extracted with diethyl ether (2 × 25 ml). The combined organic layer was washed with water, dil. HCl, water, aq. $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated to dryness under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexanes : EtOAc = 90 : 10) to give **13** (3.6 g, 96%) as a colorless oil. R_f 0.50 (20% EtOAc in hexanes). IR (KBr): ν_{max} 2983, 2922, 1362, 1218, 1177, 1063, 983, 812 cm^{-1}; $[\alpha]_D^{20}$ = +3.18 (c = 0.88, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 7.77 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 8.3 Hz, 2H), 4.08–3.97 (m, 1H), 3.95–3.78 (m, 3H), 3.31 (dt, J = 12.0, 2.3 Hz, 1H), 2.46 (s, 3H), 1.88–1.76 (m, 1H), 1.47–1.34 (m, 2H), 1.24 (s, 6H), 1.01 (d, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.6, 133.0, 129.6, 127.7, 100.8, 72.4, 65.6, 65.5, 36.8, 30.5, 24.6, 24.5, 21.4, 16.8; MS (ESI): m/z = 351 $[M + Na]^+$; HRMS: calcd. for $C_{16}H_{24}O_5SNa$ $(M + Na)^+$ 351.1237; found 351.1236.

(4*R*,6*R*)-2,2,6-Trimethyl-4-(pent-4-enyl)-1,3-dioxepane (14). A solution of 3-butenylmagnesium bromide (prepared from 4-bromo-1-butene (1.95 ml, 19.2 mmol) and Mg (634 mg, 26.4 mmol) in dry THF (25 mL) under nitrogen) was added dropwise to a stirred solution of **13** (3.15 g, 9.6 mmol) in dry THF (10 mL) at −78 °C. Subsequently, a solution of Li_2CuCl_4 (0.1 M in THF, 1 mL, 0.1 mmol) was added dropwise to the stirred mixture, which was left to stand overnight to gradually warm to room temperature. The reaction was quenched with saturated aqueous NH_4Cl (20 mL) and extracted with diethyl ether (2 × 25 mL). The ether extract was washed with brine (20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, hexanes : EtOAc = 95 : 5) to give olefin **14** (1.8 g, 88%) as a colorless oil. R_f 0.60 (10% EtOAc in hexanes); IR (KBr): ν_{max} 2934, 1378, 1219, 1060 cm^{-1}; $[\alpha]_D^{20}$ = −16.8 (c = 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 5.88–5.72 (m, 1H), 5.04–4.91(m, 2H), 3.91 (dd, J = 12.0, 1.5 Hz, 1H), 3.87–3.77 (m, 1H), 3.36 (dt, J = 12.0, 3.0 Hz, 1H), 2.06 (dd, J = 14.3, 6.8 Hz, 2H), 1.85–1.73 (m, 1H), 1.59–1.35 (m, 6H), 1.34 (s, 3H), 1.32 (s, 3H), 1.04 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.8, 114.3, 100.3, 67.8, 65.7, 41.7, 36.2, 33.8, 31.2, 25.7, 25.1, 17.1.

(*E*)-7-((4*R*,6*R*)-2,2,6-Trimethyl-1,3-dioxepan-4-yl)hept-3-en-2-one (15). A solution of **14** (1.40 g, 6.54 mmol) and $NaHCO_3$ (500

mg) in CH_2Cl_2 (65 mL) was treated at −78 °C with a stream of ozone until the starting material disappeared (monitored by TLC). The excess ozone was purged from the solution with a stream of oxygen and Ph_3P (2.07 g, 7.85 mmol) was added. The reaction was allowed to warm slowly to room temperature, at which point it was diluted with water (25 mL). The subsequent mixture was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure to give the crude aldehyde, which was used for the next reaction without further purification.

To a solution of the above aldehyde in THF (30 mL) was added methyl-(triphenylphosphoranylidene)-2-propanone (3.12 g, 9.81 mmol) and the mixture was heated under reflux for 12 h. After cooling, the solvent was removed *in vacuo*, and the residue was purified by column chromatography (silica gel, hexanes : EtOAc = 90 : 10) to give enone **15** (1.4 g, 84%) as a colorless oil. R_f 0.50 (20% EtOAc in hexanes); IR (KBr): ν_{max} 2931, 2864, 1712, 1673, 1358, 1218, 1072, 1039 cm^{-1}; $[\alpha]_D^{26}$ = +2.6 (c = 1.05, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 6.74 (dt, J = 15.8, 6.8 Hz, 1H), 6.03 (dt, J = 15.8, 1.4 Hz, 1H), 3.85 (dd, J = 12.0, 1.5 Hz, 1H), 3.82–3.72 (m, 1H), 3.31 (dt, J = 12.0, 2.3 Hz, 1H), 2.28–2.17 (m, 2H), 2.22 (s, 3H) 1.83–1.70 (m, 1H), 1.71–1.32 (m, 6H), 1.30 (s, 3H), 1.27 (s, 3H), 1.02 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.6, 148.2, 131.3, 100.3, 67.6, 65.7, 41.7, 36.2, 32.4, 31.1, 26.8, 25.1, 25.0, 24.9, 17.1; MS (ESI): m/z = 277 $[M + Na]^+$; HRMS: calcd. for $C_{15}H_{26}O_3Na$ $(M + Na)^+$ 277.1774; found 277.1776.

1-((2*S*,6*R*)-6-((*R*)-3-Hydroxy-2-methylpropyl)tetrahydro-2*H*-pyran-2-yl)propan-2-one (16). To compound **15** (450 mg, 1.77 mmol) in CH_2C1_2 (10 ml) was added *p*-TSA·H_2O (cat.). The mixture was stirred for 1 h at room temperature. After completion of the reaction (monitored by TLC), saturated $NaHCO_3$ (10 mL) was added to the reaction mixture and extracted with CH_2C1_2 (2 × 25 ml). The combined organic layer was dried over Na_2SO_4 and evaporated to dryness under reduced pressure. The residue was purified by column chromatography (silica gel, hexanes : EtOAc = 70 : 30) to give **16** (337 mg, 89%) as a colorless oil. R_f 0.40 (50% EtOAc in hexanes); IR (KBr): ν_{max} 3433, 2927, 1709, 1361, 1195, 1037 cm^{-1}; $[\alpha]_D^{28}$ = −3.3 (c = 0.90, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ = 3.85–3.74 (m, 1H), 3.57–3.48 (m, 1H), 3.46 (dd, J = 10.5, 5.3 Hz, 1H), 3.34 (dd, J = 10.5, 6.8 Hz, 1H), 2.67 (dd, J = 15.8, 7.5 Hz, 1H), 2.39 (dd, J = 15.8, 5.3 Hz 1H), 2.15 (s, 3H), 1.93–1.78 (m, 2H), 1.65–1.37 (m, 5H), 1.31–1.12 (m, 3H), 0.9 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 207.3, 75.5, 73.9, 67.6, 49.8, 40.1, 32.0, 31.1, 31.0, 30.9, 23.3, 17.2; MS (ESI): m/z = 237 $[M + Na]^+$; HRMS: calcd. for $C_{12}H_{22}O_3Na$ $(M + Na)^+$ 237.1461; found 237.1463.

1-((2*S*,6*R*)-6-((*R*)-3-(*tert*-Butyldimethylsilyloxy)-2-methylpropyl)tetrahydro-2*H*-pyran-2-yl)propan-2-one (5). To a stirred solution of alcohol **16** (850 mg, 3.97 mmol) in CH_2Cl_2 (10 mL) was added imidazole (405 mg, 5.95 mmol) followed by *tert*-butyldimethylsilyl chloride (718 mg, 4.77 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. After completion of the reaction, the reaction mixture was diluted by the addition of water (20 mL) and the aqueous phase was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4 and the organic solvent evaporated under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, hexanes : EtOAc = 95 : 5) to give **5** (1.24 g, 95%) as a colorless oil. R_f 0.30 (5% EtOAc in hexanes); IR (KBr): ν_{max} 2930, 2856, 1717, 1360, 1252, 1086, 839, 775 cm^{-1}; $[\alpha]_D^{27}$ = −3.2 (c = 1.20, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 3.77–3.65 (m, 1H), 3.44–3.30 (m, 3H), 2.64 (dd, J = 15.1, 7.8 Hz, 1H), 2.35 (dd, J = 15.1, 4.8 Hz, 1H), 2.15 (s, 3H), 1.88–1.65 (m, 2H), 1.64–1.49 (m, 2H), 1.47–1.37 (m, 1H), 1.33–1.06 (m, 4H), 0.89 (s, 9H), 0.87 (d, J = 6.5 Hz, 3H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 207.7, 76.4, 74.3, 67.7, 50.3, 39.8, 32.3, 31.9, 31.5, 31.4, 31.0, 25.9, 23.5, 17.5, −5.4; MS (ESI): m/z = 351 $[M + Na]^+$; HRMS: calcd. for $C_{18}H_{36}O_3SiNa$ $(M + Na)^+$ 351.2326; found 351.2325.

(*S*)-1-(4-Methoxybenzyloxy)hex-5-en-3-ol (18)[15]. To a stirred solution of epoxide **17** (2.40 g, 11.54 mmol) in dry THF (40 mL) was added Li_2CuCl_4 (5.80 mL of a 0.1M solution in THF, 0.58 mmol) followed by vinyl magnesium bromide (23.08 mL of a 1M solution in THF, 23.08 mmol) at −78 °C. The solution was allowed to warm to −20 °C and stirred at this temperature for 1 h. The reaction was quenched with saturated aqueous NH_4Cl (20 mL) and extracted with ether (2 × 50 mL). The combined organic layer was dried over Na_2SO_4 and evaporated to dryness under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexanes : EtOAc = 80 : 20) to give **18** (2.61 g, 96%) as a colorless oil. R_f 0.40 (30% EtOAc in hexanes); $[\alpha]_D^{20}$ = −4.6 (c = 1.00, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ = 7.22 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 5.86–5.77 (m, 1H), 5.11–5.05 (m, 2H), 4.44 (s, 2H), 3.86–3.81 (m, 1H), 3.80 (s, 3H), 3.70–3.64 (m, 1H), 3.62–3.56 (m, 1H), 2.76 (br s, 1H), 2.22 (t, J = 6.8 Hz, 2H), 1.76–1.70 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.1, 134.8, 129.9, 129.2, 117.4, 113.7, 72.8, 70.3, 68.5, 55.2, 41.8, 35.7; MS (ESI): m/z = 259.2 $[M + Na]^+$.

(*S*)-*tert*-Butyl(1-(4-methoxybenzyloxy)hex-5-en-3-yloxy)dimethylsilane (19)[15]. To a stirred solution of alcohol **18** (1.0 g, 4.24 mmol) in dry DMF (5 mL) was added imidazole (432 mg, 6.36 mmol) followed by *tert*-butyldimethylsilyl chloride (766 mg, 5.08 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 12 h. After completion of the reaction the reaction mixture was diluted by the addition of ice cold water (20 mL) and the aqueous phase was extracted with ether (2 × 25 mL). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4 and the organic solvent evaporated under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, hexanes : EtOAc = 95 : 05) to give **19** (1.51 g, 95%) as a colorless oil. R_f 0.70 (20% EtOAc in hexanes); $[\alpha]_D^{20}$ = +15.1 (c = 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.21 (d, J = 8.5 Hz, 2H), 6.83 (d, J = 8.5 Hz, 2H), 5.86–5.71 (m, 1H), 5.07–4.96 (m, 2H), 4.42 (d, J = 11.5 Hz, 1H), 4.35 (d, J = 11.5 Hz, 1H), 3.94–3.84 (m, 1H), 3.80 (s, 3H), 3.51–3.42 (m, 1H), 2.28–2.13 (m, 2H), 1.81–1.59 (m, 2H), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.0, 134.8, 130.5, 129.1, 116.8, 113.6, 72.5, 68.8, 66.6, 55.0, 42.2, 36.6, 25.8, 17.9, −4.4, −4.7; MS (ESI): m/z = 373.3 $[M + Na]^+$.

(*R*)-3-(*tert*-Butyldimethylsilyloxy)-5-(4-methoxybenzyloxy)pentanal (6)[15]. To a solution of silyl ether **19** (1.16 g, 3.31 mmol) in a 30 mL mixture of acetone–water (4 : 1) was added OsO_4 (4.2 mL, 1 mg/1 mL toluene solution, 0.016 mmol) and NMO (465 mg, 3.98 mmol) at 25 °C and the mixture was stirred for 12 h. The solvent was evaporated and the residue was extracted with ethyl acetate (30 mL). The organic layers were washed with brine (20 mL), dried over Na_2SO_4 and concentrated *in vacuo*, affording an oil which was purified by flash column chromatography (silica gel, hexanes : EtOAc = 50 : 50) to give diol (1.2 g) as a colorless oil.

To a solution of the above diol (1.20 g, 3.12 mmol) in a 30 mL mixture of THF–H_2O (4 : 1) was added $NaHCO_3$ (446 mg, 5.30 mmol) and $NaIO_4$ (2.0 g, 9.4 mmol). After stirring at 0 °C for 30 min, the solid was removed by filtration and the filtrate was extracted with ethyl acetate (2 × 30 mL). The combined organic layers were washed with brine (20 mL), dried with Na_2SO_4 and concentrated *in vacuo*. The crude aldehyde was purified by flash chromatography (10% ethyl acetate in hexanes) to give aldehyde **6** (0.98 g, 84%) as a colorless oil. R_f 0.60 (20% EtOAc in hexanes); IR (KBr): ν_{max} 2954, 2931, 2857, 1726, 1613, 1513, 1465, 1250, 1098, 1037, 836, 777 cm^{-1}; $[\alpha]_D^{20}$ = +5.2 (*c* = 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 9.79 (s, 1H), 7.24 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 4.43 (d, *J* = 11.2 Hz, 1H), 4.38 (d, *J* = 11.3 Hz, 1H), 4.37–4.32 (m, 1H), 3.80 (s, 3H), 3.51 (t, *J* = 6.2 Hz, 2H), 2.59–2.51 (m, 2H), 1.9–1.76 (m, 2H), 0.86 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.1, 159.1, 130.3, 129.2, 113.7, 72.6, 65.9, 65.6, 55.2, 51.0, 37.5, 25.7, 17.9, −4.6, −4.7; MS (ESI): *m*/*z* = 375.2 $[M + Na]^+$.

(*R*)-1-(1,3-Dithian-2-yl)-4-(4-methoxybenzyloxy)butan-2-ol (20). To a stirred solution of 1,3-dithiane (434 mg, 3.6 mmol) in THF (20 mL) at −20 °C was added *n*-BuLi (1.6 M in hexanes, 2.25 mL, 3.6 mmol) dropwise. After 30 min, epoxide **17** (0.5 g, 2.40 mmol) in THF (5 mL) was added dropwise. After being stirred for 1 h at the same temperature, the reaction was quenched with saturated aqueous NH_4Cl (15 mL) and the aqueous phase was extracted with ether (2 × 25 mL). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4 and the organic solvent evaporated under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, hexanes : EtOAc = 80 : 20) to give **20** (645 mg, 82%) as a colorless oil. R_f 0.40 (20% EtOAc in hexanes); IR (KBr): ν_{max} 3403, 2921, 2851, 1612, 1511, 1243, 1220, 772 cm^{-1}; $[\alpha]_D^{20}$ = −20.7 (*c* = 0.88, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 9.0 Hz, 2H), 6.87 (d, *J* = 9.0 Hz, 2H), 4.45 (s, 2H), 4.29 (dd, *J* = 9.0, 5.0 Hz, 1H), 4.17–4.09 (m, 1H), 3.80 (s, 3H), 3.72–3.67 (m, 1H), 3.66–3.60 (m, 1H), 3.08 (br s, 1H), 2.96–2.79 (m, 4H), 2.16–2.09 (m, 1H), 1.96–1.70 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.1, 129.7, 129.2, 113.7, 72.8, 68.4, 67.6, 55.1, 43.8, 42.7, 36.3, 30.3, 29.9, 25.8; MS (ESI): *m*/*z* = 329 $[M + H]^+$; HRMS: calcd. for $C_{16}H_{25}O_3S_2$ $(M + H)^+$ 329.1240; found 329.1230.

(*R*)-(1-(1,3-Dithian-2-yl)-4-(4-methoxybenzyloxy)butan-2-yloxy)(*tert*-butyl)dimethylsilane (21). To a cooled (0 °C) solution of **20** (330 mg, 1.0 mmol) in CH_2Cl_2 (10 mL) was added 2,6-lutidine (0.23, 2.0 mmol) and TBSOTf (0.26 mL, 1.1 mmol). The mixture was stirred at the same temperature for 30 min and was then diluted with CH_2Cl_2 (10 mL). The organic phase was washed sequentially with a saturated aqueous solution of $NaHCO_3$ (20 mL) and brine (15 mL), dried over Na_2SO_4 and evaporated to dryness. The residue was purified by flash chromatography (silica gel, 5% EtOAc in hexanes) to give the silyl ether **21** (380 mg, 86% yield) as a colorless oil. R_f 0.50 (10% EtOAc in hexanes); IR (KBr): ν_{max} 2950, 2930, 2855, 1612, 1512, 1200, 1093, 833, 774 cm^{-1}; $[\alpha]_D^{20}$ = −9.2 (*c* = 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 7.27 (d, *J* = 8.3 Hz, 2H), 6.87 (d, *J* = 8.3 Hz, 2H), 4.42 (s, 2H), 4.14–4.05 (m, 1H), 3.81 (s, 3H), 3.50 (t, *J* = 6.8 Hz, 2H), 2.89–2.77 (m, 4H), 2.16–2.05 (m, 1H), 1.94–1.75 (m, 5H), 0.88 (s, 9H), 0.10 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.9, 130.4, 129.1, 113.6, 72.5, 66.3, 66.1, 55.1, 43.7, 42.8, 37.2, 30.3, 29.9, 25.8, 17.9, −4.6, −4.7; MS (ESI): *m*/*z* = 443.2 $[M + H]^+$.

(*R*)-3-(*tert*-Butyldimethylsilyloxy)-5-(4-methoxybenzyloxy)pentanal (6). To a stirred solution of **21** (1.2 g, 2.71 mmol) in CH_3CN (27 mL) and H_2O (7 mL) at room temperature was added $NaHCO_3$ (1.14 g, 13.5 mmol) and MeI (3.4 mL, 54.2 mmol). The reaction mixture was stirred at 40 °C for 12 h. The resulting mixture was extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with saturated $NaHCO_3$ (10 mL), washed with brine (10 mL), dried with Na_2SO_4 and concentrated *in vacuo*. The crude aldehyde was purified by flash chromatography (10% ethyl acetate in hexanes) to give aldehyde **6** (790 mg, 83%) as a colorless oil.

(*R*)-4-Benzyl-3-((2*R*,3*R*,*E*)-3-hydroxy-5-iodo-2-methylpent-4-enoyl)oxazolidin-2-one (23). To a stirred solution of (*R*)-4-benzyl-3-propionyl oxazolidin-2-one **22** (1.0 g, 4.29 mmol) in 10 mL CH_2Cl_2 at −78 °C was added *n*-Bu_2BOTf (5.15 mL of a 1M solution in CH_2Cl_2, 5.15 mmol) followed by NEt_3 (0.84 mL, 6.0 mmol). The resulting solution was stirred at −78 °C for 1 h, then at 0 °C for 30 min. After cooling back to −78 °C, the aldehyde **7** (1.55 g, 8.58 mmol) in 10 mL CH_2Cl_2 solution was added dropwise. After stirring at −78 °C for 1 h, then at 0 °C for 1 h, the reaction was quenched with pH 7 buffer (5 mL), MeOH (17 mL) and 30% H_2O_2 (5 mL). The ice bath was removed, and stirring continued for 1 h. The resulting solution was concentrated, then extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layers were washed with 20 mL saturated aq. $NaHCO_3$ solution, dried over Na_2SO_4, filtered and concentrated. Purification by flash column chromatography (20% EtOAc–hexanes) afforded the aldol adduct **23** (1.32 g, 74%) as a viscous oil. R_f 0.40 (20% EtOAc in hexanes); IR (KBr): ν_{max} 3470, 2922, 1776, 1692, 1385, 1215, 1110, 1011, 771, 703 cm^{-1}; $[\alpha]_D^{20}$ = −31.4 (*c* = 1.16, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.28 (m, 3H), 7.23–7.18 (m, 2H), 6.55 (dd, *J* = 15.1, 5.2 Hz, 1H), 6.46 (d, *J* = 15.1 Hz, 1H), 4.77–4.65 (m, 1H), 4.52–4.45 (m, 1H), 4.26 (dd, *J* = 9.0, 7.5 Hz, 1H), 4.21 (dd, *J* = 9.0, 3.0 Hz, 1H), 3.89–3.80 (m, 1H), 3.24 (dd, *J* = 13.6, 3.0 Hz, 1H), 3.06 (d, *J* = 3.0 Hz, 1H), 2.80 (dd, *J* = 13.6, 9.8 Hz, 1H), 1.26 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.9, 152.9, 144.6, 134.8, 129.3, 128.9, 127.4, 78.6, 74.1, 66.2, 55.0, 41.9, 37.7, 11.1; MS (ESI): *m*/*z* = 438 $[M + Na]^+$; HRMS: calcd. for $C_{16}H_{18}INO_4Na$ $(M + Na)^+$ 438.0173; found 438.0141.

(*R*)-4-Benzyl-3-((2*R*,3*R*,*E*)-3-(*tert*-butyldimethylsilyloxy)-5-iodo-2-methylpent-4-enoyl)oxazolidin-2-one (24). To a cooled

(0 °C) solution of **23** (2.73 g, 6.58 mmol) in CH_2Cl_2 (25 mL) was added 2,6-lutidine (1.53 mL, 13.16 mmol) and TBSOTf (1.66 mL, 7.24 mmol). The mixture was stirred at 0 °C for 30 min and was then diluted with CH_2Cl_2 (15 mL). The organic phase was washed sequentially with a saturated aqueous solution of $NaHCO_3$ (20 mL) and brine (15 mL), dried over Na_2SO_4 and evaporated to dryness. The residue was purified by flash chromatography (silica gel, 5% EtOAc in hexanes) to give **24** (3.13 g, 90% yield) as a colorless oil. R_f 0.50 (10% EtOAc in hexanes); IR (KBr): ν_{max} 2929, 2856, 1782, 1698, 1381, 1212, 1108, 1072, 1015, 838, 776, 701 cm^{-1}; $[\alpha]_D^{20}$ = −44.2 (*c* = 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.28 (m, 3H), 7.24–7.18 (m, 2H), 6.59 (dd, *J* = 14.5, 6.8 Hz, 1H), 6.28 (d, *J* = 14.5 Hz, 1H), 4.68–4.55 (m, 1H), 4.29 (t, *J* = 6.8 Hz, 1H), 4.22–4.15 (m, 2H), 4.02–3.91 (m, 1H), 3.26 (dd, *J* = 13.4, 3.4 Hz, 1H), 2.78 (dd, *J* = 13.4, 9.6 Hz, 1H), 1.22 (d, *J* = 6.8 Hz, 3H), 0.88 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.0, 153.0, 146.7, 135.1, 129.3, 128.8, 127.3, 77.6, 76.5, 66.0, 55.5, 43.7, 37.7, 25.6, 18.0, 12.5, −4.5, −5.2; MS (ESI): *m*/*z* = 552.1 $[M + Na]^+$; HRMS: calcd. for $C_{22}H_{32}INO_4SiNa$ $(M + Na)^+$ 552.1037; found 552.0990.

(2*S*,3*R*,*E*)-3-(*tert*-Butyldimethylsilyloxy)-5-iodo-2-methylpent-4-en-1-ol (25). To a stirred solution of **24** (1.52 g, 2.87 mmol) in THF (25 mL) at 0 °C was sequentially added MeOH (0.14 mL, 3.58 mmol) and $LiBH_4$ (94 mg, 4.31 mmol). After 2h, the reaction was quenched with saturated aqueous NH_4Cl (50 mL) and extracted with EtOAc (2 × 30 mL). The combined organic layer was dried over Na_2SO_4 and evaporated to dryness under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexanes : EtOAc = 70 : 30) to give **25** (878 mg, 86%) as a colorless oil. R_f 0.40 (40% EtOAc in hexanes); IR (KBr): ν_{max} 3378, 2930, 2858, 1606, 1466, 1362, 1255, 1170, 1117, 1038, 837, 776 cm^{-1}; $[\alpha]_D^{20}$ = +38.8 (*c* = 1.12, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ = 6.56 (dd, *J* = 14.3, 5.5 Hz, 1H), 6.25 (d, *J* = 14.3 Hz, 1H), 4.23 (t, *J* = 5.5 Hz, 1H), 3.59 (dd, *J* = 10.0, 8.8 Hz, 1H), 3.50–3.41 (m, 1H), 2.52 (br s, 1H), 1.91–1.82 (m, 1H), 0.88 (s, 9H), 0.81 (d, *J* = 6.6 Hz, 3H), 0.05 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.0, 77.5, 76.8, 65.0, 40.8, 25.7, 18.0, 11.7, −4.6, −5.2; MS (ESI): *m*/*z* = 379 $[M + Na]^+$.

5-((2*R*,3*R*,*E*)-3-(*tert*-Butyldimethylsilyloxy)-5-iodo-2-methylpent-4-enylthio)-1-phenyl-1*H*-tetrazole (26)

DIAD (0.4 mL, 2.01 mmol) was slowly added at 0 °C to a solution of alcohol **25** (550 mg, 1.55 mmol), PPh_3 (488 mg, 1.85 mmol) and 1-phenyl-1*H*-tetrazole- 5-thiol (330 mg, 1.85 mmol) in THF (20 mL). The mixture was stirred at room temperature for 1 h before the solvent was evaporated. The residue was purified by flash column chromatography (silica gel, hexanes : EtOAc = 90 : 10) to give **26** (768 mg, 96%) as a colorless oil. R_f 0.40 (10% EtOAc in hexanes); IR (KBr): ν_{max} 2954, 2931, 2857, 1599, 1500, 1465, 1409, 1386, 1252, 1087, 1022, 838, 777 cm^{-1}; $[\alpha]_D^{20}$ = +10.7 (*c* = 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 7.63–7.50 (m, 5H), 6.54 (dd, *J* = 14.5, 6.2 Hz, 1H), 6.28 (dd, *J* = 14.5, 1.3 Hz, 1H), 4.21 (dddd, *J* = 6.0, 4.7, 3.6, 1.3 Hz, 1H), 3.48 (dd, *J* = 13.0, 6.6 Hz, 1H), 3.23 (dd, *J* = 13.0, 7.3 Hz, 1H), 2.14–2.05 (m, 1H), 1.02 (d, *J* = 6.9 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.3, 146.2, 133.6, 130.0, 129.7, 123.7, 77.4, 76.9, 39.0, 36.2, 25.7, 18.0, 13.8, −4.4, −5.0; MS (ESI): *m*/*z* = 539 $[M + Na]^+$; HRMS: calcd. for $C_{19}H_{30}IN_4OSSi$ $(M + H)^+$ 517.0949; found 517.0904.

5-((2*R*,3*R*,*E*)-3-(*tert*-Butyldimethylsilyloxy)-5-iodo-2-methylpent-4-enylsulfonyl)-1-phenyl-1*H*-tetrazole (4). A solution of $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (0.868 g, 0.7 mmol) in aq. H_2O_2 (30% w/w, 3.5 mL) was stirred at 0 °C for 15 min before it was added to a solution of **26** (0.725 g, 1.40 mmol) in EtOH (14 mL) at 0 °C, and the mixture was allowed to warm up to room temperature. After 12 h, the reaction was diluted with water (20 mL) and the resulting mixture was extracted with EtOAc (2 × 25 mL). The organic layer was washed with saturated aqueous $Na_2S_2O_3$ (20 mL) and brine (20 mL), then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by flash column chromatography (hexane–EtOAc, 90 : 10) to give **4** (621 mg, 81%) as a viscous oil. R_f 0.40 (10% EtOAc in hexanes); IR (KBr): ν_{max} 2955, 2930, 2857, 1734, 1607, 1502, 1464, 1341, 1268, 1153, 1100, 761 cm^{-1}; $[\alpha]_D^{20}$ = +6.3 (*c* = 1.00, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ = 7.72–7.66 (m, 2H), 7.64–7.58 (m, 3H), 6.51 (dd, *J* = 14.0, 6.0 Hz, 1H), 6.36 (dd, *J* = 14.0, 6.0 Hz, 1H), 4.28 (t, *J* = 5.0 Hz, 1H), 4.02 (dd, *J* = 14.0, 4.0 Hz, 1H), 3.48 (dd, *J* = 14.0, 8.0 Hz, 1H), 2.52–2.41 (m, 1H), 1.15 (d, *J* = 7.0 Hz, 3H), 0.90 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.8, 144.7, 132.9, 131.4, 129.6, 125.0, 78.6, 76.7, 57.8, 34.4, 25.7, 18.1, 14.7, −4.5, −5.0; MS (ESI): *m*/*z* = 571 $[M + Na]^+$; HRMS: calcd. for $C_{19}H_{29}IN4O_3SSiNa$ $(M + Na)^+$ 571.0667; found 571.0643.

(*R*)-6-(*tert*-Butyldimethylsilyloxy)-1-((2*S*,6*S*)-6-((*R*)-3-(*tert*-butyldimethylsilyloxy)-2-methylpropyl)tetrahydro-2*H*-pyran-2-yl)-8-(4-methoxybenzyloxy)octane-2,4-dione (27). To a solution of diisopropyl amine (0.6 mL, 4.20 mmol) in dry THF (15 mL) at 0 °C was added *n*-BuLi (1.6 M in hexane, 2.5 mL, 4.02 mmol). After 30 min, the solution was cooled to −78 °C and a solution of ketone **5** (1.2 g, 3.65 mmol) in dry THF (5 mL) was added dropwise. After 1 h at −78 °C, a solution of aldehyde **6** (1.42 g, 4.02 mmol) in dry THF (10 mL) was added dropwise. The resulting mixture was stirred for 2 h at −78 °C, and was then quenched with saturated NH_4Cl (15 mL). The aqueous phase was extracted with Et_2O (3 × 25 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (hexanes : EtOAc, 80 : 20) to give the aldol adduct (1.8 g, 74%) as a mixture of diastereomers.

To a stirred solution of the above aldol adduct (1.8 g, 2.64 mmol) in dry CH_2Cl_2 (20 mL) at room temperature was added $NaHCO_3$ (665 mg, 7.92 mmol) and Dess–Martin periodinane (1.68 g, 3.96 mmol) in one portion. The mixture was stirred for 1 h at room temperature and quenched with saturated aqueous $Na_2S_2O_3$ (10 mL). The layers were separated and the aqueous phase was extracted with ether (2 × 25 mL). The combined organic layers were washed with brine (10 mL), dried with Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (10% ethyl acetate in hexanes) to give diketone **27** (1.7 g, 96%) as a colorless oil. R_f 0.50 (20% EtOAc in hexanes); IR (KBr): ν_{max} 2928, 2855, 1729, 1612, 1513, 1462,

1248, 1089, 834, 774 cm^{-1}; $[\alpha]_D^{28}$ = −7.7 (*c* = 1.05, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 7.20 (d, *J* = 9.0 Hz, 2H), 6.82 (d, *J* = 9.0 Hz, 2H), 5.55 (s, 1H), 4.41 (d, *J* = 11.3 Hz, 1H) 4.35 (d, *J* = 11.3 Hz, 1H), 4.30–4.20 (m, 1H), 3.80 (s, 3H), 3.72–3.62 (m, 1H), 3.47 (t, *J* = 6.8 Hz, 2H), 3.39 (d, *J* = 6.0 Hz, 2H), 3.38–3.29 (m, 1H), 2.48 (dd, *J* = 14.3, 6.7 Hz, 1H), 2.38 (d, *J* = 6.8 Hz, 2H), 2.28 (dd, *J* = 14.3, 6.0 Hz, 1H), 1.88–1.67 (m, 4H), 1.64–1.36 (m, 4H), 1.30–1.06 (m, 3H), 0.90 (s, 9H), 0.87 (d, *J* = 6.8 Hz, 3H), 0.85 (s, 9H), 0.04 (s, 3H), 0.02 (s, 6H), 0.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.6, 190.6, 159.1, 130.4, 129.2, 113.7, 102.1, 76.6, 74.6, 72.6, 67.8, 67.2, 66.2, 55.2, 46.5, 45.7, 39.7, 37.4, 32.4, 31.5, 31.4, 25.9, 25.8, 23.5, 17.4, −4.7, −5.3; MS (ESI): *m*/*z* = 701 $[M + Na]^+$; HRMS: calcd. for $C_{37}H_{66}O_7Si_2Na$ $(M + Na)^+$ 701.4239; found 701.4234.

(*S*)-6-(((2*S*,6*S*)-6-((*R*)-3-Hydroxy-2-methylpropyl)tetrahydro-2*H*-pyran-2-yl)methyl)-2-(2-(4-methoxybenzyloxy)ethyl)-2*H*-pyran-4(3H)-one (28). To a stirred solution of compound **27** (750 mg, 1.10 mmol) in MeCN (10 mL) was added HF (0.5 mL, 40% aq.) at room temperature. The resulting reaction mixture was stirred at room temperature for 4 h, and was then quenched by the addition of saturated $NaHCO_3$ (15 mL). The resulting mixture was extracted with EtOAc (2 × 20 mL), and the combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexanes–EtOAc, 1 : 1) to give compound **28** (408 mg, 86%) as a colorless oil. R_f 0.20 (50% EtOAc in hexanes); IR (KBr): ν_{max} 3451, 2927, 2858, 1658, 1606, 1247, 1091, 1034 cm^{-1}; $[\alpha]_D^{20}$ = +69.4 (*c* = 0.50, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ = 7.19 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 5.37 (s, 1H), 4.59–4.51 (m, 1H), 4.41 (s, 2H), 3.80 (s, 3H), 3.61–3.47 (m, 3H), 3.45–3.34 (m, 3H), 2.46–2.35 (m, 2H), 2.26 (dd, *J* = 14.7, 4.9 Hz, 1H), 1.95–1.80 (m, 3H) 1.60–1.44 (m, 4H), 1.41–1.34 (m, 1H), 1.30–1.17 (m, 3H), 0.90 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.0, 174.2, 159.1, 130.0, 129.2, 113.7, 105.5, 75.6, 74.7, 72.7, 67.4, 65.1, 55.2, 41.5, 40.7, 40.0, 34.4, 32.2, 31.2, 31.1, 29.6, 23.4, 17.3; MS (ESI): *m*/*z* = 433.2 $[M + H]^+$; HRMS: calcd. for $C_{25}H_{37}O_6$ $(M + H)^+$ 433.2585; found 433.2560.

(2*S*,6*R*)-2-(((2*S*,6*S*)-6-((*R*)-3-Hydroxy-2-methylpropyl)tetrahydro-2*H*-pyran-2-yl)methyl)-6-(2-(4-methoxybenzyloxy)ethyl)dihydro-2*H*-pyran-4(3H)-one (3). Palladium on carbon (100 mg, 10% wet weight) was added to a solution of compound **28** (410 mg, 0.95 mmol) and K_2CO_3 (131 mg, 0.95 mmol) in EtOAc (5 mL). The reaction mixture was stirred overnight under a hydrogen atmosphere. After completion of the reaction, the mixture was filtered through celite and the resulting filtrate was concentrated *in vacuo*. Column chromatography of the residue on silica gel (40% ethyl acetate in hexanes) gave compound **3** (380 mg, 92%) as a colorless oil. R_f 0.40 (50% EtOAc in hexanes); IR (KBr): ν_{max} 3433, 2931, 2859, 1716, 1606, 1512, 1253, 1088, 1033, 751 cm^{-1}; $[\alpha]_D^{28}$ = +8.9 (*c* = 1.30, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.18 (d, *J* = 8.5 Hz, 2H), 6.82 (d, *J* = 8.5 Hz, 2H), 4.39 (s, 2H), 3.80 (s, 3H), 3.78–3.68 (m, 2H), 3.57–3.37 (m, 6H), 2.36 (t, *J* = 13.1 Hz, 2H), 2.21 (td, *J* = 13.1, 5.4 Hz, 2H), 1.99–1.72 (m, 5H), 1.60–1.35 (m, 5H), 1.31–1.16 (m, 3H), 0.90 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 207.8, 159.3, 130.4, 129.3, 113.9, 75.7, 74.5, 74.3, 74.0, 72.9, 67.7, 66.0, 55.4, 48.0, 47.7, 42.4, 40.5, 36.5, 32.3, 31.5, 31.2, 29.8, 23.7, 17.6; MS (ESI): *m*/*z* = 457 $[M + Na]^+$; HRMS: calcd. for $C_{25}H_{38}O_6Na$ $(M + Na)^+$ 457.2561; found 457.2571.

(*R*)-3-((2*R*,6*S*)-6-(((2*S*,6*R*)-4,4-Dimethoxy-6-(2-(4-ethoxybenzyloxy)ethyl)tetrahydro-2*H*-pyran-2-yl)methyl)tetrahydro-2*H*-pyran-2-yl)-2-methylpropan-1-ol (30). To a stirred solution of **3** (141 mg, 0.32 mmol) in MeOH (2.4 mL) and $(MeO)_3CH$ (0.8 mL) at room temperature was added *p*-TSA·H_2O (6.1 mg, 0.032 mmol). After being stirred for 15 min at room temperature, the reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL). The resulting mixture was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexanes : EtOAc =70 : 30) to give dimethyl ketal **30** (126 mg, 82%) as a colorless oil. R_f 0.50 (50% EtOAc in hexanes); IR (KBr): ν_{max} 3452, 2927, 2858, 1610, 1512, 1428, 1358, 1223, 1151, 1033, 751 cm^{-1}; $[\alpha]_D^{20}$ = +11.3 (*c* = 0.70, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.9 Hz, 2H), 6.87 (d, *J* = 8.9 Hz, 2H), 4.42 (s, 2H), 3.80 (s, 3H), 3.66–3.39 (m, 8H), 3.20 (s, 3H), 3.15 (s, 3H), 2.01–1.89 (m, 2H), 1.88–1.66 (m, 3H), 1.65–1.37 (m, 6H), 1.33–1.12 (m, 6H), 0.92 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.9, 130.4, 129.0, 113.6, 98.9, 75.0, 74.5, 72.5, 70.9, 70.5, 67.5, 66.4, 55.0, 47.5, 47.1, 41.8, 40.4, 38.5, 38.4, 35.8, 32.1, 30.9, 23.5, 17.5; MS (ESI): *m*/*z* = 503.3 $[M + Na]^+$.

***tert*-Butyl((1*E*,3*R*,4*S*,5*E*,7*R*)-8-((2*R*,6*S*)-6-(((2*S*,6*R*)-4,4-dimethoxy-6-(2-(4-methoxybenzyloxy)ethyl)tetrahydro-2*H*-pyran-2-yl)methyl)tetrahydro-2*H*-pyran-2-yl)-1-iodo-4,7-dimethylocta-1,5-dien-3-yloxy)dimethylsilane (31).** To a stirred solution of **30** (85 mg, 0.18 mmol) in dry CH_2Cl_2 (4 mL) at 0 °C was added $NaHCO_3$ (60 mg, 0.71 mmol) and Dess–Martin periodinane (115 mg, 0.27 mmol) in one portion. The mixture was stirred for 1 h at 0 °C and quenched with saturated aqueous $Na_2S_2O_3$ (4 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (30% EtOAc in hexanes) to give the aldehyde (73 mg, 86%) as a colorless oil, which was immediately used in the next reaction.

To a −78 °C solution of sulfone **4** (160 mg, 0.29 mmol) in a mixture of THF (0.8 mL) and HMPA (0.2 mL) was added LiHMDS (0.28 mL of a 1 M solution in THF, 0.28 mmol). After 30 min at that temperature, the above aldehyde (70 mg, 0.15 mmol) was added to a solution of THF (0.3 mL) and HMPA (0.1 mL). The reaction mixture was stirred for 2 h at −78 °C, after which it was slowly warm to room temperature over a period of 3 h and stirred at this temperature for 12 h. The mixture was subsequently diluted with ether (5 mL) and quenched by the addition of a saturated NH_4Cl solution (2 mL). The organic phase was washed with water, brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (hexanes : EtOAc, 95 : 5 to 90 : 10) to give **31** (67 mg, 56%) and the aldehyde (20 mg, 28%). R_f 0.40 (20% EtOAc in hexanes); IR (KBr): ν_{max} 2932, 2859, 1606, 1512, 1436, 1374, 1253, 1088, 1032, 751 cm^{-1}; $[\alpha]_D^{20}$ = +9.17 (*c* = 0.60, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 7.25 (d, *J* =

8.5 Hz, 2H), 6.82 (d, J = 8.5 Hz, 2H), 6.51 (dd, J = 14.5, 6.2 Hz, 1H), 6.14 (d, J = 14.5 Hz, 1H), 5.26–5.20 (m, 2H), 4.42 (s, 2H), 3.88–3.82 (m, 1H), 3.80 (s, 3H), 3.71–3.39 (m, 5H), 3.32–3.22 (m, 1H), 3.20 (s, 3H), 3.15 (s, 3H), 2.45–2.26 (m, 1H), 2.23–2.11 (m, 1H), 1.99 (t, J = 11.7 Hz, 2H), 1.91–1.67 (m, 2H), 1.64–1.37 (m, 4H), 1.33–1.12 (m, 8H), 0.97 (d, J = 6.6 Hz, 3H), 0.95 (d, J = 6.6 Hz, 3H), 0.89 (s, 9H), 0.03 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.0, 148.0, 137.1, 130.6, 129.9, 129.1, 113.7, 99.0, 79.1, 76.0, 75.5, 74.0, 72.6, 71.0, 70.8, 66.6, 55.2, 47.6, 47.3, 44.0, 43.5, 42.5, 38.8, 38.6, 36.0, 33.0, 32.1, 31.4, 29.6, 25.8, 23.6, 21.7, 18.2, 16.2, −4.4, −4.8; MS (ESI): m/z = 823.4 $[M + Na]^+$; HRMS: calcd. for $C_{39}H_{65}IO_7SiNa$ $(M + Na)^+$ 823.3436; found 823.3448.

2-((2*R*,6*S*)-6-(((2*S*,6*R*)-6-((2*R*,3*E*,5*S*,6*R*,7*E*)-6-(*tert*-Butyldimethylsilyloxy)-8-iodo-2,5-dimethylocta-3,7-dienyl)tetrahydro-2*H*-pyran-2-yl)methyl)-4,4 dimethoxytetrahydro-2*H*-pyran-2-yl)ethanol (32). To a solution of **31** (60 mg, 0.075 mmol) in CH_2Cl_2 (0.9 mL) and pH 7 buffer solution (0.1 mL) was added DDQ (20.4 mg, 0.09 mmol) at 0 °C. The reaction mixture was stirred for 30 min, and then poured into water. The aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic extracts were washed with aq. $Na_2S_2O_3$ (5 mL), aq. $NaHCO_3$ (5 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Flash chromatography (hexanes : EtOAc, 80 : 20) afforded alcohol **32** (47 mg, 92%) as a colorless oil. R_f 0.30 (20% EtOAc in hexanes); IR (KBr): ν_{max} 3454, 2927, 2858, 1612, 1514, 1452, 1233, 1142, 1033, 772 cm^{-1}; $[\alpha]_D^{20}$ = −1.8 (c = 0.50, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.50 (dd, J = 14.9, 6.0 Hz, 1H), 6.15 (d, J = 14.9 Hz, 1H), 5.29–5.19 (m, 2H), 3.86 (t, J = 6.0 Hz, 1H), 3.81–3.68 (m, 4H), 3.44–3.35 (m, 1H), 3.29–3.22 (m, 1H), 3.21 (s, 3H), 3.16 (s, 3H), 2.72 (br s, 1H), 2.39–2.25 (m, 1H), 2.17 (dd, J = 13.0, 7.0 Hz, 1H), 2.02 (d, J = 13.0 Hz, 1H), 1.92 (d, J = 13.0 Hz, 1H), 1.86–1.62 (m, 3H), 1.60–1.41 (m, 4H), 1.38–1.11 (m, 7H), 0.97 (d, J = 7.0 Hz, 3H), 0.95 (d, J = 7.0 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.0, 137.1, 130.0, 98.6, 79.0, 76.1, 75.6, 74.7, 74.1, 71.4, 61.6, 47.7, 47.3, 43.9, 43.5, 42.5, 38.6, 38.3, 37.5, 33.0, 31.9, 31.7, 29.6, 25.8, 23.5, 21.7, 18.1, 16.3, −4.4, −4.9; MS (ESI): m/z = 703 $[M + Na]^+$; HRMS: calcd. for $C_{31}H_{57}IO_6Si$ $(M + Na)^+$ 703.2861; found 703.2852.

2-((2*S*,6*S*)-6-(((2*S*,6*R*)-6-((2*R*,3*E*,5*S*,6*R*,7*E*)-6-Hydroxy-8-iodo-2,5-dimethylocta-3,7-dienyl)tetrahydro-2*H*-pyran-2-yl)methyl)-4,4-dimethoxytetrahydro-2*H*-pyran-2-yl)acetic acid (33). To a solution of above alcohol **32** (60 mg, 0.09 mmol) in H_2O–CH_2Cl_2 (1 : 1, 1 mL) were added TEMPO (4.0 mg, 0.026 mmol) and BAIB (87 mg, 0.27 mmol). After stirring at room temperature for 2 h, the reaction mixture was diluted with CH_2Cl_2 (5 mL) and then washed with saturated aqueous $Na_2S_2O_3$ (5 mL). The organic layer was dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure to give the crude carboxylic acid, which was used for the next reaction without further purification.

A solution of the above crude carboxylic acid in THF (2 mL) was cooled to 0 °C and TBAF (0.9 mL, 0.9 mmol, 1.0 M solution in THF) was added dropwise. The resulting brown solution was stirred at room temperature for 3 h. The reaction was quenched with saturated aqueous NH_4Cl (2 mL) and extracted with EtOAc (2 × 5 mL). The combined organic layer was dried over Na_2SO_4 and evaporated to dryness under reduced pressure. The residue was purified by flash column chromatography (silica gel, $CHCl_3$: MeOH = 98 : 2) to give seco acid **33** (47.5 mg, 91%) as a colorless oil. R_f 0.40 (5% MeOH in $CHCl_3$); $[\alpha]_D^{20}$ = −4.6 (c = 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.57 (dd, J = 14.0, 5.0 Hz, 1H), 6.33 (d, J = 14.0 Hz, 1H), 5.34–5.26 (m, 2H), 3.98 (t, J = 5.0 Hz, 1H), 3.93–3.85 (m, 1H), 3.73–3.65 (m, 1H), 3.43–3.35 (m, 1H), 3.28–3.22 (m, 1H), 3.21 (s, 3H), 3.17 (s, 3H), 2.56 (dd, J = 15.0, 8.0 Hz, 1H), 2.47 (dd, J = 15.0, 5.0 Hz, 1H), 2.44–2.37 (m, 1H), 2.35–2.23 (m, 1H), 2.07–1.94 (m, 2H), 1.89–1.74 (m, 2H), 1.64–1.40 (m, 6H), 1.38–1.10 (m, 4H), 1.00 (d, J = 7.0 Hz, 3H), 0.96 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.9, 146.6, 138.0, 129.7, 98.6, 77.7, 77.5, 75.7, 74.3, 71.5, 70.5, 47.7, 47.4, 43.5, 42.4, 42.2, 40.6, 38.6, 37.8, 33.2, 31.9, 31.2, 29.6, 23.6, 21.6, 15.6; MS (ESI): m/z = 603.3 $[M + Na]^+$.

Macrolactone (34). To a solution of seco acid **33** (60 mg, 0.103 mmol) in THF (5 mL) at 0 °C were added Et_3N (0.29 mL, 2.06 mmol) and 2,4,6-$Cl_3C_6H_2COCl$ (0.16 mL, 1.03 mmol). After being stirred at room temperature for 4 h, the reaction mixture was diluted with toluene (10 mL) and added dropwise to a solution of DMAP (503 mg, 4.12 mmol) in toluene (100 mL) at 80 °C over a period of 10 h. Upon complete addition, stirring was continued for an additional 12 h. After being cooled to room temperature, the mixture was concentrated to about 20 ml, diluted with EtOAc (15 mL), and the solution was successively washed with aqueous HCl, satd. aqueous $NaHCO_3$, and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes : EtOAc = 95 : 05) providing macrolactone **34** (36.5 mg, 63%) as a colorless oil. R_f 0.40 (10% EtOAc in hexanes); IR (KBr): ν_{max} 2926, 2854, 1739, 1660, 1457, 1373, 1282, 1256, 1185, 1098, 1045, 947 cm^{-1}; $[\alpha]_D^{20}$ = −11.5 (c = 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.50 (dd, J = 15.1, 6.0 Hz, 1H), 6.33 (d, J = 15.1 Hz, 1H), 5.47 (dd, J = 15.1, 9.0 Hz, 1H), 5.13 (dd, J = 7.5, 2.2 Hz, 1H), 5.07 (dd, J = 15.1, 9.8 Hz, 1H), 3.98–3.86 (m, 1H), 3.36–3.13 (m, 3H), 3.21 (s, 3H), 3.16 (s, 3H), 2.60–2.47 (m, 1H), 2.47–2.42 (m, 2H), 2.40–2.27 (m, 1H), 1.98 (dt, J = 12.8, 2.2 Hz, 1H), 1.86 (dt, J = 13.5, 2.2 Hz, 1H), 1.80–1.61 (m, 2H), 1.53–1.40 (m, 2H), 1.38–1.21 (m, 8H), 1.04 (d, J = 6.8 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.7, 142.8, 135.9, 131.7, 99.0, 79.4, 79.2, 75.9, 75.3, 71.3, 70.6, 47.6, 47.4, 43.9, 42.9, 41.0, 38.8, 37.6, 32.9, 32.3, 31.6, 29.6, 23.9, 21.7, 14.3. MS (ESI): m/z = 585 $[M + Na]^+$; HRMS: calcd. for $C_{25}H_{39}IO_6Na$ $(M + Na)^+$ 585.1684; found 585.1634.

Macrolactone (2)[4a]. The above compound **34** (25 mg, 0.044 mmol) was dissolved in MeOH (1 mL) and the resulting solution was cooled to 0 °C and p-TSA·H_2O (cat.) was added. The mixture was stirred for 15 min at 0 °C. And then solid $NaHCO_3$ was added, and the solvents were removed under reduced pressure. Flash column chromatography (silica gel, 5⟶10% EtOAc in hexanes) furnished the desired compound **2** (19.5 mg, 86%) as a colorless oil. R_f 0.30 (10% EtOAc in hexanes); IR (KBr): ν_{max} 2925, 2854, 1726, 1658, 1403, 1213, 1176, 1090, 975, 759 cm^{-1}; $[\alpha]_D^{20}$ = −14.8 (c = 0.60, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.51 (dd, J = 14.5, 6.4 Hz, 1H), 6.38 (d, J = 14.5 Hz,

1H), 5.45 (dd, J = 15.1, 9.4 Hz, 1H), 5.20 (dd, J = 6.0, 0.9 Hz, 1H), 5.11 (dd, J = 15.1, 9.4 Hz, 1H), 4.11–4.02 (m, 1H), 3.45 (t, J = 10.7 Hz, 1H), 3.31 (dd, J = 10.3, 8.7 Hz, 1H), 3.18 (t, J = 11.1 Hz, 1H), 2.62–2.55 (m, 2H), 2.55–2.46 (m, 1H), 2.45–2.29 (m, 5H), 1.88–1.73 (m, 2H), 1.66–1.36 (m, 5H), 1.29–1.10 (m, 3H), 1.06 (d, J = 7.0 Hz, 3H), 0.95 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.9, 169.8, 142.5, 136.1, 131.5, 79.7, 79.5, 76.0, 74.9, 74.3, 73.0, 47.7, 46.5, 43.9, 43.0, 41.2, 41.0, 33.1, 32.4, 31.5, 23.8, 21.7, 14.2; MS (ESI): m/z = 539 $[M + Na]^+$; HRMS: calcd. for $C_{23}H_{34}IO_5$ $(M + H)^+$ 517.1445; found 517.1427.

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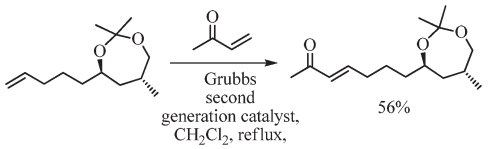

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