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Synthesis and Glycosidase Inhibitory Activities of Pyrrolidines and Piperidines with *N*-(Polyhydroxyalkyl) Side Chains

Sabrina Boutefnouchet,[a,b] István Moldvai,*[a] Eszter Gács-Baitz,[c] Claudia Bello,[d] and Pierre Vogel[d]

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Amidification of L-proline (**3**) with (+)-(*R*,*R*)-**6** and (–)-(*S*,*S*)-tartaric anhydride diacetate (**7**) gave *N*-substituted L-proline derivatives **8a**,**b**, respectively. Acids **8a**,**b** were transformed into diesters **9a**,**b** with MeOH/HCl. Similar reactions with methyl (2*S*,4*R*)-**4** and (2*R*,4*S*)-4-acetoxypipecolate (**5**) led to bicyclic lactams **14a**,**b** and **15a**. Compounds **8a**,**b** were converted into *N*-(trihydroxybutyl)pyrrolidine derivatives **8c**,**d**, **10a**,**b** and **11a**,**b**. Methyl (2*S*,4*R*)-**20a** and (2*R*,4*S*)-4-acetoxy-*N*-[(2*S*,3*S*)-1,2,3-trihydroxybutyl]pipecolate (**20b**) were obtained by displacement of (–)-(2*S*,2*S*)-2-*O*-benzyl-3,4-*O*-isopropylidene-1-deoxy-1-iodothreitol (**19**) by **4** and **5**. Compounds **20a**,**b** were converted into (2*S*,4*R*,2′*S*,2′*S*)-**21a** and (2*R*,4*S*,2′*S*,3′*S*)-4-hydroxy-2-hydromethyl-*N*-(2-benzyloxy-3,4-isopropylidenedioxy)piperidine (**21b**) and finally into unprotected pentols **22a**,**b**. Nonprotected (2*S*,2′*S*,3′*S*)-**11a** and (2*S*,2′*R*,3′*R*)-*N*-(1,2,3-trihydroxybutyl)prolinol (**11b**), as well as **22a**,**b**, did not inhibit any of the 13 glycosidases assayed. However, a triacetoxy derivative, (2*S*,3*S*)-2,3-diacetoxy-4-[(2*R*,4*S*)-4-acetoxy-2-(methoxycarbonyl)piperidin-1-yl]-4-oxobutanoic acid (**13b**) is an inhibitor (IC_{50} = 157 μM) of α-L-fucosidase from bovine kidney.

Introduction

Natural polyhydroxylated alkaloids and their synthetic analogues are well known as glycosidase inhibitors. They are sugar mimics able to recognize the active site of the enzymes. This class of compounds has many therapeutic applications in the field of diabetes, viral diseases, lysosomal storage diseases and cancer.[1] Miglitol (*N*-hydroxyethyl-1-deoxynojirimycin; **1**) is a potent inhibitor of intestinal sucrase developed by Bayer AG.[2] It has been therapeutically used since 1996 in the oral treatment of type 2 diabetes (Glyset). Salacinol (**2**) was isolated in 1997 by Yoshikawa and coworkers[3] from *Salacia reticulata*, an antidiabetic ayurvedic traditional medicine (Figure 1). Salacinol analogues have been largely developed in the last years.[4]

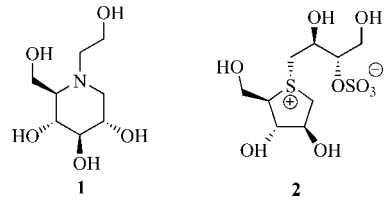

Figure 1. Structure of Miglitol and Salacinol.

Inspired by compounds **1** and **2**, we investigated new pyrrolidine and piperidine derivatives with *N*-(polyhydroxyalkyl) side chains as potential glycosidase inhibitors. Our goal was to prepare derivatives with polyhydroxylated side chains that were structurally related to the erythritolsulfate side chain of salacinol (**2**) and its analogues. Preparation and preliminary evaluation of these compounds as glycosidase inhibitors are presented.

Results and Discussion

The pyrrolidines were derived from L-proline (**3**). Methyl esters of 4-acetoxypipecolic acid [**4**: (2*S*,4*R*); **5**: (2*R*,4*S*)][5] were used as starting materials for the preparation of the piperidine derivatives (Figure 2). To introduce the *N*-(1,2,3-trihydroxybutyl) side chains, the reactions of (+)- and (–)-tartaric acid derivatives were first investigated. Both (*R*,*R*)- and (*S*,*S*)-tartaric acid are widely used as chiral building blocks, and they bear two asymmetrical carbon centres substituted by hydroxy groups.[6] Diacetyl tartaric anhydrides **6**

[a] Chemical Research Center of the Hungarian Academy of Sciences, Institute of Biomolecular Chemistry, Department of Natural Organic Compounds,
P. O. Box 17, 1525 Budapest, Hungary
Fax: +36-1-325-7554
E-mail: imoldvai@chemres.hu
[b] Laboratoire de Pharmacognosie, Université de Paris V,
4 av. de l'Observatoire, 75270 Paris cedex 06, France
[c] Chemical Research Center of the Hungarian Academy of Sciences, Institute of Structural Chemistry, NMR Laboratory,
P. O. Box 17, 1525 Budapest, Hungary
[d] Laboratory of Glycochemistry and Asymmetric Synthesis (LGSA) / Swiss Federal Institute of Technology (EPFL) Batochime
1015 Lausanne, Switzerland

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and **7** were reported to be good acylating agents and to yield chiral amides.[6] They can be easily obtained from the corresponding tartaric acids.[7]

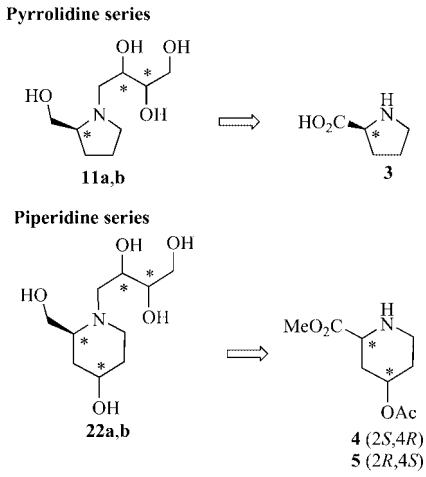


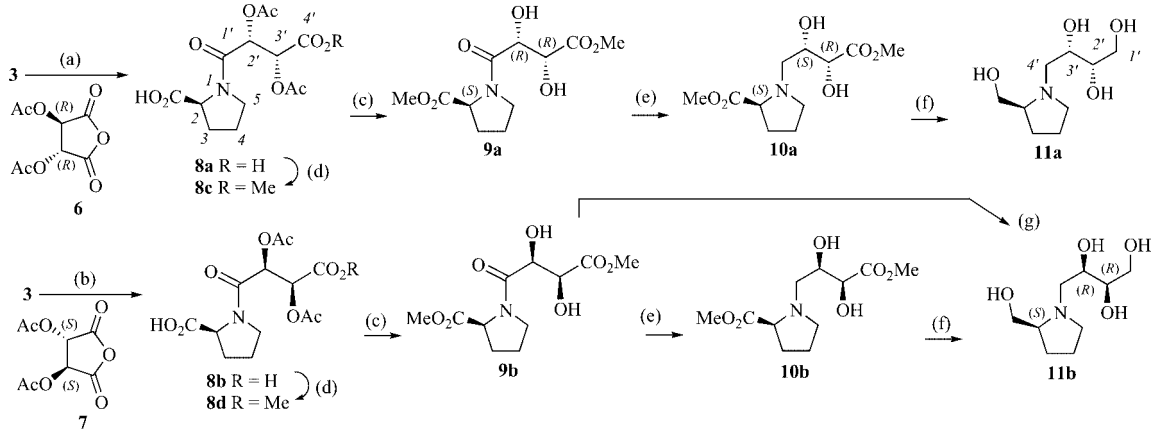
Figure 2. Retrosynthetic approaches.

L-proline (**3**) was treated with **6** and **7** to afford dicarboxylic acids **8a**,**b**, respectively, in nearly quantitative yield. Treatment of **8a**,**b** with methanolic hydrochloric acid produced corresponding dihydroxydiesters **9a**,**b** in 66 and 70% yield, respectively (Scheme 1). A mild esterification of **8a**,**b** with diazomethane afforded diacetoxydiesters **8c**,**d** in 74 and 85% yield, respectively, which were prepared for our biological studies.

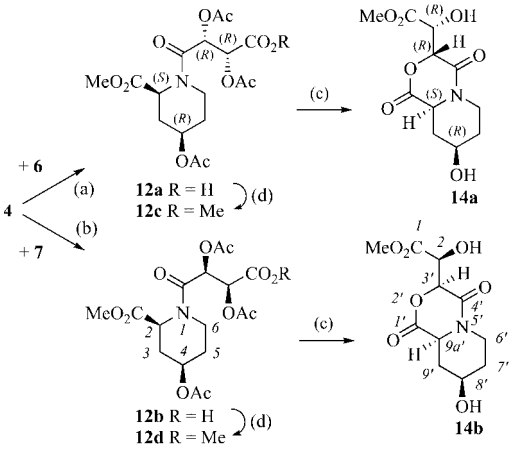
To obtain the desired *N*-(trihydroxybutyl) heterocycle, a two-step reduction procedure was applied. The amide moiety of tartaramides **9a**,**b** was first reduced with $BH_3{\cdot}SMe_2$ complex (20 °C, 2 h) into corresponding amines **10a**,**b** in 89% yield. This delivered amines with ester groups, which were subsequently reduced with lithium aluminium hydride (20 °C, 2 h) into desired pyrrolidinetetrol derivatives **11a**,**b** in 20–35% yield (Scheme 1). Compound **11b** could also be obtained by a one-step procedure by treating **9b** with $BH_3{\cdot}SMe_2$ complex for 5 d at 20 °C.

The piperidine derivatives were prepared starting from (2*S*,4*R*)-**4** and methyl (2*R*,4*S*)-4-acetoxypipecolate (**5**), which were obtained by using the efficient method developed by Beaulieu and coworkers.[8] The acylation of **4** and **5** with (+)- and (–)-diacetyl tartaric anhydrides provided desired carboxylic acids **12a** (2*S*,4*R*,2′*R*,3′*R*), **12b** (2*S*,4*R*,2′*S*,3′*S*), **13a** (2*R*,4*S*,2′*R*,3′*R*) and **13b** (2*R*,4*S*,2′*S*,3′*S*). Treatment of acids **12a**,**b** and **13a**,**b** with HCl/MeOH did not give the expected dicarboxylic esters, as in the case of **8a**,**b**, but lactones **14a**,**b** and **15a**, respectively. With **13b** only a tarry material was formed (Scheme 2).

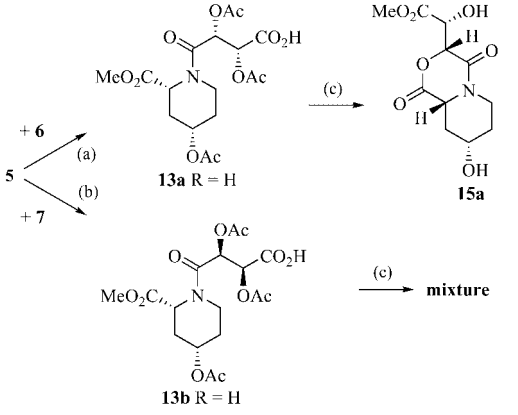
The different behaviour between pyrrolidines **8a**,**b** and piperidine **12a**,**b** and **13a**,**b** derivatives under acidic methanol treatment can be interpreted in terms of a kinetic factor that favours lactonization in the case of the piperidine derivatives; the lactonization reaction is a slower process with the pyrrolidine derivatives. The most stable conformers of *trans*-1,2-disubstituted cyclopentane place the two substituents remote from each other and corresponds to pseudo–axial–pseudo–axial orientations (dihedral angle close to 180°).[9] Thus by analogy, the conformers of type **9′a**,**b**, which are required for the intramolecular addition reaction of a hydroxy group of the nitrogen side chain to the 2-carboxylic moiety, are weakly populated for L-proline derivatives **9a**,**b** (Figure 3). This situation is completely reversed in the case of pipecolic derivatives **12a**,**b** for which the reacting conformers that are required for the lactonization process correspond to the most stable conformers where all three substituents reside in the equatorial positions. Thus, the piperidine derivatives are conformationally[10] restricted in a way that favours lactonization.[11] The equilibrium constant for the lactonization of L-proline derivatives and the pipecolic acid derivatives must be nearly the same as the cyclic strain and it is not expected to change for either type of equilibrium that exists between the bicy-



Scheme 1. Synthesis of (2*S*)-2-hydroxymethyl-*N*-(1,2,3-trihydroxybutyl)pyrrolidines and derivatives.



(a) **4** + **6**, THF, reflux, 6 h, then r.t. overnight, 77%; (b) **4** + **7**, THF, reflux 6 h, then r.t. overnight, 80%; (c) HCl / MeOH, r.t., 24 h, **14a**: 62%, **14b**: 61%; (d) CH_2N_2, CH_2Cl_2, 0 °C, 3 h, **12c**: 50%, **12d**: 47%.



(**a**) **5** + **6**, THF, reflux, 6 h, then r.t. overnight, 73%; (**b**) **5** + **7**, THF, reflux, 6 h, then r.t. overnight, 70%; (**c**) HCl / MeOH, r.t., 24 h, **15a**: 40%.

Scheme 2. Formation of lactones instead of dicarboxylic esters.

clic lactones and the monocyclic precursors. We doubt at this stage that the reactivity difference described above is due to thermodynamic control rather than to kinetic control.

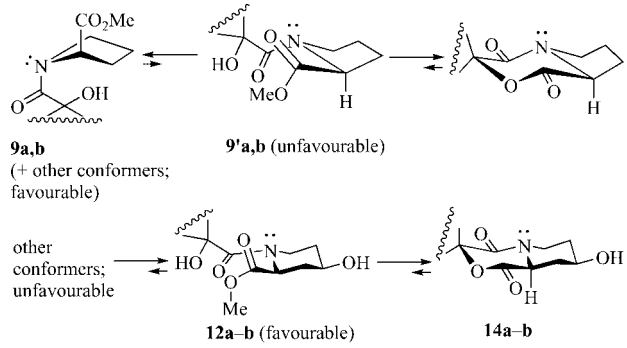
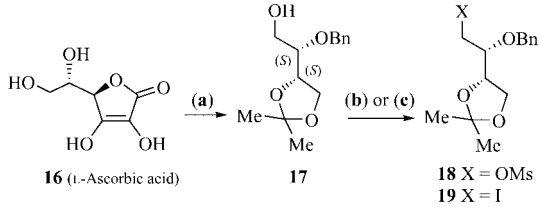


Figure 3. Conformational restriction effect favouring lactonization of the *N*-substituted pipecolic acid derivatives.

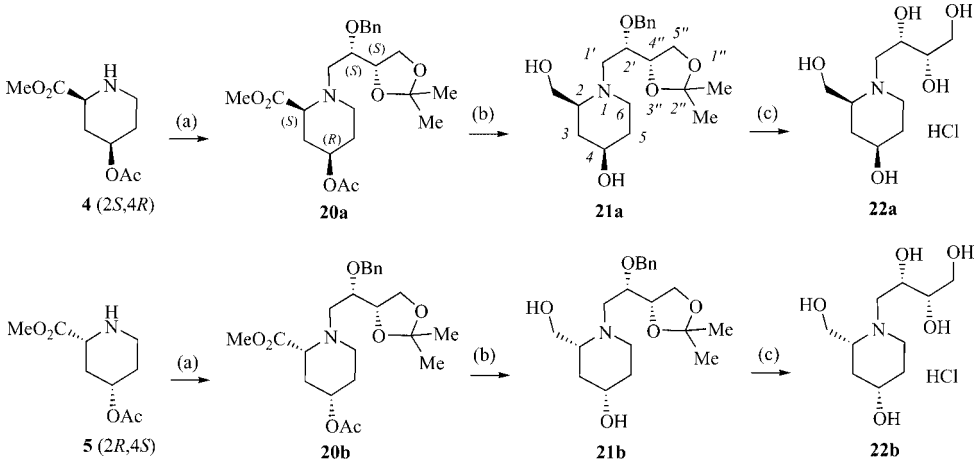
We explored the possibility of converting bicyclic lactones **14a**,**b** and **15a** into the desired piperidine derivatives. Whereas the use of $BH_3{\cdot}SMe_2$ resulted in only the recovery of the starting material (20 or 60 °C), the reduction of **14a**,**b** and **15a** with $LiAlH_4$ (3 h, 60 °C) gave inseparable tarry materials. To avoid the formation of lactones, acids **12a**,**b** were esterified with diazomethane to yield corresponding diesters **12c**,**d**. Unfortunately, deprotection of their acetyl group with potassium carbonate failed to give the desired triols and only products of degradation were observed.

We thus explored a second pathway. Alkylation of our secondary amines with a chiral protected iodobutanethrei-



(**a**) and (**b**) Ref.[12a]
(**c**) PPh_3/I_2, imidazole, benzene, r.t., 0.5 h, 72%.

Scheme 3. Synthesis of protected 1-iodo-1-deoxythreitol derivative.



(a) **4** or **5** + **19**, NEt_3, MeCN, 5 d, reflux, **20a**: 40%, **20b**: 38%. (b) $LiAlH_4$, Et_2O, 3 h, r.t., **21a**: 80%, **21b**: 75%. (c) H_2 + $Pd(OH)_2/C$ + Pd/C, HCl/MeOH, 1-2 h, r.t., **22a**: 94%, (Amberlite resin), **22b**: 86%.

Scheme 4. Synthesis of 4-hydroxy-2-hydroxymethyl-*N*-(1,2,3-trihydroxybutyl)piperidines and derivatives.

tol appeared to be a suitable alternative. The protected (2*S*,3*S*)-1-deoxy-1-iodobutanethreitol (**19**) was obtained from (*S*)-2-(benzyloxy)-2-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]ethanol (**17**) according to the procedure of Abushanab and coworkers.[12] Compound **17**, was in itself derived from L-ascorbic acid (**16**).

Although the alkylation of adenine with mesylate **18** in the presence of Cs_2CO_3 described by this group[12a] afforded the desired derivatives in good yield, we were not able to isolate the expected alkylated products by reacting **4** and **5** with mesylate **18**, independently from the base used (Na_2CO_3, Et_3N, NaH) in these reactions. We thus converted **17** into iodide **19** (PPh_3/I_2) (Scheme 3). The latter reacted with **4** and **5** to give desired piperidines **20a**,**b** in 40 and 38% yield, respectively (acetonitrile, NEt_3, reflux, 5 d) (Scheme 4). The reduction of both ester functions of **20a**,**b** was performed without any difficulties with $LiAlH_4$ in diethyl ether (2 h, 20 °C) and afforded *N*-(1,2,3-trihydroxybutyl) derivatives **21a**,**b** in 80 and 75% yield, respectively. In the final step, **21a**,**b** were submitted to catalytic hydrogenation in acidic medium (MeOH/HCl). This resulted in a one-step procedure for the removal of the benzyl protecting groups and hydrolysis of the acetonide moieties to afford pentahydroxy piperidine derivatives **22a**,**b** as hydrochloride salts in high 94 and 86% yield, respectively.

Glycosidase Inhibitory Studies

Compounds **8a**–**d**, **9a**,**b**, **10a**,**b**, **11a**,**b**, **12a**–**d**, **13a**,**b**, **21b** and **22a**,**b** were assayed for their inhibitory activities toward 13 commercially available glycosidases at 1 mM concentration and under optimal enzymatic pH.[13] No inhibition was detected for **8a**,**c**,**d**, **9b**, **10a**,**b**, **11a**,**b**, **21a**,**b** and **22a**,**b** toward the following enzymes: α-L-fucosidase from bovine kidney, α-D-galactosidase from coffee beans, β-D-galactosidase from E. coli and from *Aspergillus orizae*, α-D-glucosidase from yeast and from rice, amyloglucosidase from *Aspergillus niger*, β-D-glucosidase from almonds, α-D-mannosidase from Jack beans, β-D-mannosidase from snail, β-D-xylosidase from *Aspergillus niger* and β-D-*N*-acetylglucosaminidase from Jack beans and from bovine kidney. Contrary to our expectation, nonprotected polyhydroxylated pyrrolidines **11a**,**b** and piperidine derivatives **22a**,**b** did not recognize any of the enzymes tested. This is probably due to steric hindrance arising from the *N*-(trihydroxybutyl) group and/or from a too small number of hydroxy functions on the N-heterocycles known to be responsible for the biological activity in question. Furthermore, in the cases of **11a**,**b** the C-3′ centre is inverted compared to the C-3′ centre of the sulfur side chain of **2**. Although the C-3 and C-5 centres of **22a** have the configuration of C-3 and C-5 of D-glucose, this compound is not recognized by α-D-glucosidases. In the case of **22b**, a 3,5-diepimer of **22a** make the chances to be recognized by our enzyme even worse.

To our surprise, some of the polyols protected as polyacetates showed some inhibitory activities. Whereas methyl ester **9b** was not recognized by any of the enzymes assayed, its stereoisomer **9a** showed a weak inhibition of α-D-mannosidase from Jack beans (20% at 1 mM). This was the case for pyrrolidinedicarboxylic acid **8b**, which showed a weak inhibitory activity toward β-D-galactosidase from E. coli (17% at 1 mM). Dicarboxylic acid derivative **12a** showed a modest but selective inhibition of α-L-fucosidase from bovine kidney (56% at 1 mM). This was also the case for its enantiomer **13a** which was, though, a weaker inhibitor (20% at 1 mM). It was also the case with 4-hydroxypipecolic acid derivative **12d** (17% at 1 mM) toward the same enzyme. The most potent inhibitor discovered in this work is monocarboxylic acid **13b** derived from (2*R*,4*S*)-4-acetoxypipecolic acid, which inhibited α-L-fucosidase from bovine kidney with IC_{50} = 157 μM (94% inhibition at 1 mM).

Surely there are much better inhibitors of α-L-fucosidases.[14] Although our kinetic measurements did not establish it, the surprising result obtained with **13b** suggests that this compound is a noncompetitive inhibitor: it might be a ligand of the enzyme modifying its activity by allosteric interactions. This type of glycosidase inhibitors are becoming more frequent.[15] As diastereomers **12a**,**b** and **13a** are much less active, one must admit that the special arrangement (absolute configuration) of the methoxycarbonyl, the four acetoxy substituents and the carboxylic acid moiety of **13b** is adapted for interaction with α-L-fucosidase from bovine kidney. Noteworthy is the observation that methyl L-prolinate analogues **8a**,**b** did not affect the activity of the enzyme, which might indicate the necessity to have a (2*R*)-configured pipecolic ester. Our studies suggest that polyesters might be selective, noncompetitive inhibitors of glycosidases. The latter could be less toxic than the more classical iminoalditols (competitive inhibitors), or used together with them to enhance their inhibitory activity. This might lead to interesting biological applications.

Conclusions

Tartaramides derived from L-proline and methyl 4-acetoxypipecolates provided *N*-substituted pyrrolidines and piperidine derivatives. One of them, **13b**, the triacetoxymonocarboxylic acid derived from methyl (2*S*,4*R*)-4-acetoxypipecolate and (2*S*,3*S*)-2,3-*O*-diacetyltartaric acid anhydride, is a selective inhibitor of α-L-fucosidase. A characteristic difference was established during the esterification with HCl/MeOH of proline (**9a**,**b**) and piperidine (**12a**,**b**, **13a**) derivatives. Whereas proline derivatives afforded diesters, pipecolic acid derivatives resulted in bicyclic lactones.

Experimental Section

General: All reactions were carried out under an atmosphere of nitrogen in oven-dried glassware with magnetic stirring, unless otherwise indicated. Methanol and ethanol were dried by the Grignard reaction and distilled. Chloroform and dichloromethane were distilled from phosphorus pentoxide. Acetone was distilled from potassium permanganate. Column chromatography was performed with Merck silica gel (0.040–0.063 mm, grade 9385; 0.040–0.063 mm, grade 1.0832.9025). Analytical thin-layer chromatog-

raphy was performed with commercial silica gel plates (Merck, TLC aluminium sheets, silica gel 60 F_{254}), and the plots were visualized under UV light or developed by iodine atmosphere and immersion in a solution of *o*-toluidine. Melting points were obtained with a Carl Zeiss apparatus equipped with a microscope and are uncorrected. IR data were recorded on potassium bromide plates with a Nicolet-7795 FTIR spectrometer. Absorbance frequencies are reported in reciprocal centimetres (cm^{-1}). Optical rotations were measured with an AA-10R automatic polarimeter (Optical Activity Ltd.) by using 1.0-dm cells and the sodium D line (589 nm) at ambient temperature in the solvent and concentration indicated. MS spectra were run with an AEI-MS-902 (70 eV; direct insertion) and with a Kratos-MS-902 mass spectrometer. FAB-MS spectra were measured with a ZAB 2SEQ spectrometer. High resolution NMR measurements were carried out with Varian Unity Inova 400 and Varian NMR System 600 spectrometers equipped with 5 mm indirect detection probes and operating at 399.9 and 599.9 MHz for ^1H and at 100.5 and 150.9 MHz for ^{13}C nuclei. All spectra were acquired at 30 or 35 °C. The proton chemical shifts were measured relative to tetramethylsilane internal standard, and the carbon chemical shifts were reported by using solvents as internal standards. The structural and spectroscopic assignments were made by the combined use of 1D and 2D experiments, such as HSQC and HMBC heterocorrelation techniques by using standard Varian software. One-dimensional long-range ^1H–^{13}C correlations were obtained in a sequence of selective INEPT long-range experiments with delay values optimized for 3, 6, or 8 Hz couplings. Routine-like ^1H and ^{13}C measurements were carried out with a Varian Gemini 200 spectrometer.

(*S*)-1-[(2*R*,3*R*)-2,3-Diacetoxy-3-carboxypropanoyl]pyrrolidine-2-carboxylic Acid (8a): To a suspension of L-proline (**3**, 4.6 g, 40.0 mmol) in THF (200 mL) was added dropwise at room temp. a solution of (+)-diacetyl tartaric anhydride (**6**, 8.64 g, 40.0 mmol) in THF (400 mL). The reaction mixture was heated at reflux for 6 h and then left overnight at room temp. After evaporation, the crude product was crystallized from a mixture of hexane and ether (1:1) to yield **8a** (13.12 g, 99%) as white crystals. M.p. 175 °C. $[\alpha]_D^{25}$ = –67 (*c* = 1.03, MeOH). ^1H NMR (400 MHz, [D$_6$]DMSO) (2 rotamers): δ = 1.75–1.95 (m, 4 H, 3-H, 4-H), 2.0, 2.04 (2 s, 3 H, OCOMe), 2.06, 2.07 (2 s, 3 H, OCOMe) 3.42 (m, 1 H, 5_a-H), 3.75 (m, 1 H, 5_b-H), 4.12, 4.78 (2 dd, *J* = 8.8, 3.0 Hz, 1 H, 2-H), 5.31, 5.41 (2 d, *J* = 3.6 Hz, 1 H, 2′-H) 5.58, 5.59 (2 d, *J* = 3.6 Hz, 1 H, 3′-H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 20.9, 20.8 (2×OCO*Me*), 25.2, 24.0 (C-4), 28.7, 28.9 (C-3), 47.1, 47.9 (C-5), 59.4, 60.3 (C-2), 70.8, 71.4* (C-2′), 72.1, 72.3* (C-3′), 164.7 (C2-*C*O$_2$H), 168.3 (C-1′), 169.9, 170.0 (2×O*C*OMe), 173.4 (C-4′) ppm (*interchangeable assignments). IR (KBr): $\tilde{\nu}$ = 3318, 2940, 1754, 1715, 1632, 1461, 1375, 1224, 1150 cm^{-1}. MS: *m*/*z* = 354 [M + Na]$^+$. $C_{13}H_{17}NO_9$ (331.28): calcd. C 47.13, H 5.17, N 4.23; found C 47.06, H 5.22, N 4.17.

(*S*)-1-[(2*S*,3*S*)-2,3-Diacetoxy-3-carboxypropanoyl]pyrrolidine-2-carboxylic Acid (8b): Compound **8b** was prepared from **3** (2.3 g, 20.0 mmol) and **7** (4.32 g, 20.0 mmol) by applying the above procedure. Yield: 6.5 g (99%). M.p. 173–176 °C (white crystals). $[\alpha]_D^{25}$ = –45 (*c* = 1.04, MeOH). ^1H NMR (400 MHz, [D$_6$]DMSO) (2 rotamers): δ = 1.67–2.21 (m, 4 H, 3-H, 4-H), 1.98, 2.01 (2 s, 3 H, OCOMe), 2.05, 2.06 (2 s, 3 H, OCOMe), 3.39 (m, 1 H, 5_a-H), 3.75 (m, 1 H, 5_b-H), 4.22, 4.46 (2 dd, *J* = 6.5, 8.3 Hz, 1 H, 2-H), 5.52, 5.44 (2 d, *J* = 3.2 Hz, 1 H, 2′-H), 5.63, 5.66 (2 d, *J* = 3.2 Hz, 1 H, 3′-H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 20.9, 20.8 (2×OCO*Me*), 25.7 (C-4) 28.8 (C-3), 47.1 (C-5), 59.8 (C-2), 69.3* (C-2′), 71.4* (C-3′), 163.5 (C2-*C*O$_2$H), 168.0 (C-1′), 170.0, 170.1 (2×O*C*OMe), 173.4 (C4′) ppm. IR (KBr): $\tilde{\nu}$ = 3300, 2996, 1777, 1753, 1711, 1632, 1453, 1368, 1210 cm^{-1}. MS: *m*/*z* = 354 [M + Na]$^+$. $C_{13}H_{17}NO_9$ (331.28): calcd. C 47.13, H 5.17, N 4.23; found C 47.21, H 5.27, N 4.29.

(*S*)-Methyl 1-[(2*R*,3*R*)-2,3-Diacetoxy-3-methoxycarbonylpropionyl]pyrrolidine-2-carboxylate (8c): To a cold suspension (0 °C) of acid **8a** (3.31 g, 10.0 mmol) in CH_2Cl_2 (200 mL) was added diazomethane (24.0 mmol in 80 mL of CH_2Cl_2). The mixture was stirred for 1.5 h. The reaction mixture was decomposed with AcOH (2.0 mL) and diluted with water (30 mL). After extraction, the organic phase was washed with a dilute NH_4OH solution (5 mL cc. NH_4OH + 15 mL water) and dried. The filtrate was evaporated under reduced pressure. The residue was purified by column chromatography (AcOEt/hexane, 6:4) to yield **8c** (2.65 g, 74%) as a pale yellow oil. $[\alpha]_D^{25}$ = –54 (*c* = 1.5, MeOH). ^1H NMR (400 MHz, $CDCl_3$) (two rotamers): δ = 1.82–2.24 (m, 4 H, 3-H, 4-H), 2.12, 2.07 (2 s, 3 H, OCOMe), 2.15 (s, 3 H, OCOMe), 3.51, 3.56 (2 m, 1 H, 5_a-H), 3.67, 3.72 (2 s, 3 H, CO_2Me), 3.74, 3.73 (2 s, 3 H, CO_2Me), 3.95 (m, 1 H, 5_b-H), 4.41, 4.91 (2 dd, *J* = 8.2, 3.2 Hz, 1 H, 2-H), 5.61, 5 58 (2 d, *J* = 4.3 Hz, 1 H, 2′-H), 5.72, 5.59 (2 d, *J* = 4.3 Hz, 1 H, 3′-H) ppm. ^{13}C NMR (100 MHz,$CDCl_3$): δ = 20.60, 20.62 (2×OCOMe), 25.1, 22.1 (C-4), 28.8, 31.8 (C-3), 47.1, 47.6 (C-5), 52.4, 53.0 (2×CO2Me), 59.9, 59.5 (C-2), 70.5 (C-2′)*, 71.1 (C-3′)*, 164.6 (C-1′), 167.4 (CO), 169.7 (CO), 169.8, 170 (CO), 172.0 (CO) ppm. IR (KBr): $\tilde{\nu}$ = 2959, 1754, 1670, 1644, 1438, 1215, 1121, 1073 cm^{-1}. MS: *m*/*z* = 359 [M]$^+$. $C_{15}H_{21}NO_9$ (359.33): calcd. C 50.14, H 5.89, N 3.90; found C 50.22, H 5.80, N 3.86.

(*S*)-Methyl 1-[(2*S*,3*S*)-2,3-Diacetoxy-3-methoxycarbonylpropionyl]pyrrolidine-2-carboxylate (8d): Acid **8b** (2.0 g, 6.0 mmol) was esterified to diester **8d** as described above. Yield: 1.84 g (85%), pale yellow oil. $[\alpha]_D^{25}$ = –57 (*c* = 1.9, MeOH). ^1H NMR (400 MHz, $CDCl_3$) (two rotamers): δ = 1.88–2.27 (m, 4 H, 3-H, 4-H), 2.15, 2.11 (2 s, 3 H, OCOMe), 2.19 (s, 3 H, OCOMe), 3.63, 3.55 (2 m, 1 H, 5_a-H), 3.69, 3.75 (2 s, 3 H, CO_2Me), 3.80, 3.78 (2 s, 3 H, CO_2Me), 3.77 (m, 1 H, 5_b-H), 4.53, 4.57 (2 dd, *J* = 8.3, 3.5 Hz, 1 H, 2-H), 5.71, 5 62 (2 d, *J* = 5.2 Hz, 1 H, 2′-H)*, 5.70, 5.72 (2 d, *J* = 5.2 Hz, 1 H, 3′-H)*ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.5, 20.6 (2×OCOMe), 25.4, 22.1 (C-4), 28.7, 31.6 (C-3), 47.0, 47.3 (C-5), 52.3, 53.1 (2×CO_2Me), 59.5, 60.5 (C-2), 69.4, 69.7 (C-2′)*, 70.8 (C-3′)*, 164.0, 164.5 (C-1′), 167.1, 167.6 (CO), 171.3, 169.8 (CO), 171.9 (CO) ppm. IR (KBr): $\tilde{\nu}$ = 2958, 1755, 1675, 1436, 1374, 1216 cm^{-1}. $C_{15}H_{21}NO_9$ (359.33): calcd. C 50.14, H 5.89, N 3.90; found C 50.07, H 5.82, N 3.85.

(*S*)-Methyl 1-[(2*R*,3*R*)-2,3-Dihydroxy-3-methoxycarbonylpropionyl]pyrrolidine-2-carboxylate (9a): A solution of diacid **8a** (5.95 g, 18.0 mmol) in MeOH (100 mL) was cooled with an NaCl/ice-bath to –5 °C. Dry HCl gas was bubbled through the solution over 4–6 h while the temperature was maintained at about 0 °C, and the mixture was then left overnight at room temp. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography ($CHCl_3$/acetone, 10:2). The combined fractions were evaporated, and the residue was crystallised from diethyl ether to yield **9a** (3.72 g, 66%) as white crystals. M.p. 110 °C. $[\alpha]_D^{25}$ = –50 (*c* = 1.08, MeOH). ^1H NMR (400 MHz, [D$_6$]-DMSO/$CDCl_3$) (2 rotamers): δ = 1.7–2.2 (m, 4 H, 3-H, 4-H), 3.4–3.6 (m, 2 H, 5-H), 3.61, 3.62 (2 s, 3 H, C-2–CO_2Me), 3.70, 3.67 (2 s, 3 H, C-4′–CO_2Me), 4.22, 4.47 (2 d, *J* = 8.3 Hz, 1 H, C-2′–OH), 4.36 (dd, *J* = 8.3, 2.0 Hz, 1 H, 2′-H), 4.39, 4.44 (2 dd, *J* = 8.3, 2.7 Hz, 1 H, 2-H), 4.49, 4.84 (2 d, *J* = 8.0 Hz, C-3′–OH), 4.55, 4.89 (2 dd, *J* = 8.0, 2.0 Hz, 1 H, 3′-H) ppm. ^{13}C NMR (100 MHz, [D$_6$]-DMSO/$CDCl_3$): δ = 24.8 (C-4), 28.9, 31.7 (C-3), 46.8, 47.6 (C-5), 52.3, 52.5 (CO_2Me), 52.6, 53.0 (CO_2Me), 59.6, 59.3 (C-2), 71.4, 71.6* (C-2′), 73.3* (C-3′), 169.5, 170.0 (C-1′), 172.2 (*C*O$_2$Me),

172.4, 172.5 (CO_2Me) ppm. IR (KBr): $\tilde{\nu}$ = 3360, 3182, 2965, 1763, 1729, 1667, 1624, 1461, 1381, 1284, 1207, 1130, 1090, 991 cm^{-1}. MS: *m*/*z* = 298 $[M + Na]^+$. $C_{11}H_{17}NO_7$ (275.26): calcd. C 48.00, H 6.23, N 5.09; found C 47.89, H 6.27, N 5.13.

(*S*)-Methyl 1-[(2*S*,3*S*)-2,3-Dihydroxy-3-methoxycarbonylpropionyl]pyrrolidine-2-carboxylate (9b): Compound **9b** was prepared from **8b** (6.62 g, 20.0 mmol) as described above. Yield: 3.8 g (70%). M.p. 110 °C (white crystals). $[\alpha]_D^{25}$ = –77 (*c* = 1.06, MeOH). ^{1}H NMR (400 MHz, [D$_6$]DMSO) (2 rotamers): δ = 1.67–2.25 (m, 4 H, 3-H, 4-H), 3.38 (m, 1 H, 5$_a$-H), 3.53, 3.57 (2 s, 3 H, C-2–CO_2Me), 3.61, 3.63 (2 s, 3 H, C-4′–CO_2Me), 3.80 (m, 1 H, 5$_b$-H), 4.21, 4.27 (2 dd, *J* = 7.4, 4.0 Hz, 1 H, C-2′–OH), 4.28, 4.51 (2 dd, *J* = 9.0, 4.7 Hz, 1 H, 2′-H), 4.41, 4.65 (2 dd, *J* = 7.9, 4.0 Hz, 1 H, 2-H), 5.04, 5.25 (2 d, *J* = 7.9 Hz, 1 H, C-2′–OH), 5.40, 5.97 (2 d, *J* = 7.4 Hz, 1 H, C-3′–OH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 25.5 (C-4), 29.0 (C-3), 47.2 (C-5), 52.2 (CO_2*Me*), 52.4 (CO_2*Me*), 59.7 (C-2), 72.4* (C-2′), 72.7* (C-3′), 170.1 (C-1′), 172.8 (*C*O_2Me), 172.7 (*C*O_2Me) ppm. IR (KBr): $\tilde{\nu}$ = 3426, 3300, 2957, 1747, 1647, 1440, 1386, 1279, 1202, 1127, 1102, 994 cm^{-1}. MS: *m*/*z* = 298 $[M + Na]^+$. $C_{11}H_{17}NO_7$ (275.26): calcd. C 48.00, H 6.23, N 5.09; found C 48.13, H 6.15, N 5.00.

(*S*)-Methyl 1-[(2*S*,3*R*)-2,3-Dihydroxy-3-methoxycarbonylpropyl]pyrrolidine-2-carboxylate (10a): To a cold solution (ice-bath) of amide **9a** (2.75 g, 10.0 mmol) in dry THF (100 mL) was added borane dimethyl sulfide complex solution (8.3 mL, 2.0 M in THF; 50.0 mmol), and the mixture was stirred for 2 h while the temperature was warmed up to room temp. The reaction mixture was decomposed with MeOH (50 mL) and was further stirred overnight. The solvent was evaporated under reduced pressure. The crude product was purified by column chromatography ($CHCl_3$/MeOH/NH_4OH, 10:1:0.1) to yield **10a** (2.78 g, 89%; 84% purity) as a pale yellow oil. An aliquot was purified again by column chromatography to yield analytically pure **10a** as a pale oil. $[\alpha]_D^{25}$ = –59 (*c* = 1.0, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.8–2.23 (m, 4 H, 3-H, 4-H), 2.47 (m, 1 H, 5$_a$-H), 2.66 (dd, *J* = 3.4, 12.7 Hz, 1 H, 1′$_a$-H), 2.97 (dd, *J* = 9.8, 12.7 Hz, 1 H, 1′$_b$-H), 3.28 (m, 1 H, 5$_b$-H), 3.41 (dd, *J* = 8.7, 5.5 Hz, 1 H, 2-H), 3.72 (s, 3 H, C-2–CO_2Me), 3.82 (s, 3 H, C-4′–CO_2Me), 4.02 (ddd, *J* = 9.8, 3.4, 1.7 Hz, 1 H, 2′-H), 4.06 (d, *J* = 1.7 Hz, 1 H, 3′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.1 (C-4), 29.8 (C-3), 52.2 (CO_2*Me*), 52.7 (CO_2*Me*), 53.7 (C-5), 57.6 (C-1′), 66.0 (C-2), 69.8* (C-2′), 72.0* (C-3′), 173.5 (*C*O_2Me), 175.2 (*C*O_2Me) ppm. IR (KBr): $\tilde{\nu}$ = 3306, 2955, 1740, 1440, 1278, 1210, 1140, 1090 cm^{-1}. MS (FAB, NOBA): *m*/*z* = 262 $[M + H]^+$, 284 $[M + Na]^+$. $C_{11}H_{19}NO_6$ (261.27): calcd. C 50.57, H 7.33, N 5.36; found C 50.33, H 7.25, N 5.29.

(*S*)-Methyl 1-[(2*R*,3*S*)-2,3-Dihydroxy-3-methoxycarbonylpropyl]pyrrolidine-2-carboxylate (10b): Amide **9b** (2.75 g, 10.0 mol) was reduced to **10b** as described above. Yield: 2.78 g (89%; 84% purity). An aliquot was purified again by column chromatography to yield analytically pure **10b** as a pale yellow oil. $[\alpha]_D^{25}$ = –48 (*c* = 1.0, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.78–2.2 (m, 4 H, 3-H, 4-H), 2.62 (m, 1 H, 5$_a$-H), 2.76 (dd, *J* = 6.0, 12.5 Hz, 1 H, 1′$_a$-H), 2.87 (dd, *J* = 8.0, 12.5 Hz, 1 H, 1′$_b$-H), 3.16 (m, 1 H, 5$_b$-H), 3.35 (dd, *J* = 4.8, 9.2 Hz, 1 H, 2-H), 3.72 (s, 3 H, C-2–CO_2Me), 3.83 (s, 3 H, C-4′–CO_2Me), 3.94 (ddd, *J* = 8.1, 6.2, 1.8 Hz, 1 H, 2′-H), 4.28 (d, *J* = 1.8 Hz, 1 H, 3′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.9 (C-4), 29.8 (C-3), 52.2 (CO_2*Me*), 52.7 (CO_2*Me*), 54.4 (C-5), 57.2 (C-1′), 65.9 (C-2), 70.1 (C-2′), 71.8 (C-3′), 173.6 (*C*O_2Me), 175.5 (*C*O_2Me) ppm. IR (KBr): $\tilde{\nu}$ = 3300, 2955, 1740, 1439, 1279, 1210, 1141 cm^{-1}. MS (FAB, NOBA): *m*/*z* = 262 $[M + H]^+$. $C_{11}H_{19}NO_6$ (261.27): calcd. C 50.57, H 7.33, N 5.36; found C 50.69, H 7.19, N 5.28.

(2*S*,3*S*)-4-[(*S*)-2-(Hydroxymethyl)pyrrolidin-1-yl]butane-1,2,3-triol (11a): To a cold (ice-bath) solution of diester **10a** (250 mg, 0.95 mmol) in THF (10 mL) was added powdered $LiAlH_4$ (360 mg, 9.5 mmol) portionwise. The temperature was warmed up to room temp., and the mixture was stirred for 2 h. The reaction mixture was decomposed by the addition of water. After removal of the precipitate by filtration, the organic phase was evaporated. The crude oil was purified by column chromatography ($CHCl_3$/MeOH/NH_4OH, 50:50:1.0) to yield **11a** (40 mg, 20%) as a yellow–brown oil. $[\alpha]_D^{25}$ = –13 (*c* = 1.19, MeOH). ^{1}H NMR (400 MHz, CD_3OD): δ =1.6–1.95 (m, 4 H, 3-H, 4-H), 2.40 (m, 1 H, 5$_a$-H), 2.52 (dd, *J* = 12.7, 3.0 Hz, 1 H, 4′$_a$-H), 2.72 (m, 1 H, 2-H), 3.08 (dd, *J* = 12.7, 9.2 Hz, 1 H, 4′$_b$-H), 3.29 (m, 1 H, 5$_b$-H), 3.54–3.66 (m, 5 H, 2 × C*H*$_2$OH, 2′-H), 3.80 (m, 1 H, 3′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.3 (C-4), 28.5 (C-3), 56.1 (C-5), 59.8 (C-4′), 64.4 (2 × *C*H$_2$OH), 67.8 (C-2), 70.5 (C-3′), 74.8 (C-2′) ppm. IR (KBr): $\tilde{\nu}$ = 3371, 2948, 1456, 1398, 1043 cm^{-1}. MS (FAB, NOBA): *m*/*z* = 206 $[M + H]^+$. $C_9H_{19}NO_4$ (205.25): calcd. C 52.67, H 9.33, N 6.82; found C 52.71, H 9.42, N 6.79.

(2*R*,3*R*)-4-[(*S*)-2-(Hydroxymethyl)pyrrolidin-1-yl]butane-1,2,3-triol (11b): *Method A*: Compound **11b** was prepared from **10b** (430 mg, 1.64 mmol) as described above to yield **11b** (120 mg, 35%) as a yellow–brown oil. $[\alpha]_D^{25}$ = –21 (*c* = 1.05, MeOH). ^{1}H NMR (400 MHz, CD_3OD): δ = 1.65–2.05 (m, 4 H, 3-H, 4-H), 2.68 (m, 1 H, 5$_a$-H), 2.77 (dd, *J* = 7.0, 12.7 Hz, 1 H, 4′$_a$-H), 2.96 (m, 1 H, 2-H), 3.18 (dd, *J* = 5.5, 12.7 Hz, 1 H, 4′$_b$-H), 3.36 (m, 1 H, 5$_b$-H), 3.56–3.66 (m, 5 H, 2 × C*H*$_2$OH, 2′-H), 3.87 (t, *J* = 5.5 Hz, 1 H, 3′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.3 (C-4), 28.3 (C-3), 57.2 (C-5), 59.7 (C-4′), 64.4 (2 × *C*H$_2$OH), 68.4 (C-2), 70.5 (C-3′), 74.3 (C-2′) ppm. IR (KBr): $\tilde{\nu}$ = 3371, 2948, 1456, 1398, 1043 cm^{-1}. MS: *m*/*z* = 206 $[M + H]^+$. $C_9H_{19}NO_4$ (205.25): calcd. C 52.67, H 9.33, N 6.82; found C 52.61, H 9.27, N 6.93. *Method B*: Amide **9b** was reduced directly to **11b**. To a cold solution (ice-bath) of amide **9b** (275 mg, 1.0 mmol) in THF (10 mL) was added a solution of BH_3·SMe_2 (3.3 mL, 6.66 mmol; 2.0 M solution of BH_3·SMe_2 in THF). The temperature was warmed up to room temp., and the mixture was stirred for 5 d. The reaction mixture was decomposed with MeOH (50 mL). The solvent was evaporated under reduced pressure. The crude product was purified by column chromatography as described above to yield **11b** (60 mg, 29%).

Methyl (2*S*,4*R*)-4-Acetoxy-1-[(2*R*,3*R*)-2,3-diacetoxy-3-carboxy-propionyl]piperidine-2-carboxylate (12a): To a solution of methyl (–)-(2*S*,4*R*)-4-acetoxypipecolate (**4**, 2.0 g, 10.35 mmol) in THF (50 mL) was added a solution of (+)-diacetyl tartaric anhydride (**6**; 2.34 g, 10.85 mmol) in THF (100 mL) dropwise at room temp. The reaction mixture was heated at reflux for 6 h and then left overnight at room temp. After evaporation, the crude product was crystallized from diethyl ether/diisopropyl ether (1:1) to yield **12a** (3.34 g, 77%) as pale yellow crystals. M.p. 150 °C. $[\alpha]_D^{25}$ = –51 (*c* = 1.06, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.65–2.65 (m, 4 H, 3-H, 5-H), 1.98 (s, 3 H, OCOMe), 2.12 (s, 3 H, OCOMe), 2.15 (s, 3 H, OCOMe), 3.65 (m, 1 H, 6$_a$-H), 3.72 (s, 3 H, CO_2Me), 3.92 (m, 1 H, 6$_b$-H), 5.08 (m, 1 H, 4-H), 5.19 (dd, *J* = 6.9, 1.7 Hz, 1 H, 2-H), 5.43 (br. s, 1 H, 3′-H), 5.99 (br. s, 1 H, 2′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.7 (OCO*Me*), 20.9 (OCO*Me*), 21.1 (OCO*Me*), 28.9* (C-3), 30.3* (C-5), 38.6 (C-6), 49.9 (C-2), 52.4 (CO_2*Me*), 66.6 (C-4), 70.9* (C-2′), 73.0* (C-3′), 167.5 (C-1′), 169.8 (*C*O_2H), 170.2* (*C*O_2Me), 171.0* (O*C*OMe), 171.1* (O*C*OMe) ppm. IR (KBr): $\tilde{\nu}$ = 3458, 2959, 1744, 1648, 1442, 1373, 1223, 1081, 1060, 1019 cm^{-1}. MS (FAB, NOBA): *m*/*z* = 418 $[M + H]^+$. $C_{17}H_{23}NO_{11}$ (417.36): calcd. C 48.92, H 5.55, N 3.36; found C 48.87, H 5.49, N 3.30.

Methyl (2*S*,4*R*)-4-Acetoxy-1-[(2*S*,3*S*)-2,3-diacetoxy-3-carboxypropionyl]piperidine-2-carboxylate (12b): Compound **12b** was prepared from **4** (2.0 g, 10.35 mmol) and (–)-diacetyl tartaric anhydride **7** (2.34 g, 10.85 mmol) as described above. Yield: 3.45 g (80%). M.p. 98 °C, pale yellow crystals. $[\alpha]_D^{25}$ = –2.7 (*c* = 1.1, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.65–2.65 (m, 4 H, 3-H, 5-H), 1.98 (s, 3 H, OCOMe), 2.12 (s, 3 H, OCOMe), 2.15 (s, 3 H, OCOMe), 3.62 (m, 1 H, 6_a-H), 3.70 (s, 3 H, CO_2Me), 3.91 (m, 1 H, 6_b-H), 5.10 (m, 1 H, 4-H), 5.31 (dd, *J* = 6.9, 1.6 Hz, 1 H, 2-H), 5.41 (br. s, 1 H, 3′-H), 5.95 (br. s, 1 H, 2′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.7 (OCO*Me*), 20.9 (OCO*Me*), 21.0 (OCO*Me*), 29.2* (C-3), 30.3* (C-5), 38.5 (C-6), 49.3 (C-2), 52.5 (CO_2*Me*), 66.4 (C-4), 70.8* (C-2′), 71.7* (C-3′), 169.9 (C-1′), 170.0 (*C*O$_2$H), 170.6* (*C*O$_2$Me), 171.0* (O*C*OMe), 171.3* (O*C*OMe) ppm. IR (KBr): $\tilde{\nu}$ = 3459, 2958, 1744, 1649, 1441, 1374, 1220, 1083, 1062, 1021 cm^{-1}. MS (FAB, NOBA): *m*/*z* = 418 [M + H]$^+$, 440 [M + Na]$^+$. $C_{17}H_{23}NO_{11}$ (417.36): calcd. C 48.92, H 5.55, N 3.36; found C 49.05, H 5.43, N 3.32.

Methyl (2*S*,4*R*)-4-Acetoxy-1-[(2*R*,3*R*)-2,3-diacetoxy-3-methoxycarbonylpropionyl]piperidine-2-carboxylate (12c): To a cold solution (0 °C) of acid **12a** (250 mg, 0.6 mmol) in CH_2Cl_2 (12 mL) was added diazomethane (5.0 mmol in 20 mL of CH_2Cl_2). The mixture was stirred for 3 h. The reaction mixture was diluted with MeOH (10 mL), and the mixture was evaporated under reduced pressure. The residue was purified by column chromatography ($CHCl_3$/acetone, 10:2) to yield **12c** (130 mg, 50%) as a pale oil. $[\alpha]_D^{25}$ = –24.6 (*c* = 1.3, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.70–2.65 (m, 4 H, 3-H, 5-H), 1.98 (s, 3 H, OCOMe), 2.16 (s, 3 H, OCOMe), 2.18 (s, 3 H, CO_2Me), 3.73 (s, 3 H, CO_2Me), 3.79 (s, 3 H, CO_2Me), 3.7–3.85 (m, 2 H, 6-H), 5.11 (dddd, *J* = 4 × 2.7 Hz, 1 H, 4-H), 5.19 (d, *J* = 6.3 Hz, 1 H, 2-H), 5.67 (d, *J* = 3.8 Hz, 1 H, 2′-H)*, 5.99 (d, *J* = 3.8 Hz, 3′-H)* ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.60 + 20.64 + 21.1 (3 × OCOMe), 29.1 (C-5)*, 30.4 (C-3)*, 38.6 (C-6), 49.8 (C-2), 52.5 + 53.1 (2 × CO_2Me), 66.3 (C-4), 69.7 (C-2′)*, 70.5 (C-3′)*, 165.8 (C-1′), 167.2 (CO), 169.7 (CO), 169.8 (CO), 169.9 (CO), 170.7 (CO) ppm. IR (KBr): $\tilde{\nu}$ = 2998, 1752, 1684, 1440, 1382, 1222, 1081, 1067 cm^{-1}. $C_{18}H_{25}NO_{11}$ (431.39): C 50.12, H 5.84, N 3.25; found C 50.04, H 5.91, N 3.22.

Methyl (2*S*,4*R*)-4-Acetoxy-1-[(2*S*,3*S*)-2,3-diacetoxy-3-methoxycarbonylpropionyl]piperidine-2-carboxylate (12d): Diester **12d** was prepared from **12b** (250 mg, 0.6 mmol) as described above. Yield: 120 mg (47%). $[\alpha]_D^{25}$ = –19.3 (*c* = 1.45, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.80–2.67 (m, 4 H, 3-H, 5-H), 1.98 (s, 3 H, OCOMe), 2.17 (s, 6 H, 2 × OCOMe), 3.70 (s, 3 H, CO_2Me), 3.81 (s, 3 H, CO_2Me), 3.65–3.80 (m, 2 H, 6-H), 5.11 (dddd, *J* = 4 × 2.7 Hz, 1 H, 4-H), 5.33 (d, *J* = 6.5 Hz, 1 H, 2-H), 5.66 (d, *J* = 3.7 Hz, 1 H, 2′-H)*, 5.95 (d, *J* = 3.8 Hz, 1 H, 3′-H)* ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.62 + 20.64 + 21.1 (3 × OCOMe), 29.3 (C-5)*, 30.3 (C-3)*, 38.5 (C-6), 49.4 (C-2), 52.40 + 53.2 (2 × CO_2Me), 66.2 (C-4), 69.48 (C-2′)*, 69.51 (C-3′)*, 165.1 (C-1′), 167.1 (CO), 169.8 (CO), 170.1 (CO), 170.2 (CO), 170.8 (CO) ppm. IR (KBr): $\tilde{\nu}$ = 2958, 1751, 1676, 1437, 1375, 1217 cm^{-1}. $C_{18}H_{25}NO_{11}$ (431.39): C 50.12, H 5.84, N 3.25; found C 49.96, H 5.79, N 3.19.

Methyl (2*R*,4*S*)-4-Acetoxy-1-[(2*R*,3*R*)-2,3-diacetoxy-3-carboxypropionyl]piperidine-2-carboxylate (13a): Compound **13a** was prepared from methyl (+)-(2*R*,4*S*)-4-acetoxypipecolate (**5**, 1.5 g, 7.75 mmol) and (+)-diacetyl tartaric anhydride (**6**, 1.76 g, 8.15 mmol) as described for the preparation of compound **12a**. Yield: 2.36 g (73%). M.p. 74–78 °C as pale yellow crystals. $[\alpha]_D^{25}$ = +7.6 (*c* = 1.08, MeOH). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.84–2.65 (m, 4 H, 3-H, 5-H), 1.99 (s, 3 H, OCOMe), 2.17 (s, 3 H, OCOMe), 2.18 (s, 3 H, OCOMe), 3.67 (m, 1 H, 6_a-H), 3.70 (s, 3 H, CO_2Me), 3.79 (m, 1 H, 6_b-H), 5.11 (m, *J* = 2.7, 2.9, 3.0 Hz, 1 H, 4-H), 5.34 (dd, *J* = 6.6, 1.7 Hz, 1 H, 2-H), 5.64 (d, *J* = 3.3 Hz, 1 H, 3′-H), 5.97 (d, *J* = 3.3 Hz, 1 H, 2′-H), 6.0 (s, 1 H, CO_2H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 20.6 (2 × OCO*Me*), 21.1 (OCO*Me*), 29.2* (C-3), 30.2* (C-5), 38.6 (C-6), 49.5 (C-2), 52.6 (CO_2*Me*), 66.2 (C-4), 69.2* (C-2′), 69.6* (C-3′), 165.7 (C-1′), 168.9 (*C*O$_2$H), 170.1* (*C*O$_2$Me), 170.4* (O*C*OMe), 170.5* (O*C*OMe), 170.9* (O*C*OMe) ppm. IR (KBr): $\tilde{\nu}$ = 3300, 2974, 1748, 1677, 1638, 1441, 1375, 1218, 1123, 1084, 1021 cm^{-1}. MS (FAB, NOBA): *m*/*z* = 418 [M + H]$^+$, 440 [M + Na]$^+$. $C_{17}H_{23}NO_{11}$ (417.36): calcd. C 48.92, H 5.55, N 3.36; found C 49.13, H 5.47, N 3.40.

Methyl (2*R*,4*S*)-4-Acetoxy-1-[(2*S*,3*S*)-2,3-diacetoxy-3-carboxypropionyl]piperidine-2-carboxylate (13b): Compound **13b** was prepared from **5** (1.5 g, 7.75 mmol) and **7** as described above. Yield: 2.23 g (70%). M.p. 107–113 °C, pale yellow crystals. $[\alpha]_D^{25}$ = +35 (*c* = 1.1, MeOH). ^{1}H NMR (600 MHz, $CDCl_3$) (two rotamers): δ: 1.82–2.68 (m, 4 H, 3-H, 5-H), 1.99, 2.04 (2 s, 3 H, OCOMe), 2.18 (s, 6 H, 2 × OCOMe), 3.73 (s, 3 H, CO_2Me), 3.65–3.87 (m, 2 H, 6-H), 4.91, 5.11 (2 m, *J* = 3.0, 3.0, 2.7, 2.7 Hz, 1 H, 4-H), 5.04, 5.19 (2 dd, *J* = 6.4, 1.7 Hz, 1 H, 2-H), 5.42, 5.64 (2 d, *J* = 4.0 Hz, 1 H, 3′-H), 5.80, 5.97 (2 d, *J* = 4.0 Hz, 1 H, 2′-H), 7.12 (s, 1 H, CO_2H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 20.6 (2 × OCO*Me*), 21.1 (OCO*Me*), 29.0* (C-3), 30.3* (C-5), 38.7 (C-6), 49.9 (C-2), 52.6 (CO_2*Me*), 66.4 (C-4), 69.6* (C-2′), 70.3* (C-3′), 166.3 (C-1′), 169.0 (*C*O$_2$H), 170.0 (*C*O$_2$Me), 170.1 (2 × O*C*OMe), 170.7 (O*C*OMe) ppm. IR (KBr): $\tilde{\nu}$ = 3300, 2972, 1748, 1660, 1616, 1445, 1372, 1204, 1123, 1082, 1049 cm^{-1}. MS (FAB, NOBA): *m*/*z* = 418 [M + H]$^+$, 440 [M + Na]$^+$. $C_{17}H_{23}NO_{11}$ (417.36): calcd. C 48.92, H 5.55, N 3.36; found C 48.88, H 5.62, N 3.27.

Methyl (*R*)-2-Hydroxy-2-{(3*R*,8*R*,9a*S*)-8-hydroxy-1,4-dioxooctahydropyrido[2,1-c][1,4]oxazin-3-yl}acetate (14a): Dry HCl gas was introduced into a cold (0 °C to +5 °C) solution of acid **12a** (3.0 g, 7.2 mmol) in dry MeOH (80 mL) for about 6 h. The reaction mixture was left at room temp. overnight, and the solvent was evaporated under reduced pressure. The residue was crystallized from ethyl acetate (20 mL) to yield lactone **14a** (1.36 g, 62%) as white crystals. M.p. 92–96 °C. $[\alpha]_D^{25}$ = +38 ° (*c* = 1.0, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$/CD_3OD): δ = 1.31 (m, 1 H, 7′$_a$-H), 1.44 (ddd, *J* = 12.5, 12.3, 12.1 Hz, 1 H, 9′$_a$-H), 1.93 (m, 1 H, 7′$_b$-H), 2.46 (m, 1 H, 9′$_b$-H), 2.58 (m, 1 H, 6′$_a$-H), 3.70 (m, 1 H, 8′-H), 3.72 (s, 3 H, CO_2Me), 4.08 (dd, *J* = 12.3, 2.3 Hz, 1 H, 9$_a$′-H), 4.48 (m, 1 H, 6′$_b$-H), 4.62 (d, *J* = 0.8 Hz, 1 H, 2-H), 5.10 (d, *J* = 0.8 Hz, 1 H, 3′-H′) ppm. ^{13}C NMR (100 MHz, $CDCl_3$/CD_3OD): δ = 32.9 (C-7′), 39.2 (C-9′), 40.7 (C-6′), 53.3 (CO_2*Me*), 54.6 (C-9a′), 67.1 (C-8′), 72.9 (C-2), 79.7 (C-3′), 163.6 (C-1′), 167.1 (C-4′), 171.2 (C-1) ppm. IR (KBr): $\tilde{\nu}$ = 3327, 1769, 1743, 1669, 1653, 1453, 1376, 1330, 1277 cm^{-1}. MS (turbo spray) *m*/*z* = 274 [M + H]$^+$. $C_{11}H_{15}NO_7$ (273.24): calcd. C 48.35, H 5.53 N 5.13; found C 48.29, H 5.57, N 5.21.

Methyl (*S*)-2-Hydroxy-2-{(3*S*,8*R*,9a*S*)-8-hydroxy-1,4-dioxooctahydropyrido[2,1-c][1,4]oxazin-3-yl}acetate (14b): Acid **12b** (3.0 g, 7.2 mmol) reacted with HCl/MeOH as described above. The crude product was crystallized from diethyl ether/MeOH to yield lactone **14b** (1.35 g, 61%) as white crystals. M.p. 164–168 °C. $[\alpha]_D^{25}$ = –54 (*c* = 1.0, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$/CD_3OD): δ = 1.38 (dddd, *J* = 4.5,11.2, 13.0, 13.5 Hz, 1 H, 7′$_a$-H), 1.85 (ddd, *J* = 12.5, 12.4, 11.2 Hz, 1 H, 9′$_a$-H), 2.01 (m, 1 H, 7′$_b$-H), 2.53 (m, 1 H, 9′$_b$-H), 2.67 (td, *J* = 13.5, 2.5 Hz, 1 H, 6′$_a$-H), 3.84 (m, 1 H, 8′-H), 3.85 (s, 3 H, CO_2Me), 4.22 (dd, *J* = 12.5, 3.0 Hz, 1 H, 9a′-H), 4.61 (ddd, *J* = 13.5, 4.5, 2.0 Hz, 1 H, 6′$_b$-H), 4.71 (d, *J* = 1.5 Hz, 1 H, 2-H), 5.28 (d, *J* = 1.5 Hz, 1 H, 3′-H′) ppm. ^{13}C NMR (100 MHz,

$CDCl_3/CD_3OD$): δ = 33.9 (C-9′), 39.7 (C-7′), 41.1 (C-6′), 53.3 (CO_2Me), 55.7 (C-9a′), 68.0 (C-8′), 72.3 (C-2), 80.6 (C-3′), 162.4 (C-4′), 166.9 (C-1′), 171.9 (C-1) ppm. IR (KBr): $\tilde{\nu}$ = 3284, 1758, 1732, 1642, 1506, 1461, 1385, 1333, 1282 cm^{-1}. MS (FAB, NOBA) *m/z* (%) = 274 (52) $[M + H]^+$, 214 (6). $C_{11}H_{15}NO_7$ (273.24): calcd. C 48.35, H 5.53 N 5.13; found C 48.30, H 5.42, N 5.05.

Methyl (*R*)-2-Hydroxy-2-{(3*R*,8*S*,9a*R*)-8-hydroxy-1,4-dioxooctahydropyrido[2,1-c][1,4]oxazin-3-yl}acetate (15a): Acid **13a** (1.5 g, 3.6 mmol) was transformed into lactone **15a** as described above. Yield: 450 mg (40%), white crystals. M.p. 160–168 °C. $[\alpha]_D^{25}$ = +60 (*c* = 0.96, MeOH). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.38 (dddd, *J* = 4.5, 12.8, 13.5, 11.2 Hz, 1 H, 7′$_a$-H), 1.85 (td, *J* = 12.0, 12.0, 12.5 Hz, 1 H, 9′$_a$-H), 1.99 (m, 1 H, 7′$_b$-H), 2.51 (m, 1 H, 9′$_b$-H), 2.67 (td, *J* = 2.0, 13.5 Hz, 1 H, 6′$_a$-H), 3.84 (m, 1 H, 8′-H), 3.85 (s, 3 H, CO_2Me), 4.24 (dd, *J* = 3.0, 12.5 Hz, 1 H, 9a′-H), 4.61 (ddd, *J* = 2.0, 4.5, 13.5 Hz, 1 H, 6′$_b$-H), 4.72 (d, *J* = 1.5 Hz, 1 H, 2-H), 5.28 (d, *J* = 1.5 Hz, 1 H, 3′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 33.9 (C-9′), 39.7 (C-7′), 41.0 (C-6′), 53.2 (CO_2Me), 55.6 (C-9a′), 68.0 (C-8′), 72.3 (C-2), 80.6 (C-3′), 162.4 (C-4′), 166.9 (C-1′), 171.9 (C-1) ppm. IR (KBr): $\tilde{\nu}$ = 3283, 1758, 1732, 1642, 1506, 1461, 1385, 1333, 1282, 1132 cm^{-1}. MS (FAB, NOBA) *m/z* (%) = 274 (59) $[M + H]^+$, 214 (6). $C_{11}H_{15}NO_7$ (273.24): calcd. C 48.35, H 5.53 N 5.13; found C 48.21, H 5.63, N 5.22.

(*S*)-4-[(*R*)-1-(Benzyloxy)-2-iodoethyl]-2,2-dimethyl-1,3-dioxolane (19): To a solution of PPh_3 (21.65 g, 82.0 mol) in benzene (100 mL) was added a solution of iodine (20.09 g, 80.0 mol) in benzene(300 mL) dropwise. After complete addition, crystals of imidazole (12.78 g, 187 mmol) were added, and the mixture was stirred. After a few minutes, a solution of **17** (14.25 g, 56.0 mol) in benzene (40 mL) was added dropwise. The mixture was filtered, and the precipitate was washed with diethyl ether. The combined solvents were evaporated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc, 9:1) to afford **19** (14.7 g, 72% yield) as a colourless oil. $[\alpha]_D^{25}$ = –9.2 (*c* = 1.06, $CHCl_3$) {ref.[16] $[\alpha]_D^{27}$ = –8.6 (*c* = 1.97, $CHCl_3$)} prepared in another way from tartaric acid derivatives. For the spectroscopic data, see ref.[16]

Methyl (2*S*,4*R*)-4-Acetoxy-1-{(*S*)-2-(benzyloxy)-2-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]ethyl}piperidine-2-carboxylate (20a): To a solution of **4** (3.5 g, 18.0 mmol) in a mixture of acetonitrile and Et_3N (40.0 + 15.1 mL) was added a solution of protected iodo compound **19** (6.5 g, 18.0 mol) in acetonitrile (40 mL) dropwise at room temp. The reaction mixture was heated at refluxed for 6 d. After evaporation of the solvents, the residue was purified by column chromatography (hexane/AcOEt, 8:2) to yield **20a** (3.2 g, 40%) as colourless oil. $[\alpha]_D^{25}$ = +1.0 (*c* = 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.36 (s, 3 H, C-2′′–Me), 1.40 (s, 3 H, C-2′′–Me), 1.64 (m, 1 H, 5$_a$-H), 1.84 (m, 1 H, 5$_b$-H), 1.98 (s, 3 H, OCOMe), 1.95–2.15 (m, 2 H, 3-H), 2.36 (m, 1 H, 6$_a$-H), 2.68 (dd, *J* = 14.1, 5.0 Hz, 1 H, 1′$_a$-H), 2.81 (dd, *J* = 14.1, 5.6 Hz, 1 H, 1′$_b$-H), 3.27 (m, 1 H, 6$_b$-H), 3.33 (dd, *J* = 5.6, 5.1 Hz, 1 H, 2-H), 3.48 (ddd, *J* = 5.0, 5.6, 5.8 Hz, 1 H, 2′-H), 3.66 (s, 3 H, CO_2Me), 3.72 (dd, *J* = 8.1, 7.5 Hz, 5′′$_a$-H), 4.0 (dd, *J* = 8.1, 6.6 Hz, 1 H, 5′′$_b$-H), 4.25 (ddd, *J* = 7.5, 6.6, 5.8 Hz, 1 H, 4′′-H), 4.71 (s, 2 H, CH_2Ph), 4.84 (m, 1 H, 4-H), 7.35 (m, 5 H, PhH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.3 (OCO*Me*), 25.7 + 26.7 (2 × *Me*, acetonide), 30.3 (C-5), 33.6 (C-3), 47.0 (C-6), 51.5 (CO_2Me), 56.3 (C-1′), 61.5 (C-2), 66.2 (C-5′′), 68.5 (C-4), 72.7 (CH_2Ph), 77.5 (C-2′), 78.0 (C-4′′), 109.1 (C-2′′), 127.7 + 128.0 + 128.5 + 138.8 (6 C, *Ar*) ppm. IR (KBr): $\tilde{\nu}$ = 2985, 2951, 1740, 1455, 1371, 1247 cm^{-1}. MS (FAB, NOBA): *m/z* = 436 $[M + H]^+$, 458 $[M + Na]^+$. $C_{23}H_{33}NO_7$ (435.51): calcd. C 63.43, H 7.64, N 3.22; found C 63.37, H 7.58, N 3.19.

Methyl (2*R*,4*S*)-4-Acetoxy-1-{(*S*)-2-(benzyloxy)-2-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]ethyl}piperidine-2-carboxylate (20b): Compound **20b** was prepared from **5** (3.5 g, 8.0 mmol) and **19** (6.5 g, 18.0 mmol) as described above. Yield: 3.04 g (38%), colourless oil. $[\alpha]_D^{25}$ = –3.8 (*c* = 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.35 (s, 3 H, C-2′′–Me), 1.42 (s, 3 H, C-2′′–Me), 1.68 (m, 1 H, 5$_a$-H), 1.79 (m, 1 H, 5$_b$-H), 1.98 (s, 3 H, OCOMe), 1.96–2.06 (m, 2 H, 3-H), 2.37 (m, 1 H, 6$_a$-H), 2.58 (dd, *J* = 13.9, 6.6 Hz, 1 H, 1′$_a$-H), 2.74 (dd, *J* = 13.9, 4.7 Hz, 1 H, 1′$_b$-H), 3.17 (m, 1 H, 6$_b$-H), 3.26 (dd, *J* = 7.1, 4.9 Hz, 1 H, 2-H), 3.56 (ddd, *J* = 6.6, 6.4, 4.7 Hz, 1 H, 2′-H′), 3.65 (s, 3 H, CO_2Me), 3.75 (dd, *J* = 8.3, 7.3 Hz, 5′′$_a$-H), 4.04 (dd, *J* = 8.3, 6.6 Hz, 1 H, 5′′$_b$-H), 4.18 (ddd, *J* = 7.3, 6.6, 6.4 Hz, 1 H, 4′′-H), 4.73 (2 d, *J* = 11.9 Hz, 2 H, CH_2Ph), 4.82 (m, 1 H, 4-H), 7.34 (m, 5 H, PhH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2 (OCO*Me*), 25.5 + 26.7 (2 × *Me*, acetonide), 30.3 (C-5), 33.9 (C-3), 47.2 (C-6), 51.5 (OCO*Me*), 56.9 (C-1′), 62.4 (C-2), 66.2 (C-5′′), 68.8 (C-4), 73.1 (CH_2Ph), 77.7 (C-4′), 78.3 (C-2′), 109.1 (C-2′′), 127.7–128.5 + 138.9 (6 C, *Ar*) ppm. IR (KBr): $\tilde{\nu}$ = 2985, 2951, 1740, 1455, 1371, 1245 cm^{-1}. MS: *m/z* = 436 $[M + H]^+$, 458 $[M + Na]^+$. $C_{23}H_{33}NO_7$ (435.51): calcd. C 63.43, H 7.64, N 3.22; found C 63.50, H 7.55, N 3.26.

(2*S*,4*R*)-1-{(*S*)-2-(Benzyloxy)-2-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-ethyl}-2-hydroxymethylpiperidin-4-ol (21a): To a cold (ice-bath) solution of **20a** (1.5 g, 3.45 mmol) in diethyl ether (20 mL) was added powdered $LiAlH_4$ (523 mg, 13.8 mmol) portionwise. The ice bath was removed, and the mixture was stirred for 3 h. The reaction mixture was decomposed with water (2 mL), and the precipitate was filtered off. The solvent was evaporated under reduced pressure. The residue was purified by column chromatography ($CHCl_3$/MeOH/NH_4OH, 10:1:0.1) to yield **21a** (1.0 g, 80%) as a colourless oil. $[\alpha]_D^{25}$ = –35 (*c* = 1.0, MeOH). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.33 (s, 3 H, C-2′′–Me), 1.38 (m, 1 H, 5$_a$-H), 1.39 (s, 3 H, C-2′′–Me), 1.65 (m, 1 H, 3$_a$-H), 1.78 (m, 2 H, 3$_b$-H, 5$_b$-H), 2.16 (dd, *J* = 14.0, 3.0 Hz, 1 H, 1′$_a$-H), 2.24 (ddd, *J* = 14.1, 12.1, 2.1 Hz, 1 H, 6$_a$-H), 2.35 (m, 1 H, 2-H), 2.89 (dd, *J* = 14.1, 8.9 Hz, 1 H, 6$_b$-H), 2.95 (m, 1 H, 1′$_b$-H), 3.32 (dd, *J* = 12.1, 2.7 Hz, 1 H, CH_2OH), 3.55–3.65 (m, 2 H, 2′-H, 4-H), 3.72 (dd, *J* = 7, 8.5 Hz, 1 H, 5′′$_a$-H), 3.84 (dd, *J* = 3.5, 12 Hz, 1 H, CH_2OH), 3.95 (dd, *J* = 8.4, 6.6 Hz, 1 H, 5′′$_b$-H), 4.21 (ddd, *J* = 7.0, 6.6, 6.0 Hz, 1 H, 4′′-H), 4.72 (s, 2 H, CH_2Ph), 7.35 (m, 5 H, PhH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.4 + 26.6 (2 × *Me*, acetonide), 34.1 (C-5), 37.7 (C-3), 51.3 (C-6), 51.8 (C-1′), 60.5 (C-2), 63.2 (*C*H_2OH), 65.8 (C-5′′), 68.8 (C-4), 73.7 (*C*H_2Ph), 76.7 (C-2′), 76.9 (C-4′′), 109.5 (C-2′′), 128.1 + 128.5 + 128.6 + 138.1 (6 C, *Ar*) ppm. IR (KBr): $\tilde{\nu}$ = 3417, 2937, 1455, 1371, 1261, 1214, 1071 cm^{-1}. MS (FAB, NOBA): *m/z* = 366 $[M + H]^+$. $C_{20}H_{31}NO_5$ (365.46): calcd. C 65.73, H 8.55, N 3.83; found C 65.81, H 8.47, N 3.80.

(2*R*,4*S*)-1-{(*S*)-2′-(Benzyloxy)-2-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]ethyl}-2-hydroxymethylpiperidin-4-ol (21b): Dihydroxy compound **21b** was prepared from **20b** (1.5 g, 3.45 mmol) as described above. Yield: 1.07 g (75%). $[\alpha]_D^{25}$ = +11.5 (*c* = 1.03, MeOH), colourless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.37 (s, 3 H, C-2′′–Me), 1.45 (m, 1 H, 5$_a$-H), 1.45 (s, 3 H, C-2′′–Me), 1.58 (m, 1 H, 3$_a$-H), 1.80 (m, 2 H, 3$_b$-H, 5$_b$-H), 2.25 (td, *J* = 12.2, 2.6 Hz, 1 H, 6$_a$-H), 2.35 (m, 1 H, 2-H), 2.42 (dd, *J* = 13.4, 6.5 Hz, 1 H, 1′$_a$-H), 2.90–3.00 (m, 2 H, 1′$_b$-H, 6$_b$-H), 3.36 (dd, *J* = 12.2, 3.7 Hz, 1 H, CH_2OH), 3.55–3.70 (m, 2 H, 2′-H, 4-H), 3.87 (dd, *J* = 8.1, 7.2 Hz, 4′′$_a$-H), 3.88 (dd, *J* = 12.2, 3.1 Hz, 1 H, CH_2OH), 3.98 (dd, *J* = 8.1, 6.7 Hz, 1 H, 5′′$_b$-H), 4.38 (ddd, *J* = 7.2, 6.7, 4.2 Hz, 1 H, 4′′-H), 4.72 (2 d, *J* = 11.7 Hz, 2 H, CH_2Ph), 7.35 (m, 5 H, PhH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.5 + 26.4 (2 × *Me*, acetonide), 33.9 (C-5), 37.5 (C-3), 51.0 (C-6), 51.4 (C-1′), 61.2 (C-2), 63.4 (*C*H_2OH), 65.4 (C-5′′), 68.9 (C-4), 73.2 (*C*H_2Ph), 76.3 (C-4′′), 76.5 (C-2′), 109.4 (C-2′′), 128.0 + 128.1 + 128.6 + 138.2 (6 C, *Ar*) ppm. IR (KBr): $\tilde{\nu}$ = 3405, 2936, 1455, 1371, 1258, 1213, 1070 cm^{-1}. MS:

m/*z* = 366 [M + H]$^+$. $C_{20}H_{31}NO_5$ (365.46): calcd. C 65.73, H 8.55, N 3.83; found C 65.69, H 8.49, N 3.77.

(2*S*,3*S*)-4-[(2*S*,4*R*)-4-Hydroxy-2-(hydroxymethyl)piperidin-1-yl]-butane-1,2,3-triol Hydrochloride (22a): To a solution of **21a** (200 mg, 0.54 mmol) in MeOH (5.0 mL), which was acidified with a few drops of HCl/EtOH, was added a mixture of 20% $Pd(OH)_2$/C (20 mg) and 10% Pd/C catalyst (20 mg) in MeOH (10 mL). The reaction mixture was hydrogenated according to the usual conditions for about 2 h. The catalyst was filtered off, and the filtrate was evaporated to dryness to yield pure **22a** (140 mg, 94%) as a colourless oil. $[\alpha]_D^{25}$ = –12.6 (*c* = 0.95, MeOH). ^{1}H NMR (400 MHz, CD_3OD): δ = 1.74 (m, 1 H, 5_a-H), 1.88 (m, 1 H, 3_a-H), 2.12 (m, 2 H, 3_b-H, 5_b-H), 3.20–3.35 (m, 2 H, 1′-H), 3.43 (m, 1 H, 2-H), 3.52–3.7 (m, 4 H, 4′-H, 2′-H′, 3′-H), 3.74 (dd, *J* = 12.6, 3.2 Hz, 1 H, $4'_a$-H), 3.79 (m, 1 H, 6_a-H), 3.90 (m, 1 H, 4-H), 3.98 (dd, *J* = 12.6, 3.4 Hz, 1 H, $4'_b$-H), 4.15 (ddd, *J* = 9.8, 2.7, 2.5 Hz, 6_b-H) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 32.7 (C-5), 36.6 (C-3), 51.8 (C-4′), 57.3 (C-6), 61.3 (C-1′), 63.8 (C2-*C*H_2OH), 65.3* (C-2), 65.9* (C-2′), 66.9 (C-4), 73.9 (C-3′) ppm. IR (KBr): $\tilde{\nu}$ = 3346, 2939, 1406, 1055 cm^{-1}. MS: *m*/*z* = 236 [M + H]$^+$. $C_{10}H_{22}ClNO_5$ (271.74): calcd. C 44.20, H 8.16, Cl 13.05, N 5.15; found C 44.31, H 8.06, Cl 12.98, N 5.00.

(2*S*,3*S*)-4-[(2*R*,4*S*)-4-Hydroxy-2-(hydroxymethyl)piperidin-1-yl]-butane-1,2,3-triol Hydrochloride (22b): Protected diol **21b** (400 mg, 1.1 mmol) was hydrogenated as described above. The crude product was purified with Amberlyst resin (MeOH). Yield: 260 mg (86%), pale yellow oil. $[\alpha]_D^{25}$ = –6.3 (*c* = 1.1, MeOH). ^{1}H NMR (400 MHz, CD_3OD): δ = 1.72–2.15 (m, 4 H, 3-H, 5-H), 3.20 (td, *J* = 12.6, 2.7 Hz, 1 H, 6_a-H), 3.32 (dd, *J* = 13.6, 7.9 Hz, 1 H, $4'_a$-H), 3.44–3.54 (m, 2 H, 2-H, $4'_b$-H), 3.58–3.77 (m, 5 H, 1′-H, 2′-H, CH_2OH), 3.88 (m, 1 H, 4-H), 3.94 (m, 1 H, 6_b-H), 4.13 (ddd, *J* = 9.6, 2.5, 2.0 Hz, 1 H, 3′-H) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 33.6 (C-5), 37.3 (C-3), 52.6 (C-4′), 55.3 (C-6), 63.7 (C-2), 63.9 (C2-*C*H_2OH), 64.5 (C-1′), 68.6 (C-4), 69.7 (C-3′), 74.3 (C-2′) ppm. IR (KBr): $\tilde{\nu}$ = 3358, 2948, 1410, 1310, 1077, 1052 cm^{-1}. MS: *m*/*z* = 236 [M + H]$^+$. $C_{10}H_{22}ClNO_5$ (271.74): calcd. C 44.20, H 8.16, Cl 13.05, N 5.15; found C 44.19, H 8.22, Cl 12.99, N 5.23.

Supporting Information (see footnote on the first page of this article): Copies of ^{1}H and ^{13}C NMR spectra of **8a**–**d**, **9a**,**b**, **10a**,**b**, **11a**,**b**, **12a**–**d**, **13a**,**b**, **14a**,**b**, **15a**, **19**, **20a**,**b**, **21a**,**b** and **22a**,**b**.

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