Bicyclic Compounds Derived from Tartaric Acid and α-Amino Acids (BTAas): Synthesis of New Molecular Scaffolds Derived from the Combination of (*R*,*R*)-Tartaric Acid and L-Serine

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The synthesis of the new *N*-Fmoc-protected dipeptide isoster methyl (1*S*,2*S*,5*S*,6*R*)-2*exo*-hydroxymethyl-7,8-dioxa-3-azabicyclo[3.2.1]octane-6*exo*-carboxylate (BTS) has been achieved, starting from (*R*,*R*)-tartaric acid and *O*-benzyl-L-serine, in 11% overall yield after 9 steps. Interestingly, starting from the same α-amino acid, it was also possible to prepare the 2*endo*-substituted compound, formally derived from the combination of tartaric acid with D-serine. Each compound has a CH_2OH functional group at C-2, which is very useful for greater diversification of the 7,8-dioxa-3-azabicyclo[3.2.1]octane-6-carboxylate (BTAa) dipeptide isosters. The oxidation of the C-2 carbinol group in BTS, moreover, gave rise to a novel, conformationally constrained, α-amino acid that may find application in peptidomimetic synthesis.

Introduction

We have recently reported the synthesis of a new class of γ-amino acids named 7-*B*icycles derived from *T*artaric acid and α-*A*mino *a*cids (BTAas) (Figure 1), obtained by combination of tartaric acid and α-amino acid derivatives.[1,2] These compounds, which can be thought of as dipeptide isosters, are characterized by rigid molecular skeletons and the presence of two side chains at positions 2 and 6, with spatial orientations controlled by the stereochemistry of the reagents. Because of these features, BTAas are useful compounds for the synthesis of peptidomimetics[3−5] by insertion into biologically active peptides, although other applications can be envisioned. Of the 164 different peptide isosters that could arise from the combination of (*R*,*R*)-, (*S*,*S*)-, and *meso*-tartaric acids with glycine and 20 chiral, natural L-amino acids and their D enantiomers, we have so far prepared and used those from glycine, alanine, and phenylalanine, and also those from unnatural phenylglycine.[1,2] We have employed these compounds as monomers for the generation of oligomers[6] and as chiral auxiliaries,[7] and their 6*endo* derivatives as reverse turn inducers in peptide chains.[8]

To expand the scope and applications of BTAas further, we planned syntheses of the *B*icycles derived from (*R*,*R*)-*T*artaric acid and L-*S*erine (BTSs) (Figure 1). Moreover, the free hydroxy group on the serine C-2 side chain can easily be either derivatized or transformed into other functional groups, thus widening the range of compounds obtainable with the same scaffold. For example, oxidation of the 2-hydroxymethyl group to a carboxylic group would produce a new, conformationally constrained, α-amino acid. In this paper we thus report on the synthesis of the BTS molecular scaffold and its transformation into the corresponding α-amino acid.

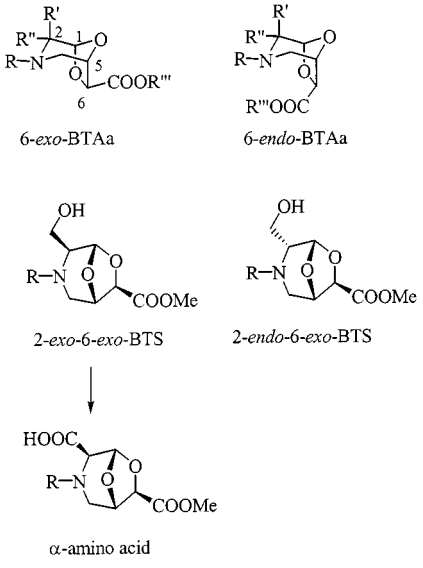

Figure 1. Structure of BTAa and BTS

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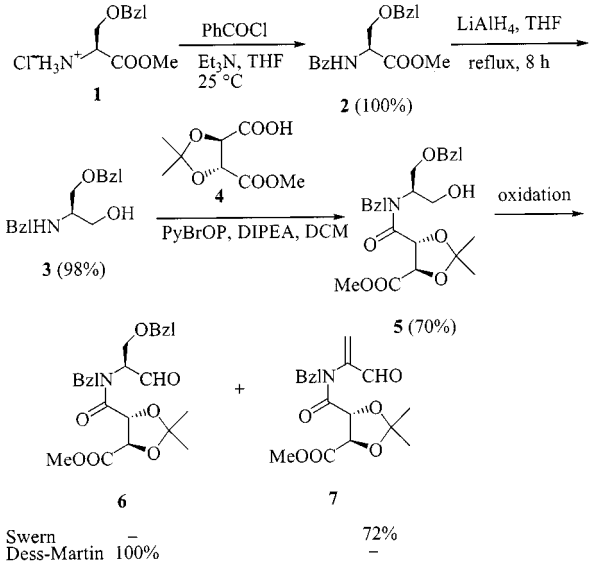
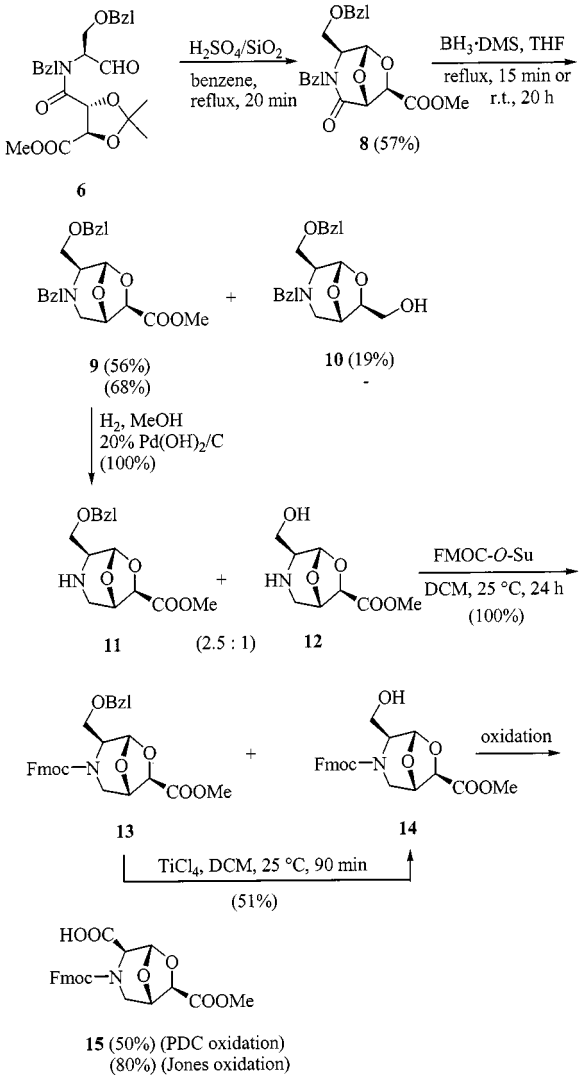
Results and Discussion

According to the synthetic methodology already reported for BTAas,[2] the key intermediate for the synthesis of *N*-Fmoc-BTS is the *O*-protected aldehyde **6** (Scheme 1). We chose benzyl protection for both amino and hydroxy groups in L-serine derivative **2**, because it can, in principle, be simultaneously removed from both groups by a single hydrogenolysis step. Starting from *O*-benzyl L-serine methyl ester hydrochloride **1**, the *N*-Bzl protected amino alcohol **3** was obtained nearly quantitatively after *N*-benzoylation and $LiAlH_4$ reduction. Compound **3** was treated with monomethyl tartrate derivative **4**, in the presence of PyBrOP as a coupling reagent and DIPEA as a base in CH_2Cl_2, to afford amide **5** in 70% yield after chromatography. No epimerization of the stereocenters in **5** occurred during the coupling reaction. Oxidation of **5** to the corresponding aldehyde **6** was troublesome, due to the great instability of this product. We initially carried out the oxidation by a Swern reaction, with DIPEA as a base, but the major product in the crude reaction mixture was the α,β-unsaturated aldehyde **7** in a 4:1 ratio (determined by ^1H NMR analysis) with the desired compound **6**. Abstraction of the α-proton from β-benzyloxy aldehyde **6** during the Swern oxidation should be base-assisted, as already reported for similar aldehydes.[9] Aldehyde **6** could also suffer from acid sensitivity, since no traces of **6** were recovered after an attempt to separate the two aldehydes by chromatography on silica gel, whereas pure **7** was obtained in 72% yield. The best method to prevent the base-assisted elimination appeared to be the use of the Dess−Martin reagent[10] to perform the oxidation and avoidance of the purification of the crude aldehyde. The oxidation of **5** was complete in 30 min at room temperature in CH_2Cl_2, affording aldehyde **6** in sufficiently pure form for the next cyclization step. This was carried out (Scheme 2) in refluxing benzene in the presence of H_2SO_4/SiO_2 as already described (20 min reflux before distilling off half of the solvent).[2] After treatment of the crude reaction mixture with $Na_2S_2O_3$, necessary to remove the residual iodinane from the previous Dess−Martin oxidation, and subsequent chromatography, compound **8** was obtained in 57% yield. Elimination of benzyl alcohol from **6** seems not to occur under the cyclization conditions, since neither the formation of α,β-unsaturated aldehyde **7** nor of its cyclization corresponding products **18** and **19** (see Scheme 4) was observed by ^1H NMR analysis of the crude reaction mixture. No epimerization of the stereocenters occurred in the course of the cyclization, as observed in other cases,[2] and lactam **8** was thus obtained as a single diastereoisomer with the C-4 side chain in *exo* orientation: the presence of a singlet for proton 5-H in the ^1H NMR spectrum was consistent with this stereochemistry for BTAa lactams.[2] Reduction of



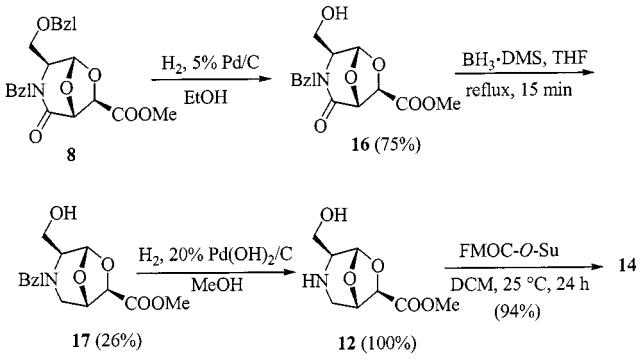
Scheme 1



Scheme 2

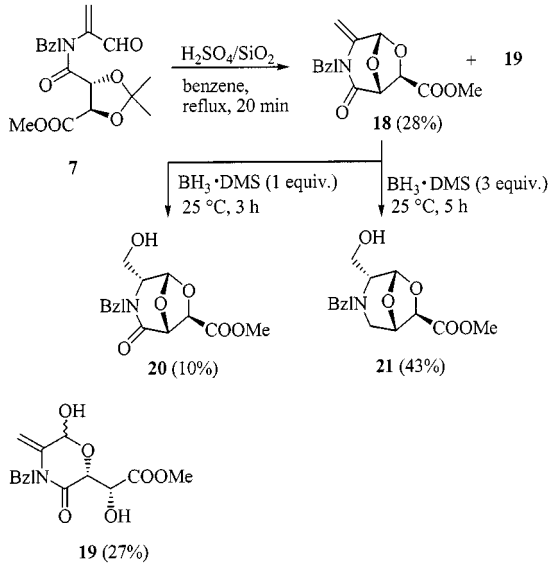
the amide bond (please note that the numbering system of the BTAa skeleton changes when the lactam moiety is reduced to an amine) by BH_3·DMS[11] in refluxing THF (15 min) was not completely selective, since compound **9** (56% after chromatography) was obtained along with the amino alcohol **10** (19%) derived from COOMe reduction. A shorter reduction time improved the selectivity but lowered the degree of conversion into **9**. However, when the reaction was instead carried out at room temperature for 20 h, the selectivity was complete, providing only **9** in 68% yield after chromatographic purification. Complete debenzylation of **9** was attempted by hydrogenolysis over $Pd(OH)_2$. However, all experiments always furnished a 1:2.5 mixture of the desired amino alcohol **12** together with compound **11**, still with the OH protection. It is possible that the initial formation of a certain amount of free amine might poison the Pd catalyst, thus preventing further *O*-Bzl deprotection. Failed or only partial *O*-Bzl deprotection by hydrogenolysis over Pd catalysts in the presence of amines has been reported.[12] The mixture of compounds **11** and **12** was not separated and was directly used for the *N*-Fmoc protection with Fmoc-*O*-succinimide in CH_2Cl_2. After 24 h at room temperature, a 1:2.5 mixture of *N*-Fmoc-protected compounds **14** and **13** was quantitatively obtained. Because of the presence of the *N*-Fmoc protecting group, *O*-debenzylation by hydrogenation had to be avoided, and we therefore tried a procedure reported for the deprotection of polybenzylated sugars, based on the use of Lewis acids such as $SnCl_4$ and $TiCl_4$, in which the coordination of the metal ion to three oxygen atoms is followed by the attack of a chloride anion at the benzylic position.[13] In our case, by carrying out the reaction on the mixture of **13** and **14** (separation of **13** and **14** was avoided) with $TiCl_4$ in CH_2Cl_2 we obtained (after 90 min at room temperature) a complete conversion of the mixture into the target compound **14** (51% yield after chromatography). Finally, oxidation of **14** to the α-amino acid **15** was performed with PDC in DMF, affording **15** in 50% yield after chromatography (the conversion was 87% after 24 h according to ^1H NMR analysis of the crude reaction mixture). A higher yield was obtained when the reaction was carried out with the Jones oxidant, which furnished **15** in 80% yield after 24 h at room temperature.

Because of the difficulties encountered in removing the *O*-benzyl group in the presence of the free amine group, we tried a selective deprotection with lactam **8** (Scheme 3). Thus, hydrogenolysis of **8** in the presence of 5% Pd/C in EtOH afforded OH-deprotected compound **16** in 75% yield after chromatography. *O*-Debenzylation was slower (48 h) when $Pd(OH)_2$ was used as catalyst in MeOH. Unfortunately, the subsequent BH_3 reduction of the lactam to an amino group did not afford the amino alcohol **17** in a yield higher than 26% under the best conditions. Successive deprotection of the N atom by hydrogenolysis in the presence of $Pd(OH)_2$ and protection as the Fmoc derivative afforded target compound **14** in 94% yield. The overall yield of **14** by this sequence was 8%, similar to the yield (11%) obtained by the first methodology.



Scheme 3

The benzyl alcohol elimination observed in the course of the oxidation of **5** to give **7** was exploited in an attempt to synthesize the 2*endo* epimer of BTS, which formally derives from the combination of (*R*,*R*)-tartaric acid and D-serine (Scheme 4). Thus, aldehyde **7** was subjected to the usual cyclization conditions, which afforded the cyclic compound **18** in 28% yield after chromatography, along with the hemiacetal intermediate **19** in 27% yield. The low yield of compound **18** was plausibly due to the presence of an sp^2 C-4 atom, which would make the second cyclization step of intermediate **19**, which decomposes under the reaction conditions, to **18** more difficult. In fact, when **19** was again subjected to the cyclization conditions we observed only 48% conversion into **18** (by ^1H NMR). This result is consistent with that obtained in the cyclization of the phenylglycine derivative analogue,[2] in which the slow cyclization step of the hemiacetal intermediate resulted in its degradation in refluxing toluene. In that case, substitution of toluene with the lower boiling benzene reduced the extent of



Scheme 4

decomposition of this intermediate. In the current case, degradation of α,β-unsaturated aldehyde by heating under acid conditions could also cause loss of starting material.

Finally, selective hydroboration with 1 equiv. of BH_3·DMS for 3 h at room temperature failed to give compound **20** in a yield higher than 10%, because of the low degree of conversion under these conditions. Instead, one-pot BH_3 reduction and hydroboration of **18** with an excess of BH_3·DMS (3 equiv.) for 5 h at room temperature afforded 2*endo*-BTS derivative **21** as a single diastereoisomer in 43% yield after chromatography. The presence of a doublet at δ = 5.86 in the ^{1}H NMR spectrum of **20**, attributable to the 5-H proton, is consistent with the 4*endo* stereochemistry of **20** (and, by extension, of the 2*endo* stereochemistry of **21**) derived from the completely selective *exo* approach of the borane onto the double bond.

Conclusion

In conclusion, we have demonstrated that, starting from (*R*,*R*)-tartaric acid and L-serine, the synthesis of the BTS scaffold with a 2*exo*-CH_2OH functional group is possible by two different methodologies, in acceptable 8 and 11% overall yields after 9 steps. Interestingly, by starting from the same natural L-amino acids, we found that it was possible to prepare the 2*endo*-substituted compound, formally derived from the combination of tartaric acid with the D-serine, by exploiting the α,β-unsaturated aldehyde formed in the Swern oxidation process. The oxidation of the C-2 carbinol group in compound **14** gave rise to a novel, conformationally constrained, α-amino acid **15**, which may find application in peptidomimetic synthesis.

Experimental Section

General: All reactions requiring dry conditions were performed under nitrogen and in anhydrous solvents. Chromatographic separations were performed under pressure on silica gel by flash-column techniques; R_f values refer to TLC carried out on 25-mm silica gel plates (Merck F254), with the same eluent as indicated for the column chromatography. Melting points are uncorrected. IR spectra were recorded with a Perkin−Elmer 881 spectrophotometer in $CDCl_3$ solution. ^{1}H NMR (200 MHz) and ^{13}C NMR (50 MHz) spectra were recorded with a Varian XL 200 instrument in $CDCl_3$ solution. Mass spectra were carried out by EI at 70 eV on 5790A-5970A Hewlett−Packard and QMD 1000 Carlo Erba instruments. Electron-Spray Mass Spectra were recorded with a PE SCIEX API 365 instrument. Microanalyses were carried out with a Perkin−Elmer 2400/2 elemental analyzer. Optical rotations were determined with a JASCO DIP-370 instrument.

Methyl (2*S*)-2-Amino-3-benzyloxypropanoate Hydrochloride (1):[14] HCl (37%, 4.2 mL) was added dropwise at 0 °C to a solution of *O*-benzyl-L-serine (5.0 g, 25.6 mmol) in 2,2-dimethoxypropane (25 mL) and the mixture was stirred at room temperature for 48 h. Evaporation of the solvent gave a crude product, which was recrystallized from MeOH/Et_2O at 0 °C. Pure **1** (5.36 g, 85%) was obtained as a white solid. M.p. 164−166 °C. $[\alpha]_D^{20}$ = +6.9 (*c* = 1.00, MeOH) (ref.[14] $[\alpha]_D$ = +6.9). ^{1}H NMR (DMSO): δ = 7.36−7.30 (m, 5 H, OCH_2*Ph*), 4.53 (AB, *J* = 6.1 Hz, 2 H, OCH_2Ph), 4.34 (t, *J* = 4.0 Hz, 1 H, 2-H), 3.85 (d, *J* = 4.0 Hz, 2 H, 3-H_2), 3.73 (s, 3 H, COO*Me*), 3.36 (br, 2 H, NH_3^+).

Methyl (2*S*)-2-(Benzoylamino)-3-benzyloxypropanoate (2): Et_3N (4.1 mL, 29.8 mmol) and benzoyl chloride (2.1 mL, 18.1 mmol) were slowly added at 0 °C under nitrogen to a solution of **1** (3.67 g, 14.9 mmol) in dry THF (27 mL). The mixture was stirred at room temperature for 15 h. Brine (10 mL) was added to this solution, and the aqueous layer was extracted with Et_2O and CH_2Cl_2 and dried with Na_2SO_4. After evaporation of the solvent, compound **2** (5.0 g) was obtained as a yellow oil, used in the next step without purification. ^{1}H NMR ($CDCl_3$): δ = 7.79−7.74 (m, 2 H, CH_{meta}), 7.51−7.32 (m, 3 H, CH_{ortho} and CH_{para}), 7.29−7.21 (m, 5 H, OCH_2*Ph*), 6.99 (br. d, *J* = 7.8 Hz, 1 H, N*H*), 4.92 (dt, *J* = 7.8, 3.0 Hz, 1 H, 2-H), 4.49 (AB, *J* = 6.3 Hz, 2 H, OCH_2Ph), 3.95 (dd, *J* = 10.0, 3.0 Hz, 1 H, 3-H), 3.76 (dd, *J* = 10.0, 3.0 Hz, 1 H, 3-H), 3.72 (s, 3 H, COO*Me*).

(2*R*)-(+)-2-(*N*-Benzylamino)-3-benzyloxy-1-propanol (3):[15] A solution of **2** (5.0 g, 15.9 mmol) in dry THF (30 mL) was added dropwise at 0 °C and under nitrogen to a suspension of $LiAlH_4$ (2.1 g, 55.3 mmol) in dry THF (40 mL). The mixture was refluxed for 8 h, and was then stirred at room temperature overnight. A solution of KOH (0.4 N, 4 mL) was then slowly added to the mixture, cooled with an ice bath, and after 5 min, 8 mL of H_2O were added and the suspension was refluxed for 30 min. The hot reaction mixture was filtered through a Celite layer and diluted with CH_2Cl_2, and the organic phase was separated and dried with Na_2SO_4. After evaporation of the solvent, compound **3** (4.23 g, 98%) was obtained as a yellow oil. $[\alpha]_D^{20}$ = +12.9 (*c* = 1.40, $CHCl_3$) (ref.[15] $[\alpha]_D$ = +13.3). ^{1}H NMR ($CDCl_3$): δ = 7.36−7.26 (m, 10 H, 2 × *Ph*), 4.48 (s, 2 H, OCH_2Ph), 3.79 (s, 2 H, NCH_2Ph), 3.76−3.44 (m, 4 H, 1-H_2, 3-H_2), 2.92 (m, 1 H, 2-H).

Methyl (2*R*,3*R*)-(−)-*N*-Benzyl-*N*′-[(1*R*)-1-benzyloxymethyl-2-hydroxyethyl]-2,3-di-*O*-isopropylidenetartramate (5): A solution of **4** (2.94 g, 14.4 mmol) in dry CH_2Cl_2 (46 mL), PyBrOP (6.72 g, 14.4 mmol), and DIPEA (5.0 mL, 28.8 mmol) were added at 0 °C under nitrogen to a solution of **3** (3.90 g, 14.4 mmol) in anhydrous CH_2Cl_2 (50 mL; CH_2Cl_2 was filtered through a short pad of Na_2CO_3 just before being used). The mixture was stirred at 0 °C for 20 min and then at room temperature overnight. After evaporation of the solvent, the oil obtained was dissolved in EtOAc and filtered through a short layer of Celite. The solution was washed with aqueous 5% $KHSO_4$, 5% $NaHCO_3$, and brine, and dried with Na_2SO_4. After evaporation of the solvent, the crude product was purified by chromatography (EtOAc/petroleum ether, 1:2, R_f = 0.1), to yield **5** (4.61 g, 70%) as a yellow oil. $[\alpha]_D^{20}$ = −39.8 (*c* = 0.67, $CHCl_3$). ^{1}H NMR ($CDCl_3$) (2:1 mixture of rotamers). **Major Rotamer:** δ = 7.34−7.24 (m, 10 H, 2 × *Ph*), 5.32 (d, *J* = 5.8 Hz, 1 H, OC*H*CON), 5.08 (d, *J* = 17.2 Hz, 1 H, NCH_2Ph), 4.83 (d, *J* = 5.8 Hz, 1 H, OC*H*COOMe), 4.63 (d, *J* = 17.2 Hz, 1 H, NCH_2Ph), 4.39 (s, 2 H, OCH_2Ph), 3.86−3.55 (m, 5 H, CH_2OH, CH_2OBzl, C*H*N), 3.74 (s, 3 H, O*Me*), 2.18 (br. s, 1 H, O−*H*), 1.43 (s, 3 H, C*Me*), 1.42 (s, 3 H, C*Me*); **Minor Rotamer:** δ = 7.34−7.24 (m, 10 H, 2 × *Ph*), 5.37 (d, *J* = 5.4 Hz, 1 H, OC*H*CON), 5.15 (d, *J* = 5.4 Hz, 1 H, OC*H*COOMe), 4.78 (d, *J* = 16.0 Hz, 1 H, NCH_2Ph), 4.60 (d, *J* = 16.0 Hz, 1 H, NCH_2Ph), 4.39 (s, 2 H, OCH_2Ph), 3.86−3.55 (m, 5 H, CH_2OH, CH_2OBzl, C*H*N), 3.77 (s, 3 H, O*Me*), 2.18 (br. s, 1 H, O−*H*), 1.45 (s, 3 H, C*Me*), 1.40 (s, 3 H, C*Me*). ^{13}C NMR ($CDCl_3$) (2:1 mixture of rotamers): δ = 171.0 (s, *C*=O,

one rotamer), 170.5 (s, *C*=O, one rotamer), 169.6 (s, *C*=O, one rotamer), 169.4 (s, *C*=O, one rotamer), 138.4 (s, Ph), 137.7 (s, Ph), 137.4 (s, Ph), 136.6 (s, Ph), 128.6 (d, Ph), 128.3 (d, Ph), 128.2 (d, Ph), 127.9 (d, Ph), 127.6 (d, Ph), 127.5 (d, Ph), 127.4 (d, Ph), 127.3 (d, Ph), 126.8 (d, Ph), 126.6 (d, Ph), 113.0 (s, CMe_2, one rotamer), 112.7 (s, CMe_2, one rotamer), 76.5 (d, O*C*HCON), 76.2 (d, O*C*HCOOMe), 73.0 (t, OCH_2Ph, one rotamer), 72.8 (t, OCH_2Ph, one rotamer), 68.9 (t, CH_2OBzl, one rotamer), 68.1 (t, CH_2OBzl, one rotamer), 62.4 (t, CH_2OH, one rotamer), 60.9 (t, CH_2OH, one rotamer), 60.8 (d, *C*HN, one rotamer), 58.2 (d, *C*HN, one rotamer), 52.3 (q, O*Me*), 51.8 (t, NCH_2Ph, one rotamer), 45.7 (t, NCH_2Ph, one rotamer), 26.2 (q, C*Me*, one rotamer), 26.1 (q, 2 C, C*Me*, both rotamers), 26.0 (q, C*Me*, one rotamer). MS *m*/*z* (%) = 457 (0.3) [M^+], 366 (3), 336 (21), 275 (0.2), 159 (10), 91 (100). IR ($CDCl_3$): $\tilde{\nu}$ = 3440 (O−H), 1740 (O−*C*=*O*), 1634 (N−*C*=*O*) cm^{-1}. $C_{25}H_{31}NO_7$ (457.5): calcd. C 65.63, H 6.83, N 3.06; found C 65.35, H 6.88, N 2.85.

Methyl (2*R*,3*R*)-*N*-Benzyl-*N*′-[(1*S*)-1-benzyloxymethyl-1-formylmethyl]-2,3-di-O-isopropylidenetartramate (6): The Dess−Martin periodinane (2.73 g, 6.44 mmol) was added under nitrogen to a solution of **5** (2.00 g, 4.37 mmol) in anhydrous CH_2Cl_2 (120 mL). The reaction mixture was stirred at room temperature for 30 min, and the homogeneous solution was then diluted with Et_2O (30 mL) and filtered quickly through a Celite layer. After evaporation of the solvent, product **6** (2.03 g) was obtained as a white solid (decomposes on heating) and used directly for the next step without purification. ^{1}H NMR ($CDCl_3$): δ = 9.38 (s, 1 H, C*H*O), 7.37−7.24 (m, 10 H, 2 × *Ph*), 5.32 (d, *J* = 6.0 Hz, 1 H, OC*H*CON), 5.24 (d, *J* = 16.0 Hz, 1 H, NCH_2Ph), 4.98 (d, *J* = 6.0 Hz, 1 H, OC*H*COOMe), 4.62 (d, *J* = 16.0 Hz, 1 H, NCH_2Ph), 4.43 (s, 2 H, OCH_2Ph), 4.07 (dd, *J* = 8.0, 2.0 Hz, 1 H, CH_2OBzl), 3.87 (m, 2 H, CH_2OBzl, C*H*N), 3.74 (s, 3 H, O*Me*), 1.46 (s, 3 H, C*Me*), 1.41 (s, 3 H, C*Me*).

Methyl (2*R*,3*R*)-(−)-*N*-Benzyl-*N*′-(1-formylvinyl)-2,3-di-*O*-isopropylidenetartramate (7): A solution of $(COCl)_2$ (378 μL, 4.40 mmol) in dry CH_2Cl_2 (10 mL) was cooled to −60 °C under nitrogen, and anhydrous DMSO (590 μL, 8.31 mmol) was added slowly at such a rate as to keep the temperature constant. After 5 min, a solution of **5** (1.77 g, 3.87 mmol) in dry CH_2Cl_2 (12 mL) was added dropwise, maintaining the temperature at −60 °C. The mixture was stirred for 15 min, DIPEA (2.77 mL, 15.9 mmol) was then added, and after 10 min the reaction mixture was left to warm to room temperature, followed by addition of water (15 mL). The organic phase was washed with water and dried with Na_2SO_4, and after evaporation of the solvent a mixture of **7** and **6** (4:1) was obtained. Purification by chromatography (Et_2O/petroleum ether, 2:1, R_f = 0.25) gave only **7** (968 mg, 72%) as a yellow oil. $[\alpha]_D^{20}$ = −14.2 (*c* = 0.31, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 9.36 (s, 1 H, C*H*O), 7.32−7.16 (m, 5 H, *Ph*), 6.10 (s, 1 H, C=CH_2), 5.97 (s, 1 H, C=CH_2), 5.17 (d, *J* = 5.2 Hz, 1 H, OC*H*CON), 4.77−4.64 (m, 3 H, NCH_2Ph, OC*H*COOMe), 3.73 (s, 3 H, O*Me*), 1.38 (s, 3 H, C*Me*), 1.36 (s, 3 H, C*Me*). ^{13}C NMR ($CDCl_3$): δ = 188.5 (d, *C*HO), 170.7 (s, *C*=O), 168.7 (s, *C*=O), 146.2 (s, *C*=CH_2), 136.1 (s, 1 C, *Ph*), 128.6 (d, 2 C, Ph), 128.6 (d, 1 C, Ph), 127.9 (d, 2 C, *Ph*), 113.5 (s, CMe_2), 113.5 (t, C=*C*H_2), 76.7 (d, O*C*HCON), 76.5 (d, O*C*HCOOMe), 52.6 (q, OCH_3), 51.3 (t, NCH_2Ph), 26.4 (q, C*Me*), 25.9 (q, C*Me*). MS *m*/*z* (%) = 347 (0.3) [M^+], 159 (12), 91 (100), 59 (15). IR ($CDCl_3$): $\tilde{\nu}$ = 1750 (O−*C*=*O*), 1707 (H-*C*=*O*), 1667 (N−*C*=*O*) cm^{-1}. $C_{18}H_{21}NO_6$ (347.4): calcd. C 62.23, H 6.09, N 4.03; found C 62.58, H 6.45, N 4.34.

(−)-Methyl (1*R*,4*S*,5*S*,7*R*)-3-Benzyl-4*exo*-(*O*-benzylhydroxymethyl)-2-oxo-6,8-dioxa-3-azabicyclo[3.2.1]octane-7*exo*-carboxylate (8): A solution of **6** (2.03 g, 4.37 mmol) in benzene (70 mL) was quickly added to a refluxing suspension of H_2SO_4/SiO_2 (2.40 g, g/g ratio 0.36) in benzene (130 mL). The mixture was allowed to react for 20 min and half of the solvent was then distilled off. The hot reaction mixture was filtered through a short layer of $NaHCO_3$, and the solvent was evaporated. The residue was dissolved in CH_2Cl_2, 60 mL of saturated aqueous $NaHCO_3$ containing 2.2 g of $Na_2S_2O_3$ was then added, and the mixture was stirred for 5 min. The organic phase was washed with saturated aqueous $NaHCO_3$ and water, and dried with Na_2SO_4. After evaporation of the solvent, the crude product was purified by chromatography (EtOAc/petroleum ether, 1:2, R_f = 0.26), yielding **8** (990 mg, 57%) as a white solid. m.p. 68−70 °C. $[\alpha]_D^{27}$ = −24.4 (*c* = 0.54, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 7.34−7.09 (m, 10 H, 2 × *Ph*), 5.90 (s, 1 H, 5-H), 5.06 (d, *J* = 16.0 Hz, 1 H, NCH_2Ph), 4.93 (s, 1 H, 7-H), 4.70 (s, 1 H, 1-H), 4.44 (s, 2 H, OCH_2Ph), 4.05 (d, *J* = 16.0 Hz, 1 H, NCH_2Ph), 3.77 (s, 3 H, O*Me*), 3.65−3.32 (m, 3 H, 4-H, CH_2OBzl). ^{13}C NMR ($CDCl_3$): δ = 168.7 (s, *C*=O), 165.7 (s, *C*=O), 137.0 (s, 1 C, Ph), 135.8 (s, 1 C, Ph), 128.5 (d, 2 C, Ph), 128.2 (d, 2 C, Ph), 127.6 (d, 1 C, Ph), 127.4 (d, 1 C, Ph), 127.3 (d, 2 C, Ph), 127.2 (d, 2 C, Ph), 101.0 (d, 5-C), 77.6 (d, 1-C), 77.2 (d, 7-C), 73.0 (t, OCH_2Ph), 67.4 (t, CH_2OBzl), 59.0 (d, 4-C), 52.4 (q, OCH_3), 46.3 (t, NCH_2Ph). MS *m*/*z* (%) = 397 (0.4) [M^+], 306 (3), 215 (0.2), 91 (100), 59 (3). IR ($CDCl_3$): $\tilde{\nu}$ = 1753 (O−*C*=*O*), 1667 (N−*C*=*O*) cm^{-1}. $C_{22}H_{23}NO_6$ (397.3): calcd. C 66.48, H 5.83, N 3.52; found C 66.84, H 5.95, N 3.33.

(−)-Methyl (1*S*,2*S*,5*S*,6*R*)-3-Benzyl-2*exo*-(benzyloxymethyl)-7,8-dioxa-3-azabicyclo[3.2.1]octane-6*exo*-carboxylate (9) and (−)-(1*S*,2*S*,5*S*,6*S*)-3-Benzyl-2*exo*-(benzyloxymethyl)-6*exo*-hydroxymethyl-7,8-dioxa-3-azabicyclo[3.2.1]octane (10): A solution of BH_3·Me_2S (10 M, 30 μL, 0.295 mmol) was added over 2 min under nitrogen to a refluxing solution of **8** (350 mg, 0.88 mmol) in anhydrous THF (10 mL) and the mixture was stirred for 15 min. The mixture was then immediately cooled with an ice bath. The solvent was evaporated and the crude product was dissolved in dioxane (11 mL), followed by addition of TMEDA (160μL, 1.06 mmol). The mixture was left to react at room temperature for 30 min, the solvent was then evaporated, and the residue was suspended in diethyl ether and carefully filtered through a short Celite layer. After evaporation of the solvent, a mixture of product **9** and amino alcohol **10** (3:1) was obtained. Purification by chromatography (EtOAc/petroleum ether, 1:2) gave pure **9** (190 mg, 56%, R_f = 0.53) and **10** (60 mg, 19%, R_f = 0.23). Compound **9** was also prepared from **8** (350 mg, 0.88 mmol) in anhydrous THF (10 mL) as described above, by adding a 10 M BH_3·DMS solution at room temperature and stirring for 20 h. **Compound 9:** $[\alpha]_D^{26}$ = −31.7 (*c* = 1.23, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 7.32−7.23 (m, 10 H, 2 × *Ph*), 5.73 (d, *J* = 1.8 Hz, 1 H, 1-H), 4.69 (s, 1 H, 6-H), 4.55 (s, 1 H, 5-H), 4.48 (s, 2 H, OCH_2Ph), 3.84 (d, *J* = 15.4 Hz, 1 H, NCH_2Ph), 3.73 (s, 3 H, O*Me*), 3.64 (m, 2 H, CH_2OBzl), 3.51 (d, *J* = 15.4 Hz, 1 H, NCH_2Ph), 3.11 (m, 1 H, 2-H), 2.81 (dd, *J* = 12.1, 1.4 Hz, 1 H, 4-H), 2.48 (dd, *J* = 12.2, 1.4 Hz, 1 H, 4-H). ^{13}C NMR ($CDCl_3$): δ = 171.5 (s, *C*=O), 138.4 (s, 1 C, Ph), 137.9 (s, 1 C, Ph), 128.3 (d, 2 C, Ph), 128.2 (d, 4 C, Ph), 127.5 (d, 1 C, Ph), 127.3 (d, 2 C, Ph), 127.1 (d, 1 C, Ph), 102.4 (d, 1-C), 76.9 (d, 6-C), 75.6 (d, 5-C), 73.2 (t, OCH_2Ph), 64.3 (t, CH_2OBzl), 60.4 (d, 2-C), 57.4 (t, 4-C), 52.2 (q, O*Me*), 49.6 (t, NCH_2Ph). MS *m*/*z* (%) = 325 (0.8), 234 (20), 91 (100), 59 (3). IR ($CDCl_3$): $\tilde{\nu}$ = 1757 (O−*C*=*O*) cm^{-1}. $C_{22}H_{25}NO_5$ (383.4): calcd. C 68.92, H 6.57, N 3.65; found C 68.56, H 6.59, N 3.38. **Compound 10:** $[\alpha]_D^{25}$ = −41.9 (*c* = 0.43, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 7.34−7.23 (m, 10 H, 2 × *Ph*), 5.56 (d, *J* = 1.6 Hz, 1 H, 1-H), 4.48 (s, 2 H, OCH_2Ph), 4.35 (t, *J* = 5.1 Hz, 1 H, 6-H), 4.17 (s, 1 H, 5-H), 3.85 (d, *J* = 13.6 Hz, 1 H, NCH_2Ph), 3.65 (m,

2 H, CH_2OBzl), 3.55 (m, 2 H, CH_2OH), 3.50 (d, J = 13.6 Hz, 1 H, NCH_2Ph), 3.09 (m, 1 H, 2-H), 2.77 (dd, J = 11.7, 1.8 Hz, 1 H, 4-H), 2.34 (dd, J = 11.7, 1.8 Hz, 1 H, 4-H), 2.63 (br. s, 1 H, O−H). ^{13}C NMR ($CDCl_3$): δ = 138.7 (s, 1 C, Ph), 138.0 (s, 1 C, Ph), 128.4 (d, 2 C, Ph), 128.3 (d, 2 C, Ph), 128.2 (d, 2 C, Ph), 127.6 (d, 1 C, Ph), 127.5 (d, 2 C, Ph), 127.0 (d, 1 C, Ph), 101.3 (d, 1-C), 77.9 (d, 6-C), 74.6 (d, 5-C), 73.3 (t, OCH_2Ph), 64.8 (t, CH_2OBzl), 64.2 (t, CH_2OH), 60.9 (d, 2-C), 57.7 (t, 4-C), 49.6 (t, NCH_2Ph). MS m/z (%) = 355 (0.4) [M$^+$], 324 (2), 234 (90), 173 (2.5), 91 (100), 59 (3). IR ($CDCl_3$): $\tilde{\nu}$ = 3591 (O−H) cm^{-1}. $C_{21}H_{25}NO_4$ (355.4): calcd. C 70.96, H 7.09, N 3.94; found C 70.98, H 7.45, N 3.96.

Methyl (1*S*,2*S*,5*S*,6*R*)-2*exo*-(Benzyloxymethyl)-7,8-dioxa-3-azabicyclo[3.2.1]octane-6*exo*-carboxylate (11) and Methyl (1*S*,2*S*,5*S*,6*R*)-2-*exo*-hydroxymethyl-7,8-dioxa-3-azabicyclo[3.2.1]octane-6*exo*-carboxylate (12): A solution of **9** (190 mg, 0.496 mmol) in MeOH (7 mL) was added to a suspension of 20% $Pd(OH)_2$/C (32 mg) in MeOH (6 mL). The reaction mixture was left under H_2 overnight at room temperature and the catalyst was then removed by filtration through a Celite layer and washed with MeOH. The solution was filtered through a column filled with Amberlyst A-21 beads to afford, after evaporation of the solvent, a 2.5:1 mixture of **11** and **12** (150 mg, quantitative yield), which was used without separation for the next step. ^{1}H NMR ($CDCl_3$) (2.5:1 mixture of **11** and **12**): δ = 7.32−7.24 (m, 5 H, *Ph*), 5.70 (br, 1 H, N−*H*), 5.59 (s 1 H, 1-H), 5.45 (s, 1 H, 1-H), 4.73 (s, 1 H, 6-H), 4.65 (s, 1 H, 6-H), 4.51 (s, 4 H, 5-H, OCH_2Ph), 3.75 (s, 6 H, O*Me*), 3.62−3.45 (m, 4 H, CH_2OH, CH_2OBzl), 3.23 (dd, J = 13.1, 2.2 Hz, 1 H, 4-H), 3.08 (m, 1 H, 4-H), 2.91 (t, J = 7.0 Hz, 1 H, 2-H), 2.75−2.63 (m, 3 H, 2-H, 4-H), 2.44 (br, 1 H, O−*H*). Compound **12** can be prepared according to the procedure described above, starting from **17** (45 mg, 0.153 mmol). After evaporation of the solvent, **12** (30 mg) was obtained in quantitative yield and used directly for the next step. ^{1}H NMR ($CDCl_3$): δ = 5.45 (s, 1 H, 1-H), 4.65 (s, 1 H, 6-H), 4.51 (s, 1 H, 5-H), 3.75 (s, 3 H, O*Me*), 3.62−3.45 (m, 2 H, CH_2OH), 3.08 (m, 1 H, 4-H), 2.75−2.63 (m, 2 H, 2-H, 4-H), 2.41 (br. s, 1 H, O−*H*).

(+)-Methyl (1*S*,2*S*,5*S*,6*R*)-3-(9-Fluorenylmethoxycarbonyl)-2*exo*-hydroxymethyl-7,8-dioxa-3-azabicyclo[3.2.1]octane-6*exo*-carboxylate (14): FMOC-*O*-Su (383 mg) was added at 0 °C to a stirred solution of the mixture of **11** and **12** (150 mg) in CH_2Cl_2 (15 mL). The solution was stirred for 10 min at 0 °C and then for 24 h at room temperature. The reaction mixture was then washed with water (4 ×15 mL) and dried with Na_2SO_4. After evaporation of the solvent, a 2.5:1 mixture of **13** and **14** (265 mg) was obtained. $TiCl_4$ (1 M, 64 μL) in CH_2Cl_2 was added to a solution of this mixture in dry CH_2Cl_2 (11 mL) and the resulting reaction mixture was stirred at room temperature for 90 min. A saturated aqueous $NaHCO_3$ solution (10 mL) was then added. After separation, the aqueous phase was extracted with CH_2Cl_2 and the combined organic phases were washed with brine and dried with Na_2SO_4. Pure **14** (117 mg, 51%, R_f = 0.13) was obtained by chromatography (CH_2Cl_2/MeOH, 40:1) as a white foamy solid. Compound **14** was also prepared by starting from **12** as follows: FMOC-*O*-Su (101 mg, 0.229 mmol) was added at 0 °C to a stirred solution of **12** (30 mg, 0.148 mmol) in CH_2Cl_2 (5 mL). The solution was stirred for 10 min at 0 °C and then for 24 h at room temperature. The reaction mixture was washed with water (4×5 mL) and dried with Na_2SO_4. Purification by chromatography as above gave **14** (59 mg, R_f = 0.13) in 94% yield. $[\alpha]_D^{22}$ = +5.2 (c = 0.25, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 3:2 mixture of rotamers): δ = 7.76 (d, J = 8.0 Hz, 2 H + 2 H), 7.55 (d, J = 8.0 Hz, 2 H + 2 H), 7.43−7.24 (m, 4 H + 4 H), 5.69 (s, 1 H, 1-H minor rotamer), 5.60 (s, 1 H, 1-H major rotamer), 4.64−4.21 (m, 5 H + 5 H), 3.91−3.24 (m, 5 H + 5 H), 3.79 (s, 3 H, O*Me* minor rotamer), 3.75 (s, 3 H, O*Me* major rotamer), 1.92 (br. s, 1 H, O−*H*). ^{13}C NMR ($CDCl_3$) (3:2 mixture of rotamers): δ = 170.3 (s, *C*=O), 156.0 (s, N*C*=O, one rotamer), 155.8 (s, N*C*=O, one rotamer), 143.5 (s, 2 C), 141.3 (s, 2 C), 127.7 (d, 2 C), 127.2 (d, 2 C), 124.6 (d, 2 C), 119.9 (d, 2 C), 100.9 (d, C-1, one rotamer), 100.2 (d, C-1, one rotamer), 75.5 (d, C-6, one rotamer), 75.3 (d, C-5), 75.1 (d, C-6, one rotamer), 67.2 (t, CH_2OCO, one rotamer), 67.1 (t, CH_2OCO, one rotamer), 60.5 (t, CH_2OH, one rotamer), 60.1 (t, CH_2OH, one rotamer), 57.1 (d, C-2, one rotamer), 57.0 (d, C-2, one rotamer), 52.6 (q, O*Me*), 47.4 (d, *C*H of FMOC, one rotamer), 47.2 (d, *C*H of FMOC, one rotamer), 45.3 (t, C-4, one rotamer), 44.8 (t, C-4, one rotamer). ESI-MS: m/z = 426 [M$^+$·H], 448 [M$^+$·Na]. IR ($CDCl_3$): $\tilde{\nu}$ = 3600 (O−H), 1740 (O−*C*=*O*), 1692 (O−*CO*-N) cm^{-1}. $C_{23}H_{23}NO_7$ (425.4): calcd. C 64.93, H 5.45, N 3.29; found C 64.46, H 5.74, N 2.88.

(+)-(1*S*,2*S*,5*S*,6*R*)-3-(9-Fluorenylmethoxycarbonyl)-6*exo*-methoxycarbonyl-7,8-dioxa-3-azabicyclo[3.2.1]octane-2*exo*-carboxylic Acid (15). − Method A: Pyridinium dichromate (PDC, 154 mg, 0.409 mmol) was added at 0 °C under nitrogen to a solution of **14** (50 mg, 0.117 mmol) in dry DMF (1 mL). After the mixture had been stirred at room temperature for 24 h, water (10 mL) was added, and the solution was extracted with Et_2O and dried with Na_2SO_4. After purification by chromatography (CH_2Cl_2/MeOH, 20:1), pure **15** (26 mg, 50%, R_f = 0.14) was obtained. **Method B:** Jones' reagent (82.5 mg of CrO_3, 150 μL of H_2SO_4, 1.1 mL of H_2O) was added at 0 °C to a solution of **14** (50 mg, 0.117 mmol) in acetone (1 mL). The mixture was stirred at room temperature for 24 h, and 2-propanol (5 mL) was added. After filtration through a short Celite layer, the solvent was evaporated. Pure product **15** (40 mg, 80%, R_f = 0.14) was obtained by chromatography according to Method A. $[\alpha]_D^{23}$ = +8.4 (c = 0.22, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 2:1 mixture of rotamers): δ = 7.72−7.68 (m, 2 H + 2 H), 7.53−7.45 (m, 2 H + 2 H), 7.38−7.24 (m, 4 H + 4 H), 6.02 (s, 1 H, 1-H, minor rotamer), 5.96 (s, 1 H, 1-H, major rotamer), 4.73−4.10 (m, 5 H + 5 H), 3.88 (m, 1 H + 1 H), 3.76 (s, 3 H, O*Me*, minor rotamer), 3.75 (s, 3 H, O*Me*, major rotamer), 3.56−3.45 (m, 2 H + 2 H). ^{13}C NMR ($CDCl_3$, 2:1 mixture of rotamers): δ = 170.9 (s, *C*=O, one rotamer), 170.1 (s, *C*=O, one rotamer), 169.1 (s), 156.1 (s, N*C*=O, one rotamer), 155.7 (s, N*C*=O, one rotamer), 143.4 (s, 2 C), 141.4 (s, 2 C), 127.8 (d, 2 C), 127.1 (d, 2 C), 124.7 (d, 2 C), 120.0 (d, 2 C), 100.1 (d, C-1, one rotamer), 99.6 (d, C-1, one rotamer), 75.6 (d, C-6), 75.2 (d, C-5), 69.7 (t, CH_2OCO, one rotamer), 67.8 (t, CH_2OCO, one rotamer), 59.1 (d, C-2, one rotamer), 58.8 (d, C-2, one rotamer), 52.7 (q, O*Me*), 47.2 (d, *C*H of FMOC, one rotamer), 47.1 (d, *C*H of FMOC, one rotamer), 45.8 (t, C-4, one rotamer), 45.2 (t, C-4, one rotamer). ESI-MS: m/z = 440 [M$^+$·H], 462 [M$^+$·Na]. IR ($CDCl_3$): $\tilde{\nu}$ = 3500 (O−H), 1756 (O−*C*=*O*), 1731 (O−*C*=*O*), 1710 [O-(*C*=*O*)−N] cm^{-1}. $C_{23}H_{21}NO_8$ (439.4): calcd. C 62.87, H 4.82, N 3.19; found C 63.11, H 4.98, N 2.95.

(−)-Methyl (1*R*,4*S*,5*S*,7*R*)-3-Benzyl-4*exo*-hydroxymethyl-2-oxo-6,8-dioxa-3-azabicyclo[3.2.1]octane-7*exo*-carboxylate (16): A solution of **8** (350 mg, 0.881 mmol) in EtOH (15 mL) was added to a suspension of 5% Pd/C (170 mg) in EtOH (15 mL). The reaction mixture was left under H_2 overnight at room temperature and the catalyst was then removed by filtration through a layer of Celite and washed with EtOH. The solution was filtered through a column filled with Amberlyst A-21 beads to give, after evaporation of the solvent, pure **16** (203 mg, 75%) as a colorless oil. $[\alpha]_D^{25}$ = −56.1 (c = 1.13, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 7.31−7.11 (m, 5 H, *Ph*), 5.88 (s, 1 H, 5-H), 5.06 (d, J = 14.0 Hz, 1 H, NCH_2Ph), 4.91 (s, 1 H, 1-H), 4.68 (s, 1 H, 7-H), 4.05 (d, J = 14.0 Hz, 1 H,

NCH_2Ph), 3.73 (s, 3 H, O*Me*), 3.76−3.63 (m, 2 H, CH_2OH), 3.23 (dd, J = 6.0, 4.0 Hz, 1 H, 4-H). ^{13}C NMR ($CDCl_3$): δ = 169.2 (s, *C*=O), 166.3 (s, *C*=O), 135.8 (s, 1 C, Ph), 128.8 (d, 2 C, Ph), 127.8 (d, 1 C, Ph), 127.4 (d, 2 C, Ph), 101.6 (d, 5-C), 77.7 (d, 1-C), 77.4 (d, 7-C), 60.5 (d, 4-C), 59.8 (t, *C*H_2OH), 52.8 (q, O*C*H_3), 46.4 (t, N*C*H_2Ph), 2.90 (br. s, 1 H, O−*H*). MS: *m*/*z* (%) = 307 (6) [M^+], 276 (4), 216 (3), 91 (100), 59 (6). IR ($CDCl_3$): ṽ = 3471 (O−H), 1752 (O−*C*=*O*), 1660 (N−*C*=*O*) cm^{-1}. $C_{15}H_{17}NO_6$ (307.2): calcd. C 58.65, H 5.58, N 4.56; found C 59.01, H 5.63, N 4.29.

(−)-Methyl (1*S*,2*S*,5*S*,6*R*)-3-Benzyl-2*exo*-hydroxymethyl-7,8-dioxa-3-azabicyclo[3.2.1]octane-6*exo*-carboxylate (17): This compound was prepared according to the synthesis of **9**, starting from **16** (180 mg, 0.586 mmol). After chromatography (EtOAc/petroleum ether, 1:1, R_f = 0.26), pure **17** (45 mg, 26%) was obtained as a yellow oil. $[\alpha]_D^{25}$ = −62.4 (*c* = 0.91, $CDCl_3$). ^{1}H NMR ($CDCl_3$): δ = 7.31−7.24 (m, 5 H, *Ph*), 5.72 (s, 1 H, 1-H), 4.74 (s, 1 H, 6-H), 4.64 (s, 1 H, 5-H), 3.88 (d, J = 13.4 Hz, 1 H, NCH_2Ph), 3.92−3.72 (m, 2 H, CH_2OH), 3.75 (s, 3 H, O*Me*), 3.68 (d, J = 13.4 Hz, 1 H, NCH_2Ph), 3.09 (m, 1 H, 4-H), 2.87 (m, 1 H, 2-H), 2.58 (m, 1 H, 4-H). ^{13}C NMR ($CDCl_3$): δ = 171.5 (s, *C*=O), 138.2, (s, 1 C, Ph), 128.4 (d, 4 C, Ph), 127.2, (d, 1 C, Ph), 103.1 (d, 1-C), 77.2 (d, 6-C), 75.8 (d, 5-C), 61.1 (d, 2-C), 59.1 (t, *C*H_2OH), 57.4 (t, 4-C), 52.5 (q, O*C*H_3), 50.8 (t, N*C*H_2Ph). MS *m*/*z* (%) = 276 (8), 216 (3), 91 (100), 59 (10). IR ($CDCl_3$): ṽ = 3614 (O−H), 1743 (O−*C*=*O*) cm^{-1}. $C_{15}H_{19}NO_5$ (293.2): calcd. C 61.45, H 6.53, N 4.78; found C 61.74, H 6.51, N 4.53.

(−)-Methyl (1*R*,5*S*,7*R*)-3-Benzyl-4-methylene-2-oxo-6,8-dioxa-3-azabicyclo[3.2.1]octane-7*exo*-carboxylate (18): A solution of **7** (608 mg, 1.75 mmol) in benzene (45 mL) was quickly added to a refluxing suspension of H_2SO_4/SiO_2 (523 mg) in benzene (50 mL). The mixture was allowed to react for 20 min and then half of the solvent was distilled off. The hot reaction mixture was filtered through a short layer of $NaHCO_3$ and the solvent was evaporated. The residue was purified by chromatography (EtOAc/petroleum ether, 1:3, R_f = 0.30) to yield **18** (140 mg, 28%) as a colorless oil and **19** (145 mg, 27%) as a yellow oil. **Compound 18:** $[\alpha]_D^{27}$ = −68.3 (*c* = 0.86, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 7.31−7.11 (m, 5 H, *Ph*), 5.92 (s, 1 H, 5-H), 5.15 (s, 1 H, 1-H), 4.85 (AB, J = 7.9 Hz, 2 H, NCH_2Ph), 4.79 (s, 1 H, 7-H), 4.42 (d, J = 2.6 Hz, 1 H, C=CH_2), 4.36 (d, J = 2.6 Hz, 1 H, C=CH_2), 3.81 (s, 3 H, O*Me*). ^{13}C NMR ($CDCl_3$): δ = 168.7 (s, *C*=O), 165.1 (s, *C*=O), 140.3 (s, 4-C), 135.2 (s, 1 C, Ph), 128.8 (d, 2 C, Ph), 127.5 (d, 1 C, Ph), 126.4 (d, 2 C, Ph), 102.5 (d, 5-C), 94.4 (t, C=*C*H_2), 78.3 (d, 1-C), 76.7 (d, 7-C), 52.9 (q, O*C*H_3), 44.0 (t, N*C*H_2Ph). MS *m*/*z* (%) = 289 (25) [M^+], 230 (4), 198 (4), 91 (100), 59 (9). IR ($CDCl_3$): ṽ = 1759 (O−*C*=*O*), 1694 (N−*C*=*O*), 1643 (*C*=*C*) cm^{-1}. $C_{15}H_{15}NO_5$ (289.3): calcd. C 62.30, H 5.23, N 4.84; found C 62.04, H 5.65, N 4.50. **Compound 19:** ^{1}H NMR ($CDCl_3$) (2:1 mixture of epimers): δ = 7.40−7.15 (m, 5 H + 5 H), 5.59 (s, 1 H, O−*C*HOH, minor epimer), 5.50 (s, 1 H, O−*C*HOH, major epimer), 5.05−4.30 (m, 4 H + 4 H), 4.94 (d, J = 15.8 Hz, 1 H, NCH_2Ph), 4.40 (d, J = 15.8 Hz, 1 H, NCH_2Ph), 3.87 (s, O*Me*, minor epimer), 3.85 (s, O*Me*, major epimer), 3.05 (br. s, 1 H, O−*H*), 2.80 (br. s, 1 H, O−*H*). MS: *m*/*z* (%) = 307 (3) [M^+], 91 (100). IR ($CDCl_3$): ṽ = 3549 (O−H), 1747 (O−*C*=*O*), 1676 (N−*C*=*O*).

(−)-Methyl (1*R*,4*R*,5*S*,7*R*)-3-Benzyl-4*endo*-hydroxymethyl-2-oxo-6,8-dioxa-3-azabicyclo[3.2.1]octane-7*exo*-carboxylate (20): BH_3·Me_2S in THF (10 M, 8.50 μL, 0.0886 mmol) was added at 0 °C to a solution of **18** (70 mg, 0.242 mmol) in dry THF (2 mL). The solution was stirred at room temperature for 3 h, and then H_2O (2 mL), NaOH (30 μL), 35% H_2O_2 (30 μL) were added successively, and the resulting mixture was heated at 50 °C for 1 h. Brine (20 mL) was added and the mixture was extracted with CH_2Cl_2 and the organic phase was dried with anhydrous Na_2SO_4. After solvent evaporation, the crude product was purified by chromatography (EtOAc/petroleum ether, 2:3, R_f = 0.10) to afford pure **20** (10 mg, 10%) and starting material **18** (26 mg, 13%). $[\alpha]_D^{20}$ = −6.13 (*c* = 0.31, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ = 7.35−7.15 (m, 5 H, *Ph*), 5.86 (d, J = 3.1 Hz, 1 H, 5-H), 5.37 (d, J = 15.4 Hz, 1 H, NCH_2Ph), 5.03 (s, 1 H, 1-H), 4.71 (s, 1 H, 7-H), 4.00 (d, J = 15.4 Hz, 1 H, NCH_2Ph), 3.80 (s, 3 H, O*Me*), 3.80−3.74 (m, 2 H, CH_2OH), 3.40 (m, 1 H, 4-H), 1.77 (br. s, 1 H, O−*H*). MS: *m*/*z* (%) = 307 (11) [M^+], 276 (8), 216 (8), 91 (100), 59 (5). IR ($CDCl_3$): ṽ = 3468 (O−H), 1756 (O−*C*=*O*), 1670 (N−*C*=*O*) cm^{-1}. $C_{15}H_{17}NO_6$ (307.2): calcd. C 58.65, H 5.58, N 4.56; found C 58.99, H 5.73, N 3.89.

(−)-Methyl (1*S*,2*R*,5*S*,6*R*)-3-Benzyl-2*endo*-hydroxymethyl-7,8-dioxa-3-azabicyclo[3.2.1]octane-6*exo*-carboxylate (21): BH_3·Me_2S in THF (10 M, 23.5 μL, 0.235 mmol) was added at 0 °C to a solution of **18** (70 mg, 0.242 mmol) in dry THF (2 mL). The solution was stirred at room temperature for 5 h, ethanol (2 mL), NaOH (30 μL), and 35% H_2O_2 (30 μL) were then added successively, and the resulting mixture was heated at 50 °C for 1 h. Water (20 mL) was then added and the mixture was extracted with Et_2O (15 mL). The organic phase was washed successively with water and brine, and dried with anhydrous Na_2SO_4. After solvent evaporation, pure **21** (30 mg, 43%) was obtained as an oil. $[\alpha]_D^{25}$ = −78.1 (*c* = 0.63, $CDCl_3$) − ^{1}H NMR ($CDCl_3$): δ = 7.45−7.24 (m, 5 H, *Ph*), 5.65 (s, 1 H, 1-H), 4.64 (s, 1 H, 6-H), 4.60 (s, 1 H, 5-H), 4.11 (d, J = 13.2 Hz, 1 H, NCH_2Ph), 3.81−3.73 (m, 2 H, CH_2OH), 3.73 (s, 3 H, O*Me*), 3.20 (d, J = 13.2 Hz, 1 H, NCH_2Ph), 2.70 (m, 1 H, 4-H), 2.55−2.45 (m, 2 H, 4-H, 2-H), 2.00 (br. s, 1 H, O−*H*). ^{13}C NMR ($CDCl_3$): δ = 171.0 (s, *C*=O), 137.4 (s, 1 C, Ph), 128.8 (d, 2 C, Ph), 128.4 (d, 2 C, Ph), 127.3 (d, 1 C, Ph), 103.7 (d, 1-C), 77.1 (d, 6-C), 75.6 (d, 5-C), 69.2 (t, *C*H_2OH), 62.8 (d, 2-C), 60.2 (t, 4-C), 56.9 (t, N*C*H_2Ph), 53.2 (q, O*C*H_3). MS: *m*/*z* (%) = 293 (3) [M^+], 276 (4), 262 (74), 234 (20), 216 (6), 105 (10), 91 (100). IR ($CDCl_3$): ṽ = 3459 (O−H), 1752 (O−*C*=*O*) cm^{-1}. $C_{15}H_{19}NO_5$ (293.2): calcd. C 61.42, H 6.53, N 4.78; found C 61.08, H 6.94, N 4.51.

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