DOI: 10.1002/ejoc.201000558

Oxygenated Stereotriads with Definite Absolute Configuration by Lipase-Mediated Kinetic Resolution: De Novo Synthesis of Imino Sugars and 6-Deoxy-*C*-glycosides

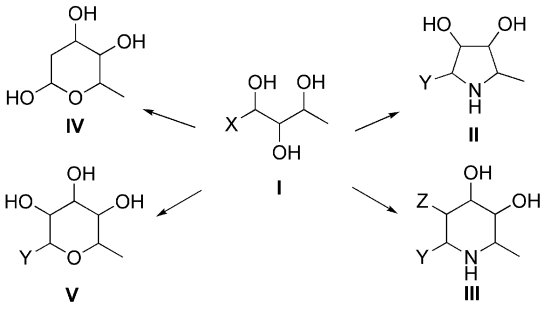
Daniela Acetti,[a] Elisabetta Brenna,*[a] and Francesco G. Gatti[a]

Keywords: Iminosugars / Enzymes / Kinetic resolution / Chirality / C-glycosides

The lipase-mediated kinetic resolution of compound **1** was investigated to prepare chiral synthons showing oxygenated stereotriads in a definite configurational arrangement. These key intermediates were embedded in biologically relevant structures, such as hydroxylated pyrrolidine **3** and C-phenyl glycosides by classical organic reactions.

Introduction

The single enantiomers of configurationally defined stereotriads are very precious building blocks of modern organic chemistry:[1] if they show adequate functionalisation, such as those of type **I** (Scheme 1), they can be incorporated into chiral molecules with multiple stereogenic centres, such as glycosidase inhibitors **II** and **III** or deoxysugar derivatives **IV** and **V**.

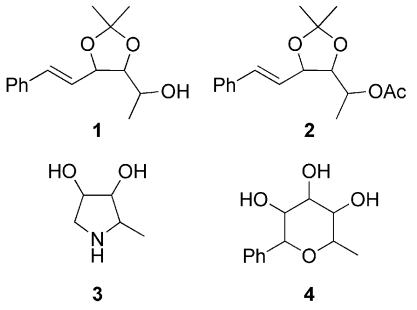


Scheme 1. X, Y, Z = suitable functional groups, or alkyl or aryl substituents.

The common strategies to synthons **I** usually start from carbohydrates available from *the chirality pool*, and they are thus finalised to the synthesis of a single configurational isomer, the one allowed by the stereochemistry of the starting natural building block. Sometimes stereodiversity has to be achieved, either to investigate the biological activity of all the different stereoisomers of a certain molecule or to obtain configurations that are complementary to those available from natural sources.

Imino sugars **II** and **III** have been widely investigated due to their potential as glycosidase inhibitors.[2] Both natural and non-natural hydroxylated pyrrolidines and piperidines were prepared to investigate the influence of substituents and configurational and conformational changes on inhibition.[3] 2,6-Dideoxypyranosides **IV** are essential components of steroidal glycosides, antibiotics and antitumour compounds.[4] They are scarcely available from microbial sources, and their preparation is still the object of intense investigation,[5]even according to de novo approaches.[6] *C*-Glycosides **V**, particularly those showing Y = aryl, have been found to possess antibacterial, antitumour and antifungal activities.[7] These characteristics, in addition to their limited availability from natural sources, makes them intriguing and timely targets for total synthesis.

In the aim of synthesising useful oxygenated synthons showing *stereochemical differentiation*, we investigated the kinetic resolution of substrate **1** (Scheme 2) mediated by lipase PS. Single stereoisomers of acetates **2** were obtained, their absolute configurations were established, and they were converted into imino sugar **3** and deoxysugar derivatives **4** to show the *structural differentiation* that these building blocks can afford.



Scheme 2.

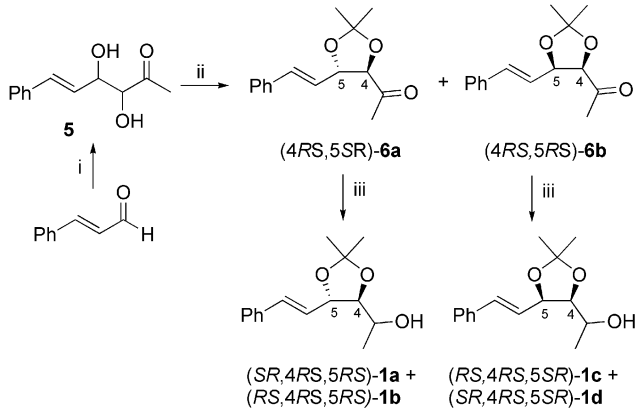
[a] Politecnico di Milano, Dipartimento di Chimica, Materiali, Ingegneria Chimica,
Via Mancinelli 7, 20131 Milano, Italy
Fax: +39-02-23993180
E-mail: elisabetta.brenna@polimi.it

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201000558.

Results and Discussion

Kinetic Resolution of Substrates 1a–d

Aldolic condensation of cinnamaldehyde and hydroxyacetone in methanol solution promoted by 40% NaOH (Scheme 3) afforded a 1:0.8 mixture of the two racemic diastereoisomers of dihydroxy ketone **5**. After acetonide protection, diastereoisomers **6a** and **6b** could be separated by column chromatography and submitted separately to $NaBH_4$ reduction to give a 1:1 mixture of alcohols **1a**/**1b** and **1c**/**1d**, respectively. The relative configuration of the two acetonide derivatives was first tentatively assigned: a crude mixture showing the ^1H NMR signals of 5-deoxy-2,3-*O*-isopropylidene-β-ribofuranose[8] was recovered from the ozonolysis and dimethyl sulfide quenching of a mixture of **1c** and **1d**. This attribution was then confirmed by the outcome of the sequence that was developed starting from these substrates.



Scheme 3. Reagents and conditions: (i) Hydroxyacetone, NaOH 40%, MeOH; (ii) 2,2-dimethoxypropane, PPTS, acetone, column chromatography; (iii) $NaBH_4$, CH_2Cl_2, MeOH.

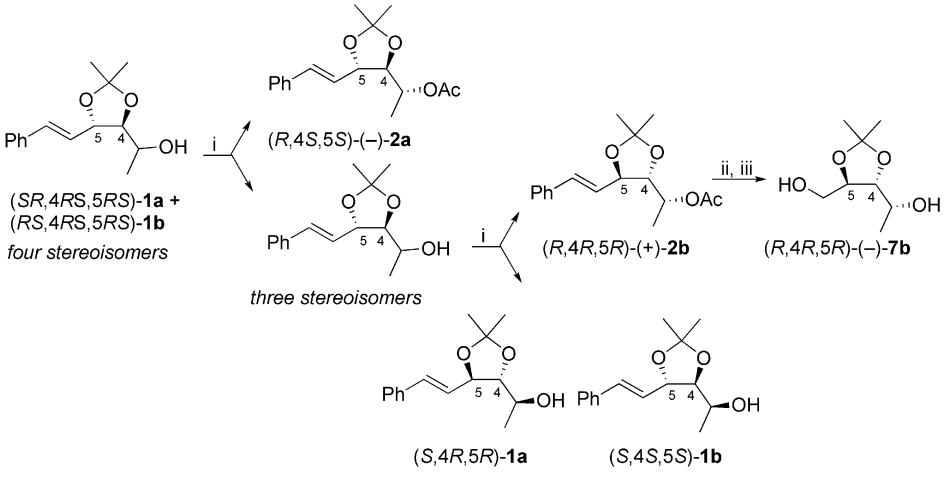
When the 1:1 mixture of *rac*-**1a** and *rac*-**1b** (four stereoisomers) was treated with lipase PS in methyl *tert*-butyl ether solution in the presence of vinyl acetate, acetate (*R*,4*S*,5*S*)-**2a** (99%*ee*, HPLC of the corresponding alcohol on a chiral column) was obtained after 48 h at room temperature (Scheme 4). The unreacted alcohols consisted of three stereoisomers, which were submitted again to lipase-mediated kinetic resolution under the same conditions to afford, after 96 h at room temperature, acetate (*R*,4*R*,5*R*)-**2b** (99%*ee*, HPLC of the corresponding alcohol on a chiral column) and a 1:1 mixture of alcohols (*S*,4*R*,5*R*)-**1a** and (*S*,4*S*,5*S*)-**1b**.

Acetate (+)-**2b** was submitted to ozonolysis followed by $NaBH_4$ quenching to obtain, after saponification (Scheme 4), the O_3,O_4-isopropylidene derivative of 1-deoxy-D-lyxitol (–)-**7b** of known absolute configuration.[9] Thus, the relative *anti* stereochemistry of C-4 and C-5 was established and (*R*) configuration was assigned to the stereogenic carbon atom bearing the OH group acetylated by lipase PS in (+)-**2b**, and by analogy in (–)-**2a**. This attribution was also confirmed by the transformation of (–)-**2a** into the corresponding known pyrrolidine (2*S*,3*S*,4*S*)-(+)-**3**.

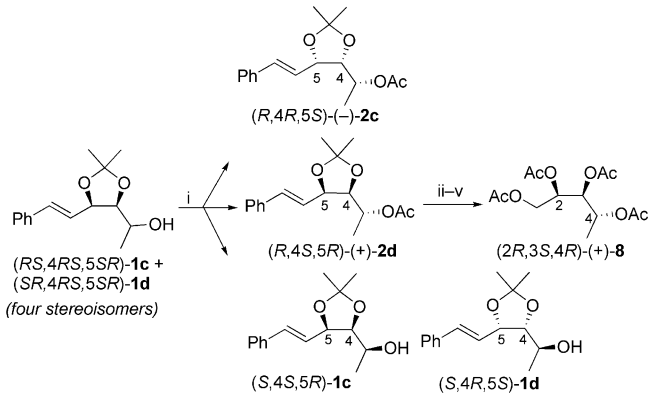
Interestingly, when *rac*-**1c** and *rac*-**1d** (Scheme 5) were treated with lipase PS under the same transesterification conditions, enantiopure acetates (*R*,4*R*,5*S*)-**2c** (99%*ee*, HPLC of the corresponding alcohol on a chiral column) and (*R*,4*S*,5*R*)-**2d** (99%*ee*, HPLC of the corresponding alcohol on a chiral column) were simultaneously obtained and separated by column chromatography. A mixture of (*S*,4*S*,5*R*)-**1c** and (*S*,4*R*,5*S*)-**1d** was left unreacted after the enzyme-mediated kinetic resolution.

Acetate (+)-**2d** was submitted to ozonolysis followed by $NaBH_4$ quenching to obtain, after deprotection and acetylation, the tetracetyl derivative of 1-deoxy-D-arabitol (+)-**8** of known absolute configuration.[10] Thus, the (*R*) configuration was established for the stereogenic carbon atom bearing the OH group acetylated by lipase PS in (+)-**2d**, and by analogy in (–)-**2c**. The relative configurations of the stereocentres in the 4- and 5-positions of starting acetonide **1d** were also confirmed.

This latter information was also supported by isolation of derivative **9**, then converted into the O_3,O_4-isopropylid-

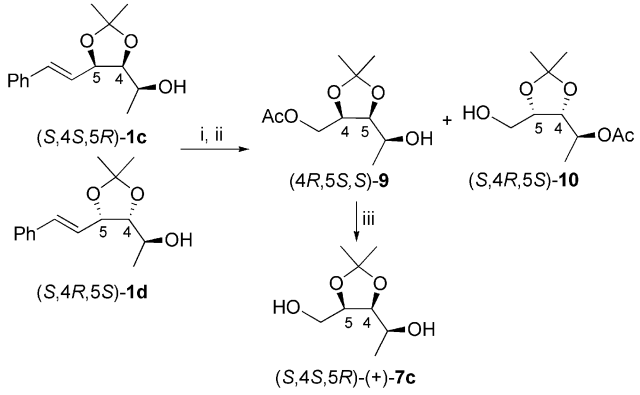


Scheme 4. Reagents and conditions: (i) Lipase PS, vinyl acetate, methyl *tert*-butyl ether, column chromatography; (ii) O_3, MeOH/CH_2Cl_2, then $NaBH_4$; (iii) KOH, MeOH.



Scheme 5. Reagents and conditions: (i) Lipase PS, vinyl acetate, methyl *tert*-butyl ether, column chromatography; (ii) O_3, MeOH/CH_2Cl_2, then $NaBH_4$; (iii) KOH, MeOH; (iv) HCl, AcOH, THF/H_2O; (v) Ac_2O, pyridine.

ene derivative of 1-deoxy-D-ribitol (+)-**7c** of known absolute configuration,[11] besides the monoacetate of 1-deoxyarabitol **10**, from the mixture of **1c** and **1d** recovered unreacted from lipase PS treatment (Scheme 6). After acetylation with Ac_2O and pyridine, the mixture of **1c** and **1d** was treated with O_3 followed by reductive quenching to afford monoacetates **9** and **10**. The migration of the acetyl group occurred only in one stereoisomer, and thus we could separate them by column chromatography. Compound **9** gave (+)-**7c** upon saponification.

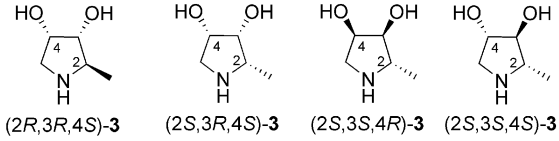


Scheme 6. Reagents and conditions: (i) Ac_2O, pyridine; (ii) O_3, MeOH/CH_2Cl_2; then $NaBH_4$, column chromatography; (iii) KOH, MeOH.

Stereoselective Synthesis of Pyrrolidine 3

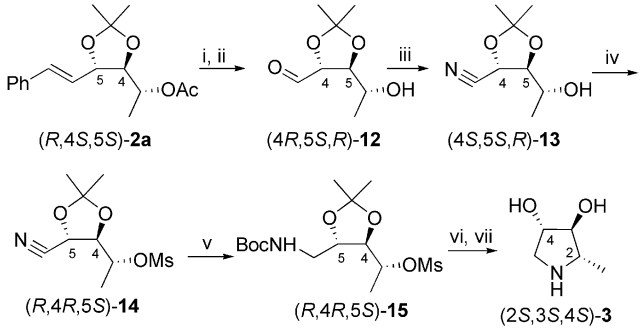
Much interest has been devoted recently to the chemistry and the biological activity of polyhydroxylated pyrrolidines **3**,[12] because they have been shown to selectively inhibit the oligosaccharide processing enzyme called glycosidases.[13] Thus, they are potentially useful as antiviral, antiadhesive, antimetastatic and antibacterial agents.[14]

Stereoisomer (2*R*,3*R*,4*S*)-**3** (Scheme 7) was prepared in 1995 by Chi-Huey Wong[15] starting from L-ribose, and by selectively converting the OH at C-4 into an amino functionality. The hydrobromic acid salt of this enantiomer was described to be obtained[16] also from the corresponding *N*-oxide, prepared from D-ribose by unsaturated hydroxylamine, employing the nitrone addition and the Cope–House cyclisation. The employment of stereoselective hetero-Diels–Alder reactions either with chiral *N*-dienylpyroglutamates or with chiral *p*-tolylsulfinyl-1,3-pentadiene with nitrosoformates, followed by osmylation and suitable chemical transformations, afforded (2*S*,3*R*,4*S*)-[17] and (2*S*,3*S*,4*R*)-**3**,[18] and a derivative of the latter.[19] Compound (2*S*,3*R*,4*S*)-**3** was also obtained[20] as a hydrochloric acid salt from 1-hydroxymethyl-4-sulfonylbutadiene, employing a Sharpless epoxidation. In 2002,[21] (2*S*,3*S*,4*S*)-**3** was prepared by MeMgBr addition to the succinimide derived from L-tartaric acid, followed by stereocontrolled triethylsilane-promoted reduction of the resulting cyclic amidol. In 2007, the same enantiomer was prepared by Chi-Huey Wong[22] by D-fructose-6-phosphate aldolase catalysed reaction of azido acetaldehyde and hydroxyacetone, followed by hydrogenation in the presence of $Pd(OH)_2/C$.



Scheme 7. Isomers of pyrrolidine **3** known in the literature.

We envisaged the possibility to synthesise pyrrolidine **3** by means of our chiral synthons: enantiopure acetate (*R*,4*S*,5*S*)-**2a** was employed as a model starting material to investigate the synthetic procedure reported in Scheme 8 and to prepare the single stereoisomer (2*S*,3*S*,4*S*)-**3**. The key steps were the conversion of aldehyde **12** into nitrile **13** by reaction with iodine and ammonium hydroxide in THF, and the final ring closure to pyrrolidine **3** by intramolecular nucleophilic substitution of the amino function on the mesylate group in derivative **15**.



Scheme 8. Reagents and conditions: (i) KOH/MeOH; (ii) O_3, –78 °C, then $(CH_3)_2S$; (iii) I_2, NH_3 30%, THF, room temp.; (iv) MsCl/Py, 0 °C; (v) Boc_2O, $NiCl_2{\cdot}6H_2O$, then $NaBH_4$ at 0 °C; (vi) HCl/MeOH; (vii) K_2CO_3/acetone.

Acetate (*R*,4*S*,5*S*)-**2a** was submitted to saponification, followed by ozonolysis and dimethyl sulfide quenching. Aldehyde (4*R*,5*S*,*R*)-**12** was recovered and reacted with NH_3 and I_2 to afford nitrile (4*S*,5*S*,*R*)-**13**, which was treated with mesyl chloride in pyridine to afford derivative (*R*,4*R*,5*S*)-**14**.[23] Reduction of the nitrile moiety with concomitant

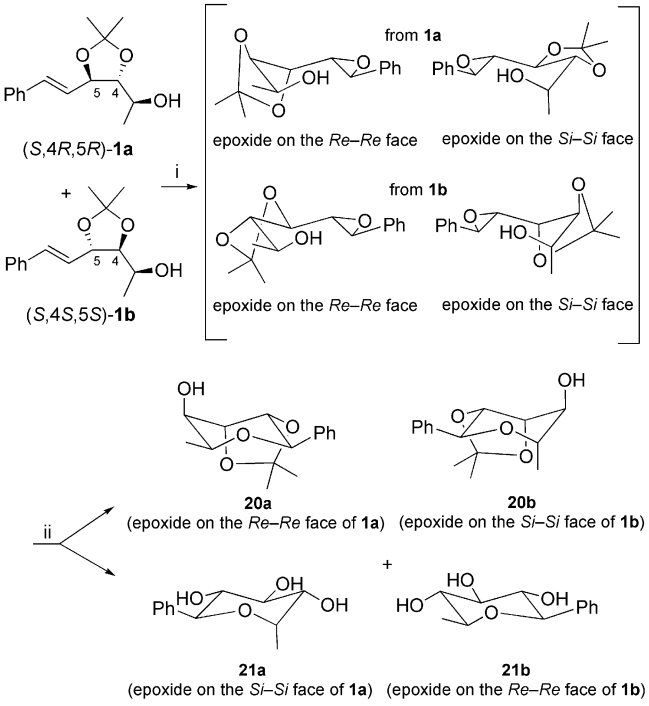
protection of the resulting amine gave derivative (*R*,4*R*,5*S*)-**15**.[24] Treatment with hydrochloric acid promoted the removal of the Boc protecting group and the acetonide moiety: subsequent reaction with potassium carbonate in acetone allowed us to obtain the enantiopure five-membered ring amino sugar (2*S*,3*S*,4*S*)-**3**.

Stereoselective Synthesis of 6-Deoxy-C-phenylglycosides

C-Aryl glycosides[25] are characterised by the presence of a carbohydrate moiety that is directly attached to an aromatic ring through a C–C bond rather than a C–O bond. This type of connectivity makes them quite stable to both enzymatic and acid hydrolysis: they are indeed potent enzyme inhibitors and substrates for carbohydrate-binding proteins.[26] Most of the existing strategies that lead to simple *C*-aryl glycosides are based on the formation of the key C–C bond between the carbohydrate and the aromatic components.[27] A few have involved the construction of the sugar fragment from nonsaccharide precursors.[28] The chemical structure of the chiral synthons prepared in this work allowed the de novo preparation of *C*-glycosides according to this second approach by epoxidation of the double bond conjugated with the aromatic ring.

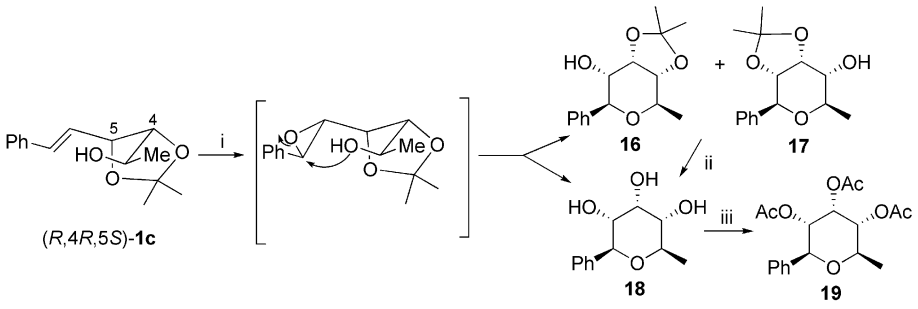
Treatment of compound (*R*,4*R*,5*S*)-**1c**, obtained upon saponification of acetate (*R*,4*R*,5*S*)-**2c** (Scheme 5), with *m*-chloroperbenzoic acid followed by column chromatography separation allowed the isolation of two fractions (Scheme 9). The first one consisted of a 1:1 mixture of the two ring-closed acetonide derivatives **16** and **17**, and the second one was found to be *C*-phenyl-β-D-alloside **18**. Intramolecular ring closure occurred during the reaction and its workup, with either migration or loss of the acetonide protection. Acetonides **16** and **17** were converted into derivative **18** by acid hydrolysis. The epoxidation reaction was totally stereoselective on the *Si–Si* face of the double bond, affording only β-D-alloside **18**, whose relative configuration was assigned by analysis of the ^{1}H NMR spectra of the corresponding triacetate derivative **19**.

When a 1:1 mixture of unreacted alcohols (*S*,4*R*,5*R*)-**1a** (99%*ee*, HPLC) and (*S*,4*S*,5*S*)-**1b** (99%*ee*) was treated with *m*-chloroperbenzoic acid (Scheme 10), the following products in order of elution could be isolated by column chromatography: acetonides **20a** and **20b**, which are the products of ketal migration to the *syn* OH groups in the ring closed derivatives obtained from the epoxidation of the *Re–Re* face of **1a** and the *Si–Si* face of **1b**, respectively; a 1:1 mixture of triols **21a** and **21b**, obtained from deprotection of the *C*-glycosides derived from the epoxidation of the *Si–Si* face and the *Re–Re* face of **1a** and **1b**, respectively.



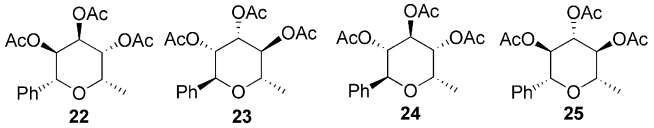
Scheme 10. Reagents and conditions: (i) *m*-chloroperbenzoic acid, CH_2Cl_2, 0 °C; (ii) workup, then column chromatography.

The ratio of these epoxidation products was calculated from the weight of the isolated products: **20a**/**20b**/mixture **21a**,**21b** = 1.4:1.0:6.8. Diastereoselectivity was not complete as observed in the case of substrate **1c**, but it was found to be in favour of the conformationally most stable glycosides for both **1a** (48%) and **1b** (54%). Compounds **20a** and **20b** were characterised as acetyl derivatives, then submitted to acid hydrolysis and extensive acetylation to afford the triacetates of β-L-guloside **22** and α-L-mannoside **23** (Scheme 11). The relative configuration of compound **22** was confirmed by NOE experiments. When the hydrogen atom at C-2 was irradiated, NOE effects were observed on



Scheme 9. Reagents and conditions: (i) *m*-chloroperbenzoic acid, CH_2Cl_2, 0 °C; then column chromatography; (ii) 37% HCl, AcOH in THF/H_2O; (iii) Ac_2O, pyridine.

H–C-3 (10%) and H–C-6 (13%). The 1:1 mixture of **21a** and **21b** was acetylated to give the corresponding acetyl derivatives of α-L-idoside **24** and β-L-glucoside **25** (Scheme 11).



Scheme 11.

Conclusions

The structural optimisation of certain biologically relevant molecular skeletons can be achieved by investigating the effect of absolute configuration on their specific activity. Methods to obtain these molecules in all the possible stereochemical arrangements are thus required to perform this screening. Lipase-mediated kinetic resolution of hydroxy derivatives has been employed as a useful and versatile method to obtain *stereochemical differentiation* and prepare chiral synthons showing controlled absolute configuration. The known preference of lipase PS for the reaction with *R* stereogenic carbon atoms was confirmed also in these kinetic resolutions.[29] Classical organic chemistry transformations allowed the *structural differentiation* necessary to embed these suitably functionalised building blocks into biologically active molecules, such as hydroxylated pyrrolidines and *C*-phenyl glycosides.

Experimental Section

General Methods: Lipase PS " Amano" SD from *Burkholderia cepacia* (Amano Enzyme Inc. Japan) was employed in this work. GC–MS analyses were performed by using a HP-5MS column (30 m × 0.25 mm × 0.25 μm). The following temperature program was employed: 60 °C (1 min)/6 °C min^{-1}/150 °C (1 min)/12 °C min^{-1}/280 °C (5 min). ^{1}H and ^{13}C NMR spectra were recorded with a 400 MHz spectrometer. The chemical shift scale was based on internal tetramethylsilane. Optical rotations were measured with a Dr. Kernchen Propol digital automatic polarimeter at 589 nm. TLC analyses were performed on Merck Kieselgel 60 F254 plates. All the chromatographic separations were carried out on silica gel columns. The enantiomeric excess values were determined by HPLC analysis by using a ChiralCel OD column, installed on a Merck–Hitachi 1-7100 instrument with a Merck–Hitachi L-4250 UV/Vis detector: 0.6 mL min^{-1}, 210 nm, hexane/isopropanol (98:2): (*R*,4*S*,5*S*)-**1a**, t_R = 40.453 min; (*R*,4*R*,5*R*)-**1b**, t_R = 26.8 min; (*S*,4*R*,5*R*)-**1a** and (*S*,4*S*,5*S*)-**1b**, t_R = 18.92 and 27.03 min; (*S*,4*S*,5*R*)-**1c**, t_R = 30.39 min; (*R*,4*R*,5*S*)-**1c**, t_R = 34.97 min; (*R*,4*S*,5*R*)-**1d**, t_R = 21.21 min; (*S*,4*R*,5*S*)-**1d**, t_R = 22.76 min.

(*R*)-1-{(4*S*,5*S*)-2,2-Dimethyl-5-[(*E*)-styryl]-1,3-dioxolan-4-yl}ethyl Acetate [(*R*,4*S*,5*S*)-2a] and (*R*)-1-{(4*R*,5*R*)-2,2-Dimethyl-5-[(*E*)-styryl]-1,3-dioxolan-4-yl}ethyl Acetate [(*R*,4*R*,5*R*)-2b]: The mixture diastereoisomers (*SR*,4*RS*,5*RS*)-**1a** and (*RS*,4*RS*,5*RS*)-**1b** (7 g, 0.028 mol) was submitted to lipase PS in vinyl acetate/methyl *tert*-butyl ether (1:4, 200 mL) at room temperature. After 36 h, the enzyme was filtered, and an oily residue was obtained after evaporation of the solvents. Column chromatography of this residue gave acetate (*R*,4*S*,5*S*)-**2a** (1.5 g, 18.5%). The starting material (5 g, 0.020 mol) was submitted again to lipase PS reaction, and after 96 h, acetate (*R*,4*R*,5*R*)-**2b** was recovered (1 g, 17%). Data for (*R*,4*S*,5*S*)-**2a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23–7.41 (m, 5 H, Ar), 6.67 (d, J = 15.9 Hz, 1 H, Ar-*CH*), 6.14 (dd, J = 7.5, 15.9 Hz, 1 H, ArCH=C*H*), 5.08 (dq, J = 6.5, 4.5 Hz, 1 H, *CH*-OAc), 4.38 (t, J = 7.9 Hz, =CH-C*H*-O), 3.84 (dd, J = 4.5, 8.1 Hz, 1 H, *CH*-O), 2.08 (s, 3 H, OAc), 1.48 (s, 3 H, CCH_3), 1.46 (s, 3 H, CCH_3), 1.30 (d, J = 6.7 Hz, 3 H, CHCH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 16.7, 21.1, 26.6, 27.1, 68.6, 78.3, 82.4, 109.4, 126.1, 126.6, 128.0, 128.5, 134.1, 136.1, 170.2 ppm. GC–MS: t_R = 23.45 min. GC–MS: *m*/*z* (%) = 275 (6) [M – 15], 230 (25), 172 (100), 159 (35), 145 (82). $[\alpha]_D^{20}$ = –16.4 (c = 1.17, $CHCl_3$). Data for (*R*,4*R*,5*R*)-**2b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22–7.42 (m, 5 H, Ar), 6.67 (d, J = 15.7 Hz, 1 H, Ar*CH*), 6.16 (dd, J = 7.7, 15.7 Hz, 1 H, ArCH=C*H*), 5.10 (m, 1 H, *CH*-OAc), 4.45 (t, J = 8.0 Hz, =CH-C*H*O), 3.83 (dd, J = 5.5, 8.0 Hz, 1 H, *CH*-O), 1.98 (s, 3 H, OAc), 1.47 (s, 3 H, CCH_3), 1.45 (s, 3 H, CCH_3), 1.31 (d, J = 6.7 Hz, 3 H, CHCH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 16.2, 20.6, 26.7, 26.5, 69.5, 79.5, 81.9, 108.9, 126.3, 127.7, 128.2, 133.4, 135.9, 169.4 ppm. GC–MS: t_R = 23.24 min. GC–MS: *m*/*z* (%) = 275 (4) [M – 15], 232 (17), 172 (100), 159 (39), 145 (87). $[\alpha]_D^{20}$ = +33 (c = 1.2, $CHCl_3$).

(*R*)-1-{(4*R*,5*S*)-2,2-Dimethyl-5-[(*E*)-styryl]-1,3-dioxolan-4-yl}ethyl Acetate [(*R*,4*R*,5*S*)-2c] and (*R*)-1-{(4*S*,5*R*)-2,2-Dimethyl-5-[(*E*)-styryl]-1,3-dioxolan-4-yl}ethyl Acetate [(*R*,4*S*,5*R*)-2d]: The mixture of racemic (*RS*,4*RS*,5*SR*)-**1c** and (*SR*,4*RS*,5*SR*)-**1d** (6 g, 0.024 mol) was submitted to lipase PS in vinyl acetate/methyl *tert*-butyl ether (1:4, 200 mL) at room temperature for 96 h. Then the enzyme was removed, and the solvents were evaporated. Column chromatography (hexane →hexane/ethyl acetate) gave the enantiomerically pure diastereoisomers acetate (*R*,4*R*,5*S*)-**2c** (1.3 g, 18.7%) and acetate (*R*,4*S*,5*R*)-**2d** (1.2 g, 17%). Data for (*R*,4*R*,5*S*)-**2c**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.15–7.42 (m, 5 H, Ar), 6.63 (d, J = 15.9 Hz, 1 H, Ar*CH*), 6.12 (dd, J = 7.6, 15.9 Hz, 1 H, ArCH=C*H*), 4.96 (m, 1 H, *CH*-OAc), 4.79 (t, J = 7.0 Hz, =CHC*H*O), 4.13 (t, J = 7.0 Hz, 1 H, *CH*-O), 1.77 (s, 3 H, OAc), 1.51 (s, 3 H, CCH_3), 1.39 (s, 3 H, CCH_3), 1.29 (d, J = 6.4 Hz, 3 H, CHOAcCH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 16.9, 20.7, 25.0, 27.4, 68.6, 78.4, 79.5, 108.6, 124.1, 126.3, 127.7, 128.3, 133.0, 136.1, 169.4 ppm. GC–MS: t_R = 23.01 min. GC–MS: *m*/*z* (%) = 290 (1) $[M]^+$, 275 (2), 230 (10), 174 (100), 159 (43), 145 (79). $[\alpha]_D^{20}$ = –4.8 (c = 1.3, $CHCl_3$). Data for (*R*,4*S*,5*R*)-**2d**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20–7.40 (m, 5 H, Ar), 6.64 (d, J = 15.9 Hz, 1 H, Ar*CH*), 6.13 (dd, J = 7.9, 15.9 Hz, 1 H, ArCH=C*H*), 4.99 (q, J = 6.5 Hz, 1 H, *CH*-OAc), 4.74 (t, J = 7.2 Hz, =CH-C*H*-O), 4.14 (t, J = 6.5 Hz, 1 H, *CH*-O), 2.02 (s, 3 H, OAc), 1.56 (s, 3 H, CCH_3), 1.41 (s, 3 H, CCH_3), 1.22 (d, J = 6.4 Hz, 3 H, CHCH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 16.9, 21.1, 25.5, 27.4, 68.4, 78.4, 80.3, 109.0, 124.2, 126.5, 127.9, 128.5, 133.9, 136.1, 169.9 ppm. GC–MS: t_R = 23.31 min. GC–MS: *m*/*z* (%) = 290 (1) $[M]^+$, 275 (3), 230 (12), 174 (100), 159 (46), 145 (91). $[\alpha]_D^{20}$ = +19.17 (c = 1.1, $CHCl_3$).

(*R*,4*S*,5*S*)-1a and (*R*,4*R*,5*S*)-1c: Saponification of acetate derivatives (*R*,4*S*,5*S*)-**2a** (1.5 g, 5 mmol) and (*R*,4*R*,5*S*)-**2c** (1.3 g, 4 mmol) with KOH (0.43 g, 7.6 mmol and 0.38 g, 6.7 mmol) in methanol (30 mL for each reaction) gave (*R*,4*S*,5*S*)-**1a** (1.25 g, 97%) and (*R*,4*R*,5*S*)-**1c** (1.1 g, 98%), respectively. Data for (*R*,4*S*,5*S*)-**1a**: $[\alpha]_D^{20}$ = –1.78 (c = 1.27, $CHCl_3$). Data for (*R*,4*R*,5*S*)-**1c**: $[\alpha]_D^{20}$ = +1.7 (c = 0.95, $CHCl_3$).

(4*R*,5*S*)-5-[(*R*)-1-Hydroxyethyl]-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde [(4*R*,5*S*,*R*)-12]: Ozonised oxygen was bubbled into a solu-

tion of (*R*,4*S*,5*S*)-**2a** (1.2 g, 4.8 mmol) in CH_2Cl_2/MeOH (2:1) at –78 °C until the appearance of a blue colour. Dimethyl sulfide (0.45 g, 7.3 mmol) was added dropwise at the same temperature. After standing 1 h at room temperature, the reaction mixture was concentrated, and the residue was chromatographed on SiO_2 (ethyl acetate/hexane) to yield (4*R*,5*S*,*R*)-**12** (0.6 g, 72%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.78 (s, 1 H, *CHO*), 3.8–4.1 (m, 3 H, C*H*-OH, 2 *CH*-O), 1.51 (s, 3 H, CCH_3), 1.41 (s, 3 H, CCH_3), 1.26 (d, J = 6.6 Hz, 3 H, CHCH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 18.6, 26.3, 26.6, 67.1, 80.5, 81.1, 110.9, 200.98 ppm. GC–MS: t_R = 8.75 min. GC–MS: *m*/*z* (%) = 159 (20) [M – 15], 145 (59), 129 (24), 101 (17), 85 (39), 59 (100). $[a]_D^{20}$ = –8.04 (c = 0.9, $CHCl_3$).

(4*S*,5*S*)-5-[(*R*)-1-Hydroxyethyl]-2,2-dimethyl-1,3-dioxolane-4-carbonitrile [(4*S*,5*S*,*R*)-13]: To a stirred solution of aldehyde **12** (0.6 g, 3.4 mmol) in THF was added 30% NH_3 (20 mL) and I_2 (0.9 g, 3.4 mmol) at room temperature. The initially dark coloured solution became colourless at the end of reaction (after 1 h). The mixture was then poured into water, extracted with ethyl acetate (3×) and the solvent was then evaporated to give nitrile (4*S*,5*S*,*R*)-**13** (0.5 g, 86%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.58 (d, J = 6.4 Hz, 1 H, O-*CH*-CN), 4.29 (dd, J = 4.2, 6.4 Hz, 1 H, *CH*-O), 3.84 (dq, J = 4.2, 6.4 Hz, 1 H, C*H*-OH), 1.53 (s, 3 H, CCH_3), 1.48 (s, 3 H, CCH_3), 1.30 (d, J = 6.4 Hz, 3 H, CHCH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 19.2, 24.7, 26.3, 64.5, 66.4, 83.7, 113.1, 117.9 ppm. GC–MS: t_R = 9.89 min. GC–MS: *m*/*z* (%) = 156 (65) [M – 15], 126 (39), 97 (23), 59 (33), 43 (100). $[a]_D^{20}$ = –6.74 (c = 0.95, $CHCl_3$).

(*R*)-1-[(4*R*,5*S*)-5-Cyano-2,2-dimethyl-1,3-dioxolan-4-yl]ethyl Methanesulfonate [(*R*,4*R*,5*S*)-14]: Nitrile (4*S*,5*S*,*R*)-**13** (0.5 g, 2.9 mmol) was dissolved in pyridine (5 mL) and methanesulfonyl chloride (0.33 g, 2.9 mmol) was added dropwise at 0 °C. After stirring for 2 h at room temperature, the reaction mixture was poured into water and extracted with ethyl acetate. The organic phase was washed with 1% HCl and dried with Na_2SO_4 to afford a residue (0.65 g, 90%) that was submitted without any further purification to the following reaction step.

(*R*)-1-{(4*R*,5*S*)-5-[(*tert*-Butoxycarbonylamino)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl}ethyl Methanesulfonate [(*R*,4*R*,5*S*)-15]: To a stirred solution of (*R*,4*R*,5*S*)-**14** (0.6 g, 2.4 mmol) in MeOH (30 mL) was added Boc_2O (1.05 g, 4.8 mmol) and a catalytic amount of $NiCl_2{\cdot}6H_2O$; then, at 0 °C, $NaBH_4$ (0.64 g, 16.8 mmol) was added portionwise over 30 min. The reaction mixture was stirred for 24 h. After the usual workup, column chromatography (hexane → hexane/ethyl acetate) gave (*R*,4*R*,5*S*)-**15** (0.6 g, 70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.78 (m, 1 H, *CH*OMs), 3.98 (ddd, J = 3.6, 5.1, 7.9 Hz, 1 H, CH_2CHO), 3.77 (dd, J = 5.3, 7.9 Hz, 1 H, *CH*-O), 3.20–3.40 (m, 2 H, CH_2NH), 3.1 (s, 3 H, SO_2CH_3), 1.35–1.49 (m, 18 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 17.4, 27.0, 28.0, 38.2, 41.8, 76.1, 77.8, 79.4, 84.7, 109.3, 146.4, 155.7 ppm. GC–MS: t_R = 24.35 min. GC–MS: *m*/*z* (%) = 282 (15) [M – 71], 223 (23), 165 (35), 127 (49), 57 (100).

(2*S*,3*S*,4*S*)-2-Methylpyrrolidine-3,4-diol [(2*S*,3*S*,4*S*)-3]: Compound (*R*,4*R*,5*S*)-**15** (0.6 g, 1.7 mmol) was treated with 37% HCl at room temperature for 24 h in methanol solution. Then, the solvent was removed, and the residue was treated with K_2CO_3 (0.25 g, 2.5 mmol) in acetone (15 mL) to obtain (2*S*,3*S*,4*S*)-**3** (0.15, 75%): ^{1}H NMR (400 MHz, CD_3OD): δ = 4.04 (m, 1 H, CH_2CHOH), 3.59 (dd, J = 3.2, 4.9 Hz, 1 H, $CH_3CHCHOH$), 3.11 (dd, J = 5.3, 12.4 Hz, 1 H, CH*H*NH), 2.93 (m, 1 H, C*H*CH_3), 2.88 (dd, J = 2.1, 12.4 Hz, 1 H, C*H*HNH), 1.29 (d, J = 6.7 Hz, 3 H, CHCH_3) ppm. ^{13}C NMR (100.6 MHz, CD_3OD): δ = 18.3, 52.9, 62.2, 79.2, 85.0 ppm. $[a]_D^{20}$ = +12.9 (c = 1.04, MeOH) {ref.[22] for (2*R*,3*R*,4*R*)-**3**: $[a]_D^{20}$ = –13.3 (c = 0.71, H_2O)}.

(3a*R*,4*R*,6*S*,7*S*,7a*S*)-2,2,4-Trimethyl-6-phenyltetrahydro-3a*H*-[1,3]-dioxolo[4,5-*c*]pyran-7-ol (16), (3a*S*,4*S*,6*R*,7*R*,7a*R*)-2,2,6-Trimethyl-4-phenyltetrahydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyran-7-ol (17), (2*R*,3*S*,4*R*,5*R*,6*S*)-2-Methyl-6-phenyltetrahydro-2*H*-pyran-3,4,5-triol (18) and (2*R*,3*R*,4*R*,5*S*,6*S*)-2-Methyl-6-phenyltetrahydro-2*H*-pyran-3,4,5-triyl Triacetate (19): Acetate (*R*,4*R*,5*S*)-**2c** (1.2 g, 4.1 mmol) was hydrolysed in MeOH (20 mL) with KOH (0.35 g, 6.2 mmol), and the corresponding alcohol (*R*,4*R*,5*S*)-**1c** (0.9 g, 89%) was submitted to epoxidation with *m*-chloroperbenzoic acid (30% water; 0.85 g, 5.4 mmol) in CH_2Cl_2 (20 mL) at 0 °C. After 2 h at room temperature, the reaction mixture was poured into water, washed with a 10% solution of sodium pyrosulfite 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 (hexane → hexane/ethyl acetate) to afford in order of elution first a 1:1 mixture of derivatives **16** and **17** (0.53 g, 43%) and at the end derivative **18** (0.25 g, 27%). Data for **16** and **17** (1:1 mixture): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42 –7.24 (m, Ar), 4.55 (t, J = 4.4 Hz, 1 H, H_{eq}), 4.52 (t, J = 4.4 Hz, 1 H, H_{eq}), 4.43 (d, J = 9.6 Hz, 1 H, *CH*Ph), 4.35 (d, J = 9.0 Hz, *CH*Ph), 4.08 (dd, J = 9.1, 4.6 Hz, 1 H), 3.86 (dd, J = 9.0, 4.5 Hz, 1 H), 3.82 (dd, J = 9.6, 4.4 Hz, 1 H), 3.70 (dq, J = 9.5, 6.1 Hz, 1 H, *CH*CH_3), 3.61 (dq, J = 9.1, 6.2 Hz, 1 H, *CH*CH_3), 3.59 (dd, J = 9.5, 4.0 Hz, 1 H), 1.64 (s, 3 H, CCH_3), 1.58 (s, 3 H, CCH_3), 1.43 (s, 3 H, CCH_3), 1.40 (s, 3 H, CCH_3), 1.38 (d, J = 6.2 Hz, 3 H, CHCH_3), 1.30 (d, J = 6.2 Hz, 3 H, CHCH_3). Data for (2*R*,3*S*,4*R*,5*R*,6*S*)-**18**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 (m, 5 H, Ar), 4.43 (d, J = 9.5 Hz, 1 H, H–C-6), 4.23 (m, 1 H, H–C-4), 3.73 (dq, J = 9.5, 6.0 Hz, 1 H, H–C-2), 3.57 (dd, J = 9.5, 2.5 Hz, 1 H, H–C-5 or H–C-3), 3.35 (dd, J = 9.5, 2.8 Hz, 1 H, H–C-3 or H–C-5),1.31 (d, J = 6.3 Hz, 3 H, CHCH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 16.9, 70.2, 73.8, 76.4, 77.7, 93.3, 126.0, 128.1, 128.6, 139.1 ppm. The compound had to be purified by converting it into the corresponding triacetate by reaction with acetic anhydride (3 mL) in pyridine (3 mL) to afford compound (2*R*,3*S*,4*R*,5*R*,6*S*)-**19** (0.36 g, 93%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (m, 5 H, Ar), 5.66 [m, 1 H, H-C(4)], 5.01 (dd, J = 10.0, 2.9 Hz, 1 H, H–C-3 or H–C5), 4.81 (dd, J = 10.0, 2.5 Hz, H–C5 or H–C-3), 4.66 (d, J = 10.0 Hz, 1 H, H–C-6), 4.03 (dq, J = 10.0, 6.0 Hz, 1 H, H–C-2), 1.23 (d, J = 6.0 Hz, 3 H, CHCH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 17.6, 20.3, 20.6, 20.7, 68.5, 70.4, 70.5, 75.3, 88.9, 126.0, 128.2, 128.8, 139.8, 168.7, 169.3, 169.9 ppm. GC–MS: t_R = 24.60 min. GC–MS: *m*/*z* (%) = 290 (1) [M – 60], 247 (2), 230 (100), 215 (69), 188 (24), 173 (52). $[a]_D$ = +13.9 (c = 0.95, $CHCl_3$). Derivatives **16** and **17** were treated with AcOH (0.5 mL) and a few drops of 37% HCl in THF solution (5 mL) for 12 h at room temperature. After the usual workup, the residue was acetylated with Ac_2O (3 mL) in pyridine (3 mL) to afford triacetate (2*R*,3*S*,4*R*,5*R*,6*S*)-**19**.

(3a*R*,4*R*,6*S*,7*R*,7a*S*)-2,2,6-Trimethyl-4-phenyltetrahydro-3a*H*-[1,3]-dioxolo[4,5-*c*]pyran-7-ol (20a), (3a*S*,4*S*,6*S*,7*S*,7a*R*)-2,2,6-Trimethyl-4-phenyltetrahydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyran-7-ol (20b), (2*S*,3*S*,4*S*,5*R*,6*S*)-2-Methyl-6-phenyltetrahydro-2*H*-pyran-3,4,5-triol (21a) and (2*S*,3*R*,4*R*,5*S*,6*R*)-2-Methyl-6-phenyltetrahydro-2*H*-pyran-3,4,5-triol (21b): A 1:1 mixture of (*S*,4*R*,5*R*)-**1a** (99%*ee*) and (*S*,4*S*,5*S*)-**1b** (99%*ee*) (2.0 g, 8.0 mmol) was submitted to epoxidation with *m*-chloroperbenzoic acid (30% water; 1.7 g, 10.8 mmol) in CH_2Cl_2 (20 mL) at 0 °C. After 2 h at room temperature, the reaction mixture was poured into water, washed with a 10% solution of sodium pyrosulfite 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 (hexane → hexane/ethyl acetate) to afford in order of elution derivatives **20a** (0.23 g, 11%), **20b** (0.17 g, 8%) and a 1:1 mixture of triols **21a** and **21b** (0.96 g, 54%). Compounds **20a**, **20b**, **21a** and **21b** were characterised as acetates derivatives, after acetylation with acetic anhydride in pyridine. Data for the acetate of (3a*R*,4*R*,6*S*,7*R*,7a*S*)-**20a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 –7.28 (m, 5 H, Ar), 5.21 (t, *J* = 1.9 Hz, 1 H, H–C-7–OAc), 4.36 (d, *J* = 9.2 Hz, 1 H, H–C-4–Ph), 4.20 (dd, *J* = 5.0, 2.2 Hz, H–C-7a), 4.10 (dd, *J* = 9.2, 5.0 Hz, 1 H, H–C-3a), 4.06 (dq, *J* = 1.6, 6.5 Hz, 1 H, H–C-6–CH_3), 2.16 (s, 3 H, OAc), 1.62 (s, 3 H, CCH_3), 1.37 (s, 3 H, CCH_3), 1.24 (d, *J* = 6.5 Hz, 3 H, CHCH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 15.9, 20.5, 26.1, 28.1, 69.6, 70.9, 74.4, 75.2, 79.4, 109.3, 126.3, 127.5, 128.1, 139.9, 169.9 ppm. $[\alpha]_D$ = +21 (*c* = 1.50, $CHCl_3$). Data for the acetate of (3a*S*,4*S*,6*S*,7*S*,7a*R*)-**20b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 –7.25 (m, 5 H, Ar), 5.09 (t, *J* = 6.5 Hz, 1 H, H–C-7–OAc), 4.86 (d, *J* = 6.0 Hz, 1 H, H–C-4–Ph), 4.44 (t, *J* = 6.0 Hz, H–C-7a or H–C-3a), 4.27 (t, *J* = 6.0 Hz, H–C-3a or H–C-7a), 3.79 (quint., *J* = 6.5 Hz, 1 H, H–C-6–CH_3), 2.09 (s, 3 H, OAc), 1.60 (s, 3 H, CCH_3), 1.37 (s, 3 H, CCH_3), 1.30 (d, *J* = 6.5 Hz, 3 H, CHCH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 16.7, 20.8, 25.8, 27.6, 69.1, 72.8, 73.3, 75.5, 76.2, 109.3, 126.6, 128.3, 129.9, 139.0, 169.7 ppm. $[\alpha]_D$ = –10.1 (*c* = 1.1, $CHCl_3$).

(2*S*,3*R*,4*S*,5*S*,6*S*)-24 and (2*S*,3*S*,4*R*,5*R*,6*R*)-25: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.20 (m, Ar), 5.46 (t, *J* = 9.5 Hz, 1 H, H–C-4 or H–C-5 of **24**), 5.30 (t, *J* = 9.4 Hz, 1 H, H–C-3 or H–C-4 or H–C-5 of **25**), 5.21 (dd, *J* = 9.9, 6.5 Hz, 1 H, H–C-3 of **24**), 5.12 (t, *J* = 9.5 Hz, 1 H, H–C-3 or H–C-4 or H–C-5 of **25**), 5.07 (t, *J* = 9.6 Hz, 1 H, H–C-4 or H–C-5 of **24**), 4.98 (t, *J* = 9.6 Hz, 1 H, H–C-3 or H–C-4 or H–C-5 of **25**), 4.64 (d, *J* = 9.7 Hz, 1 H, H–C-6 of **24**), 4.57 (quint., *J* = 6.5 Hz, 1 H, H–C-2–CH_3 of **24**), 4.37 (d, *J* = 9.8 Hz, 1 H, H–C-6 of **25**), 3.72 (dq, *J* = 9.8, 6.2 Hz, 1 H, H–C-2–CH_3 of **25**), 2.07, 2.00, 1.81 (3 s, 3 OAc of **24**), 2.06, 1.99, 1.78 (3 s, 3 OAc of **25**), 1.40 (d, *J* = 6.5 Hz, 3 H, CHCH_3); 1.27 (d, *J* = 6.1 Hz, 3 H, CHCH_3) ppm. GC–MS: t_R = 24.62 min. GC–MS: *m*/*z* (%) =290 (1) [M – 60], 230 (100), 215 (70), 188 (21), 173 (100). GC–MS: t_R = 24.99 min. GC–MS: *m*/*z* (%) = 290 (1) [M – 60], 230 (100), 215 (75), 188 (21), 173 (91).

(2*S*,3*R*,4*S*,5*R*,6*R*)-2-Methyl-6-phenyltetrahydro-2*H*-pyran-3,4,5-triyl Triacetate (22): The acetate derivative of (3a*R*,4*R*,6*S*,7*R*,7a*S*)-**20a** (0.240 g, 0.82 mmol) was treated with AcOH (0.5 mL) and a few drops of 37% HCl in THF solution (5 mL) for 12 h at room temperature. After the usual workup, the residue was acetylated with Ac_2O (3 mL) in pyridine (3 mL) to afford triacetate **22** (0.21 g, 74%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.20 (m, 5 H, Ar), 5.39 (t, *J* = 3.4 Hz, 1 H, H–C-4–OAc), 5.19 (dd, *J* = 10.2, 3.2 Hz, 1 H, H–C-5–OAc), 4.96 (dd, *J* = 3.6, 1.3 Hz, H–C-3), 4.68 (d, *J* = 10.2 Hz, 1 H, H–C-6–Ph), 4.20 [dq, *J* = 1.3, 6.5 Hz, 1 H, H–C-2–CH_3), 2.22, 2.21 and 1.79 (3 s, 9 H, 3 OAc), 1.21 (d, *J* = 6.5 Hz, 3 H, CHCH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 16.1, 20.3, 20.7, 20.8, 67.4, 69.2, 70.4, 70.9, 76.0, 127.3, 128.2, 128.3, 137.8, 168.6, 169.2, 169.9 ppm. GC–MS: t_R = 24.45 min. GC–MS: *m*/*z* (%) = 290 (0.1) [M – 60], 247 (1), 230 (100), 215 (65), 188 (22), 173 (65).

(2*S*,3*S*,4*R*,5*S*,6*S*)-2-Methyl-6-phenyltetrahydro-2*H*-pyran-3,4,5-triyl Triacetate (23): The acetate derivative of (3a*S*,4*S*,6*S*,7*S*,7a*R*)-**20b** (0.16 g, 0.52 mmol) was treated with AcOH (0.5 mL) and a few drops of 37% HCl in THF solution (5 mL) for 12 h at room temperature. After the usual workup, the residue was acetylated with Ac_2O (3 mL) in pyridine (3 mL) to afford triacetate **23** (0.13 g, 70%): ^{1}H NMR (400 MHz, $CDCl_3$):[30] δ = 7.40–7.20 (m, 5 H, Ar), 6.01 (t, *J* = 2.9 Hz, 1 H, H–C-5–OAc), 5.18 (dd, *J* = 9.2, 8.5 Hz, 1 H, H–C-3–OAc), 5.12 (dd, *J* = 9.2, 3.0 Hz, H–C-4–OAc), 5.05 (d, *J* = 2.4 Hz, 1 H, H–C-6–Ph), 3.64 (dq, *J* = 8.2, 6.2 Hz, 1 H, H–C-2–CH_3), 2.16, 2.05 and 2.01 (3 s, 9 H, 3 OAc), 1.29 (d, *J* = 6.4 Hz, 3 H, CHCH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 17.3, 20.5, 20.6, 20.8, 68.9, 69.5, 69.8 71.3, 75.5, 126.2, 128.0, 128.8, 135.8, 168.9, 169.7, 170.2 ppm. GC–MS: t_R = 24.56 min. GC–MS: *m*/*z* (%) = 290 (1) [M – 60], 230 (61), 215 (50), 188 (17), 173 (100).

Supporting Information (see footnote on the first page of this article): Experimental procedures and spectroscopic data.

[1] S. Shang, H. Iwadare, D. E. Macks, L. Ambrosini, D. Tan, *Org. Lett.* **2007**, *9*, 1895–1898; K. A. Parker, Q. Z. Me, *Org. Lett.* **2008**, *10*, 1349–1352; K. A. Parker, H. Y. Kao, *Org. Lett.* **2006**, *8*, 3541–3544; S. R. Chemler, W. R. Roush, *J. Org. Chem.* **2003**, *68*, 1319–1333.

[2] P. Compain, O. R. Martin, *Iminosugars: From Synthesis to Therapeutic Applications*, Wiley, Chichester, **2007**; A. E. Stütz, *Iminosugars as Glycosidase Inhibitors: Nojirimycin and Beyond*, Wiley-VCH, Weinheim, **1999**.

[3] T. D. Heightman, A. T. Vasella, *Angew. Chem. Int. Ed.* **1999**, *38*, 750–770; D. L. Zechel, S. G. Withers, *Acc. Chem. Res.* **2000**, *33*, 11–18; V. H. Lillelund, H. H. Jensen, X. Liang, M. Bols, *Chem. Rev.* **2002**, *102*, 515–554; G. Danoun, J. Ceccon, A. E. Greene, J.-F. Poisson, *Eur. J. Org. Chem.* **2009**, 4221–4224; E. Moreno-Clavijo, A. T. Carmona, Y. Vera-Ayoso, A. J. Moreno-Vargas, C. Bello, P. Vogel, I. Robina, *Org. Biomol. Chem.* **2009**, *7*, 1192–1202.

[4] J. F. Kennedy, C. A. White, *Bioactive Carbohydrates in Chemistry, Biochemistry and Biology*, Ellis Horwood Publishers, Chichester, **1983**; A. Kirschning, A. F. W. Bechthold, J. Rohr, *Top. Curr. Chem.* **1997**, *188*, 1–84; X. M. He, H. W. Liu, *Curr. Opin. Chem. Biol.* **2002**, *6*, 590–597.

[5] M. T. Crimmins, A. Long, *Org. Lett.* **2005**, *7*, 4157–4160; M. Handa, W. J. Smith, W. R. Roush, *J. Org. Chem.* **2008**, *73*, 1036–1039; H. Wehlan, M. Dauber, M. T. M. Fernaud, J. Schuppan, S. Keiper, R. Mahrwald, M.-E. J. Garcia, U. Koert, *Chem. Eur. J.* **2006**, *12*, 7378–7397; E. Fan, W. Shi, T. L. Lowary, *J. Org. Chem.* **2007**, *72*, 2917–2928; D. Hou, T. L. Lowary, *J. Org. Chem.* **2009**, *74*, 2278–2289.

[6] S. Hanessian, *Total Synthesis of Natural Products: The "Chiron" Approach*, Pergamon Press, Oxford, **1983**; F. M. Hauser, S. R. Ellenberger, *Chem. Rev.* **1986**, *86*, 35–67; A. Kirschning, M. Jesberger, K.-U. Schöning, *Synthesis* **2001**, 507–540; M. Brasholz, H.-U. Reißig, *Eur. J. Org. Chem.* **2009**, 3595–3504.

[7] M. R. Hansen, L. H. Hurley, *Acc. Chem. Res.* **1996**, *29*, 249–258; J. A. Moral, S.-J. Moon, S. Rodriguez-Torres, T. G. Minehan, *Org. Lett.* **2009**, *11*, 3734–3737.

[8] M. A. Glomb, D. Rösch, R. H. Nagaraj, *J. Agric. Food Chem.* **2001**, *49*, 366–372.

[9] M. A. Bukhari, A. B. Foster, J. Lehmann, J. M. Webber, *J. Chem. Soc.* **1963**, 2287–2290.

[10] J. C. Sowden, D. R. Strobach, *J. Am. Chem. Soc.* **1960**, *82*, 3707–3709.

[11] P. Munier, A. Krusinski, D. Picq, D. Anker, *Tetrahedron* **1995**, *51*, 1229–1244.

[12] B. L. Stocker, E. M. Dangerfield, A. L. Win-Mason, G. W. Haslett, M. S. M. Timmer, *Eur. J. Org. Chem.* **2010**, 1615–1637.

[13] G. Legler, *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 319–384; N. Asano, R. J. Nash, R. J. Molyneux, G. W. J. Fleet, *Tetrahedron: Asymmetry* **2000**, *11*, 1645–1680; M. E. Sinnott, *Chem. Rev.* **1990**, *90*, 1171–1202; D. L. Zechel, St. G. Withers, *Acc. Chem. Res.* **2000**, *33*, 11–18.

[14] G. C. Look, C. H. Fotsch, C.-H. Wong, *Acc. Chem. Res.* **1993**, *26*, 182; Y. Nishimura, *Stud. Nat. Prod. Chem.* **1992**, *10*, 495; Y. L. Merrer, L. Poitout, J. D. Depezay, I. Dosbaa, S. Geoffroy, M. J. Foglietti, *Bioorg. Med. Chem.* **1997**, *5*, 519–533.

[15] C.-H. Wong, L. Provencher, J. A. Porco Jr., S.-H. Jung, Y.-F. Wang, L. Chen, R. Wang, D. H. Steensma, *J. Org. Chem.* **1995**, *60*, 1492–1501.

[16] A. M. Palmer, V. Jäger, *Eur. J. Org. Chem.* **2001**, 2547–2558.
[17] M. Joubert, A. Defoin, C. Tarnus, J. Streith, *Synlett* **2000**, 1366–1368.
[18] J.-B. Behr, C. Chevrier, A. Defoin, C. Tarnus, J. Streith, *Tetrahedron* **2003**, *59*, 543–553.
[19] C. Arribas, M. C. Carreño, J. L. Garcia-Ruano, J. F. Rodriguez, M. Santos, M. A. Sanz-Tejedor, *Org. Lett.* **2000**, *2*, 3165–3168.
[20] D. Diez, M. T. Beneitez, I. S. Marcos, N. M. Garrido, P. Basabe, J. C. Urones, *Synlett* **2001**, 655–657; D. Diez, M. T. Beneitez, I. S. Marcos, N. M. Garrido, P. Basabe, J. C. Urones, *Tetrahedron: Asymmetry* **2002**, *13*, 639–646.
[21] H. J. Jeong, J. M. Lee, M. K. Kim, S.-G. Lee, *J. Heterocycl. Chem.* **2002**, *39*, 1019–1024.
[22] M. Sugiyama, Z. Hong, P.-H. Liang, S. M. Dean, L. J. Whalen, W. A. Greenberg, C.-H. Wong, *J. Am. Chem. Soc.* **2007**, *128*, 14811–14817.
[23] J. J. Shie, J. M. Fang, *J. Org. Chem.* **2003**, *68*, 1158–1160.
[24] S. Caddick, D. B. Judd, A. K. de K. Lewis, M. T. Reich, M. R. V. Williams, *Tetrahedron* **2003**, *59*, 5417–5423.
[25] C. Jaramillo, S. Knapp, *Synthesis* **1994**, 1.
[26] G. D. Daves Jr., *Acc. Chem. Res.* **1990**, *23*, 201; H. Togo, W. He, Y. Waki, M. Yokoyama, *Synlett* **1998**, 700; M. Isobe, R. Nishizawa, S. Hosokawa, T. Nishikawa, *Chem. Commun.* **1998**, 2665; L. Somsák, *Chem. Rev.* **2001**, *101*, 81; C. Taillefumier, Y. Chapleur, *Chem. Rev.* **2004**, *104*, 263.
[27] K. A. Parker, Y. H. Koh, *J. Am. Chem. Soc.* **1994**, *116*, 11149–11150; T. Hosoya, E. Takashiro, T. Matsumoto, K. Suzuki, *J. Am. Chem. Soc.* **1994**, *116*, 1004–1015; K. Toshima, G. Matsuo, T. Ishizuka, Y. Ushiki, M. Nakata, S. Matsumura, *J. Org. Chem.* **1998**, *63*, 2307–2313; K. A. Parker, A. T. Georges, *Org. Lett.* **2000**, *2*, 497–499; F. M. Hauser, X. Hu, *Org. Lett.* **2002**, *4*, 977–978; S. Vijayasaradhi, I. S. Aidhen, *Org. Lett.* **2002**, *4*, 1739–1742; C. Rousseau, O. R. Martin, *Org. Lett.* **2003**, *5*, 3763–3766; E. Brenna, C. Fuganti, P. Grasselli, S. Serra, S. Zambotti, *Chem. Eur. J.* **2002**, *8*, 1872–1878.
[28] S. J. Danishefsky, B. J. Uang, G. Quallich, *J. Am. Chem. Soc.* **1985**, *107*, 1285–1293; B. Schmidt, *Org. Lett.* **2000**, *2*, 791–794; B. Schmidt, *J. Chem. Soc. Perkin Trans. 1* **1999**, 2627–2637; F. M. Hauser, X. Hu, *Org. Lett.* **2002**, *4*, 977–97; S. Bernd, W. Holger, *Eur. J. Org. Chem.* **2000**, 3145–3163; B. Schmidt, H. Wildemann, *Synlett* **1999**, 1591–1593; B. Koo, F. E. McDonald, *Org. Lett.* **2005**, *7*, 3621–3624; K. B. Bahnck, S. D. Rychnovsky, *Chem. Commun.* **2006**, 2388 2390.
[29] R. V. Muralidhar, R. R. Chirumamilla, R. Marchant, V. N. Ramachandran, O. P. Ward, P. Nigam, *World J. Microbiol. Biotechnol.* **2002**, *18*, 81–97.
[30] Vicinal coupling constants for derivative **23** were reported by P. M. Collins, A. S. Travis, *J. Chem. Soc. Perkin Trans. 1* **1980**, 779–786.

Received: April 22, 2010
Published Online: June 29, 2010

