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Stereoselective Synthesis of Enantiopure Oxetanes, a Carbohydrate Mimic, an ε-Lactone, and Cyclitols from Biocatalytically Derived β-Hydroxy Esters as Chiral Precursors

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Biocatalytically derived enantiopure α-substituted β-hydroxy esters serve as excellent chirons for the synthesis of a diverse set of structures such as oxetanes, a carbohydrate mimic, an ε-lactone, and carbocyclic and aromatic cyclitols. The starting materials can be easily accessed in enantiopure form from α-substituted β-keto esters by biocatalytic reduction with *Klebsiella pneumoniae* (NBRC 3319). Ring-closing metathesis (RCM) is one of the key transformations used to create the carbocyclic/heterocyclic frameworks reported in this article. The synthesized cyclitols were screened for their inhibitory effect on α- and β-glucosidases.

Introduction

The enantio- and diastereoselective reduction of α-substituted β-keto esters by dynamic kinetic resolution (DKR) can be achieved using yeast and other microorganisms, and a few examples of this have been reported in the scientific literature.[1] α-Substituted β-keto esters are unique substrates for the ketoreductase class of enzymes.[2] Due to the high kinetic acidity of the protons on the α-carbon, these compounds are very prone to epimerization. For the bioreduction of α-substituted β-keto esters, starting with the enantiopure substrate is not a prerequisite for obtaining enantio- and diastereomerically pure products. Racemic substrates can serve the purpose very well. The enzyme takes up the reactive enantiomer into its active site, and transfers the "hydride" in a Prelog or anti-Prelog manner, depending on the number and kind of keto-reductases involved.[3] The slow-reacting enantiomer is easily epimerized (due to the high kinetic acidity of the proton at the 2-position) to reform the racemic mixture, and the cycle goes on. The requirements for a successful reduction by this DKR process are first, that the racemization of the β-keto ester should be faster than the bioreduction, and second, that the product hydroxy ester is not racemized under the reaction conditions.[4] Thus, the bioreduction of α-substituted β-keto esters follows a DKR pathway as shown in (Figure 1), and the reduction proceeds enantioselectively and diastereoselectively to give only a single stereoisomer out of a possible four, in one step. There has been phenomenal growth in the use of asymmetric bioreduction processes for the synthesis of enantiopure secondary alcohols using various microbial and plant ketoreductases in the last two decades.[5] α-Substituted β-keto esters act as very good substrates for several ketoreductase enzymes, and numerous literature reports demonstrate the successful application of this class of enzymes to yield β-hydroxy esters in a stereocontrolled way.[2] Enantiopure β-hydroxy esters are useful intermediates for the synthesis of the corresponding hydroxy acids, aldehydes, and other useful small organic molecules.[6] We have earlier demonstrated that fermenting cells of *Klebsiella pneumoniae* (NBRC 3319) can selectively reduce several 2-substituted ethyl 3-oxobutyrates to give the corresponding *syn*-β-hydroxy esters with remarkable stereocontrol (*de* > 99%, *ee* > 99%). The resulting α-substituted β-hydroxy esters can then be synthetically manipulated to give cyclopentane- or cyclohexane-based carbocyclic compounds.[7]

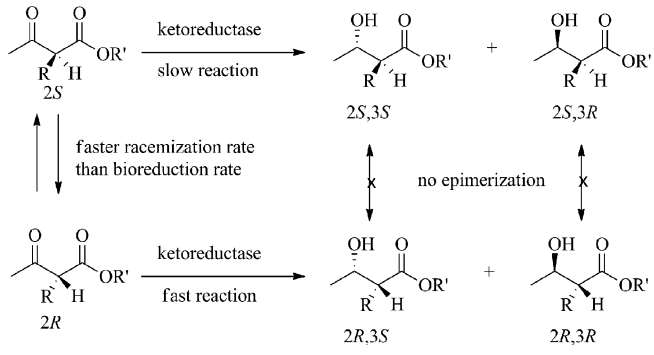

Figure 1. Enantioselective and diastereoselective bioreduction of α-substituted β-keto esters (dynamic kinetic resolution).

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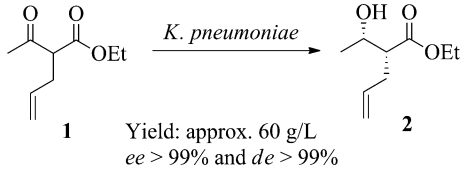
Results and Discussion

We have also shown that ethyl 2-acetylpent-4-enoate (**1**) acts as one of the best substrates for the ketoreductase from *Klebsiella pneumoniae*, as it yields the corresponding hydroxy ester (**2**) in excellent yield (yield 60 g/L; Scheme 1). The yield has been substantially improved (1.5-fold) compared to our earlier report. A subtle change in the medium composition ($CaCO_3$ was used at 10 g/L instead of 40 g/L as earlier) might be responsible for the yield enhancement. The presence of a large amount of $CaCO_3$ in the growing media makes the overall isolation process tedious and difficult. We assume that the product hydroxy esters become trapped in the insoluble $CaCO_3$ matrix, so repeated extraction with organic solvent (EtOAc) is required to isolate the product. But a modified medium composition with a new isolation procedure by centrifugation (to remove the cell debris and insoluble inorganic salts; see Experimental Section) enables us to obtain a better overall yield of the β-hydroxy ester product.

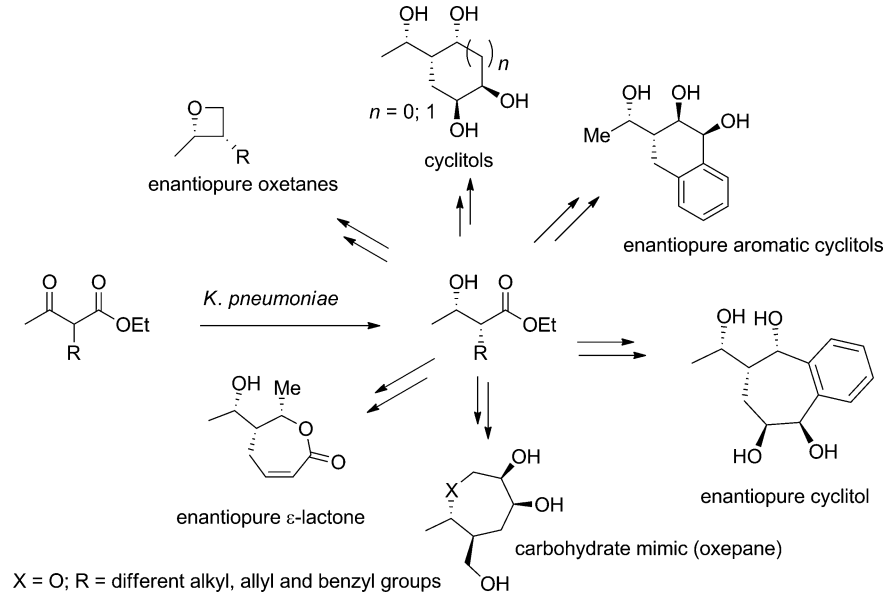


Scheme 1. Bioreduction of ethyl 2-acetylpent-4-enoate with *K. pneumoniae*.

We envisioned that the enantiopure β-hydroxy esters obtained from the bioreduction of several α-substituted β-keto esters with *Klebsiella pneumoniae* could serve as excellent chiral synthons for the synthesis of various carbocyclic and heterocyclic scaffolds, as shown in Scheme 2. The precursor presented in Figure 2 has three principal reaction sites: R^1 (OH group; useful for intramolecular cyclization reactions such as lactonization and S_N2 displacement), R^2 (stereochemically pure allyl/propargyl appendage; useful for ene–ene/ene–yne metathesis, carbophilic activation by soft transition metals and other related reactions), and R^3 (–CO_2Et group; can act as a masked –CHO or –CH_2OH group). The three reaction sites can be synthetically manipulated at the same time or in a mutually exclusive permutation–combination manner (i.e., with two reaction sites being manipulated at the same time while the other site remains untouched) to generate a diverse set of new chemical entities by adopting a purely transformation-based strategy. Following the strategy shown in Figure 2, in this article, we present the synthesis of enantiopure oxetanes (R^1–R^3 combination), an oxepane (R^1–R^2 combination), and new polyhydroxylated carbocyclic scaffolds and an ε-lactone (R^2–R^3 combination), starting from biocatalytically derived enantiopure α-substituted β-hydroxy esters (Scheme 2).

Synthesis of Enantiopure Oxetanes (R^1–R^2 Reaction Sites)

Enantiopure oxetanes are useful building blocks, and they are also found as essential structural components in some biologically active natural products.[8] We decided to carry out the asymmetric synthesis of several oxetanes, starting from biocatalytically derived *syn*-β-hydroxy esters. For that purpose, enantiopure β-hydroxy esters **3–8** were reduced with DIBAL-H (diisobutylaluminium hydride) to give the corresponding 2-substituted 1,3-propane diols (i.e., **9–14**) in excellent yields. Treatment with tosyl chloride (4-toluenesulfonyl chloride) and Et_3N resulted in a regioselective reaction of the primary hydroxy groups to give tosylates **15–20**. The tosylates were then treated with base



Scheme 2. *Klebsiella pneumoniae* (NBRC 3319) mediated synthesis of various 2-substitited β-hydroxy esters and further proposed synthetic manipulation.

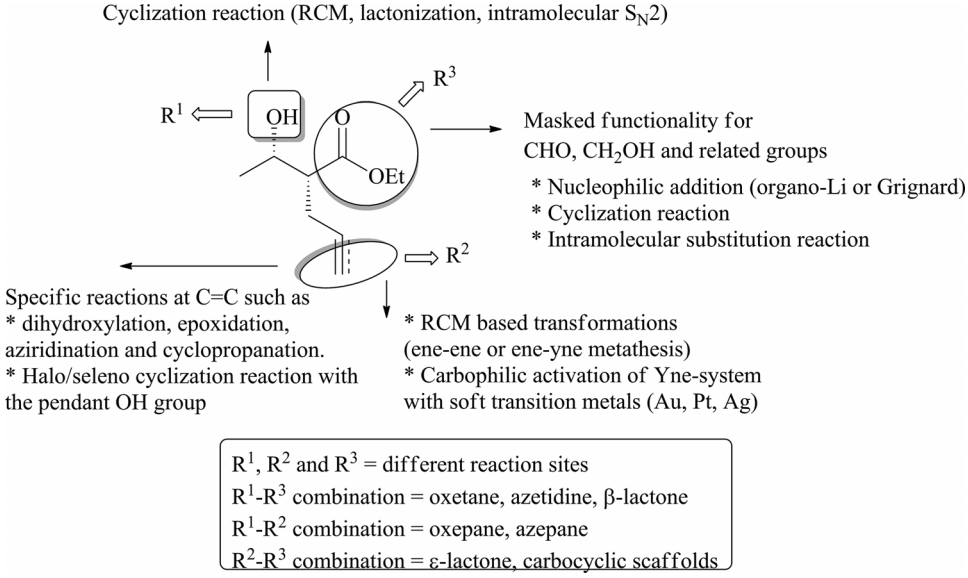
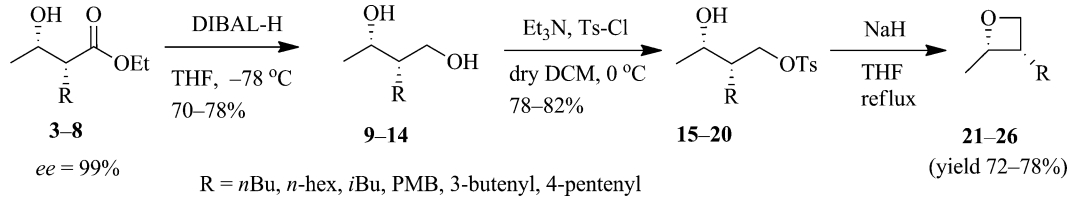


Figure 2. Enantiopure α-substituted β-hydroxy esters as potential precursors for generating molecular diversity through a transformation-based approach.

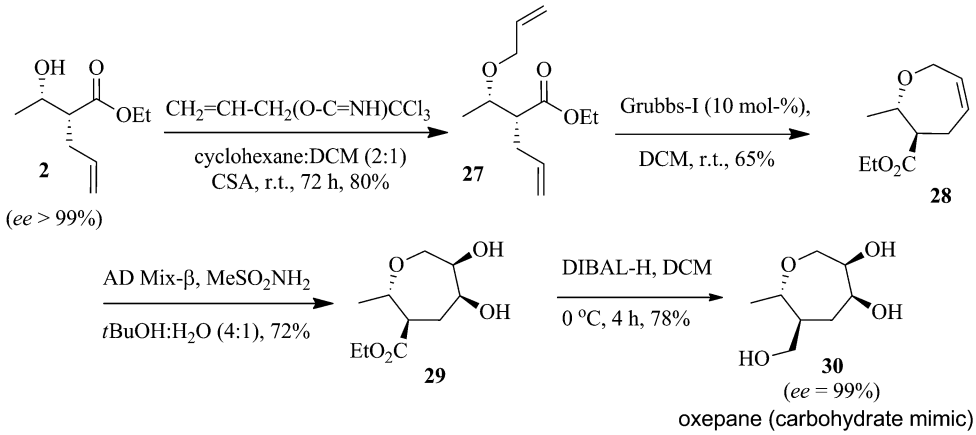


Scheme 3. Synthesis of enantiopure oxetanes.

(NaH in refluxing THF) to give the corresponding oxetanes (i.e., **21**–**26**) stereospecifically (Scheme 3). The oxetanes are fairly unstable at room temperature, so attempted purification by silica gel chromatography resulted in decomposition. Hence, the crude oxetanes were not purified prior to characterization (^1H and ^{13}C NMR spectroscopy).

Synthesis of an Enantiopure Carbohydrate Mimic (R^1–R^3 Reaction Sites)

For the stereoselective synthesis of a seven-membered-ring carbohydrate mimic chose to start from enantiopure β-hydroxy ester **2** (*ee* > 99%). The secondary hydroxy group



Scheme 4. Synthesis of an oxepane as a carbohydrate mimic; CSA = camphorsulfonic acid.

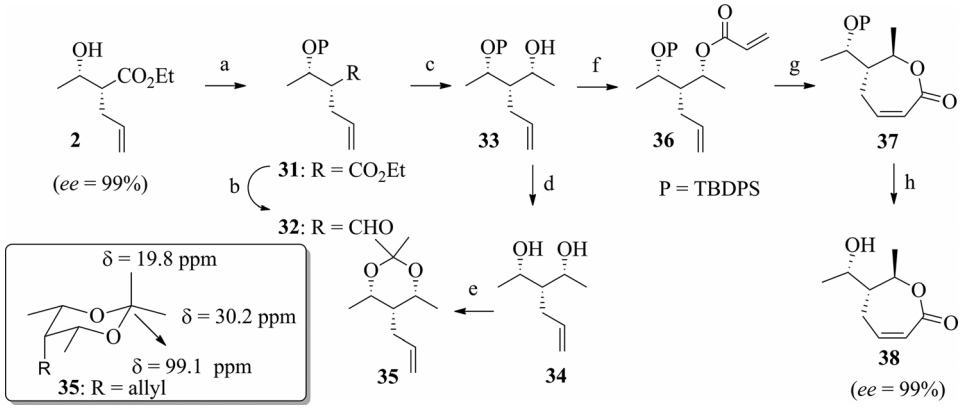
in compound **2** was protected as its *O*-allyl ether by treatment with allyl imidate[9] to give compound **27** in 80% yield. Compound **27** when subjected to a ring-closing metathesis (RCM) reaction with Grubbs I catalyst[10] at room temperature to give the corresponding cycloheptene derivative (i.e., **28**) in 65% yield. Asymmetric dihydroxylation under Sharpless conditions[11] gave compound **29** in good yield (Scheme 4). Oxepane derivative **29**, upon reduction with DIBAL-H in CH_2Cl_2 gave the corresponding hydroxylated oxepane (i.e., **30**) in 78% yield. This type of chiral hydroxylated cycloheptane-based scaffold (i.e., **30**) is new in the scientific literature. So by applying a simple four-step synthetic manipulation starting from a biocatalytically derived enantiopure β-hydroxy ester, new hydroxylated scaffolds can be synthesized in good yield with retention of enantiopurity in the final product.

Synthesis of an Enantiopure ε-Lactone (R^2–R^3 Reaction Sites)

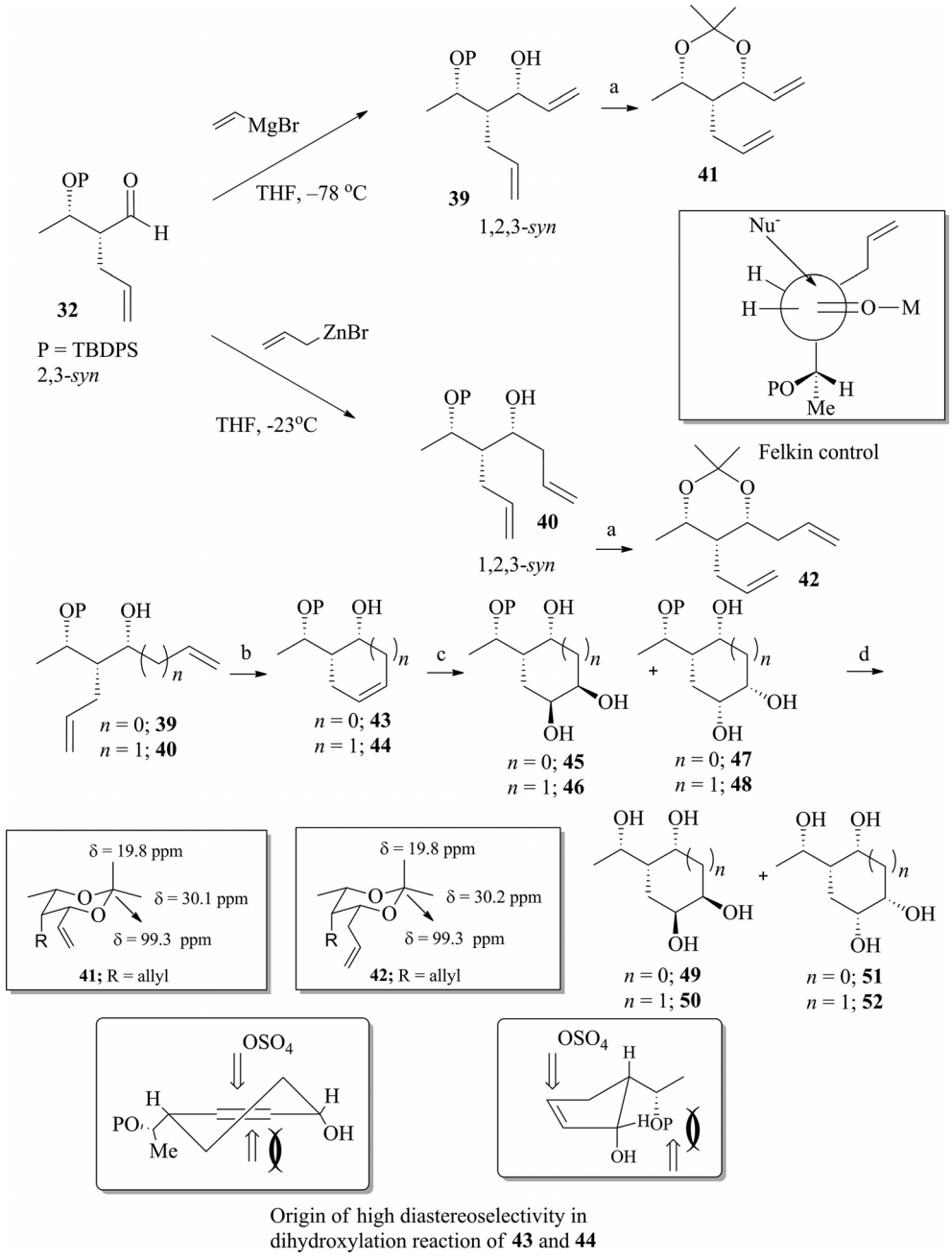
The synthesis started from known enantiopure β-hydroxy ester **2**. The free hydroxy group in compound **2** was protected as its TBDPS (*tert*-butyldiphenylsilyl) ether by treatment with imidazole and TBDPS-Cl to give compound **31** in 90% yield. Reduction of the ester functionality with DIBAL-H at –78 °C gave the corresponding aldehyde (i.e., **32**) in 82% yield. Addition of MeMgI at –78 °C to aldehyde **32** gave compound **33** as a single diastereomer. The configuration of the newly generated stereocentre was confirmed by the Rychnovsky method.[12] Deprotection of the TBDPS group in compound **33** gave known symmetrical diol **34** in 88% yield.[13] The diol functionality was then protected as its acetonide by treatment with 2,2-DMP (2,2-dimethoxypropane) to give compound **35**. Analysis by ^{13}C NMR spectroscopy revealed that the relative stereochemistry of the two hydroxy groups was *syn*, as shown in Scheme 5. Condensation of **33** with acrolyl chloride in the presence of DIPEA (diisopropylethylamine) and DMAP (4-dimethylaminopyridine) gave acrylate **36** in 88% yield. RCM reaction of compound **36** with Grubbs II catalyst (5 mol-%) in refluxing CH_2Cl_2 gave seven-membered-ring lactone **37** in 82% yield. Finally, deprotection of the TBDPS group with HF/pyridine[14] gave enantiopure ε-lactone **38** in 78% yield (Scheme 5).

Synthesis of Cyclopentane/Cyclohexane Based Cyclitols (R^2–R^3 Reaction Sites)

A strategy combining the R^2 and R^3 reaction sites (Figure 2) was devised for the synthesis of cyclitols based on cyclopentane and cyclohexane frameworks. Initially, aldehyde **32** was treated with CH_2=$CHMgBr$ at –78 °C to give compound **39** as the sole product. The reaction of aldehyde **2** with CH_2=$CHCH_2MgBr$ under similar conditions was sluggish. But aldehyde **2** reacted nicely with CH_2=$CHCH_2ZnBr$ to give compound **40** in 86% yield. The stereochemical outcome of both of these reactions can be predicted satisfactorily through a Felkin type (non-chelating conditions)[15] model, as shown in Scheme 6. The relative stereochemistry (1,3-*syn*) of compounds **39** and **40** was confirmed by the Rychnovsky method, as described above (Scheme 6). Compounds **39** and **40** were then subjected to RCM reactions with Grubbs II catalyst to give ring-closed products **43** and **44** in 90 and 84% yields, respectively. Substrate-directed dihydroxylation reactions with OsO_4 gave stereochemically pure diols **45** and **46** as major diastereomers, along with **47** and **48** as minor diastereomers, in 80–82% combined yield (Scheme 6; **45/47** = 10:1; **46/48** = 12:1). The high diastereoselectivity in the dihydroxylation reaction of **43** and **44** can be explained by assuming envelope and half-chair-like conformations for the compounds in their respective ground states; the bulky OTBDPS group effectively shields the bottom face, so dihydroxylation occurs from the top face (Scheme 6). Removal of the TBDPS protecting group with TBAF (tetrabutylammonium fluoride) gave the corresponding cyclopentane- and cyclohexane-based cyclitols (i.e., **49**–**52**; Scheme 6) in 88% yield. Tetrols **49**–**52** were subsequently converted to their corresponding tetraacetates by treatment with Et_3N and Ac_2O in order to get well-resolved ^1H NMR spectra.



Scheme 5. Synthesis of an enantiopure ε-lactone; reagents and conditions: a) imidazole, TBDPS-Cl, room temp., 8 h, 90%; b) DIBAL-H, CH_2Cl_2, –78 °C, 2 h, 82%; c) MeMgI, –78 °C to room temp., 6 h, 90%; d) TBAF, THF, room temp., 92%; e) 2,2-DMP, CSA, room temp., 8 h, 88%; f) CH_2=$CHCOCl$, DIPEA, DMAP, 88%; g) Grubbs II (5 mol-%), CH_2Cl_2, 8 h, 82%; h) HF/pyridine, 0 °C, 6 h, 78%.

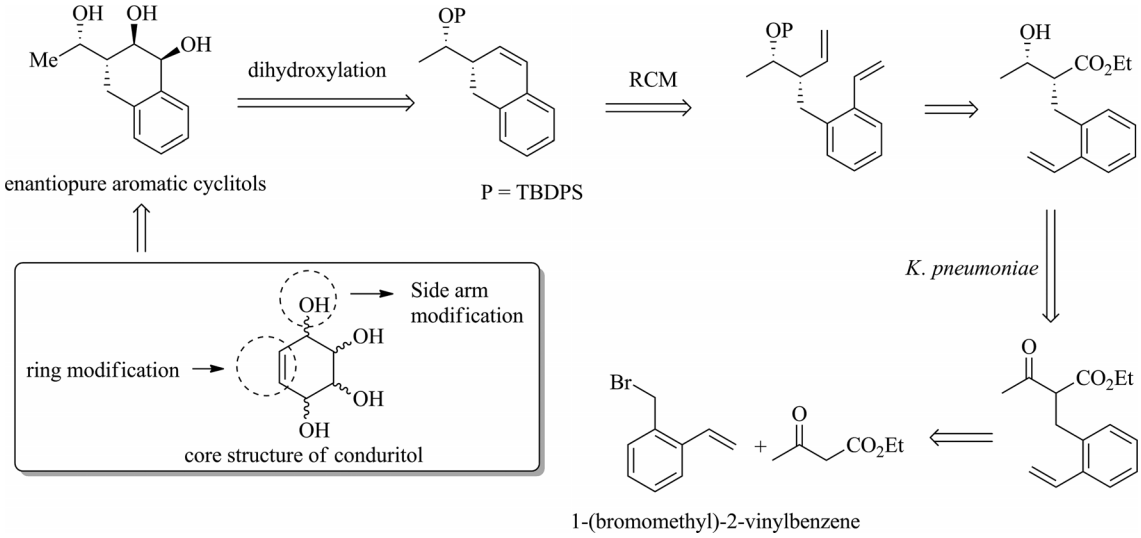


Scheme 6. Synthesis of cyclitols based on cyclopentane/cyclohexane frameworks; reagents and conditions: a) (i) TBAF, THF, room temp., 6 h; (ii) 2,2-DMP, PPTS (pyridine *p*-toluenesulfonate), room temp., 8 h; b) Grubbs I (5 mol-%), room temp., 12 h, 84–90%; c) OsO_4, NMO (*N*-methylmorpholine *N*-oxide), THF/H_2O (3:1), 80–82%; d) TBAF, THF, room temp., 2 h, 88–90%.

Synthesis of Aromatic Cyclitols (R^2–R^3 Reaction Sites)

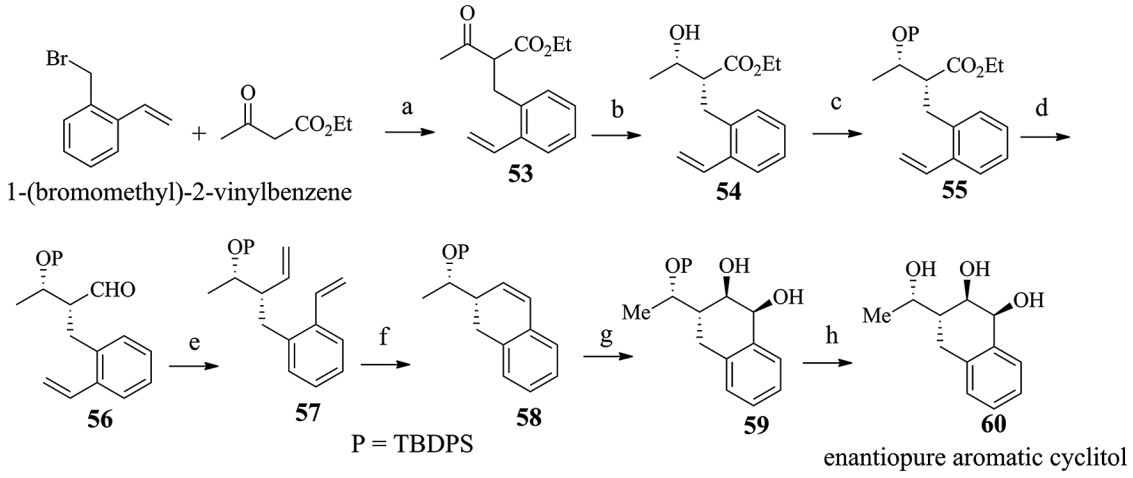
Aryl cyclitols are structural analogues of conduritols − which can be regarded as locked cyclitols − in which the ring double bond is replaced by an aromatic ring. The quest for new analogues of conduritols has mainly been focussed on ring modification and side-chain variation (Scheme 7). Aryl cyclitols are such analogues generated by ring modification.[16] Many unnatural synthetic analogues with the basic core structural units of conduritols have been synthesized. Aryl cyclitols, bicyclic mimics of conduritols with an extra aromatic ring, could have interesting properties such as stacking properties and enhanced lipophilicity.[17] We envisioned that our biocatalytically derived enantiopure β-hydroxy ester might act as an excellent precursor for such aromatic cyclitols, as shown in Scheme 7.

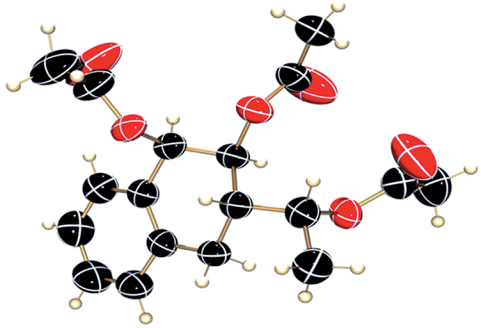
We started our synthesis from ethyl acetoacetate, which was alkylated with 1-(bromomethyl)-2-vinylbenzene in the presence of KO*t*Bu to give substituted β-keto ester **53** in 80% yield. Bioreduction of this β-keto ester with growing cells of *K. pneumoniae* gave the corresponding β-hydroxy ester (i.e., **54**) as the sole product in 76% yield (*ee* > 99%,

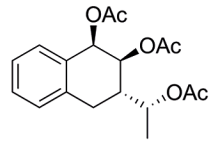


Scheme 7. Retrosynthetic analysis of an enantiopure aromatic cyclitol to start from a β-keto ester.

and *de* > 99%). The secondary hydroxy group was protected as its TBDPS ether by treatment with imidazole and TBDPS-Cl to give compound **55** in 88% yield. The ester functionality in compound **55** was then partially reduced with DIBAL-H at –78 °C to give the corresponding aldehyde (i.e., **56**) in 82% yield. Wittig olefination with $Ph_3P{=}CH_2$ gave olefinic compound **57** in 70% yield. Ring-closing metathesis was then attempted on compound **57** using Grubbs II catalyst[18] and CH_2Cl_2 as a solvent. This went smoothly, and after 12 h at room temperature the corresponding ring-closed product (i.e., **58**) was formed in 78% yield. Substrate-directed dihydroxylation[19] with OsO_4 gave







triacetate derivative of **60**

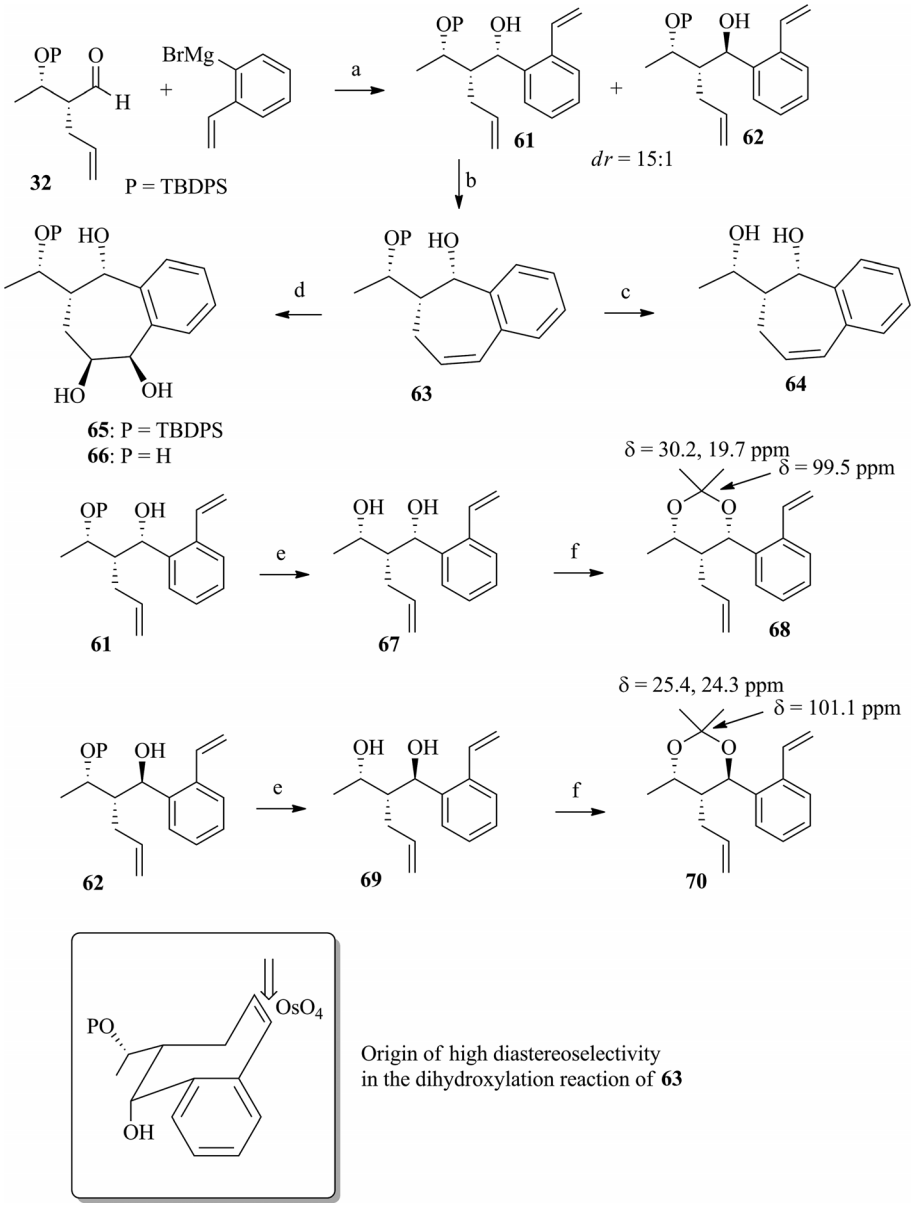
ORTEP presentation (drawn at 30% probability)

Scheme 8. Synthesis of an aromatic cyclitol; reagents and conditions: a) KO*t*Bu, THF, reflux, 12 h, 80%; b) *K. pneumoniae*, 5 d incubation, 76%; c) imidazole, TBDPS-Cl, 6 h, 88%; d) DIBAL-H, –78 °C, 82%; e) $PH_3P^+MeI^-$, LHMDS (lithium hexamethyldisilazide), –78 °C, 70%; f) Grubbs II (5 mol-%), CH_2Cl_2, room temp., 12 h, 78%; g) OsO_4, NMO, THF/water (3:1), 24 h, 70%; h) TBAF, THF, room temp., 6 h, 90%.

diol **59** as the major diastereomer in 70% yield. Subsequent removal of the TBDPS group with TBAF in THF gave enantiopure aromatic cyclitol **60** in 90% yield (Scheme 8). Triol **60** was subsequently converted into its triacetate by treatment with Et_3N and Ac_2O to obtain a well-resolved ^1H NMR spectrum. The structure of triol **60** was confirmed by X-ray crystal analysis of the corresponding triacetate derivative. The ORTEP presentation of the triacetate derivative of **60** is shown in Scheme 8.

Synthesis of Aromatic Cyclitols with a Cycloheptane Ring (R^2–R^3 Reaction Sites)

We went on to synthesize an enantiopure aromatic cyclitol containing a cycloheptane ring. The synthesis was started from the biocatalytically derived known aldehyde **32**. Addition of the Grignard reagent generated from 2-vinyl-1-bromobenzene to aldehyde **32** at –78 °C gave the stereotriad **61/62** with excellent diastereoselectivity (15:1; Scheme 9). The stereochemistry in **61/62** was confirmed by the Rychnovsky protocol by preparing the corresponding acetonide (i.e., **68/70**). A ring-closing metathesis reaction was then attempted with the major diastereomer (i.e., **61**), but this did not give any ring-closed product after repeated attempts with Grubbs I and Grubbs II catalysts. However, ring-closing metathesis with the Hoveyda–Grubbs II catalyst[20] (10 mol-%) was successful, and gave cycloheptane scaffold **63** in 82% yield. Subsequent deprotection of the TBDPS group with TBAF gave enantiopure diol **64** in 89% yield. Dihydroxylation of compound **63** with OsO_4/NMO



Scheme 9. Synthesis of cycloheptane-ring-containing aromatic cyclitol; reagents and conditions: a) Et_2O, –78 °C to room temp., 6 h, 80%; b) Hoveyda–Grubbs II (10 mol-%), CH_2Cl_2, reflux, 8 h, 88%; c) TBAF, THF, room temp., 6 h, 89%; d) (i) OsO_4, NMO, THF/water (3:1), 24 h, 70%; (ii) TBAF, THF, room temp., 8 h, 82%; e) same as (c), 86%; f) 2,2-DMP, PPTS, room temp., 12 h, 90%.

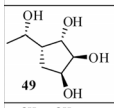
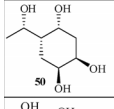
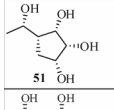
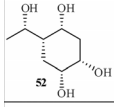
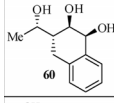
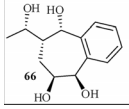
gave triol **65** in 70% yield, which, after TBDPS-group deprotection gave tetrol **66** (57% yield over two steps; Scheme 9). The high diastereoselectivity in the dihydroxylation reaction of **63** can be explained as shown in Scheme 9, by assuming a chair–boat-like conformation for the cycloheptene core. Tetrol **66** was subsequently converted to its tetraacetate by treatment with Et_3N and Ac_2O to obtain a well-resolved ^1H NMR spectrum.

Glycosidase Inhibition Study

Glycosidase inhibition is an important pharmaceutical goal, as proved by current treatments for influenza (Tamiflu) and non-insulin-dependent diabetes (Miglitol/Glyset).[21] Iminocyclitols and other designed analogues (also often called azasugars or iminosugars) are particularly well-studied glycosidase inhibitors that have shown tremendous potential for the treatment of cancer, glycosphingolipid storage disorders, and viral diseases such as HIV and hepatitis B and C.[22] Their efficacy has mainly been attributed to their structural mimicry of the glycosidase "oxocarbenium-ion-like" transition state and the special electrostatic binding interactions at the glycosidase active site. Interestingly, as well as the six-membered pyranoside isosteres, five-membered iminocyclitols have also been found to inhibit glycosidases.[23] This has prompted a huge investment of research into the synthesis and screening of cyclitol libraries.

We carried out glycosidase (α-glucosidase and β-glucosidase) inhibition studies for all the cyclitols whose synthesis is reported in this article (i.e., **49–52**, **60** and **66**), using the corresponding *para*-nitrophenyl glucosides as substrates. The results are summarized in Table 1. Cyclitol **52**, based on a cyclohexane framework, seems to show the best inhibition of both α- and β-glucosidases. The inhibition rates found were 53.0 ± 2% (for α) and 59.0 ± 1.6% (for β) for a 10 μM concentration of compound **52**. Cyclopentane-based cyclitol **51** showed moderate inhibition of both α- and β-glucosidases (the respective inhibition rates were 36.0 ± 2.5% and 30.0 ± 1.8% for a 10 μM concentration of the inhibitor). Compounds **49** and **50** (with similar stereochemical substitution patterns) showed low inhibitory activities against both α- and β-glucosidases at a 10 μM inhibitor concentration. Although the synthesized cyclitols show good inhibitory activities against glucosidases, their activities are substantially lower than clinically used anti-diabetic drugs like miglitol (IC_{50} = 1.3 μM), voglibose (IC_{50} = 0.11 μM), and acarbose (IC_{50} = 0.35 μM),[24] all of which are potent α-glucosidase inhibitors. The inhibitory activity of the synthesized cyclitols can be attributed to their mimicking of the structure of a "strained activated complex"[25] (transition-state analogue) involved in glycoside hydrolysis.

Table 1. Inhibition of glycosidases by cyclitols **49**–**52**, **60**, and **66**.

Cyclitol	Inhibition (%) α-glycosidase[a]	Inhibition (%) β-glycosidase[b]	IC_{50} (μM)[c,d] α-glycosidase	IC_{50} (μM)[c,d] β-glycosidase
 **49**	11.0 ± 3.8	22.0 ± 1.5	31.0 ± 1.5	29.2 ± 2.0
 **50**	17.0 ± 2	9.5 ± 2.5	23.5 ± 2.2	21.2 ± 1.8
 **51**	36.0 ± 2.5	30.0 ± 1.8	12.0 ± 1.1	13.8 ± 1.5
 **52**	53.0 ± 2	59.0 ± 1.6	9.5 ± 1.1	10.2 ± 0.6
 **60**	n.i.[e]	8.0 ± 1.8	n.d.	46.5 ± 2.2
 **66**	14.0 ± 1.6[f]	9.0 ± 2.0[f]	35.0 ± 2.0	49.9 ± 1.5

[a] α-glucosidase from yeast; The inhibitor concentration was 10 μM. [b] β-glucosidase from sweet almonds; The inhibitor concentration was 10 μM. [c] Concentration required for 50% inhibition of enzyme activity under the assay conditions. [d] Experiments were performed at four different concentrations for each compound. Each experiment was performed in triplicate. [e] n.i.: no inhibition (the compound was added in the concentration range of 10–100 μM). [f] For compound **66**, the inhibitor concentration was 50 μM. n.d.: not determined.

Conclusion

In conclusion, we can claim that biocatalytically derived enantiopure α-substituted β-hydroxy esters act as excellent precursors for the synthesis of stereochemically pure carbocycles and heterocycles. In the majority of cases, we have shown that RCM reactions can be successfully used for the construction of core carbocyclic frameworks from linear precursors using a distinctive transformation-based strategy. Once the cyclic scaffold is created, new functionality can be introduced by several stereoselective reactions, such as the substrate-directed dihydroxylation reaction described in this paper. The creation of further molecular diversity from biocatalytically synthesized enantiopure α-substituted β-hydroxy esters is currently in progress, and the results will be reported in due course. The synthesized cyclitols were tested for their inhibitory activity against glycosidases, and moderate to good inhibition was found.

It is also noteworthy that fermenting cells of *Klebsiella pneumoniae* (NBRC 3319) accept α-substituted acetoacetates (bearing a terminal Me group) as their main substrate, and that they produce the corresponding hydroxy esters. Our initial screening of other substrates (without the terminal Me group) was not very encouraging. But we need to screen various α-substituted β-keto esters (without a terminal Me group) to have a better understanding of the substrate spectrum of the ketoreductase from *Klebsiella pneumoniae*.

Experimental Section

General Information: Unless otherwise stated, materials were obtained from commercial suppliers and used without further purification. THF and diethyl ether were distilled from sodium benzophenone ketyl. Dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) were distilled from CaH_2. *Klebsiella pneumoniae* (NBRC 3319; microbial ketoreductase strain form) was obtained from NBRC, Japan. The microorganism is safely handled in a biosafety level 2 enviornment (BSL-2). Bioreductions were carried out in an incubator shaker at 35 °C. Reactions were monitored by thin-layer chromatography (TLC) on 0.25 mm silica gel plates (Merck), which were visualized with UV light, and using 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. Proton nuclear magnetic resonance (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectra were acquired in $CDCl_3$, unless otherwise stated. Chemical shifts are reported in parts per million (ppm, δ), downfield from tetramethylsilane (δ = 0.00 ppm), and are referenced to residual solvent [$CDCl_3$, δ = 7.26 ppm (^{1}H) and 77.16 ppm (^{13}C)]. Coupling constants (J) are reported in Hertz (Hz). Optical rotations were measured with a JASCO P1020 digital polarimeter. HPLC analysis was performed with a CHIRALPAK AD-H (Daicel) column using a UV/Vis detector and a Shimadzu prominence system. Mass spectrometric analysis was performed at the CRF, IIT-Kharagpur (TOF analyser). CCDC-988087 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

General Procedure for Bioreduction: NBRC-3319 mediated bioreduction of several α-substituted β-keto esters for the synthesis of compounds **3**–**8** is reported in our earlier article.[7]

Typical Procedure for the Reduction of Esters to Alcohols Using DIBAL-H, Synthesis of 9: Compound **3** (80 mg, 0.426 mmol) was dissolved in dry THF (3 mL), and the solution was cooled to –78 °C. A solution of DIBAL-H (1 M in cyclohexane; 1 mL, 1 mmol) was added over 15 min. The reaction mixture was stirred for a further 2 h at the same temperature, and then it was warmed to room temperature. After that, the reaction mixture was quenched with dry methanol, and stirred for a further 1.5 h. Then the mixture was filtered through a pad of Celite to remove the solid residues. The filtrate was concentrated, and the resulting residue was dissolved in EtOAc. The organic phase was then washed with brine, and dried with $MgSO_4$. The organic phase was evaporated, and the residue was purified by flash chromatography (EtOAc/hexane, 1:3) to give compound **9** (60 mg, 96%) as a colourless liquid.

(2*S*,3*S*)-2-Butylbutane-1,3-diol (9): R_f = 0.2 (EtOAc/hexane, 1:1). $[\alpha]_D^{29}$ = –13.2 (c = 1.1, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.08–4.00 (m, 1 H), 3.82–3.65 (m, 2 H), 3.00 (br., 2 H, OH), 1.79–1.65 (m, 1 H), 1.31–1.17 (m, 12 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 71.3, 64.4, 45.1, 30.1, 26.0, 23.1, 18.8, 14.2 ppm. HRMS (ESI): calcd. for $C_8H_{18}O_2Na$ [M + Na]$^+$ 169.1204; found 169.1208.

(2*S*,3*S*)-2-Hexylbutane-1,3-diol (10): R_f = 0.2 (EtOAc/hexane, 1:1). $[\alpha]_D^{29}$ = –6.8 (c = 1.1, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.09–4.05 (m, 1 H), 3.84–3.67 (m, 2 H), 2.89 (br., 2 H, OH), 1.73–1.54 (m, 3 H), 1.38–1.18 (m, 14 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 71.5, 64.6, 45.3, 32.0, 29.94, 27.94, 26.38, 22.89, 18.97, 14.33 ppm. HRMS (ESI): calcd. for $C_{10}H_{22}O_2Na$ [M + Na]$^+$ 197.1517; found 197.1515.

(2*S*,3*S*)-2-Isobutylbutane-1,3-diol (11): R_f = 0.25 (EtOAc/hexane, 1:1). $[\alpha]_D^{29}$ = –23.7 (c = 1.1, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.09–4.03 (m, 1 H), 3.79–3.64 (m, 2 H), 3.38 (br., 2 H, OH), 1.82–1.78 (m, 1 H), 1.16 (d, J = 6.4 Hz, 3 H), 1.10–0.98 (m, 2 H), 0.89 (d, J = 6.6 Hz, 3 H), 0.86 (d, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 70.9, 64.2, 42.3, 35.1, 25.4, 23.1, 22.0, 18.3 ppm. HRMS (ESI): calcd. for $C_8H_{18}O_2Na$ [M + Na]$^+$ 169.1204; found 169.1208.

(2*S*,3*S*)-2-(4-Methoxybenzyl)butane-1,3-diol (12): R_f = 0.15 (EtOAc/hexane, 1:1). $[\alpha]_D^{29}$ = +15.4 (c = 1.1, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.04 (d, J = 8.4 Hz, 2 H), 6.77 (d, J = 8.4 Hz, 2 H), 4.12–3.86 (m, 1 H), 3.71 (s, 3 H), 3.64–3.44 (m, 2 H), 2.64–2.37 (m, 2 H), 1.89–1.79 (m, 1 H), 1.19 (d, J = 6.2 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 157.8, 132.4, 129.9, 113.8, 70.1, 63.3, 55.2, 47.3, 31.3, 19.1 ppm. HRMS (ESI): calcd. for $C_{12}H_{18}O_3Na$ [M + Na]$^+$ 233.1154; found 233.1151.

(2*S*,3*S*)-2-(But-3-enyl)butane-1,3-diol (13): R_f = 0.15 (EtOAc/hexane, 1:1). $[\alpha]_D^{29}$ = –17.1 (c = 1.1, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.90–5.69 (m, 1 H), 5.08–4.95 (m, 2 H), 4.14–4.03 (m, 1 H), 3.85–3.68 (m, 2 H), 2.81 (br., 2 H, OH), 2.18–2.01 (m, 2 H), 1.77–1.69 (m, 1 H), 1.42–1.31 (m, 2 H), 1.21 (d, J = 6.4 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 138.4, 114.9, 71.1, 64.2, 44.3, 31.7, 25.0, 18.9 ppm. HRMS (ESI): calcd. for $C_8H_{16}O_2Na$ [M + Na]$^+$ 167.1048; found 167.1051.

(2*S*,3*S*)-2-(Pent-4-enyl)butane-1,3-diol (14): R_f = 0.15 (EtOAc/hexane, 1:1). $[\alpha]_D^{29}$ = –7.2 (c = 1.1, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.88–5.68 (m, 1 H), 5.02–4.91 (m, 2 H), 4.12–4.03 (m, 1 H), 3.92–3.67 (m, 2 H), 3.31 (br., 2 H, OH), 2.06–1.98 (m, 2 H), 1.76–1.68 (m, 1 H), 1.58–1.24 (m, 4 H), 1.18 (d, J = 6.4 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 138.6, 114.7, 71.0, 64.2, 44.9, 33.9, 26.9, 25.5, 18.7 ppm. HRMS (ESI): calcd. for $C_9H_{18}O_2Na$ [M + Na]$^+$ 181.1204; found 181.1209.

Typical Procedure for the Selective Tosylation of the Primary Hydroxy Group, Synthesis of 15: Compound **9** (56 mg, 0.384 mmol) was dissolved in anhydrous CH_2Cl_2 (3 mL). Triethylamine (0.045 mL, 0.384 mmol) was added at 0 °C, and the reaction mixture was then stirred for 15 min at the same temperature. After that time, *p*-toluenesulfonyl chloride (74 mg, 0.384 mmol) was added, and the reaction mixture was stirred for a further 1 h at room temperature. After TLC indicated that the reaction was complete, water was added, and the organic layer was washed with excess water and brine. The organic layer was dried ($MgSO_4$), and the solvents were evaporated to dryness. The residue was then purified by flash chromatography (EtOAc/hexane, 1:5) to give compound **15** (101 mg, 88%) as a colourless liquid.

(*S*)-2-[(*S*)-1-Hydroxyethyl]hexyl 4-Methylbenzenesulfonate (15): R_f = 0.5 (EtOAc/hexane, 1:3). $[\alpha]_D^{29}$ = –7.5 (c = 1.5, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.75 (d, J = 8.4 Hz, 2 H), 7.31 (d, J = 8.0 Hz, 2 H), 4.09–3.94 (m, 2 H), 3.91–3.83 (m, 1 H), 2.41 (s, 3 H), 1.64–1.59 (m, 1 H), 1.34–1.07 (m, 12 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 144.9, 132.8, 129.9, 127.9, 70.6, 67.2, 44.4, 29.5, 25.3, 22.8, 21.6, 20.1, 13.9 ppm. HRMS (ESI): calcd. for $C_{15}H_{24}O_4SNa$ [M + Na]$^+$ 323.1293; found 323.1297.

(*S*)-2-[(*S*)-1-Hydroxyethyl]octyl 4-Methylbenzenesulfonate (16): R_f = 0.5 (EtOAc/hexane, 1:3). $[\alpha]_D^{29}$ = –4.6 (c = 1.1, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.79 (d, J = 7.6 Hz, 2 H), 7.35 (d, J = 7.8 Hz, 2 H), 4.13–3.98 (m, 2 H), 3.95–3.87 (m, 1 H), 2.45 (s, 3 H), 1.67–1.61 (m, 2 H), 1.25–1.11 (m, 15 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 144.8, 132.9, 129.9, 127.9, 70.6, 67.3, 44.4, 31.7, 29.4, 27.3, 25.7, 22.6, 21.6, 20.1, 14.0 ppm. HRMS (ESI): calcd. for $C_{17}H_{28}O_4SNa$ [M + Na]$^+$ 351.1606; found 351.1606.

(*S*)-2-[(*S*)-1-Hydroxyethyl]-4-methylpentyl 4-Methylbenzenesulfonate (17): R_f = 0.4 (EtOAc/hexane, 1:3). $[\alpha]_D^{29}$ = –16.5 (*c* = 1.4, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 8.4 Hz, 2 H), 7.31 (d, *J* = 8.0 Hz, 2 H), 4.09–3.86 (m, 3 H), 2.46 (s, 3 H), 1.81–1.65 (m, 2 H), 1.49–1.29 (m, 1 H), 1.08 (d, *J* = 6.4 Hz, 3 H), 0.80 (d, *J* = 6.6 Hz, 3 H), 0.77 (d, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 144.9, 132.9, 129.9, 127.9, 70.7, 67.1, 41.9, 34.5, 15.6, 23.3, 21.9, 21.6, 19.9 ppm. HRMS (ESI): calcd. for $C_{15}H_{24}O_4SNa$ $[M + Na]^+$ 323.1293; found 323.1297.

(*S*)-2-[(*S*)-1-Hydroxyethyl]-2-(4-methoxybenzyl) 4-Methylbenzenesulfonate (18): R_f = 0.35 (EtOAc/hexane, 1:3). $[\alpha]_D^{29}$ = +9.5 (*c* = 0.9, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.68 (d, *J* = 8.4 Hz, 2 H), 7.29 (d, *J* = 8.4 Hz, 2 H), 6.90 (d, *J* = 8.4 Hz, 2 H), 6.69 (d, *J* = 8.4 Hz, 2 H), 4.16–3.79 (m, 3 H), 3.71 (s, 3 H), 2.81–2.50 (m, 2 H), 2.46 (s, 3 H), 1.89–1.79 (m, 1 H), 1.15 (d, *J* = 6.2 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 158.0, 144.9, 132.7, 131.3, 129.9, 127.9, 113.9, 69.7, 66.8, 55.2, 46.9, 31.2, 21.7, 20.5 ppm. HRMS (ESI): calcd. for $C_{19}H_{24}O_5SNa$ $[M + Na]^+$ 387.1242; found 387.1238.

(*S*)-2-[(*S*)-1-Hydroxyethyl]hex-5-enyl 4-Methylbenzenesulfonate (19): R_f = 0.4 (EtOAc/hexane, 1:3). $[\alpha]_D^{29}$ = –12.4 (*c* = 1.0, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 8.0 Hz, 2 H), 7.35 (d, *J* = 8.0 Hz, 2 H), 5.80–5.60 (m, 1 H), 4.99–4.91 (m, 2 H), 4.14–3.91 (m, 3 H), 2.45 (s, 3 H), 2.1–1.94 (m, 2 H), 1.68–1.55 (m, 3 H), 1.13 (d, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 144.9, 137.9, 132.9, 129.9, 127.9, 115.2, 70.3, 67.2, 43.6, 31.4, 24.8, 21.6, 20.2 ppm. HRMS (ESI): calcd. for $C_{15}H_{22}O_4SNa$ $[M + Na]^+$ 321.1136; found 321.1141.

(*S*)-2-[(*S*)-1-Hydroxyethyl]hept-6-enyl 4-Methylbenzenesulfonate (20): R_f = 0.4 (EtOAc/hexane, 1:3). $[\alpha]_D^{29}$ = –7.1 (*c* = 0.8, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 8.0 Hz, 2 H), 7.33 (d, *J* = 8.0 Hz, 2 H), 5.81–5.61 (m, 1 H), 4.98–4.89 (m, 2 H), 4.23–3.74 (m, 3 H), 2.43 (s, 3 H), 2.02–1.93 (m, 3 H), 1.65–1.53 (m, 2 H), 1.48–1.41 (m, 2 H), 1.03 (d, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 144.0, 138.3, 132.8, 129.9, 127.9, 114.8, 70.5, 67.2, 44.3, 33.8, 26.6, 25.2, 21.7, 20.1 ppm. HRMS (ESI): calcd. for $C_{16}H_{24}O_4SNa$ $[M + Na]^+$ 335.1293; found 335.1298.

Typical Procedure for Oxetane Synthesis, Synthesis of 21: Sodium hydride (60% suspension in mineral oil; 12 mg, 0.266 mmol) was dissolved in anhydrous THF (1 mL), then tosylate compound **15** (80 mg, 0.266 mmol) was added at room temperature. The resulting reaction mixture was then heated at reflux for 1 h. After that time, water was added at 0 °C and the reaction mixture was extracted with Et_2O. The organic layer was successively washed with $NaHCO_3$ solution and brine, and then dried ($MgSO_4$). The organic extract was evaporated in vacuo to give crude oxetane compound **21** as a colourless liquid. The oxetane compounds were then characterized without further purification as they tend to decompose during flash chromatography.

(2*S*,3*S*)-3-Butyl-2-methyloxetane (21): R_f = 0.7 (EtOAc/hexane, 1:15). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.11–4.98 (m, 1 H), 4.73 (dd, *J* = 7.6, 1.8 Hz, 1 H), 4.19 (t, *J* = 6.0 Hz, 1 H), 2.97–2.83 (m, 1 H), 1.66–1.24 (m, 12 H + grease) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 81.4, 74.8, 37.0, 31.9, 30.2, 27.0, 22.6, 14.0 ppm.

(2*S*,3*S*)-3-Hexyl-2-methyloxetane (22): R_f = 0.7 (EtOAc/hexane, 1:15). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.05–5.02 (m, 1 H), 4.72 (dd, *J* = 7.6, 1.6 Hz, 1 H), 4.18 (t, *J* = 6.0 Hz, 1 H), 2.90–2.85 (m, 1 H), 1.85–1.56 (m, 4 H), 1.32–1.21 (m, 12 H + grease) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 81.3, 74.8, 37.6, 31.7, 29.3, 28.5, 27.2, 22.5, 17.6, 14.0 ppm.

(2*S*,3*S*)-3-Isobutyl-2-methyloxetane (23): R_f = 0.6 (EtOAc/hexane, 1:15). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.08–5.0 (m, 1 H), 4.74 (dd, *J* = 7.7, 1.5 Hz, 1 H), 4.24 (t, *J* = 6.2 Hz, 1 H), 3.02–2.93 (m, 1 H), 1.60–1.14 (m, 11 H + grease) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 81.6, 75.3, 37.6, 31.9, 27.1, 22.7, 22.5, 14.1 ppm.

(2*S*,3*S*)-3-(4-Methoxybenzyl)-2-methyloxetane (24): R_f = 0.4 (EtOAc/hexane, 1:15). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.99 (d, *J* = 8.4 Hz, 2 H), 6.77 (d, *J* = 8.4 Hz, 2 H), 5.13–5.0 (m, 1 H), 4.64 (dd, *J* = 7.4, 1.2 Hz, 1 H), 4.25 (t, *J* = 6.3 Hz, 1 H), 3.72 (s, 3 H), 2.84 (d, *J* = 8.2 Hz, 2 H), 1.33 (d, *J* = 6.4 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 158.0, 131.5, 129.2, 113.9, 81.1, 74.1, 55.1, 38.6, 33.5, 17.8 ppm.

(2*S*,3*S*)-3-(But-3-enyl)-2-methyloxetane (25): R_f = 0.72 (EtOAc/hexane, 1:15). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.88–5.67 (m, 1 H), 5.11–4.94 (m, 3 H), 4.72 (dd, *J* = 7.6, 1.8 Hz, 1 H), 4.24 (t, *J* = 5.2 Hz, 1 H), 3.02–2.84 (m, 1 H), 2.01–1.91 (m, 2 H), 1.67–1.24 (m, 5 H + grease) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 138.2, 115.2, 81.4, 74.9, 37.3, 32.1, 22.9, 14.3 ppm.

(2*S*,3*S*)-2-Methyl-3-(pent-4-enyl)oxetane (26): R_f = 0.75 (EtOAc/hexane, 1:15). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.85–5.68 (m, 1 H), 5.10–4.93 (m, 3 H), 4.72 (dd, *J* = 7.6, 1.8 Hz, 1 H), 4.21 (t, *J* = 6.0 Hz, 1 H), 2.94–2.83 (m, 1 H), 2.09–1.99 (m, 2 H), 1.67–1.56 (m, 5 H), 1.32–1.25 (m, 2 H + grease) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 138.4, 114.7, 81.3, 74.7, 37.5, 33.7, 26.6, 22.7, 17.6 ppm.

(*R*)-Ethyl 2-[(*S*)-1-(Allyloxy)ethyl]pent-4-enoate (27): A solution of allyl alcohol (0.34 mL, 5 mmol) in anhydrous diethyl ether (10 mL) was added dropwise to a suspension of NaH (60% in oil; 12 mg, 0.5 mmol) in diethyl ether (10 mL) at room temperature under a nitrogen atmosphere. The resulting mixture was stirred at room temperature for 20 min, and then cooled to 0 °C. Trichloroacetonitrile (TCA, 0.67 mL, 5 mmol) was added dropwise over 5 min, and the reaction mixture was warmed slowly to room temperature over 1 h. The solution was evaporated to give an orange syrup, to which anhydrous hexane (10 mL) containing a few drops of MeOH was then added. The resulting suspension was then shaken vigorously and filtered through Celite, and the filtrate was concentrated to give the crude imidate.

The crude imidate was dissolved in cyclohexane (14 mL), and a solution of alcohol **2** (435 mg, 2.53 mmol) in CH_2Cl_2 (7 mL) was added. The resulting solution was cooled to 0 °C, and CSA (58 mg, 0.25 mmol) was added. The reaction mixture was stirred for 3 d at room temperature, and a white precipitate of trichloroacetamide developed slowly. The precipitate was removed by filtration, and washed with CH_2Cl_2. The filtrate was washed with $NaHCO_3$ solution, water, and brine. The organic phase was evaporated in vacuo, and the residue was purified by flash chromatography (EtOAc/hexane, 1:100) to give compound **27** (428 mg, 80%) as a colourless liquid. R_f = 0.5 (EtOAc/hexane, 1:40). $[\alpha]_D^{25}$ = +7.25 (*c* = 1.2, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.96–5.65 (m, 2 H), 5.30–4.92 (m, 4 H), 4.19–3.84 (m, 4 H), 3.74–3.57 (m, 1 H), 2.63–2.25 (m, 3 H), 1.24 (t, *J* = 7.0 Hz, 3 H), 1.17 (d, *J* = 6.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.4, 135.5, 134.9, 116.7, 116.4, 75.1, 69.9, 60.2, 51.6, 33.1, 17.5, 14.2 ppm. HRMS (ESI): calcd. for $C_{12}H_{20}O_3Na$ $[M + Na]^+$ 235.1342; found 235.1338.

Ethyl (*Z*,2*S*,3*R*)-2,3,4,7-Tetrahydro-2-methyloxepine-3-carboxylate (28): Compound **27** (350 mg, 1.651 mmol) was dissolved in anhydrous degassed CH_2Cl_2 (200 mL). Grubbs first generation metathesis catalyst (Grubbs I; 132 mg, 0.165 mmol) was then added, and the solution was stirred at room temperature for 3 h. The solvent was then evaporated, and the contents of the flask were loaded directly onto a silica gel column. The residue was purified by flash chromatography (EtOAc/hexane, 1:30) to give compound **28**

(197 mg, 65%) as a colourless liquid. R_f = 0.4 (EtOAc/hexane, 1:40). $[\alpha]_D^{29}$ = +36.82 (c = 0.8, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.77–5.53 (m, 2 H), 4.27–3.99 (m, 5 H), 2.66–2.21 (m, 3 H), 1.23 (t, J = 7.2 Hz, 3 H), 1.12 (d, J = 6.4 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.7, 129.7, 129.5, 75.2, 67.2, 60.6, 49.2, 25.1, 17.3, 14.4 ppm. HRMS (ESI): calcd. for $C_{10}H_{16}O_3Na$ $[M + Na]^+$ 207.0972; found 207.0988.

Ethyl (2*S*,3*R*,5*S*,6*R*)-5,6-Dihydroxy-2-methyloxepane-3-carboxylate (29): *t*BuOH (0.2 mL), H_2O (0.2 mL), and AD-mix-β (87 mg) were mixed, and the mixture was stirred for 15 min. $MeSO_2NH_2$ (20 mg) was then added, and stirring was continued for a further 15 min. Compound **28** (120 mg, 0.652 mmol) was then added in one portion. The slurry was then stirred vigorously at 20 °C for 24 h. After that time, sodium sulfite (25 mg) was added, and stirring was continued for a further 1 h. The reaction mixture was then extracted with EtOAc. The organic layer was dried ($MgSO_4$), and the solvents were evaporated in vacuo. The crude diol was purified by flash chromatography (EtOAc/hexane, 1:5) to give streochemically pure diol **29** (102 mg, 72%) as a colourless liquid. R_f = 0.3 (EtOAc/hexane, 1:3). $[\alpha]_D^{29}$ = +21.73 (c = 1.2, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.30–4.09 (m, 2 H), 3.98–3.79 (m, 4 H), 3.65–3.54 (m, 1 H), 2.62–2.21 (m, 3 H), 1.25 (t, J = 7.4 Hz, 3 H), 1.11 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.4, 77.0, 72.2, 70.1, 68.8, 61.2, 48.9, 24.8.17.6, 14.3 ppm.

(3*R*,4*S*,6*S*,7*S*)-6-(Hydroxymethyl)-7-methyloxepane-3,4-diol (30): Oxepane ester **29** (102 mg, 0.47 mmol) was dissolved in dry CH_2Cl_2 (37 mL) and DIBAL-H solution (1 M in toluene; 1.0 mL, 1.0 mmol) was added at –10 °C. The reaction mixture was stirred for 4 h at 0 °C. After that time, the reaction was quenched by the addition of a saturated solution of sodium potassium tartrate. The mixture was then filtered through a pad of Celite, and then extracted several times with CH_2Cl_2. The combined CH_2Cl_2 extracts were then evaporated under vacuum, and the crude alcohol was purified by flash chromatography (EtOAc/hexane, 1:10) to give pure **30** (64 mg, 78%) as a colourless liquid. R_f = 0.2 (EtOAc/hexane, 1:1). $[\alpha]_D^{29}$ = +32.0 (c = 1.0, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.37–4.06 (m, 5 H), 3.76–3.55 (m, 2 H), 2.14–1.96 (m, 1 H), 1.86–1.72 (m, 1 H), 1.63–1.55 (m, 1 H), 1.11 (d, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 75.0, 72.4, 70.2, 68.6, 61.3, 38.9, 25.0, 17.5 ppm.

Ethyl (*R*)-2-[(*S*)-1-Hydroxyethyl]pent-4-enoate (2): The following procedure was modified a little compared to our earlier reported procedure.[7] *Klebsiella pneumoniae* cells were grown in YM (yeast malt) glucose medium in a 500 mL conical flask for 24 h. Compound **1** (2 g, 11.67 mmol) was directly added to the growing cell culture. The reaction was monitored periodically by TLC analysis. It usually took 4 d for quantitative conversion. After the reaction was complete, the mixture was centrifuged (10000 rpm) for 30 min, then the supernatent was collected, and the product alcohol was extracted with EtOAc (3×). The combined organic extracts were washed with brine, and dried with $MgSO_4$. The crude alcohol was then purified by flash chromatography (EtOAc/hexane, 1:10) to give alcohol **2** (1.77 g, 88%) as a colourless liquid. R_f = 0.3 (EtOAc/hexane, 1:5). $[\alpha]_D^{25}$ = +15.3 (c = 1, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.88–5.68 (m, 1 H), 5.12–4.98 (m, 2 H), 4.17 (q, J = 7.2 Hz, 2 H), 4.10–3.94 (m, 1 H), 2.56–2.37 (m, 3 H), 1.29–1.19 (m, 6 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 174.8, 135.5, 116.7, 67.9, 60.6, 52.0, 31.9, 20.3, 14.2 ppm. HRMS (ESI): calcd. for $C_9H_{16}O_3Na$ $[M + Na]^+$ 195.0887; found 195.0988.

(*R*)-Ethyl 2-[(*S*)-1-(*tert*-Butyldiphenylsilyloxy)ethyl]pent-4-enoate (31): Imidazole (1.898 g, 27.907 mmol) and TBDPS-Cl (5 mL, 18.605 mmol) were added to a solution of alcohol **2** (1.6 g, 9.302 mmol) in dry CH_2Cl_2 (40 mL) at 0 °C. The mixture was stirred at room temperature for 6 h. After the reaction was complete, water was added, and the mixture was extracted with CH_2Cl_2 (2×). The combined organic extracts were dried with anhydrous $MgSO_4$, and evaporated in vacuo. The crude product was then purified by flash chromatography (EtOAc/hexane, 1:20) to give compound **31** (3.432 g, 90%) as a viscous liquid. R_f = 0.6 (EtOAc/hexane, 1:10). $[\alpha]_D^{25}$ = –9.04 (c = 1.2, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.76–7.69 (m, 4 H), 7.49–7.35 (m, 6 H), 5.78–5.61 (m, 1 H), 5.08–4.94 (m, 2 H), 4.19–4.04 (m, 3 H), 2.66–2.55 (m, 1 H), 2.37 (t, J = 6.6 Hz, 2 H), 1.25 (t, J = 7.0 Hz, 3 H), 1.08 (12 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.7, 136.1, 136.0, 134.6, 133.9, 129.9, 129.8, 127.8, 127.7, 116.5, 70.6, 60.3, 53.4, 33.0, 27.1, 20.8, 19.5, 14.4 ppm. HRMS (ESI): calcd. for $C_{25}H_{32}O_3SiNa$ $[M + Na]^+$ 433.2175; found 433.2199.

(*R*)-2-[(*S*)-1-(*tert*-Butyldiphenylsilyloxy)ethyl]pent-4-enal (32): TBDPS-protected β-hydroxy ester **31** (3.737 g, 9.116 mmol) was dissolved in dry CH_2Cl_2 (37 mL), and DIBAL-H solution (1 M in toluene; 9.11 mL, 9.11 mmol) was added at –10 °C. The mixture was stirred for 4 h at –10 °C. After that time, the reaction was quenched by the addition of a saturated solution of sodium potassium tartrate. The mixture was then filtered through a pad of Celite, and the filtrate was extracted several times with CH_2Cl_2. The combined CH_2Cl_2 extracts were then evaporated under vacuum, and the crude aldehyde was purified by flash chromatography (EtOAc/hexane, 1:10) to give pure **32** (2.736 g, 82%) as a colourless liquid. R_f = 0.5 (EtOAc/hexane, 1:10). $[\alpha]_D^{25}$ = –0.58 (c = 0.5, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.95 (d, J = 1.2 Hz, 1 H), 7.75–7.68 (m, 4 H), 7.50–7.38 (m, 6 H), 5.62–5.53 (m, 1 H), 5.04–4.94 (m, 2 H), 4.26–4.21 (m, 1 H), 2.56–2.40 (m, 2 H), 2.15–2.10 (m, 1 H), 1.12 (12 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 205.0, 136.1, 135.8, 134.2, 133.6, 130.1, 130.0, 128.0, 127.8, 116.7, 69.5, 58.1, 29.2, 27.2, 20.4, 19.5 ppm. HRMS (ESI): calcd. for $C_{23}H_{30}O_2SiNa$ $[M + Na]^+$ 389.1913; found 389.1936.

(2*R*,3*S*)-3-[(*S*)-1-(*tert*-Butyldiphenylsilyloxy)ethyl]hex-5-en-2-ol (33): Aldehyde **32** (300 mg, 0.82 mmol) was dissolved in dry diethyl ether, and then a freshly prepared MeMgI solution (1.23 mmol in Et_2O) was added at –78 °C. The reaction mixture was then allowed to reach room temperature. After 6 h, the reaction was quenched by the addition of saturated NH_4Cl solution, and then the mixture was extracted with diethyl ether (3×). The combined organic extracts were then dried with anhydrous $MgSO_4$, and evaporated in vacuo. The residue was purified by flash chromatography (EtOAc/hexane, 1:15) to give compound **33** (282 mg, 90%) as a colourless liquid, as the sole product. R_f = 0.4 (EtOAc/hexane, 1:10). $[\alpha]_D^{25}$ = +8.18 (c = 1.2, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.72–7.69 (m, 4 H), 7.49–7.36 (m, 6 H), 5.83–5.63 (m, 1 H), 5.05 (d, J = 17.0 Hz, 1 H), 4.9 (d, J = 10.2 Hz, 1 H), 4.18–4.02 (m, 2 H), 2.43–2.11 (m, 3 H), 1.22 (d, J = 6.6 Hz, 3 H), 1.05 (12 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 139.2, 136.1, 136.0, 134.7, 133.8, 130.0, 129.8, 127.9, 127.7, 115.5, 72.5, 69.5, 51.0, 29.7, 27.2, 22.5, 20.8, 19.4 ppm. HRMS (ESI): calcd. for $C_{24}H_{34}O_2SiNa$ $[M + Na]^+$ 405.2226; found 405.2211.

(2*R*,3*r*,4*S*)-3-Allylpentane-2,4-diol (34): Alcohol **33** was dissolved in dry THF (80 mg, 0.21 mmol), and TBAF solution (1 M in THF; 0.42 mL, 0.42 mmol) was added at room temperature. After 4 h, the solvent was evaporated using a rotary evaporator. The residue was purified by flash chromatography (EtOAc/hexane, 1:3) to give diol **34** (27 mg, 92%) as a colourless liquid. R_f = 0.3 (EtOAc/hexane, 1:2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.03–5.82 (m, 1 H), 5.08 (d, J = 17.0 Hz, 1 H), 4.93 (d, J = 10.2 Hz, 1 H), 4.17–4.06 (m, 2 H), 3.62 (br., 2 H, OH), 2.33–2.27 (m, 2 H), 1.43–1.38 (m, 1

H), 1.23 (d, J = 6.4 Hz, 6 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 140.1, 115.3, 72.4, 49.3, 26.8, 21.8 ppm. HRMS (ESI): calcd. for $C_8H_{16}O_2Na$ $[M + Na]^+$ 167.1048; found 167.1102.

(4*S*,5*r*,6*R*)-5-Allyl-2,2,4,6-tetramethyl-1,3-dioxane (35): Diol **34** (27 mg, 0.18 mmol) was dissolved in dry CH_2Cl_2 (1 mL). 2,2-DMP (0.07 mL, 0.54 mmol) was added to the solution, followed by a catalytic amount of PPTS. The reaction mixture was then stirred for 12 h at room temperature. After that time, the solvent was evaporated under vacuum, and the residue was purified by flash chromatography (EtOAc/hexane, 1:7) to give pure product **35** (26 mg, 90%) as a colourless liquid. R_f = 0.6 (EtOAc/hexane, 1:5). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.99–5.78 (m, 1 H), 5.3 (d, J = 17.2 Hz, 1 H), 4.92 (d, J = 10.0 Hz, 1 H), 4.1 (dq, J = 6.4, 2.0 Hz, 2 H), 2.28–2.22 (m, 2 H), 1.5 (m, 1 H), 1.43 (s, 3 H), 1.38 (s, 3 H), 1.15 (d, J = 6.4 Hz, 6 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 140.4, 114.5, 99.1, 69.8, 43.1, 30.2, 25.6, 19.8, 19.5 ppm.

(2*R*,3*S*)-3-[(*S*)-1-(*tert*-Butyldiphenylsilyloxy)ethyl]hex-5-en-2-yl Acrylate (36): Freshly distilled acryloyl chloride (0.128 mL, 1.579 mmol), DIPEA (0.27 mL, 1.579 mmol), and a catalytic amount of DMAP were added to a solution of alcohol **33** (200 mg, 0.526 mmol) in dry CH_2Cl_2 at 0 °C. The mixture was left at room temperature for 6 h. The reaction was then quenched by the addition water, and the mixture was extracted with CH_2Cl_2 (2× 25 mL). The combined organic extracts were then dried with anhydrous $MgSO_4$ and evaporated in vacuo, and the residue was purified by flash chromatography (EtOAc/hexane, 1:20) to give pure compound **36** (201 mg, 88%) as a colourless liquid. R_f = 0.5 (EtOAc/hexane, 1:10). $[\alpha]_D^{25}$ = –0.87 (c = 1.1, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.73–7.68 (m, 4 H), 7.43–7.40 (m, 6 H), 6.39 (dd, J = 17.2, 1.6 Hz, 1 H), 6.18–6.04 (m, 1 H), 5.80 (dd, J = 10.2, 1.4 Hz, 1 H), 5.63–5.37 (m, 2 H), 4.97–4.85 (m, 2 H), 4.01–3.93 (m, 1 H), 2.32–2.01 (m, 2 H), 1.71–1.61 (m, 1 H), 1.29 (d, J = 6.4 Hz, 3 H), 1.10–1.02 (m, 12 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 165.7, 137.7, 136.1, 134.7, 134.1, 130.3, 129.9, 129.7, 129.4, 127.8, 127.6, 115.8, 70.4, 69.5, 49.8, 31.1, 27.2, 19.5, 19.4, 19.2 ppm. HRMS (ESI): calcd. for $C_{27}H_{36}O_3SiNa$ $[M + Na]^+$ 459.2331; found 459.2348.

(6*S*,7*R*,*Z*)-6-[(*S*)-1-(*tert*-Butyldiphenylsilyloxy)ethyl]-7-methyl-6,7-dihydrooxepin-2(5*H*)-one (37): Ester **36** (100 mg, 0.23 mmol) was dissolved in CH_2Cl_2 (200 mL), which had previously been was degassed by purging a positive pressure of argon. Grubbs 2nd generation catalyst (Grubbs II; 0.0115 mol, 10 mg) was added, and the reaction mixture was heated at reflux under an argon atmosphere for 8 h. After TLC indicated that the reaction was complete, air was bubbled into the reaction mixture to quench any catalyst present in the solution. The solvent was then evaporated, and the residue was purified by flash chromatography (EtOAc/hexane, 1:20) to give pure RCM product **37** (77 mg, 83%) as a colourless liquid. R_f = 0.4 (EtOAc/hexane, 1:10). $[\alpha]_D^{25}$ = +30.51 (c = 1.5, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.67–7.64 (m, 4 H), 7.43–7.27 (m, 6 H), 6.68–6.59 (m, 1 H), 5.97 (d, J = 11.0 Hz, 1 H), 4.64–4.50 (m, 1 H), 3.89 (q, J = 5.8 Hz, 1 H), 2.74–2.35 (m, 2 H), 1.93–1.85 (m, 1 H), 1.24 (d, J = 6.4 Hz, 3 H), 1.07–1.04 (12 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 170.1, 144.1, 136.1, 136.0, 134.3, 133.2, 130.2, 129.9, 128.0, 127.7, 122.5, 69.4, 52.7, 27.2, 25.7, 22.4, 19.5, 19.1 ppm. HRMS (ESI): calcd. for $C_{25}H_{32}O_3SiNa$ $[M + Na]^+$ 431.2018; found 431.2047.

(6*R*,7*R*,*Z*)-6-[(*S*)-1-Hydroxyethyl]-7-methyl-6,7-dihydrooxepin-2(5*H*)-one (38): TBDPS-protected ε-lactone **37** (70 mg, 0.172 mmol) was dissolved in dry THF (1 mL), and HF/pyridine (7:3; 250 μL) was added dropwise to the solution at 0 °C. The reaction mixture was then warmed to room temperature, and stirring was continued for 72 h. Then the reaction mixture was quenched with a saturated solution of $NaHCO_3$, and the mixture was extracted with EtOAc (2× 20 mL). The combined organic extracts were dried with $MgSO_4$, and concentrated in a rotary evaporator. The crude residue was then purified by flash chromatography on silica (EtOAc/hexane, 1:10) to give ε-lactone **38** (23 mg, 78%) as a colourless liquid. R_f = 0.5 (EtOAc/hexane, 1:5). $[\alpha]_D^{25}$ = +15.21 (c = 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.88 (d, J = 11.2 Hz, 1 H), 4.63–4.47 (m, 1 H), 3.86 (q, J = 5.6 Hz, 1 H), 2.6–2.36 (m, 2 H), 1.89–1.83 (m, 1 H), 1.23 (d, J = 6.4 Hz, 3 H), 1.1–1.05 (12 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 170.2, 127.8, 127.6, 122.0, 68.8, 53.1, 25.4, 22.6, 18.9 ppm. HRMS (ESI): calcd. for $C_{25}H_{32}O_3SiNa$ $[M + Na]^+$ 193.0841; found 193.0822.

(3*R*,4*S*)-4-[(*S*)-1-(*tert*-Butyldiphenylsilyloxy)ethyl]hepta-1,6-dien-3-ol (39): Aldehyde **32** (400 mg, 1.093 mmol) was dissolved in dry THF (5 mL), and then vinylmagnesium bromide (1 M in THF; 1.64 mL, 1.64 mmol) was added at –78 °C. The reaction mixture was then allowed to reach room temperature. After 3 h, the reaction was quenched by the addition of saturated aqueous NH_4Cl, then the THF was evaporated under vacuum, and the mixture was extracted with diethyl ether (3×). The combined organic extracts were then dried with anhydrous $MgSO_4$, and evaporated in vacuo. The residue was purified by flash chromatography (EtOAc/hexane, 1:15) to give compound **39** (345 mg, 80%) as a colourless liquid, as the sole product. R_f = 0.5 (EtOAc/hexane, 1:10). $[\alpha]_D^{25}$ = +28.0 (c = 0.5, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.71–7.67 (m, 4 H), 7.42–7.30 (m, 6 H), 5.92–5.83 (m, 1 H), 5.51–5.75 (m, 1 H), 5.29–4.86 (m, 4 H), 4.55–4.53 (m, 1 H), 4.08 (dd, J = 6.4, 3.4 Hz, 1 H), 2.25–2.09 (m, 2 H), 1.70–1.62 (m, 1 H), 1.09–1.06 (s, 12 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 140.9, 138.5, 136.1, 134.6, 133.9, 130.0, 129.8, 127.9, 127.7, 115.8, 114.6, 73.7, 72.0, 49.7, 29.8, 27.3, 20.5, 19.4 ppm. HRMS (ESI): calcd. for $C_{25}H_{34}O_2SiNa$ $[M + Na]^+$ 417.2226; found 417.2252.

(4*S*,5*R*,6*R*)-5-Allyl-2,2,4-trimethyl-6-vinyl-1,3-dioxane (41): The TBDPS group was removed from compound **39** with TBAF, as described above for the synthesis of compound **34**, to give (2*S*,3*R*,4*R*)-3-allylhex-5-ene-2,4-diol. R_f = 0.4 (EtOAc/hexane, 1:3). $[\alpha]_D^{25}$ = +23.2 (c = 0.5, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.0–5.77 (m, 2 H), 5.30–4.92 (m, 4 H), 4.41 (d, J = 1.4 Hz, 1 H), 4.18–4.09 (m, 1 H), 2.27–2.21 (m, 2 H), 1.58 (dd, J = 5.6, 2.6 Hz, 1 H), 1.22 (d, J = 6.4 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 139.9, 139.5, 115.6, 115.0, 76.4, 71.3, 48.7, 27.4, 21.7 ppm. HRMS (ESI): calcd. for $C_9H_{16}O_2Na$ $[M + Na]^+$ 179.1048; found 179.1093.

The diol obtained in the previous step (40 mg, 0.256 mmol) was dissolved in dry CH_2Cl_2 (1 mL). 2,2-DMP (0.157 mL, 1.282 mmol) was added to the solution, followed by a catalytic amount of PPTS. The reaction mixture was then stirred for 12 h at room temperature. After that time, the solvent was evaporated under vacuum, and the residue was purified by flash chromatography (EtOAc/hexane, 1:7) to give pure product **41** (45 mg, 90%) as a viscous liquid. R_f = 0.5 (EtOAc/hexane, 1:20). $[\alpha]_D^{25}$ = +15.4 (c = 0.5, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.90–5.74 (m, 2 H), 5.31–4.87 (m, 4 H), 4.51–4.40 (m, 1 H), 4.17–4.11 (m, 1 H), 2.33–2.10 (m, 2 H), 1.72–1.59 (m, 1 H), 1.44 (d, J = 6.4 Hz, 6 H), 1.18 (d, J = 6.4 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 140.2, 137.6, 115.4, 114.6, 99.3, 74.5, 69.5, 42.7, 30.1, 26.2, 19.8, 19.6 ppm. HRMS (ESI): calcd. for $C_{12}H_{20}O_2Na$ $[M + Na]^+$ 219.1361; found 219.1356.

(1*R*,5*S*)-5-[(*S*)-1-(*tert*-Butyldiphenylsilyloxy)ethyl]cyclopent-2-enol (43): Compound **39** (260 mg, 0.66 mmol) was dissolved in anhydrous CH_2Cl_2 (degassed by argon purging; 300 mL), and Grubbs 1st generation catalyst (Grubbs I; 0.033 mol, 27.0 mg) was added.

The reaction solution was stirred under an argon atmosphere for 8 h. After that time, air was bubbled into the reaction solution to quench any remaining catalyst present in the solution. The organic solvent was then evaporated, and the residue was purified by flash chromatography (EtOAc/hexane, 1:20) to give pure product **43** (217 mg, 90%) as a colourless liquid. R_f = 0.3 (EtOAc/hexane, 1:5). $[a]_D^{25}$ = –20.53 (c = 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.72–7.70 (m, 4 H), 7.44–7.36 (m, 6 H), 6.01 (t, J = 2.8 Hz, 1 H), 5.88 (dd, J = 5.6, 2.0 Hz, 1 H), 4.67 (s, 1 H), 4.27–4.24 (m, 1 H), 2.431 (d, J = 7.6 Hz, 2 H), 2.27–2.23 (m, 1 H), 1.14 (d, J = 6.0 Hz, 3 H), 1.03 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.9, 135.8, 135.0, 134.6, 133.9, 139.6, 129.5, 127.6, 127.4, 77.4, 70.8, 48.8, 33.6, 27.0, 22.8, 19.3 ppm. HRMS (ESI): calcd. for $C_{23}H_{30}O_2SiNa$ [M + Na]$^+$ 389.1913; found 389.1923.

(1*S*,2*S*,3*S*,4*S*)-4-[(*S*)-1-(*tert*-Butyldiphenylsilyloxy)ethyl]cyclopentane-1,2,3-triol (45) and (1*R*,2*R*,3*S*,4*S*)-4-[(*S*)-1-(*tert*-Butyldiphenylsilyloxy)ethyl]cyclopentane-1,2,3-triol (47): Compound **43** (90 mg, 0.246 mmol) was dissolved in a THF/water mixture (3:1; 4 mL), and the solution was cooled to 0 °C. OsO_4 (0.05 M solution in toluene; 0.492 mL, 0.0246 mmol) and NMO (57.6 mg, 0.492 mmol) were added successively to the reaction mixture at 0 °C, and the reaction mixture was allowed to reach room temperature. The mixture was then stirred at room temperature for 12 h. When the reaction was complete, a saturated Na_2SO_3 solution was added at 0 °C to quench the reaction. Then the mixture was extracted with EtOAc (3 ×), and the combined organic extracts were dried with $MgSO_4$, and evaporated under vacuum. The product was purified by flash chromatography (EtOAc/hexane, 1:10) to give a mixture of triols **45** (72.8 mg) and **47** (7.2 mg) in a 10:1 ratio (80%) as a viscous liquid. R_f = 0.3 (EtOAc/hexane, 1:1).

Data for **45**: $[a]_D^{25}$ = +16.78 (c = 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.74–7.69 (m, 4 H), 7.45–7.39 (m, 6 H), 4.36–4.33 (m, 2 H), 4.20 (d, J = 4.4 Hz, 1 H), 2.41–2.39 (m, 1 H), 2.24–2.20 (m, 1 H), 1.82–1.76 (m, 1 H), 1.02 (s, 9 H), 0.96 (d, J = 6.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.0, 135.9, 134.5, 133.2, 130.2, 129.9, 128.1, 127.8, 79.8, 79.4, 71.5, 71.0, 44.9, 30.8, 27.2, 22.5, 19.4 ppm. HRMS (ESI): calcd. for $C_{23}H_{32}O_4SiNa$ [M + Na]$^+$ 423.1967; found 423.2000.

Data for **47**: $[a]_D^{25}$ = +20.52 (c = 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.74–7.70 (m, 4 H), 7.45–7.38 (m, 6 H), 4.39–4.33 (m, 2 H), 4.21 (d, J = 4.2 Hz, 1 H), 2.41–2.39 (m, 1 H), 2.26–2.20 (m, 1 H), 1.82–1.76 (m, 1 H), 1.02 (s, 9 H), 0.96 (d, J = 6.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.0, 135.9, 134.5, 133.8, 130.1, 130.0, 128.0, 127.7, 81.6, 79.5, 72.9, 72.0, 45.0, 30.8, 27.1, 22.5, 19.5 ppm.

(1*S*,2*S*,3*S*,4*R*)-4-[(*S*)-1-Acetoxyethyl]cyclopentane-1,2,3-triyl Triacetate (Tetraacetate of 49): A solution of triol **45** in dry THF (70 mg, 0.175 mmol) was treated with TBAF (1 M in THF; 0.35 mL, 0.35 mmol) at room temperature. After 6 h, the solvent was evaporated, and the residue was purified by flash chromatography (EtOAc/hexane, 1:5) to give tetrol **49** (27 mg, 0.167 mmol) as a viscous liquid.

Tetrol **49** (25 mg, 0.154 mmol) was dissolved in distilled Et_3N (1 mL), and Ac_2O (0.122 mL, 0.875 mmol) was added along with a catalytic amount of DMAP at room temperature. The reaction mixture was stirred at room temperature for 3 d, then the Et_3N was evaporated under vacuum, and the residue was purified by column chromatography (EtOAc/hexane, 1:10) to give the pure tetraacetate (35.6 mg, 70%) as a gummy solid. R_f = 0.4 (EtOAc/hexane, 1:5). $[a]_D^{25}$ = +63.13 (c = 0.5, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 5.35–5.27 (m, 2 H), 5.13–5.10 (m, 1 H), 4.94–4.88 (m, 1 H), 2.61–2.55 (m, 1 H), 2.23–2.13 (m, 1 H), 2.07–1.98 (m, 12 H), 1.97–1.89 (m, 1 H), 1.16 (d, J = 6.0 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 171.0, 170.3, 76.2, 75.5, 70.9, 68.1, 40.0, 28.7, 21.5, 21.0, 20.9, 20.8, 18.4 ppm. HRMS (ESI): calcd. for $C_{15}H_{22}O_8Na$ [M + Na]$^+$ 353.1212; found 353.1224.

(1*R*,2*R*,3*S*,4*R*)-4-[(*S*)-1-Acetoxyethyl]cyclopentane-1,2,3-triyl Triacetate (Tetraacetate of 51): $[a]_D^{25}$ = –8.12 (c = 0.5, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 5.45–5.27 (m, 2 H), 5.14–5.10 (m, 1 H), 4.94–4.88 (m, 1 H), 2.62–2.55 (m, 1 H), 2.23–2.13 (m, 1 H), 2.07–1.97 (m, 12 H), 1.97–1.89 (m, 1 H), 1.16 (d, J = 6.4 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 171.0, 170.3, 170.1, 76.1, 75.6, 72.8, 70.5, 40.1, 28.6, 21.5, 21.1, 21.0, 20.9, 18.3 ppm. HRMS (ESI): calcd. for $C_{15}H_{22}O_8Na$ [M + Na]$^+$ 353.1212; found 353.1224.

(4*R*,5*S*)-5-[(*S*)-1-(*tert*-Butyldiphenylsilyloxy)ethyl]octa-1,7-dien-4-ol (40): Aldehyde **32** (477 mg, 1.3033 mmol) was dissolved in THF, and then Zn dust (170 mg) and allyl bromide (0.26 mL, 2.6066 mmol) were added at 10 °C. Then, saturated aqueous NH_4Cl solution (0.1 mL) was added portionwise to the reaction mixture over 0.5 h. The reaction mixture was then allowed to reach room temperature, and stirred vigorously for 6 h. The mixture was extracted with diethyl ether (3 ×). The combined organic extracts were then dried with anhydrous $MgSO_4$ and evaporated in vacuo. The residue was purified by flash chromatography (EtOAc/hexane, 1:20) to give compound **40** (372 mg, 70%) as a colourless liquid. R_f = 0.5 (EtOAc/hexane, 1:10). $[a]_D^{25}$ = +9.95 (c = 0.5, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 7.71–7.66 (m, 4 H), 7.44–7.34 (m, 6 H), 5.78–5.59 (m, 2 H), 5.12–4.86 (m, 4 H), 4.07–4.02 (m, 2 H), 2.33–2.10 (m, 4 H), 1.57–1.49 (m, 1 H), 1.06–1.04 (12 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 138.9, 136.1, 136.0, 135.7, 134.7, 133.9, 129.9, 129.7, 127.8, 127.6, 117.9, 115.5, 72.0, 71.6, 48.9, 40.8, 29.5, 27.2, 20.5, 19.4 ppm. HRMS (ESI): calcd. for $C_{26}H_{36}O_2SiNa$ [M + Na]$^+$ 431.2382; found 431.2381.

(4*R*,5*R*,6*S*)-4,5-Diallyl-2,2,6-trimethyl-1,3-dioxane (42): The TBDPS group was removed from compound **40** with TBAF as described above for the synthesis of compound **34**, to give (2*S*,3*R*,4*R*)-3-allylhept-6-ene-2,4-diol. R_f = 0.4 (EtOAc/hexane, 1:3). $[a]_D^{25}$ = +5.71 (c = 0.5, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 6.0–5.66 (m, 2 H), 5.15–4.94 (m, 4 H), 4.14–4.03 (m, 1 H), 3.95–3.87 (m, 1 H), 2.32–2.25 (m, 4 H), 1.51–1.46 (m, 1 H), 1.21 (d, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 139.8, 135.1, 118.3, 115.4, 75.5, 72.5, 47.3, 40.2, 26.7, 21 ppm. HRMS (ESI): calcd. for $C_{10}H_{18}O_2Na$ [M + Na]$^+$ 193.1205; found 193.1212.

The acetonide protection of the diol was done by the same procedure described above for the synthesis of compound **35**, to give **42**. R_f = 0.5 (EtOAc/hexane, 1:20). $[a]_D^{25}$ = +10.04 (c = 0.5, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 5.90–5.65 (m, 2 H), 5.14–4.90 (m, 4 H), 4.10–4.06 (m, 1 H), 3.94–3.87 (m, 1 H), 2.31–2.21 (m, 4 H), 1.42–1.39 (m, 6 H), 1.36–1.25 (m, 1 H), 1.17 (d, J = 6.4 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 140.1, 134.8, 117.2, 114.7, 99.3, 74.1, 67.0, 41.2, 37.6, 30.2, 25.9, 19.8, 19.6 ppm. HRMS (ESI): calcd. for $C_{13}H_{22}O_2Na$ [M + Na]$^+$ 233.1517; found 233.1521.

(1*R*,6*S*)-6-[(*S*)-1-(*tert*-Butyldiphenylsilyloxy)ethyl]cyclohex-3-enol (44): Compound **40** (250 mg, 0.613 mmol) was dissolved in anhydrous CH_2Cl_2 (degassed by argon purging; 300 mL), and Grubbs 1st generation catalyst (Grubbs I; 0.03 mmol, 25.0 mg) was added. The reaction solution was stirred under an argon atmosphere for 10 h. After that time, air was bubbled into the reaction solution to quench the catalyst, the solvent was evaporated, and the residue was purified by flash chromatography (EtOAc/hexane, 1:20) to give pure product **44** (196 mg, 84%) as a colourless liquid. R_f = 0.3 (EtOAc/hexane, 1:5). $[a]_D^{25}$ = +76.43 (c = 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.77–7.72 (m, 4 H), 7.47–7.37 (m, 6 H),

5.86–5.81 (m, 1 H), 5.62–5.59 (m, 1 H), 4.25–4.19 (m, 2 H), 2.42–2.14 (m, 4 H), 1.64–1.60 (m, 1 H), 1.04 (s, 9 H), 0.95 (d, J = 6.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.1, 136.0, 134.7, 133.4, 130.1, 129.8, 128.0, 127.7, 126.7, 123.5, 74.8, 68.7, 44.1, 34.3, 27.2, 21.6, 20.8, 19.5 ppm. HRMS (ESI): calcd. for $C_{24}H_{32}O_2SiNa$ $[M + Na]^+$ 403.2069; found 403.2108.

(1*S*,2*R*,4*R*,5*S*)-5-[(*S*)-1-(*tert*-Butyldiphenylsilyloxy)ethyl]cyclohexane-1,2,4-triol (46) and (1*R*,2*S*,4*R*,5*S*)-5-[(*S*)-1-(*tert*-Butyldiphenylsilyloxy)ethyl]cyclohexane-1,2,4-triol (48): Compound **44** (105 mg, 0.276 mmol) was dissolved in a THF/water mixture (3:1; 4 mL), and the solution was cooled to 0 °C. OsO_4 (0.05 M solution in toluene; 0.553 mL, 0.0276 mmol) and NMO (64.7 mg, 0.552 mmol) were added at 0 °C, and the mixture was allowed to reach room temperature. The mixture was then stirred at room temperature for 12 h. When the reaction was complete, a saturated Na_2SO_3 solution was added at 0 °C to quench the reaction. The product was extracted with EtOAc (3 ×), and the combined organic extracts were dried with $MgSO_4$, and evaporated under vacuum. The residue was purified by flash chromatography (EtOAc/hexane, 1:10) to give a mixture of two diastereomeric triols, **46** (86.8 mg) and **48** (7.2 mg), in a 12:1 ratio (82%) as a viscous liquid. R_f = 0.3 (EtOAc/hexane, 1:1).

Data for **46**: $[\alpha]_D^{25}$ = +27.47 (c = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76–7.70 (m, 4 H), 7.46–7.38 (m, 6 H), 4.32–4.15 (m, 4 H), 2.12–2.06 (m, 1 H), 1.96–1.93 (m, 2 H), 1.77–1.71 (m, 2 H), 1.01 (s, 9 H), 0.92 (d, J = 6.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.0, 135.9, 134.4, 133.1, 130.2, 129.9, 128.1, 127.7, 74.8, 71.8, 69.3, 68.6, 39.9, 35.4, 27.1, 24.5, 22.0, 19.4 ppm. HRMS (ESI): calcd. for $C_{24}H_{34}O_4SiNa$ $[M + Na]^+$ 437.2124; found 437.2151.

Data for **48**: $[\alpha]_D^{25}$ = +13.4 (c = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75–7.71 (m, 4 H), 7.46–7.39 (m, 6 H), 4.28–4.26 (m, 1 H), 4.05 (s, 1 H), 3.96 (s, 1 H), 3.56 (s, 1 H), 2.35–2.30 (m, 1 H), 2.0–1.94 (m, 2 H), 1.57–1.50 (m, 1 H), 1.41–1.33 (m, 1 H), 1.02 (s, 9 H), 0.96 (d, J = 6.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.0, 135.9, 134.2, 133.0, 130.2, 129.9, 128.1, 127.8, 74.4, 71.8, 71.0, 70.5, 46.4, 35.7, 27.1, 23.8, 21.7, 19.5 ppm.

(1*S*,2*R*,4*R*,5*R*)-5-[(*S*)-1-Acetoxyethyl]cyclohexane-1,2,4-triyl Triacetate (Tetraacetate of 50): The tetraacetate of compound **50** was prepared as described above for the synthesis of the tetraacetate of **49**. R_f = 0.4 (EtOAc/hexane, 1:5). $[\alpha]_D^{25}$ = +11.53 (c = 0.5, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.40 (s, 1 H), 5.28 (s, 1 H), 5.04–4.99 (m, 1 H), 4.77–4.74 (m, 1 H), 2.11–1.91 (m, 16 H), 1.816–1.746 (m, 1 H), 1.2 (d, J = 6.0 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 170.3, 170.2, 70.9, 69.3, 68.1, 38.9, 30.2, 27.2, 21.2, 21.1, 20.9, 18.1 ppm. HRMS (ESI): calcd. for $C_{16}H_{24}O_8SiNa$ $[M + Na]^+$ 367.1369; found 367.1385.

(1*R*,2*S*,4*R*,5*R*)-5-[(*S*)-1-Acetoxyethyl]cyclohexane-1,2,4-triyl Triacetate (Tetraacetate of 52): The tetraacetate of compound **52** was prepared as described above for the synthesis of the tetraacetate of **49**. R_f = 0.4 (EtOAc/hexane, 1:5). $[\alpha]_D^{25}$ = –8.72 (c = 0.5, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.27–5.27 (m, 1 H), 5.01–5.0 (m, 1 H), 4.90–4.81 (m, 2 H), 2.06–1.98 (m, 15 H), 1.794–1.686 (m, 2 H), 1.18 (d, J = 6.0 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 170.4, 170.2, 170.1, 170.0, 70.9, 70.7, 67.2, 66.9, 42.8, 31.9, 23.9, 21.2, 21.1, 21.0, 20.9, 17.9 ppm.

Ethyl 3-Oxo-2-(2-vinylbenzyl)butanoate (53): KO*t*Bu (3.588 g, 31.98 mmol) and *t*BuOH (0.27 mL, 089 mmol) were added to a solution of ethylacetoacetate (4 mL, 31.98 mmol) in dry THF at 0 °C under an argon atmosphere. The reaction mixture was then stirred at 0 °C for 20 min, and then a solution of 1-(bromomethyl)-2-vinylbenzene (6 g, 31.98 mmol) in dry THF was added dropwise. The reaction mixture was then stirred at reflux. After 12 h, the mixture was cooled to room temperature, and then ice-cooled water was added to quench the reaction. The THF was evaporated under vacuum, and diethyl ether was added. The product was extracted with diethyl ether (3 ×), and the combined organic extracts were dried with $MgSO_4$, and concentrated. The residue was purified by flash chromatography (EtOAc/hexane, 1:25) to give pure compound **53** (6.293 g, 80%) as a colourless liquid. R_f = 0.6 (EtOAc/hexane, 1:10). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.50–7.45 (m, 1 H), 7.27–7.10 (m, 3 H), 7.06–6.92 (dd, J = 17.0, 11.0 Hz, 1 H), 5.65 (d, J = 17.0 Hz, 1 H), 5.35 (d, J = 11.0 Hz, 1 H), 4.19–4.08 (m, 2 H), 3.80–3.73 (m, 1 H), 3.29–3.22 (m, 2 H), 2.16 (s, 3 H), 1.20 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 202.7, 169.3, 137.0, 135.5, 134.3, 130.3, 128.0, 127.3, 126.3, 116.7, 61.6, 60.3, 31.4, 29.9, 14.1 ppm. HRMS (ESI): calcd. for $C_{15}H_{18}O_3Na$ $[M + Na]^+$ 269.1154; found 269.1169.

(2*R*,3*S*)-Ethyl-3-hydroxy-2-(2-vinylbenzyl)butanoate (54): Bioreduction of compound **53** with *K. pneumoniae* (NBRC 3319) was carried out as described above for the synthesis of compound **2**, to give **54** (76%) as a colourless liquid. R_f = 0.5 (EtOAc/hexane, 1:5). $[\alpha]_D^{25}$ = +29.1 (c = 1.0, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.49–7.45 (m, 1 H), 7.26–7.08 (m, 3 H), 7.05–6.91 (dd, J = 17.2, 11.0 Hz, 1 H), 5.65 (d, J = 17.4 Hz, 1 H), 5.31 (d, J = 11.0 Hz, 1 H), 4.06–3.93 (m, 3 H), 3.19–2.93 (m, 2 H), 2.75–2.65 (m, 1 H), 1.26 (d, J = 6.2 Hz, 3 H), 1.05 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 174.7, 136.9, 136.6, 134.4, 130.2, 127.8, 127.0, 126.0, 116.1, 68.3, 60.7, 53.7, 31.0, 20.5, 14.1 ppm. HRMS (ESI): calcd. for $C_{15}H_{20}O_3Na$ $[M + Na]^+$ 271.1310; found 271.1357.

(2*R*,3*S*)-Ethyl 3-(*tert*-Butyldiphenylsilyloxy)-2-(2-vinylbenzyl)butanoate (55): Imidazole (197.6 mg, 2.903 mmol) and TBDPS-Cl (0.44 mL, 1.742 mmol) were added to a solution of alcohol **54** (360 mg, 1.452 mmol) in dry CH_2Cl_2 (6 mL) at 0 °C. The mixture was stirred at room temperature for 6 h. After the reaction was complete, water was added, and the mixture was extracted with CH_2Cl_2 (2 ×). The combined organic extracts were then dried with anhydrous $MgSO_4$. The organic solvent was evaporated in vacuo, and the residue was purified by flash chromatography (EtOAc/hexane, 1:20) to give pure **55** (622.3 mg, 88%) as a viscous liquid. R_f = 0.7 (EtOAc/hexane, 1:10). $[\alpha]_D^{25}$ = +34.22 (c = 1.4, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.81–7.79 (m, 4 H), 7.49–7.46 (m, 7 H), 7.30–6.97 (m, 4 H), 5.71 (d, J = 17.4 Hz, 1 H), 5.35 (d, J = 11.0 Hz, 1 H), 4.27–4.17 (m, 1 H), 4.04 (q, J = 7.2 Hz, 2 H), 3.28–3.18 (m, 1 H), 3.07–2.91 (m, 2 H), 1.36 (3 H), 1.21–1.09 (12 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.6, 137.1, 136.9, 136.1, 134.7, 133.8, 130.2, 129.9, 129.8, 127.9, 127.7, 126.8, 126.0, 115.9, 71.1, 61.3, 55.3, 32.5, 29.9, 27.2, 21.1, 19.6, 14.2 ppm. HRMS (ESI): calcd. for $C_{31}H_{38}O_3SiNa$ $[M + Na]^+$ 509.2488; found 509.2495.

(2*R*,3*S*)-3-(*tert*-Butyldiphenylsilyloxy)-2-(2-vinylbenzyl)butanal (56): TBDPS-protected hydroxy ester **55** (600 mg, 1.232 mmol) was dissolved in dry CH_2Cl_2 (15 mL) and DIBAL-H (1 M solution in toluene; 1.23 mL, 1.23 mmol) was added at –10 °C. The mixture was stirred for 4 h at –10 °C. After that time, the reaction was quenched by the addition of a saturated solution of sodium potassium tartrate. Then the mixture was filtered through a pad of Celite, and extracted several times with CH_2Cl_2. The combined CH_2Cl_2 extracts were then evaporated under vacuum. The residue was then purified by silica gel flash chromatography (EtOAc/hexane, 1:10) to give pure **56** (446 mg, 82%) as a colourless liquid. R_f = 0.6 (EtOAc/hexane, 1:10). $[\alpha]_D^{25}$ = +17.88 (c = 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.93 (d, J = 1.2 Hz, 1 H), 7.67–7.59 (m, 4 H), 7.44–

7.35 (m, 7 H), 7.22–7.08 (m, 2 H), 7.02–6.98 (m, 1 H), 6.85 (dd, *J* = 17.4, 11.0 Hz, 1 H), 5.58 (dd, *J* = 17.4, 1.4 Hz, 1 H), 5.26 (dd, *J* = 11.0, 1.4 Hz, 1 H), 4.24–4.13 (m, 1 H), 3.21–3.10 (m, 1 H), 2.88–2.79 (m, 1 H), 2.74–2.64 (m, 1 H), 1.13 (d, *J* = 6.4 Hz, 6 H), 1.11 (9 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 204.8, 137.0, 136.8, 136.0, 134.6, 134.2, 133.4, 130.3, 130.1, 129.9, 127.9, 127.8, 126.9, 126.4, 116.3, 69.7, 59.6, 28.3, 27.2, 20.5, 19.5 ppm. HRMS (ESI): calcd. for $C_{29}H_{34}O_2SiNa$ $[M + Na]^+$ 465.2226; found 465.2239.

***tert*-Butyldiphenyl[(2*S*,3*S*)-3-(2-vinylbenzyl)pent-4-en-2-yloxy]silane (57):** $Ph_3P^+CH_3I^-$ (694 mg, 1.761 mmol) was dissolved in dry THF (5 mL), and the solution was cooled to –78 °C. LHMDS (1 M in THF; 1.76 mL, 1.76 mmol) was added at –78 °C. After 15–20 min, aldehyde **56** (390 mg, 0.88 mmol), dissolved in dry THF (4 mL), was added at –78 °C, and then the reaction mixture was warmed to room temperature. The reaction mixture was stirred for 3 h at room temperature, and then ice-cold water was added at 0 °C to quench the reaction. After that, the THF was evaporated under vacuum, the residue was extracted with diethyl ether (2 ×), and the combined organic extracts were dried with anhydrous $MgSO_4$ and evaporated under vacuum. The residue was purified by flash chromatography (EtOAc/hexane, 1:40) to give pure olefinic compound **57** (544 mg, 70%) as a colourless liquid. R_f = 0.8 (EtOAc/hexane, 1:10). $[\alpha]_D^{25}$ = +33.45 (*c* = 0.8, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.73–7.67 (m, 4 H), 7.51–7.34 (m, 7 H), 7.21–7.13 (m, 2 H), 7.10–6.90 (m, 2 H), 5.85–5.71 (m, 1 H), 5.6 (d, *J* = 17.0 Hz, 1 H), 5.30 (d, *J* = 11.0 Hz, 1 H), 5.0 (d, *J* = 10.4 Hz, 1 H), 4.83 (d, *J* = 17.0 Hz, 1 H), 3.92–3.87 (m 1 H), 3.08–3.04 (m 1 H), 3.60–3.45 (m 2 H), 1.09–1.05 (m, 12 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 138.3, 136.9, 136.1, 135.1, 134.2, 130.9, 129.7, 129.6, 127.7, 127.6, 127.4, 126.3, 125.8, 116.8, 115.4, 72.0, 52.8, 34.3, 27.3, 20.4, 19.6 ppm. HRMS (ESI): calcd. for $C_{30}H_{36}OSiNa$ $[M + Na]^+$ 463.2433; found 463.2434.

***tert*-Butyl{(*S*)-1-[(*S*)-1,2-dihydronaphthalen-2-yl]ethoxy}diphenylsilane (58):** Compound **57** (250 mg, 0.566 mmol) was dissolved in anhydrous degassed CH_2Cl_2 (250 mL), and then Grubbs 2nd generation catalyst (Grubbs II; 0.028 mol, 24.0 mg) was added. The solution was then stirred at room temperature under an argon atmosphere for 12 h. After that, air was bubbled into the reaction mixture to quench the catalyst, and then the solvent was evaporated. The residue was purified by flash chromatography (EtOAc/hexane, 1:25) to give RCM product **58** (183 mg, 78%) as a colourless liquid. R_f = 0.7 (EtOAc/hexane, 1:10). $[\alpha]_D^{25}$ = +12.33 (*c* = 1.4, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.70–7.65 (m 4 H), 7.43–7.30 (m, 6 H), 7.14–6.99 (m 4 H), 6.49 (dd, *J* = 9.8, 2 Hz, 1 H), 6.01 (dd, *J* = 9.8, 3 Hz, 1 H), 3.95–3.83 (m, 1 H), 2.94–2.74 (m, 2 H), 2.70–2.60 (m, 1 H), 1.05 (12 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 136.1, 135.1, 134.9, 134.3, 134.2, 130.7, 129.8, 129.7, 128.5, 128.1, 127.7, 127.6, 127.1, 126.5, 126.1, 71.6, 42.3, 29.8, 27.3, 20.9, 19.6 ppm. HRMS (ESI): calcd. for $C_{28}H_{32}OSiNa$ $[M + Na]^+$ 435.2120; found 435.2122.

(*S*)-3-[(*S*)-1-(*tert*-Butyldiphenylsilyloxy)ethyl]-1,2,3,4-tetrahydronaphthalene-1,2-diol (59): Compound **58** (210 mg, 0.51 mmol) was dissolved in a THF/water mixture (3:1; 4 mL), and the solution was cooled to 0 °C. OsO_4 (0.05 M solution in toluene; 1.02 mL, 0.051 mmol) and NMO (119.5 mg, 1.02 mmol) were added at 0 °C, and the reaction mixture was then allowed to reach room temperature. The reaction solution was stirred at room temperature for 24 h, and after the reaction was complete, saturated Na_2SO_3 solution was added at 0 °C to quench the reaction. The product was extracted with EtOAc (3 ×), and the combined organic extracts were dried with $MgSO_4$ and evaporated under vacuum. The product was purified by flash chromatography (EtOAc/hexane, 1:6) to give pure diol **59** (159.6 mg, 70%) as a colourless liquid. R_f = 0.3 (EtOAc/hexane, 1:5). $[\alpha]_D^{25}$ = +64.68 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.78–7.67 (m, 4 H), 7.50–7.39 (m, 6 H), 7.26–7.20 (m, 3 H), 7.09–7.05 (m, 1 H), 4.76 (d, *J* = 3.8 Hz, 1 H), 4.18–4.05 (m, 3 H), 2.68–2.49 (m, 3 H), 1.24 (d, *J* = 7.2 Hz, 3 H), 1.09 (9 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 136.1, 135.7, 135.3, 132.9, 131.1, 130.3, 130.1, 128.7, 128.6, 128.1, 127.9, 127.8, 126.6, 72.1, 71.8, 70.3, 39.6, 30.5, 27.2, 19.4, 18.3 ppm. HRMS (ESI): calcd. for $C_{28}H_{34}O_3SiNa$ $[M + Na]^+$ 469.2175; found 469.2041.

(*R*)-3-[(*S*)-1-acetoxyethyl]-1,2,3,4-tetrahydronaphthalene-1,2-diyl Diacetate (Triacetate of 60): A solution of diol **59** in dry THF (86 mg, 0.192 mmol) was treated with TBAF (1 M in THF; 0.4 mL, 0.4 mmol) at room temperature. After 6 h, the solvent was evaporated. The residue was purified by flash chromatography (EtOAc/hexane, 1:5) to give triol **60** (36 mg, 0.173 mmol) as a viscous liquid.

Triol **60** (36 mg, 0.173 mmol) was dissolved in distilled Et_3N (0.7 mL), and Ac_2O (0.073 mL, 0.78 mmol) was added along with a catalytic amount of DMAP at room temperature. The reaction mixture was stirred at room temperature for 2 d, then the Et_3N was evaporated under vacuum. The residue was purified by flash chromatography (EtOAc/hexane, 1:10) to give the pure triacetate (40 mg, 70%) as a colourless crystalline solid. R_f = 0.5 (EtOAc/hexane, 1:5). $[\alpha]_D^{25}$ = +44.28 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.26 (m, 2 H), 7.22–7.19 (m, 2 H), 6.21 (d, *J* = 3.2 Hz, 1 H), 5.36–5.33 (m, 1 H), 5.16 (dd, *J* = 11.6, 3.2 Hz, 1 H), 3.15–2.95 (m, 2 H), 2.51 (dd, *J* = 16.6, 11.4 Hz, 1 H), 2.08–1.98 (9 H), 1.32 (d, *J* = 6.0 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 170.7, 170.6, 170.5, 136.0, 132.4, 130.8, 129.5, 129.1, 126.8, 70.2, 69.9, 67.2, 37.4, 27.8, 21.4, 21.3, 21.0, 17.4 ppm. HRMS (ESI): calcd. for $C_{18}H_{22}O_6Na$ $[M + Na]^+$ 357.1314; found 357.1278.

(1*S*,2*S*)-2-[(*S*)-1-(*tert*-Butyldiphenylsilyloxy)ethyl]-1-(2-vinylphenyl)-pent-4-en-1-ol (61) and (1*R*,2*S*)-2-[(*S*)-1-(*tert*-Butyldiphenylsilyloxy)ethyl]-1-(2-vinylphenyl)pent-4-en-1-ol (62): Aldehyde **32** (588 mg, 1.606 mmol) was dissolved in dry diethyl ether, and then the freshly generated Grignard reagent from 2-vinyl-1-bromobenzene (2 mmol) was added at –78 °C. The reaction mixture was allowed to reach room temperature. The reaction mixture was then stirred at room temperature for 6 h. After the reaction was complete, it was quenched by the addition of a saturated solution of NH_4Cl. The crude product was extracted with diethyl ether (3 ×), and the combined organic extracts were dried with $MgSO_4$. The organic extract was evaporated using a rotary evaporator to give the crude alcohol as a diastereomeric mixtures. The diastereomeric ratio of the two products was 15:1, which was unchanged after purification by flash chromatography. The mixture of diastereomers (total yield 80%) containing isomer **61** (566 mg, 1.205 mmol) and isomer **62** (38 mg, 0.0803 mmol) was obtained as a colourless liquid. R_f = 0.4 (EtOAc/hexane, 1:10).

Data for **61**: $[\alpha]_D^{25}$ = –3.47 (*c* = 0.6, $CHCl_3$). ^{1}H NMR (data for **61**; 200 MHz, $CDCl_3$): δ = 7.75–7.59 (m, 4 H), 7.56–7.49 (m, 1 H), 7.47–7.46 (m, 6 H), 7.42–7.21 (m, 3 H), 7.03 (dd, *J* = 17.0 Hz, 11.0 Hz, 1 H), 5.66–5.37 (m, 3 H), 5.14–5.08 (m, 1 H), 4.87–4.71 (m, 2 H), 4.26–4.20 (m, 1 H), 2.34–2.06 (m, 2 H), 1.89–1.88 (m, 1 H), 1.10–1.04 (12 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 140.9, 138.7, 136.2, 136.0, 135.1, 135.0, 134.7, 134.3, 133.9, 129.9, 129.8, 127.8, 127.7, 127.2, 126.6, 125.9, 116.0, 115.3, 72.9, 71.5, 49.8, 27.7, 27.3, 20.9, 19.5 ppm. HRMS (ESI): calcd. for $C_{31}H_{38}O_2SiNa$ $[M + Na]^+$ 493.2539; found 493.2562.

Data for **62**: R_f = 0.45 (EtOAc/hexane, 1:10). $[\alpha]_D^{25}$ = –3.77 (*c* = 0.8, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.73–7.65 (m, 4 H), 7.47–7.39 (m, 6 H), 7.34–7.30 (m, 1 H), 7.23–7.19 (m, 3 H), 6.87

(dd, J = 17.2, 10.8 Hz, 1 H), 5.76 (s, 1 H), 5.55 (d, J = 17.6 Hz, 1 H), 5.32–5.24 (m, 1 H), 5.21 (d, J = 10.8 Hz, 1 H), 4.76–4.67 (m, 2 H), 4.13–4.10 (m, 1 H), 2.43–2.35 (m, 2 H), 2.09–2.06 (m, 1 H), 1.29–1.26 (m, 3 H), 1.11–1.0 (9 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 141.0, 137.9, 136.0, 135.7, 135.2, 135.1, 134.4, 134.1, 133.7, 130.1, 129.8, 127.6, 127.5, 127.3, 126.5, 125.7, 116.1, 115.1, 73.1, 71.5, 50.1, 27.5, 27.1, 20.8, 19.5 ppm.

(1*S*,2*R*,3*S*)-2-Allyl-1-(2-vinylphenyl)butane-1,3-diol (67): The TBDPS group was removed from compound **61** with TBAF as described above for the synthesis of compound **34**, to give diol **67**. R_f = 0.4 (EtOAc/hexane, 1:3). $[\alpha]_D^{25}$ = –7.03 (c = 2.6, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.60–7.47 (m, 1 H), 7.44–7.43 (m, 1 H), 7.35–7.29 (m, 2 H), 6.94 (dd, J = 17.2, 11 Hz, 1 H), 5.61–5.44 (m, 2 H), 5.34–5.29 (m, 2 H), 4.89–4.75 (m, 2 H), 4.22–4.12 (m, 1 H), 2.59 (br., 2 H, OH), 2.30–2.23 (m, 2 H), 1.80–1.75 (m, 1 H), 1.26 (d, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 140.3, 139.5, 135.4, 134.3, 128.0, 127.5, 126.3, 126.1, 116.7, 115.0, 74.2, 72.0, 48.9, 26.6, 21.9 ppm. HRMS (ESI): calcd. for $C_{15}H_{20}O_2Na$ [M + Na]$^+$ 255.1361; found 255.1416.

(1*R*,2*R*,3*S*)-2-Allyl-1-(2-vinylphenyl)butane-1,3-diol (69): The TBDPS group **62** was removed from compound with TBAF as described above for the synthesis of compound **34**, to give diol **69**. R_f = 0.4 (EtOAc/hexane, 1:3). $[\alpha]_D^{25}$ = +2.91 (c = 0.8, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.61 (d, J = 7.2 Hz, 1 H), 7.44 (d, J = 7.8 Hz, 1 H), 7.37–7.22 (m, 2 H), 6.86 (dd, J = 17.0, 11.0 Hz, 1 H), 5.65–5.46 (m, 3 H), 5.30 (d, J = 11.0 Hz, 1 H), 5.02–4.88 (m, 2 H), 4.21–4.08 (m, 1 H), 2.52 (br., 2 H, OH), 2.40–2.23 (m, 2 H), 2.05–1.99 (m, 1 H), 1.47 (d, J = 6.4 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 140.0, 137.8, 134.9, 134.2, 127.8, 127.3, 126.6, 126.4, 116.5, 69.2, 68.9, 47.3, 28.9, 21.9 ppm.

(4*S*,5*R*,6*S*)-5-Allyl-2,2,4-trimethyl-6-(2-vinylphenyl)-1,3-dioxane (68): Compound **67** (25 mg, 0.11 mmol) was dissolved in dry CH_2Cl_2 (0.5 mL). 2,2-DMP (0.07 mL, 0.54 mmol) was added to the reaction mixture, followed by a catalytic amount of PPTS. The reaction solution was then stirred for 12 h at room temperature. After that time, the solvent was evaporated under vacuum. The residue was purified by flash chromatography (EtOAc/hexane, 1:7) to give pure product **68** (26 mg, 90%) as a colourless liquid. R_f = 0.5 (EtOAc/hexane, 1:20). $[\alpha]_D^{25}$ = –40.3 (c = 2.3, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.60–7.56 (m, 1 H), 7.46–7.42 (m, 1 H), 7.35–7.24 (m, 2 H), 6.92 (dd, J = 17.2, 11.0 Hz, 1 H), 5.63 (dd, J = 17.2, 1.2 Hz, 1 H), 5.37–5.25 (m, 3 H), 4.67–4.64 (m, 1 H), 4.58 (s, 1 H), 4.37–4.33 (m, 1 H), 2.14–2.01 (m, 2 H), 1.69–1.63 (m, 1 H), 1.59–1.55 (m, 6 H), 1.23 (d, J = 6.4 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 139.4, 137.8, 135.0, 134.3, 127.8, 127.3, 126.6, 126.1, 116.4, 114.1, 99.5, 72.3, 69.5, 42.4, 30.3, 25.8, 19.7 ppm. HRMS (ESI): calcd. for $C_{18}H_{24}O_2Na$ [M + Na]$^+$ 295.1674; found 295.1732.

(4*S*,5*R*,6*R*)-5-Allyl-2,2,4-trimethyl-6-(2-vinylphenyl)-1,3-dioxane (70): Diol **69** was protected as its acetonide as described above for the synthesis of compound **35**, to give compound **70** (13 mg, 90%). R_f = 0.5 (EtOAc/hexane, 1:20). $[\alpha]_D^{25}$ = +76.0 (c = 2.2, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.57–7.52 (m, 1 H), 7.46–7.42 (m, 1 H), 7.34–7.20 (m, 2 H), 6.62 (dd, J = 17.0, 11.0 Hz, 1 H), 5.63 (dd, J = 17.0, 1.2 Hz, 1 H), 5.40–5.26 (m, 3 H), 4.82–4.75 (m, 2 H), 3.71–3.65 (m, 1 H), 1.97–1.66 (m, 3 H), 1.56–1.42 (m, 6 H), 1.29 (d, J = 6.2 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 137.4, 137.2, 135.1, 134.3, 127.8, 127.1, 126.8, 125.7, 116.4, 115.8, 101.1, 69.5, 68.0, 47.3, 33.4, 25.5, 24.3, 21.8 ppm.

(5*S*,6*S*,*Z*)-6-[(*S*)-1-(*tert*-Butyldiphenylsilyloxy)ethyl]-6,7-dihydro-5*H*-benzo[7]annulen-5-ol (63): Compound **61** (385 mg, 0.82 mmol) was dissolved in anhydrous CH_2Cl_2 (degassed by argon purging; 300 mL), and Hoveyda–Grubbs 2nd generation catalyst (HG-II, 0.041 mol, 25.6 mg) was added. The reaction solution was heated at reflux under an argon atmosphere for 8 h. After that time, air was bubbled into the reaction solution to quench any catalyst present in the solution. The solvent was then evaporated, and the residue was purified by flash chromatography (EtOAc/hexane, 1:20) to give pure product **63** (290 mg, 88%) as a colourless liquid. R_f = 0.6 (EtOAc/hexane, 1:5). $[\alpha]_D^{25}$ = –82.74 (c = 1.4, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.85–7.73 (m, 4 H), 7.57–7.35 (m, 11 H), 6.51 (d, J = 12.2 Hz, 1 H), 6.04–5.95 (m, 1 H), 4.14–4.09 (m, 1 H), 2.81–2.64 (m, 2 H), 1.26 (d, J = 6.4 Hz, 3 H), 1.19 (9 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 142.1, 136.1, 136.0, 134.8, 134.6, 134.0, 132.4, 131.3, 129.9, 129.4, 128.8, 128.0, 127.8, 127.7, 127.1, 78.9, 73.0, 46.9, 28.3, 27.2, 19.8, 19.5 ppm. HRMS (ESI): calcd. for $C_{29}H_{34}O_2SiNa$ [M + Na]$^+$ 465.2226; found 465.2232.

(5*S*,6*R*,*Z*)-6-[(*S*)-1-Hydroxyethyl]-6,7-dihydro-5*H*-benzo[7]annulen-5-ol (64): A solution of alcohol **63** (50 mg, 0.113 mmol) in dry THF (0.5 mL) was treated with TBAF (1 M solution in THF; 0.23 mL, 0.23 mmol) at room temperature. After 4 h, the solvent was evaporated, and the residue was purified by flash chromatography (EtOAc/hexane, 1:5) to give diol **64** (20.4 mg, 80%) as a colourless liquid. R_f = 0.2 (EtOAc/hexane, 1:5). $[\alpha]_D^{25}$ = –66.2 (c = 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.17–7.09 (m, 4 H), 6.30 (d, J = 12.4 Hz, 1 H), 5.92–5.82 (m, 1 H), 4.84 (s, 1 H), 4.04–4.01 (m, 1 H), 2.65–2.40 (m, 1 H), 2.38–2.28 (m, 1 H), 1.98–1.85 (m, 1 H), 1.12 (d, J = 6.4 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 140.7, 134.9, 132.1, 131.6, 129.8, 128.6, 128.3, 127.0, 79.4, 72.6, 45.9, 24.9, 20.8 ppm. HRMS (ESI): calcd. for $C_{13}H_{16}O_2Na$ [M + Na]$^+$ 227.1048; found 227.1053.

(8*S*,9*S*)-8-[(*S*)-1-(*tert*-Butyldiphenylsilyloxy)ethyl]-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-5,6,9-triol (65): Compound **63** (335 mg, 0.758 mmol) was dissolved in a THF/water mixture (3:1; 4 mL), and the solution was cooled to 0 °C. OsO_4 (0.05 M solution in toluene; 1.516 mL, 0.076 mmol) and NMO (177.6 mg, 1.516 mmol) were added to the reaction mixture at 0 °C, and the mixture was allowed to reach room temperature. The reaction solution was then stirred at room temperature for 24 h. After the reaction was complete, saturated Na_2SO_3 solution was added at 0 °C to quench the reaction. The product was extracted with EtOAc (3×), and the combined organic extracts were dried with $MgSO_4$, and evaporated under vacuum. The residue was purified by flash chromatography (EtOAc/hexane, 1:3) to give pure triol **65** (252.5 mg, 70%) as a viscous liquid. R_f = 0.3 (EtOAc/hexane, 1:1). $[\alpha]_D^{25}$ = – 27.92 (c = 2.4, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.70 (d, J = 6.4 Hz, 4 H), 7.64 (d, J = 8 Hz, 1 H), 7.46–7.30 (m, 7 H), 7.23–7.16 (m, 2 H), 5.61 (s, 1 H), 5.08 (s, 1 H), 4.24 (s, 1 H), 4.04 (s, 1 H), 2.44–2.41 (m, 1 H), 1.88–1.72 (m, 2 H), 1.08 (9 H), 1.04 (d, J = 5.6 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 139.7, 138.8, 136.0, 135.9, 134.4, 133.6, 130.0, 129.9, 128.4, 128.2, 127.9, 127.7, 127.4, 127.1, 78.0, 75.1, 73.7, 41.7, 29.3, 27.2, 20.6, 19.4 ppm. HRMS (ESI): calcd. for $C_{29}H_{36}O_4SiNa$ [M + Na]$^+$ 499.2281; found 499.2273.

(8*R*,9*S*)-8-[(*S*)-1-Acetoxyethyl]-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-5,6,9-triyl Triacetate (Tetraacetate of 66): A solution of triol **65** in dry THF (110 mg, 0.23 mmol) was treated with TBAF (1 M solution in THF; 0.46 mL, 0.46 mmol) at room temperature. After 6 h, the solvent was evaporated, and the residue was purified by column chromatography (EtOAc/hexane, 1:5) to give tetrol **66** (50 mg, 0.21 mmol) as a colourless liquid.

Tetrol **66** (50 mg, 0.21 mmol) was dissolved in distilled Et_3N (0.8 mL), and Ac_2O (0.175 mL, 1.26 mmol) was added along with a catalytic amount of DMAP at room temperature. The reaction

mixture was stirred at room temperature for 2 d, then the Et_3N was evaporated under vacuum, and the crude product was purified by flash chromatography (EtOAc/hexane, 1:10) to give the pure tetraacetate (60 mg, 70%) as a gummy solid. R_f = 0.4 (EtOAc/hexane, 1:5). $[\alpha]_D^{25}$ = –44.1 (*c* = 2.5, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 7.43–7.23 (m, 4 H), 6.318 (s, 2 H), 5.44–5.39 (m, 1 H), 4.90 (dd, *J* = 6.2, 5.0 Hz, 1 H), 2.15–2.09 (m, 10 H), 1.95 (s, 3 H), 1.79 (s, 3 H), 1.21 (d, *J* = 8.0 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 170.3, 170.2, 170.0, 169.8, 136.6, 133.8, 128.5, 128.3, 71.3, 69.7, 54.0, 31.8, 29.8, 29.4, 28.3, 21.3, 21.2, 21.1, 18.0 ppm. HRMS (ESI): calcd. for $C_{21}H_{28}O_8Na$ $[M + Na]^+$ 429.1525; found 429.1550.

General Method for Glycosidase Inhibition Study: The inhibitory activities of cyclitols **49**–**52**, **60**, and **66** were determined using a spectrophotometric glycosidase assay with *p*-nitrophenyl glucosides (α or β) as substrates. The residual hydrolytic activities of the glycosidases were measured spectrophotometrically (Shimadzu UV/Vis spectrophotometer). A typical enzymatic assay (final volume 3 mL) contained 0.03–0.06 units mL^{-1} of the enzyme (1 unit = 1 enzyme unit liberating 1 μmol of *p*-nitrophenol per minute from the *p*-nitrophenyl glycoside). Each assay was performed with the *p*-nitrophenyl glucoside derivatives as substrate in a potassium phosphate buffer (67 mM, pH 6.8). The assays were performed with four different concentrations of the substrates (1, 2, 3, and 4 mM in the aq. buffer solution). Enzyme and inhibitors (buffered solutions of the cyclitols; for compounds **60** and **66**, a very small amount of DMSO was added to tackle the solubility issue) were preincubated for 1–2 min at 37 °C, depending on the enzyme, and the reaction was started by addition of the substrate. The *p*-nitrophenolate formed was measured by UV spectroscopy at 400 nm at 30 s intervals. A suitable control assay was performed in each case without adding the inhibitors.

Supporting Information (see footnote on the first page of this article): ^1H and ^{13}C NMR spectra of all the compounds reported in this article, X-ray crystallographic information, and HPLC chromatograms.

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