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Synthesis of L- and D-4,6-Dideoxyhexoses and 4,6-Dideoxy-*C*-phenylglycosides from Enzyme-Generated Products

Daniela Acetti,[a] Elisabetta Brenna,*[a] Claudio Fuganti,[a] Francesco G. Gatti,[a] Luciana Malpezzi,[a] and Stefano Serra[b]

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Optically active 1,3-diols **1** were prepared by biocatalysed routes. The synthetic versatility of compounds **1** as chiral building blocks was shown. The oxidative cleavage of the double bond afforded a carbonyl moiety, which allowed for elongation by Grignard addition and further derivatisation to make deoxy sugars readily available. The epoxidation of the same double bond allowed the direct intramolecular opening of the epoxide ring to generate deoxy *C*-phenylglycosides.

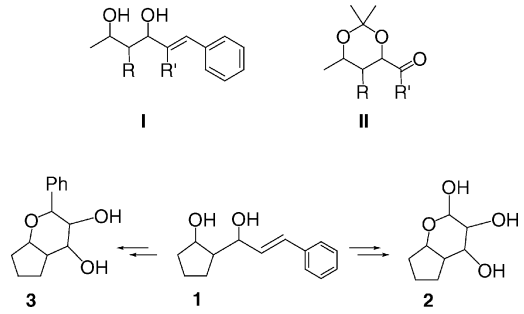
Introduction

A growing trend in pharmaceutical research is the development of step-economical syntheses of novel structures with improved or new activities. This target is achieved by optimizing new reactions and synthetic strategies, which allows for a shorter route to a target molecule, or by designing less complex molecules with comparable or superior function, which can be prepared in practical and novel manners.[1] Both approaches have stimulated the development of synthetic building blocks whose synthesis is well optimized and that can be assembled to afford the desired compound.

The 1,3-diol structural motif, for example, occurs as an important subunit in a number of biologically active products and intermediates used for the synthesis of complex molecules.[2] Several synthetic procedures even to complex 1,3-polyol arrays have been developed with great success.[3] The total synthesis of palytoxin represents one of the most outstanding examples.[4]

The strategies for the creation of 1,3-dioxygenated stereocentres have been recently reviewed[5] and include (i) reduction of β-hydroxy ketones,[6] (ii) Tishchenko reaction,[7] (iii) stereoselective reduction of 1,3-diketones,[8] (iv) Prins reaction,[9] and other miscellaneous reactions.[10]

It seems desirable to develop synthetic procedures to procure 1,3-diol chiral synthons in all their possible configurations, which can be assembled into chiral molecules with several stereogenic centres. We have recently optimized[11] an enzymatic method for the kinetic resolution of 1,3-diols of type **I** (Scheme 1), to be converted into chiral synthons **II**, showing two or three stereogenic centres with controlled stereochemistry and one carbonyl group suitable of further functionalisation.



Scheme 1.

We wish herein to report on the synthesis of the single stereoisomers of new 1,3-diols **1** with defined stereochemistry at three adjacent stereogenic centres and on their use as chiral synthons to prepare biologically active molecules such as 4,6-dideoxyhexoses **2** and 4,6-dideoxy-*C*-phenylglycosides **3**, which contain non-oxygenated carbon atoms in positions 4 and 6 in the sugar ring. Deoxy sugars and *C*-glycosides are integral components of several therapeutically relevant products, and their presence is often critical in conferring bioactivity.[12] These derivatives have recently received great attention, and their synthesis is a rather challenging task.[13] The preparation of modified carbohydrate moieties can also be exploited for the development of novel sugar mimics able to antagonize oligosaccharides at the protein receptor level and to interfere with the recognition events, on which the transmission or the onset of a disease is based. The design of glycomimetic structures is aimed

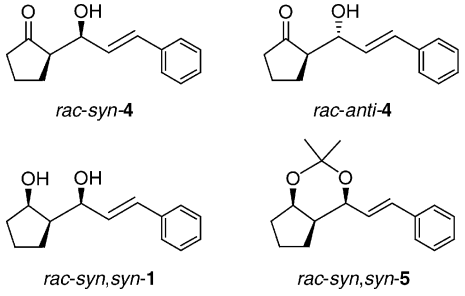
[a] Politecnico di Milano, Dipartimento di Chimica, Materiali ed Ingegneria Chimica; Istituto di Chimica del Riconoscimento Molecolare – CNR,
Via Mancinelli 7, 20131 Milano, Italy
Fax: +39-02-23993180
E-mail: elisabetta.brenna@polimi.it
[b] Istituto di Chimica del Riconoscimento Molecolare – CNR, Dipartimento di Chimica, Materiali ed Ingegneria Chimica,
Via Mancinelli 7, 20131 Milano, Italy

at reducing the carbohydrate-likeness of the mimics and to increase their drug-like properties.[14] Ganglioside GM1, for example, interacts with cholera toxin using galactose and *N*-acetylneuraminic acid residues at the oligosaccharide non-reducing end.[15] It was discovered that the terminal galactose could potentially serve as an "anchor" point for antagonist design,[16] and aryl galactosides[17] and galactose dendrimers[18] were developed as effective cholera toxin antagonists. The interest in this field encouraged us to investigate the synthetic versatility of our chiral building blocks by preparing a modified carbohydrate related to galactose.

Results and Discussion

Synthesis of Optically Active Diols 1

The aldol condensation of cyclopentanone and cinnamaldehyde gave a mixture of the two diastereomeric hydroxy ketones *syn*- and *anti*-**4**[19] (Scheme 2), which were submitted to $NaBH_4$ reaction to afford the four racemic diastereomeric diols **1**.



Scheme 2.

Diol *syn*,*syn*-**1** could be isolated from this reduction mixture by column chromatography, and its relative stereochemistry was assigned on the basis of the NMR spectra of the corresponding acetonide *syn*,*syn*-**5**. Diol *syn*,*syn*-**1** and the mixture of the other three diastereomers were submitted separately to lipase PS mediated transesterification in *tert*-butyl methyl ether in the presence of vinyl acetate as an acyl donor (Scheme 3).

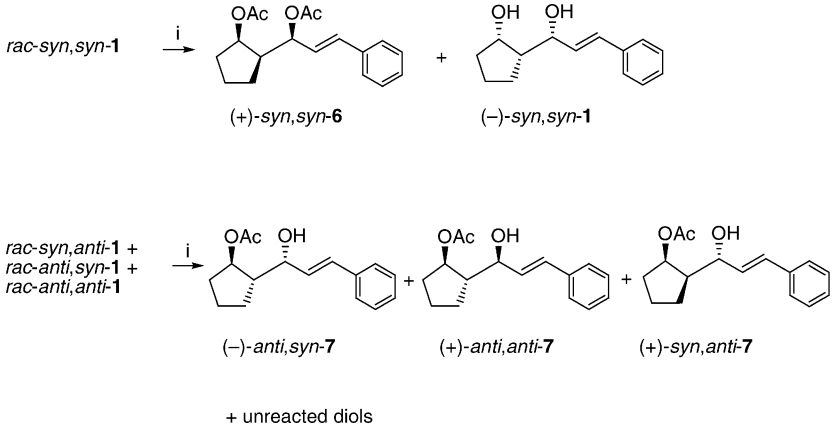
Enzymatic acetylation of *rac*-*syn*,*syn*-**1** gave diacetate (+)-*syn*,*syn*-**6** and unreacted alcohol (–)-*syn*,*syn*-**1**. The absolute stereochemistry was established by analogy with that determined for *anti* derivatives (see Configuration Assignment below). The enantiomeric excess of both diacetate (+)-*syn*,*syn*-**6** and unreacted diol (–)-*syn*,*syn*-**1** was found to be >99% by GC analysis of the corresponding acetonides (+)- and (–)-*syn*,*syn*-**5** on a chiral column.

Lipase-catalysed acetylation of the mixture of the other three diols afforded monoacetates (–)-*anti*,*syn*-**7**, (+)-*anti*,*anti*-**7**, and (+)-*syn*,*anti*-**7**, which could be separated by column chromatography, and a mixture of the unreacted starting diols. The absolute configuration (see Configuration Assignment below) was assigned by degradation of a mixture of (–)-*anti*,*syn*-**7** and (+)-*anti*,*anti*-**7**. The enantiomeric excess of *anti*,*anti*-**7** was 98% by GC analysis of the corresponding acetonide on a chiral column.

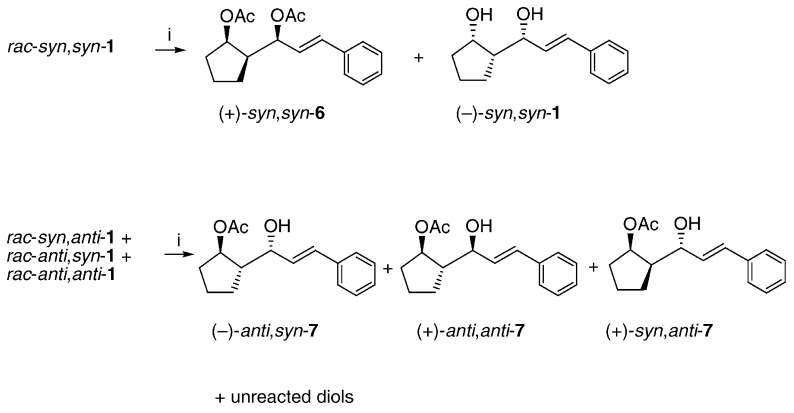
We also experimented with the Baker's yeast reduction of *syn*- and *anti*-**4**, which afforded a 1:1 mixture of diols *anti*,*anti*-**1** and *syn*,*anti*-**1** (Scheme 4), which were converted into the corresponding acetonides and separated by column chromatography. The *anti*,*anti*-acetonide thus recovered was enantiomerically pure (GC) and of opposite configuration to that of the acetonide prepared from monoacetate (+)-*anti*,*anti*-**7**.

We could draw the conclusion that Baker's yeast promoted the stereoselective reduction of *anti*-**4**. To the best of our knowledge, this reduction of compound **4** represents the first example of a Baker's yeast reduction of a β-hydroxy ketone to an optically active 1,3-diol. Literature in this field reports only several examples of Baker's yeast reduction of β-diketones to β-hydroxy ketones.[20]

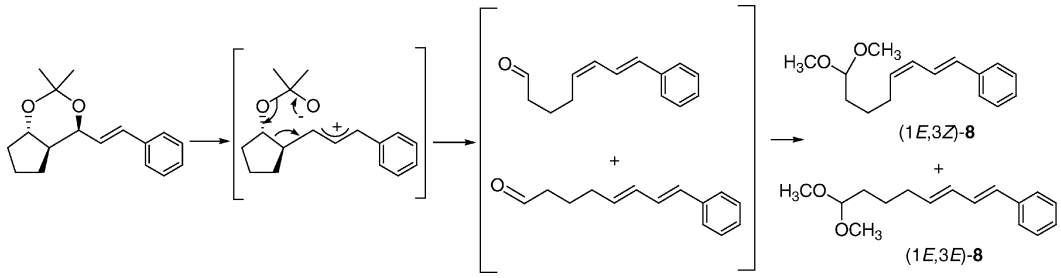
When the mixture of the four racemic diols was treated with dimethoxypropane in acetone in the presence of pyridinium *p*-toluenesulfonate, only three diastereomeric acetonides were recovered, *anti*,*anti*-, *syn*,*anti*-, and *syn*,*syn*-**5**, besides two degradation products, (1*E*,3*Z*)- and (1*E*,3*E*)-**8** (Scheme 5). These products could be explained by admitting an acid-catalysed Grob fragmentation mainly of the missing acetonide *anti*,*syn*-**5** via an allylic carbocationic intermediate through a non-synchronous mechanism, as has been recently highlighted by Barluenga et al.[21]



Scheme 3. (i) Lipase PS, *tert* -butyl methyl ether, vinyl acetate; column chromatography.



Scheme 4. (i) Baker's yeast, H_2O/ethanol, glucose; column chromatography.



Scheme 5. Acid-catalysed Grob fragmentation.

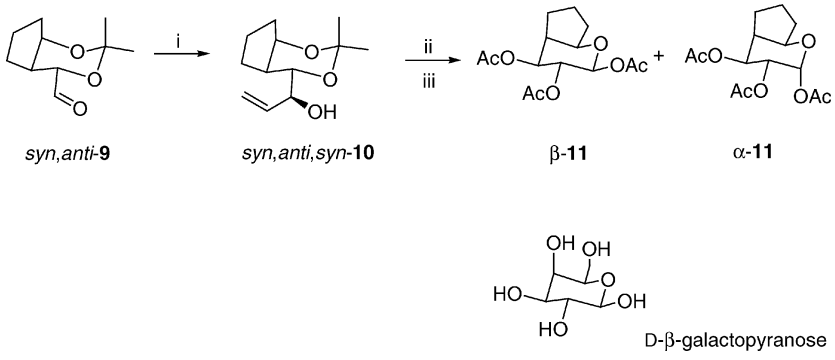
In order to show the synthetic potential of diols **1** as chiral building blocks, we employed them to prepare two important sets of compounds, 4,6-dideoxyhexoses **2** (in particular galactose) and 4,6-dideoxy-*C*-phenylglycosides **3**. A complete preliminary investigation of the synthetic route was performed on racemic materials.

Synthesis of Dideoxy Sugars

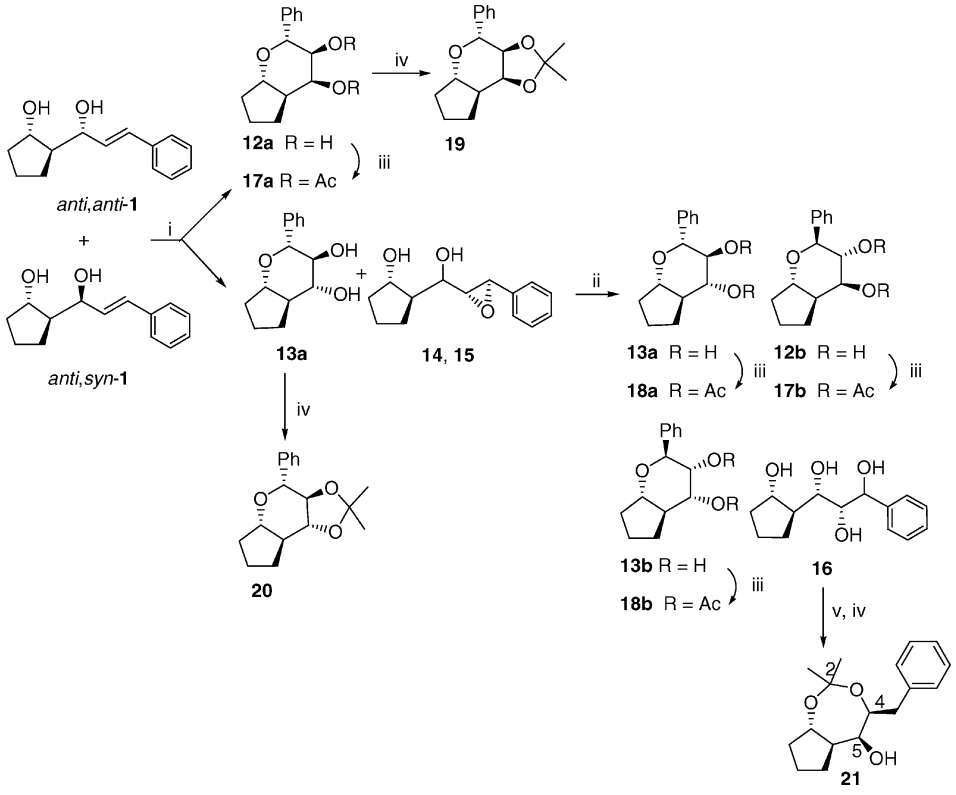
The three acetonides **5** were submitted, separately, to ozonolysis and PPh_3 treatment to afford aldehydes *syn*,*syn*-, *syn*,*anti*-, and *anti*,*anti*-**9**, which contain three adjacent stereocentres with controlled configuration and a carbonyl moiety,[22] which could be employed to further functionalise the molecule. Aldehyde *syn*,*anti*-**9**, for example (Scheme 6), was treated with vinylmagnesium bromide to afford only diastereomer *syn*,*anti*,*syn*-**10** with total control of the configuration of the new stereogenic centre, probably through a chelation-controlled nucleophilic addition similar to those described by Still et al.[23] for α-alkoxy ketones. Ozonolysis with PPh_3 quenching followed by treatment with Ac_2O in pyridine, allowed us to isolate a 6:4 mixture of the two anomers of 4,6-dideoxygalactopyranose triacetate **11**. This compound is structurally related to galactose; the OH groups at C(4) and C(6) of galactose are substituted by CH_2 moieties, connected by a C–C bond to form a five-membered fused ring.

Synthesis of *C*-Glycosides

A mixture of diols *anti*,*anti*- and *anti*,*syn*-**1** was epoxidised with *m*-chloroperbenzoic acid in CH_2Cl_2 to afford,



Scheme 6. (i) Vinylmagnesium bromide, THF; (ii) O_3, MeOH/CH_2Cl_2, then PPh_3; (iii) THF, H_2O, 10% HCl.



Scheme 7. (i) *m*CPBA, CH_2Cl_2; (ii) THF/H_2O, $HClO_4$; (iii) Ac_2O, pyridine; (iv) 2,2-dimethoxypropane, acetone, pyridinium *p*-toluenesulfonate; (v) H_2, Pd/C, EtOH, $HClO_4$.

after workup and purification by column chromatography, compound **12a** and a mixture containing compound **13a** and the two epoxide derivatives **14** and **15** (Scheme 7). This latter mixture was dissolved in THF/H_2O, treated with $HClO_4$ and acetic acid, and the products were separated by column chromatography. Compound **13a** was recovered unreacted; the two epoxides were converted into compounds **12b** and **13b** and recovered as their corresponding diacetates, and tetraol **16** was recovered as the last eluted fraction. The structures of *C*-phenylglycosides **12a**,**b** and **13a**,**b** were established by means of ^1H and ^{13}C NMR analysis and by their conversion into their corresponding acetate and acetonide derivatives, **17**–**20**.

Tetraol **16** was submitted to hydrogenolysis and then treated with dimethoxypropane in acetone, to afford, unexpectedly, the seven-membered ring **21**. The structure was established by X-ray crystallography (Figure 1).[24]

Compounds **12a** and **13a**, which are, respectively, a β-*C*-phenyl-4,6-dideoxyalloside and -glucoside, were readily formed during the epoxidation reaction (Scheme 8). The intramolecular opening of the two diastereomeric epoxides was highly favoured, leading to an all-equatorial arrangement of the substituents in **13a** and to the presence of only one axial OH group in **12a**. The other two diastereomers **12b** and **13b**, which are, respectively, a β-*C*-phenyl-4,6-dideoxyaltroside and an α-*C*-phenyl-4,6-dideoxymannoside, could be obtained by acid-catalysed opening of derivatives **14** and **15**. Tetraol **16**, recovered from the hydrolysis reaction, derived from the opening of the same epoxide giving rise to compound **12b**.

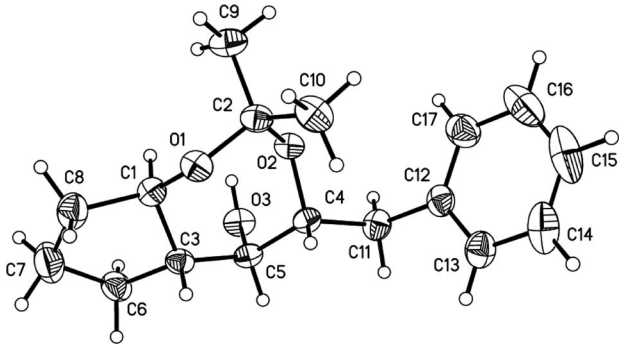
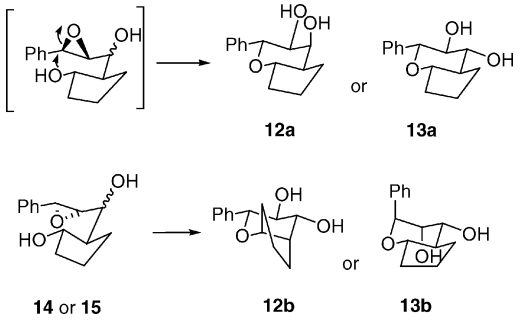


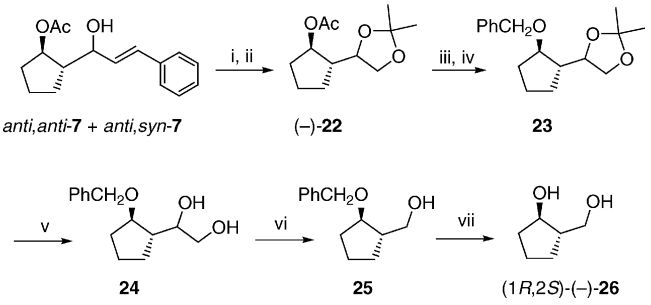
Figure 1. X-ray crystal structure of **21**.



Scheme 8.

Configuration Assignment

A 1:1 mixture of monoacetates (+)-*anti*,*anti*-**7** and (–)-*anti*,*syn*-**7** was submitted to ozonolysis followed by $NaBH_4$ quenching to afford, after reaction with dimethoxypropane in acetone and pyridinium *p*-toluenesulfonate, compound (–)-**22** (Scheme 9). This latter was saponified and treated with $PhCH_2Br$, after treatment with NaH in THF, to give derivative **23**, which was then deprotected, affording diol **24**. Oxidative cleavage of the 1,2-diol with periodic acid in THF, followed by $NaBH_4$ reduction of the intermediate aldehyde, allowed us to obtain compound **25**, which was debenzylated to afford compound (1*R*,2*S*)-(–)-**26**, whose absolute configuration was known in the literature.[25] Thus, the absolute configuration of the cyclopentane ring of (+)-*anti*, *anti*- and (–)-*anti*,*syn*-**7** was determined. The absolute configuration of the *syn* derivatives was assigned on the basis of analogy with that determined for the *anti* derivatives.



Scheme 9. (i) O_3, CH_2Cl_2/MeOH (1:1), then $NaBH_4$; (ii) 2,2-dimethoxypropane, acetone, pyridinium *p*-toluenesulfonate, reflux; (iii) 25% aqueous KOH, MeOH; (iv) NaH, $PhCH_2Cl$, THF; (v) AcOH, a few drops HCl, THF/H_2O (2:1); (vi) $HClO_4$, THF, then a few drops of ethylene glycol, MeOH and $NaBH_4$ at –10 °C; (vii) H_2, 50 psi, Pd/C, ethyl acetate.

The relative configuration of diols **1** was assigned by analysis of the NMR spectra of the corresponding acetonides **5**.

Conclusions

The work shows the synthetic versatility of diols of type **1**. The lipase-mediated resolution and the enantiospecific generation of a stereogenic centre by Baker's yeast are useful methods for the preparation of optically active starting diols **1**. The oxidative cleavage of the double bond affords a carbonyl moiety, which allows elongation by Grignard addition and further derivatisation, to make deoxy sugars readily available. The epoxidation of the same double bond allows the direct intramolecular opening of the epoxide ring, to generate deoxy *C*-phenylglycosides.

This work shows the accessibility of hydroxylated six-membered rings starting from an aldol condensation by means of simple reactions employing biocatalysis to produce optically pure products. The combination of our procedure with known techniques for the diastereoselective reduction of the starting aldol to *syn*- or *anti*-1,3-diols[26] can be employed to synthesize target diastereomers selectively.

Some topics that arose during the development of this work deserve future investigations, such as the bias towards Grob fragmentation of the *anti*,*syn*-acetonide **5** and the steric requirements leading to the unexpected preference for the dioxepinol derivative **21**, rather than for a five- or six-membered acetonide, in the reaction of tetraol **16** with dimethoxypropane in acetone under acid catalysis.

Experimental Section

General Methods: Lipase PS *Burkholderia cepacia* was employed in this work. GC-MS analyses were performed by using an HP-5MS column (30m × 0.25mm × 0.25μm). The following temperature program was employed: 60 °C (1 min) / 6 °C/min / 150° (1 min) / 12 °/min / 280° (5 min). ^1H and ^{13}C NMR spectra were recorded with a 400 MHz spectrometer. The chemical shift scale was based on internal tetramethylsilane. The enantiomeric excess of acetonides **5** was determined by GC analysis using a Chirasil DEX CB, 25 m × 0.25 mm (Chrompack) column, installed on a DANI HT 86.10 gas chromatograph with the following temperature program: 60 °C (3 min) / 3 °C/min / 180 °C (10 min). The following retention times were observed: (4*S*,4a*R*,7a*R*,*E*)-*anti*,*anti*-**5** t_R = 36.17 min, (4*R*,4a*S*,7a*S*,*E*)-*anti*,*anti*-**5** t_R = 36.32 min, (4*R*,4a*R*,7a*S*,*E*)-*syn*,*syn*-**5** t_R = 35.71 min, and (4*S*,4a*S*,7a*R*,*E*)-*syn*,*syn*-**5** t_R = 36.12 min. Optical rotations were measured with a Dr. Kernchen Propol digital automatic polarimeter at 589 nm and are given in 10^{-1} deg cm^2 g^{-1}. TLC analyses were performed with Merck Kieselgel 60 F254 plates. All the chromatographic separations were carried out with silica gel columns.

Preparation of Diols 1, Acetonides 5 and Aldehydes 9

(*RS*)-2-[(*SR*,*E*)-1-Hydroxy-3-phenylallyl]cyclopentanone (*syn*-4) and (*RS*)-2-[(*RS*,*E*)-1-Hydroxy-3-phenylallyl]cyclopentanone (*anti*-4): A stirred solution of cyclopentanone (42 g, 0.5 mol) and cinnamaldehyde (66 g, 0.5 mol) in methanol (300 mL) at –10 °C was treated with aqueous sodium hydroxide (40%, 1 mL). After 5 min, the slightly yellow solution was poured into excess iced H_2O, containing acetic acid (3 mL). The reaction mixture was extracted with a 2:1 mixture of ethyl acetate/hexane. The organic phase was washed with saturated $NaHCO_3$ solution and dried with sodium sulfate. The oil obtained upon evaporation of the solvent was chromatographed (SiO_2) with increasing amounts of ethyl acetate in hexane, providing oily **4** (63 g, 58%) as a 1:1 mixture of *syn* and *anti* diastereomers. ^1H NMR[19] (400 MHz, $CDCl_3$): δ = 7.20–7.42 (m, 10 H, aromatic hydrogen atoms of both diastereomers), 6.64 (d, J = 15.8 Hz, 2 H, 2 CH= of both diastereomers), 6.20 (dd, J = 6.3, 15.8 Hz, 1 H, C=CC*H* of one diastereomer), 6.15 (dd, J = 7.1, 15.8 Hz, 1 H, C=CC*H* of the other diastereomer), 4.76 (m, 1 H, C*H*OH of one diastereomer), 4.38 (dt, J = 0.9, 7.1 Hz, 1 H, C*H*OH of the other diastereomer), 1.59–2.46 (m, 14 H, hydrogen atoms of the cyclopentane ring of both diastereomers) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 222.4, 222.3, 136.6, 136.5, 129.5, 129.0, 128.9, 128.6, 128.5, 128.3, 127.8, 127.7, 126.6, 126.5, 73.5, 71.1, 54.1, 53.9, 39.1, 38.6, 26.6, 23.6, 20.7, 20.5 ppm.

2-[(2*E*)-1-Hydroxy-3-phenylallyl]cyclopentan-1-ol (*syn*,*syn*-, *syn*, *anti*-, *anti*,*syn*-, *anti*,*anti*-1): To a stirred solution of the 1:1 mixture of *syn*- and *anti*-**4** (22 g, 0.1 mol) in ethanol (150 mL) at 0 °C was added sodium borohydride (3.7 g, 0.1 mol) portionwise over 30 min. After 10 h, the mixture was poured into iced H_2O and extracted with ethyl acetate/hexane (4:1). The oily residue (18 g) obtained upon concentration of the washed and dried organic phase was chromatographed with ethyl acetate/hexane (4:6 → 6:4), pro-

viding, in order, *syn*,*syn*-**1** (3.92 g, 18%) and a mixture of the other three diols **1** (14.8 g, 68%).

***syn*,*syn*-1:** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19–7.41 (m, 5 H, aromatic hydrogen atoms), 6.62 (d, J = 15.9 Hz, 1 H, CH=), 6.27 (dd, J = 6.2, 15.9 Hz, 1 H, =C*H*CHOH), 4.76 (m, 1 H, =CHC*H*OH), 4.40 (m, 1 H, CH_2C*H*OH), 1.53–2.02 (m, 7 H, hydrogen atoms of cyclopentane ring) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 136.9, 131.6, 129.7, 128.5, 127.4, 126.4, 76.4, 72.6, 49.6, 36.0, 22.4, 21.9 ppm.

***anti*,*syn*-1:** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19–7.42 (m, 5 H, aromatic hydrogen atoms), 6.62 (d, J = 15.8 Hz, 1 H, CH=), 6.29 (dd, J = 6.5, 15.8 Hz, 1 H, =C*H*CHOH), 4.37 (t, J = 6.5 Hz, 1 H, =CHC*H*OH), 4.14 (q, J = 6.4 Hz, 1 H, CH_2C*H*OH), 1.37–2.10 (m, 7 H, hydrogen atoms of the cyclopentane ring) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 136.6, 131.3, 130.3, 128.5, 127.6, 126.4, 74.9, 74.1, 53.3, 34.7, 25.5, 21.8 ppm.

***syn*,*anti*-1:** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20–7.41 (m, 5 H, aromatic hydrogen atoms), 6.63 (d, J = 15.9 Hz, 1 H, CH=), 6.30 (dd, J = 7.0, 15.9 Hz, 1 H, =C*H*CHOH), 4.49 (dt, J = 2.2, 4.8 Hz, 1 H, CH_2C*H*OH), 4.42 (t, J = 7.0 Hz, 1 H, =CHC*H*OH), 1.52–2.02 (m, 7 H, hydrogen atoms of the cyclopentane ring) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 136.9, 131.8, 130.5, 128.5, 127.6, 126.5, 74.3, 73.9, 50.5, 35.2, 26.4, 22.4 ppm.

***anti*,*anti*-1:** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20–7.41 (m, 5 H, aromatic hydrogen atoms), 6.54 (d, J = 15.9 Hz, 1 H, CH=), 6.17 (dd, J = 7.1, 15.9 Hz, 1 H, =C*H*CHOH), 4.08–4.20 (m, 2 H, =CHC*H*OH, CH_2C*H*OH), 1.49–2.02 (m, 7 H, hydrogen atoms of the cyclopentane ring) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 136.6, 131.2, 130.9, 128.5, 127.7, 126.4, 78.2, 78.1, 52.8, 33.9, 26.6, 21.1 ppm.

2,2-Dimethyl-4-styrylhexahydrocyclopenta[*d*][1,3]dioxine (*syn*,*syn*-, *syn*,*anti*-, *anti*,*syn*-, *anti*,*anti*-5), (1*E*,3*Z*)- and (1*E*,3*E*)-(8,8-Dimethoxyocta-1,3-dienyl)benzene [(1*E*,3*Z*)-8, (1*E*,3*E*)-8]: To a mixture of diols *syn*,*syn*-, *syn*,*anti*-, *anti*,*syn*-, and *anti*,*anti*-**1** (4.6 g, 0.02 mol), dissolved in acetone (30 mL) and 2,2-dimethoxypropane (15 mL) at 50–60 °C, pyridinium *p*-toluenesulfonate (50 mg, 0.198 mmol) was added. Once the reaction was completed (< 10 min), the mixture was diluted with ethyl acetate/hexane (1:1) and washed with saturated $NaHCO_3$ solution. The residue obtained upon concentration was chromatographed (SiO_2) with hexane/ethyl acetate (98:2 → 95:5), eluting in order, *syn*,*syn*-**5** (0.77 g, 15%), *syn*,*anti*-**5** (0.67 g, 13%), a 6:4 mixture of (1*E*,3*E*)-**8** and (1*E*,3*Z*)-**8** (0.54 g, 11%), and *anti*,*anti*-**5** (1.0 g, 19%).

***syn*,*syn*-5:** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19–7.38 (m, 5 H, aromatic hydrogen atoms), 6.61 (d, J = 15.9 Hz, 1 H, CH=), 6.17 (dd, J = 15.9, 6.2 Hz, 1 H, =C*H*CHO), 4.80 (m, 1 H, =CHC*H*O), 4.35 (m, 1 H, CH_2C*H*O), 1.54–2.01 (m, 7 H, hydrogen atoms of the cyclopentane ring), 1.53 (s, 3 H, CH_3), 1.44 (s, 3 H, CH_3) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 137.0, 130.2, 129.4, 128.4, 127.4, 126.4, 98.1, 73.2, 69.9, 43.4, 33.0, 30.1, 21.9, 21.7, 19.5 ppm. GC/MS: t_R = 23.90 min; *m*/*z* (%) = 258 (6) $[M]^+$, 243 (7), 200 (17), 183 (16), 133 (21), 104 (100). Enantiopure (+)- and (–)-*syn*,*syn*-**5**, obtained from (+)-*syn*,*syn*-**6** and (–)-*syn*,*syn*-**1**, showed, respectively: $[\alpha]_D^{20}$ = +53.3 (c = 0.96, $CHCl_3$) and $[\alpha]_D^{20}$ = –50.1 (c = 1.01, $CHCl_3$).

***syn*,*anti*-5:** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19–7.39 (m, 5 H, aromatic hydrogen atoms), 6.59 (d, J = 15.8 Hz, 1 H, CH=), 6.20 (dd, J = 15.8, 6.6 Hz, 1 H, =*C*HCHO), 4.30 (dt, J = 2.5, 6.6 Hz, 1 H, CH_2C*H*O), 4.04 (dd, J = 7.3, 9.8 Hz, 1 H, =CHC*H*O), 2.18 (m, 1 H, CH of the cyclopentane ring), 1.44–1.92 (m, 6 H, hydrogen atoms of the cyclopentane ring), 1.42 (s, 3 H, CH_3), 1.39 (s, 3 H, CH_3) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 136.9, 130.9, 129.2, 128.4, 127.5, 126.4, 99.7, 73.2, 72.3, 47.1, 34.1, 28.8, 25.8, 24.2, 24.1 ppm. GC/MS: t_R = 23.57 min; *m*/*z* (%) = 258 (5) $[M]^+$, 243 (1), 200 (21), 183 (5), 133 (76), 104 (100).

(1*E*,3*E*)-8 and (1*E*,3*Z*)-8: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.15–7.42 (m, 10 H, aromatic hydrogen atoms of both stereoisomers), 7.03 [dd, J = 11.0, 15.8 Hz, 1 H, H-2 of (3*Z*)-**8**], 6.73 [dd, J = 10.5, 15.8 Hz, 1 H, H-2 or H-3 of (3*E*)-**8**], 6.51 [d, J = 15.8 Hz, 1 H, H-1 of (3*Z*)-**8**], 6.43 [d, J = 15.8 Hz, 1 H, H-1 of (3*E*)-**8**], 6.20 [m, 2 H, H-3 or H-2 of (3*E*)-**8** and H-3 of (3*Z*)-**8**], 5.79 [dt, J = 15.8, 7.0 Hz, 1 H, H-4 of (3*E*)-**8**], 5.48 [dt, J = 10.0, 7.0 Hz, 1 H, H-4 of (3*Z*)-**8**], 4.36 [m, 2 H, *CH*$(OCH_3)_2$ of both diastereomers], 3.31 (s, 12 H, 2 OCH_3 of both diastereomers), 2.27 [q, J = 7.0 Hz, 2 H, *C*H_2C=C of (3*Z*)-**8**], 2.17 (q, J = 7.0 Hz, 2 H, *C*H_2C=C of (3*E*)-**8**], 1.63 (m, 4 H, CH_2 of both diastereomers), 1.50 (m, 4 H, CH_2 of both diastereomers) ppm. GC/MS: (1*E*,3*E*)-**8**: t_R = 24.38 min; *m*/*z* (%) = 246 (7) $[M]^+$, 214 (10), 183 (12), 156 (100); (1*E*,3*Z*)-**8**: t_R = 23.87 min; *m*/*z* (%) = 246 (8) $[M]^+$, 214 (10), 183 (15), 156 (100).

***anti*,*anti*-5:** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18–7.38 (m, 5 H, aromatic hydrogen atoms), 6.60 (d, J = 15.8 Hz, 1 H, CH=), 6.17 (dd, J = 15.8, 6.6 Hz, 1 H, =*C*HCHO), 4.29 (dd, J = 6.6, 9.5 Hz, 1 H, =CHC*H*O), 3.63 (dt, J = 6.9, 10.4 Hz, 1 H, CH_2C*H*O), 1.96 (m, 1 H, CH of the cyclopentane ring), 1.53 (s, 3 H, CH_3), 1.51 (s, 3 H, CH_3), 1.12–1.79 (m, 6 H, hydrogen atoms of the cyclopentane ring) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 136.7, 131.0, 128.8, 128.3, 127.5, 126.4, 100.0, 77.5, 75.2, 47.5, 30.0, 29.1, 22.4, 20.3, 18.1 ppm. GC/MS: t_R = 24.00 min; *m*/*z* (%) = 258 (1) $[M]^+$, 240 (1), 200 (38), 183 (32), 133 (19), 104 (100).

Baker's Yeast Reduction of *syn* and *anti*-4: To a stirred mixture of Baker's yeast (500 g) and D-glucose (200 g) in tap H_2O (2 L) at 30 °C was added dropwise over 30 min a solution of *syn*- and *anti*-**4** (21.6 g, 0.1 mol) in ethanol (40 mL). After 2 d, under these conditions, acetone (1 L) was added followed by ethyl acetate/hexane (4:1, 1 L). After 1 d of stirring, the mixture was filtered through a large Buchner funnel with a thick Celite pad previously washed with acetone. The two phases were then separated, and the aqueous phase was extracted twice with the ethyl acetate/hexane mixture. The oily residue obtained upon evaporation of the washed and dried organic phase was chromatographed with increasing amounts of ethyl acetate in hexane, obtaining ketone **4** (13.2 g, 61%) and a diol fraction (4.3 g, 20%). The latter mixture, on treatment with 2,2-dimethoxypropane (as was described above), afforded products *syn*,*anti*-**5** {$[\alpha]_D^{20}$ = +4.72 (c = 0.98, $CHCl_3$)} and *anti*,*anti*-**5** {$[\alpha]_D^{20}$ = –1.19 (c = 1.01, $CHCl_3$)}, in a 1:1 ratio after separation by column chromatography. The enantiomeric excess of *anti*,*anti*-**5** was determined by GC analysis on a chiral column to be >99%.

Acetylation of Diols *syn*,*syn*-, *syn*,*anti*-, *anti*,*syn*-, and *anti*,*anti*-1, Mediated by Lipase Amano PS: In a typical experiment, a solution of *syn*,*syn*-**1** (3.0 g, 0.014 mol) in vinyl acetate/*tert*-butyl methyl ether (1:1, 40 mL), was stirred with lipase Amano PS (3.0 g) at room temperature for 2 d. The filtered solution was concentrated, and the residue was chromatographed with increasing amounts of ethyl acetate in hexane. Under these conditions, *syn*,*syn*-**1** afforded diacetyl derivative (+)-*syn*,*syn*-**6** (0.42 g, 10%), followed by an inseparable mixture of isomeric monoacetates and, finally, by the unconverted starting diol (–)-*syn*,*syn*-**1** (1.06 g, 36%).

(+)-*syn*,*syn*-6: $[\alpha]_D^{20}$ = +8.84 (c = 0.95, $CHCl_3$); *ee* > 99%, determined by GC analysis on a chiral column of the corresponding acetonide, prepared by saponification of the diacetate and subsequent treatment with 2,2-dimethoxypropane. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20–7.36 (m, 5 H, aromatic hydrogen atoms), 6.57 (d,

J = 16.0 Hz, 1 H, CH=), 6.12 (dd, *J* = 7.7, 16.0 Hz, 1 H, C=*CH*CHOAc), 5.52 (t, *J* = 8.6 Hz, 1 H, C=CHC*H*OAc), 5.17 (dt, *J* = 2.2, 5.1 Hz, 1 H, CH_2CHOAc), 2.25 (m, 1 H, CH of the cyclopentane ring), 2.07 (s, 3 H, OAc), 2.03 (s, 3 H, OAc), 1.58–2.01 (m, 6 H, hydrogen atoms of the cyclopentane ring) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 170.3 170.0, 136.3, 132.9, 128.5, 127.9, 126.7, 126.5, 76.4, 74.8, 47.9, 32.9, 27.1, 21.9, 21.2, 21.1 ppm.

(–)-*syn*,*syn*-1: $[\alpha]_D^{20}$ = –5.47 (*c* = 0.50, $CHCl_3$); *ee* > 99%, determined by GC analysis of the corresponding acetonide on a chiral column. NMR spectra are in agreement with those of the racemic sample.

The mixture of diols *syn*,*anti*-, *anti*,*syn*-, and *anti*,*anti*-**1** provided, under the above conditions, the following products in order of elution: *anti*,*syn*-**7** (0.40 g, 11%), *anti*,*anti*-**7** (0.55 g, 15%), *syn*,*anti*-**7** (0.22 g, 6%), and a mixture of unreacted starting diols (0.67 g, 22%).

(–)-*anti*,*syn*-7: $[\alpha]_D^{20}$ = –1.76 (*c* = 0.90, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18–7.39 (m, 5 H, aromatic hydrogen atoms), 6.61 (d, *J* = 16.1 Hz, 1 H, CH=), 6.20 (dd, *J* = 6.4, 16.1 Hz, 1 H, C=C*H*CHOH), 5.05 (m, 1 H, CH_2CHOAc), 4.34 (m, 1 H, C=CHC*H*OH), 2.21 (m, 1 H, CH of the cyclopentane ring), 1.99 (s, 3 H, OAc), 1.48–1.95 (m, 6 H, hydrogen atoms of the cyclopentane ring) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 171.5, 136.8, 130.8, 130.3, 128.5, 127.5, 126.4, 77.8, 73.0, 51.9, 32.6, 25.9, 23.1, 21.2 ppm.

(+)-*anti*,*anti*-7: $[\alpha]_D^{20}$ = +6.06 (*c* = 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.13–7.37 (m, 5 H, aromatic hydrogen atoms), 6.56 (d, *J* = 16.0 Hz, 1 H, CH=C), 6.17 (dd, *J* = 7.1, 15.7 Hz, 1 H, C=C*H*CHOH), 5.14 (m, 1 H, CH_2CHOAc), 4.09 (m, 1 H, C=CH*CH*OH), 2.14 (m, 1 H, CH of the cyclopentane ring), 1.94 (s, 3 H, OAc), 1.50–1.88 (m, 6 H, hydrogen atoms of the cyclopentane ring) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 171.1, 136.5, 130.4, 130.3, 128.0, 126.9, 125.9, 78.1, 73.8, 51.9, 32.4, 27.4, 23.3, 20.7 ppm.

(+)-*syn*,*anti*-7: $[\alpha]_D^{20}$ = +29.3 (*c* = 0.69, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19–7.41 (m, 5 H, aromatic hydrogen atoms), 6.64 (d, *J* = 15.9 Hz, 1 H, CH=), 6.21 (dd, *J* = 6.6, 15.9 Hz, 1 H, C=*CH*CHOH), 5.39 (m, 1 H, CH_2CHOAc), 4.07 (m, 1 H, C=CH*CH*OH), 2.11 (s, 3 H, OAc), 1.40–1.97 (m, 7 H, hydrogen atoms of the cyclopentane ring) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 171.7, 136.8, 130.7, 130.3, 128.3, 127.3, 126.3, 77.1, 71.8, 51.9, 32.2, 25.9, 21.7, 21.0 ppm.

2,2-Dimethylhexahydrocyclopenta[*d*][1,3]dioxine-4-carbaldehyde (*syn*,*syn*-, *syn*,*anti*-, and *anti*,*anti*-9): Ozonised oxygen was passed through a solution of acetonide **5** (2.6 g, 10 mmol) in CH_2Cl_2 (30 mL) at –78 °C until the appearance of a blue colour. A solution of triphenylphosphane (2.6 g, 10 mmol) in CH_2Cl_2 (15 mL) was then added dropwise at the same temperature. After standing at room temp. for 1 h, the reaction mixture was concentrated to dryness, and the oily residue was treated with a small amount of diethyl ether. The phosphane oxide, which precipitated upon scratching the side of the flask, was removed by filtration. The liquid phase was concentrated, and the residue was chromatographed on SiO_2 eluting with ethyl acetate in hexane, yielding benzaldehyde and aldehyde **9** (1.1 g, 60%).

***syn*,*syn*-9:** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.59 (s, 1 H, CHO), 4.52 (d, *J* = 3.4 Hz, 1 H, CHC*H*–O), 4.35 (q, *J* = 2.5 Hz, 1 H, CH_2CH–O), 1.52–2.05 (m, 7 H, hydrogen atoms of cyclopentane ring), 1.48 (s, 3 H, CH_3), 1.46 (s, 3 H, CH_3) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 202.0, 98.4, 74.3, 73.3, 39.1, 32.4, 29.6, 22.1, 21.7, 19.0 ppm. GC/MS: t_R = 12.57 min; *m*/*z* (%) = 184 (1) $[M]^+$, 169 (22), 155 (45), 97 (38), 79 (34), 59 (100). Optically active (–)-*syn*,*syn*-**9** was prepared from the acetonide of (–)-*syn*,*syn*-**1**: $[\alpha]_D^{20}$ = –38.5 (*c* = 0.94, $CHCl_3$).

***syn*,*anti*-9:** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.71 (s, 1 H, CHO), 4.26 (dt, *J* = 2.5, 6.5 Hz, 1 H, CH_2CH–O), 3.87 (d, *J* = 9.9 Hz, 1 H, CHC*H*–O), 2.27 (m, 1 H, CH of cyclopentane ring), 1.44–1.89 (m, 6 H, hydrogen atoms of cyclopentane ring), 1.42 (s, 3 H, CH_3), 1.36 (s, 3 H, CH_3) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 201.0, 99.9, 77.0, 72.2, 42.0, 33.4, 28.6, 25.7, 23.9, 23.5 ppm. GC/MS: t_R = 11.69 min; *m*/*z* (%) = 184 (1) $[M]^+$, 169 (19), 155 (42), 97 (37), 79 (31), 59 (100).

***anti*,*anti*-9:** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.58 (d, *J* = 1.1 Hz, 1 H, CHO), 4.09 (dd, *J* = 1.1, 10.5 Hz, 1 H, CHC*H*–O), 3.63 (dt, *J* = 6.8, 10.3 Hz, 1 H, CH_2CH–O), 1.41–2.01 (m, 7 H, hydrogen atoms of cyclopentane ring), 1.52 (s, 3 H, CH_3), 1.50 (s, 3 H, CH_3) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 200.6, 100.3, 80.8, 75.2, 42.5, 29.6, 28.4, 22.0, 20.0, 18.4 ppm. GC/MS: t_R = 12.51 min; *m*/*z* (%) = 183 (1) $[M - 1]^+$, 169 (33), 155 (53), 97 (86), 79 (44), 59 (100).

Conversion of *syn*,*anti*-Aldehyde 9 into Deoxyhexose Derivatives 2

(*RS*)-1-[(4*RS*,4a*RS*,7a*SR*)-2,2-Dimethylhexahydrocyclopenta[*d*](1,3)-dioxin-4-yl]prop-2-en-1-ol (*syn*,*anti*,*syn*-10): To the Grignard reagent prepared in THF (150 mL) under nitrogen from Mg turnings (2.3 g, 100 mmol) and vinyl bromide (22 g, 20 mmol) was added at 0 °C *syn*,*anti*-**9** (2.0 g, 11.6 mmol) in THF (50 mL). After one night at room temperature, a saturated solution of ammonium chloride was added with caution at 0 °C. Dilution with iced H_2O and solvent extraction provided, after chromatographic purification, *syn*,*anti*,*syn*-**10** (2.0 g, 78%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.86 (ddd, *J* = 6.3, 10.5, 17.1 Hz, CH=), 5.37 (m, 1 H,C=C*H*H), 5.21 (m, 1 H, C=C*H*H), 4.21 (dt, *J* = 2.5, 6.0 Hz, 1 H, CH_2CHO), 3.99 (m, 1 H, *CH*OH), 3.33 (dd, *J* = 5.4, 9.5 Hz, 1 H, CHC*H*O), 2.17 (m, 1 H, C*H* of the cyclopentane ring), 1.33–1.88 (m, 6 H, hydrogen atoms of the cyclopentane ring), 1.37 (s, 3 H, CH_3), 1.32 (s, 3 H, CH_3) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 133.6, 116.8, 99.9, 75.9, 74.9, 72.7, 43.6, 33.3, 29.7, 25.0, 24.4, 24.1 ppm. GC/MS: t_R = 15.39 min; *m*/*z* (%) = 197 (20) $[M - 15]^+$, 155 (34), 97 (38), 59 (100).

(2*RS*,3*SR*,4*RS*,4a*RS*,7a*SR*)-Octahydrocyclopenta[*b*]pyran-2,3,4-triyl Triacetate (11): Compound *syn*,*anti*,*syn*-**10** (1.8g, 9.0 mmol), dissolved in methanol/H_2O (8:2, 20 mL), was treated in a H_2O bath with 4 drops of concentrated HCl. After 3 h, the hydrolysis was complete. Most of the methanol was evaporated under vacuum, and the residue was neutralised upon addition of $NaHCO_3$ solution. Five extractions of the salted solution with ethyl acetate provided, after concentration and chromatography of the residue through a short path of SiO_2 of the residue using ethyl acetate as eluent, a triol derivative (1.2 g, 77%). This material was dissolved in CH_2Cl_2 (15 mL) and ozonised, as described above. The addition of 1 mol-equiv. of triphenylphosphane and concentration of the reaction mixture provided a semi-solid residue. This was treated with Ac_2O (10 mL) and pyridine (10 mL) overnight, providing, after evaporation of the reagents under vacuum, an oil, which was chromatographed on SiO_2 eluting with 35% ethyl acetate in hexane to yield a triacetyl derivative (0.9 g, 67%) as a 6:4 mixture of β and α anomers. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.25 (d, *J* = 3.5 Hz, 1 H, H-2 of the α anomer), 5.58 (d, *J* = 7.9 Hz, 1 H, H-2 of the β anomer), 5.49 (dd, *J* = 6.0, 10.5 Hz, 1 H, H-3 or H-4 of the α anomer), 5.16–5.27 (m, 3 H, H-3 and H-4 of the β anomer + H-4 or H-3 of the α anomer), 4.40 (t, *J* = 4.1 Hz, 1 H, H-7a of the α anomer), 4.18 (t, *J* = 3.5 Hz, 1 H, H-7a of the β anomer), 2.55 (m, 1 H, CH of the cyclopentane ring α anomer), 2.44 (m, 1 H, CH of

the cyclopentane ring β anomer), 2.02, 2.05, 2.14 (3 s, 9 H, 3 OAc of the α anomer), 2.03, 2.04, 2.09 (3 s, 9 H, 3 OAc of the β anomer), 1.55–1.96 (m, 12 H, hydrogen atoms of the cyclopentane ring of both anomers) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): β anomer: δ = 170.3, 169.7, 169.2, 92.2, 78.1, 72.6, 68.7, 44.4, 31.8, 23.8, 21.4, 20.8, 20.7 ppm; α anomer: δ = 170.5, 170.1, 169.3, 90.8, 75.4, 68.9, 67.0, 44.1, 32.0, 23.6, 21.8, 20.6, 20.5 ppm. GC/MS: t_R = 22.57, 22.63 min; *m*/*z* (%) = 241 (1) $[M - 59]^+$, 198 (18), 156 (15), 110 (100).

(2*RS*,3*SR*,4*SR*,4a*RS*,7a*SR*)-2-Phenyloctahydrocyclopenta[*b*]pyran-3,4-diol (12a), (2*RS*,3*SR*,4*RS*,4a*RS*,7a*SR*)-2-Phenyloctahydrocyclopenta[*b*]pyran-3,4-diol (13a), (2*SR*,3*RS*,4*SR*,4a*RS*,7a*SR*)-2-Phenyloctahydrocyclopenta[*b*]pyran-3,4-diol (12b), (2*SR*,3*RS*,4*RS*,4a*RS*,7a*SR*)-2-Phenyloctahydrocyclopenta[*b*]pyran-3,4-diol (13b), and (1*RS*,2*SR*)-1-[(1*RS*,2*RS*)-2-Hydroxycyclopentyl]-3-phenylpropane-1,2,3-triol (16): A mixture of racemic *anti*,*anti*- and *anti*,*syn*-**1** (4.36 g, 0.02 mol) was treated with *m*-chloroperbenzoic acid (4.31 g, 0.025 mol) in CH_2Cl_2 (100 mL) at 0 °C. After 2 h at room temperature, the reaction mixture was poured into H_2O, washed with a 10% solution of sodium bisulfite and a saturated solution of $NaHCO_3$, and extracted with CH_2Cl_2. The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure to give a residue, which was chromatographed with increasing amounts of ethyl acetate in hexane, to afford compound **12a** (0.70 g, 12%) and a 1:1:0.5 mixture of compounds **13a**, **14**, and **15** (2.01 g). ^{1}H NMR signals of epoxide rings: **14**: δ = 3.97 (d, *J* = 1.9 Hz), 3.09 (dd, *J* = 1.9, 3.1 Hz) ppm; **15**: δ = 3.83 (d, *J* = 1.9 Hz), 3.02 (dd, *J* = 1.9, 5.4 Hz) ppm.

This latter mixture was dissolved in THF/H_2O and treated with CH_3COOH (1 mL) and a few drops of $HClO_4$. After 30 min, the reaction mixture was diluted with H_2O and extracted with diethyl ether. The organic phase was washed with a saturated $NaHCO_3$ solution, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was chromatographed, eluting with increasing amounts of ethyl acetate in hexane. In order of elution, the following products were obtained: **13a** (0.76 g, 13%), **12b** (0.35 g, 6%), **13b** (0.29 g, 5%), and **16** (0.50 g, 8%).

12a: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.27 (m, 5 H, aromatic hydrogen atoms), 4.51 (d, *J* = 9.5 Hz, 1 H, H-2), 4.22 (m, 1 H, H-4), 3.94 (dt, *J* = 7.3, 10.4 Hz, 1 H, H-7a), 3.59 (dd, *J* = 3.1, 9.5 Hz, 1 H, H-3), 2.00–1.50 (m, 7 H, hydrogen atoms of the cyclopentane ring) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 139.4, 128.6, 128.4, 127.7, 79.3, 76.6, 73.9, 68.5, 47.9, 28.2, 21.1, 19.8 ppm.

13a: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.27 (m, 5 H, aromatic hydrogen atoms), 4.19 (d, *J* = 9.3 Hz, 1 H, H-2), 3.51 (dd, *J* = 8.3, 10.0 Hz, 1 H, H-3 or H-4), 3.48 (dt, *J* = 7.1, 10.3 Hz, 1 H, H-7a), 3.38 (t, *J* = 9.0 Hz, 1 H, H-4 or H-3), 2.00–1.20 (m, 7 H, hydrogen atoms of the cyclopentane ring) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 138.7, 128.7, 128.5, 127.7, 83.9, 82.5, 78.0, 77.5, 49.5, 28.4, 24.3, 20.1 ppm.

12b: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.25 (m, 5 H, aromatic hydrogen atoms), 4.15 (t, *J* = 3.2 Hz, 1 H, H-7a), 4.06 (dd, *J* = 6.4, 9.3 Hz, 1 H, H-4), 4.02 (t, *J* = 9.3 Hz, 1 H, H-2), 3.61 (t, *J* = 9.3 Hz, 1 H, H-3), 2.40–1.20 (m, 7 H, hydrogen atoms of the cyclopentane ring) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 138.8, 128.6, 128.3, 127.3, 81.6, 80.8, 73.7, 73.6, 47.0, 29.6, 23.4, 22.1 ppm.

13b: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.25 (m, 5 H, aromatic hydrogen atoms), 5.24 (br. s, H-2), 4.51 (br. s, 1 H, H-3), 3.61 (br. d, *J* = 9.0 Hz, 1 H, H-4), 3.23 (dt, *J* = 7.4, 10.3 Hz, 1 H, H-7a), 2.50–1.00 (m, 7 H, hydrogen atoms of the cyclopentane ring) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 138.8, 128.7, 127.5, 126.3, 80.7, 75.9, 72.7, 69.8, 45.6, 28.4, 24.2, 18.7 ppm.

16: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47–7.20 (m, 5 H, aromatic hydrogen atoms), 4.98 (d, *J* = 4.3 Hz, 1 H, PhC*H*OH), 4.02 (q, *J* = 7.4 Hz, 1 H, cyclopentane-*CH*OH), 3.70 (m, 1 H, *CH*OH), 3.60 (m, 1 H, *CH*OH), 2.00–1.00 (m, 7 H, hydrogen atoms of the cyclopentane ring) ppm.

The structures of compounds **12a**,**b** and **13a**,**b** were confirmed by observing the downfield shift only of protons H-3 and H-4 of the sugar ring upon acetylation with Ac_2O in pyridine. The structure of compound **16** was confirmed by observing the downfield shift of all four protons linked to oxygen atoms upon acetylation with Ac_2O in pyridine.

(2*RS*,3*SR*,4*SR*,4a*RS*,7a*SR*)-2-Phenyloctahydrocyclopenta[*b*]pyran-3,4-diol Acetonide (19): Compound **12a** was converted into the corresponding acetonide according to the procedure already described for the preparation of acetonides **5**. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.27 (m, 5 H, aromatic hydrogen atoms), 4.49 (dd, *J* = 3.5, 4.5 Hz, 1 H, H-4), 4.44 (d, *J* = 8.7 Hz, 1 H, H-2), 3.97 (dd, *J* = 4.5, 8.4 Hz, 1 H, H-3), 3.80 (dt, *J* = 7.1, 10.6 Hz, 1 H, H-7a), 2.06–1.55 and 1.65 (m + s, 10 H, 7 hydrogen atoms of the cyclopentane ring + CH_3), 1.40 (s, 3 H, CH_3) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 140.8, 128.3, 127.6, 126.6, 110.3, 81.4, 78.1, 77.5, 74.4, 44.8, 28.4, 28.2, 26.4, 21.8, 19.6 ppm.

(2*RS*,3*SR*,4*RS*,4a*RS*,7a*SR*)-2-Phenyloctahydrocyclopenta[*b*]pyran-3,4-diol Acetonide (20): Compound **13a** was converted into its corresponding acetonide according to the procedure already described for the preparation of acetonides **5**. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55–7.23 (m, 5 H, aromatic hydrogen atoms), 4.52 (d, *J* = 9.2 Hz, 1 H, H-2), 3.54 (dd, *J* = 8.3, 10.2 Hz, 1 H, H-3 or H-4), 3.47–3.38 (t + dt, t *J* = 9.2 Hz, dt *J* = 7.3, 9.5 Hz, 2 H, H-4 or H-3 + H-7a), 3.38 (t, *J* = 9.0 Hz, 1 H, H-4 or H-3), 2.20–1.50 (m, 7 H, hydrogen atoms of the cyclopentane ring), 1.46 (s, 3 H, CH_3), 1.40 (s, 3 H, CH_3) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 138.4, 128.4, 128.2, 126.7, 110.1, 83.7, 83.0, 81.4, 80.9, 48.7, 27.6, 26.8, 26.6, 24.1, 20.2 ppm.

(4*RS*,5*RS*,5a*SR*,8a*RS*)-4-Benzyl-2,2-dimethylhexahydro-4*H*-cyclopenta[*d*][1,3]dioxepin-5-ol (21): Tetraol **16** (0.30 g, 1.19 mmol) in ethyl acetate (20 mL) was hydrogenated at 80 psi in the presence of 10% Pd/C (30 mg) at room temp. for 24 h. The reaction mixture was filtered through a short column of SiO_2, containing an upper layer of Celite, obtaining, upon concentration of the organic phase, a crude reaction product, which was treated with 2,2-dimethoxypropane. Column chromatography (hexane/ethyl acetate, 7:3) afforded derivative **21** (0.18 g, 55%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.10 (m, 5 H, aromatic hydrogen atoms), 3.97 (m, 2 H, 2 CHO), 3.60 (dd, *J* = 1.14, 10.3 Hz, 1 H, *CH*OH), 2.91 (dd, *J* = 8.6, 13.4 Hz, 1 H, PhC*H*H), 2.83 (dd, *J* = 6.3, 13.4 Hz, 1 H, PhC*H*H), 2.18 (d, *J* = 10.3 Hz, 1 H, O*H*), 1.91–1.31 (m, 7 H, hydrogen atoms of the cyclopentane ring), 1.51 (s, 3 H, CH_3), 1.31 (s, 3 H, CH_3) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 138.9, 129.7, 128.2, 126.2, 101.4, 74.8, 71.5, 68.8, 52.4, 39.3, 30.4, 25.0, 24.4, 22.6, 19.9 ppm.

Configuration Assignment of Optically Active Monoacetates *anti*, *anti*- and *anti*,*syn*-7

(1*R*,2*R*)-2-(2,2-Dimethyl-1,3-dioxolan-4-yl)cyclopentyl Acetate (22): Ozonised oxygen was passed through a solution of a 1:1 mixture of optically active *anti*,*anti*- and *anti*,*syn*-**7** at –78 °C, produced in the enzymatic incubation of a 1:1 mixture of diols **1** with PS (5.2 g, 20 mmol) in MeOH/CH_2Cl_2 (1:1, 80 mL). At the end of the reaction, solid sodium borohydride was added in small portions under

nitrogen at the same temperature over 1 h until the decomposition of the ozonide was complete (TLC). The reaction mixture was brought to room temperature, diluted with cold H_2O and extracted with CH_2Cl_2. The washed and dried organic phase was treated with 2,2-dimethoxypropane (30 mL), acetone (20 mL) and a few crystals of pyridinium 4-toluenesulfonate and kept at a gentle reflux for 3 h. The cooled mixture was washed with a saturated solution of $NaHCO_3$, dried, and the solvents were evaporated to dryness to leave a residue (ca. 5 g), which was purified by column chromatography with increasing amounts of ethyl acetate in hexane, to give compound **22** as a 1:1 mixture of two diastereomers (2.65 g, 58%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.12 (m, 1 H, CHOAc of one diastereomer), 4.90 (m, 1 H, CHOAc of the other diastereomer), 4.10 (m, 1 H, CH–O), 3.99 (m, 3 H, CH–O), 3.63 (m, 2 H, CH–O), 1.47–2.15 (m + 2 s at δ = 2.01 and 2.00 ppm, 26 H, 14 hydrogen atoms of cyclopentane ring and 2 OAc of both diastereomers), 1.49, 1.39, 1.33, and 1.32 (4 s, 12 H, 4 OCH_3) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 170.6, 170.4, 108.9, 108.6, 78.4, 77.8, 77.2, 67.9, 67.6, 62.9, 48.2, 47.9, 32.7, 32.6, 27.1, 26.6, 26.2, 26.5, 25.4, 24.5, 23.1, 21.2, 21.1 ppm. GC/MS: t_R = 16.66 min; *m*/*z* (%) = 213 (59) $[M - 15]^+$, 170 (1), 153 (15), 111 (100).

4-[(1*R*,2*R*)-2-(Benzyloxy)cyclopentyl]-2,2-dimethyl-1,3-dioxolane (23) and 1-[(1*S*,2*R*)-2-(Benzyloxy)cyclopentyl]ethane-1,2-diol (24): Compound **22** (2.28 g, 10 mmol) in MeOH (20 mL) was treated in an H_2O bath with aqueous KOH (25%, 2 mL) for 2 h. The mixture was diluted with iced H_2O, brought to pH = 7 with dilute acetic acid, and extracted twice with Et_2O. The crude oily residue obtained upon concentration of the solution was dissolved in dry THF (50 mL) and treated whilst stirring under nitrogen at room temp. with NaH (60% suspension in oil, 0.48 g, 12 mmol). After 6 h, a solution of benzyl bromide (2.65 g, 15 mmol) in THF (10 mL) was added dropwise. After 24 h of stirring, the reaction mixture was diluted with a few drops of MeOH and then with iced H_2O. The oily residue obtained upon concentration of the ethereal extract of the latter reaction mixture was chromatographed to provide the *O*-benzyl ether **23** (1.9 g, 68%). Compound **23** (1.7 g, 6.15 mmol), dissolved in THF/MeOH (2:1, 30 mL), was treated in an H_2O bath for 1 h with acetic acid (1 mL) and 3 drops of concentrated HCl. The reaction mixture was concentrated to dryness, and the residue was chromatographed on SiO_2 eluting with ethyl acetate diol **24** (1.12 g, 77%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.62–4.41 (m, 4 H, CH_2OPh of both diastereomers), 4.01 (m, 1 H, CH–O), 3.83 (m, 1 H, CH–O), 3.73–3.48 (m, 6 H, CH–O and C*H*$_2$OH of both diastereomers), 1.48–2.00 (m, 14 H, hydrogen atoms of cyclopentane ring of both diastereomers) ppm.

[(1*S*,2*R*)-2-(Benzyloxy)cyclopentyl]methanol (25): Compound **24** (1.12 g, 4.7 mmol), dissolved in THF (10 mL), was added at once at room temp. to a stirred mixture of THF (80 mL) and periodic acid (1.25 g, 5.5 mmol). After 5 min, a few drops of ethylene glycol (0.2 mL) were added to the cloudy reaction mixture. After cooling to –10 °C and dilution with MeOH (20 mL), sodium borohydride was then added in small portions until the reduction of the intermediate aldehyde (TLC) was complete. The mixture was poured with caution into iced H_2O and extracted twice with Et_2O. Concentration of the washed and dried organic extract yielded **25** (0.82 g, 81%). $[\alpha]_D^{20}$ = –48.8 (*c* = 0.95, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21–7.35 (m, 5 H, Ar), 4.54 (d, *J* = 11.9 Hz, 1 H, C*H*HAr), 4.45 (d, *J* = 11.6 Hz, 1 H, CH*H*Ar), 3.72–3.78 (q, *J* = 5.4 Hz, 2 H, C*H*O), 3.54 (m, 2 H, C*H*$_2$OH), 1.16–1.21 (m, 7 H, $CH_2CH_2CH_2CH$) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 138.6, 128.2, 127.5, 127.4, 83.8, 71.1, 65.5, 47.7, 31.4, 26.5, 22.3 ppm.

(1*R*,2*S*)-2-(Hydroxymethyl)cyclopentanol [(*R*,*S*)-(–)-26]: The *O*-benzyl ether **25** (0.75 g, 3.6 mmol), dissolved in ethyl acetate (20 mL), was hydrogenated at 50 psi in the presence of 10% Pd/C (200 mg) at room temp. for 24 h. The reaction mixture was filtered through a short column of SiO_2 containing an upper layer of Celite, providing, upon concentration of the organic phase, diol (–)-**26** (0.35 g, 83%). $[\alpha]_D^{20}$ = –13.9 (*c* = 1.0, $CHCl_3$) {ref.[25a] (1*R*,2*S*)-(–)-**26**: $[\alpha]_D^{20}$ = –22.7 (*c* = 0.75, $CHCl_3$); ref.[25b] $[\alpha]_D^{20}$ = –13.7 (*c* = 1.0, $CHCl_3$); ref.[25c] (1*S*,2*R*)-(+)-**26**: $[\alpha]_D^{20}$ = +13.4 (*c* = 1.0, $CHCl_3$); ref.[25d] $[\alpha]_D^{20}$ = +38.7 (*c* = 1.0, MeOH)}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.0 (q, *J* = 6.1 Hz, 1 H, C*H*OH), 3.67 (dd, *J* = 5.5, 10.6 Hz, 1 H, CH*H*OH), 3.50 (dd, *J* = 8.7, 10.6 Hz, 1 H, C*H*HOH), 1.13–2.05 (m, 7 H, $CH_2CH_2CH_2CH$) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 77.2, 65.6, 49.7, 34.4, 26.4, 21.8 ppm.

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