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Total synthesis of both enantiomers of *trans*-β-hydroxypipecolic acid

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Abstract: *trans*-β-Hydroxypipecolic acids of both L- and D-series, L-**1** and D-**1**, have been straightforwardly prepared in 14% and 15% yields, respectively, starting from glyceraldehyde imines D-**7** and L-**7** as useful three-carbon chirons. The key feature of these parallel syntheses lies on the highly diastereoselective character of the initial coupling manoeuver between silyloxy furan TBSOF and imines **7**, which ultimately accounts for the relative, and hence absolute configuration of the target pipecolic acids. © 1997 Elsevier Science Ltd

Introduction

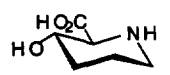
3-Hydroxypipecolic acids, six-membered cyclic α-amino-β-hydroxy acids [e.g. (2*S*,3*S*)-isomer L-**1**, Figure 1], constitute non-natural variants of a structural motif often encountered in a variety of functional molecules — e.g. naturally occurring (2*S*,4*R*)-4-hydroxypipecolic acid **2**,[1] the uronic acid derivative of deoxynojirimycin **3**,[2] and potent β-glucuronidase inhibitor D-glucaro-δ-lactam **4**[3] — and may be regarded as an "expanded" hydroxylated proline (e.g. **5**), or a conformationally restricted serine derivative (e.g. **6**).

As a consequence, a practical route providing an easy access to these multifunctional, chiral substances in a structurally defined form should be highly desirable,[4] also considering that these compounds might be precious scaffolds to be incorporated into conformationally restricted peptidomimetics of biological relevance.

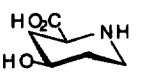
Results and discussion

Planning

A variable plan addressing the synthesis of a given 3-hydroxypipecolic acid of type **A** is illustrated in Scheme 1. Here, the piperidine ring of the target amino acid **A**, derived from



L-1



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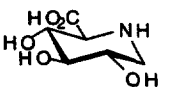

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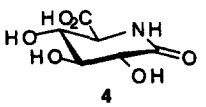

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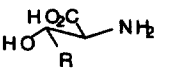

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Figure 1.

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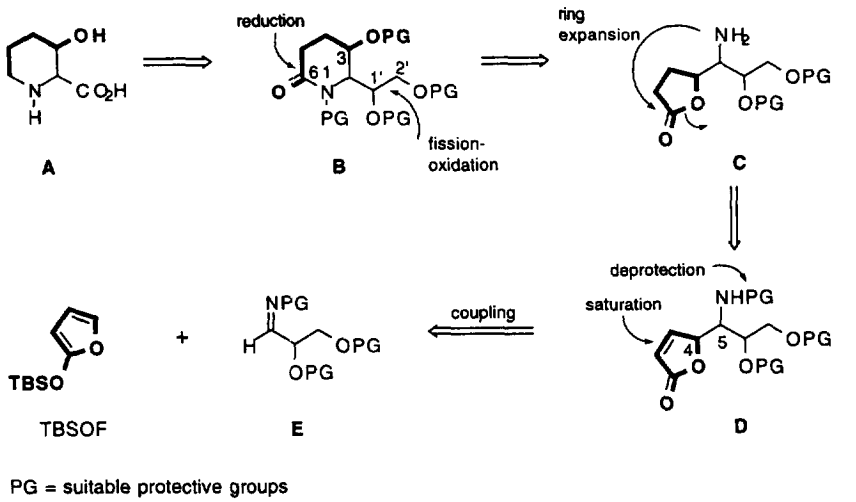
piperidinone **B** by oxidative fission of the C-1′–C-2′ linkage and C-6 carbonyl reduction, is built up via γ-lactone-to-δ-lactam expansion (**C**→**B**). Lactone **C** is obtained by saturation and selective deprotection of butenolide **D**, which is, in turn, available by Lewis acid-catalyzed coupling of 2-[(*tert*-butyldimethylsilyl)oxy]furan (hereafter TBSOF) with properly protected glyceraldehyde imine **E**. Accordingly, while TBSOF represents the nucleophilic synthon supplying for the hydroxylated C-3–C-6 portion of the pipecolic acid structure (bold lines in Scheme 1), glyceraldehyde imine **E** may be viewed as a (chiral) glycine cation surrogate.[5]



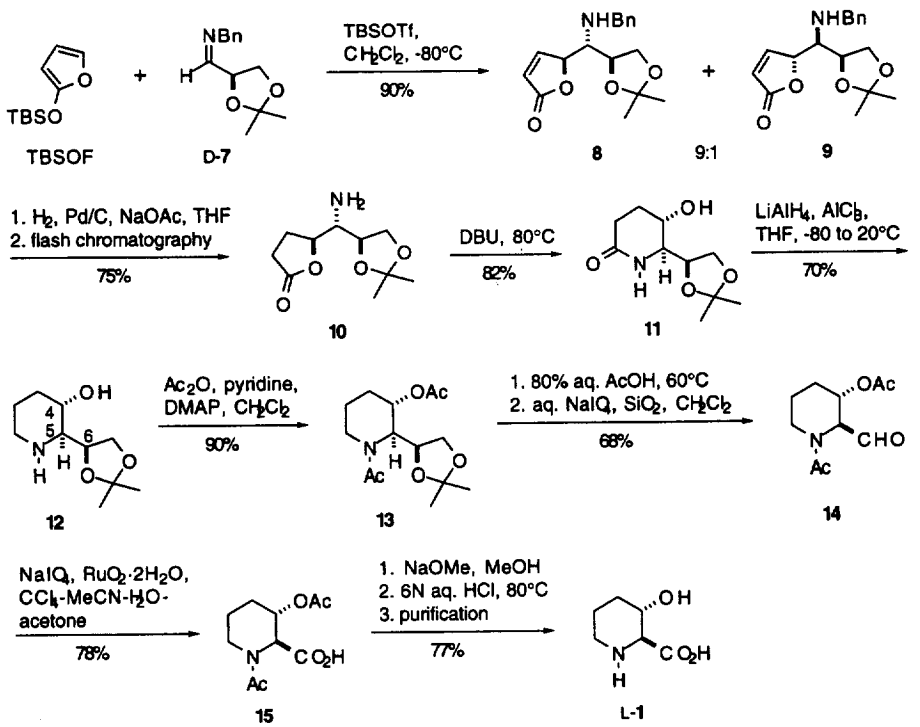
Scheme 1.

The asymmetric induction issue—i.e. the selective formation of a given structurally defined isomer—can be addressed by controlling the stereochemical course of the crucial coupling step (TBSOF+**E**→**D**), wherein two stereocenters (C-4 and C-5) are newly generated. Thus, the *syn* versus *anti* configuration of the C-4 and C-5 carbon atoms within **D** will dictate the relative stereodisposition of the carboxyl and hydroxyl components embodied in **A** (*cis* versus *trans*), while the single chiral element within **E** will control the absolute configuration of the target (facial diastereoselection).

Synthesis of trans-*3-hydroxypipecolic acids* L-*1 and* D-*1*

The stereoselective synthesis of pipecolic acid L-**1** commenced with the key coupling reaction between 2-silyloxyfuran TBSOF and 2,3-*O*-isopropylidene-D-glyceraldehyde *N*-benzyl imine (D-**7**) (Scheme 2).[6] Treatment of freshly prepared imine D-**7** with TBSOF in the presence of 0.5–0.6 molar equivalents of TBSOTf[7] in CH_2Cl_2 at −80°C gave rise to 4,5-*anti*-5,6-*anti*-configured butenolide **8** as the predominant isomer, along with a small amount of the 4,5-*anti*-5,6-*syn*-disposed diastereoisomer **9**[8] (90:10 dr, 90% combined yield). The stereochemical assignment of the major lactone **8** was only tentative at this point, based on chiroptical considerations,[9] but its structure is firmly ascertained at a later stage of the synthesis (*vide infra*). Conveniently, the 9:1 crude mixture of butenolides **8** and **9** was subjected to catalytic hydrogenation (Pd/C, THF, NaOAc), which provided saturation of the double bond with concomitant removal of the benzyl protective group. There was obtained crystalline amino lactone **10** in 75% yield, after easy flash chromatographic purification.

At this juncture, furanone-to-piperidinone expansion had to be performed, and this was readily achieved by treating compound **10** with neat 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at 80°C. Pure piperidinone **11** was obtained in a good 82% yield, which was cleanly transformed to crystalline piperidine **12** (70% yield) by alane reduction at −80°C ($LiAlH_4$, $AlCl_3$, THF).[10]



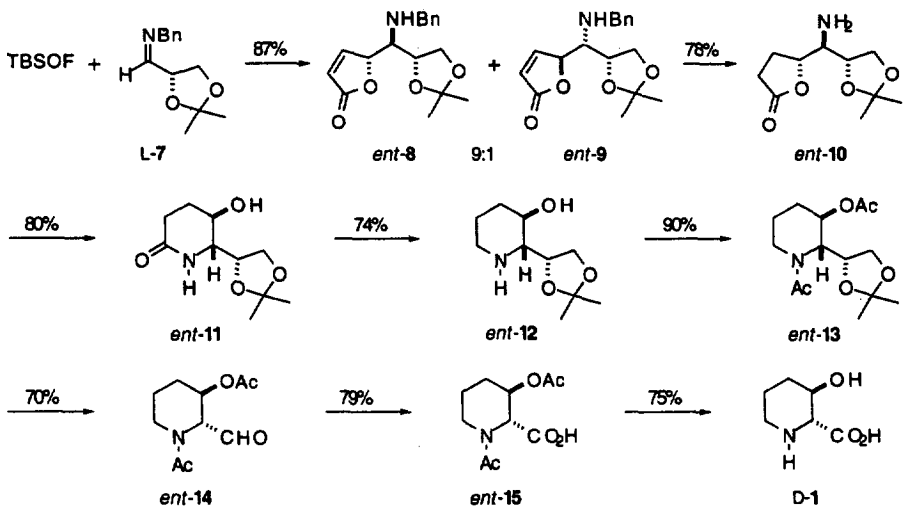
Scheme 2.

The assignment of the relative *trans*-disposition of the substituents at the C-4 and C-5 positions within **12** followed from ^{1}H NMR spectral analysis that showed a diagnostic coupling constant between the H-4 and H-5 protons ($J_{4,5}$=8.8 Hz), thus confirming a *trans*-diaxial configuration for these nuclei. Unambiguous relative and absolute configuration of **12** was confirmed by a single crystal X-ray analysis (*vide infra*), thus corroborating the structures of all the related products in Scheme 2.

Having the hydroxylated piperidine moiety at hand, all that remained was the unmasking of the side diol appendage to a carboxylic function. Thus, protection of both NH and OH groups in **12** was first carried out by acetylation (Ac_2O, pyridine, DMAP), furnishing *N,O*-bis-acetylated compound **13** in 90% yield. Notably, the ^{1}H and ^{13}C NMR spectra in $CDCl_3$ at room temperature showed compound **13** to be a 1:1 mixture of two isomeric components, probably arising from amide isomerism.

Fully protected piperidine **13** was readily transformed into aldehyde **14** by a two-step procedure involving acidic deprotection (80% aq. AcOH, 60°C), followed by aqueous sodium periodate oxidation (68% yield for the two steps to **14**). Crude aldehyde **14** was directly oxidized to protected pipecolic acid **15** ($RuO_2 \cdot 2H_2O$, solid $NaIO_4$, 78% yield), which was finally converted to pipecolic acid L-**1** by a two-step deprotective protocol involving NaOMe treatment in methanol to furnish a mono *N*-acetyl intermediate, followed by exposure to 6 N aq. HCl at 80°C and chromatographic purification. (2*S*,3*S*)-3-Hydroxypipecolic acid (L-**1**) was recovered as an off-white solid material (mp 230–238°C, decomp.) in 77% yield from **15**, which corresponds to 14% overall yield for the entire ten-step sequence from D-**7**.

Very conveniently, (2*R*,3*R*)-3-hydroxypipecolic acid D-**1** was prepared by starting from 2,3-*O*-isopropylidene-L-glyceraldehyde *N*-benzyl imine L-**7** and TBSOF through intermediates *ent*-**8**–*ent*-**15** by just paralleling the synthetic procedure described above for its enantiomer L-**1** (Scheme 3). There was obtained pipecolic acid D-**1** (D-series) as a white solid material (mp 234–239°C, decomp.) in 15% overall yield for the whole sequence from L-**7**.



Scheme 3. (See Scheme 2 for reaction conditions.)

Mechanistic considerations

The diastereoselective behavior of the opening move in this synthesis, i.e. the vinylogous Mukaiyama-aldol addition[11] of TBSOF to chiral imine derivatives, solely dictates the generation of all the stereocenters within the target compounds and the related intermediates. Irrespective of the nature of the Lewis acid employed, the reaction strongly favored the formation of the 4,5-*anti*-5,6-*anti*-configured adducts (**8** and *ent*-**8**), being the optimal conditions observed when a catalytic amount of TBSOTf (0.5–0.6 equivalents) was used.[7]

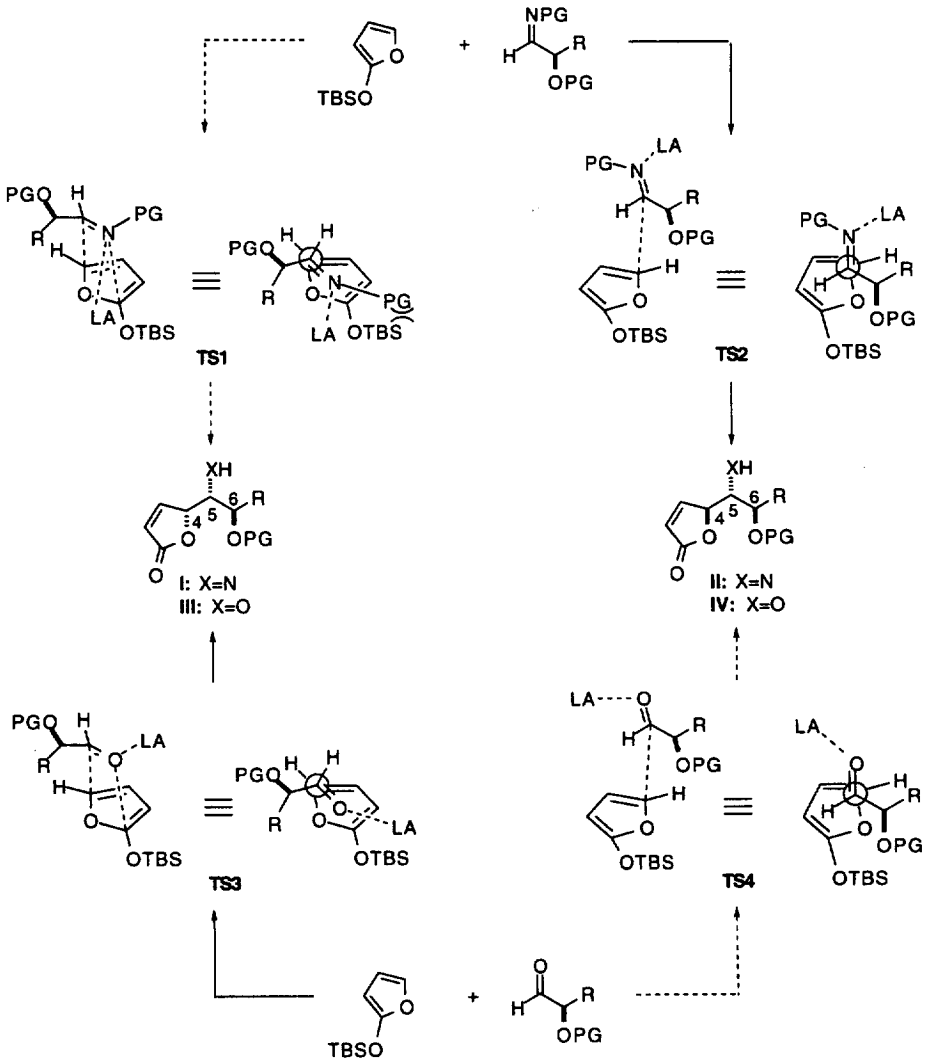
Of note, this behavior markedly differs from the general outcome of the Lewis acid-assisted reactions involving TBSOF (and related silyloxy furan, pyrrole, and thiophene reagents) and aldehyde electrophiles, which lead to 4,5-*syn*-5,6-*anti*-configured adducts, preferentially.[6] Although a complete rationale accounting for the observed stereochemical behavior is hard to construct, one can formulate a mechanistic path as that outlined in Scheme 4, accounting for the preferential formation of the 4,5-*anti*-adducts **II** (for α-alkoxyimine derivatives) and 4,5-*syn*-adducts **III** (for α-alkoxyaldehydes).

For aldehydes, a Diels–Alder like transition state **TS3** leading to compounds **III** seems to be preferred over **TS4** (open chain), whilst for imine derivatives, an open chain model of type **TS2**, giving rise to adducts **II**, appears more favorable over **TS1**. Likely, **TS2** seems to be stabilized over **TS1** due to diminished steric congestion, whereas **TS3** is advantaged over **TS4** owing to favorable orbital overlapping and less severe congestion. Instead, the facial diastereoselection governing the 5,6-relative configuration of the adducts is substrate-independent, with 5,6-*anti*-configured adducts (Felkin type approach) favored using both aldehyde and imine substrates.

X-Ray structural analysis

An ORTEP plot of compound **12** with its numbering scheme is displayed in Figure 2. The absolute configuration of the stereocenters has been assigned as 2*S*,1*S*,6*S* (crystallographic numbering; 4*S*,5*S*,6*S* elsewhere) based on the chirality of the related precursor D-**7**. The overall conformation of the molecule is determined by one intramolecular interaction[12a,b] between C6–H6 and O1 [2.910(8) Å] and by an intramolecular hydrogen bond N1-H1N···O2 [2.835(7) Å].

The orientation of the O1-H group with respect to the dioxolane ring is shown by the following torsion angle C6C1C2O1=54.4(7)°. The H1···H2, H6···H1A and H1A···H1N distances are 2.61, 2.31, and 2.23 Å, respectively, with torsion angles of −175.7, 60.7, and 71.4° in antiperiplanar, synclinal, and synclinal conformation. As expected, the arrangement of H2 and H1A atoms is *trans*-



Scheme 4.

diaxial with a torsion angle H2-C2-C1-H1A of 178.5°, in agreement with the ^{1}H NMR measurements (*vide supra*).

The piperidine ring is in the $^1C_4$ chair conformation [puckering parameters: q_2=0.056(7) Å, q_3=−0.563(7) Å, ϕ_2=174.1(7.0)°, Q=0.565(7) Å, Θ_2=174.3(7)°],[12c] as unprotected nojirimycin[12d] and other simple piperidine derivatives.[12e] The dioxolane ring shows a conformation closest to twist with a twofold axis passing through the C6 atom [puckering parameters: q_2=0.294(6) Å, ϕ_2=78.3(1.2)°].[12c,f] The dihedral angle between the dioxolane ring and the mean plane of the piperidine is 96.5(2)°. Bond lengths and angles in the piperidine and dioxolane rings are in good agreement with the values reported for similar moieties.[12e,g] The packing is mainly governed by O1-H1···N1(x,y,z+1) hydrogen bond of 3.033(8) Å with the O-H···N angle of 165.3(4)°. A weak interaction C7-H7B···O1(x,y,z-1)=3.47(1) Å is also present, so chains of molecules run along the crystallographic *c* axis (Figure 3).

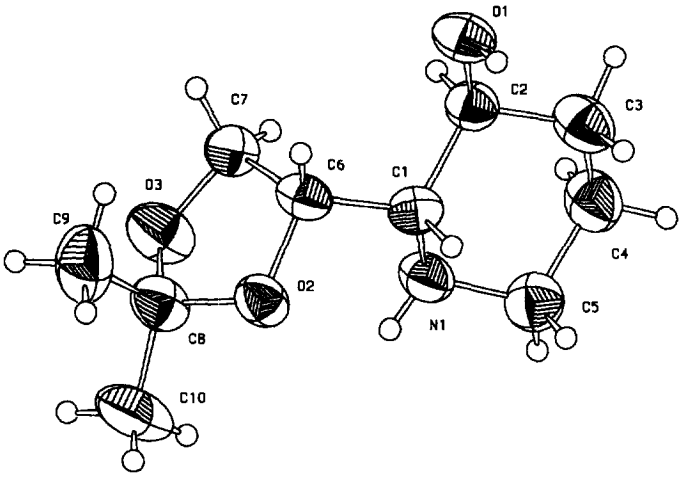


Figure 2. ORTEP view of the molecule **12** in its correct absolute configuration showing the atomic numbering scheme. Thermal ellipsoids enclose 50% of probability and the hydrogen atoms are drawn with an arbitrary diameter.

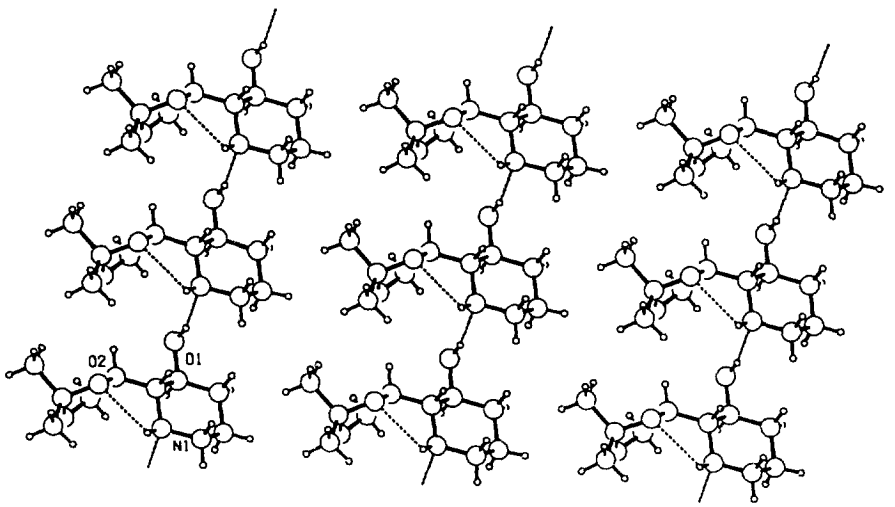


Figure 3. Projection of the structure on the (010) plane showing the most significant hydrogen bonds.

Conclusion

Practical methodology for the synthesis of enantiopure (2*S*,3*S*)- and (2*R*,3*R*)-3-hydroxypipecolic acids L-**1** and D-**1** has been presented, that exploits glyceraldehyde imines D-**7** and L-**7** as synthetic equivalents of chiral α-glycine cation. The highly diastereoselective and regioselective character of the key operation, namely the vinylogous aldol addition of silyloxy furan TBSOF to imines **7**, dictated the formation of *trans*-disposed 3-hydroxy pipecolic acids, while imparting chirality into the targets and related intermediates. The high yields of each reaction step and the availability of almost all the isolated intermediates as crystalline solids render this protocol an efficient way to access these rare amino acids on both small and large scales.

The potentiality of the chemistry here disclosed overrides the production of simple pipecolic acids of type **1**, being certain synthetic intermediates envisioned as valuable building blocks en route to a variety of multifunctional structures of biological relevance. As an example, proper dihydroxylation

of the double bond within **8** could secure preparation of piperidinose sugars of the nojirimycin family, while enolate-driven α-alkylation of **11** would pave the way to acyclic hydroxyethylene dipeptide isosteres, a promising progeny of aspartic protease inhibitors.

Experimental

General procedures

Melting points were determined (uncorrected) on an Electrothermal apparatus. Optical rotations were measured on a Perkin-Elmer 241 polarimeter and are given in units of 10^{-1} deg cm^2 g^{-1}. The ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded using a Bruker AC-300 spectrometer. Chemical shifts are quoted in parts per million (δ) relative to tetramethylsilane (0.0 ppm) or to the specific solvent as an internal standard, and coupling constants (*J*) are measured in hertz (Hz). Analytical thin-layer chromatography was carried out on Merck Kieselgel 60 F_{254} glass-backed plates. Flash chromatography was performed on 32–63 μm silica gel (ICN Biomedicals), using the reported solvent mixtures. The compounds were visualized by dipping the plates in an aqueous H_2SO_4 solution of cerium sulfate and ammonium molybdate, followed by heating. All the solvents were dried according to common methods and distilled before use. All the reactions were carried out under an oxygen-free nitrogen atmosphere. Elemental analyses were performed by the Microanalytical Laboratory of University of Sassari.

Materials

2-[(*tert*-Butyldimethylsilyl)oxy]furan (TBSOF) was prepared on a multigram scale from 2-furaldehyde (Aldrich) according to a described protocol.[6d] 2,3-*O*-Isopropylidene-D- and L-glyceraldehyde *N*-benzylimines (D-**7** and L-**7**) were obtained by reacting benzylamine (Aldrich) and 2,3-*O*-isopropylidene-D- and L-glyceraldehyde, respectively, in CH_2Cl_2, in the presence of anhydrous $MgSO_4$. The crude materials were used as such in the subsequent coupling processes.

*5-(N-Benzylamino)-6,7-O-isopropylidene-2,3,5-trideoxy-*D-ribo-*hept-2-enonic acid 1,4-lactone* **8** *and 5-(N-benzylamino)-6,7-O-isopropylidene-2,3,5-trideoxy-*D-lyxo-*hept-2-enonic acid 1,4-lactone* **9**

To a stirring solution of imine D-**7** (4.55 g, 20.64 mmol) in anhydrous CH_2Cl_2 (80 mL) under nitrogen atmosphere cooled to −80°C were sequentially added TBSOF (4.09 g, 20.6 mmol) and TBSOTf (2.37 mL, 10.32 mmol), and the resulting mixture was allowed to react for 3 h at −80°C. The reaction was then quenched at the same temperature by the addition of saturated aqueous $NaHCO_3$ and, after ambient temperature was reached, the mixture was extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were washed with brine (2×15 mL), dried with $MgSO_4$, filtered, and evaporated to give an oily yellowish crude residue (5.64 g, 90%), whose ^{1}H NMR spectrum revealed the presence of a ~9:1 mixture of isomeric **8** and **9**. While almost all the recovered residue was used as such in the subsequent hydrogenation step, a small portion (0.60 g) was subjected to flash chomatographic purification (hexanes/EtOAc 60:40), in order for the predominant lactone **8** to be fully characterized. There was obtained pure **8** (498 mg, 83%), along with 54 mg (9%) of the isomeric product **9**.

Compound **8**: white crystals, mp 66–67°C; R_f=0.37 (hexanes/EtOAc 60:40); $[\alpha]_D^{20}$=−35.2 (c=0.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53 (dd, *J*=5.8, 1.6 Hz, 1H), 7.28 (m, 5H), 6.16 (dd, *J*=5.8, 2.1 Hz, 1H), 5.35 (app. quint., *J*=2.1 Hz, 1H), 4.07 (dd, *J*=8.3, 6.3 Hz, 1H), 3.95 (m, 1H), 3.7–3.9 (m, 4H), 3.08 (dd, *J*=7.5, 4.2 Hz, 1H), 1.39 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 154.3, 139.5, 128.1 (5C), 122.2, 109.6, 83.6, 75.5, 67.5, 61.2, 52.9, 26.5, 25.0. Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.04; H, 7.15; N, 4.50.

*5-(*N*-Benzylamino)-6,7-*O*-isopropylidene-2,3,5-trideoxy-*L*-ribo-hept-2-enonic acid 1,4-lactone* ent-***8*** *and 5-(*N*-benzylamino)-6,7-*O*-isopropylidene-2,3,5-trideoxy-*L*-lyxo-hept-2-enonic acid 1,4-lactone* ent-***9***

The title compounds were prepared according to the synthetic procedure described for their enantiomers **8** and **9**, by employing 2,3-*O*-isopropylidene-L-glyceraldeyde *N*-benzylimine L-**7** in place of D-**7**. Starting with TBSOF (3.57 g, 18.0 mmol), there were obtained 4.8 g (87%) of a crude oily residue containing a 9:1 mixture of *ent*-**8** and *ent*-**9**, which was used as such in the next hydrogenation step. A small amount of this material (0.6 g) was flash chromatographed (hexanes/EtOAc 60:40), furnishing 450 mg (75%) of pure *ent*-**8**, along with 50 mg (8%) of pure *ent*-**9**.

Compound *ent*-**8**: white crystals, mp 64–65°C; R_f=0.37 (hexanes/EtOAc 60:40); $[\alpha]_D^{20}$=+36.0 (c=0.8, $CHCl_3$); The ^1H NMR and ^{13}C NMR spectra coincided with those of its enantiomer **8**. Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.34; H, 7.07; N, 4.56.

*5-Amino-6,7-*O*-isopropylidene-2,3,5-trideoxy-*D*-ribo-heptonic acid 1,4-lactone* ***10***

To a stirring solution of crude material **8+9** (5.0 g, 16.48 mmol) in anhydrous THF (150 mL) was added 10% Pd on carbon (0.5 g) and a small amount of sodium acetate (120 mg) at room temperature. The reaction vessel was evacuated and thoroughly purged with hydrogen (three times), and the resulting heterogeneous mixture was stirred under a balloon of hydrogen for 24 h. After hydrogen evacuation, the catalyst was filtered off, and the filtrate was concentrated under vacuum to afford a crude oily residue that was subjected to flash chromatographic purification (EtOAc/MeOH 90:10). Pure amino lactone **10** (2.7 g) was recovered in 75% yield as a white crystalline solid: mp 62–65°C, R_f=0.3 (EtOAc/MeOH 90:10); $[\alpha]_D^{20}$=+19.1 (c=0.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.59 (ddd, *J*=8.0, 7.3, 4.7 Hz, 1H), 4.07 (dd, *J*=7.7, 6.2 Hz, 1H), 3.99 (ddd, *J*=6.9, 6.2, 5.9 Hz, 1H), 3.88 (dd, *J*=7.7, 5.9 Hz, 1H), 3.24 (dd, *J*=6.9, 4.7 Hz, 1H), 2.54 (m, 2H), 2.21 (m, 2H), 2.01 (bs, 2H), 1.40 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.9, 109.2, 81.0, 75.6, 66.4, 54.8, 28.5, 26.4, 25.0, 22.1. Anal Calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51. Found: C, 55.92; H, 8.07; N, 6.40.

*5-Amino-6,7-*O*-isopropylidene-2,3,5-trideoxy-*L*-ribo-heptonic acid 1,4-lactone* ent-***10***

Saturated amino lactone *ent*-**10** was prepared from crude mixture *ent*-**8**+*ent*-**9** (4.2 g, 13.84 mmol), by adopting the above hydrogenation procedure to **10**. After flash chromatographic purification (EtOAc/MeOH 90:10) there were obtained 2.3 g (78%) of pure *ent*-**10** as white crystals: mp 62–63°C; R_f=0.28 (EtOAc/MeOH 90:10); $[\alpha]_D^{20}$=−18.5 (c=0.5, $CHCl_3$). The ^1H and ^{13}C NMR spectra coincided with those reported for its enantiomer **10**. Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51. Found: C, 55.89; H, 7.79; N, 6.35.

*5-Amino-6,7-*O*-isopropylidene-2,3,5-trideoxy-*D*-ribo-heptonic acid 1,5-lactam* ***11***

2.7 g (12.5 mmol) of amino lactone **10** were dissolved in 10 mL of DBU and the resulting mixture was warmed to 80°C for 4 h. The solution was then concentrated under vacuum leaving a brown residue that was purified by flash chromatography eluting with EtOAc/MeOH (75:25). Pure lactam **11** was obtained (2.2 g, 82%) as a white crystalline solid: mp 110–113°C; R_f=0.6 (EtOAc/MeOH 75:25); $[\alpha]_D^{20}$=+22.3 (c=0.8, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.47 (bs, 1H), 4.50 (bs, 1H), 4.23 (app. q, *J*=6.4, 6.3, 6.1 Hz, 1H), 4.06 (dd, *J*=8.4, 6.4 Hz, 1H), 3.79 (dd, *J*=8.4, 6.3 Hz, 1H), 3.75 (m, 1H), 3.42 (td, *J*=6.5, 1.4 Hz, 1H), 2.46 (dt, *J*=18.0, 5.8 Hz, 1H), 2.29 (ddd, *J*=18.0, 9.5, 6.3 Hz, 1H), 1.98 (m, 1H), 1.86 (m, 1H), 1.41 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 109.5, 76.3, 65.8, 65.2, 59.4, 28.1, 27.4, 26.2, 24.8. Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51. Found: C, 55.74; H, 8.02; N, 6.60.

*5-Amino-6,7-*O*-isopropylidene-2,3,5-trideoxy-*L*-ribo-heptonic acid 1,5-lactam* ent-***11***

The title compound was prepared employing 2.3 g (10.68 mmol) of γ-lactone *ent*-**10** by following the procedure described for its enantiomer **11**. There were obtained 1.84 g (80%) of pure lactam *ent*-**11** as a white crystalline solid: mp 108–110°C; R_f=0.6 (EtOAc/MeOH 75:25); $[\alpha]_D^{20}$=−20.8 (c=0.8,

$CHCl_3$). The ^1H and ^{13}C NMR spectra coincided with those of its enantiomer **11**. Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51. Found: C, 55.64; H, 8.09; N, 6.38.

6,7-O-Isopropylidene-1,2,3,5-tetradeoxy-1,5-imino-D-ribo-*heptitol* ***12***

To a reaction vessel containing anhydrous $AlCl_3$ (2.0 g, 15.33 mmol) cooled to 0°C under a nitrogen atmosphere, were added 60 mL of dry THF and the resulting colorless solution was stirred at the same temperature for 5 min. Lithium aluminium hydride (46.0 mL of a 1.0 M solution in THF, 46.0 mmol) was then added, and a vigorous bubbling was observed. The colorless AlH_3 solution so obtained was warmed to room temperature and allowed to stir for 20 min, after which time was recooled to −80°C. A pre-cooled (−80°C) solution of lactam **11** (2.2 g, 10.22 mmol) in dry THF (60 mL) was added via syringe to the above alane solution and the resulting cloudy mixture was stirred at −80°C for 1 h, warmed to 20°C, and stirred an additional 20 min. The colorless solution so obtained, once recooled to 0°C, was quenched with MeOH and the resulting slurry was thoroughly extracted with EtOAc (5×30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuum to furnish a colorless crystalline residue that was purified by flash chromatography (EtOAc/MeOH 70:30) providing 1.44 g (70%) of piperidine **12** as a white crystalline solid: mp 112–115°C; R_f=0.32 (EtOAc/MeOH 70:30); $[\alpha]_D^{20}$=+28.1 (c=0.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.12 (app. q, *J*=6.3 Hz, 1H), 4.06 (dd, *J*=7.7, 6.3 Hz, 1H), 3.90 (dd, *J*=7.7, 6.3 Hz, 1H), 3.36 (ddd, *J*=10.3, 8.8, 4.6 Hz, 1H), 2.93 (dquint, *J*=12.3, 2.0 Hz, 1H), 2.47 (td, *J*=12.3, 3.1 Hz, 1H), 2.45 (dd, *J*=8.8, 6.6 Hz, 1H), 2.33 (bs, 2H), 2.03 (m, 1H), 1.65 (m, 1H), 1.40 (s, 3H), 1.33 (s, 3H), 1.1–1.3 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 111.9, 78.8, 67.4, 63.6, 55.2, 45.5, 33.0, 29.6, 26.3, 25.2. Anal Calcd for $C_{10}H_{19}NO_3$: C, 59.68; H, 9.52; N, 6.96. Found: C, 59.70; H, 9.46; N, 6.90.

6,7-O-Isopropylidene-1,2,3,5-tetradeoxy-1,5-imino-L-ribo-*heptitol* ent-***12***

The title compound was prepared according to the above procedure to **12**, by employing 1.84 g (8.55 mmol) of *ent*-**11**. Piperidine *ent*-**12** was recovered (1.28 g, 74%) as a white crystalline solid: mp 114–116°C; R_f=0.32 (EtOAc/MeOH 70:30); $[\alpha]_D^{20}$=−27.0 (c=0.3, $CHCl_3$). The ^1H and ^{13}C NMR spectra were coincident with those of its enantiomeric counterpart **12**. Anal. Calcd for $C_{10}H_{19}NO_3$: C, 59.68; H, 9.52; N, 6.96. Found: C, 59.82; H, 9.67; N, 6.79.

4,5-(O,N-Diacetyl)-6,7-O-isopropylidene-1,2,3,5-tetradeoxy-1,5-imino-D-ribo-*heptitol* ***13***

To a solution of piperidine **12** (1.0 g, 4.96 mmol) in dry CH_2Cl_2 (50 mL) under nitrogen atmosphere were sequentially added pyridine (2.4 mL, 29.8 mmol), acetic anhydride (1.87 mL, 19.87 mmol), and a catalytic amount of DMAP (50 mg). The mixture was stirred at room temperature for 2 h, quenched with aqueous saturated $NaHCO_3$ solution, and extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuum to provide a crude oily residue that was purified by flash chromatography (EtOAc/MeOH 95:5). There were obtained 1.28 g (90%) of fully protected piperidine **13** as white crystals: mp 85–87°C, R_f=0.4 (EtOAc/MeOH 95:5); $[\alpha]_D^{20}$=−50.1 (c=0.8, $CHCl_3$);^1H NMR (300 MHz, $CDCl_3$, 50:50 mixture of rotamers) δ 5.20 (m, 1H), 4.77 (bd, *J*=7.0 Hz, 0.5H), 4.61 (bd, *J*=9.7 Hz, 0.5H), 4.40 (ddd, *J*=9.2, 5.9, 4.3 Hz, 0.5H), 4.21 (app. q, *J*=6.5 Hz, 0.5H), 3.95 (dd, *J*=8.8, 5.9 Hz, 0.5H), 3.94 (dd, *J*=8.3, 6.5 Hz, 0.5H), 3.82 (dd, *J*=8.5, 6.5 Hz, 0.5 H), 3.78 (bd, *J*=10.0 Hz, 0.5H), 3.72 (dd, *J*=9.0, 4.2 Hz, 0.5H), 3.64 (bd, *J*=14.0 Hz, 0.5H), 3.23 (td, *J*=13.4, 2.8 Hz, 0.5H), 2.52 (td, *J*=13.1, 3.1 Hz, 0.5H), 2.11 (s, 3×0.5H), 2.05 (s, 3×0.5H), 2.04 (s, 3×0.5H), 1.99 (s, 3×0.5H), 1.6–1.9 (m, 4H), 1.48 (s, 3×0.5H), 1.44 (s, 3×0.5H), 1.33 (s, 3×0.5H), 1.31 (s, 3×0.5H); ^{13}C NMR (75 MHz, $CDCl_3$, 50:50 mixture of isomers) δ 171.2, 170.2, 170.0, 168.0, 110.3, 110.0, 74.5, 73.0, 68.0, 67.3, 67.1, 66.4, 59.1, 53.4, 42.9, 37.1, 29.5 (2C), 27.0, 26.3, 25.2 (2C), 24.7, 23.9, 21.8, 21.4, 20.2, 19.2. Anal. Calcd for $C_{14}H_{23}NO_5$: C, 58.93; H, 8.12; N, 4.91. Found: C, 59.01; H, 8.20; N, 4.83.

4,5-(O,N-Diacetyl)-6,7-O-isopropylidene-1,2,3,5-tetradeoxy-1,5-imino-L-ribo-*heptitol* ent-**13**

The above procedure to **13** was followed, by starting with 1.0 g (4.96 mmol) of piperidine *ent*-**12**. There was obtained pure *ent*-**13** (1.3 g, 90%) as a white crystalline solid: mp 86–88°C, R_f=0.4 (EtOAc/MeOH 95:5); $[\alpha]_D^{20}$=+52.0 (c=0.8, $CHCl_3$). The ^1H and ^{13}C NMR spectra were coincident with those of its enantiomeric counterpart **13**. Anal. Calcd for $C_{14}H_{23}NO_5$: C, 58.93; H, 8.12; N, 4.91. Found: C, 59.10; H, 8.28; N, 4.80.

*(2S,3S)-1,3-*N,O-*Diacetyl-2-formyl-3-hydroxypiperidine* **14**

Protected piperidine **13** (1.3 g, 4.55 mmol) was dissolved in 13 mL of 80% aqueous acetic acid and the resulting solution was warmed to 60°C and stirred for 5 h. The solution was then concentrated under vacuum to furnish an oily crude residue that was purified by flash chromatography eluting with EtOAc/MeOH 85:15. There was obtained a pure terminal diol intermediate (804 mg, 72%) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$, 75:25 mixture of isomers) δ 5.42 (m, 0.75H), 5.32 (m, 0.25H), 4.54 (m, 0.25H), 4.50 (bd, *J*=10.5 Hz, 0.75H), 3.95 (m, 0.75H), 3.3–3.8 (m, 5.25H), 3.01 (td, *J*=13.3, 3.2 Hz, 0.75H), 2.49 (td, *J*=13.3, 2.9 Hz, 0.25H), 2.12 (s, 3×0.75H), 2.07 (s, 3×0.25H), 2.01 (s, 3×0.25H), 1.98 (s, 3×0.75H), 1.5–1.9 (m, 4H). The diol was then dissolved in CH_2Cl_2 (25 mL) and treated with a 0.65 M aqueous $NaIO_4$ solution (25 mL) and chromatography grade SiO_2 (20 g). The resulting heterogeneous mixture was vigorously stirred at room temperature for 20 min, after which time the slurry was filtered under suction and the silica thoroughly washed with CH_2Cl_2. The filtrates were evaporated to afford aldehyde **14** (664 mg, 95%) as a colorless oil: R_f=0.5 (EtOAc/MeOH 90:10); $[\alpha]_D^{20}$=−40.9 (c=0.7, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 80:20 mixture of isomers, major isomer) δ 9.51 (s, 1H), 5.48 (m, 1H), 5.42 (m, 1H), 3.80 (bd, *J*=13.4 Hz, 1H), 3.15 (td, *J*=12.0, 3.1 Hz, 1H), 2.19 (s, 3H), 2.02 (s, 3H), 1.5–2.0 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, major isomer) δ 196.9, 170.8, 169.8, 65.0, 61.9, 44.3, 25.8, 20.9, 20.7, 19.8.

*(2R,3R)-1,3-*N,O-*Diacetyl-2-formyl-3-hydroxypiperidine* ent-**14**

The title compound was prepared following the two-step procedure described to transform **13** into **14**, starting with 1.2 g (4.2 mmol) of piperidine *ent*-**13**. There were obtained 628 mg (70%) of aldehyde *ent*-**14** as an oil: R_f=0.5 (EtOAc/MeOH 90:10); $[\alpha]_D^{20}$=+39.0 (c=0.5, $CHCl_3$). The ^1H and ^{13}C NMR spectra coincided with those of its enantiomer **14**.

*(2S,3S)-*N,O-*1,3-Diacetyl-3-hydroxypipecolic acid* **15**

Aldehyde **14** (650 mg, 3.04 mmol) was dissolved in 25 mL of a CCl_4–MeCN–acetone–H_2O solvent mixture (1:1:0.3:1.4 ratio) and treated with 1.0 g of solid $NaIO_4$ and a catalytic amount of $RuO_2 \cdot 2H_2O$ (20 mg). The resulting mixture was stirred at room temperature for 1 h, quenched with propan-2-ol and filtered on a Celite pad. The filtrate was evaporated and the residue was purified by flash chromatography eluting with EtOAc/MeOH/30% aq. NH_3 6:4:0.3 to furnish 543 mg (78%) of protected pipecolic acid **15** as a foamy solid: R_f=0.4 (EtOAc/MeOH/30% aq. NH_3 6:4:0.3); $[\alpha]_D^{20}$=−36.7 (c=0.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 70:30 mixture of isomers, major isomer) δ 7.67 (bs, 1H), 5.39 (m, 1H), 5.09 (m, 1H), 3.65 (bd, *J*=12.8 Hz, 1H), 3.22 (bt, *J*=12.0 Hz, 1H), 2.08 (s, 3H), 1.95 (s, 3H), 1.4–1.9 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, major isomer) δ 173.0, 172.0, 170.8, 69.2, 56.9, 43.8, 25.3, 21.5, 21.2, 21.1. Anal. Calcd for $C_{10}H_{15}NO_5$: C, 52.40; H, 6.60; N, 6.11. Found: C, 52.51; H, 6.49; N, 6.03.

*(2R,3R)-1,3-*N,O-*Diacetyl-3-hydroxypipecolic acid* ent-**15**

The title compound was prepared starting with 600 mg (2.81 mmol) of aldehyde *ent*-**14** according to the procedure described for **15**. There were obtained 510 mg (79%) of protected pipecolic acid *ent*-**15** as a foamy solid: R_f=0.4 (EtOAc/MeOH/30% aq. NH_3 6:4:0.3); $[\alpha]_D^{20}$=+35.9 (c=0.5, $CHCl_3$). The ^1H and ^{13}C NMR spectra coincided with those of its enantiomer **15**. Anal. Calcd for $C_{10}H_{15}NO_5$: C, 52.40; H, 6.60; N, 6.11. Found: C, 52.28; H, 6.70; N, 5.98.

(2S,3S)-3-Hydroxypipecolic acid L-*1*

To a solution of protected pipecolic acid **15** (520 mg, 2.27 mmol) in 30 mL of methanol were added 10 mL of a 1% methanolic NaOMe solution portionwise until complete disappearance of the starting material (about 3 h). The reaction mixture was then concentrated in vacuum to give a crude residue that was purified by flash chromatography eluting with EtOAc/MeOH/30% aq. NH_3 (6:4:0.3). There was obtained a partially *O*-deprotected pipecolic acid intermediate (382 mg, 90%) as a gummy solid: ^{1}H NMR (300 MHz, CD_3OD, 50:50 isomeric mixture) δ 5.05 (m, 0.5H), 4.50 (m, 1H), 4.40 (bd, *J*=12.7 Hz, 0.5H), 4.30 (m, 0.5H), 3.74 (bd, *J*=13.0 Hz, 0.5H), 3.40 (td, *J*=13.0, 3.9 Hz, 0.5H), 2.85 (td, *J*=13.0, 3.0 Hz, 0.5H), 2.14 (s, 3×0.5H), 2.05 (s, 3×0.5H), 1.6–1.8 (m, 2H), 1.3–1.5 (m, 2H).

This intermediate (382 mg, 2.04 mmol) was dissolved in a 6 N aqueous HCl solution (10 mL) and the resulting mixture gradually warmed to 80°C. After being stirred at this temperature for 10 h, the solution was concentrated under vacuum to give a crude residue that was purified by flash chromatography eluting with EtOAc/MeOH/30% aq. NH_3 (5:5:0.7). Pure pipecolic acid L-**1** was recovered (255 mg, 86%) as an off-white solid material: mp 230–238°C (decomp.); R_f=0.32 (EtOAc/MeOH/30% aq. NH_3 5:5:1); $[\alpha]_D^{20}$=+12.9 (c=0.23, 10% aq. HCl) {lit.[4a] $[\alpha]_D^{20}$=+13 (c=0.4, 10% aq. HCl); lit.[4b] $[\alpha]_D^{20}$=+15 (c=0.5, 10% aq. HCl)}; ^{1}H NMR (300 MHz, D_2O) δ 4.05 (ddd, *J*=10.5, 7.2, 3.0 Hz, 1H, H-3), 3.49 (d, *J*=7.2 Hz, 1H, H-2), 3.27(m, 1H, H-6_{eq}), 2.98 (ddd, *J*=12.9, 9.0, 3.3 Hz, 1H, H-6_{ax}), 1.91 (m, 2H, H-4_{eq}, H-5_{eq}), 1.64 (m, 2H, H-4_{ax}, H-5_{ax}); ^{13}C NMR (75 MHz, CD_3OD) δ 176.4, 67.3, 62.9, 43.9, 30.2, 20.1. Anal. Calcd for $C_6H_{11}NO_3$:C, 49.65; H, 7.64; N, 9.65. Found: C, 49.77; H, 7.80; N, 9.52.

(2R,3R)-3-Hydroxypipecolic acid D-*1*

The title compound was prepared by starting with 500 mg (2.18 mmol) of protected pipecolic acid *ent*-**15** by paralleling the two-step procedure described to transform **15** into L-**1**. After chromatographic purification (flash chromatography, EtOAc/MeOH/30% aq. NH_3 5:5:0.7), there was obtained pipecolic acid D-**1** (237 mg, 75%) as a white solid material: mp 234–239°C (decomp.); R_f=0.32 (EtOAc/MeOH/30% aq. NH_3 5:5:1); $[\alpha]_D^{20}$=−13.0 (c=0.2, 10% aq. HCl) {lit.[4a] $[\alpha]_D^{20}$=−14 (c=0.5, 10% aq. HCl)}. The ^{1}H NMR and ^{13}C NMR spectral data were identical to those reported for its enantiomer L-**1**. Anal. Calcd for $C_6H_{11}NO_3$:C, 49.65; H, 7.64; N, 9.65. Found: C, 49.52; H, 7.80; N, 9.77.

Structure determination of compound 12

Crystal data: $C_{10}H_{18}NO_3$, *M*=200.2, triclinic, space group *P*1, *a*=9.769(5), *b*=5.535(2), *c*=5.196(2) Å, α=103.31(1), β=77.68(1), γ=97.28(1)°, *V*=266.2(2) Å^3, *Z*=1, *F*(000)=109, *Dc*=1.249 Mg m^{-3}, μ(Cu-Kα)=7.5 cm^{-1}. The intensity data were collected at room temperature on a Siemens AED diffractometer over a 3–70° θ range; *h*, −11 to 11; *k*, −6 to 6; *l*, 0 to 6, by using the Cu-Kα radiation (λ=1.54178 Å) and θ–2θ scanning. Of the 1012 unique data measured, 589 had $I>2\sigma(I)$ and were used in the subsequent structural solution. The data were corrected for Lorentz and polarization effects, but not for absorption in view of small crystal dimensions (0.43×0.47×0.70 mm). The structural determination was carried out by SIR92.[13a] The structure was then refined by full-matrix least-squares methods (SHELXL-96)[13b] using anisotropic temperature factors for all the non-hydrogen atoms. All H-atoms were calculated at idealized positions with the exception of the hydrogen of the piperidine nitrogen which was located with a difference Fourier map and not refined. At convergence, the discrepancy indices R and wR were 0.066 and 0.154, respectively $(w=1/[\sigma^2(F_o^2)+(0.1360P)^2+0.0P]$ where $P=(\mathrm{Max}(F_o^2,0)+2F_o^2)/3$. Scattering factors for C, H, N and O were taken from the literature.[13c] Molecular-geometry calculations were carried out by using the computer program PARST[13d] and the structure drawing by using the ORTEP and PLUTON program.[13e,f] Lists of refined coordinates,

e.s.d.'s, and thermal parameters obtained from the crystallographic analysis have been deposited at the Cambridge Crystallographic Data Centre (CCDC).

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7. The actual experimental conditions in the coupling reaction resulted after an extensive optimization procedure. Of note, when stoichiometric $BF_3 \cdot OEt_2$ (CH_2Cl_2, −80°C) or catalytic TMSOTf (CH_2Cl_2, −80°C), $InCl_3$ (THF, 0°C), $Yb(OTf)_3$ (CH_2Cl_2, 0°C) were used, a decrease in efficiency and/or diastereoselectivity was observed, being compounds **8** and **9** flanked by two other isomers (diastereomeric ratios ranging from 60:40 to 80:20).
8. When **8** was treated with Et_3N in CH_2Cl_2, no base-promoted interconversion into **9** was observed, thus confirming that these compounds were not epimeric at C-4. The 4,5-*anti*-stereodisposition within **9** was deduced by the ^1H NMR spectrum of an advanced *trans*-configured piperidine intermediate related to compound **12**.
9. As a rule, lactones having 4*R* absolute configuration are dextrorotatory, while those having 4*S* absolute configuration are levorotatory. With few exceptions, this empirical guideline proved widely applicable also to a variety of closely related substances. Casiraghi, G.; Colombo, L.; Rassu, G.; Spanu, P.; Gasparri Fava, G.; Ferrari Belicchi, M. *Tetrahedron* **1990**, *46*, 5807.
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