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Synthesis of a bicyclic δ-amino acid as a constrained Gly-Asn dipeptide isostere

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Summary. δ-Amino acids are very attractive in drug discovery, especially in the peptidomimetic area, because of their capability to act as dipeptide isosteres and reverse turn mimetics. Herein we report the synthesis of a rigid δ-amino acid constrained by a 3-aza-6,8-dioxabicyclo[3.2.1]octane-based scaffold, which can be considered as a Gly-Asn dipeptide mimetic. Key steps are the condensation of glycidol and tartaric acid derivatives, and the intramolecular *trans*-acetalization of the oxidized adduct to give the bicyclic δ-amino acid. Starting from L-tartaric acid derivative, it was achieved the corresponding Gly-D-Asn isostere, whereas from the enantiomeric D-tartaric acid derivative the corresponding Gly-L-Asn isostere could be obtained, thus giving access to both enantiomeric dipeptide sequences.

Keywords: Amino acids – Peptides – Peptidomimetics – Bicyclic compounds – Chiral pool

Introduction

A field of interest in biomedical research is oriented towards the development of therapeutics based on peptides and proteins, by introducing both structural and functional specific modifications, and maintaining the features responsible for biological activity. In this context, the area of peptidomimetics provides new dimensions to the field of molecular diversity and drug discovery (Giannis and Kolter, 1993; Gante, 1994; Adessi and Soto, 2002). In particular, the development of new leads for drug discovery has taken advantage of the use of unnatural amino acids in different fields of medicinal chemistry, for the development of peptidomimetics possessing high molecular diversity and the capability to generate high-ordered structures (Cole, 1994; Juaristi and Lopez-Ruiz, 1999; Trabocchi et al., 2005; Trabocchi et al., 2007). The possibility of having a large collection of δ-amino acids, both linear and cyclic, is of special interest in the generation of different molecular entities able to interact with biological targets. The most interesting feature displayed by δ-amino acids is their structural analogy with dipeptides, and many δ-amino acids as peptidomimetics have been constructed to mimic dipeptide sequences with added structural constraints (Trabocchi et al., 2005). Relevant examples of δ-amino acids include linear (Wipf et al., 1998; Gardner et al., 1999; Shankaramma et al., 1999; Casimir et al., 2000), cyclic (Poitout et al., 1995; Graf von Roedern et al., 1996; Suhara et al., 1996; Wattersom et al., 2003; Durrat et al., 2004), bicyclic (Hanessian et al., 1997; Van Well et al., 2003), and spiro (Genin and Johnson, 1992; Khalil et al., 1999; Alonso et al., 2001) compounds, and different templates have been applied for the generation of such amino acids. Moreover, since the β-turn is a common structural feature of proteins associated with the dipeptide unit, much research about δ-amino acids has been concentrated on the creation of reverse turn mimetics, where the central amide bond is replaced by a rigid moiety (Kim and Germanas, 1997a, b; Belvisi et al., 1999; Estiarte et al., 2000; Trabocchi et al., 2002). Also, the folding properties of δ-peptides have been investigated (Szabo et al., 1998), as they proved to generate stable secondary structures. Among this class, sugar amino acid-based scaffolds gathered interest in both oligomer synthesis (Smith et al., 1999; Locardi et al., 2001) and peptidomimetics, due to the attractive feature of presenting many functional groups anchored in a rigid scaffold, and in well-defined positions.

Our last achievements in the generation of constrained bicyclic amino acids using derivatives from the chiral

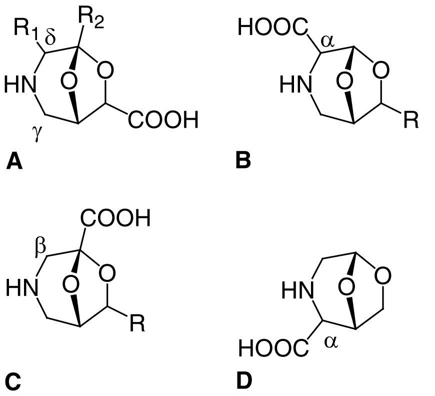


Fig. 1. 6,8-Dioxa-3-azabicyclo[3.2.1]octane-based amino acids: $\tilde{\gamma}/\delta$ (**A**), α (**B** and **D**), β (**C**)

pool were based on a general synthetic approach consisting in a coupling reaction between sugar and amino carbonyl derivatives, followed by intramolecular cyclization to give 6,8-dioxa-3-azabicyclo[3.2.1]octane-based scaffolds. This method allowed us to obtain a new class of bicyclic α- (Trabocchi et al., 2003a; Lalli et al., 2006), β- (Danieli et al., 2005), and γ/δ-amino acids (Guarna et al., 1999, 2002; Cini et al., 2002; Trabocchi et al., 2003b) by simply changing the starting material and tuning the reaction conditions according to the reactivity of the intermediate compounds (Fig. 1).

Recently, we reported the synthesis of bicyclic β-amino acids from glycidol and sugar derivatives (Fig. 1C) (Danieli et al., 2005). Starting from these molecules, by simply changing the sugar moiety with a tartaric acid derivative in the synthetic scheme, we designed a new type of δ-amino acid structure having the amino group at position 5 and the carboxyl function at position 7 (Fig. 2).

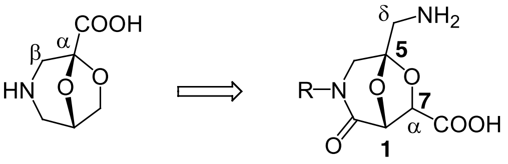


Fig. 2. Conceptual approach to a new δ-amino acid using the reported synthetic strategy for parent β-amino acids

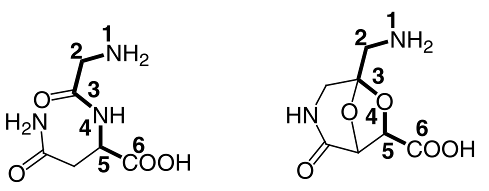


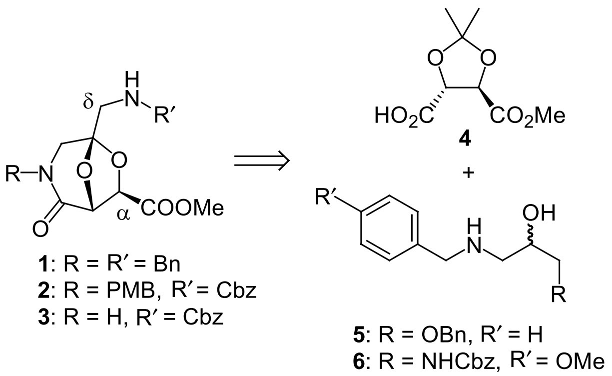
Fig. 3. Atom-by-atom correlation of the bicyclic δ-amino acid (*right*) with the Gly-Asn dipeptide sequence (*left*)

This new bicyclic amino acid shows a straightforward atom-by-atom correlation with respect to a general dipeptide sequence Gly-Asn, as shown in Fig. 3.

In particular, the carbonyl group at position **3** of the dipeptide Gly-Asn is mimicked by the acetal moiety in the bicyclic molecule, thus acting as a transition-state analogue, which is fundamental for peptidomimetic-based enzyme inhibitors (Giannis and Kolter, 1993; Gante, 1994). The replacement of the amide nitrogen atom at position **4** of the dipeptide by an oxygen atom, allows the maintenance of an heteroatom at such position. Moreover, the stereochemistry of Asn can be mimicked by proper choice of the tartaric acid stereoisomer, as the use of L-tartaric derivative **3** (see Fig. 4) forces the carbon atom at position **5** to have the same stereochemistry as for D-Asn, whereas the use of enantiomeric D-tartaric derivative provides the stereochemistry required for the L-Asn isostere.

Results and discussion

The synthesis of the new bicyclic δ-amino acid derivatives **1**–**3** consisted in amide bond formation between the tartaric acid derivative **4** with the amino alcohols **5** or **6** resulting from regioselective epoxide ring opening mediated by $LiNTf_2$, as reported (Cossy et al., 2002; Danieli et al., 2005). Subsequent alcohol oxidation and acid-catalyzed cyclization gave the corresponding bicyclic scaffold. The desired δ-amino ester **1**, deriving from amino alcohol **5**, was achieved after manipulation of the benzyloxy group of the parent bicyclic scaffold to give the amine, whereas more conveniently, δ-amino esters **2** and **3** where obtained directly with the Cbz-protected amino groups after acidic cyclization (see Fig. 4 for the retrosynthetic analysis).



1: R = R′ = Bn
2: R = PMB, R′ = Cbz
3: R = H, R′ = Cbz

5: R = OBn, R′ = H
6: R = NHCbz, R′ = OMe

Fig. 4. Retrosynthetic strategy to δ-amino esters **1**–**3**

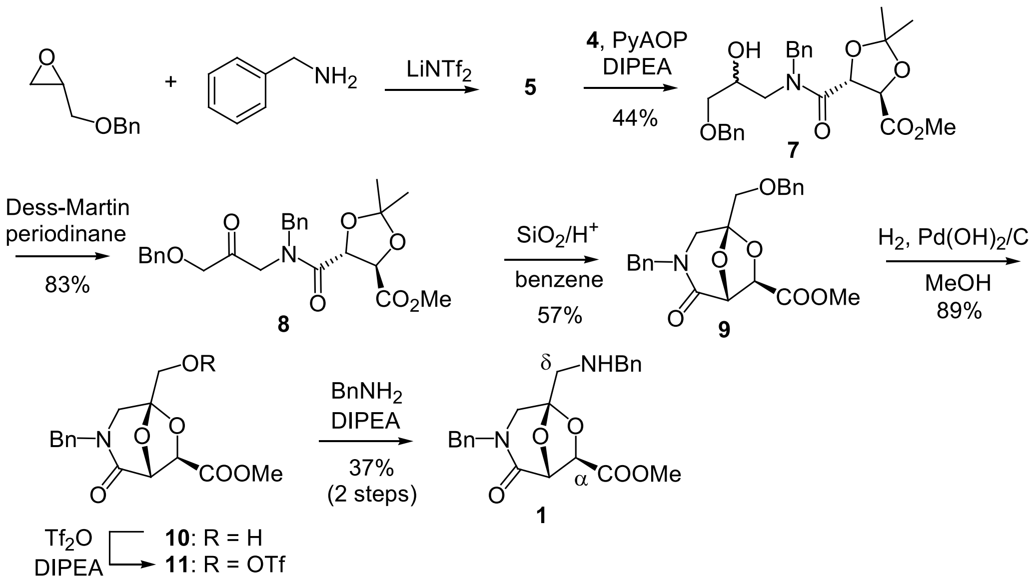


Fig. 5.

Table 1. COOH activators employed in the coupling reaction of acid **4** with amino alcohol **5**

Entry	Reagent system	Time (h)	Temperature (K)	Yield (%)
1	EDC, cat. DMAP	20	25	22
2	EDC-Cl, DIPEA	18	25	3
3	EDC-Cl, HOBt, NMM	24	25	18
4	1. DCC; 2. DIPEA	3 + 24	25	18
5	PyBrOP, DIPEA	16	25	26
6	PyAOP, DIPEA	12	25	44
7	HATU, TEA, DMF	16	25	15

Coupling reaction between amino alcohol **5** and tartaric acid derivative **4** to give **7** proved to be troublesome in terms of yield (Fig. 5).

Initially, EDC was added to acid **4** and the reaction was left in DCM for 20 h at room temperature and in the presence of catalytic DMAP, giving the desired amide in only 22% yield (Table 1, entry 1). Activation of COOH of **4** with EDC-Cl did not yield any improvement, nor the preactivation with DCC followed by addition of the amine and DIPEA as base (Table 1, entries 1–4). Use of other activating agents for the carboxylic function was thus investigated in order to obtain the adduct **7** in good yield. PyBrOP reagent, which is reported as a good coupling reagent for amide bond formation with relatively unreactive secondary amines Frérot et al., 1991), failed to give superior yields compared to carbodiimides (Table 1, entry 5). Finally, the use of PyAOP allowed to obtain compound **7** in higher yield (Table 1, entry 6), probably due to the effect of the nitrogen atom in the six-membered ring of the 1-hydroxy-7-aza-benzotriazolyl system in coordinating the amino group of **7** by virtue of hydrogen-bonding (Carpino, 1993). Interestingly, reaction conducted with the parent activator HATU and using DMF as solvent resulted in lower yield (Table 1, entry 7). Although the ester by-product was obtained in comparable quantity, the two products were separated easily by chromatography.

Subsequent secondary alcohol oxidation of the diastereomeric mixture of **7** using Dess-Martin periodinane gave the corresponding ketone **8** in 83% yield, and as a single stereoisomer, owing to the loss of the stereocenter at the carbon atom bearing the hydroxyl function. Acid-catalyzed cyclization was carried out in refluxing toluene, giving **9** in 40% yield. Better results were obtained when benzene was used as the solvent, in order to lower both the reaction temperature and the product degradation, giving **9** in 57% yield. Deprotection of the hydroxyl function of **9** was achieved by hydrogenolysis over $Pd(OH)_2/C$ in methanol, giving pure **10** after overnight stirring. Having in hands the bicyclic scaffold **10**, the hydroxylic function at position 5 was converted to the corresponding triflate **11**, and successively allowed to react with benzylamine, giving the final δ-amino acid derivative **1**, protected as *N*-benzylamino ester, in 37% yield over two steps.

Following a modification of the synthetic scheme, we next devised a more convenient route to access the title Gly-Asn dipeptide isostere by introducing the amino group at the beginning of the synthesis rather than by hydroxylic group manipulation. Thus, oxiranyl-methana-

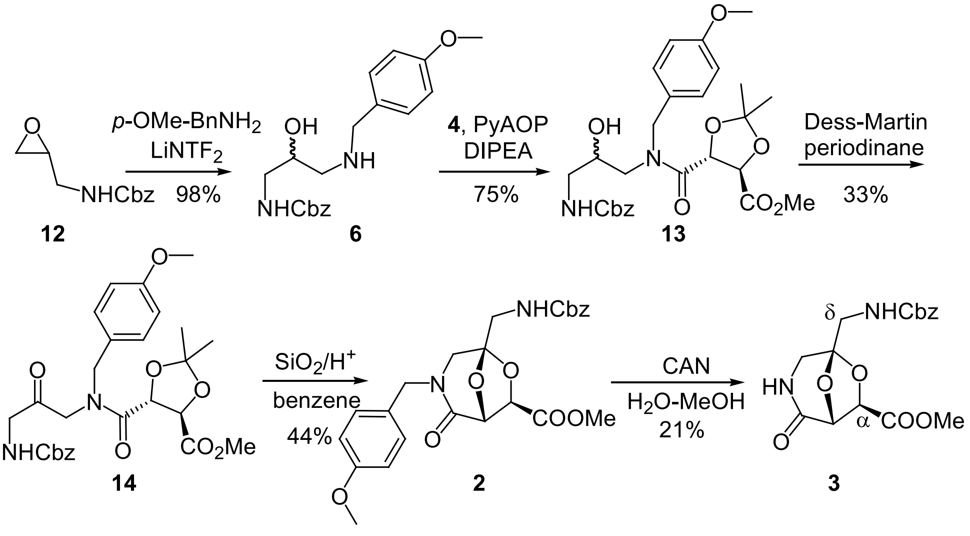


Fig. 6.

mine was taken into account as building block instead of *O*-benzyl-glycidol. Specifically, Fmoc-protected epoxide derivative was initially considered so as to achieve the corresponding Fmoc-derived dipeptide isostere for solid-phase chemistry. According to reported procedures, allylamine was Fmoc-protected and successively treated with *m*CPBA in water – acetone to give the corresponding epoxide (Bischofberger et al., 1988; Volkmer-Engert et al., 1997). Unfortunately, when the resulting oxiranyl derivative was treated with a stoichiometric amount of *p*-methoxy-benzylamine in the presence of 0.5 equivalents of $LiNTf_2$, according to literature, substantial Fmoc-deprotection was observed, thus preventing the application of this protecting group in the new synthetic route. Thus, Cbz protecting group was selected, and after synthesizing the corresponding epoxide **12** in 72%, according to the above described method (Bischofberger et al., 1988; Volkmer-Engert et al., 1997), the amino alcohol **6** resulting from $LiNTf_2$-mediated epoxide ring-opening with *p*-methoxy-benzylamine was cleanly obtained in 98% overall yield (Fig. 6).

Successively, the construction of the bicyclic scaffold was performed in the usual way, by reacting the amino alcohol **6** with the protected monoester tartaric acid derivative **4** in the presence of PyAOP as carboxylic acid activator. Subsequent alcohol oxidation of **13** and acid-catalyzed cyclization of the resulting ketone **14** allowed to achieve the title bicyclic scaffold **2** in 11% overall yield. Finally, in order to achieve the bicyclic dipeptide isostere as Gly-D-Asn mimetic, the elimination of the *p*-methoxybenzyl derivative was required with the aim of having the correct Asn side-chain mimetic, as shown in Fig. 3. Thus, the lactam moiety was treated with cerium ammonium nitrate (CAN), giving the molecule **3** with the deprotected amide function in 21% yield.

The same protocol was applied for the synthesis of the enantiomeric δ-amino acid as Gly-L-Asn isostere coming from the coupling between **6** and methyl di-*O*-isopropylidene-D-tartaric acid derivative ***S*,*S*-4**, giving the fully protected ***S*,*S*-2** in 25% overall yield. Particularly, the coupling and oxidation steps were performed in higher yields with respect to the other stereoisomer, indicating a more favourable stereochemical effect for the L-isostere. Also, coupling with PyAOP in both cases produced the title adduct in higher yields compared to **7**, corresponding to the other synthetic strategy.

Conclusion

In conclusion, the facile synthesis of a bicyclic δ-amino acid was achieved by coupling glycidol and tartaric acid derivatives, followed by alcohol oxidation and intramolecular acid *trans*-acetalization. Further derivatization of the hydroxymethyl function to give the aminomethyl group allowed to obtain the δ-amino acid structure. More interestingly, the application of oxiranyl-methanamine instead of glycidol allowed to simplify the overall synthesis, thus achieving the title Gly-Asn dipeptide isostere in few steps and avoiding the tedious manipulation of the glycidol-derived hydroxylic function to achieve the corresponding amino group. This constrained Gly-Asn isostere may find application in the generation of peptidomimetics having this particular dipeptidic sequence, expecially where the conformational restriction is desired, and also, as δ-amino acids are often involved in β-turns, the application as a turn inducer is under investigation.

Experimental

Melting points are uncorrected. Chromatographic separations were performed on silica gel using flash-column techniques; R_f values refer to TLC carried out on 25-mm silica gel 60 F_{254} plates with the same eluant as indicated for column chromatography. ^{1}H and ^{13}C NMR spectra of all compounds were recorded at 200 and 50.33 MHz, respectively, using $CDCl_3$ solutions. EI mass spectra were carried out at 70 eV ionizing voltage. Acid silica gel (H_2SO_4–SiO_2) was prepared as reported (Guidi et al., 1997).

*(4R,5R)-5-[Benzyl-(3-benzyloxy-2(R/S)-hydroxy-propyl)-carbamoyl]-2,2-dimethyl-[1,3]dioxolane-4-carboxylic acid methyl ester (**7**)*

Acid **4** (750 mg, 3.68 mmol) and PyAOP (1.19 g, 3.68 mmol, 1 eq) were dissolved in anhydrous CH_2Cl_2 (20 ml), and the resulting mixture was added to a solution of amine **5** (1.00 g, 3.68 mmol, 1 eq) in anhydrous CH_2Cl_2 (10 ml). After adding DIPEA (1.89 ml, 11.0 mmol, 3 eq), the mixture was left overnight stirring at room temperature, then it was successively washed with a 5% citric acid solution, a saturated $NaHCO_3$ solution, and dried over Na_2SO_4. Purification by flash chromatography (EtOAc: petroleum ether = 1:2) yielded a yellow oil corresponding to **7** as a diastereometic mixture, each as a mixture of rotamers (740 mg, 1.62 mmol, 44%). ^{1}H-NMR ($CDCl_3$, 200 MHz) $\delta = 7.36$–7.17 (m, 10 H), 5.38–5.36 (m, 0.34 H), 5.33–5.31 (m, 0.64 H), 5.20 (d, $J = 6.0$ Hz, 0.17 H), 5.02 (d, $J = 6.0$ Hz, 0.17 H), 4.98–4.95 (m, 1.85 H), [4.77 (d, $J = 16.0$ Hz) and 4.73 (d, $J = 16.1$ Hz), 1 H], 4.51 (m, 2 H), 3.78, 3.77, and 3.75 (s, 3 H), 3.68–3.56 (m, 1 H), 3.48–3.27 (m, 4 H), 1.46 and 1.45 (s, 6 H) ppm. ^{13}C-NMR ($CDCl_3$, 50 MHz) Major diastereomer $\delta = 171.0$ (s), 170.5 (s), 137.9 (s), 136.1 (s), 128.8 (d, 2 C), 128.3 (d, 2 C), 127.7 (d, 4 C), 126.8 (d, 2 C), 113.1 (s), 76.2 (d), 73.5 (d), 72.0, 70.0, 69.0, 52.2, 50.5, 49.3, 26.4 (q, 2 C) ppm. MS m/z (%) 457 (M^+, 2.1), 336 (16), 270 (22), 91 (100). Anal. Calcd for $C_{25}H_{31}NO_7$: C, 65.63; H, 6.83; N, 3.06. Found: C, 65.71; H, 6.89; N, 2.89.

*(4R,5R)-5-[Benzyl-(3-benzyloxy-2-oxo-propyl)-carbamoyl]-2,2-dimethyl-[1,3]dioxolane-4-carboxylic acid methyl ester (**8**)*

Compound **7** (116 mg, 0.253 mmol) was dissolved in CH_2Cl_2 (2.5 ml), then Dess-Martin periodinane (129 mg, 0.304 mmol) was added and the mixture was stirred at room temperature for 1 h. Successively, cold diethyl ether (3 ml) and a saturated $NaHCO_3$ solution containing 25% $Na_2S_2O_3$ (3 ml) were added, and the mixture was vigorously stirred for 10 min. Then it was diluted with additional diethyl ether, and the organic phase was separated, washed with a saturated $NaHCO_3$ solution, brine and dried over anhydrous Na_2SO_4. Solvent evaporation afforded a crude product, that was purified by column chromatography (EtOAc:petroleum ether = 1:1) to give **8** (96 mg, 0.20 mmol, 83%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$, 200 MHz) 2:3 mixture of rotamers A and B $\delta = 7.37$–7.26 (m, 8 H), 7.23–7.19 (m, 2 H), 5.38 (d, $J = 5.1$ Hz, 1 H, A), 5.34 (d, $J = 5.5$ Hz, 1 H, B), 5.03 (d, $J = 5.5$ Hz, 1 H, B), 4.87 (d, $J = 15.0$ Hz, 1 H, A), 4.78 (s, 2 H, A), 4.77 (s, 1 H, A), 4.53 (s, 2 H, B), 4.53–4.48 (d, $J = 19.0$ Hz, 1 H, B), 4.24–4.15 (m, 4 H, A + B), 4.07 (s, 2 H, B), 4.02 (s, 2 H, A), 3.80 (s, 3 H, A), 3.79 (s, 3 H, B), 1.48 (s, 3 H), 1.47 (s, 3 H), 1.41 (s, 3 H), 1.34 (s, 3 H) ppm. ^{13}C-NMR ($CDCl_3$, 50 MHz) $\delta = 203.3$ (s, A), 202.5 (s, B), 170.6 (s), 168.6 (s), 136.7 (s, A), 136.5 (s, B), 136.0 (s, A), 135.6 (s, B), 128.8 (d, 2 C, A), 128.7 (d, 2 C, B), 128.5 (d, 2 C, A), 128.4 (d, 2 C, B), 128.2 (d, 2 C, A), 128.0 (d, 2 C, B), 127.9 (d, 2 C, A), 127,9 (d, 2 C, B), 127.7 (d, 2 C, A), 127.3 (d, 2 C, B), 113.3 (s, A), 113.1 (s, B), 77.2 (d, A), 76.3 (d), 76.1 (d, B), 74.3 (t), 74.0 (t, A), 73.7 (t, B), 53.0 (t, A), 52.7 (q), 52.5 (t, B), 52.0 (t, A), 50.7 (t, B), 26.5 (q, 2 C) ppm. MS m/z (%) 455 (M^+, 1.0), 334 (69), 306 (22), 91 (100). Anal. Calcd for $C_{25}H_{29}NO_7$: C, 65.92; H, 6.42; N, 3.08. Found: C, 66.01; H, 6.49; N, 3.00.

*(1R,5R,7R)-3-Benzyl-5-benzyloxymethyl-2-oxo-6,8-dioxa-3-aza-bicyclo[3.2.1]octane-7-exo-carboxylic acid methyl ester (**9**)*

Compound **8** (400 mg, 0.878 mmol) was dissolved in benzene (4 ml) to give a solution that was quickly added to a refluxing suspension of H_2SO_4/SiO_2 (141 mg) in benzene (7 ml). After 30 min, one-third of the solvent was distilled-off, the warm mixture was filtered through celite and the solvent was evaporated to give a crude oil that was purified by flash column chromatography (EtOAc:petroleum ether = 1:3), affording **9** (200 mg, 0.50 mmol, 57%) as a viscous oil. $[\alpha]_D^{20} = -19.6$ (*c* 1.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 400 MHz) $\delta = 7.36$–7.26 (m, 8 H), 7.22–7.20 (m, 2 H), 4.98 (s, 1 H), 4.78 (s, 1 H), 4.64 (d, $J = 14.8$ Hz, 1 H), 4.60 (d, $J = 4.5$ Hz, 2 H), 4.47 (d, $J = 14.8$ Hz, 1 H), 3.80 (d, $J = 7.0$ Hz, 2 H), 3.77 (s, 3 H), 3.57 (d, $J = 12.3$ Hz, 1 H), 3.19 (d, $J = 12.3$ Hz, 1 H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) $\delta = 169.2$ (s), 165.4 (s), 137.7 (s), 135.4 (s), 128.8 (d, 2 C), 128.4 (d, 2 C), 127.9 (d. 3 C), 127.8 (d, 3 C), 107.4 (s), 78.8 (d), 78.0 (d), 73.8 (t), 70.8 (t), 52.7 (q), 51.7 (t), 48.7 (t) ppm. MS m/z (%) 397 (M^+, 1.0), 306 (2), 291 (10), 91 (100). Anal. Calcd for $C_{22}H_{23}NO_6$: C, 66.49; H, 5.83; N, 3.52. Found: C, 66.55; H, 5.89; N, 3.49.

*(1R,5R,7R)-3-Benzyl-5-hydroxymethyl-2-oxo-6,8-dioxa-3-aza-bicyclo[3.2.1]octane-7-carboxylic acid methyl ester (**10**)*

To a solution of **9** (150 mg, 0.378 mmol) in MeOH (4 ml) was added 20% $Pd(OH)_2/C$ (57 mg). The suspension was stirred under a hydrogen atmosphere at room temperature for 12 h, the it was filtered over celite and the solvent was evaporated to afford **10** (103 mg, 0.33 mmol, 89%) as a colourless oil and enough pure for the next step. ^{1}H-NMR ($CDCl_3$, 200 MHz) $\delta = 7.32$–7.27 (m, 3 H), 7.21–7.17 (m, 2 H), 4.95 (s, 1 H), 4.78 (s, 1 H), 4.54 (s, 2 H), 3.81 (s, 2 H), 3.80 (s, 3 H), 3.31 (d, $J = 11.7$ Hz, 1 H), 3.10 (d, $J = 11.7$, 1 H) ppm. ^{13}C-NMR ($CDCl_3$, 50 MHz) $\delta = 170.2$ (s), 165.1 (s), 135.1 (s), 128.8 (d, 2 C), 127.9 (d, 3 C), 108.0 (s), 79.0 (d), 77.6 (d), 62.0 (t), 53.2 (q), 51.6 (t), 48.7 (t) ppm. MS m/z (%) 307 (M^+, 8), 248 (2), 218 (3), 91 (100).

*(1R,5R,7R)-3-Benzyl-5-benzylamino-methyl-2-oxo-6,8-dioxa-3-aza-bicyclo[3.2.1]octane-7-exo-carboxylic acid methyl ester (**1**)*

Triflic anhydride (80 µl, 0.488 mmol) was dropwise added to a stirring solution of **10** (100 mg, 0.325 mmol) and triethylamine (99 µl, 0.715 mmol) in anhydrous CH_2Cl_2 (1.7 ml) at 0 °C. The mixture was stirred at 0 °C for 40 min, then it was washed with a saturated $NaHCO_3$ solution and brine. The organic phase was then dried over Na_2SO_4, and the solvent was evaporated to give **11** as a crude red oil that was used in the next step, without further purification. ^{1}H-NMR ($CDCl_3$, 200 MHz) $\delta = 7.35$–7.31 (m, 3 H), 7.25–7.17 (m, 2 H), 5.04 (s, 1 H), 4.83 (s, 1 H), 4.67 (s, 2 H), 4.64 (d, $J = 14.6$ Hz, 1 H), 4.48 (d, $J = 14.6$ Hz, 1 H), 3.79 (s, 3 H), 3.46 (d, $J = 11.7$ Hz, 1 H), 3.20 (d, $J = 11.7$ Hz, 1 H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) $\delta = 168.2$ (s), 164.4 (s), 150.1 (s), 134.8 (s), 128.9 (d, 2 C), 128.1 (d), 127.9 (d, 2 C), 104.5 (s), 79.1 (d), 78.5 (d), 73.0 (t), 53.1 (d), 51.0 (t), 48.8 (t) ppm. To a solution of benzylamine (64 µl, 0.592 mmol) and diisopropylethylamine (51 µl, 0.296 mmol) in anhydrous CH_2Cl_2 (0.5 ml), was dropwise added, at 0 °C, a solution of **11** (130 mg, 0.296 mmol) in anhydrous CH_2Cl_2 (1 ml). The mixture was stirred under a nitrogen atmosphere, at room temperature for 12 h, then it was poured into a 5% aqueous solution of $NaHCO_3$. The organic layer was separated, then it was washed with brine, dried over Na_2SO_4, and evaporated under vacuum to give a crude oil that was purified by flash column chromatography (EtOAc:petroleum ether = 2:1) to give **1** (40 mg, 0.10 mmol, 37% over two steps) as a pale yellow oil. $[\alpha]_D^{20} = -15.2$ (*c* 0.5, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 400 MHz) $\delta = 7.35$–7.26 (m, 8 H), 7.21–7.19 (m, 2 H), 4.97 (s, 1 H), 4.75 (s, 1 H), 4.59 (d, $J = 14.6$ Hz, 1 H), 4.49 (d, $J = 14.6$ Hz, 1 H), 3.91 (d, $J = 13.5$ Hz, 1 H), 3.83 (d, $J = 13.5$ Hz, 1 H), 3.77 (s, 3 H), 3.43 (d, $J = 12.2$ Hz, 1 H), 3.16 (d, $J = 12.2$ Hz, 1 H) 3.04 (s, 2 H), 2.17 (br, 1 H) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz) $\delta = 169.5$ (s), 165.3 (s), 138.9 (s), 135.3 (s), 128.8 (d), 128.4 (d, 2 C), 128.1 (d, 2 C), 127.9 (d, 2 C), 127.8 (d), 127.2 (d), 108. 3 (s), 78.9 (d), 77.9 (d), 53.8 (t), 52.9 (q), 52.8 (t), 51.0 (t), 48.7 (t) ppm. MS *m/z* (%) 396 (M^+, 1.0), 366 (1), 336 (2), 306 (1), 91 (100). Anal. Calcd for $C_{22}H_{24}N_2O_5$: C, 66.65; H, 6.10; N, 7.07. Found: C, 66.71; H, 5.99; N, 7.09.

*[2-Hydroxy-3-(4-methoxy-benzylamino)-propyl]-carbamic acid benzyl ester (**6**)*

p-Methoxy-benzylamine (1.01 ml, 7.71 mmol, 1.1 eq) and $LiNTF_2$ (1.07 g, 3.51 mmol, 0.5 eq) were added to a solution of epoxide **12** (1.452 g, 7.01 mmol) in anhydrous CH_2Cl_2 (3.5 ml) under a nitrogen atmosphere. The mixture was left stirring for 22 h at room temperature, then, a saturated $NaHCO_3$ solution was added and the organic phase was separated and dried over Na_2SO_4, giving 3.30 g of crude product, which was further purified by flash chromatography, (EtOAc + 0.5% Et_3N, then MeOH), thus yielding pure **6** (2.37 g, 6.89 mmol, 98%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$, 200 MHz) $\delta = 7.30$–7.20 (m, 5 H), 7.17–7.13 (d, $J = 8.5$ Hz, 2 H), 6.81–6.77 (d, $J = 8.5$ Hz, 2 H), 5.92 (m, 1 H), 5.00 (s, 2 H), 3.77 (s, 2 H), 3.74 (m, 1 H), 3.71 (s, 3 H), 3.35–3.05 (m, 2 H), 2.70–2.45 (m, 2 H) ppm. ^{13}C-NMR ($CDCl_3$, 50 MHz) $\delta = 179.1$ (s), 158.7 (s), 157.1 (s), 136.0 (s), 129.5 (d, 2 C), 129.3 (d, 2 C), 128.2 (d, 2 C), 127.8 (d), 127.6 (d, 2 C), 68.3 (d), 66.7 (t), 55.1 (q), 52.3 (t), 51.3 (t), 46.5 (t) ppm. Anal. Calcd for $C_{19}H_{24}N_2O_4$: C, 66.26; H, 7.02; N, 8.13. Found: C, 66.32; H, 7.11; N, 7.99.

*(4R,5R)-5-[(3-Benzyloxycarbonylamino-2(R/S)-hydroxy-propyl)-(4-methoxy-benzyl)-carbamoyl]-2,2-dimethyl-[1,3]dioxolane-4-carboxylic acid methyl ester (**13**)*

Compound **13** was prepared as reported for **7**, starting from acid **4** (392 mg, 1.92 mmol) and amine **6** (661 mg, 1.92 mmol, 1 eq). Purification by flash chromatography (EtOAc, R_f 0.80) yielded a yellow oil corresponding to **13** as a diastereometic mixture, each as a mixture of rotamers (763 mg, 1.44 mmol, 75%). ^{1}H-NMR ($CDCl_3$, 200 MHz) $\delta = 7.26$ (m, 5 H), 7.06 (d, $J = 8.8$ Hz, 2 H), 6.81 (d, $J = 8.8$ Hz, 2 H), 5.85 and 5.80 (br, 1 H), 5.23–5.05 (m, 1 H), 5.00 (s, 2 H), 4.84 (d, $J = 5.9$ Hz, 1 H), 4.69 (m, 2 H), 3.95 (m, 1 H), 3.75 and 3.72 (s, 3 H), 3.72 and 3.70 (s, 3 H), 3.68–2.95 (m, 4 H), 1.22–1.14 (s, 6 H) ppm. ^{13}C-NMR ($CDCl_3$, 50 MHz) $\delta = 171.5$, 169.0, 159.0, 143.4, 138.7, 136.6, 129.1, 128.3, 127.9, 127.7, 76.7, 76.0, 75.7, 69.1, 68.8, 67.8, 66.7, 55.1, 52.5, 51.4, 49.1, 44.2, 26.1, 25.9 ppm. MS *m/z* (%) 530 (M^+, 0.2), 343 (22), 121 (100), 91 (41.7). Anal. Calcd for $C_{27}H_{34}N_2O_9$: C, 61.12; H, 6.46; N, 5.28. Found: C, 61.17; H, 6.51; N, 5.19.

*(4R,5R)-5-[(3-Benzyloxycarbonylamino-2-oxo-propyl)-(4-methoxy-benzyl)-carbamoyl]-2,2-dimethyl-[1,3]dioxolane-4-carboxylic acid methyl ester (**14**)*

Compound **14** was prepared as reported for **8**, starting from a solution of **13** (763 mg, 1.44 mmol) in CH_2Cl_2 (14.5 ml). Flash chromatography purification (EtOAc – petroleum ether 1:1, R_f 0.28) afforded pure **14** (254 mg, 0.48 mmol, 33%) as a pale yellow oil. $[\alpha]_D^{24} = -5.2$ (*c* 0.9, $CDCl_3$) ^{1}H-NMR ($CDCl_3$, 200 MHz) $\delta = 7.26$–7.25 (m, 5 H), 7.13–7.06 (m, 2 H), 6.84–6.75 (m, 2 H), 5.56 (m, 1 H), 5.32 (m, 1 H), 5.29 (d, $J = 12.8$ Hz, 1 H), 5.05 (s, 2 H), 5.04 (d, $J = 12.8$ Hz, 1 H), 4.77–4.64 (m, 2 H), 4.39–4.17 (m, 1 H), 3.99–3.90 (m, 2 H), 3.72 (s, 3 H), 3.70 (s, 3 H), 1.42 (s, 6 H) ppm. ^{13}C-NMR ($CDCl_3$, 50 MHz) $\delta = 200.0$ (s), 170.2 (s), 168.0 (s), 158.9 (s), 155.8 (s), 135.8 (s), 129.5 (d, 2 C), 128.5 (d, 2 C), 127.7 (d, 2 C), 127.6 (d), 126.8 (d, 2 C), 76.0 (d), 75.7 (d), 66.6 (t), 60.3 (s), 55.0 (q), 52.5 (q), 52.3 (t), 51.2 (t), 50.0 (t), 26.3 (q), 26.1 (q) ppm. MS *m/z* (%) 528 (M^+, 0.2), 364 (3.7), 322 (11.7), 136 (3.9). Anal. Calcd for $C_{27}H_{32}N_2O_9$: C, 61.35; H, 6.10; N, 5.30. Found: C, 61.42; H, 6.13; N, 5.09.

*(1R,5R,7R)-5-(Benzyloxycarbonylamino-methyl)-3-(4-methoxy-benzyl)-2-oxo-6,8-dioxa-3-aza-bicyclo[3.2.1]octane-7-carboxylic acid methyl ester (**2**)*

Compound **2** was prepared as reported for **9**, starting from a solution of **14** (209 mg, 0.40 mmol) in benzene (3 ml). Flash chromatography purification (EtOAc – petroleum ether 2:1, R_f 0.53) yielded pure **2** (80 mg, 0.18 mmol, 44%) as a pale yellow oil. $[\alpha]_D^{27} = -17.4$ (*c* 4.0, $CDCl_3$). ^{1}H-NMR ($CDCl_3$, 200 MHz) $\delta = 7.33$–7.31 (m, 5 H), 7.14–7.10 (m, 2 H), 6.90–6.83 (m, 2 H), 6.05 (m, 1 H), 5.11 (s, 2 H), 4.94 (s, 1 H), 4.74 (s, 1 H), 4.48–4.44 (m, 2 H), 4.04 (m, 1 H), 3.78 (s, 6 H), 3.73 (s, 2 H), 3.47 (dd, $J = 14.3$, 3.3 Hz, 1 H), 3.30 (d, $J = 11.8$ Hz, 1 H), 3.10 (d, $J = 12.0$ Hz, 1 H) ppm. ^{13}C-NMR ($CDCl_3$, 50 MHz) $\delta = 169.4$ (s), 168.3 (s), 164.6 (s), 159.0 (s), 156.6 (s), 145.8 (s), 129.8 (d, 2 C), 129.2 (d, 2 C), 128.3 (d, 2 C), 127.8 (d), 126.9 (d, 2 C), 106.8 (s), 78.8 (d), 77.7 (d), 76.0 (t), 66.9 (t), 66.6 (t), 55.2 (q), 52.8 (q), 47.9 (t) ppm. MS *m/z* (%) 456 (M^+, 0.2), 335 (3.7), 322 (4.1), 136 (2.3). Anal. Calcd for $C_{24}H_{26}N2O_8$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.32; H, 5.61; N, 5.89.

*(1R,5R,7R)-5-(Benzyloxycarbonylamino-methyl)- 2-oxo-6,8-dioxa-3-aza-bicyclo[3.2.1]octane-7-carboxylic acid methyl ester (**3**)*

Compound **2** (107 mg, 0.23 mmol) was dissolved in acetonitrile (1.2 ml), followed by addition of a solution of cerium ammonium nitrate (CAN) (252 mg, 0.46 mmol, 2 eq) in water (1.2 ml). After stirring at room temperature for 3 h, the mixture was diluted with EtOAc and the organic phase was separated. The aqueous phase was successively treated with EtOAc, and the organic extracts were combined and dried over Na_2SO_4, giving 126 mg of crude **3** after solvent evaporation. Flash chromatography purification (EtOAc:petroleum ether = 4:1, then CH_2Cl_2 – MeOH 10:1) afforded pure **3** (17 mg, 0.048 mmol, 21%) as a yellow oil. $[\alpha]_D^{22} = -16.3$ (*c* 3.4, $CDCl_3$). ^{1}H-NMR ($CDCl_3$, 200 MHz) $\delta = 7.31$ (m, 5 H), 6.11, 6.00 (br, 1 H), 5.10 (s, 2 H), 4.78 (s, 1 H), 4.73 (s, 1 H), 3.76 (m, 1 H), 3.72 (s, 3 H), 3.53 (dd, $J = 14.4$, 3.6 Hz, 1 H), 3.46 (d, $J = 12.9$ Hz, 1 H), 3.29 (d, $J = 12.8$ Hz, 1 H) ppm. ^{13}C-NMR ($CDCl_3$, 50 MHz) $\delta = 169.4$ (s), 166.5 (s), 156.6 (s), 136.2 (s), 128.1 (d, 2 C), 127.7 (d), 127.6 (d, 2 C), 106.2 (s), 78.5 (d), 77.6 (d), 66.6 (t), 52.7 (q), 48.1 (t), 43.0 (t) ppm. MS *m/z* (%) 350 (M^+, 2.7), 243 (17), 201 (44), 183 (27), 91 (100). Anal. Calcd for $C_{16}H_{18}N_2O_7$: C, 54.86; H, 5.18; N, 8.00. Found: C, 54.95; H, 5.23; N, 7.92.

*(4S,5S)-5-[(3-Benzyloxycarbonylamino-2(R/S)-hydroxy-propyl)-(4-methoxy-benzyl)-carbamoyl]-2,2-dimethyl-[1,3]dioxolane-4-carboxylic acid methyl ester (**S,S-13**)*

Prepared from ***S,S*-4** (392 mg, 1.92 mmol) and **6** (661 mg, 1.92 mmol) as reported for **7**, giving 838 mg (1.58 mmol) of a yellow oil corresponding to (***S,S*-13**) as a diastereomeric mixture in 82% yield, with identical NMR data as for **13**. Anal. Calcd for $C_{27}H_{34}N_2O_9$: C, 61.12; H, 6.46; N, 5.28. Found: C, 61.16; H, 6.53; N, 5.23.

*(4S,5S)-5-[(3-Benzyloxycarbonylamino-2-oxo-propyl)-(4-methoxy-benzyl)-carbamoyl]-2,2-dimethyl-[1,3]dioxolane-4-carboxylic acid methyl ester (**S,S-14**)*

Prepared from (***S,S*-13**) (838 mg, 1.58 mmol) as reported for **8**, giving 427 mg (0.81 mmol) of pure (***S,S*-14**) as a pale yellow oil in 51% yield, with identical NMR data as for **14**. $[\alpha]_D^{25} = +4.6$ (*c* 1.3, $CDCl_3$). Anal.

Calcd for $C_{27}H_{32}N_2O_9$: C, 61.35; H, 6.10; N, 5.30. Found: C, 61.39; H, 6.15; N, 5.13.

*(1S,5S,7S)-5-(Benzyloxycarbonylamino-methyl)-3-(4-methoxy-benzyl)-2-oxo-6,8-dioxa-3-aza-bicyclo[3.2.1]octane-7-carboxylic acid methyl ester (**S,S-2**)*

Prepared from (***S,S*-14**) (394 mg, 0.75 mmol) as reported for **9**, giving 211 mg (0.46 mmol) pure (***S,S*-2**) as a yellow oil in 62% yield, with identical NMR data as for **2**. $[\alpha]_D^{25} = +19.1$ (*c* 1.1, $CDCl_3$). Anal. Calcd for $C_{24}H_{26}N2O_8$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.34; H, 5.63; N, 5.91.

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