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Synthesis of a new enantiopure bicyclic γ/δ-amino acid (BTKa) derived from tartaric acid and α-amino acetophenone

Antonio Guarna,* Ilaria Bucelli, Fabrizio Machetti, Gloria Menchi, Ernesto G. Occhiato, Dina Scarpi and Andrea Trabocchi

Dipartimento di Chimica Organica "U. Schiff", Università di Firenze and Istituto di Chimica dei Composti Organometallici—CNR, via della Lastruccia 13, 50019 Sesto Fiorentino, Firenze, Italy

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Abstract—The synthesis of a novel enantiopure γ/δ-amino acid having the 3-aza-6,8-dioxabicyclo[3.2.1]octane structure was realized by the combination of tartaric acid derivatives and α-amino acetophenone followed by a trans-acetalisation process. This amino acid, which has a rigid skeleton and carries substituents at the 3, 5 and 7 positions of the scaffold, could find different applications in organic and peptidomimetic synthesis. Two different synthetic strategies were studied, one of them allowing the multigram scale preparation of the amino acid.

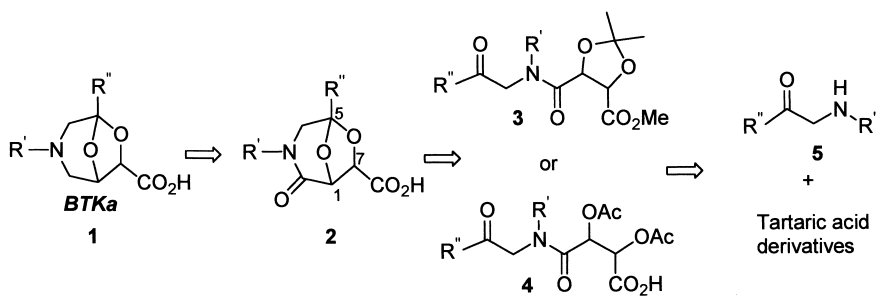
1. Introduction

Recently we have reported on the synthesis of a new class of γ/δ-amino acids named BTAa (Bicycles from Tartaric acid and Amino acid) obtained by the combination of tartaric acid and α-amino acid derivatives.[1–3] These compounds present a high degree of molecular diversity which can be varied through modifications of the configuration of the stereocenters and the functionalities introduced on the scaffold by choice of suitable starting reagents. These compounds could find different applications in organic and peptidomimetic synthesis: for example, we have used them as monomers for the generation of oligomers,[4] as chiral auxiliaries in asymmetric synthesis,[5] and, the 7-*endo* derivatives, as reverse turn inducers in peptide chains.[6]

2. Results and discussion

The methodology we have developed for the preparation of BTAa is based on the coupling between (*R*,*R*)-, (*S*,*S*)- or *meso*-tartaric acid derivatives with various α-amino alcohols or α-amino aldehydes derived from the corresponding α-amino acids.[1,2] In order to expand the range of scaffolds in our hands, we envisaged that new functionalised scaffolds **1** and **2** bearing a substituent at C-5 could be prepared starting from α-amino ketones **5** and tartaric acid derivatives (Scheme 1).

The coupling between compound **5** and tartaric acid derivatives would lead to intermediates **3** or **4**, which after trans-acetalisation, could give the scaffold **2**. Subsequent



Scheme 1.

Keywords: amino acids and derivatives; amino ketones; peptide mimetics.

* Corresponding author. Tel.: +39-55-4573481; fax: +39-55-4573569; e-mail: antonio.guarna@.unifi.it

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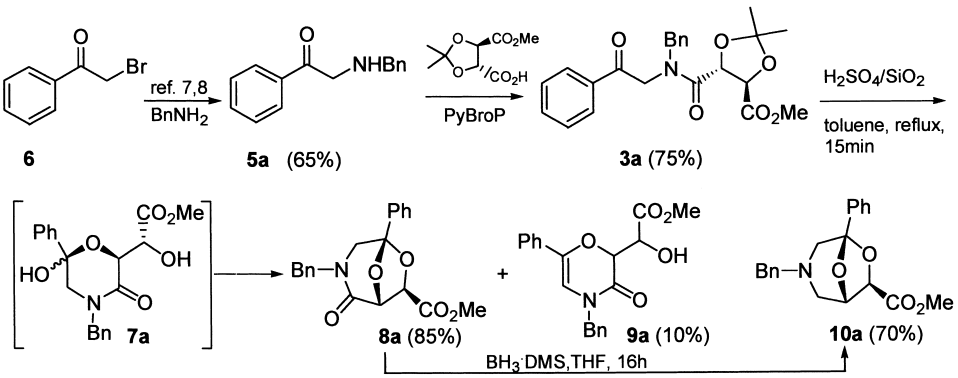
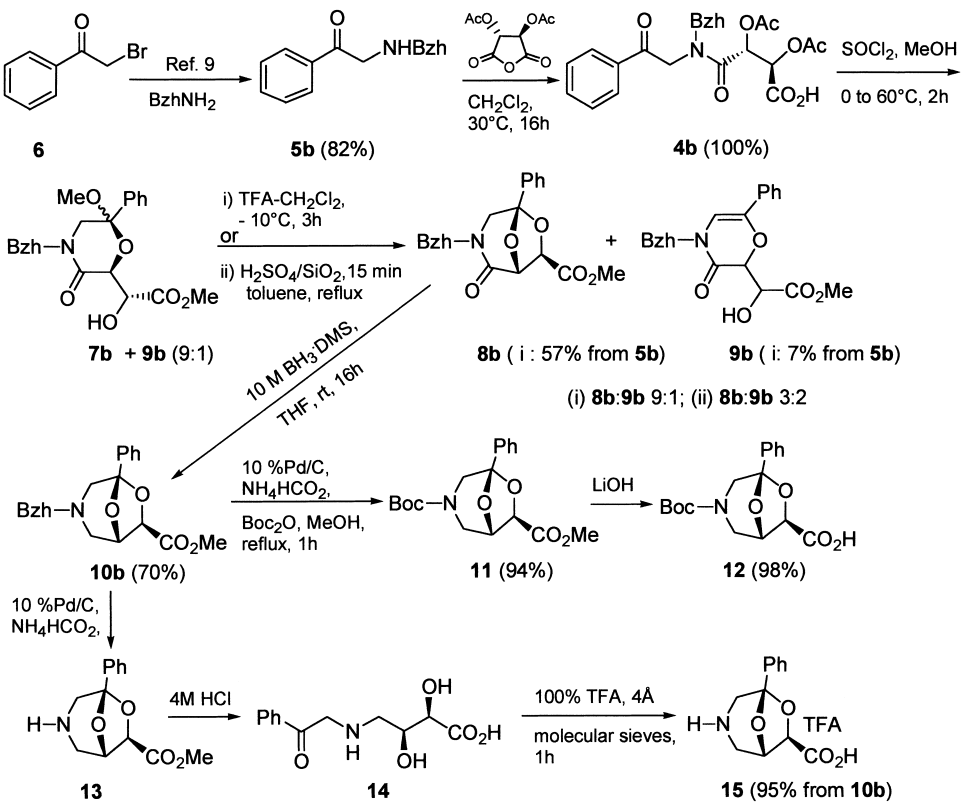


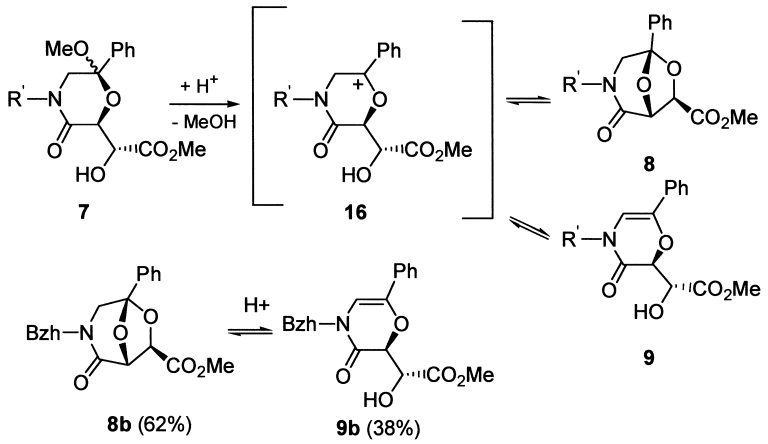
Scheme 2.

amide reduction would produce the desired amino acid **1** (which was named BTKa, Bicycles from Tartaric acid and Keto-amines). This new scaffold bears three different points of substitution and therefore should be useful for the development of chemical libraries. As a first example, we report here the synthesis of the compound derived from α-aminoacetophenone and tartaric acid.

α-Amino acetophenones are easily prepared by reaction of aliphatic and aromatic amines with commercially available α-halo-acetophenones. Thus, α-amino acetophenone **5a** (Scheme 2) was prepared in 65% yield, by reacting benzylamine with α-bromoacetophenone as reported in the literature.[7,8] Condensation of this amino ketone with (*R*,*R*)-tartaric acid monomethyl ester using PyBroP as a coupling reagent, in the presence of DIPEA in dichloromethane,[1] furnished amide **3a** in good yield (75%) after chromatographic purification. This compound was subjected to the trans-acetalisation conditions developed in our previous work,[1] i.e. boiling a toluene solution of the amide in the presence of a suspension of concentrated H_2SO_4 absorbed on silica gel and distilling off part of the solvent. Cyclisation took place under these conditions to give, after chromatography, the corresponding lactam **8a** in 85% yield and the side product 2-oxomorpholine **9a** (<10%). The latter compound derived from loss of water from the reaction intermediate **7a**. The supposed intermediate hemiacetal **7a** has not been isolated, although its formation is reasonable taking into account that the corresponding methyl acetal **7b** is obtained during the synthesis of BTKa using the synthetic methodology depicted in Scheme 3 (see later). In the ^{1}H NMR spectra of the crude reaction mixtures, the presence of two singlets at about 5.2 and 5.0 ppm, assigned to proton H-1 and H-7, respectively, is diagnostic of the formation of the bicyclic skeleton. The presence of by-product **9a** is instead revealed by the presence of a



Scheme 3.



Scheme 4.

singlet at about 6.0 ppm, due to the =CH proton. In the case of compound **8a**, the lactam moiety was selectively reduced by BH_3·DMS in THF at room temperature to give amino ester **10a** in 70% yield.

Although the yields in the coupling process between the α-amino ketone and the tartaric acid mono methyl ester derivative in the above process were acceptable, the strategy is however unsuitable for a large scale preparation of the scaffold due to the high cost of the condensation reagent PyBroP. For this reason, we applied a less expensive methodology to the α-amino ketones (Scheme 3) based on the use of tartaric acid anhydride for direct condensation followed by the two-step, acid catalysed trans-acetalisation of the coupling product. We applied this procedure to α-amino ketone **5b**, derived from the reaction between α-bromo-acetophenone **6** and benzhydrylamine ($BzhNH_2$).[9] The condensation of **5b** with tartaric anhydride was carried out in CH_2Cl_2 to give the product **4b** in quantitative yield which, dissolved in MeOH and treated with thionyl chloride, afforded crude lactam **7b** in a 9:1 mixture with monocyclic compound **9b** derived from methanol elimination. Trans-acetalisation of **7b** was first carried out on this mixture under the usual conditions, i.e. by heating a toluene solution for about 15 min in the presence of a suspension of H_2SO_4 on silica gel, and distilling off part of the solvent.

Analysis of the reaction mixture by ^1H NMR spectroscopy revealed the presence of two major products in a 3:2 ratio, of which one was scaffold **8b** and the other the corresponding monocyclic compound **9b**. The formation of **9b** during the acid-catalysed reaction could be accounted for by the equilibrium shown in Scheme 4, in which the cation **16** is supposed to be the common intermediate between **9** and **8**. The 3:2 ratio is the equilibrium composition, since after heating pure **8b** (obtained after chromatography) in toluene in the presence of H_2SO_4 on silica gel, the same **8b/9b** mixture in 3:2 ratio is obtained. A better result in the cyclisation process was obtained by treating the 9:1 mixture of **7b/9b** with a 1:1 mixture of TFA and dichloromethane, at −10°C for 3 h. After that time, the analysis of the reaction mixture revealed the presence of scaffold **8b** in a 9:1 ratio with **9b**, suggesting that under these conditions, in any case, further methanol elimination from **7b** does not occur. Chromatography of the crude reaction mixture afforded then pure **8b** in 57% yield from **5b**. In the case of **8b**, this was reduced to amine **10b** in 70% after chromatography. The *N*-benzhydryl protecting group was then removed from amine **10b** by treatment with ammonium formate in MeOH on 10% Pd–C, obtaining free amine **13**. The hydrolysis of the ester group was performed in 4 M HCl at room temperature but, after 16 h, we recovered quantitatively only product **14** as HCl salt derived from ring opening and hydrolysis of **13**. However, it was possible to obtain the amino acid **15** by treatment of **14** with TFA in the presence of molecular sieves. The synthesis of the amino acid **15** was carried out in a multigram scale, starting from 80 g of **5b** and obtaining **15** as TFA salt in 37% overall yield. Alternatively, the *N*-Boc protected amino acid **12** was obtained in high yield via one pot conversion of *N*-Bzh amino ester **10b** into the corresponding *N*-Boc amino ester **11**, by treatment with ammonium formate and 10% Pd–C in the presence of $(Boc)_2O$ in refluxed methanol, followed by hydrolysis of **11** with LiOH.

3. Conclusion

In conclusion we have realized the synthesis of a novel enantiopure γ/δ-amino acid (BTKa) having the 3-aza-6,8-dioxabicyclo[3.2.1]octane structure by combining a tartaric acid derivative and an α-amino acetophenone. One of the two synthetic strategies allowed the multigram scale preparation of the amino acid. These amino acids, which have a rigid skeleton and carries substituents at the 3, 5 and 7 position of the scaffold (and whose spatial orientation depends on the stereochemistry of the tartaric acid used), could find different applications in organic and peptidomimetic synthesis. Moreover, since a great range of these scaffolds can be prepared by simply changing the α-amino ketone, their use in processes of discovering biologically active compounds based on screening of a large number of them is also conceivable.

4. Experimental

4.1. General

Melting points are uncorrected. Chromatographic separations

were performed under pressure on silica gel using flash-column techniques; Large scale purifications were performed with Biotage Inc. apparatus with a prepacked cartridge system flash 75i M™ 15 cm column. R_f values refer to TLC carried out on 25-mm silica gel plates (Merck F254), with the same eluant indicated for column chromatography. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 200 and 50.33 MHz, respectively, unless otherwise stated. EI mass spectra were carried out at 70 eV ionising voltage. IR spectra were recorded with a FT-IR-1600 Perkin–Elmer spectrophotometer. Microanalyses were carried out with a Perkin–Elmer 240 C instrument. Optical rotations were measured with JASCO DIP-360 digital polarimeter. THF was distilled from Na/benzophenone. CH_2Cl_2 was distilled from CaH_2. All reactions requiring anhydrous conditions were performed in oven-dried glassware. Acid silica gel (H_2SO_4/SiO_2) was prepared as reported.[1]

4.1.1. 2-Benzylamino-1-phenyl-ethanone hydrobromide (5a). This compound was prepared in 65% yield according to the known procedure.[7]

White solid. Mp 203–204°C. ^1H NMR (DMSO-d_6) δ 9.42 (br, 1H), 8.00 (d, J=1.4 Hz, 2H), 7.82–7.40 (m, 8H), 4.86 (s, 2H), 4.25 (s, 2H). ^{13}C NMR (DMSO-d_6) δ 192.2 (s), 134.8 (s), 133.6 (s), 131.6 (d), 130.2 (d), 129.1 (d), 128.8 (d), 128.5 (d), 128.2 (d), 51.9 (t), 50.2 (t). IR (KBr): 1684 cm^{-1}. Anal. calcd for $C_{15}H_{15}NO{\cdot}HBr$ (306.20): C, 58.84; H, 5.27; N, 4.57. Found: C, 58.44; H, 5.36; N, 4.27.

4.1.2. 2-(Benzhydryl-amino)-1-phenyl-ethanone (5b). This compound was prepared in 82% yield according to the known procedure and its analytical and spectroscopical data were identical to those reported by Marchand-Brynaert.[9]

4.1.3. (4*R*,5*R*) 5-[Benzyl-(2-oxo-2-phenyl-ethyl)-carbamoyl]-2,2-dimethyl-[1,3]dioxolane-4-carboxylic acid methyl ester (3a). To a solution of **5a** (1.20 g, 5.33 mmol) in anhydrous CH_2Cl_2 (10 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*)-tartaric acid monomethyl ester (2.49 g, 5.33 mmol), and DIPEA (2.73 mL, 16.0 mmol). The mixture was stirred at room temperature for 2 h, 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 on silica gel (EtOAc/petroleum ether 1:3, R_f 0.32), yielding **3a** (1.64 g, 75%).

Colourless oil. $[\alpha]_D^{22}=-8.8$ (*c* 1.31, $CHCl_3$). ^1H NMR δ (mixture of rotamers) 7.90–7.85 (m, 2H), 7.61–7.22 (m, 8H), 5.39 (d, J=5.1 Hz, 1H), 5.11 (d, J=5.1 Hz, 1H), 4.88–4.64 (m, 4H), 3.80 and 3.78 (s, 3H), 1.52 and 1.49 (s, 3H), 1.35 and 1.31 (s, 3H). ^{13}C NMR δ (mixture of rotamers) 193.8, 193.3, 170.9, 168.8, 136.3, 135.9, 135.0, 133.8, 133.6, 128.8, 128.7, 128.6, 128.4, 127.9, 127.7, 127.4, 113.3, 113.1, 77.6, 76.4, 76.3, 52.6, 52.1, 51.6, 51.3, 50.5, 26.3, 26.2, 25.9. MS *m*/*z* (%): 396 (1), 352 (2), 306 (5), 292 (23), 120 (45), 91 (100). IR ($CDCl_3$) 3034, 2982, 2956, 1752, 1701, 1655, 1449 cm^{-1}. Anal. calcd for $C_{23}H_{25}NO_6$ (411.45): C, 67.14; H, 6.12; N, 3.40. Found: C, 67.44; H, 6.32; N, 3.16.

4.1.4. (2*R*,3*R*) 2,3-Diacetoxy-*N*-benzhydryl-*N*-(2-oxo-2-phenyl-ethyl)-succinamic acid (4b). Di-*O*-acetyl-L-tartaric anhydride (57.3 g, 265.4 mmol) was added portionwise to a cooled (0°C) stirred solution of 2-(benzhydryl-amino)-1-phenyl-ethanone (**5b**, 80 g, 265.4 mol) in anhydrous CH_2Cl_2 (2 L) and then the reaction mixture was allowed to warm to 30°C. After 16 h the mixture was concentrated and CH_2Cl_2 was evaporated off from the residue. The amide **4b** (137 g, 100%) was thereby obtained as a viscous oil and resulted sufficiently pure to be used in the next step without further purification. A sample for elemental analysis was obtained by flash chromatography on silica gel (eluent EtOAc/petroleum ether 1:1, R_f 0.25).

White solid. Mp 99–100°C. $[\alpha]_D^{25}=-1.1$ (*c* 1, $CHCl_3$). ^1H NMR δ (mixture of rotamers) 7.85–7.00 (m), 6.91 (s), 6.66 (s), 6.20–6.16 (m), 6.14–5.90 (m), 5.80–5.77 (m), 5.64–5.55 (m), 5.50–5.40 (m), 5.32–5.26 (m), 5.20–5.16 (m), 5.04–4.82 (m), 4.80–4.76 (m), 4.60–4.50 (m), 4.40–4.20 (m), 4.98 (br s), 4.89 (br s), 4.53 (br s), 4.38 (br s). ^{13}C NMR δ (mixture of rotamers, aromatic signals not reported) 193.8, 191.3, 170.7, 170.2, 170.0, 169.9, 169.2, 168.1, 167.0, 70.7, 69.9, 69.4, 66.2, 64.7, 62.9, 51.4, 50.8, 20.6, 20.4, 20.0. MS *m*/*z* (%): 300 (3), 224 (16), 166 (100), 105 (44). IR ($CDCl_3$) 1751, 1222 cm^{-1}. Anal. calcd for $C_{29}H_{27}NO_8$ (517.17): C, 67.30; H, 5.26; N, 2.71. Found: C, 67.44; H, 5.04; N, 2.90.

4.1.5. (1*R*,5*S*,7*R*)-3-Benzyl-2-oxo-5-phenyl-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-*exo*-carboxylic acid methyl ester (8a). A solution of **3a** (1.65 g, 4.00 mmol) in toluene (40 mL) was quickly added to a refluxing suspension of H_2SO_4/SiO_2 (30% w/w, 700 mg) in toluene (60 mL). The mixture was allowed to react for 15 min, and afterwards, 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 on silica gel (EtOAc/petroleum ether 1:4, R_f 0.3) affording pure **8a** (1.20 g, 85%).

White solid. Mp 122–124°C. $[\alpha]_D^{25}=-64.3$ (*c* 0.8, $CHCl_3$). ^1H NMR δ 7.62–7.59 (m, 2H), 7.41–7.24 (m, 8H), 5.16 (s, 1H), 4.92 (s, 1H), 4.64 (part A of AB system, J=15.0 Hz, 1H), 4.52 (part B of AB system, J=15.0 Hz, 1H), 3.74 (s, 3H), 3.59 (part A of AB system, J=12.0 Hz, 1H), 3.40 (part B of AB system, J=12.0 Hz, 1H). ^{13}C NMR δ 169.0 (s), 165.4 (s), 135.3 (s), 129.5 (d), 128.8 (d), 128.3 (d), 127.9 (d), 127.8 (d), 125.4 (d), 107.7 (s), 79.1 (d), 78.4 (d), 55.5 (t), 52.6 (q), 48.6 (t). IR ($CDCl_3$): 1762, 1673, 1601 cm^{-1}. MS (*m*/*z*, %): 353 (M^+, <1), 294 (7), 120 (56), 105 (100), 91 (98), 77 (28). Anal. calcd for $C_{20}H_{19}NO_5$ (353.37): C, 67.98; H, 5.42; N, 3.96. Found: C, 68.16; H, 5.64; N, 3.66.

4.1.6. (1*R*,5*S*,7*R*)-3-Benzhydryl-2-oxo-5-phenyl-6,8-dioxa-3-aza-bicyclo[3.2.1]octane-7-*exo*-carboxylic acid methyl ester (8b) and (4-benzhydryl-3-oxo-6-phenyl-3,4-dihydro-2*H*-[1,4]oxazin-2-yl)-hydroxy-acetic acid methyl ester (9b). Thionyl chloride (16 mL, 219 mmol) was added dropwise to a cooled (0°C) stirred solution of crude product **4b** (137 g) in CH_3OH (1.6 L) and then the

reaction mixture was heated at 60°C. After 2 h the volatile were removed under reduced pressure and the resulting residue was dissolved in a 1:1 mixture of CH_2Cl_2–TFA (720 mL). The mixture was cooled at −10°C and allowed to react for 3 h. The reaction mixture was concentrated under reduced pressure and the residue washed with Et_2O. The residue oil was chromatographed over a short pad of silica gel (EtOAc/petroleum ether 1:4). The first fraction (R_f 0.34) containing pure **8b** (65.0 g, 57% yield from **5b**) was followed by a second fraction (R_f 0.1) containing **9b** (7.8 g, 7% yield from **5b**).

Compound **8b**. White solid. Mp 62–63°C. $[\alpha]_D^{25}=-3.6$ (*c* 1.0, $CHCl_3$). ^1H NMR δ 7.60–7.53 (m, 2H), 7.40–7.28 (m, 10H), 7.24–7.17 (m, 3H), 7.07 (s, 1H), 5.22 (s, 1H), 5.02 (s, 1H), 3.75 (s, 3H), 3.41 (part A of AB system, *J*=12.4 Hz, 1H), 3.29 (part B of AB system, *J*=12.4 Hz, 1H). ^{13}C NMR δ 168.9 (s), 165.5 (s), 137.5 (s), 137.1 (s), 135.4 (s), 129.5 (d), 129.3 (d) 128.7 (d), 128.6 (d), 128.3 (d), 128.0 (d), 127.7 (d), 127.6 (d), 125.4 (d), 107.9 (s), 79.3 (d), 78.7 (d), 58.8 (d), 52.7 (t), 52.5 (q). MS *m/z* (%): 429 (M^+, 71), 370 (2), 311 (2), 167 (100), 152 (27), 105 (31), 77 (16). IR ($CDCl_3$) 3064, 3034, 2596, 1761, 1667 cm^{-1}. Anal. calcd for $C_{26}H_{23}NO_5$ (429.46): C, 72.71; H, 5.40; N, 3.26. Found: C, 72.69; H, 5.36; N, 3.59.

Compound **9b**. White solid. Mp 120–121°C. $[\alpha]_D^{20}=-6.0$ (*c* 6.3, $CHCl_3$). ^1H NMR δ 7.40–7.20 (m, 15H), 7.16 (s, 1H), 5.99 (s, 1H), 5.08 (d, *J*=2.0 Hz, 1H), 4.99 (d, *J*=2.0 Hz, 1H), 3.90 (s, 3H). ^{13}C NMR δ 172.0 (s), 161.6 (s), 138.9 (s), 138.1 (s), 137.9 (s), 132.1 (s), 128.8 (d), 128.7 (d), 128.6 (d), 128.4 (d), 128.3 (d), 128.1 (d), 128.0 (d), 127.8 (d), 123.6 (d), 103.0 (d), 78.2 (d), 71.9 (d), 60.0 (d), 53.1 (q). MS *m/z* (%): 429 (M^+, 4), 210 (15), 167 (100), 152 (36), 105 (27), 77 (18). IR ($CDCl_3$) 3534, 3062, 3027, 2949, 1744, 1678 cm^{-1}. Anal. calcd for $C_{26}H_{23}NO_5$ (429.46): C, 72.71; H, 5.40; N, 3.26. Found: C, 72.93; H, 5.41; N, 3.03.

4.1.7. (1*S*,5*S*,7*R*)-3-Benzyl-5-phenyl-6,8-dioxa-3-aza-bicyclo[3.2.1]octane-7-*exo*-carboxylic acid methyl ester (10a). To a solution of **8a** (4.43 g, 12.6 mmol) in anhydrous THF (85 mL) cooled at 0°C was added dropwise 10 M $BH_3{\cdot}Me_2S$ (2.39 mL, 23.9 mmol). The reaction mixture was stirred at room temperature for 16 h and then EtOH (3 mL), 3 M NaOH (3 mL) and H_2O (100 mL) were added successively. The mixture was extracted with Et_2O (3×100 mL) and the combined organic phase concentrated obtaining a crude oil that after chromatography (EtOAc/petroleum ether 1:3, R_f 0.30) furnished 2.99 g of **10a** (70%).

White solid. Mp 98°C. $[\alpha]_D^{25}=+13.0$ (*c* 1.0, $CHCl_3$). ^1H NMR δ 7.72–7.58 (m, 2H), 7.52–7.19 (m, 8H), 5.00 (s, 1H), 4.86 (s, 1H), 3.74 (part A of AB system, *J*=13.2 Hz, 1H), 3.61 (part B of AB system, *J*=13.2 Hz, 1H), 3.78 (s, 3H), 3.16 (d, *J*=11.2 Hz, 1H), 2.93 (d, *J*=11.2 Hz, 1H), 2.63 (d, *J*=11.2 Hz, 2H). ^{13}C NMR δ 171.6 (s), 137.3 (s), 128.9 (d), 128.7 (d), 128.3 (d), 128.1 (d), 127.2 (d), 125.6 (d), 107.9 (s), 78.4 (d), 77.6 (d), 61.4 (t), 60.2 (t), 54.0 (t), 52.3 (q). IR ($CDCl_3$): 1757, 1733 cm^{-1}. MS (*m/z*, %): 339 (M^+, 2), 280 (13), 218 (78), 158 (100), 105 (83), 91 (100), 77 (73). Anal. calcd for $C_{20}H_{21}NO_4$ (339.39): C, 70.78; H, 6.24; N, 4.13. Found: C, 70.98; H, 6.06; N, 3.94.

4.1.8. (1*S*,5*S*,7*R*)-3-Benzhydryl-5-phenyl-6,8-dioxa-3-aza-bicyclo[3.2.1]octane-7-*exo*-carboxylic acid methyl ester (10b). Amide **8b** (11.0 g, 25.6 mmol) was reduced as reported for **8a** to afford after chromatography purification (EtOAc/petroleum ether 1:8, R_f 0.30) 7.4 g of **10b** (70%).

White solid. Mp 101–102°C. $[\alpha]_D^{25}=-12.0$ (*c* 1.0, $CHCl_3$). ^1H NMR δ 7.62–7.57 (m, 2H), 7.48–7.43 (m, 3H), 7.36–7.15 (m, 10H), 5.14 (s, 1H), 4.83 (s, 1H), 4.46 (s, 1H), 3.77 (s, 3H), 3.17 (d, *J*=11.4 Hz, 1H), 2.91 (d, *J*=10.6 Hz, 1H), 2.53 (d, *J*=10.6 Hz, 1H), 2.43 (d, *J*=11.4 Hz, 1H). ^{13}C NMR δ 171.7 (s), 141.5 (s), 141.1 (s), 137.4 (s), 128.9 (d), 128.7 (d), 128.6 (d), 128.1 (d), 127.9 (d), 127.8 (d), 127.3 (d), 127.2 (d), 125.7 (d), 108.8 (s), 78.4 (d), 77.2 (d), 75.1 (d), 58.7 (t), 53.2 (t), 52.4 (q). MS *m/z* (%) 414 (M^+-1, 2), 293 (7), 167 (100), 105 (26), 91 (7), 77 (15). IR ($CDCl_3$) 3073, 3030, 2957, 2814, 1757, 1731 cm^{-1}. Anal. calcd for $C_{26}H_{25}NO_4$ (415.48): C, 75.16; H, 6.06; N, 3.37. Found: C, 74.93; H, 5.90; N, 3.60.

4.1.9. (1*S*,5*S*,7*R*)-5-Phenyl-6,8-dioxa-3-aza-bicyclo-[3.2.1]octane-7-*exo*-carboxylic acid trifluoro acetate (15). To a degassed solution of benzhydryl aminoester **10b** (7.4 g, 17.8 mmol) in MeOH (200 mL) were added ammonium formate (6.7 g, 107 mmol), and 10% Pd/C (3.0 g). The resulting suspension was heated to reflux under N_2. After 1 h the mixture was cooled, filtered through a short pad of Celite and rinsed with MeOH. The filtrate was concentrate and the residue clear oil. **13**: ^1H NMR δ 7.65–7.60 (m, 2H), 7.46–7.38 (m, 3H), 4.87 (s, 1H), 4.75 (s, 1H), 3.75 (s, 3H), 3.39–3.28 (m, 2H), 3.04–2.90 (m, 2H). MS *m/z* (%) 249 (M^+, 2), 190 (13), 127 (66), 105 (74), 104 (100), 77 (99). dissolved in 4 M HCl (700 mL), washed with petroleum ether (3×200 mL) and stirred at room temperature. After 16 h the mixture was concentrated and the residue. **14**: ^{13}C NMR (D_2O) δ 192.6 (s), 174.4 (s), 135.0 (s), 128.7 (d, 2C), 128.5 (d, 2C), 127.8 (d), 71.5 (s), 67.0 (d), 52.4 (t), 49.6 (t)] dissolved in TFA (100 mL) and stirred at room temperature in the presence of 4 Å molecular sieves. After 1 h the mixture was concentrated and the residue was washed with Et_2O obtaining pure **15** (6.0 g, 95% combined yield from **10b**).

White solid. Mp 170°C (dec). $[\alpha]_D^{25}=+1.1$ (*c* 1.0, EtOH). ^1H NMR (D_2O) δ 7.52–7.48 (m, 2H), 7.36–7.32 (m, 3H), 5.04 (s, 1H), 4.85 (s, 1H), 3.45 (m, 4H); ^{13}C NMR (DMSO-d_6) δ 171.6 (s), 136.6 (s), 130.4 (d), 129.1 (d), 126.6 (d), 106.4 (s), 76.7 (d), 76.5 (d), 48.7 (t), 44.3 (t). MS *m/z* (%): 235 (M^+, 12), 190 (7) 114 (94), 105 (100); IR (KBr) 3033, 2826, 1682, 1207, 1139 cm^{-1}. Anal. calcd for $C_{14}H_{14}F_3NO_6$ (349.26): C, 48.14; H, 4.04; N, 4.01. Found: C 48.04; H, 4.16; N, 3.80.

4.1.10. (1*S*,5*S*,7*R*)-3-(*tert*-Butoxycarbonyl)-5-phenyl-6,8-dioxa-3-aza-bicyclo[3.2.1]octane-7-*exo*-carboxylic acid methyl ester (11). To a degassed solution of benzhydryl aminoester **10b** (16.5 g, 39.7 mmol) in MeOH (660 mL) were added ammonium formate (17.5 g, 278 mmol), $(Boc)_2O$ (26.3 g, 119 mmol) and 10% Pd/C (6.6 g). The resulting suspension was heated to reflux under N_2. After 1 h the mixture was cooled, filtered through a short pad of Celite® and rinsed with MeOH. The filtrate was concentrate and the residue was purified by silica gel chromatography

eluting with EtOAc/petroleum ether 1:1, R_f 0.3, to give **11** (13.0 g, 94%).

White solid. Mp 68–69°C. $[\alpha]_D^{25}=+43.5$ (*c* 1.45, $CHCl_3$). ^1H NMR δ 7.70–7.60 (m, 2H), 7.48–7.35 (m, 3H), 4.85 and 4.80 (rotamers, br s, 1H), 4.71 and 4.68 (rotamers, br s, 1H), 4.20–4.04 (m, 1H), 4.02–3.90 (m, 1H), 3.71 (s, 3H), 3.42–3.10 (m, 2H), 1.44 (s, 9H). ^{13}C NMR δ 170.8 (s), 155.3 (s), 136.5 (s), 129.3 (d, 2C), 128.3 (d, 2C), 125.6 (d), 106.8 (s), 80.6 (s), 77.3 (d), 76.8 (d), 52.4 (q), 51.8 (t), 45.4 (t), 28.3 (q, 3C). MS *m/z* (%): 349 (M^+, <1), 293 (18), 276 (9), 104 (99), 56 (100). IR ($CDCl_3$) 3018, 2980, 2927, 1759, 1690, 1415 cm^{-1}. Anal. calcd for $C_{18}H_{23}NO_6$ (349.38): C, 61.88; H, 6.64; N, 4.01. Found: C, 61.68; H, 6.44; N, 4.14.

4.1.11. (1*S*,5*S*,7*R*)-3-(*tert*-Butoxycarbonyl)-5-phenyl-6,8-dioxa-3-aza-bicyclo[3.2.1]octane-7-*exo*-carboxylic acid (12). The Boc-protected amino ester **11** (10.0 g, 28.6 mmol) was dissolved in MeOH (60 mL) and LiOH (1.29 g, 31 mmol) was added. The mixture was stirred at room temperature for 16 h diluted with H_2O (35 mL) and washed with Et_2O. The aqueous phases were adjusted to pH 4 with 5% HCl and then extracted with CH_2Cl_2 (3×40 mL). The organic extracts were dried over Na_2SO_4, concentrated and put under high vacuum to yield 9.2 g (98%) of acid **12**.

White solid. Mp 129–130°C. $[\alpha]_D^{25}=+57.3$ (*c* 0.98, $CHCl_3$). ^1H NMR (CD_3OD) δ 7.72–7.60 (m, 2H), 7.45–7.38 (m, 3H), 4.94 (s, 1H), 4.74 (s, 1H), 4.18–3.95 (m, 2H), 3.45–3.04 (m, 2H), 1.50 (s, 9H). ^{13}C NMR (CD_3OD) δ 173.6 (s), 156.9 (s), 138.2 (s), 130.1 (d, 2C), 129.1 (d, 2C), 126.8 (d), 108.2 and 107.8 (rotamers, s), 82.0 (s), 78.6 (d), 78.0 (d), 53.1 and 51.8 (rotamers, t), 48.0 and 46.7 (rotamers, t), 28.3 (q, 3C). MS *m/z* (%): 279 (7), 262 (5), 234 (4), 105 (100), 77 (42), 57 (100). IR ($CDCl_3$) 1776, 1692 cm^{-1}. Anal. calcd for $C_{17}H_{21}NO_6$ (335.35): C, 60.89; H, 6.31; N, 4.18. Found: C, 61.18; H, 6.32; N, 4.37.

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