Synthesis and Reactivity of Bicycles Derived from Tartaric Acid and α-Amino Acids: A Novel Class of Conformationally Constrained Dipeptide Isosteres Based upon Enantiopure 3-Aza-6,8-dioxabicyclo[3.2.1]octane-7-carboxylic Acid

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3-Aza-6,8-dioxabicyclo[3.2.1]octane-7-carboxylic acids (named BTAa) derived from (*R*,*R*)-, (*S*,*S*)-, or *meso*-tartaric acid and natural (L), unnatural (D), or unusual α-amino acids are described as conformationally constrained dipeptide isosteres. The general strategy developed for their preparation has required the trasformation of the amino acids into the corresponding *N*-benzylamino alcohols, followed by the PyBroP-promoted condensation with the monomethyl ester of the suitable 2,3-di-*O*-isopropylidenetartaric acid. Oxidation of the hydroxy group to aldheyde and subsequent acid-catalyzed trans-acetalization with the two hydroxy groups of the tartaric acid moiety provided 3-aza-2-oxo-6,8-dioxabicyclo[3.2.1]octane-7-carboxylic acid methyl esters [named BTAa(O)] in good yield and, in most cases, as single enantiopure diastereoisomers. This strategy has been applied to the preparation of BTAa(O) starting from (*R*,*R*)-, (*S*,*S*)-, or *meso*-tartaric acid and glycine, L- and D-phenylalanine, L- and D-alanine, and (±)-phenylglycine. In the cases of glycine, L- and D-phenylalanine, and L- and D-alanine, the selective reduction by BH_3·DMS of the amide group succeeding to the cyclization step, or the reduction of both amide and ester functions followed by reoxidation of the hydroxy to carboxylic group, provided in good yield the 3-aza-3-benzyl-6,8-dioxabicyclo[3.2.1]-octane-7-carboxylic acids (or their methyl ester) BTAa, having the side chain of the amino acid precursors at position 4. The stability and rigidity of the bicyclic skeleton, the complete control of all the stereocenters, the possibility of introducing the side chains of L- or D-amino acids, and the demonstrated compatibility with the conditions required for solid-phase peptide synthesis make the BTAa compounds potential dipeptide isosteres useful for the synthesis of modified peptides.

Introduction

Peptide isosteres are compounds that can replace one or more amino acids in a bioactive peptide leading to modified structures possibly displaying more favorable pharmacological properties than the prototype. In several cases, the modified peptide shows a higher metabolic stability, better bioavailability, and higher receptor affinity or selectivity.[1]

The isosteric substitution can occur at different levels, from the simple modification of a single amino acid or substitution of a single amide bond up to the complete replacement of the amino acid backbone. The use of a dipepetide isostere,[1−3] replacing two neighboring amino acids (Xaa-Yaa) at the same time, is a possible approach to attaining modified peptides, whose flexibility, in comparison with that of regular peptides, may be limited by introducing conformational restrictions.[1]

In designing a novel class of conformationally restricted dipeptide isosteres, the following requirements should be taken into account:

(1) The synthesis should be easy and include only few steps, starting from commercially available enantiopure precursors, in both enantiomeric forms. Moreover, there must be a stereochemistry control in each step of the synthesis in order to have, starting from the appropriate precursor, the desired configuration of the stereocenters in the final compound.

(2) A high number of positions should be functionalized in order to increase the molecular diversity.

(3) The side chain of the L- or D-amino acids should be introduced into at least one of the positions equivalent to those of the Xaa-Yaa dipeptide prototype.

(4) The functionalities and protecting groups should be compatible with the conditions required for solid-phase peptide synthesis.

(5) The structure should have a limited number of accessible conformations.

We have envisioned that some of the these features could be found in the bicyclic structure based upon the 3-aza-6,8-dioxabicyclo[3.2.1]octane-7-carboxylic acid skeleton shown in Figure 1. As shown in Scheme 1, these novel amino acids can be prepared by reduction of the corresponding 2-oxo derivatives, which, in turn, derive from the condensation between α-amino aldehydes and tartaric acid derivatives.[4,5] Because α-amino aldehydes are usually prepared from the corresponding α-amino

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(1) Giannis, A.; Kolter, T. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1244−1267 and references therein.

(2) Chung, Y. J.; Ryu, E. J.; Keum, G.; Kim, B. H. *Bioorg. Med. Chem.* **1996**, *4*, 209−225.

(3) Norman, B. H.; Kroin, J. S. *J. Org. Chem.* **1996**, *61*, 4990−4998.

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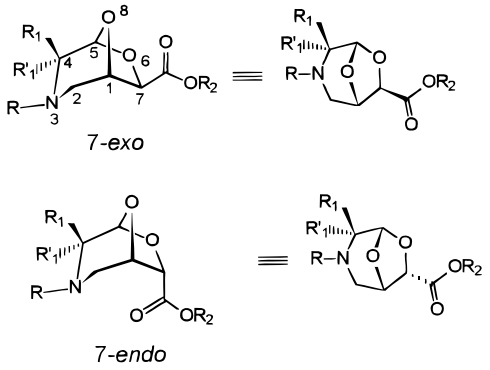
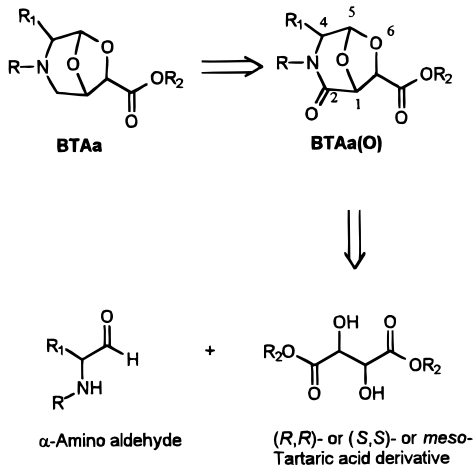


Figure 1.

Scheme 1



acids, we named this novel class of dipeptide isosteres BTAa, meaning bicyclic compounds derived from tartaric acid and amino acids. By analogy, the corresponding amide precursors were named BTAa(O).

Comparison of an extended structure of a peptide with that of the modified one by introduction of dipeptide isostere BTAa (Figure 2) allows the following comments to be made:

The number of bonds between atoms 1 and 6 is the same in both peptides, but in the modified peptide the first amino acid contains a bisubstituted nitrogen with two arms, one bearing the same side chain as the unmodified peptide and the other one linked to the side chain of the second amino acid making a seven-membered ring.

The position 3 (bearing the oxo group in the unmodified peptide) in the first amino acid is now sp^3-hybridized and the oxygen lies out of plane, forming a second rigid ring. The N-4 atom of the unmodified peptide is substituted in the modified one by the O-4 atom.

The configuration of the two stereocenters at C-2 and C-5 can either be identical to that of the original peptide or inverted by choosing suitable amino acid and tartaric acid precursors.

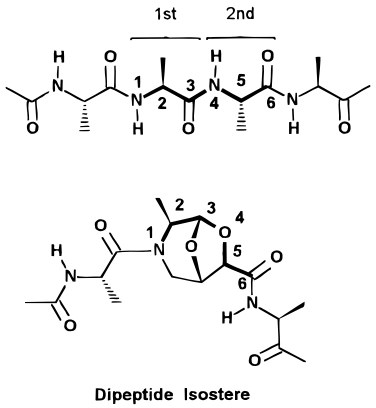


Figure 2.

The combination of all these elements determines whether the polar and steric requirements of the native peptide are maintained and, at the same time, can confer modifications of the overall peptide structure. Moreover, since the amide bond between the two amino acids is now substituted by the acetal system, this can represent a transition-state isostere of a scissile peptide bond in a substrate−enzyme complex. A variety of transition-state isosteres have been developed, including hydroxyethylenes, reduced amides, hydroxyethylamines, and phosphinates, the high interest in these isosteres being also related to their use in the synthesis of HIV protease inhibitors, as recently reported.[6]

The most interesting feature of the new dipeptide isostere BTAa is the possibility of setting the configuration of the stereocenters by choosing the suitable starting material. In Chart 1 the stereochemical relationships between compounds BTAa and the amino acid precursors and (*R*,*R*)-, (*S*,*S*)-, and *meso*-tartaric acids are illustrated.

The amino acid chosen as a starting material (L or D) determines the nature and the configuration of the substituent at C-4, whereas the stereochemistry of the tartaric acid allows us to set the configuration of the other two stereocenters of the skeleton. Thus, the combination of L- and D-amino acids with (*R*,*R*)-, (*S*,*S*)-, and *meso*-tartaric acid would produce eight possible stereoisomers. Therefore, to simplify the nomenclature, we assign the abbreviation BTX (with the capital X from the single letter code of the amino acid used) to the stereoisomer derived from natural (*R*,*R*)-tartaric acid and a natural L-amino acid, whereas the lower case letters t and x are used for compounds deriving from unnatural (*S*,*S*)-tartaric acid and unnatural D-amino acids, respectively. Thus, the combination of the two enantiomers of a chiral amino acid with the two enantiomers of tartaric acid produces the four different stereoisomers BTX, BTx, BtX, and Btx. These stereoisomers have the carboxylic group in the exo position, whereas the amino acid side chain can be in the exo or endo position depending on the absolute configuration of the tartaric acid and amino acid precursors used.

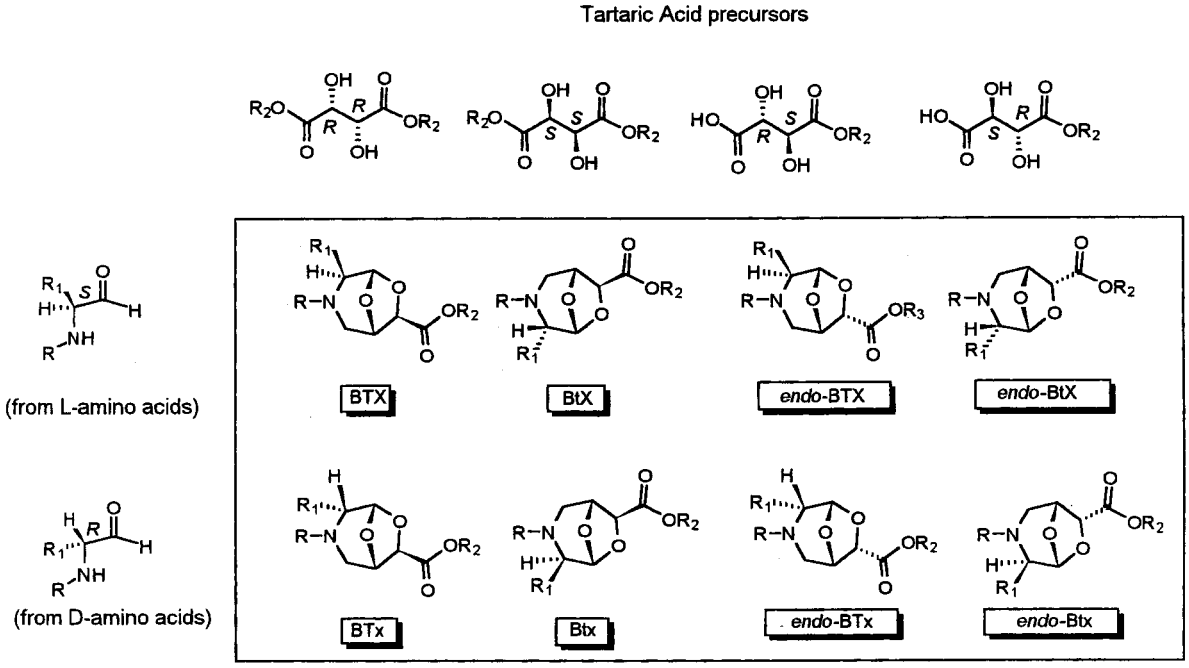
The introduction of the carboxylic group in the endo position could be possible by starting from meso tartaric acid. Also in this case, four different stereoisomers would

(4) Guidi, A.; Guarna, A.; Giolitti, A.; Macherelli, M.; Menchi, G. *Arch. Pharm. Med. Chem.* **1997**, *330*, 201−202.

(5) This skeleton is not new in the literature. Indeed, it has been already reported by Vogel et al., but only examples of glycine derivatives as amido esters were described by the authors. (a) Dienes, Z.; Vogel, P. *J. Org. Chem.* **1996**, *61*, 6958−6970. (b) Moismann, H.; Dienes, Z.; Vogel, P. *Tetrahedron* **1995**, *51*, 6495−6510. (c) Dienes, Z.; Antonsson, T.; Vogel, P. *Tetrahedron Lett.* **1993**, *34*, 1013−1016. (d) Reymond, J.-L.; Vogel, P. *J. Chem. Soc., Chem. Commun.* **1990**, 1070−1072. (e) Reymond, J.-L.; Vogel, P. *Tetrahedron: Asymmetry* **1990**, *1*, 729−736.

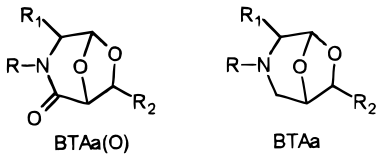
(6) (a) Tucker, T. J.; Lumma, W. C., Jr.; Payne, L. S.; Wai, J. M.; de Solms, S. J.; Giuliani, E. A.; Darke, P. L.; Heimbach, J. C.; Zugay, J. A.; Scleif, W. A.; Quintero, J. C.; Emini, E. A.; Huff, J. R.; Anderson, P. S. *J. Med. Chem.* **1992**, *35*, 2525−2533 and references therein. (b) Smallheer, J. M.; Seitz, S. S. *Heterocycles* **1996**, *43*, 2367−2376.

Chart 1[a]



[a] Nomenclature for BTAa: relationship between absolute configuration of tartaric acid and amino acid derivative precursors with the stereochemistry of BTAa.

Table 1. Panel of Compounds BTAa and BTAa(O) Prepared



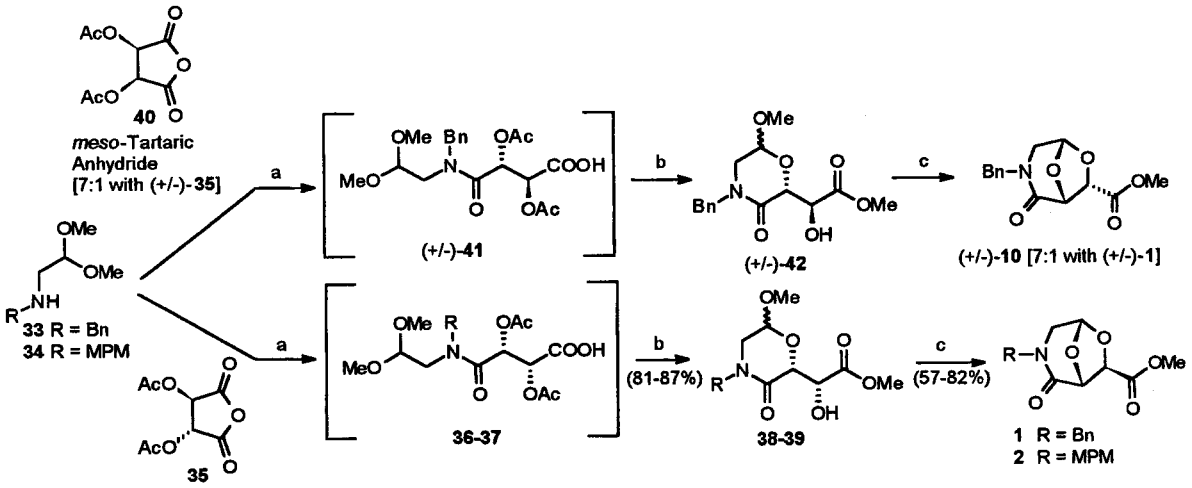
BTAa(O)				BTAa			
compd	R	R_1	R_2	compd	R	R_1	R_2
1	Bn	H	CO_2Me (exo)	**16**	Bn	H	CO_2Me (exo)
2	MPM	H	CO_2Me (exo)	**17**	Bn	Bn (exo)	CO_2Me (exo)
3	MPM	Bn (exo)	CO_2Me (exo)	**18**	Bn	Bn (endo)	CO_2Me (exo)
4	Bn	Bn (exo)	CO_2Me (exo)	**19**	Bn	Me (exo)	CO_2Me (exo)
5	Bn	Bn (endo)	CO_2Me (exo)	**20**	Bn	Me (endo)	CO_2Me (exo)
6	Bn	Me (exo)	CO_2Me (exo)	(±)-**21**	Bn	H	CO_2Me (endo)
7	Bn	Me (endo)	CO_2Me (exo)	**22**	H	H	CO_2Me (exo)
8	Bn	Ph (exo)	CO_2Me (exo)	**23**	H	Bn (exo)	CO_2Me (exo)
9	Bn	Ph (endo)	CO_2Me (exo)	**24**	H	Bn (endo)	CO_2Me (exo)
(±)-**10**	Bn	H	CO_2Me (endo)	(±)-**25**	H	H	CO_2Me (endo)
11	Bn	Bn (endo)	CO_2Me (endo)	**26**	Fmoc	H	CO_2Me (exo)
12	Bn	Me (endo)	CO_2Me (endo)	**27**	Fmoc	Bn (exo)	CO_2Me (exo)
13	H	H	CO_2Me (exo)	**28**	H	H	CO_2H (exo)
14	H	Bn (exo)	CO_2Me (exo)	**29**	Bn	H	CO_2H (exo)
15	MPM	H	CO_2H (exo)	**30**	Fmoc	H	CO_2H (exo)
				31	Fmoc	Bn (exo)	CO_2H (exo)
				32	Fmoc	Me (endo)	CO_2H (endo)

be produced by combination with the enantiomers of a chiral amino acid, all of them having the carboxylic group in the endo position. Therefore, they are named *endo*-BTX, *endo*-BTx, *endo*-BtX, and *endo*-Btx. If the synthesis is extended to all 19 chiral natural L-amino acids and the corresponding D-amino acids, 152 different compounds could be synthesized besides the four steroisomers derived from glycine (in total 156 different dipeptide isosteres).

We report herein the preparation of several enantiopure amido-esters BTAa(O), starting from (*R*,*R*)- or *meso*-tartaric acid and glycine, L- and D-phenylalanine, L- and D-alanine, and (±)-phenylglycine. In the cases of glycine, L- and D-phenylalanine, L- and D-alanine, the corresponding 3-aza-3-benzyl-6,8-dioxabicyclo[3.2.1]octane-7-carboxylic acids BTAa (orthogonally protected as *N*-benzyl and methyl ester) have been synthesized, having the 7-carboxylic group in either the exo or endo position. All the corresponding compounds derived from (*S*,*S*)-tartaric acid have been also prepared, but their synthesis is not discussed in the text. A complete panel of the BTAa(O) (**1**−**15**) and BTAa (**16**−**32**) prepared and characterized is reported in Table 1 to which we refer in the discussion throughout the text.

Finally, examples of selective protection/deprotection reactions and the preparation of some *N*-Fmoc-protected

Scheme 2[a]



[a] Key: (a) CH_2Cl_2, 60 min, 25 °C; (b) $SOCl_2$, MeOH, 2 h, 50 °C; (c) H_2SO_4/SiO_2, toluene, reflux, 15 min, then distillation of one-third of the solvent.

amino acids are reported. In the case of the glycine derivative BTG, the coupling with proline on the solid phase has been realized to assess the compatibility of these new dipeptide isosteres with the conditions required for solid-phase peptide synthesis.

Results and Discussion

Synthesis of BTAa(O). In the synthesis of the 3-aza-2-oxo-6,8-dioxabicyclo[3.2.1]octane-7-carboxylic acid skeleton of BTAa(O) (Scheme 1) from α-amino aldehydes and tartaric acid derivatives two different processes are involved:

Process 1: formation of an amide bond between the amino group of the amino aldehyde and one of the two carboxylic groups of the tartaric acid.

Process 2: formation of the acetal bridge between the two hydroxy groups of the tartaric acid moiety and the aldehyde function.

Therefore, the method to achieve these two distinct processes would be strongly dependent on the nature of the protecting groups of the amino aldehyde and tartaric acid precursors. These groups would be very important not only in the cyclization process but also in the further transformations of BTAa(O) into BTAa.

The synthesis of (1*R*,5*S*,7*R*)- and (1*S*,5*R*,7*S*)-3-alkyl-3-aza-2-oxo-6,8-dioxabicyclo[3.2.1]octane-7-carboxylic acid derivatives having R = Me, Et, Pr; R_1 = H; R_2 = Et, H and obtained from *N*-alkylglycine derivatives and 2,3-di-*O*-acetyltartaric anhydride has been previously reported by Vogel et al., who named these compounds (alkyl)-RADO or -SADO, respectively.[5] The synthesis was limited to a few examples of *N*-alkyl derivatives, and while some transformations were carried out on the carboxylic function, no attempts at converting the amide moiety into other functionalities were made. We initially extended this method to prepare Bn-BTG(O)-OMe **1**, MPM-BTG(O)-OMe **2** (MPM = 4-methoxybenzyl), and *endo*-Bn-BTG(O)-OMe (±)-**10** to introduce easily removable N protecting groups and to modify the configuration at C-7 of the carboxylic group (Scheme 2). Alternative synthetic methods, more suitable for the use of chiral amino acid derivatives as precursors, were then explored.

Thus, 2-(*N*-benzylamino)acetaldehyde dimethyl acetal **33** (Scheme 2), prepared according to a reported method,[7] was treated with commercially available (*R*,*R*)-2,3-di-*O*-acetyltartaric anhydride **35** in CH_2Cl_2, affording the corresponding amide **36**. Crude **36** was dissolved in MeOH and, when treated with thionyl chloride, afforded cyclic acetal **38** as a mixture of epimers in 87% yield. The final cyclization process to give Bn-BTG(O)-OMe **1** was carried out by quickly adding a toluene solution of **38** to a refluxing toluene suspension of H_2SO_4 adsorbed on SiO_2 (H_2SO_4/SiO_2). After 15 min, one-third of the solvent was distilled off, the hot reaction mixture was filtered through a short pad of $NaHCO_3$, and the solvent was removed to give Bn-BTG(O)-OMe **1** in 57% yield (after FCC). The procedure was then extended to MPM-BTG-OMe **2** (which was obtained in 66% overall yield), to have a N-protecting group removable by oxidation.

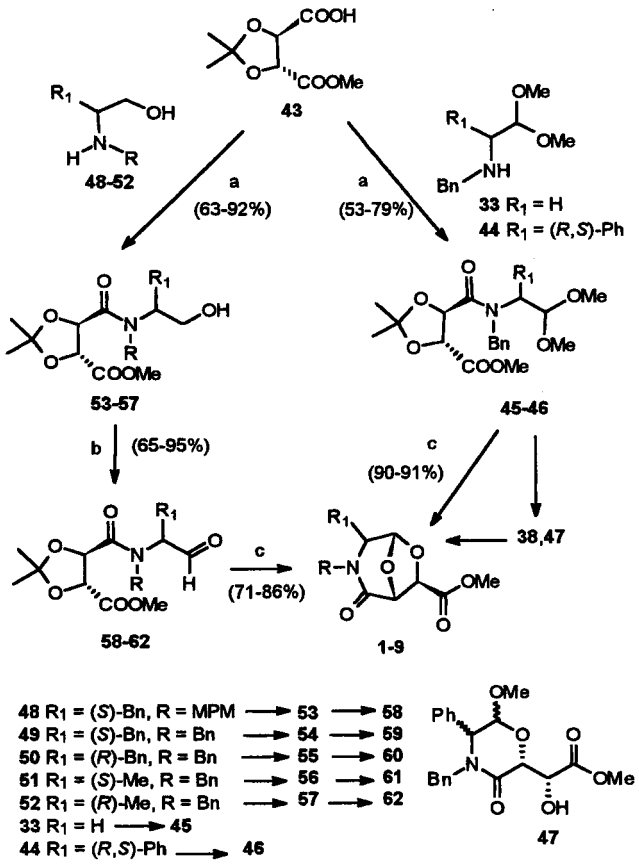
The cyclization procedure described above is the result of the optimization of the method described by Vogel for the synthesis of Me-BTG(O)-OMe. In particular, the addition of compound **38** to the refluxing toluene and the time of reflux were crucial points to obtaining good yields. A slow heating of the reaction mixture containing **38** and H_2SO_4/SiO_2 up to reflux, or a prolonged refluxing time, decreased the yield.

The same procedure (Scheme 2) was also applied to the synthesis of racemic mixture of *N*-benzyl-7-*endo*-carboxylic acid derivative (±)-**10** starting from *meso*-tartaric acid and acetal **33**. This required the synthesis of *meso*-2,3-di-*O*-acetyltartaric anhydride **40**, which, to the best of our knowledge, has not been previously described. Treatment of *meso*-tartaric acid under the conditions used for the synthesis of (*R*,*R*)-2,3-di-*O*-acetyltartaric anhydride[8] provided the desired product **40** in a 7:1 ratio with a racemic mixture of 2,3-di-*O*-acetyltartaric anhydride **35**. Owing to the instability of **40**, no attempts of purification were made. The succeding synthetic steps were identical to those performed for the synthesis of Bn-BtG(O)-OMe **1**. The final product was a racemic mixture (18% overall yield) of (±)-**10** containing, in a 7:1 ratio, the racemic mixture of the 7-exo diastereoisomer **1**

(7) Kermak, W. O.; Perkin, W. H.; Robinson, R. *J. Chem. Soc., Trans.* **1922**, *121*, 1872−1896.

(8) Lucas, H. J.; Baumgarten, W. *J. Am. Chem. Soc.* **1941**, *63*, 1653−1657.

Scheme 3[a]



[a] Key: (a) PyBrOP, DIPEA, CH_2Cl_2, 2−12 h, 25 °C; (b) Swern oxidation; (c) H_2SO_4/SiO_2, toluene or benzene, reflux, 15 or 20 min, then distillation of one-third of the solvent.

derived from the initial epimerization of the *meso*-tartaric anhydride. The absence of changes in the diasteromeric ratio indicated that no other racemization processes occurred during the synthetic procedure.

Since the procedure described above is not suitable to the synthesis of BTAa(O) derived from chiral amino acids, we developed a different methodology that we employed for the synthesis of different Bn-BTAa(O)-OMe: the diastereoisomer **1** deriving from glycine and (*R*,*R*)-tartaric acid; the two diastereoisomers **4**−**5** obtainable from (*R*,*R*)-tartaric acid and L- and D-phenylalanine; the two diastereoisomers **6**−**7** derived from L- and D-alanine and (*R*,*R*)-tartaric acid; one of the two 7-endo diastereoisomers (**11**) derived from *meso*-tartaric acid and D-phenylalanine; one of the two 7-endo diastereoisomers derived from *meso*-tartaric acid and L-alanine (**12**), and the two diastereoisomers **8**−**9** derived from α-phenylglycine and (*R*,*R*)-tartaric acid.

In Scheme 3 the synthesis of 7-*exo*-BTAa(O) **1**−**9** derivatives is reported. It was based on the amide bond formation between the monomethyl ester of (*R*,*R*)-2,3-di-*O*-isopropylidentartaric acid **43** and the *N*-benzyl-α-amino aldheyde derivatives **33** and **44** or *N*-benzyl-*β*-amino alcohols **48**−**52**, to give the condensation products **45**−**46** or **53**−**57**, respectively. In the case of the dimethyl acetal derivatives **45**−**46**, the treatment with H_2SO_4/SiO_2 in refluxing solvent was sufficient to achieve the cyclization, whereas with alcohols **53**−**57** the cyclization was realized after their transformation into aldehydes **58**−**62** by Swern oxidation. In both the sequences, the condensation between tartaric acid derivative **43** and the amino acid derivatives was promoted by the activating agent PyBroP (bromotripyrrolidinophosphonium hexafluorophosphate)[9] in the presence of base. This reagent has been reported to be a very useful coupling reagent in peptide synthesis because it promotes amide bond formation with relatively unreactive secondary amines and, at the same time, avoids the racemization of the amino acids.[9]

With regard to the synthesis of **1**, intermediate **45**, obtained in 79% yield after the coupling of **43** with **33**, was treated in the usual way with H_2SO_4/SiO_2 in refluxing toluene. Monitoring of the reaction revealed that after 10 min **45** had already lost the protection on the tartaric acid moiety, and as a consequence, cyclic acetal **38** shown in Scheme 2 (as a 5:1 mixture of epimers at the acetalic carbon) was formed as the major product, besides a certain amount (20−30%) of final Bn-BTG(O)-OMe **1**. Prolonging the reflux time up to 40 min did not affect the ratio of **38** to **1**, whereas the reaction was completed only by distillation of one-third of the toluene from the reaction mixture. Presumably, this removes MeOH eliminated during the trans-acetalization, shifting the reaction equilibrium toward the final product. Thus, repeating the reaction on **45** with a removal of toluene up to one-third of the initial volume after 15 min of reflux afforded the cyclization product in very high yield (91%) and in almost pure form.[10]

Having in our hands a good procedure to perform the two final steps, we applied the complete sequence to the synthesis of compounds **3**−**7** and the two diastereoisomers **8**−**9** derived from unnatural (±)-α-phenylglycine and (*R*,*R*)-tartaric acid (Scheme 3).

The synthesis of **3**−**7** required the preparation of amino alcohols **48**−**52** obtained starting from the methyl ester of the corresponding L- or D-amino acids. These were treated with benzoyl chloride (or *p*-methoxybenzoyl chloride), then both the amide and ester groups were reduced with $LiAlH_4$ to give the corresponding *β*-amino alcohols **48**−**52** in very high yield. The condensation of amino alcohols **48**−**52** with (*R*,*R*)-2,3-di-*O*-isopropylidenetartrate monomethyl ester (*R*,*R*)-**43** was carried out by using PyBroP and DIPEA (diisopropylethylamine) in CH_2Cl_2, affording amides **53**−**57** in high yield (63−92%). The condensation reaction was completely chemoselective because the reaction of the OH group of **48**−**52** with the carboxylic group of **43** to give an ester was never observed. Compounds **53**−**57** were purified and characterized and were found to be mixtures of rotamers in solution (by ^1H NMR). Then, amido alcohols **53**−**57** were transformed into the corresponding aldehydes **58**−**62** by Swern oxidation in 65−95% yield in the presence of DIPEA as a base. The use of Et_3N instead of DIPEA caused in some cases a partial epimerization at the α stereocenter of the aldehyde. Aldehydes **58**−**62** were, with some exceptions, sufficiently stable to permit their purification by flash column chromatography on silica gel (FCC). More surprisingly, when some epimerization occurred, the epimers were easily separatd by FCC. No

(9) Frérot, E.; Coste, J.; Pantaloni, A.; Dufour, M.-N.; Jouin, P. *Tetrahedron* **1991**, *47*, 259−270.

(10) Some attempts were made to find the conditions for direct condensation of compound **33** with dimethyltartrate. The best yield of **1** (16%) was achieved by heating for 30 min a mixture of compound **33** and dimethyltartrate (previously activated by reaction with trimethylortoformate) in toluene in the presence of the H_2SO_4/SiO_2 system.

epimerization was instead observed at the stereocenters of the tartaric acid moiety in aldehydes **58**−**62** during the course of the oxidation reaction.

At this point, the cyclization of the aldehydes to give final compounds **3**−**7** was performed by using the H_2SO_4/SiO_2 system in refluxing toluene (or benzene in the case of **61** and **62**) and removing one-third of the solvent by distillation. To obtain complete conversion, it was necessary to reflux the reaction mixtures for at least 20 min before distilling off the solvent, i.e., longer than in the case of the synthesis of Bzl-BTG(O)-OMe **1**. Interestingly, when the side chain in the final product BTAa(O) was in the 4-endo position, a longer reaction time was necessary for a complete cyclization in comparison with that required for the corresponding 4-*exo*-BTAa.

All the R-BTAa(O)-OMe, once formed, were stable under the cyclization conditions because no epimerization of the sterocenters at C-4 and/or C-7 was observed either by prolonging the reaction time or by reheating the compounds in refluxing toluene containing H_2SO_4/SiO_2. A certain degree of epimerization was, however, observed during the cyclization of aldehyde **61** (derived from natural alanine), since compound **6** was obtained as a 3:1 mixture with its epimer **7** (separable by chromatography). The cyclization of **61**, however, took place without epimerization when it was carried out in benzene. Epimerization also occurred to a similar extent (20%) when performing the reaction on **62**, but once again it was avoided by carrying out the reaction in benzene.

The observation that the formation of 4-endo compounds was slower in comparison with that of the corresponding 4-exo derivatives suggested the possibility of realizing a kinetic enrichment of the 4-exo diastereoisomer Bn-BTF(O)-OMe **4** starting from a 1:1 epimeric mixture of the two aldehydes **59** and **60** obtained from racemic Phe as described above. In fact, while under the usual cyclization conditions a 1:1 mixture of **4** and **5** was obtained starting from a 1:1 mixture of **59** and **60**, reducing the reaction time (and so the conversion) or increasing the amount of H_2SO_4/SiO_2 provided an increase of the **4**/**5** ratio up to 5:1 under the best conditions found. However, owing to the difficulties in achieving a complete separation of diasteroisomers **4** and **5** by chromatography, this method does not appear to be of synthetic utility. More convenient should be the separation by FCC of epimeric aldehydes prepared from racemic amino acids, followed by the cyclization of the separated aldehydes to obtain pure compounds BTAa(O). This goal was achieved with the 1:1 mixture of the two epimeric aldehydes **59** and **60** (from racemic Phe), which were separated by chromatography in good yield (36 and 38%, respectively) and cyclized to the corresponding BTF(O) and BTf(O). In the condensation of the racemic *N*-benzylphenylalaninol (**49** + **50**) with tartaric acid derivative (*R*,*R*)-**43**, no diastereoselectivity was observed in the formation of **54** and **55**.

The approach just described for the synthesis of BTAa-(O) could be also very useful in the case of unnatural amino acid precursors, which are usually prepared in racemic form.

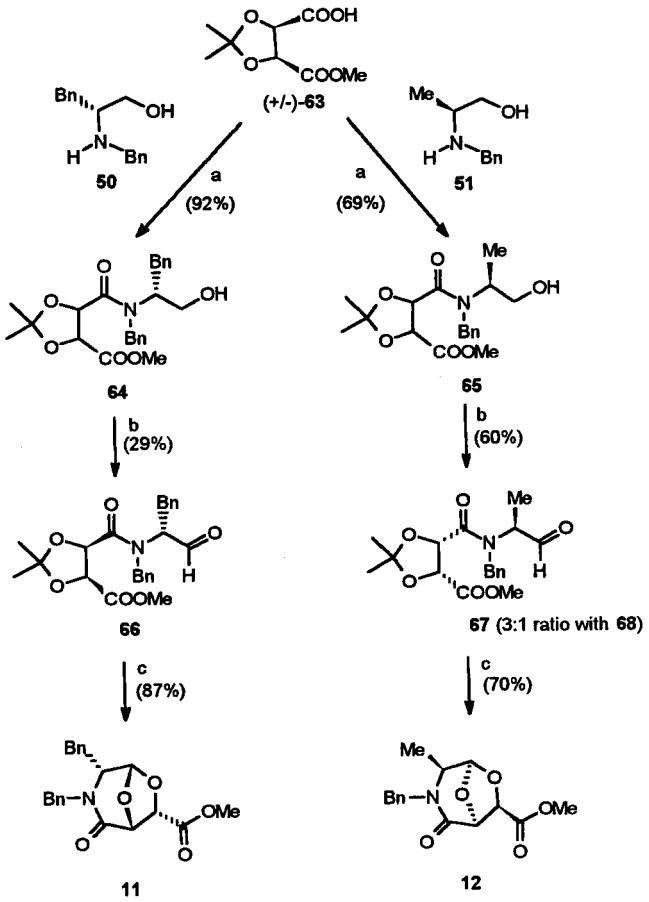
To test this hypothesis, we realized the synthesis of enantiopure methyl (1*R*,4*S*,5*S*,7*R*)- and (1*R*,4*R*,5*S*,7*R*)-3-aza-2-oxo-4-phenyl-6,8-dioxabicyclo[3.2.1]octane-7-carboxylates (**8** and **9**, respectively) through the use of the dimethyl acetal of *N*-benzyl-α-phenylglycine aldehyde **44** (Scheme 3). This compound was prepared according to a reported procedure,[11] starting from phenylacetaldehyde.

The condensation of **44** with tartaric acid derivative (*R*,*R*)-**43**, performed by using PyBroP in the usual way, afforded a 1:1 mixture of epimers **46** in 53% yield. These epimers were not separable by FCC, and thus, the mixture was subjected to different reaction conditions to convert it into the final product. The usual method of cyclization performed in boiling toluene with H_2SO_4/SiO_2 (1 equiv) for 20 min produced the desired product in very low yield as a mixture of 4-*exo*/*endo*-phenyl diastereoisomers **8** and **9**, together with the partially cyclized intermediate **47** and several decomposition products. Intermediate **47** was isolated and submitted again to the cyclization procedure for a further 10 min. In this way, it was completely converted affording desired compounds **8** and **9** as a 4:1 exo/endo diastereoisomeric mixture (12% yield). This result suggested that the large amount of decomposition products could arise from the instability of starting amides **46** more than that of **47** or the final products. Thus, heating the mixture of amides **46** under less drastic conditions [i.e., boiling benzene and in the presence of the SiO_2/H_2SO_4 (1 equiv) system for 20 min] gave a mixture of the final compounds (as a 2:1 exo/endo mixture in 75% yield), in a 6:1 ratio with **47**. Finally, using a 2-fold amount of SiO_2/H_2SO_4, the conversion of **46** to **8**/**9** was complete in boiling benzene after 20 min, although affording the final product as a 1:1 *exo*/*endo* mixture. In conclusion, from this set of experiments it was clear that the kinetic enrichment into the 4-*exo* compound **8** could be achieved only by decreasing the conversion. Unfortunately, all attempts to separate the epimeric mixture **46** or final products **8**/**9** by FCC failed. Compound **8** was thus characterized as a 4:1 mixture with its epimer **9**.

The reaction sequence depicted in Scheme 3 was then applied to the synthesis of two 7-endo compounds, i.e., 7-*endo*-Bn-BTf(O)-OMe **11** and 7-*endo*-Bn-BtA(O)-OMe **12**, derived from the initial condensation of racemic (*RS*,*SR*) methyl hydrogen 2,3-di-*O*-isopropylidenetartrate [(±)-(*R*,*S*)-**63**] with (*R*)-*N*-benzyl-phenylalaninol **50** and (*S*)-*N*-benzyl-alaninol **51**, respectively (Scheme 4). The partial hydrolysis of dimethyl *meso*-2,3-di-*O*-isopropylidenetartrate was achieved by treatment with 1 equiv of LiOH in MeOH/H_2O for 30 min at 0 °C. Under these conditions, it was possible to limit significantly the extent of epimerization to (*R*,*R*)- and (*S*,*S*)-**43**, although the conversion was not complete. Pure (±)-(*R*,*S*)-**63** (48% yield) was extracted with dichloromethane when the pH of the reaction mixture was adjusted to 4. The use of KOH as a base, under the conditions reported for the monohydrolysis of dimethyl (*R*,*R*)-2,3-di-*O*-isopropylidenetartrate,[12] produced a complex reaction mixture containing to a large extent products of epimerization. The condensation of (±)-(*R*,*S*)-**63** with amino alcohol **50** afforded a 1:1 mixture of diasteroisomers **64** (92%) having the opposite configurations of the tartaric moiety stereocenters. This mixture was not separable, and thus, it was transformed directly into the two corresponding diasteromeric aldehydes by Swern oxidation. One of the two aldehydes in part decomposed during the chromatographic separation, so that only epimer **66** (29%) was

(11) Boon, W. R. *J. Chem. Soc.* **1957**, 2146−2158.
(12) Musich, J. A.; Rapoport, H. *J. Am. Chem. Soc.* **1978**, *100*, 4865−4872.

Scheme 4[a]



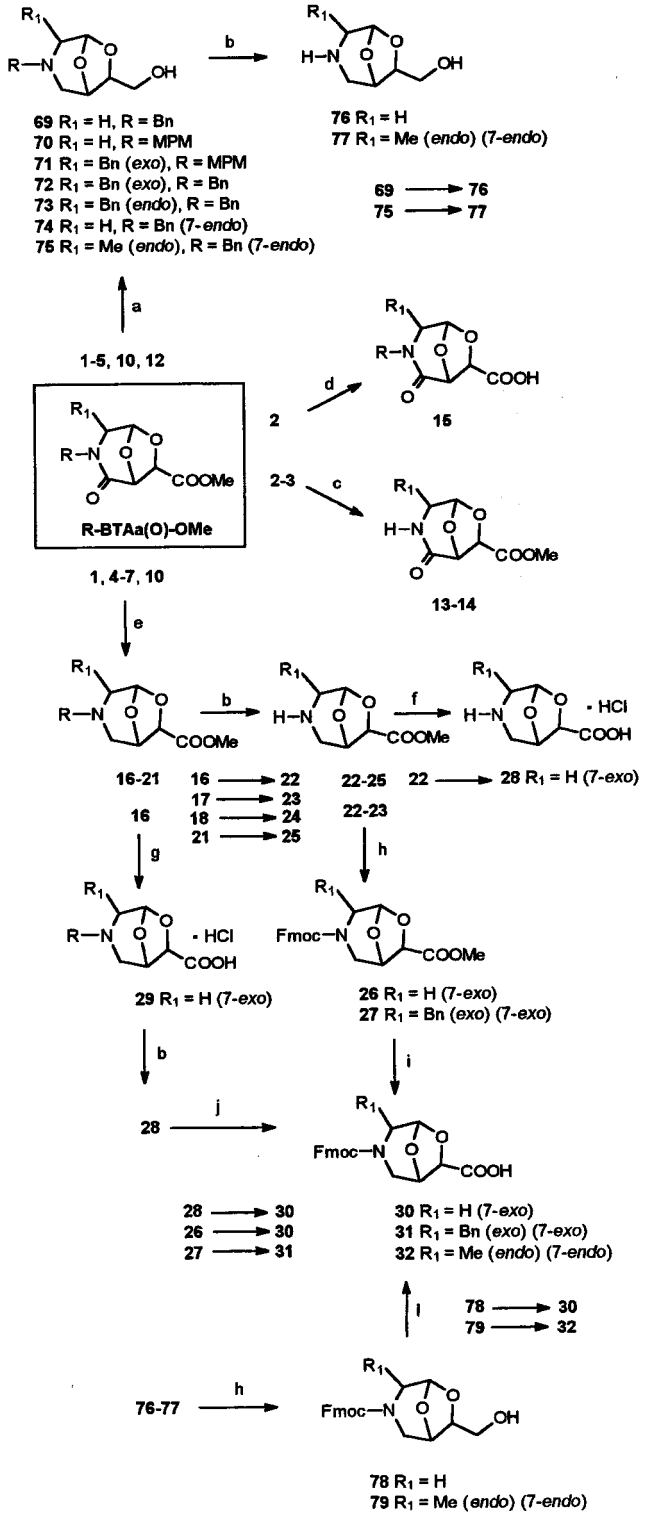
[a] Key: (a) PyBrOP, DIPEA, CH_2Cl_2, 12 h, 25 °C; (b) Swern oxidation; (c) H_2SO_4/SiO_2, benzene, reflux, 20 min, then distillation of one-third of the solvent.

recovered in pure form. This aldehyde was then treated in the usual way with H_2SO_4/SiO_2 in refluxing benzene, affording pure 7-*endo*-Bn-BTf-OMe **11** in 23% overall yield and without any epimerization. With the same methodology we prepared 7-endo compound **12**. After oxidation of amido alcohol **65** (Scheme 4) to the 1:1 mixture of corresponding aldehydes, an attempt at separating the two diastereoisomers by chromatography afforded aldehyde **67** as a 3:1 mixture with its epimer **68**. Also, in this case one of the two aldehydes decomposed to a certain extent. After cyclization in benzene of the mixture and chromatography of the crude, **12** was obtained in 70% yield as a 5:1 mixture in which the major isomer had the 4-methyl in the endo position [7-*endo*-Bn-BtA(O)-OMe]. The assignment of the endo position for the 4-substituent in **11** and **12** will be discussed later.

Reactivity of BTAa(O) and Transformation into BTAa. Several reactions were carried out to test the stability of R-BTAa(O)-OMe derivatives or transform them into compounds suitable for peptide synthesis such as *N*-Fmoc-protected amino acids or amino esters (Scheme 5). In particular, although the stability of the acetal bridge has been already demonstrated by Vogel during the transformations of the carbomethoxy into the corresponding carboxylic or amide group,[5] the stability under the conditions required for transformation into amino acids or amino esters had yet to be assessed.

The conversion of R-BTAa(O)-OMe into H-BTAa(O)-OMe by removal of the N-protecting group was feasible

Scheme 5[a]



[a] Key: (a) $LiAlH_4$, THF, reflux, 2 h; (b) H_2, $Pd(OH)_2/C$, MeOH, 12 h; (c) CAN, CH_3CN, H_2O, 5 h, 25 °C; (d) 1 M NaOH, 3 h, then 2 M HCl; (e) $BH_3 \cdot Me_2S$, THF, reflux, 40 min, then TMEDA, Et_2O, 15 min; (f) 4 N HCl, 18 h; (g) KOH, MeOH, 3 h, then 5 N HCl; (h) Fmoc-*O*-Su, CH_2Cl_2, 0 °C, 10 min, then 25 °C, 24 h; (i) 4 N HCl, DMSO, 1−3 d, 25 °C; (j) Fmoc-*O*-Su, acetone, H_2O, Na_2CO_3, 0 °C, then 25 °C, 12 h; (l) PDC, DMF, 24 h.

only by oxidation with CAN (cerium ammonium nitrate)[13] when R was MPM (4-methoxybenzyl), i.e., on compounds

(13) Yamamura, M.; Suzuky, T.; Hashimoto, H.; Yoshimura, J.; Okamoto, T. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1413−1420.

2−**3**, affording amido esters **13**−**14** in 72−85% yield. Instead, when the protecting group was the benzyl (in **1**), the deprotection attempted by hydrogenation over $Pd(OH)_2/C$ failed to give the corresponding amido esters.

As already found by Vogel, the N-protected R-BTAa-(O)-OMe derivatives were easily transformed into the corresponding acids either under acid conditions with aqueous 2 N HCl or basic conditions with KOH/MeOH. However, N-deprotected amido esters **13**−**14** showed a quite surprising reactivity: they were unstable both under acid (1 N HCl) and basic conditions (aqueous NaOH), undergoing a complete degradation of the bicyclic skeleton. The same instability was observed when H-BTAa(O)-OMe **13**−**14** were treated with strong bases (such as NaH or *n*-BuLi) in attempting a possible alkylation of the nitrogen or with $LiAlH_4$ in order to obtain the corresponding amino alcohols. This behavior is clearly related to the presence of a secondary amide because the corresponding N-protected amides R-BTAa-(O)-OMe were stable under similar conditions. Indeed, the reduction of R-BTAa(O)-OMe (R = Bn, or MPM) with $LiAlH_4$ in THF at 0 °C afforded the corresponding amino alcohols R-BTAa-CH_2OH **69**−**75** in fair to good yield without decomposition or racemization. The N-deprotection of R-BTAa-CH_2OH was performed on *N*-benzyl derivatives **69** and **75**, affording amino alcohols **76** and 7-*endo*-**77** quantitatively only by reduction with $Pd(OH)_2/C$ in MeOH. On the contrary, the *N*-MPM protecting group in **70**−**71** was not removed by hydrogenolysis, while CAN treatment decomposed the amino alcohols.

Owing to the instability of the deprotected H-BTAa-(O)-OMe, the selective reduction of the internal amide bond was therefore carried out on Bn-BTAa(O)-OMe to give the corresponding amino esters Bn-BTAa-OMe **16**−**21**, the two protections of BTAa being in this case orthogonal. The reduction was carried with $BH_3 \cdot Me_2S$ (BMS) in THF at reflux, followed by treatment with TMEDA.[14] Bn-BTAa-OMe compounds were purified by FCC, separating the amount of Bn-BTAa-CH_2OH often present as byproduct. The precise control of the refluxing time was a crucial point for limiting the formation of this side product, albeit in all cases (with the reduction of **1** as an exception) it was impossible to avoid the formation of ∼30% of the corresponding amino alcohol. The reduction of the amide function or the concomitant reduction of the ester group did not lead to any epimerization of the stereocenters.

At this point we had in our hands six different orthogonally protected BTAa amino acids (**16**−**21**). They were stable under quite different conditions, either when protected as *N*-benzyl and esters or when one or both the functionalities were deprotected. To verify the possibility of inserting these amino acids into peptides by using solid-phase peptide synthesis, we evaluated four different strategies (Scheme 5) to transform them in *N*-Fmoc-protected amino acids (Fmoc-BTA-OH), usually employed in peptide synthesis. In particular, we prepared three different *N*-Fmoc amino acids, i.e., Fmoc-BTG-OH **30**, Fmoc-BTF-OH **31**, and 7-*endo*-Fmoc-BtA-OH **32**.

The first two methods included the complete deprotection of Bn-BTAa-OMe to free amino acids, either by initial debenzylation followed by hydrolysis of the ester group or by inverting this sequence. Thus, Bn-BTAa-OMe **16**−**18** and **21** (see Table 1) were quantitatively N-deprotected with H_2 and $Pd(OH)_2/C$ in MeOH affording the corresponding H-BTAa-OMe **22**−**25** (the same deprotection failed when the protecting group was MPM). Acid or basic hydrolysis was then performed in particular on amino ester **22** to give amino acid **28** in high yield as its hydrochloride salt. The fully deprotected amino acid **28** was also prepared as its hydrochloride salt (96%) by acid hydrolysis of the corresponding *N*-benzyl ester **16** to give **29** followed by debenzylation with $H_2/Pd(OH)_2$ in MeOH (100%). The *N*-Fmoc derivative **30** (84% yield) was finally prepared by reaction of **28** with Fmoc-*O*-succinimide (Fmoc-*O*-Su) and Na_2CO_3 in acetone/water. Removal of the solvent *in vacuo* allowed the recovery of Fmoc-BTG-OH **30** sufficiently pure for the further coupling step.

As an alternative to the complete deprotection, the amino esters H-BTAa-OMe can be protected as *N*-Fmoc and then hydrolyzed by acidic treatment. Thus, Fmoc-BTG-OMe **26**, prepared by reaction of H-BTG-OMe **22** with Fmoc-*O*-Su in CH_2Cl_2, underwent hydrolysis of the ester group by treatment with 4 N HCl in DMSO at room temperature. However, the hydrolysis was slow (24 h) and the yield (72%) lowered by the difficulty involved in completely recovering the product from the solution, as well as by the uncomplete conversion to Fmoc-BTG-OH. With this strategy, Fmoc-BTF-OH **31** (66%) was prepared as well. Also in this case, the hydrolysis of intermediate **27** was very slow (3 days) making this procedure not as useful as the two previously described. Finally, as the best methodology, we found that *N*-benzylamino alcohols can be very productively employed for the conversion of BTAa in *N*-Fmoc amino acids. This strategy also avoided the use of BH_3·DMS for the reduction of the amido esters BTAa(O)-OMe to amino esters BTAa-OMe. Thus, protection of amino alcohols **76** and **77** (Scheme 5) as Fmoc derivatives **78** (66%) and **79** (69%) was accomplished with Fmoc-*O*-Su in CH_2Cl_2. Then, oxidation of alcohols **78** and **79** to carboxylic acids by PDC in DMF at room temperature gave **30** and **32** in 89% and 91% yield, respectively.

Peptide Coupling of BTAa. The compatibility of these new dipeptide isosteres with the conditions required for peptide synthesis was not, in principle, obvious. Indeed, the peptide coupling reaction of a hindered amino acid bearing a secondary amino group (as in proline) is often difficult to realize, and the resistance of BTAa's to the acid (TFA) conditions required for the cleavage of the peptide from the resin had to be ascertained.

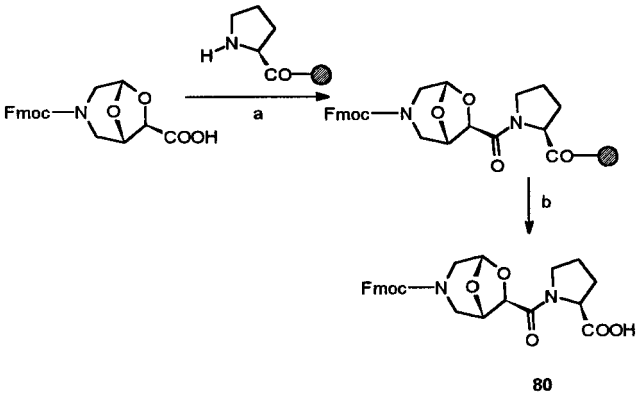
To verify the possible use of BTAa in peptide synthesis, we synthesized the dipeptide BTG-ProOH **80** on a Wang-type resin (Scheme 6).

H-Pro-{Wang resin} suspended in DMF was treated during 4 days with a 2-fold excess of Fmoc-BTG-OH in the presence of *N*,*N*′-diisopropylcarbodiimide (DIPCDI), 1-hydroxybenzotriazole (HOBt), and DIPEA. The dipeptide Fmoc-BTG-Pro-OH **80** (76%) was then cleaved from the resin by treatment with TFA/H_2O (95:5) for 4 h. The HPLC analysis showed a single peak, and FAB-MS was in agreement with the molecular weight.

Structure Assignment and Conformational Analysis. The attribution of the correct stereochemistry to R-BTAa(O)-OMe and R-BTAa-OMe (Figure 1) is possible by ^{1}H NMR spectroscopy. Amides **1**−**9**, having a 7-*exo*-carbomethoxy group, are characterized by the presence in their ^{1}H NMR spectrum of three diagnostic signals,

(14) Brown, H. C.; Choi, Y. M.; Narasimhan, S. *J. Org. Chem.* **1982**, *47*, 3153−3163.

Scheme 6[a]



[a] Key: (a) DMF, diisopropylcarbodiimide, HOBt, DIPEA, 4 days, then Ac_2O, DMF, DMAP, 3 h; (b) TFA, H_2O, 4 h.

attributable to the bridgehead protons 1-H and 5-H (equatorially orientated) and 7-H. 1-H and 7-H always resonate as singlets in the 4.67 and 5.10 ppm range. In the ^{1}H NMR spectrum of compounds (±)-**10** and **11**−**12**, bearing a 7-*endo*-carbomethoxy group, the occurrence of a coupling between 1-H and 7-H ($J \approx 5.1$ Hz) is diagnostic of the configurational change at the C-7. In all cases, the more deshielded proton is 5-H, which resonates in the 5.17−5.87 ppm range and can be a singlet or doublet depending on the stereochemistry at C-4. Thus, in the 4-exo-substituted amido esters **3**, **4**, **6**, **8**, and **14**, 5-H resonates always as a singlet, while in the 4-endo-substituted amides **5**, **7**, **9**, **11**, and **12**, it is a doublet, having a small coupling constant (1.8−2.6 Hz) with the exo proton on C-4. This coupling is diagnostic for 4-endo-substituted compounds and is always visible for the *exo*-4-H protons. The coupling between 5-H and *exo*-4-H is also visible in the spectrum of Bn-BTG(O)-OMe **1** and H-BTG(O)-OMe **13**, wherein 5-H resonates as a doublet at 5.85 (J = 2.2 Hz) and 5.87 (J = 1.8 Hz) ppm, respectively.

N-Benzylamines **16**−**21** possess the same pattern of ^{1}H NMR signals as the corresponding amides, although the 1-H proton undergoes an upfield shift and always resonates as a broad singlet (or a doublet in the case of (±)-**21** due to the endo stereochemistry of the COOMe group) in the range 4.47−4.61 ppm. The coupling constants of 1-H with the protons on C-2 and C-7 are in fact very small (0−1.8 Hz) in compounds **16**−**20** and not detectable at 200 MHz. Similarly, values of coupling constants close to 0 Hz between 5-H and either *endo*- or *exo*-4-H make the bridgehead 5-H proton appearing as a singlet between 5.25 and 5.62 ppm. The only exception is the 4-*exo*-methyl derivative **19**, in which 5-H is a doublet (J = 1.8 Hz) at 5.37 ppm because of the coupling with *endo*-4-H. In the case of amines **16**−**21**, the occurrence of 5-H as a doublet in the ^{1}H NMR spectrum is not indicative of the presence a 4-endo substituent. The same considerations apply in secondary amines **22**−**25** and **28**.

In the amines, the six-membered ring should have a chairlike conformation, as suggested by the very low coupling constants of protons 1-H and 5-H with the vicinal protons on C-2 and C-4, respectively. By molecular modeling[15] of amine **16** it was found that the chairlike conformation of the six-membered ring is thermodynamically favored (by ∼6 kcal/mol) with respect to the boatlike one. In the latter conformation, the calculated coupling constants between 1-H and the two protons on C-2 would be very different from those found experimentally, since at least one of them is about 9 Hz (and the other about 4 Hz). On the other hand, in the chairlike conformation, the dihedral angles between protons on C-1 and C-2 (and C-5 and C-4) are very close to 60°, thus accounting for the very low coupling constants observed. The repulsion between the N-3 and O-8 lone pairs in the boatlike conformation should greatly contribute to the high strain energy of this conformation for amines **16**−**21** which should, therefore, be considered as conformationally biased.

Both the introduction of an *N*-Fmoc protecting group and the formation of an amide bond with the 7-carboxy group cause an increase of the complexity of the ^{1}H NMR spectra. This is due to the occurrence in solution of isomers generated by hindered rotation about the N−C=O bonds. Thus, in the ^{1}H NMR spectrum of **26**, the signals attributable to the protons on C-2 and C-4 are split and it is possible to calculate a 1:1 ratio between the two rotamers. Moreover, while in the ^{1}H NMR spectrum of Fmoc-BTG-OMe **26** proton 5-H is a singlet, in the spectrum of Fmoc-BTG-Pro **80** the signal of the same proton is split in two singlets at 5.65 and 5.61 ppm (the ratio between the areas is 2:1), apparently undergoing the field effects of two different conformations assumed by the newly introduced proline residue. It is known in fact that proline amides display an equal tendency to assume both the *cis*- and *trans*-amide conformations.[16]

Since the aim of the present work is to prepare a novel class of constrained dipeptide isosteres, it would also be important to evaluate, once a BTAa isostere has been introduced in a peptide, how the byciclic structure could affect the orientation of the peptide chains at N-3 and C-7. With this in mind, we performed a complete conformational analysis on simple 7-exo and 7-endo model compounds shown in Figure 3 in which an *N*-acetyl group should mimic the first peptide bond and the C-7′−NHMe bond the linkage of the acid moiety of the BTAa with a second peptide. This analysis resulted in the observation that, in both 7-endo and 7-exo models, only one orientation is favored (by ∼7 kcal/mol) for the amide group at C-7, since an apparently strong H bond ($d \approx 2.1$ Å) formed between O-6 and N−H forces the C=O group to assume an antiperiplanar orientation with respect to the C-7−O-6 bond (dihedral angle $\Phi_1 \approx \pm 175°$). Thus, the presence of O-6 in BTAa is an important factor that could govern the initial orientation of the peptide chain at C-7. In the case of the 7-exo models, the formation of an H bond with O-8 is also possible but the corresponding conformation always collapsed to the one showed in Figure 3 when minimized. Concerning the substitution at N-3, the two conformations with the C=O group eclipsed or antiperiplanar to the N-3−C-2 bond (Φ_2 about 0 and −180°) were equally populated. Only in the case of the 4-endo-substituted compounds was the latter orientation favored (by 1.1 kcal/mol), due to a greater steric hindrance between the methyl group

(15) MacroModel (v4.5) molecular modeling software was used for the molecular mechanics calculations (Amber force field) and Monte Carlo conformational search using the default values of this software. Mohamadi, F.; Richards, N. G.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440−467.

(16) Curran, T. P.; McEnaney, P. M. *Tetrahedron Lett.* **1995**, *36*, 191−194.

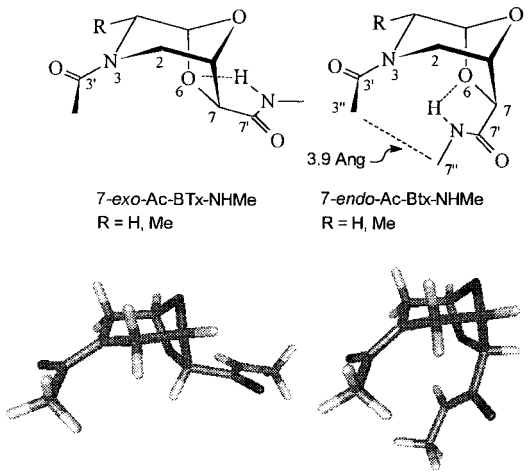


Figure 3. Left: lowest energy conformer of 7-exo model compound Ac-BTx-NHMe. Right: lowest energy conformer of 7-endo model compound Ac-Btx-NHMe. Dihedral angles Φ_1 = O-6−C-7−C-7′═O, Φ_2 = C-2−N-3−C-3′═O.

and the 4-endo substituent. These observations suggest an important difference between 7-*endo*- and 7-*exo*-BTA: the first class of compounds could be introduced into a peptide to induce β-turnlike folding, since the distance between atoms C-3″ and C-7″ is ∼3.9 Å, i.e., much lower than the maximum distance of 7 Å between the corresponding atoms in a peptide required for the formation of a β-turn.[17] 7-*exo*-BTA, on the other hand, should maintain a more planar and extended structure. Experiments aimed at confirming these hypotheses are now in progress.

Conclusions

Employing α-amino acid and tartaric acid derivatives, we have developed a simple and straightforward method for synthesizing novel potential dipeptide isosteres containing the 3-aza-6,8-dioxabicyclo[3.2.1]octane-7-carboxylic acid structure. We found, as key features, that complete control of all the stereocenters is possible by appropriate choice of the starting precursors; the synthesis can be applied to natural, unnatural, and unusual amino acids, as well as to chiral or *meso*-tartaric acids, also in racemic form, and allows the preparation of single diastereoisomers either by separation of the intermediates or by kinetic enrichment during the cyclization process. Despite the presence of the acetal moiety, the skeleton of BTAa compounds is stable under different reactions conditions, allowing a large number of synthetic transformations, including oxidation, reduction, protection, and deprotection of the functionalities. The Fmoc-protected amino acids (Fmoc-BTAa-OH) can be coupled to other amino acids bound to a resin, and the resulting peptide can be recovered without modifications of the BTAa skeleton by the usual methods of solid-phase peptide synthesis. Finally, the possibility of choosing the orientation of the 7-carboxy group could allow the selection of a particular orientation of the peptide chains if BTAa are introduced into peptides. All the features above summarized indicate that BTAa could represent a novel class of dipeptide isosteres potentially useful for peptidomimetic synthesis. The synthesis of peptides containing them is now in progress and the results of the conformational and biological proprieties of the modified peptides will be reported in due course.

(17) Ball, J. B.; Hughes, R. A.; Alewood, P. F.; Andrews, P. R. *Tetrahedron* **1993**, *49*, 3467−3478.

Experimental Section

Melting points are uncorrected. Chromatographic separations were performed under pressure on silica gel using flash-column techniques; R_f values refer to TLC carried out on 25-mm silica gel plates (Merck F254), with the same eluant indicated for column chromatography. ^{1}H and ^{13}C NMR spectra were recorded at 200 and 50.33 MHz, respectively, unless otherwise stated. EI mass spectra were carried out at 70 eV ionizing voltage. THF was distilled from Na/benzophenone. CH_2Cl_2 was distilled from CaH_2. All reactions requiring anhydrous conditions were performed in flame-dried glassware. Compounds **33**−**34, 44**,[7,11] (*R*,*R*)- and (*S*,*S*)-**43**,[12] and **48**−**52**[18−21] were prepared as reported. Acid silica gel (H_2SO_4/SiO_2) was prepared as reported.[4] Resin WANG-Pro-FMOC was purchased from Advanced Chemtech. HPLC analysis of compound **80** was performed with a RP18 5 μm column, using CH_3CN-H_2O as eluant.

(2*R*,6*R*/*S*)-(+)-(4-Benzyl-6-methoxy-3-oxomorpholin-2-yl)-(*R*)-hydroxyacetic Acid Methyl Ester (38). To a solution of anhydride **35** (8.4 g, 38.9 mmol) in dry CH_2Cl_2 (100 mL) was added, under nitrogen atmosphere, **33** (8.0 g, 41.0 mmol) and the mixture stirred at room temperature for 60 min. After evaporation of the solvent, the crude product was dissolved in methanol (135 mL), thionyl chloride (2.7 mL, 37.0 mmol) was added dropwise, and the mixture was heated at 50 °C for 2 h. The solvent was then removed, and the crude product was purified by chromatography (EtOAc−petroleum ether, 1:2, R_f 0.05) to give **38** (11.0 g, 87%) as a dark oil. The same compound was obtained as a 1:1 mixture with **1** after **45** (200 mg, 0.52 mmol) was heated in a refluxing suspension of H_2SO_4/SiO_2 (105 mg) in toluene (32 mL) for 10 min. The two products were separated by chromatography (EtOAc−petroleum ether, 1:2) obtaining pure **38** (80 mg) in 40% yield as a 5:1 mixure of epimers: $[\alpha]^{20}_D$ +97.1 (*c* 0.38, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.35−7.10 (m, 5 H), 4.92 (s, 1 H), 4.83 (s, 1 H), 4.79 (d, J = 14.7 Hz, 1 H), 4.60 (s, 1 H), 4.47 (d, J = 14.7 Hz, 1 H), 3.82 (s, 3 H), 3.50 (dd, J = 12.4, 3.3 Hz, 1 H), 3.35 (s, 3 H), 3.08 (d, J = 12.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 172.1 (s), 165.5 (s), 135.6 (s), 128.8 (d, 2 C), 127.9 (d, 2 C), 127.7 (d), 94.9 (d), 72.1 (d), 71.5 (d), 55.0 (q), 52.8 (q), 49.8 (t), 49.3 (t); MS *m*/*z* 309 (M^+, 6), 91 (100); IR ($CDCl_3$) 3547 (br), 1743, 1655 cm^{-1}. Anal. Calcd for $C_{15}H_{19}NO_6$: C, 58.25; H, 6.19; N, 4.53. Found: C, 58.30; H, 6.00; N, 4.22.

(2*R*,6*R*/*S*)-(+)-(6-Methoxy-4-*p*-methoxybenzyl-3-oxomorpholin-2-yl)-(*R*)-hydroxyacetic Acid Methyl Ester (39). Compound **39** was prepared according to the procedure for **38** from **35** (10 g, 47 mmol) and **34** (14 g, 55.3 mmol). The crude product was purified by chromatography (EtOAc−petroleum ether, 1:1, R_f 0.1) to give **39** (13.0 g, 81%) as a red solid: mp 110 °C; $[\alpha]^{20}_D$ +124.5 (*c* 1.45, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.20 (d, J = 9.0 Hz, 2 H), 6.55 (d, J = 9 Hz, 2 H), 4.83 (d, J = 1.9 Hz, 1 H), 4.73 (d, J = 2.5 Hz, 1 H), 4.60 (d, J = 15 Hz, 1 H), 4.50 (d, J = 1.9 Hz, 1 H), 4.30 (d, J = 15 Hz, 1 H), 3.81 (s, 1 H), 3.68 (s, 3 H), 3.63 (s, 3 H), 3.38 (dd, J = 12.5, 2.5 Hz, 1 H), 3.23 (s, 3 H), 2.96 (d, J = 12.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 172.1 (s), 165.0 (s), 158.6 (s), 128.8 (d, 2 C), 127.2 (s), 113.6 (d, 2 C), 94.4 (d), 72.0 (d), 71.1 (d), 54.7 (q), 54.5 (q), 52.1 (q), 48.6 (t, 2 C); MS *m*/*z* 339 (M^+, 2), 121 (100); IR ($CDCl_3$) 3450, 1752, 1673 cm^{-1}. Anal. Calcd for $C_{16}H_{21}NO_7$: C, 56.63; H, 6.24; N, 4.13. Found: C, 56.74; H, 6.25; N, 4.00.

***meso*-2,3-Di-*O*-acetyltartaric Anhydride (40).** Compound **40** was prepared according to the procedure reported

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for the preparation of **35**, by adding, under a nitrogen atmosphere, *meso*-tartaric acid (5.0 g, 33.3 mmol) to a solution of acetic anhydride (10.5 mL, 0.111 mol) and of 37% HCl (0.3 mL). Distillation of the formed acetic acid afforded **40** (3.70 g, 51%) as a dark oil that was immediately used in the next step without further purification: ^{1}H NMR ($CDCl_3$) δ 5.50 (s, 2 H), 2.18 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 169.4 (s, 2 C), 165.3 (s, 2 C), 65.9 (d, 2 C), 19.5 (q, 2 C).

(±)-(*R*,*S*)-2,3-Di-*O*-isopropylidenetartaric Acid Monomethyl Ester [(±)-(*R*,*S*)-63]. $LiOH·H_2O$ (0.56 g, 13.3 mmol) was slowly added to a stirring solution of *meso*-2,3-di-*O*-isopropylidenetartaric acid dimethyl ester (2.65 g, 12.1 mmol) in MeOH (80 mL) and water (27 mL) cooled at 0 °C. After 30 min at 0 °C, the MeOH was evaporated, and further water (30 mL) was added to the residual suspension. After a first extraction with Et_2O, the pH of the aqueous phase was adjusted to 3.5 with 5% HCl and extracted with Et_2O and then CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and concentrated, affording (±)-(*R*,*S*)-**63** (1.18 g, 48%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 4.86 (AB system, J = 7.3 Hz, 2 H), 3.76 (s, 3 H), 1.65 (s, 3 H), 1.42 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 172.3 (s), 168.5 (s), 113.3 (s), 76.3 (d), 75.8 (d), 52.6 (q), 26.5 (q), 25.6 (q).

(−)-*N*-Benzyl-*N*′-(2,2-dimethoxyethyl)-(2*R*,3*R*)-2,3-di-*O*-isopropylidenetartramic Acid Methyl Ester (45). To a solution of **33** (669 mg, 3.43 mmol) in anhydrous CH_2Cl_2 (3.5 mL) (CH_2Cl_2 was filtered through a short pad of anhydrous Na_2CO_3 just before being used) were added, under a nitrogen atmosphere, (*R*,*R*)-**43** (700 mg, 3.43 mmol), PyBrOP (1.60 g, 3.43 mmol), and DIPEA (1.17 mL, 6.86 mmol). The mixture was stirred at room temperature for 2 h, and then the solvent was removed to give an oil that was dissolved in EtOAc. This solution was washed with aqueous 5% $KHSO_4$, 5% $NaHCO_3$, and brine and dried over Na_2SO_4. After evaporation of the solvent, the crude product obtained was purified by chromatography (EtOAc−petroleum ether, 1:3, R_f 0.23), yielding **45** (1.038 g, 79%) as a colorless oil: $[\alpha]^{25}_D$ −30.9 (*c* 0.76, $CHCl_3$); ^{1}H NMR ($CDCl_3$) (1:1 mixture of rotamers) δ 7.40−7.10 (m, 5 H), 5.35 (d, J = 5.5 Hz, 0.5 H), 5.33 (d, J = 5.9 Hz, 0.5 H), 5.14 (d, J = 5.9 Hz, 0.5 H), 4.94 (AB system, J = 16.8 Hz, 0.5 H), 4.86 (d, J = 5.5 Hz, 0.5 H), 4.84 (d, J = 12.1 Hz, 0.5 H), 4.72 (AB system, J = 16.8 Hz, 0.5 H), 4.58 (d, J = 12.1 Hz, 0.5 H), 4.55 (m, 0.5 H), 4.35 (dd, J = 6.9, 3.7 Hz, 0.5 H), 3.78 (s, 1.5 H), 3.75 (m, 0.5 H), 3.74 (s, 1.5 H), 3.59 (dd, J = 13.6, 4.4 Hz, 0.5 H), 3.38 (s, 1.5 H), 3.36 (s, 1.5 H), 3.35 (m, 0.5 H), 3.34 (s, 1.5 H), 3.33 (s, 1.5 H), 3.21 (dd, J = 13.6, 5.9 Hz, 0.5 H), 1.44 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 170.9 (s), 170.8 (s), 168.9 (s), 168.5 (s), 137.0 (s), 136.4 (s), 128.7 (d, 2 C), 128.6 (d, 2 C), 128.0 (d, 2 C), 127.6 (d), 127.4 (d), 126.8 (d, 2 C), 113.0 (s), 112.9 (s), 103.0 (d), 102.9 (d), 76.1 (d, 2 C), 55.6 (q), 55.2 (q), 54.7 (q), 54.5 (q), 52.5 (q), 51.7 (q), 49.9 (t), 48.7 (t), 48.0 (t), 26.3 (q), 26.2 (q); MS *m*/*z* 381 (M^+, 0.1), 75 (100); IR ($CDCl_3$) 1754, 1652. Anal. Calcd for $C_{19}H_{27}NO_7$: C, 59.83; H, 7.13; N, 3.67. Found: C, 59.82; H, 7.15; N, 3.83.

***N*-Benzyl-*N*′-[(2,2-dimethoxy)-1-phenylethyl]-(2*R*,3*R*)-2,3-di-*O*-isopropylidenetartramic Acid Methyl Ester (46).** Prepared according to the procedure reported for **45**. Starting from **44** (0.865 g, 3.19 mmol) and (*R*,*R*)-**43** (0.651 g, 3.19 mmol), **46** was obtained after chromatographic purification (EtOAc−petroleum ether, 1:3, R_f 0.20) as a 1:1 diastereomeric mixture (0.774 g, 53%): ^{1}H NMR ($CDCl_3$) (each diastereoisomer as a 2:1 mixture of rotamers) δ 7.57−7.00 (m, 5 H), 5.62 (d, J = 8.8 Hz, 0.6 H), 5.45 (m, 1.2 H), 5.37 (d, J = 5.9 Hz, 0.4 H), 5.29 (d, J = 5.5 Hz, 0.4 H), 4.97 (d, J = 7.3 Hz, 0.4 H), 4.84−4.40 (m, 3 H), [3.82 (s), 3.74 (s), and 3.68 (s), 3 H], [3.40 (s), 3.30 (s), 3.23 (s), 3.17 (s), 3.14 (s), and 3.13 (s), 6 H], 1.60−1.30 (m, 6 H); MS *m*/*z* 457 (M^+, 0.2), 91 (100), 75 (100); IR ($CDCl_3$) 1751, 1647 cm^{-1}.

***N*-(*p*-Methoxybenzyl)-*N*′-[(1*S*)-1-benzyl-2-hydroxyethyl]-(2*R*,3*R*)-2,3-di-*O*-isopropylidenetartramic Acid Methyl Ester (53).** Prepared according to the procedure reported for **45**, but the reaction was left under stirring for 12 h. Starting from (*R*,*R*)-**43** (268 mg, 1.32 mmol) and **48** (624 mg, 1.39 mmol), **53** was obtained after chromatography (EtOAc−hexane,1:1, R_f 0.41) as a colorless oil (565 mg, 87%): ^{1}H NMR ($CDCl_3$) (2:1 mixture of rotamers) major rotamer δ 7.35−7.00 (m, 8 H), 6.85 (m, 2 H), 5.29 (d, J = 6.2 Hz, 1 H), 4.88 (d, J = 6.2 Hz, 1 H), 4.68 (d, J = 16.5 Hz, 1 H), 3.99 (d, J = 16.5 Hz, 1 H), 3.79 (s, 3 H), 3.77 (s, 3 H), 3.65 (m, 2 H), 3.50 (m, 1 H), 3.05 (m, 2 H), 1.54 (s, 3 H), 1.44 (s, 3 H); minor rotamer δ 7.35−7.20 (m, 8 H), 6.85 (m, 2 H), 5.43 (d, J = 5.4 Hz, 1 H), 5.17 (d, J = 5.4 Hz, 1 H), 4.82 (d, J = 15.4 Hz, 1 H), 4.44 (d, J = 15.4 Hz, 1 H), 3.79 (s, 3 H), 3.77 (s, 3 H), 2.92 (dd, J = 14.0, 5.1 Hz, 1 H), 2.72 (dd, J = 14.0, 9.2 Hz, 1 H), 1.54 (s, 3 H), 1.44 (s, 3 H); ^{13}C NMR ($CDCl_3$) major rotamer δ 170.7 (s), 169.3 (s), 159.3 (s), 138.3 (s), 129.3 (d, 2 C), 129.0 (s), 128.6 (d, 2 C), 128.5 (d, 2 C), 126.5 (d), 114.3 (d, 2 C), 113.1 (s), 76.8 (d), 76.3 (d), 64.3 (d), 63.7 (t), 55.3 (q), 52.7 (q), 52.2 (t), 34.1 (t), 26.4 (s), 26.1 (s). Anal. Calcd for $C_{25}H_{31}NO_7$: C, 65.63; H, 6.83; N, 3.06. Found: C, 65.48; H, 6.90; N, 2.98.

***N*-Benzyl-*N*′-[(1*S*)-1-benzyl-2-hydroxyethyl]-(2*R*,3*R*)-2,3-di-*O*-isopropylidenetartramic Acid Methyl Ester (54).** Prepared according to the procedure reported for **45**, but the reaction was left under stirring for 12 h. Starting from (*R*,*R*)-**43** (906 mg, 4.44 mmol) and **49** (1.07 g, 4.44 mmol), **54** was obtained after chromatography (EtOAc−petroleum ether, 1:1, R_f 0.37) as a colorless oil (1.32 g, 69%): $[\alpha]^{25}_D$ −72.3 (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) (2:1 mixture of rotamers) major rotamer δ 7.40−7.05 (m, 10 H), 5.28 (d, J = 6.0 Hz, 1 H), 4.81 (d, J = 6.0 Hz, 1 H), 4.75 (d, J = 16.4 Hz, 1 H), 4.00 (d, J = 16.4 Hz, 1 H), 3.79 (s, 3 H), 3.70 (m, 1 H), 3.60 (m, 1 H), 3.46 (m, 1 H), 3.04 (m, 2 H), 1.52 (s, 3 H), 1.49 (s, 3 H); minor rotamer δ 7.40−7.05 (m, 10 H), 5.41 (d, J = 5.5 Hz, 1 H), 5.13 (d, J = 5.5 Hz, 1 H), 4.95 (d, J = 15.2 Hz, 1 H), 4.42 (d, J = 15.2 Hz, 1 H), 3.79 (s, 3 H), 2.93 (dd, J = 13.7, 5.0 Hz, 1 H), 2.71 (dd, J = 13.7, 8.9 Hz, 1 H), 1.52 (s, 3 H), 1.49 (s, 3 H); ^{13}C NMR ($CDCl_3$) major rotamer δ 170.6 (s), 169.4 (s), 138.3 (s), 136.2 (s), 129.2 (d, 2 C), 129.0 (d, 2 C), 128.8 (d, 2 C), 127.9 (d), 127.3 (d, 2 C), 127.1 (d), 113.1 (s), 76.6 (d), 76.1 (d), 64.5 (d), 63.6 (t), 52.6 (t), 52.5 (q), 34.0 (t), 26.2 (q), 26.0 (q); MS *m*/*z* 427 (M^+, 1), 91 (100); IR ($CDCl_3$) 1730, 1642 cm^{-1}. Anal. Calcd for $C_{24}H_{29}NO_6$: C, 67.43; H, 6.84; N, 3.28. Found: C 67.29; H 6.91; N, 3.12.

***N*-Benzyl-*N*′-[(1*R*)-1-benzyl-2-hydroxyethyl]-(2*R*,3*R*)-2,3-di-*O*-isopropylidenetartramic Acid Methyl Ester (55).** Prepared according to the procedure reported for **45**, but the reaction was left under stirring for 12 h. Starting from (*R*,*R*)-**43** (513 mg, 2.52 mmol) and **50** (608 mg, 2.52 mmol), **55** was obtained after chromatography (EtOAc−petroleum ether, 1:1, R_f 0.38) as a colorless oil (675 mg, 63%): $[\alpha]^{25}_D$ +49.4 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) (2:1 mixture of rotamer) major rotamer δ 7.40−7.05 (m, 10 H), 5.30 (d, J = 5.8 Hz, 1 H), 4.80 (d, J = 5.8 Hz, 1 H), 4.66 (d, J = 16.1 Hz, 1 H), 3.93 (d, J = 16.1 Hz, 1 H), 3.80 (s, 3 H), 3.70−3.60 (m, 3 H), 3.05 (m, 2 H), 1.44 (s, 3 H), 1.41 (s, 3 H); ^{13}C NMR ($CDCl_3$) major rotamer δ 170.6 (s), 169.5 (s), 138.5 (s), 136.2 (s), 129.2 (d, 2 C), 128.8 (d, 2 C), 128.6 (d, 2 C), 128.0 (d), 127.6 (d, 2 C), 127.4 (d), 113.2 (s), 76.7 (d), 76.2 (d), 63.1 (d), 61.3 (t), 52.6 (t), 52.5 (q), 33.9 (t), 26.3 (q), 26.1 (q); MS *m*/*z* 427 (M^+, 4), 91 (100); IR ($CDCl_3$) 1730, 1642 cm^{-1}. Anal. Calcd for $C_{24}H_{29}NO_6$: C, 67.43; H, 6.84; N, 3.28. Found: C, 67.11; H, 6.81; N, 3.02.

***N*-Benzyl-*N*′-[(1*S*)-2-hydroxy-1-methylethyl]-(2*R*,3*R*)-2,3-di-*O*-isopropylidenetartramic Acid Methyl Ester (56).** Prepared according to the procedure reported for **45**, but the reaction was left under stirring for 12 h. Starting from (*R*,*R*)-**43** (1.53 g, 7.5 mmol) and **51** (1.24 g, 7.5 mmol), **56** was obtained after chromatography (Et_2O, R_f 0.3) as a colorless oil (2.025 g, 76%): $[\alpha]^{20}_D$ −21.9 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) (1:1 mixture of rotamers) δ 7.39−7.28 (m, 5 H), 5.43 (d, J = 5.4 Hz, 0.5 H), 5.33 (d, J = 6.2 Hz, 0.5 H), 5.18 (d, J = 5.4 Hz, 0.5 H), 4.90 (d, J = 17.4 Hz, 1 H), 4.77 (d, J = 14.6 Hz, 1 H), 4.75 (d, J = 5.8 Hz, 0.5 H), 4.52 (d, J = 17.4 Hz, 1 H), 4.39 (d, J = 14.6 Hz, 1 H), 4.00 (m, 0.5 H), 3.78 (s, 1.5 H), 3.74 (s, 1.5 H), 3.68 (m, 1 H), 3.47 (m, 1 H), 3.14 (m, 0.5 H), [1.49 (s) and 1.43 (s), 3 H], [1.45 (s) and 1.41 (s), 3 H], 1.17 (d, J = 6.6 Hz, 1.5 H), 1.15 (d, 6.6 Hz, 1.5 H); ^{13}C NMR ($CDCl_3$) δ 171.2 (s), 170.6 (s), 169.5 (s), 169.3 (s), 138.6 (s), 136.9 (s), 128.7 (d, 2 C), 128.5 (d, 2 C), 127.6 (d, 2 C), 126.9 (d, 2 C), 126.8 (d), 126.4 (d), 113.0 (s), 112.7 (s), 76.5 (d, 2 C), 76.1 (d), 76.0 (d), 64.9 (t), 63.8 (t), 55.8 (q, 2 C), 54.5 (d), 52.4 (d), 49.5 (t), 44.4 (t), 26.3

(q), 26.2 (q), 26.1 (q), 26 (q), 15.4 (q), 13.5 (q); MS *m*/*z* 351 (M^+, 1), 91 (100); IR ($CDCl_3$) 1754, 1639 cm^{-1}. Anal. Calcd for $C_{18}H_{25}NO_6$: C, 61.52; H, 7.17; N, 3.99. Found: C, 61.29; H, 7.05; N, 3.87.

***N*-Benzyl-*N*′-[(1*R*)-2-hydroxy-1-methylethyl]-(2*R*,3*R*)-2,3-di-*O*-isopropylidenetartramic Acid Methyl Ester (57).** Prepared according to the procedure reported for **45**, but the reaction was left under stirring for 12 h. Starting from (*R*,*R*)-**43** (682 mg, 3.34 mmol) and **52** (552 mg, 3.34 mmol), **57** was obtained after chromatography (Et_2O, R_f 0.3) as a colorless oil (1.29 g, 92%): $[\alpha]^{20}_D$ −15.9 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) (1:1 mixture of rotamers) δ 7.39−7.28 (m, 5 H), 5.38 (d, J = 5.4 Hz, 0.5 H), 5.21 (d, J = 6.2 Hz, 0.5 H), 5.00 (d, J = 5.4 Hz, 0.5 H), 4.80−4.30 (m, 4.5 H), 4.05 (m, 0.5 H), 3.60−3.35 (m, 3 H), [1.43 (s) and 1.37 (s), 3 H], [1.42 (s) and 1.41 (s), 3 H], 1.17 (d, J = 6.6 Hz, 1.5 H), 1.15 (d, 6.6 Hz, 1.5 H); ^{13}C NMR ($CDCl_3$) δ 170.6 (s, 2 C), 169.4 (s), 168.1 (s), 138.3 (s), 136.9 (s), 128.7 (d, 2 C), 128.4 (d, 2 C), 127.7 (d, 2 C), 126.9 (d, 2 C), 126.8 (d), 126.7 (d), 113.1 (s, 2 C), 76.3 (d, 2 C), 76.1 (d, 2 C), 64.8 (t), 64.1 (t), 56.0 (q, 2 C), 54.2 (d), 52.1 (d), 49.7 (t), 44.7 (t), 26.0 (q, 4 C), 15.9 (q), 13.8 (q); MS *m*/*z* 351 (M^+, 1), 91 (100); IR ($CDCl_3$) 1754, 1639 cm^{-1}. Anal. Calcd for $C_{18}H_{25}NO_6$: C, 61.52; H, 7.17; N, 3.99. Found: C, 61.29; H, 7.05; N, 3.87.

***N*-Benzyl-*N*′-[(1*R*)-1-benzyl-2-hydroxyethyl]-(2*R*,3*S*)/(2*S*,3*R*)-2,3-di-*O*-isopropylidenetartramic Acid Methyl Ester (64).** Prepared according to the procedure reported for **45**, but the reaction was left under stirring for 12 h. Starting from (±)-(*R*,*S*)-**63** (577 mg, 2.83 mmol) and **50** (682 mg, 2.83 mmol), **64** was obtained after chromatography (EtOAc-petroleum ether, 1:1, R_f 0.32) as a colorless oil (2.60 g, 92%). ^1H NMR ($CDCl_3$) (1:1 mixture of diastereoisomers) δ 7.47 (m, 10 H), 5.05 (d, J = 6.6 Hz, 0.5 H), 5.03 (d, J = 6.6 Hz, 0.5 H), 4.81 (d, J = 6.6 Hz, 0.5 H), 4.78 (d, J = 6.6 Hz, 0.5 H), 4.66 (d, J = 16.1 Hz, 0.5 H), 4.64 (d, J = 16.7, 0.5 H), 4.25 (d, J = 16.7 Hz, 0.5 H), 4.12 (d, J = 16.1 Hz, 0.5 H), 3.85 (s, 3 H), 3.64 (m, 2 H), 3.46 (m, 2 H), 3.06−2.80 (m, 2 H), [1.59(s), 1.56 (s), 1.40 (s), and 1.36 (s), 6 H].

***N*-Benzyl-*N*′-[(1*S*)-2-hydroxy-1-methylethyl]-(2*R*,3*S*)/(2*S*,3*R*)-2,3-di-*O*-isopropylidenetartramic Acid Methyl Ester (65).** Prepared according to the procedure reported for **45**, but the reaction was left under stirring for 12 h. Starting from (±)-(*R*,*S*)-**63** (2.26 g, 11.09 mmol) and **51** (1.83 g, 11.09 mmol), compound **65** (2.706 g, 69%) was obtained after chromatography (EtOAc−petroleum ether, 2:1, R_f 0.25) as a yellow oil: ^1H NMR ($CDCl_3$) (1:1 mixture of diastereoisomer) δ 7.40−7.15 (m, 5 H), 5.40 (d, J = 6.6 Hz, 0.25 H), 5.23 (d, J = 6.6 Hz, 0.25 H), 4.94 (d, J = 7.0 Hz, 0.5 H), 4.82−4.40 (m, 3 H), 3.78 (s, 1.5 H), 3.76 (s, 1.5 H), 3.68−3.36 (m, 3 H), 1.57 (m, 6 H), 1.29 (d, J = 7.0 Hz, 1.5 H), 1.11 (d, J = 7.0 Hz, 1.5 H).

***N*-(*p*-Methoxybenzyl)-*N*′-[(1*S*)-1-benzyl-1-formyl]-(2*R*,3*R*)-2,3-di-*O*-isopropylidentartramic Acid Methyl Ester (58).** A solution of $(COCl)_2$ (120 μL, 1.40 mmol) in 3 mL of dry CH_2Cl_2 was cooled to −60 °C under a nitrogen atmosphere, and anhydrous DMSO (180 μL, 2.59 mmol) was added slowly in order to keep the temperature constant. After 5 min, a solution of **53** (565 mg, 1.23 mmol) in 4 mL of dry CH_2Cl_2 was added dropwise still mantaining the temperature at −60 °C. The mixture was stirred for 15 min, DIPEA (1.07 mL, 6.27 mmol) was added and, after 10 min, the reaction mixture was left to warm to room temperature, followed by addition of water (10 mL). The organic phase was extracted with CH_2Cl_2 and dried over Na_2SO_4, and after evaporation of the solvent a crude yellow oil was obtained. Purification by chromatography (Et_2O−*n*-hexane, 1:1, R_f 0.27) gave **58** (532 mg, 95%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 9.38 (s, 1 H), 7.27 (m, 2 H), 7.16 (m, 3 H), 6.99 (d, J = 8.8 Hz, 2 H), 6.83 (d, J = 8.8 Hz, 2 H), 5.33 (d, J = 6.2 Hz, 1 H), 4.95 (d, J = 6.2 Hz, 1 H), 4.81 (d, J = 16.1 Hz, 1 H), 3.79 (s, 3 H), 3.77 (s, 3 H), 3.53 (dd, J = 9.9, 4.3 Hz, 1 H), 3.39 (dd, J = 12.8, 4.3 Hz, 1 H), 3.39 (d, J = 16.1 Hz, 1 H), 3.08 (dd, J = 12.8, 9.9 Hz, 1 H), 1.45 (s, 3 H), 1.39 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 196.7 (d), 170.4 (s), 167.8 (s), 159.4 (s), 137.5 (s), 129.2 (d, 2 C), 129.0 (s), 128.7 (d, 2 C), 128.5 (d, 2 C), 127.0 (d), 114.3 (d, 2 C), 113.9 (s), 75.9 (d), 75.7 (d), 67.3 (d), 55.1 (q), 52.5 (t), 51.9 (q), 32.4 (t), 26.2 (q), 25.8 (q); IR ($CDCl_3$) 3631, 1745, 1642, cm^{-1}. Anal. Calcd for $C_{25}H_{29}NO_7$: C, 65.92; H, 6.42; N, 3.07. Found: C, 66.0; H, 6.46; N, 2.98.

***N*-Benzyl-*N*′-[(1*S*)-1-benzyl-1-formyl]-(2*R*,3*R*)-2,3-di-*O*-isopropylidenetartramic Acid Methyl Ester (59).** Prepared as reported for **58**. Starting from **54** (1.32 g, 3.09 mmol), purification of the crude reaction mixture by chromatography (Et_2O−*n*-hexane, 1:1, R_f 0.23) gave **59** (881 mg, 67%) as a colorless oil: $[\alpha]^{25}_D$ −142.2 (*c* 0.26, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 9.44 (s, 1 H), 7.40−7.00 (m, 10 H), 5.33 (d, J = 6.2 Hz, 1 H), 4.92 (d, J = 6.2 Hz, 1 H), 4.89 (d, J = 18.7 Hz, 1 H), 3.79 (s, 3 H), 3.53 (dd, J = 9.8, 4.3 Hz, 1 H), 3.44 (d, J = 18.7 Hz, 1 H), 3.41 (dd, J = 13.9, 4.3 Hz, 1 H), 3.12 (dd, J = 13.9, 9.8 Hz, 1 H), 1.54 (s, 3 H), 1.45 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 196.6 (d), 170.3 (s), 168.0 (s), 137.5 (s), 135.2 (s), 129.2 (d, 2 C), 128.8 (d, 2C), 128.6 (d, 2 C), 128.0 (d), 127.6 (d, 2C), 127.5 (d), 113.2 (s), 76.4 (d), 75.6 (d), 67.8 (d), 52.4 (t), 52.3 (q), 32.4 (t), 26.1 (q), 25.8 (q); MS *m*/*z* 425 (M^+, 0.1), 91 (100); IR ($CDCl_3$) 3695, 1738, 1709, 1645 cm^{-1}. Anal. Calcd for $C_{24}H_{27}NO_6$: C, 67.75; H, 6.40; N, 3.29. Found: C, 67.53; H, 6.31; N, 3.12.

***N*-Benzyl-*N*′-[(1*R*)-1-benzyl-1-formyl]-(2*R*,3*R*)-2,3-di-*O*-isopropylidenetartramic Acid Methyl Ester (60).** Compound **60** was prepared according to the procedure for **58**. Starting from **55** (677 mg, 1.58 mmol), the crude product was purified by chromatography (Et_2O−*n*-hexane, 1:1, R_f 0.32) affording **60** (437 mg, 65%) as a yellow oil: $[\alpha]^{25}_D$ +125.9 (*c* 0.94, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 9.32 (s, 1 H), 7.40−7.00 (m, 10 H), 5.34 (dd, J = 8.8, 4.4 Hz, 1 H), 4.90 (d, J = 15.4 Hz, 1 H), 3.86 (s, 3 H), 3.36 (dd, J = 13.9, 4.4 Hz, 1 H), 3.19 (d, J = 15.4 Hz, 1 H), 3.16 (dd, J = 13.9, 8.8 Hz, 1 H), 1.49 (s, 3 H), 1.43 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 196.9 (d), 170.6 (s), 168.2 (s), 137.7 (s), 135.5 (s), 129.5 (d, 2 C), 129.3 (d, 2 C), 128.8 (d, 2 C), 128.4 (d), 127.5 (d, 2 C), 127.0 (d), 113.5 (s), 76.1 (d), 75.8 (d), 67.0 (d), 53.4 (t), 52.3 (q), 32.7 (t), 26.3 (q), 26.1 (q); MS *m*/*z* 425 (M^+, 0.25), 91 (100); IR ($CDCl_3$) 3693, 1736, 1711, 1641 cm^{-1}. Anal. Calcd for $C_{24}H_{27}NO_6$: C, 67.75; H, 6.40; N, 3.29. Found: C, 67.61; H, 6.74; N, 3.08.

***N*-Benzyl-*N*′-[(1*S*)-1-formyl-1-methyl]-(2*R*,3*R*)-2,3-di-*O*-isopropylidenetartramic Acid Methyl Ester (61).** Compound **61** was prepared according to the procedure reported for **58**. Starting from **56** (936 mg, 2.67 mmol), after purification of the crude reaction mixture by chromatography (Et_2O−petroleum ether, 2:1, R_f 0.39), **61** (839 mg, 90%) was obtained as an oil: $[\alpha]^{25}_D$ −31.2 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 9.43 (s, 1 H), 7.36−7.31 (m, 5 H), 5.31 (d, J = 6.0 Hz, 1 H), 5.04 (d, J = 16.4 Hz, 1 H), 4.93 (d, J = 6.0 Hz, 1 H), 4.51 (d, J = 16.4 Hz, 1 H), 3.76 (s, 3 H), 3.59 (q, J = 7.0 Hz, 1 H), 1.43 (s, 3 H), 1.42 (s, 3 H), 1.30 (d, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 197.4 (d), 170.5 (s), 168.2 (s), 135.7 (s), 129.0 (d, 2 C), 128.3 (d), 127.2 (d, 2 C), 113.3 (s), 75.9 (d), 75.8 (d), 61.7 (q), 52.5 (d), 51.0 (t), 26.2 (q), 26.1 (q), 11.0 (q); MS *m*/*z* 349 (M^+, 2), 91 (100); IR ($CDCl_3$) 1739, 1644 cm^{-1}. Anal. Calcd for $C_{18}H_{23}NO_6$: C, 61.88; H, 6.64; N, 4.01. Found: C, 61.77; H, 6.29; N, 3.87.

***N*-Benzyl-*N*′-[(1*R*)-1-formyl-1-methyl]-(2*R*,3*R*)-2,3-di-*O*-isopropylidenetartramic Acid Methyl Ester (62).** Compound **62** was prepared according to the procedure reported for **58**. Starting from **57** (1.175 g, 3.35 mmol), after purification of the crude reaction mixture by chromatography (Et_2O−petroleum ether, 2:1, R_f 0.36), **62** (910 mg, 78%) was obtained as an oil: $[\alpha]^{25}_D$ +22.0 (*c* 0.55, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 9.38 (s, 1 H), 7.36−7.22 (m, 5 H), 5.28 (d, J = 5.5 Hz, 1 H), 5.01 (d, J = 5.5 Hz, 1 H), 4.97 (d, J = 15.8 Hz, 1 H), 4.56 (d, J = 15.8 Hz, 1 H), 3.79 (s, 3 H), 3.53 (q, J = 7.3 Hz, 1 H), 1.48 (s, 3 H), 1.44 (s, 3 H), 1.33 (d, J = 7.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 197.2 (d), 170.6 (s), 168.2 (s), 135.7 (s), 128.9 (d, 2 C), 128.2 (d), 127.6 (d, 2 C), 113.3 (s), 76.0 (d), 75.8 (d), 61.5 (q), 52.6 (d), 51.3 (t), 26.2 (q), 26.0 (q), 11.1 (q); MS *m*/*z* 349 (M^+, 2), 91 (100); IR ($CDCl_3$) 1739, 1647 cm^{-1}. Anal. Calcd for $C_{18}H_{23}NO_6$: C, 61.88; H, 6.64; N, 4.01. Found: C, 61.77; H, 6.29; N, 3.87.

***N*-Benzyl-*N*′-[(1*R*)-1-benzyl-1-formyl]-(2*S*,3*R*)-2,3-di-*O*-isopropylidenetartramic Acid Methyl Ester (66).** Starting from the 1:1 diastereomeric mixture **64** (692 mg, 1.62 mmol), the Swern oxidation was carried out as reported for **58**. After chromatography (Et_2O−petroleum ether, 2:1, R_f 0.42), alde-

hyde **66** (200 mg, 29%) was obtained as a white solid. The other diastereoisomer in part decomposed during the purification process obtaining only **66** in pure form. **66**: mp 138.5 °C; $[\alpha]^{25}_D$ +9.2 (*c* 0.22, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 9.28 (s, 1 H), 7.40−7.00 (m, 10 H), 5.14 (d, J = 6.3 Hz, 1 H), 4.91 (d, J = 14.3 Hz, 1 H), 4.86 (d, J = 6.3 Hz, 1 H), 3.83 (s, 3 H), 3.50−3.35 (m, 3 H), 3.30 (d, J = 14.3 Hz, 1 H), 3.05 (dd, J = 13.9, 9.9 Hz, 1 H), 1.59 (s, 3 H), 1.39 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 196.9 (d), 169.4 (s), 168.3 (s), 138.2 (s), 135.5 (s), 129.3 (d, 2 C), 129.0 (d, 2 C), 128.9 (d, 2 C), 128.4 (d), 128.2 (d, 2 C), 126.9 (d), 113.2 (s), 76.2 (d), 75.4 (d), 67.0 (d), 52.6 (t), 52.5 (q), 32.6 (t), 27.0 (q), 25.8 (q); MS *m*/*z* 396 (M^+-29, 10), 91 (100); IR ($CDCl_3$) 1731, 1649 cm^{-1}. Anal. Calcd for $C_{24}H_{27}NO_6$: C, 67.75; H, 6.40; N, 3.29. Found: C, 67.62; H, 6.24; N, 3.08.

***N*-Benzyl-*N*′-[(1*S*)-1-methyl-1-formyl]-(2*R*,3*S*)-2,3-di-*O*-isopropylidenetartramic Acid Methyl Ester (67).** Starting from the 1:1 diastereomeric mixture **65** (3.08 g, 8.76 mmol), the Swern oxidation was carried out as reported for **58**. After chromatography (Et_2O−petroleum ether, 2:1, R_f 0.23), aldehyde **67** (1.844 g, 60%) was obtained in a 3:1 mixture with its diastereoisomer **68**. The minor diastereoisomer partially decomposed during the purification process: ^{1}H NMR ($CDCl_3$) (major isomer **67**) δ 9.38 (s, 1 H), 7.40−7.20 (m, 5 H), 5.12 (d, J = 6.6 Hz, 1 H), 4.90 (d, J = 16.9 Hz, 1 H), 4.83 (d, J = 6.6 Hz, 1 H), 4.49 (d, J = 16.9 Hz, 1 H), 3.75 (s, 3 H), 3.50 (m, 1 H), 1.59 (s, 3 H), 1.37 (s, 3 H), 1.29 (d, J = 6.6 Hz, 3 H).

Methyl (1*R*,5*S*,7*R*)-3-Benzyl-2-oxo-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-*exo*-carboxylate (1). Method A. A solution of **38** (11.0 g, 35.5 mmol) in toluene (60 mL) was quickly added to a refluxing suspension of H_2SO_4/SiO_2 (3.0 g) in toluene (120 mL). The mixture was allowed to react for 15 min, and then one-third of the solvent was distilled off. The hot reaction mixture was filtered through a short layer of $NaHCO_3$, and after evaporation of the solvent, the crude product was purified by chromatography (EtOAc−petroleum ether, 1:2, R_f 0.14), affording pure **1** as a white solid (5.6 g, 57%). **Method B**. A solution of **45** (1.038 g, 2.72 mmol) in toluene (30 mL) was quickly added to a refluxing suspension of H_2SO_4/SiO_2 (500 mg) in toluene (60 mL). The mixture was allowed to react for 15 min, and afterward, one-third of the solvent was distilled off. The hot reaction mixture was filtered through a short layer of $NaHCO_3$, and after evaporation of the solvent, the crude product was purified by chromatography as above affording pure **1** (686 mg, 91%): mp 82 °C; $[\alpha]^{25}_D$ −48.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.40−7.08 (m, 5 H), 5.85 (d, J = 2.2 Hz, 1 H), 4.97 (s, 1 H), 4.75 (s, 1 H), 4.53 (s, 2 H), 3.79 (s, 3 H), 3.36 (dd, J = 12.5, 2.2 Hz, 1 H), 3.10 (d, J = 12.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 169.1 (s), 165.5 (s), 135.2 (s), 129.0 (d, 2 C), 128.9 (d, 2 C), 127.9 (d), 100.0 (d), 77.7 (d), 77.5 (d), 52.8 (q), 51.0 (t), 48.3 (t); MS *m*/*z* 277 (M^+, 20), 91 (100); IR ($CDCl_3$) 1750, 1668 cm^{-1}. Anal. Calcd for $C_{14}H_{15}NO_5$: C, 60.64; H, 5.45; N, 5.05. Found: C, 60.27; H, 5.56; N, 4.74

Methyl (1*R*,5*S*,7*R*)-3-(*p*-Methoxybenzyl)-2-oxo-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-*exo*-carboxylate (2). Compound **2** was prepared according to method A reported above for the synthesis of **1**. From **39** (13.0 g, 38.3 mmol), after purification by chromatography (EtOAc−petroleum ether, 1:2, R_f 0.18), pure **2** (10.5 g, 82%) was obtained as a white solid: mp 139−140 °C; $[\alpha]^{25}_D$ −48.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.09 (d, J = 8.4 Hz, 2 H), 6.81 (d, J = 8.4 Hz, 2 H), 5.81 (d, J = 2.2 Hz, 1 H), 4.91 (s, 1 H), 4.69 (s, 1 H), 4.57 (s, 2 H), 3.74 (s, 3 H), 3.30 (dd, J = 12.3, 2.2 Hz, 1 H), 3.05 (d, J = 12.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 169.3 (s), 165.4 (s), 159.2 (s), 129.5 (d, 2 C), 126.9 (s), 113.9 (d, 2 C), 99.9 (d), 77.6 (d), 77.4 (d), 55.4 (q), 52.8 (q), 50.9 (t), 47.6 (t); MS *m*/*z* 307 (M^+, 20), 121 (100); IR ($CDCl_3$) 1756, 1670 cm^{-1}. Anal. Calcd for $C_{15}H_{17}NO_6$: C, 58.63; H, 5.58; N, 4.56. Found: C, 58.67; H, 5.80; N, 4.20.

Methyl 3-Benzyl-2-oxo-6,8-dioxa-3-azabicyclo[3.2.1]-octane-7-*endo*-carboxylate [(±)-10]. To a solution of **40** (3.7 g, 17.12 mmol) in anhydrous CH_2Cl_2 (50 mL) was added **33** (3.34 g, 17.11 mmol) dissolved in CH_2Cl_2 (10 mL) and the mixture stirred at room temperature for 30 min. The solvent was then evaporated and the crude product dissolved in 60 mL of methanol, followed by the dropwise addition of thionyl chloride (1.6 mL, 12.6 mmol). The reaction mixture was allowed to react at 50 °C for 2 h, and after evaporation of the solvent, the crude dark oil (**42**) was dissolved in toluene (30 mL) to give a solution that was quickly added to a refluxing suspension of H_2SO_4/SiO_2 (400 mg) in toluene (50 mL). After 15 min, one-third of the solvent was distilled off, the warm solution was filtered through a short layer of $NaHCO_3$, and the solvent evaporated to give a yellow oil. Purification by chromatography (Et_2O, R_f 0.46) gave (±)-**10** (870 mg, 18%) as a 7:1 mixture with (±)-**1**: oil; ^{1}H NMR ($CDCl_3$) δ 7.35−7.10 (m, 5 H), 5.70 (d, J = 2.6 Hz, 1 H), 4.90 (d, J = 5.2 Hz, 1 H), 4.60 (d, J = 5.2 Hz, 1 H), 4.49 (AB system, J = 15.1 Hz, 2 H), 3.73 (s, 3 H), 3.32 (dd, J = 12.1, 2.6 Hz, 1 H), 3.20 (d, J = 12.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 167.8 (s), 164.5 (s), 135.1 (s), 128.7 (d, 2 C), 128.3 (d, 2 C), 127.7 (d), 99.9 (d), 78.3 (d), 76.2 (d), 52.6 (t), 51.1 (q), 48.3 (t); MS *m*/*z* 277 (M^+, 8), 91 (100); IR ($CDCl_3$) 1760, 1672 cm^{-1}.

Methyl (1*R*,4*S*,5*S*,7*R*)-3-(*p*-Methoxybenzyl)-2-oxo-4-*exo*-benzyl-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-*exo*-carboxylate (3). Prepared according to method B reported for the synthesis of **1**, but refluxed for 20 min before one-third of the solvent was distilled off. Starting from **58** (532 mg, 1.17 mmol), pure **3** (398 mg, 86%) was obtained after chromatography (EtOAc−*n*-hexane, 1:3, R_f 0.35) as a colorless oil: $[\alpha]^{25}_D$ −41.8 (*c* 2.16, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.40−7.00 (m, 7 H), 6.86 (d, J = 8.8 Hz, 2 H), 5.49 (s, 1 H), 5.29 (d, J = 15.1 Hz, 1 H), 4.94 (s, 1 H), 4.67 (s, 1 H), 3.95 (d, J = 15.1 Hz, 1 H), 3.77 (s, 3 H), 3.72 (s, 3 H), 3.32 (dd, J = 10.9, 4.0 Hz, 1 H), 3.17 (dd, J = 13.6, 4.0 Hz, 1 H), 2.75 (dd, J = 13.6, 10.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 169.0 (s), 165.5 (s), 159.2 (s), 135.8 (s), 129.1 (d, 2 C), 129.0 (d, 2 C), 128.9 (d, 2 C), 127.7 (s), 127.0 (d), 114.3 (d, 2 C), 101.1 (d), 77.9 (d), 77.5 (d), 60.3 (d), 55.2 (q), 52.6 (q), 45.2 (t), 36.1 (t); MS *m*/*z* 397 (M^+, 9), 121 (100); IR ($CDCl_3$)) 1754, 1664 cm^{-1}. Anal. Calcd for $C_{22}H_{23}NO_6$: C, 66.49; H, 5.83; N, 3.52. Found: C, 66.58; H, 6.22; N, 3.23.

Methyl (1*R*,4*S*,5*S*,7*R*)-3-Benzyl-2-oxo-4-*exo*-benzyl-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-*exo*-carboxylate (4). Prepared according to method B reported for the synthesis of **1**, but refluxed for 20 min before one-third of the solvent was distilled off. Starting from **59** (881 mg, 2.07 mmol), pure **4** (631 mg, 83%) was obtained after chromatography (EtOAc−*n*-hexane, 1:3, R_f 0.31) as an oil: $[\alpha]^{25}_D$ −42.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.40−7.15 (m, 8 H), 7.03 (m, 2 H), 5.51 (s, 1 H), 5.33 (d, J = 15.0 Hz, 1 H), 4.97 (s, 1 H), 4.71 (s, 1 H), 4.03 (d, J = 15.0 Hz, 1 H), 3.75 (s, 3 H), 3.32 (dd, J = 10.7, 3.7 Hz, 3 H), 3.15 (dd, J = 13.5, 3.7 Hz, 1 H), 2.75 (dd, J = 13.5, 10.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 169.1 (s), 165.8 (s), 137.9 (s), 135.9 (s), 129.3 (d, 2 C), 129.0 (d, 2C), 128.9 (d, 2 C), 128.8 (d, 2 C), 127.2 (d), 127.0 (d), 101.2 (d), 78.0 (d), 76.8 (d), 60.8 (d), 52.1 (q), 46.0 (t), 36.3 (t); MS *m*/*z* 367 (M^+, 13), 91 (100); IR ($CDCl_3$) 1758, 1666 cm^{-1}. Anal. Calcd for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76; N, 3.81. Found: C, 69.02; H, 5.93; N, 3.67.

Methyl (1*R*,4*R*,5*S*,7*R*)-3-Benzyl-2-oxo-4-*endo*-benzyl-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-*exo*-carboxylate (5). Prepared according to method B reported for the synthesis of **1**, but refluxed for 30 min before one-third of the solvent was distilled off. Starting from **60** (437 mg, 1.03 mmol), pure **5** (269 mg, 71%) was obtained after chromatography (EtOAc−*n*-hexane, 1:3, R_f 0.21) as a colorless oil: $[\alpha]^{25}_D$ −27.7 (*c* 0.24, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.40−7.15 (m, 8 H), 7.00 (m, 2 H), 5.38 (d, J = 15.4 Hz, 1 H), 5.34 (s, 1 H), 4.97 (s, 1 H), 4.76 (s, 1 H), 4.14 (d, J = 15.4 Hz, 1 H), 3.78 (s, 3 H), 3.50 (ddd, J = 12.8, 11.3, 2.6 Hz, 1 H), 3.09 (dd, J = 12.8, 4.1 Hz, 1 H), 2.72 (dd, J = 12.8, 11.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 169.1 (s), 166.7 (s), 135.8 (s), 135.4 (s), 129.3 (d, 2 C), 129.0 (d, 4 C), 128.0 (d, 2 C), 127.8 (d), 127.0 (d), 101.0 (d), 77.6 (d), 76.6 (d), 60.1 (d), 52.7 (q), 44.6 (t), 34.3 (t); MS *m*/*z* 367 (M^+, 9), 91 (100); IR ($CDCl_3$) 1756, 1667 cm^{-1}. Anal. Calcd for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76; N, 3.81. Found: C, 68.34; H, 5.82; N, 3.66.

Methyl (1*R*,4*S*,5*S*,7*R*)-3-Benzyl-2-oxo-4-*exo*-methyl-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-*exo*-carboxylate (6). Prepared according to method B reported for the synthesis of **1,** but benzene was used as a solvent and the mixture refluxed for 20 min before one-third of the solvent was distilled off.

Starting from **61** (255 mg, 0.73 mmol), pure **6** (181 mg, 85%) was obtained after chromatography (EtOAc−petroleum ether, 1:2, R_f 0.27) as an oil: $[\alpha]^{15}_D$ −64.6 (*c* 0.79, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.32−7.14 (m, 5 H), 5.54 (s, 1 H), 5.21 (d, J = 15.4 Hz, 1 H), 4.94 (s, 1 H), 4.74 (s, 1 H), 3.93 (d, J = 15.4 Hz, 1 H), 3.78 (s, 3 H), 3.26 (q, J = 7.0 Hz, 1 H), 1.22 (d, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 169.1 (s), 165.6 (s), 135.9 (s), 128.8 (d, 2 C), 127.7 (d), 127.5 (d, 2 C), 103.9 (d), 77.8 (d), 77.4 (d), 55.4 (q), 52.7 (d), 45.6 (t), 15.8 (q); MS *m*/*z* 291 (M^+, 28), 91 (100); IR ($CDCl_3$) 1755, 1674 cm^{-1}. Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.80; H, 5.75; N, 4.49.

Methyl (1*R*,4*R*,5*S*,7*R*)-3-Benzyl-2-oxo-4-*endo*-methyl-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-*exo*-carboxylate (7). Prepared according to method B reported for the synthesis of **1** but benzene was used as a solvent and the mixture was refluxed for 20 min before one-third of the solvent was distilled off. Starting from **62** (229 mg, 0.65 mmol), pure **7** (160 mg, 84%) was obtained after chromatography (EtOAc−petroleum ether, 1:3, R_f 0.24) as an oil: $[\alpha]^{15}_D$ +12.6 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.34−7.03 (m, 5 H), 5.55 (d, J = 2.6 Hz, 1 H), 5.21 (d, J = 15.1 Hz, 1 H), 4.98 (s, 1 H), 4.69 (s, 1 H), 3.95 (d, J = 15.1 Hz, 1 H), 3.76 (s, 3 H), 3.41 (dq, J = 6.6, 2.6 Hz, 1 H), 1.13 (d, J = 6.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 169.1 (s), 166.0 (s), 135.4 (s), 129.7 (d, 2 C), 127.6 (d), 127.5 (d, 2 C), 102.9 (d), 77.7 (d, 2 C), 54.1 (q), 52.7 (d), 44.0 (t), 13.7 (q); MS *m*/*z* 291 (M^+, 44), 91 (100); IR ($CDCl_3$) 1750, 1668 cm^{-1}. Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.72; H, 5.67; N, 4.71.

Methyl (1*R*,4*S*,5*S*,7*R*)-3-Benzyl-2-oxo-4-*exo*-phenyl-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-*exo*-carboxylate (8) and Methyl (1*R*,4*R*,5*S*,7*R*)-3-Benzyl-2-oxo-4-*endo*-phenyl-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-*exo*-carboxylate (9). Prepared according to method B reported for the synthesis of **1** but benzene was used as a solvent, a double amount of H_2SO_4/SiO_2 was used, and the mixture was refluxed for 20 min before one-third of the solvent was distilled off. Starting from the 1:1 diastereomeric mixture **46** (70 mg, 0.15 mmol), the 1:1 epimeric mixture of **8** and **9** (48 mg, 90%) was obtained as an oil. When the reaction was carried out heating **46** (300 mg, 0.656 mmol) in toluene as described for **1** (method B) a 0.5:0.5:1 mixture of **47** and **8** (this last in 3:1 mixture with **9**) (42 mg) was obtained after chromatography (EtOAc−petroleum ether, 1:1.5, R_f 0.5), along with a larger amount of decomposition products. This mixture was dissolved again in toluene (10 mL) in the presence of H_2SO_4/SiO_2 (19 mg), and two-thirds of the solvent was distilled off, affording **8** (27 mg, 12%) as a 4:1 mixture with epimeric compound **9**. Compound **8** (characterized as a 4:1 mixture with **9**): $[\alpha]^{20}_D$ −17.0 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.40−7.00 (m, 10 H), 5.61 (s, 1 H), 5.41 (d, J = 15.1 Hz, 1 H), 5.10 (s, 1 H), 4.81 (s, 1 H), 4.17 (s, 1 H), 3.78 (s, 3 H), 3.33 (d, J = 15.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 168.8 (s), 165.7 (s), 135.7 (s), 134.7 (s), 129.2 (d, 2 C), 129.1 (d), 128.9 (d, 2 C), 128.5 (d), 128.1 (d, 2 C), 127.8 (d, 2 C), 104.2 (d), 77.9 (d), 77.5 (d), 63.9 (d), 52.8 (q), 45.7 (t); MS *m*/*z* 353 (M^+, 1), 91 (100); IR ($CDCl_3$) 1761, 1667 cm^{-1}.

Methyl (1*R*,4*R*,5*S*,7*S*)-3-Benzyl-2-oxo-4-*endo*-benzyl-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-*endo*-carboxylate (11). Prepared according to method B reported for the synthesis of **1** but benzene was used as a solvent and the mixture was refluxed for 20 min before one-third of the solvent was distilled off. Starting from **66** (98 mg, 0.23 mmol), pure **11** (74 mg, 87%) was obtained after chromatography (EtOAc-petroleum ether, 1:3, R_f 0.28) as an oil: $[\alpha]^{25}_D$ −2.4 (*c* 0.38, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.40−7.00 (m, 10 H), 5.37 (d, J = 15.4 Hz, 1 H), 5.17 (d, J = 2.9 Hz, 1 H), 4.95 (d, J = 5.1 Hz, 1 H), 4.62 (d, J = 5.1 Hz, 1 H), 4.10 (d, J = 15.4 Hz, 1 H), 3.80 (s, 3 H), 3.51 (ddd, J = 8.0, 5.1, 2.9 Hz, 1 H), 3.17 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 168.2 (s), 165.6 (s), 136.1 (s), 135.4 (s), 129.5 (d, 2 C), 128.9 (d, 2 C), 128.7 (d, 2 C), 128.2 (d), 127.9 (d, 2 C), 126.9 (d), 101.4 (d), 77.6 (d), 76.7 (d), 60.3 (d), 52.7 (q), 44.7 (t), 33.7 (t); MS *m*/*z* 367 (M^+, 2), 91 (100); IR ($CDCl_3$) 1759, 1666 cm^{-1}. Anal. Calcd for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76; N, 3.81. Found: C, 68.38; H, 5.44; N, 3.52.

Methyl (1*S*,4*S*,5*R*,7*R*)-3-Benzyl-2-oxo-4-*endo*-methyl-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-*endo*-carboxylate (12). Prepared according to method B reported for the synthesis of **1** but benzene was used as a solvent and the mixture was refluxed for 20 min before one-third of the solvent was distilled off. Starting from **67** (1.824 g, 5.22 mmol), crude **12** (1.063 g, 70%) was obtained as a 5:1 diastereomeric mixture used directly in the next reduction step: ^{1}H NMR ($CDCl_3$) (major isomer) δ 7.40−7.15 (m, 5 H), 5.44 (d, J = 2.6 Hz, 1 H), 5.24 (d, J = 15.0 Hz, 1 H), 4.93 (d, J = 5.2 Hz, 1 H), 4.61 (d, J = 5.2 Hz, 1 H), 3.91 (d, J = 15.0 Hz, 1 H), 3.76 (s, 3 H), 3.43 (dq, J = 6.9, 2.6 Hz, 1 H), 1.29 (d, J = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 167.9 (s), 165.0 (s), 135.6 (s), 128.7 (d, 2 C), 127.9 (d, 2 C), 127.6 (d), 103.3 (d), 77.7 (d), 76.3 (d), 54.4 (d), 52.6 (q), 44.1 (t), 13.1 (q); MS *m*/*z* 291 (M^+, 4), 91 (100).

Methyl (1*R*,5*S*,7*R*)-2-Oxo-6,8-dioxa-3-azabicyclo[3.2.1]-octane-7-*exo*-carboxylate (13). Compound **2** (500 mg, 1.6 mmol) was left to react for 5 h at room temperature with CAN (2.5 g, 4.5 mmol) in CH_3CN (12 mL) and H_2O (4 mL). The solution was then adjusted to pH 7 with Na_2CO_3 and filtered over a Celite layer washing with acetone. The organic phase was extracted with Et_2O and CH_2Cl_2 and dried over Na_2SO_4. Evaporation of the solvent gave a crude product that was purified by recrystallization from Et_2O−petroleum ether at 0 °C, yielding **13** (260 mg, 85%) as a white solid: mp 163−165 °C; $[\alpha]^{25}_D$ −6.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 5.88 (br s, 1 H), 5.87 (d, J = 1.8 Hz, 1 H), 4.82 (s, 1 H), 4.73 (s, 1 H), 3.78 (s, 3 H), 3.49 (dd, J = 12.1, 1.8 Hz, 1 H), 3.28 (d, J = 12.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 169.1 (s), 167.6 (s), 99.4 (d), 77.8 (d), 77.4 (d), 52.9 (q), 47.0 (t); MS *m*/*z* 187 (M^+, 2), 71 (100); IR ($CDCl_3$) 1757, 1690 cm^{-1}. Anal. Calcd for $C_7H_9NO_5$: C, 44.92; H, 4.84; N, 7.48. Found: C, 44.60; H, 4.91; N, 7.19.

Methyl (1*R*,4*S*,5*S*,7*R*)-2-Oxo-4-*exo*-benzyl-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-*exo*-carboxylate (14). Prepared from **3** (80 mg, 0.20 mmol) as reported for **13**. Pure **14** (30 mg, 72%) was obtained after recrystallization from Et_2O−petroleum ether at 0 °C: $[\alpha]^{25}_D$ −93.1 (*c* 1.0, $CDCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.35−7.13 (m, 5 H), 5.68 (s, 1 H), 4.86 (s, 1 H), 4.70 (s, 1 H), 3.77 (s, 3 H), 3.56 (ddd, J = 9.2, 6.2, 2.2 Hz, 1 H), 2.90 (dd, J = 13.5, 6.2 Hz, 1 H), 2.80 (dd, J = 13.5, 9.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 169.0 (s), 166.5 (s), 135.4 (s), 129.1 (d, 4 C), 127.3 (d), 101.5 (d), 77.7 (d), 77.3 (d), 58.1 (d), 52.8 (q), 39.3 (t); MS *m*/*z* 277 (M^+, 2), 91 (100); IR ($CDCl_3$) 1758, 1691 cm^{-1}. Anal. Calcd for $C_{14}H_{15}NO_5$: C, 60.64; H, 5.45; N, 5.05. Found: C, 60.36; H, 5.73; N, 4.70.

Methyl (1*S*,5*S*,7*R*)-3-Benzyl-6,8-dioxa-3-azabicyclo[3.2.1]-octane-7-*exo*-carboxylate (16). To a refluxing solution of **1** (604 mg, 2.18 mmol) in anhydrous THF (12 mL) was added, under a nitrogen atmosphere, a 1 M solution of $BH_3{\cdot}Me_2S$ (0.4 mL) in 10 min and the mixture stirred for 30 min. After this time, the mixture was immediately cooled with an ice bath. The solvent was evaporated and the crude dissolved in 1,4-dioxane (30 mL), followed by addition of TMEDA (0.4 mL, 2.65 mmol), and left to react at room temperature for 15 min. The solvent was evaporated, and the residue was suspended in diethyl ether and carefully filtrered through a short layer of Celite. After evaporation of the solvent, the residue was purified by chromatography (EtOAc−petroleum ether, 2:3, R_f 0.5), affording pure **16** (512 mg, 89%) as a colorless oil: $[\alpha]^{25}_D$ −61.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.30 (m, 5 H), 5.62 (s, 1 H), 4.78 (s, 1 H), 4.60 (s, 1 H), 3.74 (s, 3 H), 3.52 (AB system, J = 13.2 Hz, 2 H), 2.86 (d, J = 11.6 Hz, 1 H), 2.77 (d, J = 11.5 Hz, 1 H), 2.51 (dd, J = 11.5, 1.5 Hz, 1 H), 2.30 (d, J = 11.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 171.7 (s), 137.3 (s), 128.9 (d, 2 C), 128.4 (d, 2 C), 127.4 (d), 101.5 (d), 76.9 (d), 76.0 (d), 61.4 (t), 56.3 (t), 54.7 (t), 52.5 (q); MS *m*/*z* 263 (M^+, 6), 91 (100); IR ($CDCl_3$) 1755 cm^{-1}. Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.50; H, 6.59; N, 4.92.

Methyl (1*S*,4*S*,5*S*,7*R*)-3-Benzyl-4-*exo*-benzyl-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-*exo*-carboxylate (17). Compound **17** was prepared according to the synthesis of **16**, starting from **4** (317 mg, 0.86 mmol). The crude was obtained as a 2:1 mixture of **17** and amino alcohol **72**. These were separated by chromatography (EtOAc−petroleum ether, 1:4), obtaining pure **17** (170 mg, 56%, R_f 0.40) and **72** (78 mg, 28%, R_f 0.12). **17**: $[\alpha]^{25}_D$ −31.2 (*c* 0.12, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.40−7.00 (m, 10 H), 5.28 (s, 1 H), 4.73 (s, 1 H), 4.61 (s, 1 H),

3.81 (d, J = 13.2 Hz, 1 H), 3.72 (s, 3 H), 3.64 (d, J = 13.2 Hz, 1 H), 3.00 (ddd, J = 11.0, 4.4, 1.8 Hz, 1 H), 2.98 (dd, J = 11.7, 1.8 Hz, 1 H), 2.92 (dd, J = 12.8, 4.4 Hz, 1 H), 2.77 (dd, J = 12.8, 11.0 Hz, 1 H), 2.56 (dd, J = 11.7, 1.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 171.9 (s), 138.2 (s), 129.1 (d, 2 C), 128.7 (d, 4 C), 128.5 (d, 2 C), 127.4 (d), 126.2 (d), 102.4 (d), 77.4 (d), 76.0 (d), 62.3 (d), 57.5 (t), 52.4 (q), 49.7 (t), 29.1 (t); MS m/z 353 (M^+, 0.3), 91 (100); IR ($CDCl_3$) 1731 cm^{-1}. Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.22; H, 6.48; N, 3.73.

Methyl (1*S*,4*R*,5*S*,7*R*)-3-Benzyl-4-*endo*-benzyl-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-*exo*-carboxylate (18). Compound **18** was prepared according to the synthesis of **16**. Starting from **5** (269 mg, 0.73 mmol), the crude was obtained as a 2:1 mixture of **18** and amino alcohol **73**. These were separated by chromatography (EtOAc−petroleum ether, 1:3), yielding pure **18** (131 mg, 51%, R_f 0.44) and **73** (60 mg, 25%, R_f 0.24). **18**: mp 75−75 °C; $[\alpha]^{25}_D$ −120.0 (c 0.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.35−7.08 (m, 10 H), 5.26 (s, 1 H), 4.67 (s, 1 H), 4.56 (br s, 1 H), 4.26 (d, J = 14.0 Hz, 1 H), 3.73 (s, 3 H), 3.24 (d, J = 14.0 Hz, 1 H), 3.17 (dd, J = 12.1, 3.3 Hz, 1 H), 2.74 (m, 2 H), 2.67 (m, 1 H), 2.51 (dd, J = 12.1, 1.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 171.6 (s), 138.3 (s), 137.9 (s), 129.5 (d, 2 C), 128.7 (d, 4 C), 128.5 (d, 2 C), 127.3 (d), 126.5 (d), 102.1 (d), 77.2 (d), 75.6 (d), 64.6 (d), 57.5 (t), 54.3 (t), 52.4 (q), 35.8 (t); MS m/z 353 (M^+, 1), 91 (100); IR ($CDCl_3$) 1747 cm^{-1}. Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.57; H, 6.78; N, 3.74.

Methyl (1*S*,4*S*,5*S*,7*R*)-3-Benzyl-4-*exo*-methyl-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-*exo*-carboxylate (19). Compound **19** was prepared according to the synthesis of **16**, starting from **6** (150 mg, 0.51 mmol). The crude was obtained as a 2:1 mixture of **19** with the corresponding amino alcohol. Pure **19** (91 mg) was obtained by chromatography (EtOAc−petroleum ether, 2:3, R_f 0.50) in 65% yield as a colorless oil: $[\alpha]^{20}_D$ −32.3 (c 0.70, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.32−7.16 (m, 5 H), 5.37 (d, J = 1.9 Hz, 1 H), 4.72 (s, 1 H), 4.54 (s, 1 H), 3.72 (s, 3 H), 3.53 (AB, J = 13.4 Hz, 2 H), 2.93 (dq, J = 6.6, 1.9 Hz, 1 H), 2.78 (dd, J = 12.0, 1.9 Hz, 1 H), 2.44 (d, J = 12.0 Hz, 1 H), 0.95 (d, J = 6.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 171.7 (s), 138.2 (s), 128.5 (d, 2 C), 128.3 (d, 2 C), 127.1 (d), 105.0 (d), 77.1 (d), 75.4 (d), 57.1 (t), 56.0 (d), 52.3 (q), 43.1 (t), 7.5 (q); MS m/z 277 (M^+, 1), 91 (100). Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.61; H, 6.72; N, 4.77.

Methyl (1*S*,4*R*,5*S*,7*R*)-3-Benzyl-4-*endo*-methyl-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-*exo*-carboxylate (20). Compound **20** was prepared according to the synthesis of **16**, starting from **7** (142 mg, 0.49 mmol). The crude was obtained as a 2:1 mixture of **20** with the corresponding amino alcohol. Pure **20** (85 mg) was obtained by chromatography (EtOAc−petroleum ether, 2:3, R_f 0.50) in 63% yield as a colorless oil: $[\alpha]^{20}_D$ −78.0 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.27−7.13 (m, 5 H), 5.25 (s, 1 H), 4.55 (s, 1 H), 4.50 (s, 1 H), 3.97 (d, J = 13.6 Hz, 1 H), 3.66 (s, 3 H), 3.05 (d, J = 13.6 Hz, 1 H), 2.59 (dd, J = 11.7, 1.4 Hz, 1 H), 2.46−2.33 (m, 2 H), 1.13 (d, J = 6.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 171.5 (s), 138.1 (s), 128.6 (d, 2 C), 128.2 (d, 2 C), 127.0 (d), 104.8 (d), 77.0 (d), 75.5 (d), 58.2 (t), 56.8 (d), 53.6 (q), 49.0 (t), 15.3 (q); MS m/z 277 (M^+, 1), 91 (100). Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 65.12; H, 6.83; N, 5.01.

Methyl 3-Benzyl-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-*endo*-carboxylate [(±)-**21**]**.** Prepared according to the synthesis of **16**. Starting from (±)-**10** (870 mg, 3.14 mmol), the crude product was obtained as a 2:1 mixture of **21** and amino alcohol **74** and then separated by chromatography (EtOAc−petroleum ether, 1:1.5), affording pure **21** (321 mg, 39%, R_f 0.48) and **74** (143 mg, 19%, R_f 0.15). **21**: ^{1}H NMR ($CDCl_3$) δ 7.22 (m, 5 H), 5.45 (s, 1 H), 4.62 (d, J = 5.4 Hz, 1 H), 4.47 (d, J = 5.4 Hz, 1 H), 3.67 (s, 3 H), 3.41 (AB system, J = 13.2 Hz, 2 H), 2.62 (m, 2 H), 2.43 (d, J = 11.4 Hz, 1 H), 2.27 (d, J = 11.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 168.3 (s), 137.2 (s), 128.9 (d, 2 C), 128.3 (d, 2 C), 127.3 (d), 100.8 (d), 76.2 (d), 74.9 (d), 61.6 (t), 56.9 (t), 52.7 (t), 51.9 (q); MS m/z 263 (M^+, 33), 91 (100); IR ($CDCl_3$) 1759 cm^{-1}. Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.51; H, 6.32; N, 5.28. **74**: ^{1}H NMR ($CDCl_3$) δ 7.25 (m, 5 H), 5.45 (s, 1 H), 4.31 (s, 1 H), 4.11 (d, J = 10.8 Hz, 1 H), 4.10 (m, 1 H), 3.85 (d, J = 10.8 Hz, 1 H), 3.65 (d, J = 12.4 Hz, 1 H), 3.39 (d, J = 12.4 Hz, 1 H), 3.02 (d, J = 11.0 Hz, 1 H), 2.83 (d, J = 11.4 Hz, 1H), 2.80 (dd, J = 11.4, 2.2 Hz, 1H), 2.29 (d, J = 11.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 137.8 (s), 129.5 (d, 2 C), 128.6 (d, 2 C), 127.9 (d), 99.1 (d), 78.4 (d), 74.5 (d), 61.9 (t), 59.3 (t), 55.7 (t), 53.4 (t); MS m/z 235 (M^+, 24), 91 (100); IR ($CDCl_3$) 3610, 3200 (br) cm^{-1}. Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.00; H, 7.32; N, 5.59.

(1*S*,5*S*,7*S*)-3-Benzyl-7-*exo*-hydroxymethyl-6,8-dioxa-3-azabicyclo[3.2.1]octane (69). To a suspension of $LiAlH_4$ (85 mg, 2.2 mmol) in anhydrous THF (12 mL) was added dropwise at 0 °C and under a nitrogen atmosphere a solution of **1** (270 mg, 0.97 mmol) in dry THF (12 mL). The mixture was refluxed for 2 h, and then, after cooling to 0 °C, diethyl ether (3 mL) and a saturated Na_2SO_4 solution (3 mL) were added. The mixture was filtered through a short layer of anhydrous Na_2SO_4, and the residue was suspended in 1 M KOH solution (50 mL), saturated with NaCl, and extracted with Et_2O and EtOAc. The organic phases were combined, dried over anhydrous Na_2SO_4, concentrated, and purified by chromatography (EtOAc−petroleum ether, 1:1, R_f 0.28) to give pure **69** (163 mg, 64%) as a colorless oil: $[\alpha]^{25}_D$ −92.2 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.29 (m, 5 H), 5.43 (s, 1 H), 4.41 (t, J = 5.5 Hz, 1 H), 4.23 (s, 1 H), 3.62−3.40 (m, 4 H), 2.94 (br s, 1 H), 2.81 (d, J = 11.0 Hz, 1 H), 2.66 (d, J = 11.4 Hz, 1 H), 2.45 (dd, J = 11.4, 1.9 Hz, 1 H), 2.29 (d, J = 11.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 137.5 (s), 128.9 (d, 2 C), 128.3 (d, 2 C), 127.2 (d), 100.2 (d), 78.4 (d), 74.5 (d), 64.1 (t), 61.7 (t), 56.8 (t), 54.9 (t); MS m/z 235 (M^+, 2), 91 (100); IR ($CDCl_3$) 3438 (br) cm^{-1}. Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.70; H, 7.52; N, 5.60.

(1*S*,5*S*,7*S*)-3-(*p*-Methoxybenzyl)-7-*exo*-hydroxymethyl-6,8-dioxa-3-azabicyclo[3.2.1]octane (70). Prepared according to the synthesis of **69**. Starting from **2** (1.0 g, 3.3 mmol), pure **70** (840 mg, 97%) was obtained after chromatography (EtOAc−petroleum ether, 1:1, R_f 0.30) as a colorless oil: $[\alpha]^{25}_D$ −71.6 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.19 (d, J = 8.4 Hz, 2 H), 6.81 (d, J = 8.4 Hz, 2 H), 5.42 (s, 1 H), 4.38 (t, J = 5.5 Hz, 1 H), 4.21 (s, 1 H), 3.78 (s, 3 H), 3.56 (m, 2 H), 3.44 (AB system, J = 12.8 Hz, 2 H), 2.79 (d, J = 10.6 Hz, 1 H), 2.65 (d, J = 11.3 Hz, 1 H), 2.41 (dd, J = 11.3, 1.5 Hz, 1 H), 2.26 (d, J = 10.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 158.8 (s), 130.0 (d, 2 C), 129.4 (s), 113.7 (d, 2 C), 100.2 (d), 78.4 (d), 74.4 (d), 64.2 (t), 61.0 (t), 56.7 (t), 55.2 (q), 54.7 (t); MS m/z 265 (M^+, 1), 121 (100); IR ($CDCl_3$) 3591, 3482 (br) cm^{-1}. Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.36; H, 7.22; N, 5.28. Found: C, 63.62; H, 7.42; N, 4.89.

(1*S*,4*S*,5*S*,7*S*)-3-(*p*-Methoxybenzyl)-4-*exo*-benzyl-7-*exo*-hydroxymethyl-6,8-dioxa-3-azabicyclo[3.2.1]octane (71). Prepared from **3** (159 mg, 0.40 mmol) as reported for **69**. After purification by chromatography (EtOAc−petroleum ether, 1:4, R_f 0.16), pure **71** (124 mg, 87%) was obtained as a colorless oil: $[\alpha]^{25}_D$ −33.8 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.40−7.05 (m, 8 H), 6.89 (d, J = 8.8 Hz, 2 H), 5.12 (d, J = 1.4 Hz, 1 H), 4.38 (t, J = 5.5 Hz, 1 H), 4.26 (s, 1 H), 3.83 (s, 3 H), 3.78 (d, J = 13.9 Hz, 1 H), 3.60 (d, J = 13.9 Hz, 1 H), 3.56 (m, 2 H), 3.00 (m, 1 H), 2.95 (d, J = 11.4 Hz, 1 H), 3.00−2.80 (m, 2 H), 2.47 (dd, J = 11.4, 1.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 158.8 (s), 138.7 (s), 130.3 (s), 129.7 (d, 2 C), 129.4 (d, 2 C), 129.1 (d, 2 C), 128.5 (d), 126.0 (s), 113.7 (d, 2 C), 101.1 (d), 78.1 (d), 74.9 (d), 64.4 (t), 62.6 (d), 56.9 (t), 55.2 (q), 49.6 (t), 29.1 (t); MS m/z 355 (M^+, 1), 121 (100). Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 70.68; H, 7.36; N, 3.74.

(1*S*,4*S*,5*S*,7*S*)-3-Benzyl-4-*exo*-benzyl-7-*exo*-hydroxymethyl-6,8-dioxa-3-azabicyclo[3.2.1]octane (72). Prepared from **4** (292 mg, 0.79 mmol) according to the synthesis of **69**. After purification by chromatography (EtOAc−petroleum ether, 1:4, R_f 0.12) pure **72** (194 mg, 75%) was obtained as a colorless oil: $[\alpha]^{25}_D$ −59.4 (c 0.17, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.40−7.00 (m, 10 H), 5.11 (s, 1 H), 4.39 (t, J = 5.1 Hz, 1 H), 4.24 (s, 1 H), 3.81 (d, J = 13.6 Hz, 1 H), 3.00−2.80 (m, 2 H), 3.63 (d, J = 13.6 Hz, 1 H), 3.52 (m, 2 H), 3.00 (m, 1 H), 2.94 (d, J = 11.6 Hz, 1 H), 2.45 (dd, J = 11.6, 1.8 Hz, 1 H); ^{13}C NMR

($CDCl_3$) δ 138.6 (s), 138.4 (s), 129.2 (d, 2 C), 128.7 (d, 2 C), 128.6 (d, 2 C), 128.4 (d, 2 C), 127.3 (d), 126.1 (d), 101.2 (d), 78.1 (d), 74.9 (d), 64.4 (t), 62.7 (t), 57.6 (d), 49.7 (t), 29.2 (t); MS *m*/*z* 325 (M^+, 0.1), 91 (100). Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.49; H, 7.25; N, 4.19.

(1*S*,4*R*,5*S*,7*S*)-3-Benzyl-4-*endo*-benzyl-7-*exo*-hydroxymethyl-6,8-dioxa-3-azabicyclo[3.2.1]octane (73). Prepared from **5** (200 mg, 0.54 mmol) according to the procedure reported for **69**. After purification by chromatography (EtOAc−petroleum ether, 1:1.5, R_f 0.44), pure **73** (141 mg, 80%) was obtained as a white solid: mp 104−105 °C; $[\alpha]^{25}_D$ −107 (*c* 0.04, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.40−7.05 (m, 10 H), 5.05 (s, 1 H), 4.31 (t, J = 4.8 Hz, 1 H), 4.29 (s, 1 H), 4.27 (d, J = 13.9 Hz, 1 H), 3.56 (m, 2 H), 3.23 (d, J = 13.9 Hz, 1 H), 3.17 (dd, J = 11.3, 3.3 Hz, 1 H), 2.80−2.60 (m, 3 H), 2.47 (dd, J = 11.3, 1.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 138.6 (s), 138.1 (s), 129.5 (d, 2 C), 128.7 (d, 2 C), 128.6 (d, 2 C), 128.4 (d, 2 C), 127.1 (d), 126.4 (d), 100.8 (d), 77.8 (d), 74.6 (d), 64.6 (d), 64.4 (t), 57.7 (t), 54.5 (t), 36.1 (t); MS *m*/*z* 325 (M^+, 0.5), 234 (100), 91 (100). Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.99; H, 7.49; N, 4.05.

(1*R*,4*S*,5*R*,7*S*)-3-Benzyl-4-*exo*-methyl-7-*endo*-hydroxymethyl-6,8-dioxa-3-azabicyclo[3.2.1]octane (75). Prepared as described for compound **69**. Starting from **12** (1.29 g, 4.43 mmol), pure **75** (680 mg, 62%) was obtained after chromatography (CH_2Cl_2−MeOH, 40:1, R_f 0.17) as a light yellow oil: $[\alpha]^{25}_D$ −3.4 (*c* 1.28, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.40−7.15 (m, 5 H), 5.16 (s, 1 H), 4.25 (m, 1 H), 4.10−3.90 (m, 2 H), 4.00 (s, 1 H), 3.70 (dd, J = 13.6, 2.9 Hz, 1 H), 3.24 (d, J = 12.8 Hz, 1 H), 2.76 (d, J = 12.1 Hz, 1 H), 2.57 (m, 2 H), 1.27 (d, J = 6.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 135.2 (s), 129.9 (d, 2 C), 128.4 (d, 2 C), 127.8 (d), 102.4 (d), 77.8 (d), 74.5 (d), 59.2 (t), 58.6 (d), 57.7 (t), 51.3 (t), 15.1 (q); MS *m*/*z* 249 (M^+, 2), 91 (100). Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.11; H, 7.91; N, 5.44.

Methyl (1*S*,5*S*,7*R*)-6,8-Dioxa-3-azabicyclo[3.2.1]octane-7-*exo*-carboxylate (22). Compound **16** (512 mg, 1.95 mmol) was dissolved in MeOH (100 mL), and 20% $Pd(OH)_2$/C (140 mg) was added. The stirring suspension was left overnight at room temperature under a H_2 atmosphere, and then the catalyst was removed by filtration over a Celite layer and washed with MeOH. The solution was then filtered through a column filled with Amberlyst A-21 beads giving, after evaporation of the solvent, pure **22** (334 mg, 99%) as a colorless oil: $[\alpha]^{25}_D$ −55.0 (*c* 0.64, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 5.53 (s, 1 H), 4.72 (s, 1 H), 4.49 (s, 1 H), 3.71 (s, 3 H), 3.17 (dd, J = 13.6, 1.8 Hz, 1 H), 2.83 (m, 2 H), 2.68 (d, J = 13.6 Hz, 1 H), 2.55 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 170.9 (s), 101.9 (d), 77.2 (d), 75.3 (d), 52.0 (q), 48.3 (t), 47.4 (t); MS *m*/*z* 173 (M^+, 7), 57 (100); IR ($CDCl_3$) 3345, 1755 cm^{-1}. Anal. Calcd for $C_7H_{11}NO_4$: C, 48.55; H, 6.40; N, 8.09. Found: C, 48.19; H, 6.21; N, 8.00.

Methyl (1*S*,4*S*,5*S*,7*R*)-4-*exo*-Benzyl-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-*exo*-carboxylate (23). Prepared from **17** (339 mg, 0.96 mmol) as reported for **22**. Pure **23** (221 mg, 87%) was obtained as a colorless oil: $[\alpha]^{25}_D$ −75.8 (*c* 0.07, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.32−7.10 (m, 5 H), 5.42 (s, 1 H), 4.73 (s, 1 H), 4.58 (br s, 1 H), 3.75 (s, 3 H), 3.43 (d, J = 13.6 Hz, 1 H), 2.88 (m, 3 H), 2.69 (d, J = 13.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 171.6 (s), 138.5 (s), 129.1 (d, 2 C), 128.6 (d, 2 C), 126.5 (d), 104.1 (d), 78.3 (d), 75.3 (d), 57.2 (d), 52.5 (q), 44.1 (t), 35.3 (t); MS *m*/*z* 263 (M^+, 2), 172 (100%); IR ($CDCl_3$) 1751 cm^{-1}. Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.48; H, 6.34; N, 5.11.

Methyl (1*S*,4*R*,5*S*,7*R*)-4-*endo*-Benzyl-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-*exo*-carboxylate (24). Prepared from **18** (120 mg, 0.34 mmol) as reported for **22**. Pure **24** (70 mg, 78%) was obtained as a colorless oil: $[\alpha]^{25}_D$ −27.0 (*c* 0.38, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.30−7.10 (m, 5 H), 5.36 (s, 1 H), 4.72 (s, 1 H), 4.56 (br s, 1 H), 3.76 (s, 3 H), 3.15 (dd, J = 12.8, 1.8 Hz, 1 H), 3.02 (dd, J = 8.1, 6.2 Hz, 1 H), 2.83 (d, J = 12.8 Hz, 1 H), 2.63 (dd, J = 13.6, 6.2 Hz, 1 H), 2.60 (dd, J = 13.6, 6.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 171.6 (s), 137.5 (s), 129.2 (d, 2 C), 128.6 (d, 2 C), 126.6 (d), 103.9 (d), 77.3 (d), 75.8 (d), 58.5 (d), 52.5 (q), 48.1 (t), 38.3 (t); MS *m*/*z* 263 (M^+, 1), 172 (100); IR ($CDCl_3$) 1750 cm^{-1}. Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.71.; H, 6.23.; N, 4.99.

Methyl 6,8-Dioxa-3-azabicyclo[3.2.1]octane-7-*endo*-carboxylate [(±)-**25**]. Prepared from (±)-**21** (322 mg, 1.22 mmol) as reported for **22**. Pure (±)-**25** (196 mg, 93%) was obtained as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 5.34 (s, 1 H), 4.48 (d, J = 4.6 Hz, 1 H), 4.37 (d, J = 4.6 Hz, 1 H), 3.72 (s, 3 H), 3.35 (d, J = 14.2 Hz, 1 H), 2.94 (br s, 1 H), 2.88 (m, 2 H), 2.65 (d, J = 14.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 170.1 (s), 101.9 (d), 76.5 (d), 75.1 (d), 52.1 (q), 48.7 (t), 45.6 (t). Anal. Calcd for $C_7H_{11}NO_4$: C, 48.55; H, 6.40; N, 8.09. Found: C, 48.18; H, 6.32; N, 7.91.

(1*S*,5*S*,7*S*)-7-*exo*-Hydroxymethyl-6,8-dioxa-3-azabicyclo-[3.2.1]octane (76). Prepared from **69** (163 mg, 0.62 mmol) as reported for **22**. Pure **76** (89 mg, 99%) was obtained as a white solid: mp 116−117 °C; $[\alpha]^{25}_D$ −70.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 5.40 (s, 1 H), 4.38 (t, J = 5.9 Hz, 1 H), 4.17 (s, 1 H), 3.60 (m, 2 H), 3.22 (dd, J = 13.5, 1.8 Hz, 1 H), 2.92 (d, J = 13.5 Hz, 1 H), 2.77−2.65 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 101.4 (d), 78.5 (d), 75.1 (d), 64.3 (t), 49.4 (t), 48.1 (t); MS *m*/*z* 145 (M^+, 3), 100 (100). Anal. Calcd for $C_6H_{11}NO_3$: C, 49.65; H, 7.64; N, 9.58. Found: C, 49.45; H, 7.32; N, 9.30.

(1*R*,4*S*,5*R*,7*S*)-4-*endo*-Methyl-7-*endo*-hydroxymethyl-6,8-dioxa-3-azabicyclo[3.2.1]octane (77). Prepared from **75** (650 mg, 2.61 mmol) as described for **22**. Crude **77** (380 mg, 91%) was obtained as a colorless oil and used directly in the next step: ^{1}H NMR ($CDCl_3$) δ 5.15 (s, 1 H), 4.26 (m, 1 H), 4.15 (dd, J = 11.4, 4.4 Hz, 1 H), 4.12 (s, 1 H), 3.82 (d, J = 11.4 Hz, 1 H), 3.25 (dd, J = 12.2, 2.2 Hz, 1 H), 3.05 (m, 2 H), 1.04 (d, J = 6.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 102.3 (d), 78.0 (d), 73.8 (d), 58.9 (t), 52.5 (d), 45.1 (t), 16.6 (q).

(1*R*,5*S*,7*R*)-3-(*p*-Methoxybenzyl)-2-oxo-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-*exo*-carboxylic Acid (15). To a suspension of **2** (50 mg, 0.163 mmol) in water (10 mL) was added under stirring a 1 M aqueous solution of NaOH (10 mL). After 3 h, the suspension was filtered over a Celite layer. To the resulting solution was added 2 M HCl (5 mL) and then NaCl up to saturation, and finally compound **15** was extracted with Et_2O. The organic layer was dried over Na_2SO_4, concentrated, and evaporated, affording **15** (44 mg, 91%) as a white solid: mp 170 °C; $[\alpha]^{25}_D$ −43.4 (*c* 1.0, DMSO); ^{1}H NMR (DMSO-d_6) δ 7.16 (d, J = 8.6 Hz, 2 H), 6.92 (d, J = 8.6 Hz, 2 H), 5.94 (d, J = 2.3 Hz, 1 H), 4.88 (s, 1 H), 4.77 (s, 1 H), 4.42 (AB system, J = 14.6 Hz. 2 H), 3.75 (s, 3 H), 3.33 (dd, J = 12.5, 2.3 Hz, 1 H), 3.04 (d, J = 12.5 Hz, 1 H); ^{13}C NMR (DMSO-d_6) δ 170.6 (s), 165.5 (s), 158.9 (s), 129.5 (d, 2 C), 128.4 (s), 114.3 (d, 2 C), 99.6 (d), 77.3 (d), 77.2 (d), 55.3 (q), 50.9 (t), 46.7 (t); MS *m*/*z* 293 (M^+, 39), 121 (100). Anal. Calcd for $C_{14}H_{15}NO_6 \cdot H_2O$: C, 54.02; H, 5.50; N, 4.50. Found: C, 54.37; H, 5.66; N, 4.12.

(1*S*,5*S*,7*R*)-6,8-Dioxa-3-azabicyclo[3.2.1]octane-7-*exo*-carboxylic Acid HCl Salt (28). Method A. To a stirred solution of **16** (51.8 mg, 0.197 mmol) in MeOH (3 mL) cooled at 0 °C was added dropwise a solution of KOH (11 mg, 0.197 mmol) in MeOH (3 mL). After 3 h, the solvent was evaporated, water (3 mL) was added, and to the resulting solution a few drops of 5 N HCl were added up to pH 1. The solution was concentrated again, yielding a white solid containing salt **29** (71 mg): ^{1}H NMR (D_2O) δ 7.51 (m, 5 H), 5.91 (s, 1 H), 5.04 (s, 1 H), 4.92 (s, 1 H), 4.39 br s, 2 H), 3.70−3.30 (m, 4 H). Salt **29** was added to a suspension of 20% $Pd(OH)_2$/C (60 mg) in MeOH (5 mL) and left under H_2 atmosphere. After 16 h, the suspension was filtered through a Celite layer and concentrated, obtaining **28** (38 mg, 100%) as HCl salt. **Method B**. Compound **28** was also obtained by dissolving **22** (60 mg, 0.35 mmol) in 4 N HCl (1.5 mL). After stirring 18 h at room temperature, the solution was concentrated obtaining pure **28** (66 mg, 96%) as the HCl salt: $[\alpha]^{20}_D$ −35.2 (*c* 0.5, H_2O); ^{1}H NMR (D_2O) δ 5.95 (s, 1 H), 5.03 (s, 1 H), 4.98 (s, 1 H), 3.57 (m, 2 H), 3.34 (m, 2 H). Anal. Calcd for $C_6H_{10}NO_4Cl$: C, 36.84; H, 5.15; N, 7.16. Found: C, 36.64; H, 5.22; N, 6.98.

Methyl (1*S*,5*S*,7*R*)-3-(9-Fluorenylmethoxycarbonyl)-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-*exo*-carboxylate (26). To a stirred solution of **22** (250 mg, 1.44 mmol) in CH_2Cl_2 (10 mL) cooled at 0 °C was added FMOC-*O*-Su (489 mg, 1.45 mmol). The solution was left under stirring for 10 min at 0 °C

and then 24 h at room temperature. The reaction mixture was filtered through a Celite layer, washed with water, dried over Na_2SO_4, and finally concentrated to give **26** (557 mg, 98%) as a white foamy solid: mp 54−55 °C; ^{1}H NMR ($CDCl_3$) (1:1 mixture of rotamers) δ 7.75 (d, J = 7.0 Hz, 2 H), 7.54 (d, J = 7.0 Hz, 2 H), 7.45−7.20 (m, 4 H), 5.66 (s, 1 H), 4.71−4.00 (m, 6 H), 3.78 (s, 3 H), 3.77−2.92 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 170.5 (s, 1 C), 156.0 (s), 143.6 (s, 2 C), 141.3 (s, 2 C), 128.1 (d), 127.7 (d), 127.0 (d), 124.9 (d), 124.7 (d), 120.0 (d), 100.2 (d), 99.7 (d), 75.6 (d), 75.4 (d), 74.9 (d), 67.6 (t), 67.1 (t), 52.5 (q), 47.8 (t), 47.0 (d), 46.5 (t); MS m/z 178 [$(C_{14}H_{10})^+$, 100]. Anal. Calcd for $C_{22}H_{21}NO_6$: C, 66.83; H, 5.35; N, 3.54. Found: C, 66.61; H, 5.52; N, 3.24.

(1*S*,5*S*,7*R*)-3-(9-Fluorenylmethoxycarbonyl)-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-*exo*-carboxylic acid (30). Method A. Salt **28** (28 mg, 0.1 mmol) was suspended in a solution of Na_2CO_3 (22 mg, 0.21 mmol) in water (0.5 mL) and, after cooling to 0 °C, a solution of FMOC-*O*-Su (37 mg, 0.11 mmol) in acetone (250 μL) was slowly added under stirring. Then an additional 250 μL of acetone was added and the solution left under stirring at room temperature overnight. Then water (2 mL), 1 M solution of $NaHSO_4$ up to pH 3, and NaCl up to saturation were added, and the resulting solution was extracted with CH_2Cl_2. After evaporation of the solvent, **30** (32 mg, 84%) was obtained as a yellowish oil. **Method B.** Compound **26** (395 mg, 1 mmol) was dissolved in DMSO (10 mL), and 4 N HCl in water (1 mL, 4 mmol) was added under stirring at room temperature. After 24 h, water (40 mL) was added and the pH of the solution adjusted to 9 with 3 M NaOH. The solution was extracted with Et_2O and EtOAc, and the aqueous layer was treated with 5% HCl to adjust the pH to 2−3 and finally extracted with Et_2O. The organic layer was dried over Na_2SO_4 and evaporated, affording **30** (275 mg, 72%) as a yellowish oil. **Method C.** *N*-FMOC amino alcohol **78** (75 mg, 0.20 mmol) was dissolved in DMF (1.3 mL) and, after cooling to 0 °C, treated with pyridinium dichromate (PDC) (376 mg, 1 mmol). After the mixture was stirred at room temperature for 24 h, water (12 mL) was added, and the solution was adjusted to pH 10 by 20% NaOH and extracted with Et_2O. Then 5% HCl was added up to pH 2−3 and the solution extracted again with Et_2O. The last organic layer was dried over Na_2SO_4 and evaporated affording pure **30** (68 mg, 89%): ^{1}H NMR ($CDCl_3$) (1:1 mixture of rotamers) δ 8.53 (br s, 1 H), 7.74 (d, J = 7.7 Hz, 2 H), 7.53 (d, J = 7.7 Hz, 2 H), 7.45−7.20 (m, 4 H), 5.67 (s, 1 H), 4.72−2.89 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 172.5 (s, 1 C), 155.9 (s), 143.5 (s, 2 C), 143.4 (s, 2 C), 127.8 (d), 127.6 (d), 126.9 (d), 125.0 (d), 124.8 (d), 124.6 (d), 119.9 (d), 100.0 (d), 99.4 (d), 75.4 (d), 75.3 (d), 74.9 (d), 67.5 (t), 67.1 (t), 47.6 (t), 47.3 (d), 46.9 (t), 46.5 (t); FAB-MS m/z 382 (M^+ + 1), 179 [$(C_{14}H_{11})^+$, 100].

Methyl (1*S*,4*S*,5*S*,7*R*)-3-(9-Fluorenylmethoxycarbonyl)-4-*exo*-benzyl-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-*exo*-carboxylate (27). Prepared as described for compound **26**. Starting from **23** (200 mg, 0.76 mmol), pure **27** (359 mg, 97%) was obtained after chromatography (CH_2Cl_2−MeOH, 30:1, R_f 0.82) as a white solid: mp 55−56 °C; $[\alpha]^{20}_D$ −20.7 (c 0.19, $CHCl_3$); ^{1}H NMR ($CDCl_3$) (2.5:1 mixture of rotamers) δ 7.78−7.65 (m, 2 H), 7.60−7.45 (m, 2 H), 7.40−7.00 (m, 8 H), 6.90 (m, 1 H), [5.34 (s) and 5.25 (d, J = 1.5 Hz), 1 H], 4.70−3.88 (m, 6 H), [3.75 (s) and 3.73 (s), 3 H], 3.65−3.25 (m, 2 H), 2.76−2.48 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 170.6 and 168.5 (s), 155.8 (s), 143.8 (s), 143.5 (s), 141.4 (s), 136.6 (s), 129.3 (d), 129.2 (d), 128.7 (d), 128.6 (d), 127.8 (d), 127.7 (d), 127.2 (d), 126.7 (d), 124.7 (d), 120.2 (d), 120.1 (d), 101.1 and 100.8 (d), 75.9 (d), 75.3 (d), 66.8 (t), 57.4 (d), 52.6 (q), 47.4 (d), 44.0 (t), 34.8 (t); MS (electron-spray) m/z 486 (M^+ + 1, 45), 426 (10), 336 (16), 264 (59), 179 (100); IR ($CDCl_3$) 1745, 1699 cm^{-1}. Anal. Calcd for $C_{29}H_{27}NO_6$: C, 71.74; H, 5.60; N, 2.89. Found: C, 71.62; H, 5.84; N, 2.51.

(1*S*,4*S*,5*S*,7*R*)-3-(9-Fluorenylmethoxycarbonyl)-4-*exo*-benzyl-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-*exo*-carboxylic Acid (31). The hydrolysis of **27** (350 mg, 0.72 mmol) was carried out as reported for **26**, but the resulting solution was stirred at room temperature for 3 d after the addition of 4 N HCl. Hydrolysis was not complete (30% of remaining ester **27** by ^{1}H NMR analysis of the crude), and pure carboxylic acid **31** (223 mg, 66%) was obtained after chromatography through a short layer of silica gel (CH_2Cl_2−MeOH, 30:1, R_f 0.11) as a white solid: mp 80−82 °C; $[\alpha]^{20}_D$ −17.4 (c 0.37, $CHCl_3$); ^{1}H NMR ($CDCl_3$) (1.75:1 mixture of rotamers) δ 7.72 (m, 2 H), 7.53 (m, 2 H), 7.40−7.15 (m, 8 H), 6.83 (m, 1 H), [5.35 (d, J = 1.2 Hz) and 5.22 (d, J = 1.2 Hz), 1 H], [4.70−4.40 (m) and 4.31 (s), 4 H], 4.20−3.90 (m, 2 H), 3.67−3.20 (m, 2 H), 2.80−2.40 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 173.1 and 172.8 (s), 155.8 and 155.2 (s), 143.8 (s), 143.4 (s), 141.4 (s), 136.4 (s), 129.3 (d), 128.8 (d), 128.7 (d), 128.1 (d), 127.9 (d), 127.8 (d), 127.2 (d), 126.9 (d), 126.8 (d), 124.7 (d), 124.6 (d), 120.2 (d), 120.1 (d), 101.4 and 100.9 (d), 76.1 and 75.6 (d), 74.8 (d), 66.9 and 66.7 (t), 57.2 and 56.8 (d), 47.5 and 47.4 (d), 44.4 and 43.9 (t), 34.7 and 34.5 (t); MS (electron-spray) m/z 472 (M^+ + 1, 60), 413 (11), 250 (43), 264 (59), 179 (100); IR ($CDCl_3$) 1785, 1703 cm^{-1}.

(1*S*,5*S*,7*S*)-3-(9-Fluorenylmethoxycarbonyl)-7-*exo*-hydroxymethyl-6,8-dioxa-3-azabicyclo[3.2.1]octane (78). Prepared as described for compound **26**. Starting from amino alcohol **76** (190 mg, 1.32 mmol), pure **78** (332 mg, 66%) was obtained after chromatography (CH_2Cl_2−MeOH, 40:1, R_f 0.23) as a colorless oil: $[\alpha]^{20}_D$ −27.3 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) (1.8:1 mixture of rotamers) δ 7.74 (d, J = 7.0 Hz, 2 H), 7.54 (d, J = 7.0 Hz, 2 H), 7.40−7.20 (m, 4 H), 5.49 (s, 1 H), 4.60−4.15 (m, 5 H), 4.00−3.65 (m, 2 H), 3.54 (m, 2 H), 3.27 (m, 1 H), 3.02 (dd, J = 25.0, 12.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 155.0 (s), 143.9 (s, 2 C), 141.4 (s, 2 C), 127.8 (d, 2 C), 127.1 (d, 2 C), 125.1 (d, 1 C), 124.9 (d, 1 C), 120.1 (d, 2 C), 99.2 and 98.7 (d), 78.2 and 78.1 (d), 73.2 and 72.8 (d), 67.7 and 67.1 (t), 64.0 (t), 48.2 (t), 47.0 (d), 46.9 (t); MS (electron-spray) m/z 368 (M^+ + 1, 72), 179 (100); IR ($CDCl_3$) 1692 cm^{-1}. Anal. Calcd for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76; N, 3.81. Found: C, 68.41; H, 5.94; N, 3.49.

(1*R*,4*S*,5*R*,7*S*)-3-(9-Fluorenylmethoxycarbonyl)-4-*endo*-methyl-7-*endo*-hydroxymethyl-6,8-dioxa-3-azabicyclo-[3.2.1]octane (79). Prepared as described for compound **26**. Starting from amino alcohol **77** (367 mg, 2.30 mmol), pure **79** (606 mg, 69%) was obtained after chromatography (CH_2Cl_2−MeOH, 40:1, R_f 0.10) as an oil: $[\alpha]^{20}_D$ −36.5 (c 0.17, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.72 (d, J = 6.9 Hz, 2 H), 7.53 (d, J = 7.4 Hz, 2 H), 7.40−7.20 (m, 4 H), 5.12 (d, J = 2.5 Hz, 1 H), 4.60−4.40 (m, 3 H), 4.18 (t, J = 5.8 Hz, 1 H), 4.03 (m, 1 H), 3.78 (m, 1 H), 3.60 (m, 1 H), 3.40−3.23 (m, 3 H), 1.13 (d, J = 6.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 157.2 (s), 143.8 (s, 2 C), 141.3 (s, 2 C), 127.6 (d, 2 C), 127.0 (d, 2 C), 124.6 (d, 2 C), 119.9 (d, 2 C), 101.4 (d), 76.6 (d), 71.6 (d), 66.9 (t), 61.0 (t), 53.5 (d), 47.1 (d), 44.0 (t), 16.5 (q); MS (electron-spray) m/z 382 (M^+ + 1, 100), 179 (55). Anal. Calcd for $C_{22}H_{23}NO_5$: C, 69.28; H, 6.08; N, 3.67. Found: C, 69.01; H, 6.37; N, 3.42.

(1*R*,4*S*,5*R*,7*R*)-3-(9-Fluorenylmethoxycarbonyl)-4-*endo*-methyl-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-*endo*-carboxylic Acid (32). Prepared by oxidation with PDC in DMF of **79** (313 mg, 0.82 mmol) as reported for **30**, Method C. Pure acid **32** (295 mg, 91%) was obtained after chromatography (CH_2Cl_2−MeOH, 40:1, 0.5% AcOH, R_f 0.12) as a low-melting solid: $[\alpha]^{20}_D$ −5.6 (c 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.98 (s, 1 H), 7.73 (d, J = 7.0 Hz, 2 H), 7.53 (d, J = 7.0 Hz, 2 H), 7.40−7.20 (m, 4 H), 5.28 (d, J = 3.0 Hz, 1 H), 4.78 (t, J = 5.0 Hz, 1 H), 4.58−4.14 (m, 5 H), 3.66 (d, J = 13.4 Hz, 1 H), 3.48 (m, 2 H), 1.33 (d, J = 6.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 170.0 (s), 156.5 (s), 143.5 (s, 2 C), 140.8 (s, 2 C), 127.3 (d, 2 C), 126.7 (d, 2 C), 124.6 (d, 2 C), 119.5 (d, 2 C), 102.3 (d), 75.8 (d), 71.6 (d), 66.9 (t), 61.0 (t), 53.4 (d), 46.7 (d), 44.1 (t), 15.4 (q); MS (electron-spray) m/z 396 (M^+ + 1, 100), 179 (58).

BTG-Pro-OH (80). Resin WANG-Pro-H (80 mg, 52 μmol, loading capacity 0.65 mmol/g) was suspended in DMF (150 mL), and compound **30** (40 mg, 0.105 mmol) was added. To this suspension was then added a solution (1.253 mL) prepared dissolving diisopropylcarbodiimide (65 μL) and 1-hydroxybenzotriazole (57 mg) in 5 mL of DMF, followed by the addition of *N*,*N*′-diisopropyl-*N*-ethylamine (27 μL). The resulting reaction mixture was left under stirring 4 days. After filtration, the resin was washed and then treated with Ac_2O (20 μL) in DMF (1 mL), in the presence of a catalytic amount of

4-(dimethylamino)pyridine (40 μL, 0.1 M solution in DMF) for 3 h. The resin was then washed with DMF, MeOH, and CH_2Cl_2 and dried. The resin was then suspended in a mixture of CF_3COOH (0.95 mL) and water (50 μL) and left under stirring for 4 h. After filtration, the suspension was concentrated and lyophilized, obtaining **80** as a white solid (38 mg, 76%). HPLC analysis of **80** showed the presence of only one a peak, having the following FAB-MS spectrum: *m*/*z* 479 ($M^+ + 1$, 60), 179 [$(C_{14}H_{11})^+$, 100].

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Supporting Information Available: Tables 2 and 3 containing the most significant ^{1}H NMR resonance data of compounds **1**−**14**, **16**−**25**, and **28**−**29**. This material is available free of charge via the Internet at http://pubs.acs.org.

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