Tetrahedron: *Asymmetry* xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

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

Enantiopure hydroxymethylated cycloalkenols as privileged small molecular multifunctional scaffolds for the asymmetric synthesis of carbocycles

Rajan Kumar, Rohan Kalyan Rej, Joydev Halder, Haridas Mandal, Samik Nanda *

Department of Chemistry, Indian Institute of Technology, Kharagpur, 721302, India

ARTICLE INFO

Article history:
Received 13 April 2016
Accepted 5 May 2016
Available online xxxx

ABSTRACT

Enantiopure hydroxymethylated cycloalkenols bearing a quaternary stereocenter have been synthesized by a Pybox mediated enantioselective desymmetrization method. The synthesized cycloalkenols serve as starting precursors for the construction of several chiral small ring carbocyclic frameworks by a distinct functional group transformation.

1. Introduction

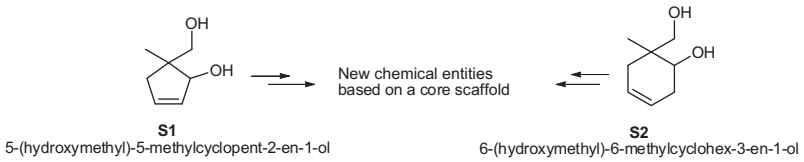
Biological space, consists of DNA, RNA, carbohydrates, proteins, lipids and related molecules seem to be modest in size; the human genome is in the order of 3×10^4 genes of which only a fraction is targeted by current therapeutics.[1] Meanwhile, chemical space is infinite, and there are an estimated 10^{60} organic compounds with a molecular weight cutoff of 500 D.[2] Our limited understanding of certain areas of chemical space that are best suited to interact with biological space is a major bottleneck of drug discovery. In recent years, there have been various attempts at narrowing this gap by statistical analyses to define descriptors for small-molecule drug-like space.[3] The ever-increasing demand for the production of natural products and their analogues for pharmaceutical applications is the basis of research efforts on the development of convenient synthetic pathways.[4] For this purpose various synthetic strategies e.g. diversity oriented synthesis, target oriented synthesis and biology oriented synthesis have been successfully utilized.[5] Natural products and their analogues provide the inspiration for a variety of strategies used in the diversity oriented synthesis of novel small molecule libraries.[6] Diversity oriented synthesis has emerged as a powerful approach to obtain complex molecules for biological studies. The utility of diversity oriented synthesis relies on the development of chemical methodologies for the synthesis of novel structural types with high levels of skeletal and stereochemical complexity.[7] There are two main strategies involved in diversity oriented synthesis; one is a reagent based strategy while the other is a substrate-based strategy.[8] In the former strategy, a core scaffold is subjected to different reagents and conditions to afford diversity in the products while in the latter strategy, a diverse collection of products is obtained by reacting different substrates to the same sequence of reagents and conditions. In the former approach, which sometimes can be regarded as scaffold oriented synthesis, the synthesized libraries are mainly based on the core scaffold from individual natural products or specific substructures found across a class of natural products or a new chemotype together. The core scaffolds are then synthetically manipulated to give a new scaffold mainly by a linear or divergent route. From our recent work in the area of scaffold oriented synthesis, we identified hydroxymethylated cycloalkenone derivatives as potential multifunctional scaffolds, which can be successfully applied to the asymmetric synthesis of natural products,[9] designed cyclitols[10] and novel carbasugars.[11] In continuation of our earlier work, we herein report our research findings based on the scaffold oriented synthesis of novel chemical entities from two relatively new hydroxymethylated cycloalkenol based scaffold containing a quaternary stereocenter (Scheme 1).

2. Results and discussion

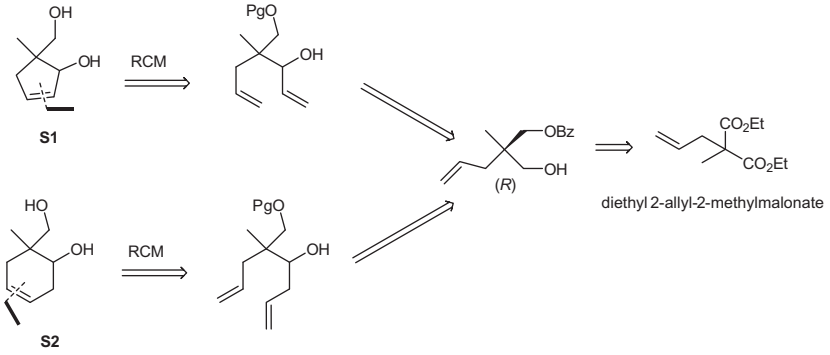
The initial hurdle was to access both hydroxymethylated cycloalkenol scaffolds **S1** and **S2** bearing a quaternary stereocenter in enantiopure form. The ring closing metathesis reaction was thought to be explored to construct the internal olefinic unsaturation present in both the scaffolds. The ring closing metathesis precursor was thought to be accessed from diethyl 2-allyl-2-methylmalonate as shown in Scheme 2.

* Corresponding author. Tel.: +91 3222 283328; fax: +91 3222 282252.
E-mail address: snanda@chem.iitkgp.ernet.in (S. Nanda).

http://dx.doi.org/10.1016/j.tetasy.2016.05.003
0957-4166/



Scheme 1. Hydroxymethylated 2-cycloalkenols bearing a quaternary stereocenter.



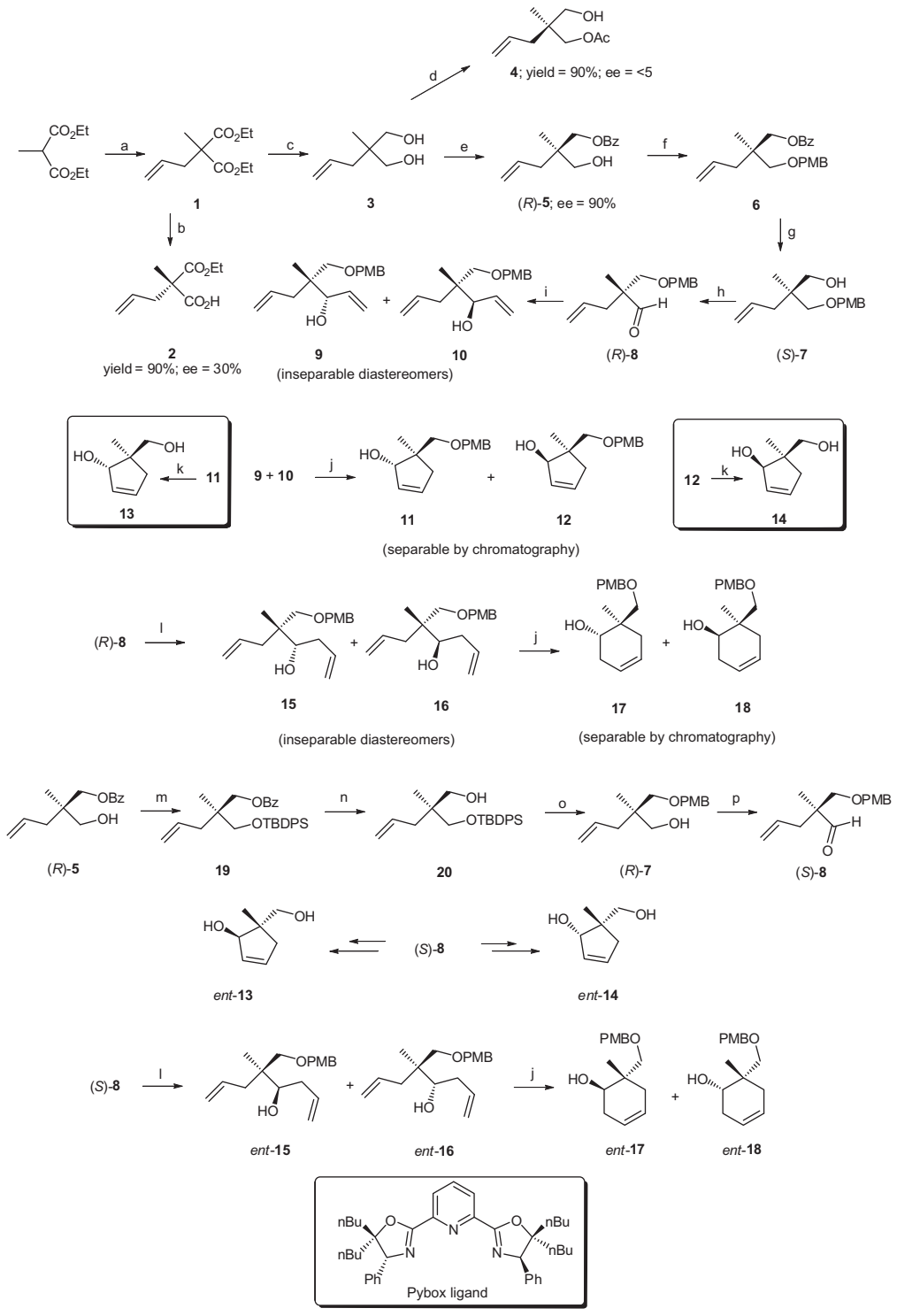
Scheme 2. Retrosynthetic analysis for both the scaffolds.

2.1. Synthesis of all of the stereoisomers of S1 and S2

In our initial attempt to fix the quaternary stereocenter present in diethyl 2-allyl-2-methylmalonate **1**, PLE (pig liver *esterase*) mediated hydrolysis through an enantioselective enzymatic desymmetrization strategy was unsuccessful.[12] The corresponding half ester **2** was obtained in 90% yield but with low enantioselectivity (ee = 30%) in favor of the (*S*)-stereoisomer. The lipase (Amano-PS) mediated enantioselective enzymatic desymmetrization through an irreversible transesterification of the prochiral diol **3** (obtained after reducing both the $-CO_2Et$ groups of compound **1**) also failed to produce any reasonable enantioselection. As a result, the direct enantioselective desymmetrization using a chemical catalyst was explored as reported by Lee et al.[13] 2,2-Disubstituted 1,3-propane diol **3** was treated with a C_2-symmetric Pybox ligand and $CuCl_2$ in the presence of PhCOCl to afford compound (*R*)-**5** in 98% yield and with 90% ee. This desymmetrization method fixed the quaternary stereocenter of our desired scaffolds. The free alcohol group in compound **5** was then protected with PMB-imidate to furnish compound **6** in 88% yield. Removal of benzoate group with methanolic K_2CO_3 afforded compound **7** in 90% yield. Oxidation of compound **7** under Swern conditions[14] afforded aldehyde (*R*)-**8** in 90% yield. Vinylmagnesium bromide addition on compound **8** at −78 °C afforded compounds **9** and **10** as an inseparable diastereomeric mixture in 82% yield. At this stage we did not assign the absolute configuration of both diastereomers. The diastereomeric mixture was subjected to ring closing metathesis reaction with G-I catalyst[15] (Grubbs 1st generation metathesis catalyst) to afford compounds **11** and **12** in 80% yield. Deprotection of the PMB groups in compounds **11** and **12** was achieved by treatment with DDQ[16] to afford the known cyclic diols **13** and **14**.[17] The absolute configurations for compounds **13** and **14** were then assigned ambiguously. Hence two stereoisomers of scaffold **S1** bearing a quaternary stereocenter was easily synthesized from the (*S*)-enantiomer of compound **7**. Protecting group manipulation was carried out as shown in Scheme 3, and afforded (*S*)-**8** from (*R*)-**5** in good yield. Enantiopure (*S*)-**8** was then synthetically manipulated to furnish *ent*-**13** and *ent*-**14** separately by following the same procedure. Hence all of the stereoisomers of scaffold **S1** can be easily accessed. For accessing the stereoisomers of scaffold **S2**, we started from enantiopure aldehyde (*R*)-**8**. Allylation of aldehyde **8** under Barbier conditions[18] afforded an inseparable mixture of diastereomers **15** and **16** in 88% yield. The ring closing metathesis reaction of the mixture of **15** and **16** with G-I catalyst afforded cyclic compounds **17** and **18**, which were then separated by column chromatography. By applying a similar procedure, *ent*-**17** and *ent*-**18** were also synthesized from aldehyde (*S*)-**8**. Hence all of the stereoisomers of scaffold **S2** were also synthesized as shown in Scheme 3. The absolute configurations of diols **17** and **18** were assigned by comparing their spectroscopic data and specific rotations with those reported in the literature.[17a]

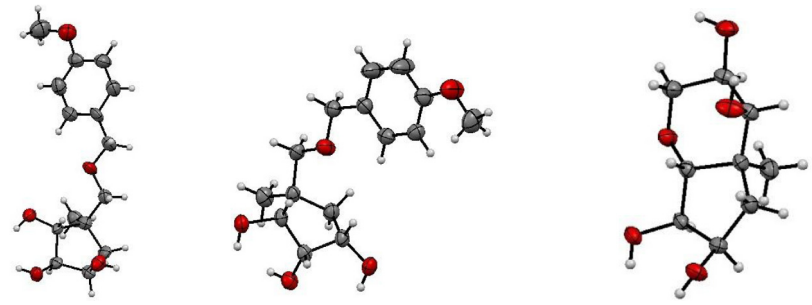
2.2. Scaffolding of hydroxymethylated cyclopent-2-enol S1

The creation of a diverse set of small molecular compounds was initiated with **11**. Compound **11** was subjected to substrate directed epoxidation with *m*CPBA in DCM solvent to afford the epoxide **21** in 90% yield as the sole product. Epoxide opening with 0.2 M H_2SO_4 in dioxane:water (1:1) afforded triol **22** as a single product. PMB deprotection and subsequent esterification of the tetraol furnished tetraacetate **23** in 80% yield. Later on **11** was subjected to dihydroxylation with OsO_4/NMO to afford diol **24** and **25** in a 3:2 ratio. The structure and relative stereochemistry for both the diols were confirmed by X-ray crystallographic analysis. The ORTEP (Oakridge Thermal Ellipsoid Plot) diagrams for diols **24** and **25** are shown in Figure 1. Next we decided to create an extra ring fused with the original cyclopentane ring present in **11**. For this purpose, the free hydroxyl group in **11** was protected as its TBS ether by treatment with imidazole and TBS-Cl to furnish compound **26** in 95% yield. Dihydroxylation of compound **26** with OsO_4/NMO afforded diols **27** and **28** in 78% yield (3:1). The diol functionality in compound **27** was protected as its acetonide by treatment with 2,2-DMP in the presence of a catalytic amount of CSA to afford acetonide **29** in 92% yield. Treatment of compound **29** with DDQ furnished alcohol **30** after removal of the PMB group in 88% yield. Oxidation under Swern conditions afforded aldehyde **31** in 90% yield. Aldehyde **31** was then subjected to Wittig olefination with $Ph_3P^+MeI^-$ in presence of LHMDS to afford the olefinic compound **32** in 74% yield. Treatment of compound **32** with TBAF afforded alcohol **33** in 88% yield. Treatment of compound **33** in the



Scheme 3. Reagents and conditions: (a) NaH, allyl bromide, reflux, 6 h, 90%; (b) PLE, phosphate buffer (pH = 8.0), 24 h; (c) LAH, THF, 90%; (d) lipase-PS (Amano), vinyl acetate, $^{i}Pr_2O$, MS (4 Å), rt, 20 h; (e) (i) Pybox ligand, $CuCl_2$, THF, 4 h; (ii) PhCOCl, Et_3N, THF, −78 °C, 12 h, 98%; (f) PMB—O—(C═NH)—CCl_3, CSA, rt, 6 h, 88%; (g) K_2CO_3, MeOH, rt, 6 h, 90%; (h) $(COCl)_2$, Me_2SO, −78 °C, Et_3N, 90%; (i) CH_2═CHMgBr, −78 °C, 2 h, 82%; (j) G-I, DCM, reflux, 6 h, 80%; (k) DDQ, DCM:phosphate buffer (19:1), rt, 2 h, 90%; (l) Allyl bromide, Zn, NH_4Cl, THF, 88% (m) imidazole, TBDPS-Cl, rt, 90%; (n) K_2CO_3, MeOH, 6 h, 90%; (o) (i) same as (f), (ii) TBAF, THF, rt, 79%; (p) same as h, 90%.

presence of NaH and allylbromide afforded the *O*-allylated compound **34** in 78% yield. The ring closing metathesis reaction of compound **34** in presence of G-II catalyst (Grubbs 2nd generation metathesis catalyst, 5 mol %) in refluxing DCM afforded the ring closing product **35** in 80% yield. Finally dihydroxylation with OsO_4/NMO afforded diol **36** as the sole product in 82% yield. The acetonide group in compound **36** was removed with PTSA to afford the tetraol **37**, whose structure and relative configuration were assigned with the help of single crystal X-ray structure analysis. Tetraol **37** was subsequently converted into tetraacetate **38** for obtaining sharp resolution in the respective ^{1}H NMR spectrum (Scheme 4). Compound **11** was subjected to substrate directed Simmons-Smith cyclopropanation to afford bicyclic compound **39** as the sole product. The free hydroxyl group in **39** was protected



Compound **24** Compound **25** Compound **37**

Figure 1. ORTEP presentation of triols **24** and **25** and tetraol **37**.

as its TBS ether by treatment with imidazole and TBS-Cl to furnish compound **40** in 90% yield. Treatment of compound **40** with DDQ furnished alcohol **41** in 88% yield after removal of the PMB group. Oxidation under Swern conditions afforded aldehyde **42** in 90% yield. Aldehyde **42** was then subjected to Wittig olefination with $Ph_3P^+MeI^-$ in the presence of LHMDS to afford the olefinic compound **43** in 74% yield. Treatment of compound **43** with TBAF afforded alcohol **44** in 86% yield. Treatment of compound **44** in presence of NaH and allylbromide afforded the *O*-allylated compound **45** in 70% yield. The ring closing metathesis reaction of compound **45** in the presence of G-II catalyst (5 mol %) in refluxing DCM afforded the ring closing product, which upon treatment with OsO_4/NMO afforded diol **46** as the sole product in 53% overall yield after two steps. The crystal structures of triol **24**, **25** and tetraol **37** were obtained with the help of single crystal X-ray analysis, and the corresponding ORTEP presentations are shown in Figure 1, which also establishes the relative stereochemistry of the different functional groups present in those compounds.

2.3. Scaffolding of the hydroxymethylated cyclohex-3-enol S2

The creation of a diverse set of small molecular compound libraries was initiated with **19**. Compound **19** was subjected to substrate directed epoxidation with *m*CPBA in DCM solvent to afford epoxides **47** and **48** in 80% yield (2:1). Epoxide opening of compounds **47** and **48** with 0.2 M H_2SO_4 in dioxane:water (1:1) followed by removal of the PMB group with DDQ afforded tetraols **49** and **50**, respectively. Compound **19** was next subjected to substrate directed Simmons-Smith cyclopropanation to afford bicyclic compound **51** as the sole product in 75% yield. Next we decided to create an extra ring fused with original cyclohexane ring present in **19**. For this purpose, the free hydroxyl group in **19** was protected as its TBS ether by treatment with imidazole and TBS-Cl to furnish compound **52** in 86% yield. Dihydroxylation of compound **52** with OsO_4/NMO afforded diols **53** and **54** in 81% yield (1:2). The diol functionality in compound **54** was protected as its acetonide by treatment with 2,2-DMP in the presence of a catalytic amount of CSA to afford acetonide **55** in 90% yield. Treatment of compound **55** with DDQ furnished alcohol **56** after removal of the PMB group in 88% yield. Oxidation under Swern conditions followed by Wittig olefination with $Ph_3P^+MeI^-$ in the presence of LHMDS afforded olefinic compound **57** in 64% yield (for two step). Treatment of compound **57** with TBAF afforded alcohol **58** in 88% yield. Treatment of compound **58** in the presence of NaH and allylbromide afforded the *O*-allylated compound **59** in 78% yield. The ring closing metathesis reaction of compound **59** in the presence of G-II catalyst (5 mol %) in refluxing DCM afforded the ring closing product **60** in 80% yield. Finally dihydroxylation with OsO_4/NMO afforded diol **61** as the sole product in 82% yield. The acetonide group in compound **61** was removed with PTSA to afford tetraol **62** in 90% yield (Scheme 5).

3. Conclusion

In conclusion, all of the stereoisomers of the hydroxymethylated cycloalkenol scaffolds based on cyclopentane and cyclohexane frameworks bearing quaternary stereocenters have been synthesized. The scaffolds can be further synthetically manipulated by a distinctive transformation based strategy in a linear way to access several carbocycles via a stereoselective fashion. We believe that most of the reactions reported herein can be carried out efficiently on a multigram scale, and so their use on an industrial scale can be amended at a later stage. The synthesized small ring carbocycles might exhibit some biological activity and could contribute to the chemical space project.

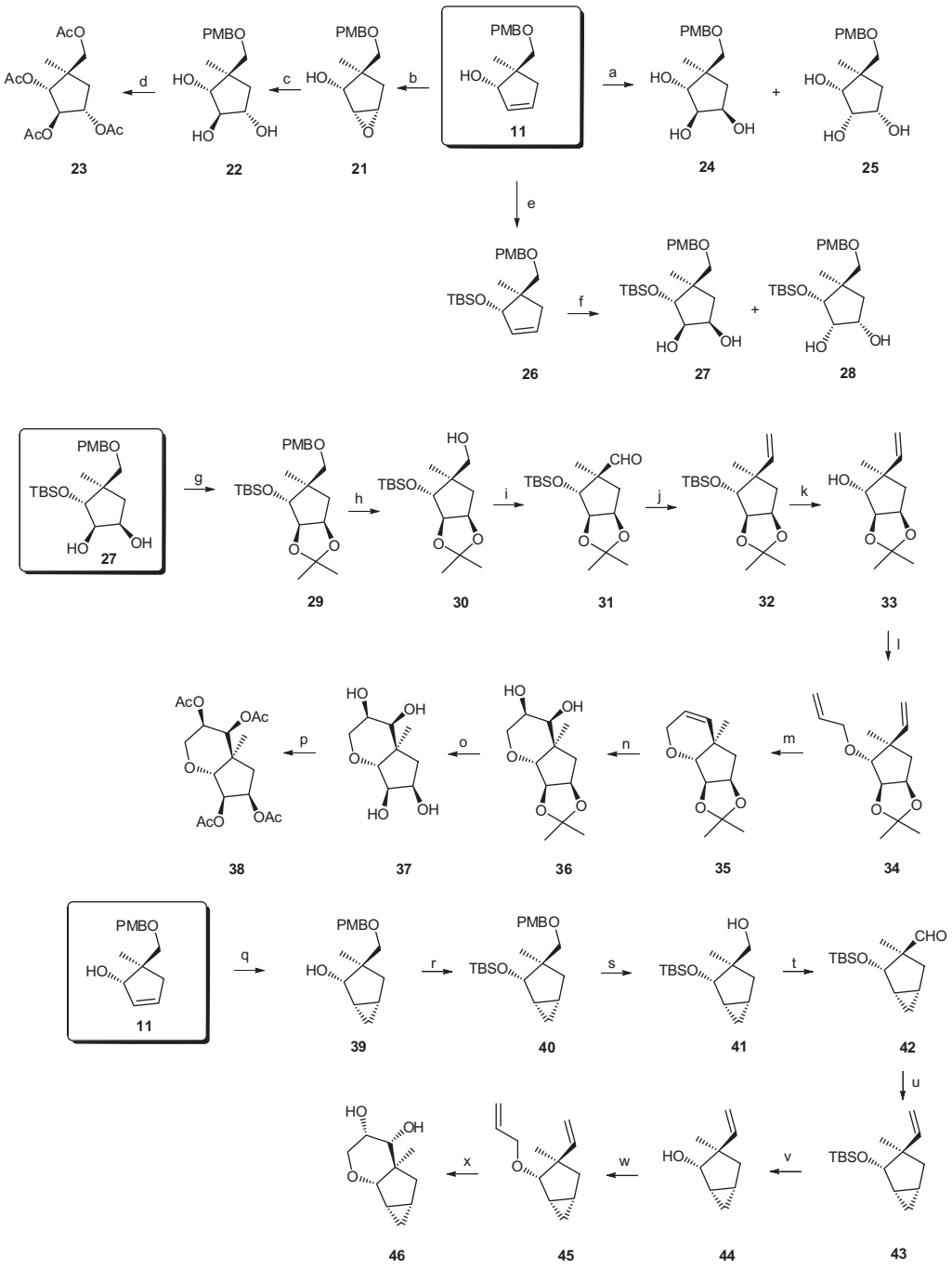
4. Experimental

4.1. General

All oxygen and/or moisture-sensitive reactions were carried out under an N_2 atmosphere in glassware that had been flame-dried under a vacuum (w0.5 mmHg) and purged with N_2 prior to use. Unless otherwise stated, materials were obtained from commercial suppliers and used without further purification. Lipase (Amano-PS) was purchased from Sigma Aldrich Co, USA and used as obtained. THF and diethyl ether were distilled from sodium benzophenone ketyl. Dichloromethane (DCM) was distilled from calcium hydride. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates with UV light, ethanolic anisaldehyde, and phosphomolybdic acid/heat as developing agents. Silica gel 100–200 mesh was used for column chromatography. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated. NMR spectra were recorded on 600, 400 and 200 MHz spectrometers at 25 °C in $CDCl_3$ using TMS as the internal standard. Chemical shifts are shown in δ. ^{13}C NMR spectra were recorded with a complete proton decoupling environment. The chemical shift value is listed as δ_H and δ_C for ^1H and ^{13}C, respectively. Coupling constants (J) are reported in Hertz (Hz) and the resonance multiplicity abbreviations used are s, singlet; d, doublet; t, triplet; q, quartet; dt, doublet of triplets; dd, doublet of doublets; ddd, doublet of doublet of doublets; m, multiplet; comp, overlapping multiplets of magnetically non-equivalent protons. Mass spectrometric analysis was performed in the CRF, IIT-Kharagpur (TOF analyzer). Optical rotations were measured on a digital polarimeter.

4.2. General procedure for the substrate directed epoxidation with *m*CPBA

Unsaturated alcohols (0.31 mmol) were dissolved in DCM (5 mL) along with $NaHCO_3$ (52 mg, 0.62 mmol). To a stirred suspension, *meta*-chloroperoxybenzoic acid (108 mg, 0.62 mmol)



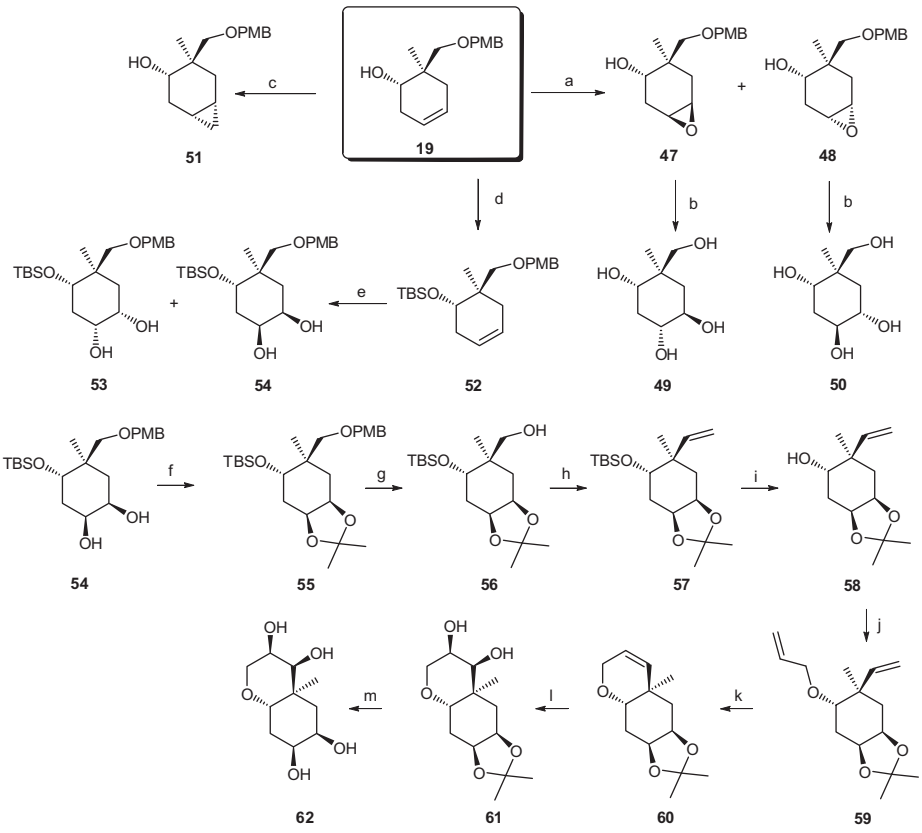
Scheme 4. Reagents and conditions: (a) OsO_4 (0.5 M in toluene), NMO, 75%; (b) *m*CPBA, DCM, rt, 90%; (c) 0.2 M H_2SO_4, dioxane:water (1:1), 8 h, 88%; (d) (i) DDQ, DCM/phosphate buffer (19:1), rt, (ii) Ac_2O, Et_3N, DMAP (5 mol %), rt, 12 h, 80%; (e) imidazole, TBS-Cl, 95%; (f) same as a, 78%; (g) 2,2-DMP, CSA, DCM, rt, 92%; (h) same as d, 88%; (i) $(COCl)_2$, DMSO, −78 °C, Et_3N, 90%; (j) $Ph_3P^+MeI^-$, LHMDS, 0 °C, 74%; (k) TBAF, THF, rt, 88%; (l) NaH, allylbromide, rt, 78%; (m) G-II, DCM, reflux, 8 h, 80%; (n) same as a, 82%; (o) PTSA, DCM, rt, 90%; (p) Ac_2O, Et_3N, DMAP (5 mol %), rt, 12 h, 95%; (q) CH_2Br_2, Zn–Cu couple, diethylether, 30 h, reflux, 75%; (r) same as e, 90%; (s) same as d, 88%; (t) same as i, 90%; (u) same as j, 74%; (v) same as k, 86%; (w) same as l, 70%; (x) (i) same as m, (ii) same as a, 53% (in two steps).

was added at room temperature. The resulting suspension was stirred vigorously for 19 h. Next a 20% aqueous solution of sodium sulfite (10 mL) was added and the resulting two-phase mixture was stirred vigorously for 15 min. The two layers were separated and the aqueous layer was extracted with DCM (30 mL). The combined organic layers were washed with a 20% aqueous solution of sodium sulfite (10 mL) and saturated aqueous $NaHCO_3$ (5 mL), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by flash column chromatography to afford the epoxide.

4.3. General procedure for the acid induced epoxide ring opening

Epoxide compounds (0.085 mmol) were added to a 1:1 mixture of 0.2 M sulfuric acid/1,4-dioxane (5 mL) and the reaction mixture was stirred at room temperature for 8 h. The reaction was then diluted with a saturated solution of $NaHCO_3$ (5 mL) and extracted with ethyl acetate (30 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography to afford the diols.

Please cite this article in press as: Kumar, R.; et al. *Tetrahedron: Asymmetry* (2016), http://dx.doi.org/10.1016/j.tetasy.2016.05.003



Scheme 5. Reagents and conditions: (a) *m*CPBA, DCM, rt, 80%; (b) (i) 0.2 N H_2SO_4, dioxane:water (1:1), 8 h, (ii) DDQ, DCM/phosphate buffer (19:1), rt; (c) CH_2Br_2, Zn–Cu couple, diethylether, 30 h, reflux, 75%; (d) imidazole, TBS-Cl, 86%; (e) OsO_4 (0.5 M in toluene), NMO, 81%; (f) 2,2-DMP, CSA, DCM, rt, 90%; (g) DDQ, DCM/phosphate buffer (19:1), 88%; (h) (i) $(COCl)_2$, DMSO, −78 °C, Et_3N, (ii) $Ph_3P^+MeI^-$, LHMDS, 0 °C, 64%; (i) TBAF, THF, rt, 88%; (j) NaH, allylbromide, rt, 78%; (k) G-II, DCM, reflux, 8 h, 80%; (l) same as e, 82%; (m) PTSA, DCM, rt, 90%.

4.4. General procedure for the cyclopropanation reaction

To a hot, rapidly stirred solution of cupric acetate monohydrate (140 mg, 0.7 mmol) in 2 mL of glacial acetic acid was added zinc dust (790 mg, 12 mmol). After approximately 0.5 min, all of the copper had deposited on the zinc. The couple was allowed to settle for 10 min, then the acetic acid was decanted while taking care to not lose the silt-like couple. The dark reddish gray couple was then washed with one portion (2 mL) of acetic acid followed by three portions (10 mL) of ether. The moist couple was thus ready for use. Methylene bromide (124 mg, 0.72 mmol) and iodine (0.15 g, 0.6 mmol) in anhydrous ether (5 mL) were added to a mixture of the zinc–copper couple. The iodine color disappeared immediately; the initial gray-colored mixture was then refluxed for 30 min. During this period, the mixture turned darker; the color change was accompanied by a gentle exothermic reaction. External heating was discontinued and the compound (60 mg, 0.18 mmol, in anhydrous ether 2 mL) was added dropwise over 30 min. During the addition, the mixture continued to reflux. Heating was resumed and the mixture was refluxed for 30 h. The reaction mixture was then cooled and filtered. The ether solution was extracted with hydrochloric acid (3 mL) to remove the dissolved zinc iodide, aqueous sodium bicarbonate (5 mL) and saturated aqueous sodium chloride. The combined ether extract was evaporated. The product was purified by flash chromatography to afford the compounds.

4.5. General procedure for the PMB deprotection

The PMB protected compound (9.23 mmol) was dissolved in 40.0 ml of DCM/phosphate buffer (pH = 7; 19:1) and the solution was cooled to 0 °C. Next, DDQ (2.51 g, 11.07 mmol) was added portion wise to the solution and the mixture was stirred at this temperature for 2 h. The reaction mixture was then filtered through a pad of Celite. The residue was then washed with 25 mL of DCM. The combined organic solution was washed successively with saturated aqueous $NaHCO_3$ solution, water and brine solution. The organic layer was then dried over anhydrous Na_2SO_4 and evaporated in vacuo. Purification by silica gel chromatography afforded the required alcohol.

4.6. General procedure for the TBS protection

To a stirred solution of alcohol (11.80 mmol) in dry DCM (30.0 ml) were added imidazole (2.0 g, 29.40 mmol) and *tert*-butyldimethylsilylchloride (2.1 g, 13.93 mmol) at room temperature and the mixture was stirred for 3 h. The solvent was removed and the residue partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated. The residue was purified by silica gel column chromatography to afford the TBS protected compound.

4.7. General procedure for the TBDMS/TBDPS deprotection

To an ice-cooled solution of the TBS protected compound (2.66 mmol) in dry THF (10.0 ml) was added a 1 M solution of TBAF (3.99 ml, 3.99 mmol) and stirred for 2 h at room temperature. After completion of the reaction, water was added to the reaction mixture and THF was removed under vacuum. The aqueous layer was then extracted with ethyl acetate and washed with saturated aqueous NH_4Cl, and brine, dried over anhydrous Na_2SO_4, and

concentrated in vacuum. The residue was purified by silica gel column chromatography to afford the alcohol.

4.8. General procedure for the Swern oxidation

Oxalyl chloride (1.16 ml, 13.26 mmol) was taken in DCM (32.0 ml) and the reaction vessel was kept at −78 °C. Dimethyl sulphoxide (DMSO, 1.88 ml, 26.52 mmol) was then added and the reaction mixture was kept at the same temperature for 25 min. The alcohol (2.02 g, 8.84 mmol) in DCM was then added and the mixture was kept for a further 45 min at the same temperature, after which triethyl amine (Et_3N 7.37 ml, 53.00 mmol) was added and the reaction mixture was gradually warmed to the room temperature for 1 h. The reaction was then quenched by adding water and extracted with DCM. The organic layer was washed successively with water, saturated aqueous $NaHCO_3$ solution and brine. The organic layer was dried (Na_2SO_4) and evaporated. The residue was purified by silica gel column chromatography to afford the aldehyde.

4.9. General procedure for enzymatic esterification

To a solution of diol (2.5 mmol) in 8 mL of vinyl acetate, 100 mg of lipase were added. The suspension was magnetically stirred at room temperature and the reaction course was followed by HPLC analysis. The reaction was interrupted by filtration of the enzyme and the filtrate was evaporated under reduced pressure. The residue was characterized by HPLC analysis.

4.10. General procedure for the OsO_4 oxidation

The compound (8.2 mmol) was dissolved in 32 ml of THF/H_2O (3:1) and the solution was cooled to 0 °C. To this solution, NMO (1.4 g, 12.3 mmol) and a 0.05 M solution of OsO_4 in toluene (16 mL, 0.82 mmol) were added consecutively and the reaction was protected from light by covering the reaction flask with black paper. The mixture was stirred for 12 h at the same temperature. The reaction was quenched by the addition of a saturated aq. Na_2SO_3 solution (8 mL) and then stirred for 1 h at room temperature. Next, 20 mL of water and 40 mL of EtOAc were added to this mixture and the organic layer was separated. The aqueous part was washed with EtOAc (2 × 50 mL). The combined organic layer was washed with brine solution (40 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The two diastereomeric diols were purified by flash column chromatography.

4.10.1. Diethyl 2-allyl-2-methylmalonate 1

To an ice-cooled solution of NaH (60% dispersion in mineral oil, 0.659 g, 16.48 mmol) in dry THF (32 mL), diethyl 2-methylmalonate (2.8 g, 16.08 mmol) in THF (16 mL) was added and the reaction mixture was kept at the same temperature for a further 45 min, after which allyl bromide (1.43 mL, 16.48 mmol) was added and the reaction mixture was stirred at reflux for 6 h. The reaction mixture was then cooled to room temperature and water was added carefully to the reaction mixture to quench any excess NaH, and the layers were separated and extracted with 400 mL of ether, washed with brine. It was then dried over anhydrous Na_2SO_4, and the solvent was removed in vacuum. The crude residue was purified by flash column chromatography (EtOAc/hexane, 1:40) to afford compound **1** (3.1 g) in 90% yield. R_f = 0.6 (EtOAc/hexane, 1:40). ^1H NMR (200 MHz, $CDCl_3$), δ_H: 5.70–5.63 (m, 1H), 5.14–5.06 (m, 2H), 4.18 (q, 4H, J = 7.1 Hz), 2.61 (d, 2H, J = 7.4 Hz), 1.39 (s, 3H), 1.24 (t, 6H, J = 7.1 Hz). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 171.7, 132.5, 118.9, 61.1, 53.3, 39.9, 19.5, 13.9. HRMS (ESI) for $C_{11}H_{18}O_4Na$ $[M+Na]^+$, calculated: 237.1103; found: 237.1109.

4.10.2. (*S*)-2-(Ethoxycarbonyl)-2-methylpent-4-enoic acid 2

To a suspension of diester **1** (0.025 g, 0.12 mmol) in a pH 8 phosphate buffer (3 mL) was added PLE (15 units), and the reaction mixture was stirred at 30 °C for 24 h. After diester **1** disappeared, 2 N HCl was added to the reaction mixture to make a pH 3 solution. The aqueous layers were extracted with EtOAc (1.5 mL × 3), dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash column chromatography (EtOAc/hexane, 1:2) to afford known compound **2** (0.02 g) in 90% yield.[19] R_f = 0.1 (EtOAc/hexane, 1:2).

4.10.3. 2-Allyl-2-methylpropane-1,3-diol 3

To a solution of LAH (2.7 g, 71.14 mmol,) in dry ether (150 mL) a solution of diethyl 2-allyl-2-methylmalonate (10 g, 46.67 mmol) in dry ether (100 mL) at 0 °C was added via a cannula. The reaction was then allowed to warm up to rt and stirred for 12 h. TLC analysis indicated the disappearance of the starting material and the reaction was quenched by the dropwise addition of a saturated Na_2SO_4 solution. The precipitated white aluminum salt was filtered off and the aluminum salt was washed thoroughly with ether (3 × 100 mL). The filtrate was washed with satd aq NaCl (50 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography (EtOAc/hexane, 1:3) to afford compound **3** (5.46 g) in 90% yield. R_f = 0.2 (EtOAc/hexane, 1:3). ^1H NMR (200 MHz, $CDCl_3$), δ_H: 5.92–5.71 (m, 1H), 5.11 (d, 1H, J = 1.4 Hz), 5.09–5.01 (m, 1H), 3.45 (s, 4H), 2.85 (br s, 2H), 2.08 (d, 2H, J = 7.6 Hz), 0.81 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 134.3, 118.0, 69.9, 39.4, 38.8, 18.6. HRMS (ESI) for $C_7H_{14}O_2Na$ $[M+Na]^+$, calculated: 153.0892; found: 153.0897.

4.10.4. (*S*)-2-(Hydroxymethyl)-2-methylpent-4-enyl acetate 4

Compound **4** was prepared according to the general procedure for the enzymatic esterification starting from compound **3** (0.5 g, 3.84 mmol). Purification by silica gel chromatography (EtOAc/hexane, 1:5) afforded compound **4** (0.595 g) in 90% yield. R_f = 0.3 (EtOAc/hexane, 1:5). ^1H NMR (400 MHz, $CDCl_3$), δ_H: 5.82–5.75 (m, 1H), 5.08–5.04 (m, 2H), 3.93 (t, 2H, J = 12 Hz), 3.27 (s, 2H), 2.30 (br s, 1H), 2.06 (s, 3H), 2.05–2.03 (m, 2H), 0.86 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 171.8, 133.5, 118.2, 68.0, 66.6, 39.1, 38.7, 20.8, 18.5. HRMS (ESI) for $C_9H_{16}O_3Na$ $[M+Na]^+$, calculated: 195.0997; found: 195.0999.

4.10.5. (*R*)-2-(Hydroxymethyl)-2-methylpent-4-enyl benzoate 5

At first, DCM (8 mL) was added to a mixture of the Pybox ligand (0.059 g, 0.1 mmol) and $CuCl_2$ (0.013 g, 0.1 mmol) at room temperature and then the mixture was stirred at that temperature for 4 h. To the generated catalyst solution, substrate **3** (0.13 g, 1.0 mmol) was added with DCM (3 mL) through a cannula at room temperature. After cooling the resulting solution to −78 °C, benzoyl chloride (174 μL, 1.5 mmol) and Et_3N (153 μL, 1.1 mmol) were added in sequence, and the monobenzoylation proceeded at −78 °C for 12 h. The reaction was then quenched with saturated aqueous NH_4Cl (5 mL) at −78 °C and then H_2O (2 mL) at room temperature. The mixture was extracted with DCM and organic layer was washed with brine and dried over anhydrous $MgSO_4$. The organic layer was concentrated in vacuo to afford the crude residue, which upon purification by silica gel chromatography (EtOAc/hexane, 1:5) afforded compound **5** (0.23 g) in 98% yield. R_f = 0.5 (EtOAc/hexane, 1:5). $[\alpha]_D^{28}$ = +5.2 (*c* 1.0, MeOH). ^1H NMR (200 MHz, $CDCl_3$), δ_H: 7.91 (d, 2H, J = 8.2 Hz), 7.42–7.25 (m, 3H), 5.79–5.69 (m, 1H), 5.49 (d, 2H, J = 13.2 Hz), 4.07 (m, 2H), 3.34 (s, 2H), 2.03 (d, 2H, J = 7.2 Hz), 0.85 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 166.9, 133.5, 133.0, 129.9, 129.5, 128.3, 118.2, 68.2, 66.5, 39.3, 38.8, 18.6. HRMS (ESI) for $C_{14}H_{18}O_3Na$ $[M+Na]^+$, calculated: 257.1154; found: 257.1159.

4.10.6. (*R*)-2-((4-Methoxybenzyloxy)methyl)-2-methylpent-4-enyl benzoate 6

A solution of 4-methoxybenzyl alcohol (2.2 g, 16.0 mmol) in 30 mL of ether was added to a suspension of 60% NaH (0.08 g, 2.0 mmol) in 10 mL of ether at room temperature. The resulting mixture was stirred at room temperature for 30 min and cooled to 0 °C. Trichloroacetonitrile (TCA;1.6 mL, 16.0 mmol) was then added and the reaction mixture was allowed to warm slowly to room temperature over 6 h. The solution was concentrated to an orange syrup, which was dissolved in anhydrous hexane (15 mL) containing a few drops of MeOH. This suspension was shaken vigorously and filtered through Celite, and the filtrate was concentrated to afford the crude imidate. The crude imidate was taken in cyclohexane (50 mL) and a solution of alcohol **5** (3.74 g, 16 mmol) in 30 mL of DCM was added. The resulting solution was cooled to 0 °C and CSA (0.37 g, 1.6 mmol) was added to it. The reaction mixture was stirred overnight at room temperature, and a white precipitate of trichloroacetamide slowly developed. The solution was filtered off, and washed with DCM. The filtrate was washed with saturated aqueous $NaHCO_3$ solution, water and brine. Purification by means of silica gel chromatography (EtOAc/hexane, 1:5) yielded compound **6** (5.0 g) in 88% yield. R_f = 0.4 (EtOAc/hexane, 1:5). $[\alpha]_D^{28}$ = +6.8 (*c* 0.8, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$), δ_H: 8.05–8.01 (m, 2H), 7.57–7.43 (m, 3H), 7.28 (d, 2H, *J* = 8.6 Hz), 6.87 (d, 2H, *J* = 8.6 Hz), 5.88–5.77 (m, 1H), 5.13 (d, 2H, *J* = 11.6 Hz), 4.19 (s, 2H), 4.27 (s, 2H), 3.80 (s, 3H), 3.37 (s, 2H), 2.25 (d, 2H, *J* = 7.4 Hz), 1.06 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 166.3, 158.9, 133.6, 132.8, 130.5, 130.3, 129.5, 129.0, 128.8, 128.3, 118.1, 113.6, 73.6, 72.8, 68.6, 55.1, 39.2, 38.5, 19.3. HRMS (ESI) for $C_{22}H_{26}O_4Na$ $[M+Na]^+$, calculated: 377.1729; found: 377.1730.

4.10.7. (*S*)-2-((4-Methoxybenzyloxy)methyl)-2-methylpent-4-en-1-ol 7

A solution of compound **6** (0.5 g, 1.41 mmol) in 5 mL of MeOH at 0 °C was treated with K_2CO_3 (0.0584 g, 0.42 mmol). The mixture was stirred at room temperature for 6 h. The mixture was then poured into 5 mL of saturated aqueous ammonium chloride solution and concentrated in vacuo. The mixture was extracted with ethyl acetate and the organic layer was washed with brine and dried over anhydrous $MgSO_4$. The organic layer was concentrated in vacuo to afford the crude residue, which upon purification by silica gel chromatography (EtOAc/hexane, 1:3) afforded compound **7** (0.317 g) in 90% yield. R_f = 0.2 (EtOAc/hexane, 1:3). $[\alpha]_D^{28}$ = −4.2 (*c* 1.0, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$), δ_H: 7.24 (d, 2H, *J* = 8.6 Hz), 6.88 (d, 2H, *J* = 8.6 Hz), 5.90–5.69 (m, 1H), 5.05 (d, 2H, *J* = 12.6 Hz), 4.43 (s, 2H), 3.80 (s, 3H), 3.48 (s, 2H), 3.32 (s, 2H), 2.13 (d, 2H, *J* = 7.4 Hz), 0.83 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 159.1, 134.2, 130.0, 129.0, 117.6, 113.7, 77.7, 73.1, 69.9, 55.1, 38.9, 38.8, 18.8. HRMS (ESI) for $C_{15}H_{22}O_3Na$ $[M+Na]^+$, calculated: 273.1467; found: 273.1469.

4.10.8. (*R*)-2-((4-Methoxybenzyloxy)methyl)-2-methylpent-4-enal 8 or (*S*)-2-((4-methoxybenzyloxy)methyl)-2-methylpent-4-enal 8

Compound **8** was prepared according to the general procedure for the Swern oxidation from compound **7** (1.26 g, 5.03 mmol). Purification by silica gel chromatography (EtOAc/hexane, 1:10) afforded aldehyde **7** (1.13 g) in 90% yield. R_f = 0.5 (EtOAc/hexane, 1:10). ^{1}H NMR (200 MHz, $CDCl_3$), δ_H: 9.61 (s, 1H), 7.26 (d, 2H, *J* = 8.8 Hz), 6.91 (d, 2H, *J* = 8.8 Hz), 5.83–5.66 (m, 1H), 5.15–5.08 (m, 2H), 4.46 (s, 2H), 3.82 (s, 3H), 3.48 (d, 2H, *J* = 4.4 Hz), 2.35 (d, 2H, *J* = 7.4 Hz), 1.09 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 205.1, 159.2, 132.7, 130.1, 129.1, 118.7, 113.8, 73.0, 72.9, 55.2, 50.1, 36.9, 16.4. HRMS (ESI) for $C_{15}H_{20}O_3Na$ $[M+Na]^+$, calculated: 271.1310; found: 271.1315.

4.10.9. (3*S*,4*R*)-4-((4-Methoxybenzyloxy)methyl)-4-methylhepta-1,6-dien-3-ol 9 and (3*R*,4*R*)-4-((4-methoxybenzyloxy)methyl)-4-methylhepta-1,6-dien-3-ol 10

Aldehyde **8** (2.0 g, 8.05 mmol) was taken in 16 ml of anhydrous THF. Next, a solution of vinylmagnesium bromide (1.0 M in THF, 8.85 mL, 8.85 mmol) was added at −78 °C. The reaction mixture was kept at the same temperature for 2 h, after which a saturated NH_4Cl solution was added. The solution was then extracted with EtOAc, and the organic layer was washed with water and brine. The organic layer was dried ($MgSO_4$) and evaporated to afford the crude alcohol. Purification of the crude product by silica gel chromatography (EtOAc/hexane, 1:8) afforded compound **9** and **10** as an inseparable diastereomeric mixture (1.82 g) in 82% yield. R_f = 0.3 (EtOAc/hexane, 1:8). ^{1}H NMR (200 MHz, $CDCl_3$), δ_H: 7.27 (d, 2H, *J* = 8.4 Hz), 6.96 (d, 2H, *J* = 8.4 Hz), 5.99–5.81 (m, 2H), 5.27–5.11 (m, 4H), 4.45 (s, 2H), 4.03–4.00 (m, 1H), 3.84 (s, 3H), 3.49–3.43 (m, 1H), 3.32–3.28 (m, 1H), 2.26 (d, 1H, *J* = 7.4 Hz), 2.05–2.01 (m, 1H), 0.93 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 159.4, 137.7, 137.3, 134.5, 129.9, 129.4, 118.1, 117.9, 116.6, 116.5, 113.9, 79.9, 79.0, 77.2, 76.8, 75.9, 73.4, 73.4, 60.5, 55.4, 41.1, 39.9, 37.1, 31.7, 22.8, 21.1, 19.3, 18.1, 14.3, 14.2.

4.10.10. (1*S*,5*R*)-5-((4-Methoxybenzyloxy)methyl)-5-methylcyclopent-2-enol 11 and (1*R*,5*R*)-5-((4-methoxybenzyloxy)methyl)-5-methylcyclopent-2-enol 12

The starting diastereomeric mixture **9** and **10** (1.82 g, 6.58 mmol) was taken in anhydrous degassed DCM (500 mL). A small amount of 1st generation Grubbs' catalyst was then added and the solution was stirred at reflux for 6 h. The reaction mixture was then cooled to room temperature and the solution was evaporated under reduced pressure. The contents of the flask were loaded directly onto a silica gel column. Two diastereomeric alcohols (compound **11** and compound **12** in 1:1 ratio) were purified by flash column chromatography (EtOAc/hexane, 1:5) to afford alcohol **11** (653.55, mg) in 40% yield and alcohol **12** (653.55 mg) in 40% yield. R_f of **11** = 0.4 (EtOAc/hexane, 1:5). $[\alpha]_D^{28}$ = +24.6 (*c* 0.5, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$), δ_H: 7.24 (d, 2H, *J* = 8.6 Hz), 6.87 (d, 2H, *J* = 8.6 Hz), 5.87–5.83 (m, 1H), 5.74 (td, 1H, *J* = 2.0, 4.0 Hz), 4.63 (s, 1H), 4.50 (s, 2H), 3.84 (s, 3H), 3.34 (d, 2H, *J* = 2.6 Hz), 2.24 (dd, 2H, *J* = 2.2, 4.0 Hz), 1.12 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 159.2, 132.6, 132.5, 130.7, 129.2, 113.9, 81.4, 77.8, 73.1, 55.4, 46.6, 42.7, 18.8. HRMS (ESI) for $C_{15}H_{20}O_3Na$ $[M+Na]^+$, calculated: 271.1310; found: 271.1313. R_f of **12** = 0.5 (EtOAc/hexane, 1:5). $[\alpha]_D^{28}$ = +73.2 (*c* 1.2, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$), δ_H: 7.24 (d, 2H, *J* = 8.6 Hz), 6.87 (d, 2H, *J* = 8.6 Hz), 5.87–5.71 (m, 2H), 4.45 (s, 2H), 4.37–4.34 (m, 1H), 3.79 (s, 3H), 3.48 (dd, 2H, *J* = 8.8, 16.4 Hz), 2.43 (dd, 1H, *J* = 2.1, 16.9 Hz), 1.94 (d, 1H, *J* = 17.0 Hz), 1.08 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 159.3, 133.4, 132.1, 130.2, 129.3, 113.9, 84.7, 75.1, 73.1, 55.2, 44.4, 42.7, 24.7. HRMS (ESI) for $C_{15}H_{20}O_3Na$ $[M+Na]^+$, calculated: 271.1310; found: 271.1312.

4.10.11. (1*S*,5*R*)-5-(Hydroxymethyl)-5-methylcyclopent-2-enol 13

Compound **13** was prepared according to the general procedure for the PMB deprotection from compound **11** (0.65 g, 2.61 mmol). Purification by silica gel chromatography (EtOAc/hexane, 1:5) afforded compound **13** (0.301 g) in 90% yield. R_f = 0.2 (EtOAc/hexane, 1:5). $[\alpha]_D^{28}$ = +48.8 (*c* 0.6, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$), δ_H: 5.86–5.81 (m, 1H), 5.69 (td, 1H, *J* = 1.8, 3.8 Hz), 4.57–4.50 (m, 1H), 3.47 (d, 2H, *J* = 2.2 Hz), 2.90 (br s, 2H), 2.16–2.12 (m, 2H), 1.06 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 133.0, 132.5, 80.8, 70.4, 47.3, 42.3, 18.1. HRMS (ESI) for $C_7H_{12}O_2Na$ $[M+Na]^+$, calculated: 151.0735; found: 151.0738.

4.10.12. (1*R*,5*R*)-5-(Hydroxymethyl)-5-methylcyclopent-2-enol 14

Compound **14** was prepared according to the general procedure for the PMB deprotection from compound **12** (0.65 g, 2.61 mmol). Purification by silica gel chromatography (EtOAc/hexane, 1:5) afforded compound **14** (0.301 g) in 90% yield. R_f = 0.3 (EtOAc/hexane, 1:5). $[\alpha]_D^{28}$ = +42.2 (*c* 0.8, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$), δ_H: 5.94–5.90 (m, 1H), 5.70 (dd, 1H, *J* = 2.2, 5.6 Hz), 4.39–4.30 (m, 1H), 3.62 (dd, 2H, *J* = 11.0, 18.8 Hz), 3.38 (br s, 2H), 2.43 (dd, 1H, *J* = 2.2, 17.2 Hz), 2.02–1.89 (m, 1H), 1.11 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 134.7, 131.7, 85.2, 68.2, 45.2, 41.9, 24.1. HRMS (ESI) for $C_7H_{12}O_2Na$ $[M+Na]^+$, calculated: 151.0735; found: 151.0737.

4.10.13. (4*S*,5*R*)-5-((4-methoxybenzyloxy)methyl)-5-methylocta-1,7-dien-4-ol 15 and (4*R*,5*R*)-5-((4-methoxybenzyloxy)methyl)-5-methylocta-1,7-dien-4-ol 16

Zn-dust (1.79 g, 27.4 mmol) followed by allyl bromide (2.2 ml, 26 mmol) were added to a cold (0 °C) and well-stirred solution of aldehyde **8** (3.4 g, 13.7 mmol), in tetrahydrofuran (5 ml) and then a saturated aqueous solution of NH_4Cl (3.0 ml) was added dropwise over a period of 30 min. The reaction mixture was then stirred at ambient temperature for 12 h until the aldehyde was totally consumed. The mixture was then filtered and the precipitate was washed thoroughly with ether. The combined filtrate was then diluted with water (10 ml) and extracted with ether (200 ml). The combined organic layer was washed successively with HCl (5%, 10 ml), water (20 ml) and brine (10 ml). The organic layer was dried ($MgSO_4$) and evaporated to afford the crude alcohol. Purification of the crude product by silica gel chromatography (EtOAc/hexane, 1:10) afforded compound **15** and **16** as an inseparable diastereomeric mixture (3.5 g) in 88% yield. R_f = 0.3 (EtOAc/hexane, 1:10). ^{1}H NMR (200 MHz, $CDCl_3$), δ_H: 7.23 (d, 2H, *J* = 8.4 Hz), 6.87 (d, 2H, *J* = 8.4 Hz), 5.99–5.75 (m, 2H), 5.13–5.02 (m, 4H), 4.41 (s, 2H), 3.78 (s, 3H), 3.54–3.40 (m, 2H), 3.38–3.21 (m, 1H), 2.37–2.03 (m, 4H), 0.87 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 159.2, 136.8, 134.5, 134.4, 130.0, 129.2, 117.7, 117.6, 116.4, 113.8, 77.8, 77.5, 76.4, 75.8, 73.2, 55.1, 41.1, 40.0, 37.0, 36.5, 36.3, 19.1, 17.9.

4.10.14. (1*S*,6*R*)-6-((4-Methoxybenzyloxy)methyl)-6-methylcyclohex-3-enol 17 and (1*R*,6*R*)-6-((4-methoxybenzyloxy)methyl)-6-methylcyclohex-3-enol 18

The starting diastereomeric mixture **15** and **16** (1.82 g, 6.26 mmol) was taken in anhydrous degassed DCM (500 mL). A small amount of 1st generation Grubbs' catalyst was then added to it and the solution was stirred at reflux for 8 h. The reaction mixture was then cooled to room temperature and the solution was evaporated under reduced pressure. The contents of the flask were directly loaded onto a silica gel column. Two diastereomeric alcohols (compound **17** and compound **18** in 1:1 ratio) were purified by flash column chromatography (EtOAc/hexane, 1:8) to afford alcohol **17** (0.656 g) in 40% yield and alcohol **18** (0.656 g) in 40% yield. R_f of **17** = 0.4 (EtOAc/hexane, 1:8). $[\alpha]_D^{28}$ = +22.8 (*c* 0.8, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$), δ_H: 7.22 (d, 2H, *J* = 8.2 Hz), 6.85 (d, 2H, *J* = 8.2 Hz), 5.65–5.54 (m, 2H), 4.42 (s, 2H), 3.77 (s, 3H), 3.69–3.60 (m, 1H), 3.53 (d, 1H, *J* = 8.8 Hz), 3.27 (d, 1H, *J* = 9.0 Hz), 2.33–2.02 (m, 3H), 1.72–1.64 (m, 1H), 0.89 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 159.2, 129.8, 129.1, 125.0, 123.5, 113.8, 77.6, 73.3 (2C), 55.1, 36.9, 32.5, 31.7, 21.5. HRMS (ESI) for $C_{16}H_{22}O_3Na$ $[M+Na]^+$, calculated: 285.1467; found: 285.1471. R_f of **18** = 0.5 (EtOAc/hexane, 1:8). $[\alpha]_D^{28}$ = +58.8 (*c* 1.1, MeOH). ^{1}H NMR (600 MHz, $CDCl_3$), δ_H: 7.26 (d, 2H, *J* = 9.0 Hz), 6.95 (d, 2H, *J* = 9.0 Hz), 5.58 (td, 1H, *J* = 0.8, 2.2 Hz), 5.57–5.51 (m, 1H), 4.49 (q, 2H, *J* = 12.8 Hz), 3.90–3.87 (m, 1H), 3.83 (s, 3H), 3.35 (s, 2H), 2.32 (dd, 1H, *J* = 1.2, 16.8 Hz), 2.30–2.06 (m, 1H), 1.93–1.90 (m, 1H), 1.74–1.70 (m, 1H), 0.99 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 159.2, 130.0, 129.1, 124.2, 113.8, 79.6, 73.2, 72.5, 55.2, 37.5, 34.7, 31.0, 15.0. HRMS (ESI) for $C_{16}H_{22}O_3Na$ $[M+Na]^+$, calculated: 285.1467; found: 285.1470.

4.10.15. (*S*)-2-((*tert*-Butyldiphenylsilyloxy)methyl)-2-methylpent-4-enyl benzoate 19

To a stirred solution of alcohol (*R*)-**5** (0.209 g, 0.89 mmol) in DCM (10 mL) were added imidazole (0.122 g, 1.78 mmol, 2.0 equiv) and TBDPSCl (0.278 mL, 1.07 mmol, 1.2 equiv) successively at room temperature. After the reaction was completed, saturated aqueous NH_4Cl (10 mL) was added to the reaction mixture, and the aqueous layers were extracted with DCM (8 mL × 3). The combined organic layers were washed with brine (5 mL × 1), dried (Na_2SO_4), filtered and concentrated under reduced pressure, which upon purification by silica gel chromatography (EtOAc/hexane, 1:20) afforded compound **19** (379.47 mg) in 90% yield. R_f = 0.4 (EtOAc/hexane, 1:20). $[\alpha]_D^{28}$ = +10.2 (*c* 0.5, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$), δ_H: 7.96 (d, 2H, *J* = 7.6 Hz), 7.65–7.59 (m, 4H), 7.58–7.56 (m, 1H), 7.45–7.39 (m, 4H), 7.31–7.26 (m, 4H), 5.86–7.75 (m, 1H), 5.07 (d, 2H, *J* = 13.2 Hz), 4.25 (s, 2H), 3.54 (s, 2H), 2.20 (d, 2H, *J* = 7.2 Hz), 1.05 (s, 9H), 0.99 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 166.6, 135.8, 135.8, 133.7, 133.5, 133.0, 130.5, 129.7, 128.5, 127.8, 118.4, 68.2, 67.4, 39.7, 39.1, 27.0, 19.5, 19.0. HRMS (ESI) for $C_{30}H_{36}O_3SiNa$ $[M+Na]^+$, calculated: 495.2332; found: 495.2336.

4.10.16. (*S*)-2-((*tert*-Butyldiphenylsilyloxy)methyl)-2-methylpent-4-en-1-ol 20

A solution of compound **19** (0.666 g, 1.41 mmol) in 6 mL of MeOH at 0 °C was treated with K_2CO_3 (0.116 g, 0.84 mmol). The mixture was stirred at room temperature for 6 h. The mixture was then poured into 6 mL of saturated aqueous ammonium chloride solution and concentrated in vacuo. The mixture was extracted with ethyl acetate and the organic layer was washed with brine and dried over anhydrous $MgSO_4$. The organic layer was concentrated in vacuo to afford the crude residue, which upon purification by silica gel chromatography (EtOAc/hexane, 1:20) afforded compound **20** (467.72 mg) in 90% yield. R_f = 0.3 (EtOAc/hexane, 1:20). $[\alpha]_D^{28}$ = +6.8 (*c* 0.3, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$), δ_H: 7.73–7.69 (m, 4H), 7.45–7.43 (m, 6H), 5.91–5.70 (m, 1H), 5.12–5.04 (m, 2H), 3.55–3.50 (m, 4H), 2.46 (br s, 1H), 2.26–2.06 (m, 2H), 1.12 (s, 9H), 0.85 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 135.9, 135.8, 134.4, 133.2, 130.0, 127.9, 117.8, 70.5, 69.5, 40.0, 38.7, 27.1, 19.4, 18.6. HRMS (ESI) for $C_{23}H_{32}O_2SiNa$ $[M+Na]^+$, calculated: 391.2070; found: 391.2074.

4.10.17. (*R*)-2-((4-Methoxybenzyloxy)methyl)-2-methylpent-4-en-1-ol 7

PMB protection of compound **20** (0.52 g, 1.41 mmol) according to the experimental procedure of compound **6** afforded a crude material (0.606 g, 1.24 mmol). The crude compound was used for the next step without further purification. Compound (*R*)-**6** was prepared according to the general procedure for the TBDPS deprotection starting from crude compound (0.606 g, 1.24 mmol). Purification by silica gel chromatography (EtOAc/hexane, 1:3) afforded (*R*)-**7** (0.28 g) in 79% yield for two steps. R_f = 0.2 (EtOAc/hexane, 1:3). $[\alpha]_D^{28}$ = +4.6 (*c* 1.0, MeOH). ^{1}H NMR, ^{13}C NMR and HRMS (ESI) for (*R*)-**6** were identical as for (*S*)-**7**.

4.10.18. (1*R*,2*R*,3*R*,5*S*)-3-((4-Methoxybenzyloxy)methyl)-3-methyl-6-oxabicyclo[3.1.0]hexan-2-ol 21

Compound **21** was prepared according to the general procedure for the substrate directed epoxidation with *m*CPBA from compound **11** (0.4 g, 1.61 mmol). Purification by silica gel chromatography (EtOAc/hexane, 1:3) afforded epoxide **21** (0.382 g) in 90% yield. R_f = 0.3 (EtOAc/hexane, 1:3). $[\alpha]_D^{28}$ = −23.9 (*c* 0.5, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$), δ_H: 7.27 (d, 2H, *J* = 8.6 Hz), 6.91 (d, 2H,

J = 8.6 Hz), 4.47 (s, 2H), 4.24–4.21 (m, 1H), 3.85 (s, 3H), 3.58–3.52 (m, 1H), 3.48–3.40 (m, 1H), 3.24 (d, 1H, J = 8.6, Hz), 3.13 (d, 1H, J = 8.6, Hz), 1.91 (d, 2H, J = 5.2 Hz), 1.05 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 159.2, 130.4, 129.2, 113.8, 77.1, 76.7, 72.9, 60.8, 55.3, 55.1, 41.2, 36.7, 21.1. HRMS (ESI) for $C_{15}H_{20}O_4Na$ $[M+Na]^+$, calculated: 287.1260; found: 287.1265.

4.10.19. (1*S*,2*R*,3*R*,4*R*)-4-((4-Methoxybenzyloxy)methyl)-4-methylcyclopentane-1,2,3-triol 22

Compound **22** was prepared according to the general procedure for the acid induced epoxide ring opening from compound **21** (0.382 g, 1.45 mmol). Purification by silica gel chromatography (EtOAc/hexane, 1:1) afforded triol **22** (0.360 g) in 88% yield. R_f = 0.3 (EtOAc/hexane, 1:1). $[\alpha]_D^{28}$ = +16.8 (c 1.0, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$), δ_H: 7.27 (d, 2H, J = 8.6 Hz), 6.91 (d, 2H, J = 8.6 Hz), 4.51 (s, 2H), 4.20–4.14 (m, 1H), 4.00 (dd, 2H, J = 2.1, 5.1 Hz), 3.84 (s, 3H), 3.36 (d, 1H, J = 8.4 Hz) 3.21 (d, 1H, J = 8.4 Hz), 2.48 (br s, 3H), 2.10–2.03 (m, 1H), 1.72–1.63 (m, 1H), 1.03 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 159.3, 129.8, 129.4, 113.9, 79.4, 77.6, 75.2, 74.9, 73.2, 55.3, 43.3, 41.4, 20.2. HRMS (ESI) for $C_{15}H_{22}O_5Na$ $[M+Na]^+$, calculated: 305.1365; found: 305.1369.

4.10.20. (1*S*,2*R*,3*R*,4*R*)-4-(Acetoxymethyl)-4-methylcyclopentane-1,2,3-triyl triacetate 23

Compound **23** (0.280 g) was prepared from compound **22** (0.300 g, 1.06 mmol) in 80% yield, according to the general procedure for the PMB deprotection followed by esterification of crude material as described in experimental part of compound **38**. ^{1}H NMR (200 MHz, $CDCl_3$), δ_H: 5.37–5.22 (m, 3H), 4.14 (d, 1H, J = 10.8 Hz), 3.97 (d, 1H, J = 10.8 Hz), 2.14 (s, 12H), 1.96 (d, 2H, J = 4.6 Hz), 1.06 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 171.1, 170.4, 170.3, 170.2, 77.1, 75.6, 70.2, 69.6, 40.4, 38.6, 21.1, 21.0, 20.8, 20.4. HRMS (ESI) for $C_{15}H_{22}O_8Na$ $[M+Na]^+$, calculated: 353.1213; found: 353.1218.

4.10.21. (1*R*,2*R*,3*R*,4*R*)-4-((4-Methoxybenzyloxy)methyl)-4-methylcyclopentane-1,2,3-triol 24 and (1*S*,2*S*,3*R*,4*R*)-4-((4-methoxybenzyloxy)methyl)-4-methylcyclopentane-1,2,3-triol 25

Compound **24** and **25** were prepared according to the general procedure for the OsO_4 oxidation from compound **11** (0.5 g, 2.01 mmol). Two diastereomeric diols (compound **24** and compound **25** in 3:2 ratio) were purified by flash column chromatography (EtOAc/hexane, 2:1) to afford diol **24** (0.255 g) in 45% yield and diol **25** (0.170 g) in 30% yield. R_f of **24** = 0.2 (EtOAc/hexane, 2:1). $[\alpha]_D^{28}$ = +38.8 (c 1.2, MeOH). ^{1}H NMR of **21** (200 MHz, $CDCl_3$), δ_H: 7.24 (d, 2H, J = 8.4 Hz), 6.88 (d, 2H, J = 8.4 Hz), 4.48 (s, 2H), 4.02–3.90 (m, 2H), 3.81 (s, 4H), 3.35 (d, 1H, J = 8.4 Hz), 3.19 (d, 1H, J = 8.4 Hz), 2.57 (br s, 3H), 1.80–1.78 (m, 2H), 0.96 (s, 3H). ^{13}C NMR of **24** (50 MHz, $CDCl_3$), δ_C: 159.2, 129.9, 129.3, 113.8, 79.1, 78.5, 78.0, 73.1, 69.1, 55.2, 41.0, 40.8, 20.0. HRMS (ESI) for $C_{15}H_{22}O_5Na$ $[M+Na]^+$, calculated: 305.1365; found: 305.1368. R_f of **25** = 0.3 (EtOAc/hexane, 2:1). $[\alpha]_D^{28}$ = −12.8 (c 0.5, MeOH). ^{1}H NMR of **25** (200 MHz, $CDCl_3$), δ_H: 7.21 (d, 2H, J = 8.6 Hz), 6.87 (d, 2H, J = 8.6 Hz), 4.41 (s, 2H), 4.14–4.01 (m, 2H), 3.80 (s, 4H), 3.13 (d, 1H, J = 8.8, Hz), 3.08 (d, 1H, J = 8.8 Hz), 2.93 (br s, 3H), 2.06–1.91 (m, 1H), 1.58 (dd, 1H, J = 3.5, 14.3 Hz), 1.10 (s, 3H). ^{13}C NMR of **25** (50 MHz, $CDCl_3$), δ_C: 159.3, 130.5, 129.2, 113.9, 78.2, 77.8, 74.7, 73.5, 73.1, 55.4, 44.3, 41.9, 20.8. HRMS (ESI) for $C_{15}H_{22}O_5Na$ $[M+Na]^+$, calculated: 305.1365; found: 305.1370.

4.10.22. *tert*-Butyl((1*S*,5*R*)-5-((4-methoxybenzyloxy)methyl)-5-methylcyclopent-2-enyloxy)dimethylsilane 26

Compound **26** was prepared according to the general procedure for the TBS protection from compound **11** (0.4 g, 1.61 mmol). Purification by silica gel chromatography (EtOAc/hexane, 1:20) afforded **26** (0.554 g) in 95% yield. R_f = 0.5 (EtOAc/hexane, 1:20). $[\alpha]_D^{28}$ = +55.4 (c 0.8, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$), δ_H: 7.28 (d, 2H, J = 8.4 Hz), 6.89 (d, 2H, J = 8.4 Hz), 5.79–5.76 (m, 1H), 5.95–5.57 (m, 1H), 4.63 (s, 1H), 4.47 (s, 2H), 3.82 (s, 3H), 3.25 (dd, 2H, J = 8.8, 12.8 Hz), 2.40–2.05 (m, 2H), 1.02 (s, 3H), 0.91 (s, 9H), 0.06 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 159.2, 133.1, 131.6, 131.0, 129.2, 113.8, 80.2, 76.7, 73.0, 55.4, 46.9, 42.4, 26.1, 19.4, 18.4, −4.3, −4.6. HRMS (ESI) for $C_{21}H_{34}O_3SiNa$ $[M+Na]^+$, calculated: 385.2175; found: 385.2179.

4.10.23. (1*R*,2*R*,3*R*,4*R*)-3-(*tert*-Butyldimethylsilyloxy)-4-((4-methoxybenzyloxy)methyl)-4-methylcyclopentane-1,2-diol 27 and (1*S*,2*S*,3*R*,4*R*)-3-(*tert*-butyldimethylsilyloxy)-4-((4-methoxybenzyloxy)methyl)-4-methylcyclopentane-1,2-diol 28

Compounds **27** and **28** were prepared according to the general procedure for the OsO_4 oxidation from compound **26** (0.8 g, 2.20 mmol). Two diastereomeric diols (compound **24** and compound **25** in 3:1 ratio) were purified by flash column chromatography (EtOAc/hexane, 1:5) to afford diol **27** (0.509 g) in 58.5% yield and diol **28** (0.170 g) 19.5% yield. R_f of **27** = 0.2 (EtOAc/hexane, 1:5). $[\alpha]_D^{28}$ = +10.8 (c 1.1, MeOH). ^{1}H NMR of **27** (200 MHz, $CDCl_3$), δ_H: 7.22 (d, 2H, J = 8.6 Hz), 6.88 (d, 2H, J = 8.6 Hz), 4.52 (s, 2H), 4.02–4.00 (m, 2H), 3.95–3.88 (m, 1H), 3.81 (s, 3H), 3.12 (dd, 2H, J = 8.6, 14.5 Hz), 2.73 (d, 1H, J = 5.0 Hz), 2.50 (d, 1H, J = 9.6 Hz), 1.03 (s, 3H), 0.92 (s, 9H), 0.06 (s, 6H). ^{13}C NMR of **27** (50 MHz, $CDCl_3$), δ_C: 159.3, 130.5, 129.2, 113.9, 77.4, 76.6, 74.2, 73.0, 72.8, 55.4, 44.6, 42.9, 26.0, 21.6, 18.3, −4.6. HRMS (ESI) for $C_{21}H_{36}O_5SiNa$ $[M+Na]^+$, calculated: 419.2230; found: 419.2235. R_f of **28** = 0.3 (EtOAc/hexane, 1:5). $[\alpha]_D^{28}$ = +38.8 (c 1.2, MeOH). ^{1}H NMR of **28** (200 MHz, $CDCl_3$), δ_H: 7.25 (d, 2H, J = 8.6 Hz), 6.89 (d, 2H, J = 8.6 Hz), 4.50 (s, 2H), 3.93–3.88 (m, 2H), 3.81 (s, 3H), 3.27–3.20 (m, 2H), 3.19 (d, 1H, J = 8.4 Hz), 1.85–1.81 (m, 2H), 0.88 (s, 9H), 0.86 (s, 3H), 0.09 (s, 6H). ^{13}C NMR of **28** (50 MHz, $CDCl_3$), δ_C: 159.7, 129.8, 129.4, 114.1, 80.7, 79.8, 76.8, 73.4, 70.5, 55.4, 42.5, 41.4, 26.0, 21.0, 18.3, −4.0, −4.7. HRMS (ESI) for $C_{21}H_{36}O_5SiNa$ $[M+Na]^+$, calculated: 419.2230; found: 419.2234.

4.10.24. *tert*-Butyl((3a*R*,4*R*,5*R*,6a*R*)-5-((4-methoxybenzyloxy)methyl)-2,2,5-trimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yloxy)dimethylsilane 29

Compound **27** (1.96 g, 4.94 mmol) was taken in 24 mL of dry DCM. 2,2-Dimethoxypropane (DMP, 1.85 mL, 14.82 mmol) was then added to it followed by addition of a catalytic amount of CSA (0.151 g, 0.5 mmol,). The reaction mixture was then stirred at room temperature for 6 h. After completion of the reaction, water was added to the reaction mixture, after which it was extracted with DCM and washed with brine. The organic layer was dried over Na_2SO_4 and evaporated to dryness. The product was purified by silica gel column chromatography (EtOAc/hexane, 1:20) to afford compound **29** (1.98 g) in 92% yield. R_f = 0.4 (EtOAc/hexane, 1:20). $[\alpha]_D^{28}$ = +22.6 (c 0.8, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$), δ_H: 7.21 (d, 2H, J = 6.4 Hz), 6.87 (d, 2H, J = 6.4 Hz), 4.66 (td, 1H, J = 4.4, 6.8 Hz), 4.48 (s, 2H), 4.36 (dd, 1H, J = 3.9, 7.1 Hz), 3.98 (d, 1H, 4 Hz), 3.81 (s, 3H), 3.24 (s, 2H), 1.88 (d, 2H, J = 4.4 Hz), 1.45 (s, 3H), 1.28 (s, 3H), 0.94 (s, 3H), 0.89 (s, 9H), 0.11 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 159.1, 131.1, 129.1, 113.8, 111.6, 87.7, 79.8, 78.1, 74.9, 72.9, 55.4, 48.5, 39.4, 27.1, 26.0, 24.7, 19.1, 18.2, −4.2, −4.9. HRMS (ESI) for $C_{24}H_{40}O_5SiNa$ $[M+Na]^+$, calculated: 459.2543; found: 459.2548.

4.10.25. ((3a*R*,4*R*,5*R*,6a*R*)-4-(*tert*-Butyldimethylsilyloxy)-2,2,5-trimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-5-yl)methanol 30

Compound **30** was prepared according to the general procedure for the PMB deprotection from compound **29** (1.98 g, 4.54 mmol).

Purification by silica gel chromatography (EtOAc/hexane, 1:10) afforded compound **30** (1.26 g) in 88% yield as a colorless oil. R_f = 0.2 (EtOAc/ hexane, 1:10). $[\alpha]_D^{28}$ = +44.2 (*c* 0.8, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$), δ_H: 4.69–4.61 (m, 1H), 4.34 (dd, 1H, *J* = 3.6, 7.0 Hz), 3.87 (d, 1H, *J* = 3.6 Hz), 3.45 (s, 2H), 2.14 (br s, 1H), 1.79–1.75 (m, 2H), 1.46 (s, 3H), 1.26 (s, 3H), 0.92 (s, 3H), 0.88 (s, 9H), 0.10 (s, 3H), 0.06 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 111.6, 87.6, 80.4, 78.2, 68.4, 49.2, 38.8, 26.9, 25.9, 24.5, 18.8, 18.1, −4.2, −5.0. HRMS (ESI) for $C_{16}H_{32}O_4SiNa$ $[M+Na]^+$, calculated: 339.1968; found: 339.1966.

4.10.26. (3a*R*,4*R*,5*S*,6a*R*)-4-(*tert*-Butyldimethylsilyloxy)-2,2,5-trimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxole-5-carbaldehyde 31

Compound **31** was prepared according to the general procedure for the Swern oxidation from compound **30** (1.26 g, 3.99 mmol). Purification by silica gel chromatography (EtOAc/hexane, 1:20) afforded aldehyde **31** (1.13 g) in 90% yield. R_f = 0.5 (EtOAc/hexane, 1:20). ^{1}H NMR (200 MHz, $CDCl_3$), δ_H: 9.62 (s, 1H), 4.69 (t, 1H, *J* = 5.7 Hz), 4.32–4.30 (m, 2H), 2.30 (d, 1H, *J* = 14.4 Hz), 1.86 (dd, 1H, *J* = 5.6, 14.4 Hz), 1.34 (s, 3H), 1.24 (s, 3H), 1.04 (s, 3H), 1.03 (s, 9H), 0.13 (s, 3H), 0.09 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 203.8, 110.7, 87.3, 79.5, 79.2, 58.3, 38.8, 25.9, 25.4, 23.9, 18.2, 16.5, −4.4, −4.8. HRMS (ESI) for $C_{16}H_{30}O_4SiNa$ $[M+Na]^+$, calculated: 337.1811; found: 337.1815.

4.10.27. *tert*-Butyldimethyl((3a*R*,4*R*,5*R*,6a*R*)-2,2,5-trimethyl-5-vinyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yloxy)silane 32

To a suspension of methyltriphenylphosphonium iodide (0.646 g, 1.60 mmol) in dry THF (5 mL) was added LiHMDS (1.0 M solution in THF, 1.60 mL) at 0 °C. The yellow mixture was stirred at 0 °C for 15 min. A solution of aldehyde **31** (0.251 g, 0.80 mmol) in 2 mL of THF was added to the reaction mixture. The yellow suspension was stirred at room temperature for a further 4 h. The reaction was then quenched by the addition of water, and the layers were separated and extracted with 25 mL of ether, and washed with brine. It was then dried over anhydrous Na_2SO_4, and concentrated under vacuum. The crude residue was purified by flash column chromatography (EtOAc/hexane, 1:35) to afford compound **32** (0.185 g) in 74% yield. R_f = 0.5 (EtOAc/hexane, 1:35). $[\alpha]_D^{28}$ = +8.7 (*c* 0.4, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$), δ_H: 5.89 (dd, 1H, *J* = 10.6, 17.6 Hz), 5.01–4.93 (m, 2H), 4.67 (td, 1H, *J* = 4.8, 7.0 Hz), 4.35 (dd, 1H, *J* = 4.3, 7.0 Hz), 3.86 (d, 1H, *J* = 4.3 Hz), 2.00–1.90 (m, 1H), 1.84–1.77 (m, 1H), 1.47 (s, 3H), 1.27 (s, 3H), 0.99 (s, 3H), 0.89 (s, 9H), 0.10 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 145.7, 112.1, 112.1, 87.2, 83.9, 77.9, 49.9, 42.2, 27.1, 26.0, 24.8, 20.0, 18.2, −4.2, −4.7. HRMS (ESI) for $C_{17}H_{32}O_3SiNa$ $[M+Na]^+$, calculated: 335.2019; found: 335.2023.

4.10.28. (3a*S*,4*R*,5*R*,6a*R*)-2,2,5-Trimethyl-5-vinyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-ol 33

Compound **33** was prepared according to the general procedure for the TBS deprotection from compound **32** (0.185 g, 0.59 mmol). Purification by silica gel chromatography (EtOAc/hexane, 1:20) afforded alcohol **33** (0.102 g) in 88% yield. R_f = 0.3 (EtOAc/hexane, 1:20). $[\alpha]_D^{28}$ = +20.2 (*c* 0.9, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$), δ_H: 5.88 (dd, 1H, *J* = 10.5, 17.7 Hz), 5.02–4.97 (m, 2H), 4.68 (td, 1H, *J* = 5.4, 7.1 Hz), 4.45 (dd, 1H, *J* = 4.8, 7.1 Hz), 3.85 (d, 1H, *J* = 4.8 Hz), 2.71 (br s, 1H), 2.04–1.97 (m, 1H), 1.93–1.80 (m, 1H), 1.47 (s, 3H), 1.27 (s, 3H), 1.01 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 145.1, 112.8, 112.7, 86.4, 83.1, 77.4, 49.5, 42.5, 27.0, 24.6, 19.1. HRMS (ESI) for $C_{11}H_{18}O_3Na$ $[M+Na]^+$, calculated: 221.1154; found: 221.1159.

4.10.29. (3a*R*,4*R*,5*R*,6a*R*)-4-(Allyloxy)-2,2,5-trimethyl-5-vinyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxole 34

To an ice-cooled solution of NaH (60% dispersion in mineral oil, 0.16 g, 4.02 mmol) in dry THF (8 mL), alcohol **33** (0.4 g, 2.01 mmol) in THF (2 mL) was added and the reaction mixture was kept for a further 45 min at the same temperature, after which allyl bromide (0.35 mL, 4.02 mmol) was added and the reaction mixture was stirred at room temperature for further 8 h. Water was then added carefully to the reaction mixture to quench any excess NaH. The layers were separated and extracted with 50 mL of ether, and then washed with brine. It was then dried over anhydrous $MgSO_4$, and the solvent was removed in vacuum. The crude residue was purified by flash column chromatography (EtOAc/hexane, 1:40) to afford compound **34** (0.373 g) in 78% yield. R_f = 0.4 (EtOAc/hexane, 1:40). $[\alpha]_D^{28}$ = −12.6 (*c* 1.1, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$), δ_H: 5.94–5.80 (m, 2H), 5.29–5.14 (m, 2H), 4.98–4.92 (m, 2H), 4.67 (dd, 1H, *J* = 7.1, 12.9 Hz), 4.48 (dd, 1H, *J* = 4.4, 7.1 Hz), 4.18–4.11 (m, 1H), 4.10–4.00 (m, 1H), 3.59 (d, 1H, *J* = 4.4 Hz), 1.94 (dd, 1H, *J* = 7.0, 13.2 Hz), 1.80 (dd, 1H, *J* = 7.0, 13.0 Hz), 1.46 (s, 3H), 1.27 (s, 3H), 1.03 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 145.5, 134.8, 116.6, 112.6, 112.0, 89.7, 85.2, 77.6, 70.9, 49.3, 42.9, 27.0, 24.7, 20.0. HRMS (ESI) for $C_{14}H_{22}O_3Na$ $[M+Na]^+$, calculated: 261.1467; found: 261.1471.

4.10.30. (3a*R*,3b*R*,7a*R*,8a*R*)-2,2,7a-Trimethyl-3a,3b,5,7a,8,8a-hexahydro-[1,3]dioxolo[4′,5′:4,5]cyclopenta[1,2-*b*]pyran 35

Starting compound **34** (0.050 g, 0.21 mmol) was taken in anhydrous degassed DCM (30 mL). Grubbs second generation metathesis catalyst (G-II, 7 mg, 0.008 mmol) was then added and the solution was stirred at reflux for 8 h. The reaction mixture was then cooled to room temperature and the solution was evaporated under reduced pressure, after which the contents of the flask were directly loaded onto a silica gel column. The crude material was then purified by silica gel column chromatography (EtOAc/hexane, 1:20) to afford product **35** (0.035 g) in 80% yield as a liquid. R_f = 0.3 (EtOAc/hexane, 1:20). ^{1}H NMR (400 MHz, $CDCl_3$), δ_H: 5.92 (dt, 1H, *J* = 2.2, 10.0 Hz), 5.44 (dt, 1H, *J* = 2.4, 10.0 Hz), 4.74 (td, 1H, *J* = 5.6, 7.2 Hz), 4.41 (t, 1H, *J* = 7.8 Hz), 4.34 (dd, 2H, *J* = 2.4, 4.8 Hz), 3.56 (d, 1H, *J* = 8.0 Hz), 2.06 (dd, 1H, *J* = 7.4, 12.6 Hz), 1.54–1.53 (m, 1H), 1.51 (s, 3H), 1.31 (s, 3H), 0.95 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 134.6, 124.8, 113.7, 86.5, 80.3, 77.7, 68.2, 41.8, 38.2, 27.4, 24.7, 21.8. HRMS (ESI) for $C_{12}H_{18}O_3Na$ $[M+Na]^+$, calculated: 233.1154; found: 233.1152.

4.10.31. (3a*R*,3b*R*,6*R*,7*S*,7a*R*,8a*R*)-2,2,7a-Trimethyloctahydro-[1,3]dioxolo[4′,5′:4,5]cyclopenta[1,2-*b*]pyran-6,7-diol 36

Compound **36** was prepared according to the general procedure for the OsO_4 oxidation from compound **35** (0.140 g, 0.66 mmol). Purification by silica gel chromatography (EtOAc/hexane, 1:1) afforded diol **36** (0.132 g) as the sole product in 82% yield. R_f = 0.2 (EtOAc/hexane, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$), δ_H: 4.78 (dd, 1H, *J* = 7.4, 13.0 Hz), 4.41 (t, 1H, *J* = 7.4 Hz), 4.14 (dd, 1H, *J* = 7.2, 14.4 Hz), 4.00–3.86 (m, 1H), 3.87 (dd, 1H, *J* = 6.0, 10.8 Hz), 3.77–3.71 (m, 1H), 3.46 (t, 1H, *J* = 10.8 Hz), 2.48 (br s, 1H), 2.21 (br s, 1H), 1.93–1.90 (m, 2H), 1.53 (s, 3H), 1.30 (s, 3H), 0.97 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 114.0, 81.9, 80.2, 78.0, 73.0, 68.3, 64.1, 46.8, 35.5, 27.4, 24.9, 18.7. HRMS (ESI) for $C_{12}H_{20}O_5Na$ $[M+Na]^+$, calculated: 267.1209; found: 267.1212.

4.10.32. (3*R*,4*S*,4a*R*,6*R*,7*R*,7a*R*)-4a-Methyloctahydrocyclopenta[*b*]pyran-3,4,6,7-tetraol 37

To a stirred solution of alcohol **36** (0.22 g, 0.09 mmol) in anhydrous DCM (2 mL) was added *p*-toluenesulfonic acid monohydrate (0.034 g, 0.18 mmol) at room temperature and stirred for 6 h. After completion of the reaction, 20 mg of solid $NaHCO_3$ were added to

the reaction mixture and the solvent was evaporated in vacuo to afford compound **37** (0.016 g) in 90% yield, which was used for the next step without further purification. R_f = 0.3 (MeOH/$CHCl_3$, 1:3).

4.10.33. (3*R*,4*S*,4a*S*,6*R*,7*R*,7a*R*)-4a-Methyloctahydrocyclopenta[*b*]pyran-3,4,6,7-tetrayl tetraacetate 38

A solution of tetraol **37** (0.050 g, 0.24 mmol) in triethylamine (0.33 mL, 2.4 mmol), at 0 °C was treated with 4-dimethylaminopyridine (0.013 g, 0.11 mmol), and acetic anhydride (0.12 mL, 1.3 mmol). The mixture was stirred at room temperature for 12 h, and then treated with saturated aqueous $NaHCO_3$ solution (2 mL), and extracted with DCM (2 × 10 mL). The combined organic phases were washed with brine (2 mL), dried (Na_2SO_4), and concentrated. The crude residue was purified by flash column chromatography (EtOAc/hexane, 1:5) to afford compound **38** (0.084 g) in 95% yield. R_f = 0.3 (EtOAc/hexane, 1:5). $[\alpha]_D^{28}$ = +78.2 (*c* 1.2, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$), δ_H: 5.37 (dd, 1H, *J* = 8.0, 14.4 Hz), 5.29–5.22 (m, 2H), 5.06 (dd, 1H, *J* = 8.0, 10.4 Hz), 3.95 (dd, 2H, *J* = 5.6, 10.4 Hz), 3.60 (t, 1H, *J* = 10.8 Hz), 2.17 (s, 3H), 2.09 (s, 3H), 2.09 (s, 3H), 2.07 (s, 3H), 1.59–1.50 (m, 1H), 1.48–1.46 (m, 1H), 1.16 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 170.2, 169.9, 169.7, 79.2, 71.6, 71.4, 67.8, 65.7, 64.9, 39.5, 35.9, 20.9, 20.8, 20.6, 18.7. HRMS (ESI) for $C_{17}H_{24}O_9Na$ $[M+Na]^+$, calculated: 395.1318; found: 395.1320.

4.10.34. (1*S*,2*S*,3*R*,5*S*)-3-((4-Methoxybenzyloxy)methyl)-3-methylbicyclo[3.1.0]hexan-2-ol 39

Compound **39** was prepared according to the general procedure for the cyclopropanation reaction from compound **11** (0.450 g, 1.8 mmol). Purification by silica gel chromatography (EtOAc/hexane, 1:5) afforded **39** (0.354 g) in 75% yield. R_f = 0.4 (EtOAc/hexane, 1:5). $[\alpha]_D^{28}$ = −23.8 (*c* 0.4, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$), δ_H: 7.24 (d, 2H, *J* = 8.8 Hz), 6.88 (d, 2H, *J* = 8.4 Hz), 4.44 (s, 2H), 4.38 (d, 1H, *J* = 5.2 Hz), 3.80 (s, 3H), 3.11 (d, 2H, *J* = 4.4 Hz), 1.86 (dd, 1H, *J* = 5.8, 13.4 Hz), 1.58–1.50 (m, 2H), 1.25–1.23 (m, 1H), 1.08 (s, 3H). 0.65 (t, 1H, *J* = 4.2 Hz), 0.49–0.47 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 158.7, 130.3, 128.8, 113.4, 78.9, 77.8, 72.5, 54.8, 45.5, 38.2, 24.9, 21.0, 15.4, 9.4. HRMS (ESI) for $C_{16}H_{22}O_3Na$ $[M+Na]^+$, calculated: 285.1467; found: 285.1470.

4.10.35. *tert*-Butyl((1*S*,2*S*,3*R*,5*S*)-3-((4-methoxybenzyloxy)methyl)-3-methylbicyclo[3.1.0]hexan-2-yloxy)dimethylsilane 40

Compound **40** was prepared according to the general procedure for the TBS protection from compound **39** (0.9 g, 3.43 mmol). Purification by silica gel chromatography (EtOAc/hexane, 1:40) afforded **40** (1.16 g) in 90% yield. R_f = 0.4 (EtOAc/hexane, 1:40). $[\alpha]_D^{28}$ = −32.6 (*c* 1.0, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$), δ_H: 7.25 (d, 2H, *J* = 8.8 Hz), 6.87 (d, 2H, *J* = 8.6 Hz), 4.44 (s, 2H), 4.27 (d, 1H, *J* = 5.4 Hz), 3.80 (s, 3H), 3.17 (s, 2H), 1.94 (dd, 1H, *J* = 6.2, 13.2 Hz), 1.49–1.40 (m, 2H), 1.29–1.23 (m, 1H), .097 (s, 9H), 0.90 (s, 3H), 0.66 (dd, 1H, *J* = 4.1, 8.3 Hz), 0.48 (td, 1H, *J* = 4.6, 8.4 Hz), 0.06 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 159.1, 131.1, 129.1, 113.8, 77.9, 76.5, 73.0, 55.3, 49.6, 38.2, 26.2, 26.1, 21.0, 18.4, 17.2, 11.4, −4.2, −4.8. HRMS (ESI) for $C_{22}H_{36}O_3SiNa$ $[M+Na]^+$, calculated: 399.2332; found: 399.2338.

4.10.36. ((1*S*,2*S*,3*R*,5*S*)-2-(*tert*-Butyldimethylsilyloxy)-3-methylbicyclo[3.1.0]hexan-3-yl)methanol 41

Compound **41** was prepared according to the general procedure for the PMB deprotection from compound **40** (1.16 g, 3.08 mmol). Purification by silica gel chromatography (EtOAc/hexane, 1:20) afforded compound **41** (695.1 mg) in 88% yield as a colorless oil. R_f = 0.3 (EtOAc/hexane, 1:20). $[\alpha]_D^{28}$ = −22.8 (*c* 0.5, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$), δ_H: 4.23 (d, 1H, *J* = 5.4 Hz), 3.34–3.33 (m, 2H), 1.81 (dd, 1H, *J* = 6.2, 13.4 Hz), 1.56–1.50 (m, 2H), 1.20 (dd, 1H, *J* = 4.2, 6.2 Hz), 0.90 (s, 9H), 0.87 (s, 3H), 0.70 (dd, 1H, *J* = 4.1, 8.5 Hz), 0.53 (dd, 1H, *J* = 4.7, 8.1 Hz), 0.09 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 77.2, 71.4, 50.3, 37.8, 26.2, 26.0, 20.1, 18.3, 17.2, 11.6, −4.1, −4.8. HRMS (ESI) for $C_{14}H_{28}O_2SiNa$ $[M+Na]^+$, calculated: 279.1757; found: 279.1760.

4.10.37. (1*S*,2*S*,3*S*,5*S*)-2-(*tert*-Butyldimethylsilyloxy)-3-methylbicyclo[3.1.0]hexane-3-carbaldehyde 42

Compound **42** was prepared according to the general procedure for the Swern oxidation from compound **41** (0.65 g, 2.53 mmol). Purification by silica gel chromatography (EtOAc/hexane, 1:20) afforded aldehyde **42** (0.579 g) in 90% yield. R_f = 0.6 (EtOAc/hexane, 1:20). ^{1}H NMR (200 MHz, $CDCl_3$), δ_H: 9.36 (s, 1H), 4.62 (d, 1H, *J* = 5.2 Hz), 2.27 (dd, 1H, *J* = 5.9, 13.7 Hz), 1.58–1.52 (m, 2H), 1.27–1.22 (m, 1H), 0.99 (s, 3H), 0.86 (s, 9H), 0.73–0.69 (m, 1H), 0.51 (dd, 1H, *J* = 5.2, 8.2 Hz) 0.06 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 203.3, 75.0, 58.6, 36.1, 26.7, 25.9, 18.3, 17.5, 17.0, 10.8, −4.3, −4.9. HRMS (ESI) for $C_{14}H_{26}O_2SiNa$ $[M+Na]^+$, calculated: 277.1600; found: 277.1608.

4.10.38. *tert*-Butyldimethyl((1*S*,2*S*,3*R*,5*S*)-3-methyl-3-vinylbicyclo[3.1.0]hexan-2-yloxy)silane 43

To a suspension of methyltriphenylphosphonium iodide (0.646 g, 1.60 mmol) in dry THF (5 mL) was added LiHMDS (1.0 M solution in THF, 1.60 mL) at 0 °C. The yellow mixture was stirred at 0 °C for 15 min. A solution of aldehyde **42** (0.203 g, 0.80 mmol) in 2 mL of THF was added to the reaction mixture. The yellow suspension was stirred at room temperature for 4 h. The reaction was then quenched with the addition of water, and the layers were separated and extracted with 25 mL of ether, and washed with brine. It was then dried over anhydrous Na_2SO_4, and concentrated under vacuum. The crude residue was purified by flash column chromatography (EtOAc/hexane, 1:40) to afford compound **43** (0.149 g) in 74% yield. R_f = 0.8 (EtOAc/hexane, 1:40). $[\alpha]_D^{28}$ = −17.8 (*c* 1.2, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$), δ_H: 5.91 (dd, 1H, *J* = 10.6, 17.4 Hz), 4.98–4.85 (m, 2H), 4.08 (d, 1H, *J* = 5.2 Hz), 1.93 (dd, 1H, *J* = 6.3, 13.1 Hz), 1.57–1.52 (m, 2H), 1.29–1.25 (m, 1H), 0.92 (s, 3H), 0.91 (s, 9H), 0.61–0.60 (m, 1H), 0.54 (dd, 1H, *J* = 3.4, 8.2 Hz), 0.06 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 148.6, 109.7, 79.8, 54.0, 40.6, 26.5, 26.2, 21.4, 18.5, 18.4, 13.2, −4.2, −4.7. HRMS (ESI) for $C_{15}H_{28}OSiNa$ $[M+Na]^+$, calculated: 275.1807; found: 275.1809.

4.10.39. (1*S*,2*S*,3*R*,5*S*)-3-Methyl-3-vinylbicyclo[3.1.0]hexan-2-ol 44

Compound **44** was prepared according to the general procedure for the TBS deprotection from compound **43** (0.15 g, 0.59 mmol). Purification by silica gel chromatography (EtOAc/hexane, 1:30) afforded alcohol **44** (0.07 g) in 86% yield. R_f = 0.4 (EtOAc/hexane, 1:30). $[\alpha]_D^{28}$ = −12.2 (*c* 1.0, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$), δ_H: 5.89 (dd, 1H, *J* = 10.6, 17.4 Hz), 4.95 (dd, 1H, *J* = 1.0, 17.4 Hz), 4.88 (dd, 1H, *J* = 1.0, 10.6 Hz), 4.26 (d, 1H, *J* = 5.4 Hz), 2.04 (dd, 1H, *J* = 6.1, 13.5 Hz), 1.53 (dd, 2H, *J* = 1.6, 13.6 Hz), 1.42 (dd, 1H, *J* = 1.9, 4.1 Hz), 0.99 (s, 3H), 0.77 (dd, 1H, *J* = 4.0, 8.8 Hz), 0.55 (td, 1H, *J* = 5.2, 8.4 Hz). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 148.4, 109.6, 79.5, 50.2, 40.5, 25.7, 21.4, 16.8, 11.1. HRMS (ESI) for $C_9H_{14}ONa$ $[M+Na]^+$, calculated: 161.0943; found: 161.0948.

4.10.40. (1*S*,2*S*,3*R*,5*S*)-2-(Allyloxy)-3-methyl-3-vinylbicyclo[3.1.0]hexane 45

To an ice-cooled solution of NaH (60% dispersion in mineral oil, 0.16 g, 4.02 mmol) in dry THF (8 mL), alcohol **44** (0.277 g,

2.01 mmol) in THF (2 mL) was added and the reaction mixture was kept for a further 45 min at the same temperature, after which allyl bromide (0.35 mL, 4.02 mmol) was added and the reaction mixture was stirred at room temperature for 8 h. Water was added carefully to the reaction mixture to quench any excess NaH, and the layers were separated and extracted with 50 mL of ether, and washed with brine. It was then dried over anhydrous $MgSO_4$, and the solvent was removed in vacuum. The crude residue was purified by flash column chromatography (EtOAc/hexane, 1:40) to afford compound **45** (0.25 g) in 70% yield. R_f = 0.8 (EtOAc/hexane, 1:40). $[\alpha]_D^{28}$ = −29.8 (*c* 1.0, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$), δ_H: 5.97–5.87 (m, 2H), 5.28 (dd, 1H, *J* = 2.0, 17.2 Hz), 5.13 (dd, 1H, *J* = 1.2, 10.4 Hz), 4.98–4.88 (m, 2H), 4.07–4.03 (m, 1H), 3.86–3.82 (m, 2H), 1.96 (dd, 1H, *J* = 6.0, 13.2 Hz), 1.57–1.55 (m, 2H), 1.29–1.23 (m, 1H), 1.01 (s, 3H), 0.74 (dd, 1H, *J* = 4.2, 8.2 Hz), 0.64 (dd, 1H, *J* = 4.6, 8.2 Hz). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 148.7, 135.6, 115.9, 109.7, 85.7, 69.5, 53.1, 41.1, 23.1, 21.0, 18.4, 13.0. HRMS (ESI) for $C_{12}H_{18}ONa$ $[M+Na]^+$, calculated: 201.1256; found: 201.1259.

4.10.41. (3*S*,4*R*,4a*R*,5a*S*,6a*S*,6b*S*)-4a-Methyloctahydro-2*H*-cyclopropa[4,5]cyclopenta[1,2-*b*]pyran-3,4-diol 46

Compound **45** (0.037 g, 0.21 mmol) was taken in anhydrous degassed DCM (30 mL). Grubbs second generation metathesis catalyst (G-II, 0.007 g, 0.008 mmol) was added and the solution was stirred at reflux for 8 h. The reaction mixture was then cooled to room temperature and the solution was evaporated under reduced pressure. The crude material was used for the next step without further purification. Compound **46** was prepared according to the general procedure for the OsO_4 oxidation starting from the crude material (23.34 mg, 0.16 mmol). Purification by silica gel chromatography (EtOAc/hexane, 1:1) afforded exclusively compound **46** (0.020 g) in 53% overall yield for two steps. R_f = 0.3 (EtOAc/hexane, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$), δ_H: 4.26 (d, 1H, *J* = 4.8 Hz), 3.96–3.91 (m, 1H), 3.89–3.87 (m, 1H), 3.65–3.60 (m, 1H), 3.42 (t, 1H, *J* = 10.6 Hz), 2.06 (dd, 2H, *J* = 4.6, 12.6 Hz), 1.64 (br s, 2H), 1.50 (d, 1H, *J* = 12.8 Hz), 1.48–1.41 (m, 1H), 1.04–1.03 (m, 1H), 0.93 (s, 3H), 0.39 (dd, 1H, *J* = 7.6, 14.8 Hz). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 79.9, 75.4, 69.3, 64.2, 39.1, 31.2, 22.6, 16.8, 12.8, 9.1. HRMS (ESI) for $C_{10}H_{16}O_3Na$ $[M+Na]^+$, calculated: 207.0997; found: 207.0999.

4.10.42. (1*S*,3*S*,4*R*,6*R*)-4-((4-Methoxybenzyloxy)methyl)-4-methyl-7-oxabicyclo[4.1.0]heptan-3-ol 47 and (1*R*,3*S*,4*R*,6*S*)-4-((4-methoxybenzyloxy)methyl)-4-methyl-7-oxabicyclo[4.1.0]heptan-3-ol 48

Compounds **47** and **48** were prepared according to the general procedure for the substrate directed epoxidation with *m*CPBA from compound **19** (0.1 g, 0.38 mmol). The two diastereomeric epoxides (compound **47** and compound **48** in a 2: 1 ratio) were purified by flash column chromatography (EtOAc/hexane, 1:2) to afford epoxide **47** (0.056 g) in 53.5% yield and epoxide **48** (0.028 g) in 26.50% yield. R_f of **47** = 0.4 (EtOAc/hexane, 1:2). $[\alpha]_D^{28}$ = +13.8 (*c* 0.3, MeOH). ^{1}H NMR (600 MHz, $CDCl_3$), δ_H: 7.24 (d, 2H, *J* = 8.4 Hz), 6.89 (d, 2H, *J* = 8.4 Hz), 4.37 (dd, 2H, *J* = 11.7, 17.1 Hz), 3.82 (s, 3H), 3.59–3.55 (m, 1H), 3.24–3.20 (m, 1H), 3.19–3.14 (m, 2H), 2.99–2.90 (m, 1H), 2.20–2.11 (m, 1H), 2.10–2.07 (m, 1H), 1.89 (d, 1H, *J* = 16.2 Hz), 1.73 (dd, 1H, *J* = 4.8, 16.2 Hz), 1.15 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 159.1, 130.1, 129.0, 113.7, 77.0, 73.0, 70.9, 55.2, 52.9, 52.0, 36.8, 30.4, 28.3, 21.2. HRMS (ESI) for $C_{16}H_{22}O_4Na$ $[M+Na]^+$, calculated: 301.1416; found: 301.1419. R_f of **48** = 0.3 (EtOAc/hexane, 1:2). $[\alpha]_D^{28}$ = −18.2 (*c* 1.1, MeOH). ^{1}H NMR (600 MHz, $CDCl_3$), δ_H: 7.23 (d, 2H, *J* = 8.4 Hz), 6.88 (d, 2H, *J* = 8.4 Hz), 4.47 (d, 1H, *J* = 11.4 Hz), 4.41 (d, 1H, *J* = 12.0 Hz), 3.80 (s, 4H), 3.26–3.22 (m, 3H), 3.09 (t, 1H, *J* = 4.5 Hz), 2.36–2.33 (m, 1H), 1.76–1.70 (m, 3H), 0.96 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 159.4, 129.9, 129.3, 114.0, 79.0, 73.3, 69.9, 55.4, 53.8, 50.0, 36.8, 33.9, 29.6, 16.1. HRMS (ESI) for $C_{16}H_{22}O_4Na$ $[M+Na]^+$, calculated: 301.1416; found: 301.1421.

4.10.43. (1*R*,2*R*,4*S*,5*R*)-5-(Hydroxymethyl)-5-methylcyclohexane-1,2,4-triol 49

According to the general procedure for the acid induced epoxide ring opening, compound **47** (0.028 g, 0.10 mmol) afforded a triol which was used for the next step without further purification. PMB deprotection of the crude triol (0.026 g, 0.08 mmol) according to the general procedure for the PMB deprotection and then purification by silica gel chromatography (EtOAc/hexane, 2:1) afforded tetraol **49** (0.010 g) in 60% yield (for two step). R_f = 0.2 (EtOAc/hexane, 2:1). ^{1}H NMR (600 MHz, $CDCl_3$), δ_H: 4.32–4.30 (m, 1H), 3.95–3.93 (m, 1H), 3.66–3.662 (m, 2H), 3.52 (d, 1H, *J* = 9.0 Hz), 2.55 (d, 1H, *J* = 12.0 Hz), 2.12–2.10 (m, 1H), 1.80 (d, 1H, *J* = 15.6 Hz), 1.44–1.41 (m, 1H), 1.14 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 79.0, 75.7, 74.1, 68.8, 45.1, 34.7, 31.5, 19.2. HRMS (ESI) for $C_8H_{16}O_4Na$ $[M+Na]^+$, calculated: 199.0947; found: 199.0950.

4.10.44. (1*S*,2*S*,4*S*,5*R*)-5-(Hydroxymethyl)-5-methylcyclohexane-1,2,4-triol 50

According to the experimental procedure of compound **49**, compound **48** (0.028 g, 0.10) afforded tetraol **50** (0.012 g) in 70% yield (for two step). R_f = 0.4 (MeOH/$CHCl_3$, 1:3). $[\alpha]_D^{28}$ = +33.5 (*c* 1.1, MeOH). ^{1}H NMR (600 MHz, C_5D_5N), δ_H: 4.34–4.30 (m, 1H), 4.22–4.21 (m, 1H), 3.94 (d, 1H, *J* = 10.8 Hz), 3.74 (d, 1H, *J* = 10.2 Hz), 3.58–3.50 (m, 1H), 2.61–2.60 (m, 1H), 2.28–2.26 (m, 1H), 2.16–2.10 (m, 1H), 1.98–1.96 (m, 1H), 1.62 (s, 3H). ^{13}C NMR (150 MHz, C_5D_5N), δ_C: 71.4, 71.0, 69.4, 49.4, 40.9, 36.1, 34.8, 29.7. HRMS (ESI) for $C_8H_{16}O_4Na$ $[M+Na]^+$, calculated: 199.0947; found: 199.0955.

4.10.45. (1*R*,3*S*,4*R*,6*S*)-4-((4-Methoxybenzyloxy)methyl)-4-methylbicyclo[4.1.0]heptan-3-ol 51

Compound **51** was prepared according to the general procedure for the cyclopropanation reaction from compound **19** (0.028 g, 0.11 mmol). Purification by silica gel chromatography (EtOAc/hexane, 1:5) afforded **51** (0.022 g) in 75% yield. R_f = 0.3 (EtOAc/hexane, 1:5). $[\alpha]_D^{28}$ = −28.0 (*c* 1.1, MeOH). ^{1}H NMR (600 MHz, $CDCl_3$), δ_H: 7.25 (d, 2H, *J* = 7.8 Hz), 6.89 (d, 2H, *J* = 7.8 Hz), 4.45 (dd, 2H, *J* = 12.0, 16.8 Hz), 3.82 (s, 3H), 3.68–3.66 (m, 1H), 3.34 (d, 1H, *J* = 9.0 Hz), 3.21 (d, 1H, *J* = 8.4 Hz), 2.18–2.06 (m, 1H), 1.65–1.62 (m, 2H), 1.30–1.27 (m, 3H), 0.90 (s, 3H), 0.74–0.72 (m, 1H), 0.58–0.57 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$), δ_C: 159.1, 130.3, 129.1, 113.8, 79.3, 73.2, 73.1, 55.2, 37.0, 30.9, 28.2, 19.3, 13.2, 8.1, 7.7. HRMS (ESI) for $C_{17}H_{24}O_3Na$ $[M+Na]^+$, calculated: 299.1623; found: 299.1628.

4.10.46. *tert*-Butyl((1*S*,6*R*)-6-((4-methoxybenzyloxy)methyl)-6-methylcyclohex-3-enyloxy)dimethylsilane 52

Compound **52** was prepared according to the general procedure for the TBS protection from compound **19** (2.5 g, 9.5 mmol).). Purification by silica gel chromatography (EtOAc/hexane, 1:30) afforded compound **52** (3.10 g) in 86% yield. $[\alpha]_D^{28}$ = +38.8 (*c* 0.9, MeOH). R_f = 0.5 (EtOAc/hexane, 1:30). ^{1}H NMR (600 MHz, $CDCl_3$), δ_H: 7.26 (d, 2H, *J* = 8.4 Hz), 6.89 (d, 2H, *J* = 8.4 Hz), 5.56–5.48 (m, 2H), 4.49 (d, 1H, *J* = 11.4 Hz), 4.35 (d, 1H, *J* = 11.4 Hz), 3.91 (dd, 1H, *J* = 6.0, 8.4 Hz), 3.82 (s, 3H), 3.38 (d, 1H, *J* = 8.4 Hz), 3.12 (d, 1H, *J* = 8.4 Hz), 2.29 (d, 1H, *J* = 17.4 Hz), 2.21–2.18 (m, 1H), 2.03–2.01 (m, 1H), 1.83–1.80 (m, 1H), 0.98 (s, 9H), 0.90 (s, 3H), 0.04 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 159.1, 131.2, 129.1, 125.9, 123.8, 113.8, 76.3, 73.0, 69.7, 55.4, 38.8, 34.7, 32.5, 26.0, 18.2, 15.8, −3.8, −4.8. HRMS (ESI) for $C_{22}H_{36}O_3SiNa$ $[M+Na]^+$, calculated: 399.2332; found: 399.2336.

4.10.47. (1*R*,2*S*,4*R*,5*S*)-5-(*tert*-Butyldimethylsilyloxy)-4-((4-methoxybenzyloxy)methyl)-4-methylcyclohexane-1,2-diol 53 and (1*S*,2*R*,4*R*,5*S*)-5-(*tert*-butyldimethylsilyloxy)-4-((4-methoxybenzyloxy)methyl)-4-methylcyclohexane-1,2-diol 54

Compound **53** and **54** were prepared according to the general procedure for the OsO_4 oxidation starting from compound **52** (1.5 g, 3.98 mmol). Two diastereomeric diols **53** and compound **54** in a 1:2 ratio were purified by flash column chromatography (EtOAc/hexane, 1:5) to afford diol **53** (0.441 g) in 27% yield and diol **54** (0.882 g) in 54% yield. R_f of **53** = 0.3 (EtOAc/hexane, 1:5). $[\alpha]_D^{28}$ = +32.8 (*c* 0.6, MeOH). ^{1}H NMR (600 MHz, $CDCl_3$), δ_H: 7.22 (d, 2H, *J* = 8.4 Hz), 6.89 (d, 2H, *J* = 8.4 Hz), 4.43 (d, 1H, *J* = 12.0 Hz), 4.37 (d, 1H, *J* = 12.0 Hz), 3.87–3.81 (m, 1H), 3.65 (s, 5H), 3.19 (t, 2H, *J* = 9.0 Hz), 2.05–2.01 (m, 1H), 1.74–1.72 (m, 1H), 1.64–1.57 (m, 2H), 1.02 (s, 3H), 0.93 (s, 9H), 0.15 (s, 3H), 0.10 (s, 3H). ^{13}C NMR^{13}C NMR (150 MHz, $CDCl_3$), δ_C: 159.1, 130.4, 128.9, 113.7, 75.1, 72.9, 69.9, 68.1, 55.2, 34.6, 33.2, 25.9, 25.8, 17.9, −4.3, −4.9. HRMS (ESI) for $C_{22}H_{38}O_5SiNa$ $[M+Na]^+$, calculated: 433.2387; found: 433.2388. R_f of **54** = 0.2 (EtOAc/hexane, 1:5). $[\alpha]_D^{28}$ = +44.2 (*c* 1.0, MeOH). ^{1}H NMR (600 MHz, $CDCl_3$), δ_H: 7.24 (d, 2H, *J* = 8.6 Hz), 6.89 (d, 2H, *J* = 8.6 Hz), 4.49 (d, 1H, *J* = 12.0 Hz), 4.36 (d, 1H, *J* = 12.0 Hz), 4.13 (d, 1H, *J* = 6.6 Hz), 3.99–3.93 (m, 1H), 3.81 (s, 4H), 3.29 (d, 1H, *J* = 9.0 Hz), 3.11 (d, 1H, *J* = 9.0 Hz), 1.95–1.91 (m, 2H), 1.68–1.64 (m, 1H), 1.57–1.54 (m, 1H), 0.93 (s, 9H), 0.85 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 159.2, 130.6, 129.3, 113.9, 77.2, 73.1, 69.4, 68.5, 55.4, 40.3, 36.2, 35.6, 26.0, 18.2, 16.9, −3.9, −4.8. HRMS (ESI) for $C_{22}H_{38}O_5SiNa$ $[M+Na]^+$, calculated: 433.2387; found: 433.2389.

4.10.48. *tert*-Butyl((3a*S*,5*S*,6*R*,7a*R*)-6-((4-methoxybenzyloxy)methyl)-2,2,6-trimethylhexahydrobenzo[*d*][1,3]dioxol-5-yloxy)dimethylsilane 55

Compound **54** (2.02 g, 4.91 mmol) was taken in 24 mL of dry DCM. 2,2-Dimethoxypropane (DMP, 1.85 mL, 14.82 mmol) was then added followed by a catalytic amount of CSA (0.13 g, 0. 56 mmol). The reaction mixture was then stirred at room temperature for 6 h. After completion of the reaction water was added to the reaction mixture, which was then extracted with DCM and washed with brine. The organic layer was dried over $MgSO_4$ and evaporated to dryness. The product was purified by silica gel column chromatography (EtOAc/hexane, 1:20) to afford compound **55** (2.0 g) in 90% yield. R_f = 0.3 (EtOAc/hexane, 1:20). $[\alpha]_D^{28}$ = +23.8 (*c* 1.0, MeOH). ^{1}H NMR (600 MHz, $CDCl_3$), δ_H: 7.28 (d, 2H, *J* = 8.6 Hz), 6.87 (d, 2H, *J* = 8.6 Hz), 4.50 (d, 1H, *J* = 12.0 Hz), 4.34 (d, 1H, *J* = 11.4 Hz), 4.27–4.26 (m, 1H), 4.18–4.17 (m, 1H), 3.98 (dd, 1H, *J* = 4.5, 9.3 Hz), 3.82 (s, 3H), 3.24 (s, 2H), 1.99–1.96 (m, 1H), 1.86–1.83 (m, 1H), 1.72–1.70 (m, 2H), 1.44 (s, 3H), 1.32 (s, 3H), 0.99 (s, 9H), 0.86 (s, 3H), 0.07 (s, 3H), 0.04 (s, 3H). ^{13}C NMR^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 159.0, 130.9, 128.6, 113.6, 107.6, 76.4, 73.7, 72.7, 68.8, 55.0, 39.6, 35.0, 32.5, 28.5, 26.2, 25.8, 18.0, 16.5, −4.1, −5.0. HRMS (ESI) for $C_{25}H_{42}O_5SiNa$ $[M+Na]^+$, calculated: 473.2700; found: 473.2704.

4.10.49. ((3a*R*,5*R*,6*S*,7a*S*)-6-(*tert*-Butyldimethylsilyloxy)-2,2,5-trimethylhexahydrobenzo[*d*][1,3]dioxol-5-yl)methanol 56

Compound **56** was prepared according to the general procedure for the PMB deprotection from compound **55** (2.0 g, 4.43 mmol). Purification by silica gel chromatography (EtOAc/hexane, 1:5) afforded compound **56** (1.29 g) in 88% yield as a colorless oil. R_f = 0.3 (EtOAc/hexane, 1:5). $[\alpha]_D^{28}$ = +22.8 (*c* 1.0, MeOH). ^{1}H NMR (600 MHz, $CDCl_3$), δ_H: 4.31 (dd, 1H, *J* = 4.8, 9.0 Hz), 4.24 (dd, 1H, *J* = 6.3, 12.3 Hz), 4.01–4.00 (m, 1H), 3.45–3.40 (m, 1H), 3.38–3.37 (m, 1H), 2.39 (br, s 1H), 1.84–1.83 (m, 1H), 1.68–1.62 (m, 3H), 1.50 (s, 3H), 1.33 (s, 3H), 0.90 (s, 9H), 0.88 (s, 3H), 0.11 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 108.0, 73.8, 72.5, 70.5, 69.4, 40.0, 35.1, 33.0, 28.1, 25.9, 18.1, 16.9, −3.9, −4.8. HRMS (ESI) for $C_{17}H_{34}O_4SiNa$ $[M+Na]^+$, calculated: 353.2124; found: 353.2127.

4.10.50. *tert*-Butyldimethyl((3a*S*,5*S*,6*R*,7a*R*)-2,2,6-trimethyl-6-vinylhexahydrobenzo[*d*][1,3]dioxol-5-yloxy)silane 57

Oxalyl chloride (1.16 ml, 13.26 mmol) was taken in DCM (32.0 ml) and the reaction vessel was kept at −78 °C. Dimethyl sulphoxide (DMSO, 1.88 ml, 26.52 mmol) was then added and the reaction mixture was kept at the same temperature for 25 min. Alcohol **56** (2.92 g, 8.84 mmol) in DCM was then added to it and the mixture was kept for a further 45 min at the same temperature, after which triethyl amine (7.37 ml, 53.00 mmol) was added and the reaction mixture was gradually warmed to the room temperature for 1 h. The reaction was then quenched by adding water and extracted with DCM. The organic layer was washed successively with water, saturated aqueous $NaHCO_3$ solution and brine. The organic layer was dried ($MgSO_4$) and evaporated. The residue was used for next step without further purification. To a suspension of methyltriphenylphosphonium iodide (5.7 g, 14.19 mmol) in dry THF (40 mL) was added LiHMDS (1.0 M solution in THF, 14.2 mL) at 0 °C. The yellow mixture was stirred at 0 °C for 30 min. A solution of the crude aldehyde (2.32 g, 7.1 mmol) in 16 mL of THF was added to the reaction mixture. The yellow suspension was stirred at room temperature for a further 4 h. Next, the reaction was quenched by the addition of water, and the layers were separated and extracted with 200 mL of ether, and washed with brine. It was then dried over anhydrous Na_2SO_4, and concentrated under vacuum. The crude residue was purified by flash column chromatography (EtOAc/hexane, 1:10) to afford compound **57** (1.85 g) in 64% yield (for two step). R_f = 0.6 (EtOAc/hexane, 1:10). $[\alpha]_D^{28}$ = +12.4 (*c* 0.8, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$), δ_H: 5.98 (dd, 1H, *J* = 10.7, 17.7 Hz), 5.00–4.92 (m, 2H), 4.27–4.22 (m, 2H), 3.70–3.64 (m, 1H), 2.05 (dd, 1H, *J* = 3.8, 10.8 Hz), 1.98–1.68 (m, 3H), 1.46 (s, 3H), 1.30 (s, 3H), 0.99 (s, 3H), 0.85 (s, 9H), 0.04 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 146.8, 111.6, 107.7, 73.5, 72.7, 72.6, 41.1, 36.7, 32.8, 28.5, 26.1, 25.8, 18.1, 18.0, −4.2, −4.8. HRMS (ESI) for $C_{18}H_{34}O_3SiNa$ $[M+Na]^+$, calculated: 349.2175; found: 349.2177.

4.10.51. (3a*S*,5*S*,6*R*,7a*R*)-2,2,6-Trimethyl-6-vinylhexahydrobenzo[*d*][1,3]dioxol-5-ol 58

Compound **58** was prepared according to the general procedure for the TBS deprotection from compound **57** (1.85 g, 5.66 mmol). Purification by silica gel chromatography (EtOAc/hexane, 1:10) afforded alcohol **58** (1.06 g) in 88% yield. R_f = 0.2 (EtOAc/hexane, 1:0). $[\alpha]_D^{28}$ = +8.6 (*c* 0.6, MeOH). ^{1}H NMR (600 MHz, $CDCl_3$), δ_H: 5.79 (dd, 1H, *J* = 10.8, 17.4 Hz), 5.17–5.10 (m, 2H), 4.35–4.30 (m, 1H), 4.21–4.18 (m, 1H), 3.80 (dd, 1H, *J* = 2.1, 11.1 Hz), 2.33 (dd, 1H, *J* = 2.4, 15.0 Hz), 1.86–1.81 (m, 1H), 1.74 (dd, 1H, *J* = 6.3, 13.5 Hz), 1.57–1.53 (m, 1H), 1.51 (s, 3H), 1.34 (s, 3H), 0.99 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 145.9, 113.7, 107.9, 73.9, 72.0, 69.9, 41.8, 38.9, 30.8, 28.5, 26.2, 14.1. HRMS (ESI) for $C_{12}H_{20}O_3Na$ $[M+Na]^+$, calculated: 235.1310; found: 235.1315.

4.10.52. (3a*R*,5*R*,6*S*,7a*S*)-6-(Allyloxy)-2,2,5-trimethyl-5-vinylhexahydrobenzo[*d*][1,3]dioxole 59

To an ice-cooled solution of NaH (60% dispersion in mineral oil, 0.16 g, 4.02 mmol) in dry THF (8 mL), alcohol **58** (0.426 g, 2.01 mmol) in THF (2 mL) was added and the reaction mixture was kept for further 45 min at the same temperature, after which allyl bromide (0.35 mL, 4.02 mmol) was added and the reaction mixture was stirred at room temperature for a further 8 h. Water was then added carefully to the reaction mixture to quench any excess NaH, and the layers were separated and extracted with 50 mL of ether, and washed with brine. It was then dried over

anhydrous $MgSO_4$, and the solvent was removed in vacuum. The crude residue was purified by flash column chromatography (EtOAc/hexane, 1:20) to afford compound **59** (0.395 g) in 78% yield. R_f = 0.4 (EtOAc/hexane, 1:20). $[\alpha]_D^{28}$ = +25.4 (*c* 1.0, MeOH). ^{1}H NMR (600 MHz, $CDCl_3$), δ_H: 6.04–6.01 (m, 1H), 5.99–5.87 (m, 1H), 5.26 (d, 1H, *J* = 16.8 Hz), 5.14 (d, 1H, *J* = 10.2 Hz), 5.04–5.00 (m, 2H), 4.32–4.31 (m, 1H), 4.22–4.20 (m, 1H), 4.06 (dd, 1H, *J* = 5.1, 12.9 Hz), 3.94 (dd, 1H, *J* = 5.1, 12.9 Hz), 3.43 (dd, 1H, *J* = 3.6, 9.6 Hz), 2.25 (d, 1H, *J* = 11.4 Hz), 1.89–1.84 (m, 1H), 1.73 (dd, 1H, *J* = 5.7, 14.1 Hz), 1.65 (dd, 1H, *J* = 8.4, 13.8 Hz), 1.50 (s, 3H), 1.34 (s, 3H), 1.02 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 146.8, 135.4, 116.3, 111.7, 108.0, 79.0, 73.7, 72.7, 71.0, 40.9, 38.0, 29.0, 28.6, 26.3, 17.7. HRMS (ESI) for $C_{15}H_{24}O_3Na$ $[M+Na]^+$, calculated: 275.1623; found: 275.1625.

4.10.53. (3a*S*,4a*S*,8a*R*,9a*R*)-2,2,8a-Trimethyl-4,4a,6,8a,9,9a-hexahydro-3a*H*-[1,3]dioxolo[4,5-g]chromene 60

The starting compound **59** (0.211 g, 0.84 mmol) was taken in anhydrous degassed DCM (120 mL). Grubbs second generation metathesis catalyst (G-II, 0.028 g, 0.032 mmol) was added and the solution was stirred at reflux for 8 h. The reaction mixture was then cooled to room temperature and the solution was evaporated under reduced pressure. The contents of the flask were directly loaded onto a silica gel column. The crude material was then purified by silica gel column chromatography (EtOAc/hexane, 1:20) to afford product **60** (0.15 g) in 80% yield as a liquid. R_f = 0.2 (EtOAc/hexane, 1:20). $[\alpha]_D^{28}$ = +38.2 (*c* 1.0, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$), δ_H: 5.55–5.50 (m, 2H), 4.36–4.32 (m, 1H), 4.22–4.15 (m, 3H), 3.61 (dd, 1H, *J* = 4.6, 12.4 Hz), 2.19 (dd, 1H, *J* = 3.6, 14.6 Hz), 1.92–1.71 (m, 3H), 1.46 (s, 3H), 1.31 (s, 3H), 0.92 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 135.6, 124.1, 107.8, 74.7, 74.2, 72.4, 66.8, 39.1, 34.7, 29.0, 28.4, 26.2, 17.0. HRMS (ESI) for $C_{13}H_{20}O_3Na$ $[M+Na]^+$, calculated: 247.1310; found: 247.1317.

4.10.54. (3a*S*,4a*S*,7*R*,8*S*,8a*R*,9a*R*)-2,2,8a-Trimethyloctahydro-3a*H*-[1,3]dioxolo[4,5-*g*]chromene-7,8-diol 61

Compound **61** was prepared according to the general procedure for the OsO_4 oxidation from compound **60** (0.4 g, 1.78 mmol). Purification by silica gel chromatography (EtOAc/hexane, 1:1) afforded diol **61** (0.377 g) as the sole product in 82% yield. R_f = 0.2 (EtOAc/hexane, 1:1). R_f = 0.3 (EtOAc/hexane, 2:1). $[\alpha]_D^{28}$ = +44.2 (*c* 0.8, MeOH). ^{1}H NMR (600 MHz, $CDCl_3$), δ_H: 4.33–4.21 (m, 1H), 4.20–4.19 (m, 1H), 4.10–4.08 (m, 1H), 3.82–3.70 (m, 1H), 3.69–3.67 (m, 1H), 3.36–3.34 (m, 1H), 3.31–3.30 (m, 1H), 2.31–2.30 (m, 1H), 2.28 (d, 1H, *J* = 4.8 Hz), 2.19–2.09 (m, 1H), 1.97–1.92 (m, 1H), 1.53 (s, 3H), 1.34 (s, 3H), 0.91 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 107.9, 76.8, 76.1, 73.8, 71.9, 71.7, 69.4, 39.6, 38.2, 28.5, 26.2, 10.9. HRMS (ESI) for $C_{13}H_{22}O_5Na$ $[M+Na]^+$, calculated: 281.1365; found: 281.1369.

4.10.55. (3*R*,4*S*,4a*R*,6*R*,7*S*,8a*S*)-4a-Methyloctahydro-2*H*-chromene-3,4,6,7-tetraol 62

To a stirred solution of alcohol **61** (0.093 g, 0.36 mmol) in anhydrous DCM (8 mL) was added *p*-toluenesulfonic acid monohydrate (0.136 g, 0.72 mmol) at room temperature and stirred for 6 h. After completion of the reaction, 80 mg of solid $NaHCO_3$ were added to the reaction mixture and the solvent was evaporated in vacuo. The residue was then purified by flash column chromatography ($MeOH/CHCl_3$, 1:3) to afford compound **62** (0.07 g) in 90% yield. R_f = 0.4 ($MeOH/CHCl_3$, 1:3). $[\alpha]_D^{28}$ = +69.2 (*c* 1.0, MeOH). ^{1}H NMR (600 MHz, C_5D_5N), δ_H: 5.47 (br s 4H), 4.72–4.70 (m, 1H), 4.41 (s, 1H), 4.38–4.36 (m, 1H), 4.27–4.25 (m, 1H), 4.11 (dd, 1H, *J* = 5.7, 9.9 Hz), 3.98–3.96 (m, 1H), 3.87 (s, 1H), 3.04 (t, 1H, *J* = 12.3 Hz), 2.36 (d, 1H, *J* = 12.6 Hz), 1.91 (t, 1H, *J* = 12.3 Hz), 1.68 (dd, 1H, *J* = 4.2, 12.6 Hz), 1.13 (s, 3H). ^{13}C NMR (150 MHz, C_5D_5N), δ_C:75.4, 70.5, 70.2, 68.6, 68.1, 64.8, 40.1, 35.8, 33.5, 16.0. HRMS (ESI) for $C_{10}H_{18}O_5Na$ $[M+Na]^+$, calculated: 241.1052; found: 241.1055.

Acknowledgements

Institutional support from IIT Kharagpur (SGIRG grant) is thankfully acknowledged. DST-India is thanked for the NMR machine (IRPHA scheme). Two of the authors R.K. and J.H. are thankful to UGC, India for research fellowship.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetasy.2016.05.003.

References

1. Mander, L.; Liu, H. In *Comprehensive Natural Products II: Chemistry and Biology* In ; Newnes, 2010; Vol. 1,. ISBN: 0080453821.
2. (a) Kirkpatrick, P.; Ellis, C. *Nature* **2004**, *432*, 823–865; (b) Reymond, J. L.; Awale, M. *ACS Chem. Neurosci.* **2012**, *3*, 649–657; (c) Ruddigkeit, L.; Van Deursen, R.; Blum, L. C.; Reymond, J. L. *J. Chem. Inf. Model.* **2012**, *52*, 2864–2875.
3. (a) Reymond, J. L. *Acc. Chem. Res.* **2015**, *48*, 722–730; (b) Reymond, J. L.; Van Deursen, R.; Blum, L. C.; Ruddigkeit, L. *MedChemComm* **2010**, *1*, 30–38.
4. (a) Harvey, A. L.; Edrada-Ebel, R.; Quinn, R. J. *Nat. Rev. (Drug Discovery)* **2015**, *14*, 111–129; (b) Huigens, R. W.; Morrison, K. C.; Hicklin, R. W.; Flood, T. A., Jr; Richter, M. F.; Hergenrother, P. J. *Nat. Chem.* **2015**, *5*, 195–202; (c) Morrison, K. C.; Hergenrother, P. J. *Nat. Prod. Rep.* **2014**, *31*, 6–14; (d) Wilson, R. M.; Danishefsky, S. J. *J. Org. Chem.* **2006**, *71*, 8329–8351.
5. (a) Schreiber, S. L. *Science* **2000**, *287*, 1964–1969; (b) Bon, R. S.; Waldmann, H. *Acc. Chem. Res.* **2010**, *43*, 1103–1114; (c) Kumar, K.; Waldmann, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 3224–3242.
6. (a) Welsch, M. E.; Snyder, S. A.; Stockwel, B. R. *Curr. Opin. Chem. Biol.* **2010**, *14*, 347–361; (b) Kluge, A. F.; Petter, R. C. *Curr. Opin. Chem. Biol.* **2010**, *14*, 421–427; (c) Jenkins, I. D.; Lacrampe, F.; Ripper, J.; Alcaraz, L.; Le, P. V.; Nikolakopoulos, G.; Leone, P. A.; White, R. H.; Quinn, R. J. *J. Org. Chem.* **2009**, *74*, 1304–1313.
7. Galloway, W. R. J. D.; Bender, A.; Welch, M.; Spring, D. R. *Chem. Commun.* **2009**, 2446–2462.
8. (a) Serba, C.; Winssinger, N. *Eur. J. Org. Chem.* **2013**, 4195–4214; (b) Burke, M. D.; Berger, E. M.; Schreiber, S. L. *Science* **2003**, *302*, 613–618.
9. (a) Mahapatra, T.; Nanda, S. *Tetrahedron: Asymmetry* **2009**, *20*, 610–615; (b) Mahapatra, T.; Bhunya, R.; Nanda, S. *Tetrahedron Lett.* **2009**, *50*, 5392–5394.
10. (a) Mahapatra, T.; Nanda, S. *Tetrahedron: Asymmetry* **2010**, *21*, 2199–2205; (b) Mahapatra, S.; Nanda, S. *Tetrahedron: Asymmetry* **2011**, *22*, 406–412; (c) Mahapatra, T.; Jana, N.; Nanda, S. *Adv. Synth. Catal.* **2011**, *353*, 2152–2168; (d) Bhuniya, R.; Nanda, S. *Org. Biomol. Chem.* **2012**, *10*, 536–547.
11. Rej, R.; Jana, N.; Kar, S.; Nanda, S. *Tetrahedron: Asymmetry* **2012**, *23*, 364–372.
12. Tsuna, K.; Noguchi, N.; Nakada, M. *Chem. Eur. J.* **2013**, *19*, 5476–5486.
13. Lee, J. Y.; You, Y. S.; Kang, S. H. *J. Am. Chem. Soc.* **2011**, *133*, 1772–1774.
14. Mancuso, A. J.; Brownfain, D. S.; Swern, D. *J. Org. Chem.* **1979**, *44*, 4148–4150.
15. Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **1995**, *34*, 2039–2041.
16. Horita, K.; Yoshioka, T.; Tanaka, Y.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021.
17. (a) Kozawa, I.; Akashi, Y.; Takiguchi, K.; Sasaki, D.; Sawamoto, D.; Takao, K.; Tadano, K. *Synlett* **2007**, 399–402; (b) Kato, K.; Tanaka, H.; Miyasaka, T.; Baba, M.; Yamaguchi, K.; Akita, H. *Chem. Pharm. Bull.* **1999**, *47*, 1256–1264.
18. Jogi, A.; Maeorg, U. *Molecules* **2001**, *6*, 964–968.
19. Tellitu, I.; Beitia, I.; Diaz, M.; Alonso, A.; Moreno, I.; Dominguez, E. *Tetrahedron* **2015**, *71*, 8251–8255.