Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 5251–5258

TETRAHEDRON

Enantiospecific synthesis of 3-aza-6,8-dioxa-bicyclo[3.2.1]octane carboxylic acids from erythrose

Andrea Trabocchi, Gloria Menchi, Massimo Rolla, Fabrizio Machetti, Ilaria Bucelli and Antonio Guarna*

Dipartimento di Chimica Organica 'Ugo Schiff', Università di Firenze, and Istituto di Chimica dei Composti Organometallici-C.N.R., Polo Scientifico di Sesto Fiorentino, Via della Lastruccia 13, I-50019 Sesto Fiorentino, Firenze, Italy

Received 31 January 2003; revised 22 April 2003; accepted 16 May 2003

Abstract—New methodology for the synthesis of enantiopure 3-aza-6,8-dioxa-bicyclo[3.2.1]octane-carboxylic acids belonging to 7-*endo*-BTAa sub-class of γ/δ amino acids is described. The novelty is the use of 2,3-*O*-isopropylidene-erythrose instead of *meso*-tartaric acid derivative, thus allowing us to perform an enantiospecific synthesis. Reductive amination of erythrolactol with aminoacetaldehyde diethylacetal or benzylamine, and subsequent acid cyclisation gave directly the amino alcohol scaffold. Protection of nitrogen as urethane and final alcohol oxidation afforded the Fmoc-, Boc-, and Cbz-amino acids. The new synthetic route was applied to multigram scale, thus resulting in a marked improvement of the synthesis of enantiopure 7-*endo*-BTG and 7-*endo*-BTK amino acids.

1. Introduction

During the last decade much interest has grown towards the synthesis of new reverse turn inducers and the conformational preferences imposed by turn-analogues when inserted in protein secondary structure models.[1] In the course of development of a new class of 3-aza-6,8-dioxa-bicyclo[3.2.1]octane γ/δ amino acids named BTAa and BTK,[2,3] 7-*endo*-BTAa sub-family compounds proved to be very interesting as dipeptide isostere reverse turn inducers (Fig. 1).[4,5]

These amino acids are obtained from reduction of the corresponding endocyclic amides 7-*endo*-BTAa(O), which in turn derive from the combination of amino acids and *meso*-tartaric acid derivatives. When aminoacetaldehyde diethylacetal is used a racemic mixture of 7-*endo*-BTG(O) and 7-*endo*-BtG(O) results (Scheme 1). Moreover, *meso*-tartaric acid derivatives are prone to epimerization to the more stable *trans* isomers, thus limiting their use as building blocks in the synthesis of scaffolds.[2]

Our need for multigram quantities of these scaffolds carrying a 7-*endo*-carboxyl group as precursors for chemical libraries, led us to develop an alternative synthetic method in order to achieve enantiopure scaffolds with increased purity and quantity, with a simpler and friendly synthetic protocol. In this paper, we present a novel strategy to prepare both enantiomers of 7-*endo*-BTG and 7-*endo*-BTK scaffolds, which is based upon the use of an erythrose derivative instead of a *meso*-tartaric acid one. 2,3-*O*-Isopropilidene-erythrose **1** and **6** (Scheme 2) are known in literature as valid building blocks, which find many applications in reactions with organometallic reagents,[6] in Wittig olefinations,[7] and in the synthesis of chiral compounds such as pyrrolidines,[8] nucleoside analogues,[9] and nitrones.[10] However, to our knowledge, no examples of reductive amination of these compounds have been reported. Many syntheses of compounds **1** and **6** starting from carbohydrates have been described,[11] and in particular both protected erythrolactols are easily obtained in gram quantities from cheap commercially available D- and L-arabinose.[8]

Starting from D-erythrolactol **1**, it was possible to obtain the scaffolds 7-*endo*-BTG **2** and 7-*endo*-BTK **3** belonging to the 'T' series,[12] and from L-erythrolactol **6** the corresponding

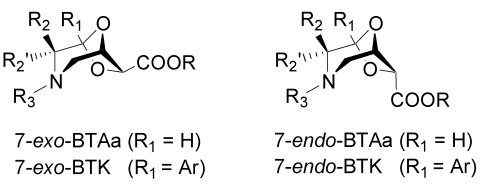
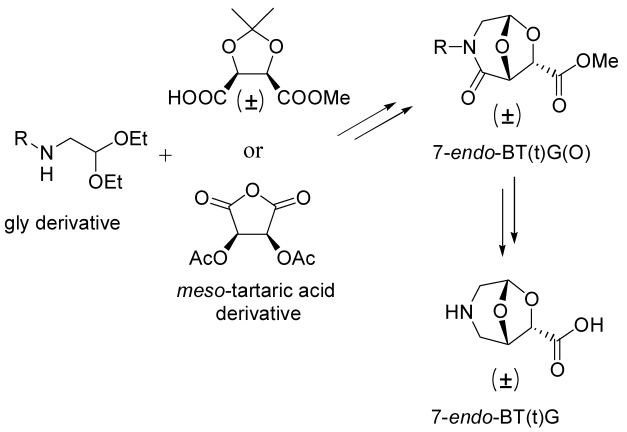


Figure 1.

Keywords: amino acids and derivatives; peptide mimetics; amination; bicyclic heterocyclic compounds.

* Corresponding author. Tel.: +39-055-457-3481; fax: +39-055-457-3569; e-mail: antonio.guarna@unifi.it

0040–4020/03/$ - see front matter
doi:10.1016/S0040-4020(03)00773-7



Scheme 1.

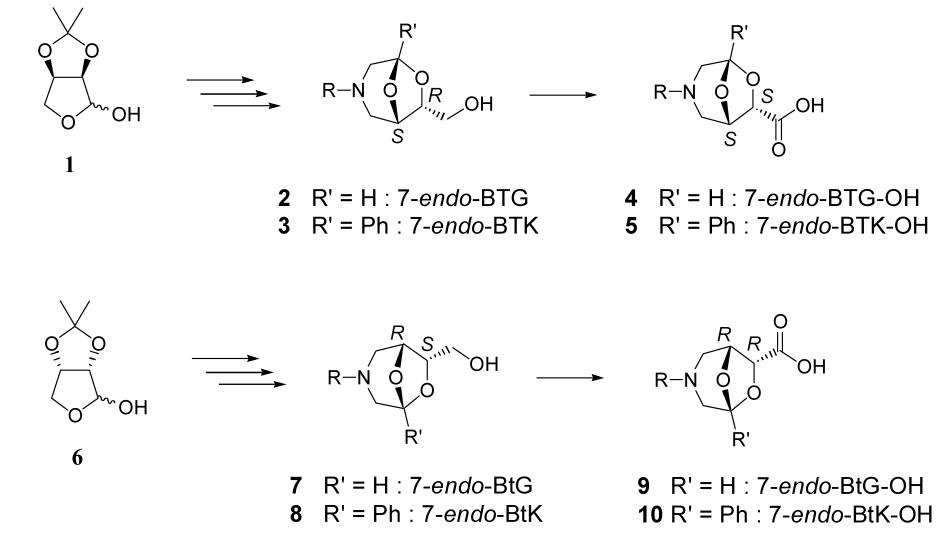
enantiomer 7-*endo*-BtG **7** and 7-*endo*-BtK **8** of the 't' series, as shown in Scheme 2. Thus, either enantiomers **2** and **3**, or **7** and **8** were synthesised by simply choosing the appropriate sugar compound **1** or **6**, obtaining 7-*endo*-BT(t)G scaffolds by reaction with aminoacetaldehyde-diethylacetal, or 7-*endo*-BT(t)K with the α-aminoketone derivative.

2. Results and discussion

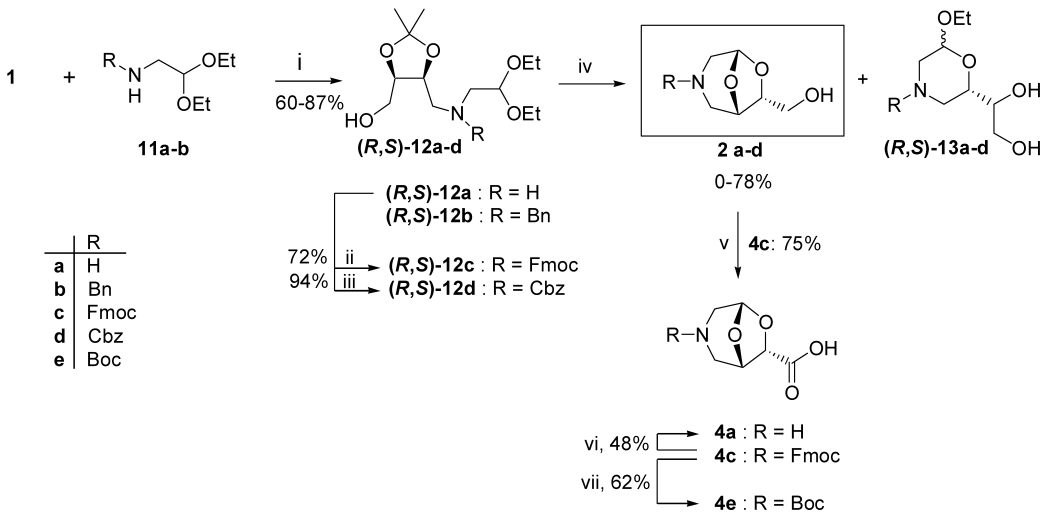
2.1. Synthesis of 7-*endo*-BTG

The synthetic strategy consisted of a reductive amination process of the erythrolactol **1** with aminoacetaldehyde diethylacetal **11a** followed by protection of the amine function as urethane, and final acid cyclisation of resulting (*R*,*S*)-**12c** with TFA to give 7-*endo*-BTG alcohol **2** (Scheme 3).[13] In a first attempt the reductive amination was conducted stepwise via imine preformation by reacting the erythrolactol **1** with **11a** in MeOH, but starting reagents were obtained after 24 h, as shown by TLC. Direct use of $NaBH_4$ in the presence of 1 equiv. of acetic acid led to a complex mixture. We next found $NaBH(OAc)_3$ to be a valid reagent for the reductive amination process, which is known to work in the presence of acid sensitive groups such as acetals.[14]

Though in the work of Abdel-Magid et al.[14] no examples of reductive amination on lactols have been reported, the reaction proved to be very efficient even in large scale, giving the amino adduct (*R*,*S*)-**12a**, in 60% yield, and 10–15% of N-acetylated amine as by-product which were easily separated by chromatography. The reaction was monitored by TLC thus showing the presence of mainly amine (*R*,*S*)-**12a** after 6 h at room temperature, though the reaction times were prolonged overnight in order to achieve completion. The reaction of **1** with amine **11b** yielded 87% of (*R*,*S*)-**12b** after stirring overnight. Benzylamine showed similar reactivity with **1**, as completion was achieved after 16 h reacting (41% yield, see Scheme 4). Cyclisation of unprotected (*R*,*S*)-**12a** with TFA gave, after stirring for 2 h at room temperature a mixture of desired **2a** and partially cyclised compound (*R*,*S*)-**13a** in about 1:1 ratio (Scheme 3), as clearly shown by the presence of two acetal carbon signals on ^{13}C NMR spectrum. Attempts using forcing reaction conditions by prolonging time and increased TFA amounts failed. Compound (*R*,*S*)-**12b** also failed to cyclise, giving only the monocyclic intermediate (*R*,*S*)-**13b**. Attempts were made with TFA and prolonged reaction times up to 24 h, or with H_2SO_4–SiO_2 or PTSA as acid catalysts, giving always incomplete conversions. The presence of free amine in both cases suggested an impediment towards double cyclisation. When compound (*R*,*S*)-**12a** was protected at the amine function with Fmoc group before acid cyclisation, giving (*R*,*S*)-**12c**, a marked improvement was achieved. The cyclisation was initially conducted in refluxing toluene with H_2SO_4–SiO_2 as acid catalyst in analogy with reported conditions,[2] giving **2c** with 34% yield after purification. The low yield was probably due to partial degradation of intermediates in *trans*-acetalisation process when carried out at high temperature. An improvement was achieved by treating compound (*R*,*S*)-**12c** with pure TFA at room temperature, which cyclised



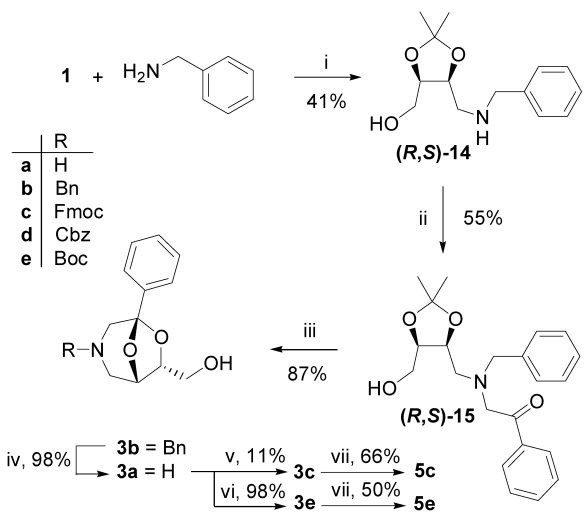
Scheme 2.



Scheme 3. (i) $NaBH(OAc)_3$, THF, room temperature, overnight; (ii) Fmoc-*O*-Su, H_2O–acetone, $Na_2CO_3{\cdot}H_2O$, 0°C then room temperature, overnight; (iii) Cbz-Cl, TEA, THF, 0°C, 30 min, then room temperature, overnight; (iv) TFA, room temperature, overnight; (v) Jones reagent, room temperature, overnight; (vi) piperidine, CH_2Cl_2, room temperature, 4 h, then Ambersep 900-OH, and elution with 0.5N HCl; (vii) piperidine, CH_2Cl_2, room temperature, 4 h, then $(Boc)_2O$, EtOH, 0°C, then room temperature, overnight.

completely to give **2c** in 78% yield after reacting overnight. Cyclisation performed on (*R*,*S*)-**12d**, where the amine function was protected with Cbz, led to partial deprotection at the amine function, thus giving Cbz-scaffold **2d** with lower yield (16%) with respect to Fmoc analogue **2c** (Scheme 3); this was probably due to less tolerance of Cbz group towards strongly acid conditions.[15] The bicyclic *N*-Fmoc-amino alcohol **2c** was oxidized with Jones reagent affording pure Fmoc-amino acid **4c** in 75% yield (Scheme 3).

Boc-7-*endo*-BTG amino acid **4e** was obtained from Fmoc-amino acid **4c**, because of incompatibility of Boc protecting group with acid cyclisation. Thus, **4c** was treated with piperidine (3 equiv.) in dichloromethane at room temperature, giving the corresponding deprotected amino acid **4a** (Scheme 3). Attempts to remove piperidine and other organic by-products by conventional acid–base washings resulted to be not very efficient in terms of purity of **4a**; on the contrary, a clean purification was obtained using Ambersep basic ion-exchange resin. Compound **4a** was immobilized on the resin, and subsequent washings of all non-acidic by-products and final elution with 0.5N HCl afforded pure **4a** as hydrochloride salt in 48% yield. The hygroscopic compound **4a** was then treated with $(Boc)_2O$ in EtOH–CH_2Cl_2 to give pure **4e** in poor yield. Consequently, the conversion of Fmoc-7-*endo*-BTG-OH (**4c**) into the corresponding Boc-amino acid **4e** was performed in one pot, by deprotection with piperidine and subsequent addition of $(Boc)_2O$ without any purification of the intermediates, giving pure **4e** in 62% yield.



Scheme 4. (i) $NaBH(OAc)_3$, THF, room temperature, 16 h; (ii) $PhCOCH_2$-Br, K_2CO_3, H_2O–CH_3CN, room temperature, overnight; (iii) TFA-CH_2Cl_2 1:1, room temperature, 1 h; (iv) NH_4CO_2H, 10% Pd/C, reflux, 1 h; (v) Fmoc-*O*-Su, H_2O–acetone, Na_2CO_3, 0°C, then room temperature, overnight; (vi) $(Boc)_2O$, DIPEA, CH_2Cl_2–EtOH 3:1, room temperature, overnight; (vii) PDC, DMF, room temperature, 2 days.

The synthetic protocol was also applied to the corresponding enantiomeric 7-*endo*-BtG scaffold starting from L-erythrose derivative **6**, and the optical rotatory values of all the intermediate compounds were in agreement with those of compounds **2**, **4** and (*R*,*S*)-**12**.

2.2. Synthesis of 7-*endo*-BTK

The same approach was also applied to the synthesis of 7-*endo*-BTK scaffolds **3**,**5** and **8**,**10**. In this case, a different pathway was followed, in which the carbonyl and amine functions were introduced separately (Scheme 4). Amine moiety was introduced by reaction of **1** with benzylamine, as above described, and the resulting compound (*R*,*S*)-**14** was alkylated with phenacyl bromide in water-acetonitrile using K_2CO_3 as base, thus giving (*R*,*S*)-**15** in 55% yield. The phenacyl moiety of (*R*,*S*)-**15** cyclised with milder conditions than corresponding acetaldehyde diethylacetal group of (*R*,*S*)-**12b**, probably due to the stabilising effect of the phenyl ring. Thus, cyclisation was performed with a 1:1 TFA–dichloromethane solution, giving **3b** after 1 h with excellent conversion.

Subsequent Pd-catalysed debenzylation of **3b** afforded free 7-*endo*-BTK amino alcohol **3a**, which was further protected either as Boc and Fmoc derivatives **3e** and **3c** (Scheme 4). Final oxidation of the *N*-protected amino alcohol to corresponding amino acid with Jones reagent led to ring opening, in agreement with previous considerations about BTK lability in strongly acid conditions.[3] Thus, the oxidation was conducted with PDC in DMF.[16]

3. Conclusion

In conclusion, a new method for the enantiospecific synthesis of formal glycine-derived 7-*endo*-BTAa and 7-*endo*-BTK was developed starting from erythrose derivatives, thus obtaining both enantiomers of *N*-protected amino acids. It was possible to synthesise either 7-*endo*-BT(t)G or 7-*endo*-BT(t)K from D(L)-erythrolactol by choosing suitable aminocarbonyl derivatives. Moreover, the mild reaction conditions and the cheap reagents used allowed us to perform the synthesis of both enantiomers of 7-*endo*-BT(t)G and 7-*endo*-BT(t)K amino acids on multigram scale.

4. Experimental

4.1. General

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 eluent 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, unless otherwise stated. EI mass spectra were carried out at 70 eV ionizing voltage. Acid silica gel (H_2SO_4–SiO_2) was prepared as reported.[17]

4.1.1. (4*R*,5*S*)-(5-[(2,2-Diethoxy-ethylamino)methyl]-2,2-dimethyl-[1,3]-dioxolan-4-yl(-methanol [(*R*,*S*)-12a]. To a solution of **1** (18.3 g, 114 mmol) and 2,2-diethoxy-ethylamine (**11a**) (16.6 mL, 114 mmol) in THF (600 mL) under a nitrogen atmosphere and at 0°C, $NaBH(OAc)_3$ (31.4 g, 148.2 mmol) was added in portions, and the mixture was stirred overnight at room temperature, then it was diluted with saturated $NaHCO_3$ solution (400 mL) and the organic products were extracted with EtOAc (2 600 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and evaporated to give a crude oil that was purified by flash chromatography (CH_2Cl_2–MeOH, 30:1, R_f 0.11), thus obtaining (*R*,*S*)-**12a** as a pale yellow oil (19.0 g, 60%). $[\alpha]_D^{20}=-8.7$ (*c* 0.54, $CHCl_3$); ^{1}H NMR δ 4.83 (br, 2H), 4.59 (t, *J*=5.5 Hz, 1H), 4.32 (m, 2H), 3.75–3.45 (m, 6H), 3.05–2.83 (m, 2H), 2.79 (d, *J*=5.5 Hz, 2H), 1.44 (s, 3H), 1.34 (s, 3H), 1.21 (t, *J*=7.0 Hz, 6H); ^{13}C NMR δ 111.6 (s), 100.9 (d), 77.2 (d), 75.2 (d), 63.0 (t), 62.9 (t), 60.2 (t), 51.4 (t), 48.2 (t), 27.4 (q), 24.9 (q), 15.3 (q, 2C); MS *m*/*z* 278 (M^++1, 0.7), 103 (100); IR ($CHCl_3$) 3450, 2987, 1670 cm^{-1}. Anal. calcd for $C_{13}H_{27}NO_5$: C, 56.30; H, 9.81; N, 5.05. Found: C, 56.41; H, 9.96; N, 5.01.

4.1.2. (4*R*,5*S*)-{5-[*N*-(9-Fluorenylmethoxycarbonyl)-*N*-(2,2-diethoxy-ethyl)-aminomethyl]-2,2-dimethyl-[1,3]dioxolan-4-yl}-methanol [(*R*,*S*)-12c]. To a solution of (*R*,*S*)-**12a** (16.8 g, 60.6 mmol) in acetone (400 mL) was added, at 0°C and under a nitrogen atmosphere, Fmoc-*O*-Su (20.6 g, 61.2 mmol) and a solution of $Na_2CO_3{\cdot}H_2O$ (7.54 g, 60.6 mmol) in water (400 mL). The mixture was stirred overnight at room temperature, then it was saturated with NaCl, extracted with CH_2Cl_2 (3×400 mL), and dried over anhydrous Na_2SO_4, to give, after solvent evaporation, a crude oil that was purified by flash chromatography (CH_2Cl_2–MeOH, 40:1, R_f 0.20), thus affording compound (*R*,*S*)-**12c** as a pure yellow oil (21.80 g, 72%). $[\alpha]_D^{20}=-34.2$ (*c* 0.38, MeOH); ^{1}H NMR δ 7.73 (d, *J*=7.3 Hz, 2H), 7.56 (m, 2H), 7.34 (m, 4H), 4.63 (m, 2H), 4.47–4.14 (m, 3H), 4.19 (t, *J*=4.9 Hz, 1H), 3.74–3.02 (m, 10H), 1.42–1.04 (m, 12H); ^{13}C NMR mixture of rotamers δ 156.1 (s), 143.8 (d, 2C), 141.3 (d, 2C), 126.8 (d, 2C), 124.5 (d, 2C), 124.4 (d, 2C), 119.7 (d, 2C), 108.6 (s), 102.0 and 101.5 (d), 76.1 (d), 75.6 (d), 66.3 and 65.9 (t), 63.6 and 63.0 (t), 62.8 and 62.7 (t), 61.0 and 60.6 (t), 50.8 and 50.5 (t), 48.4 and 47.9 (t), 47.3 (d), 27.8 (q, 2C), 25.1 (q), 24.8 (q); MS *m*/*z* 483 (M^+-17, 0.1), 179 (76); IR ($CHCl_3$) 3454, 3011, 1710 cm^{-1}. Anal. calcd for $C_{28}H_{37}NO_7$: C, 67.31; H, 7.46; N, 2.80. Found: C, 67.39; H, 7.52; N, 2.71.

4.1.3. (1*S*,5*S*,7*R*)-3-(9-Fluorenylmethoxycarbonyl)-7-*endo*-hydroxymethyl-6,8-dioxa-3-aza-bicyclo[3.2.1]octane (2c). Compound (*R*,*S*)-**12c** (19.3 g, 38.6 mmol) was dissolved in trifluoroacetic acid (80 mL) and stirred overnight at room temperature. After TFA evaporation, the crude powder was dissolved in MeOH and filtered through $NaHCO_3$ and, after solvent evaporation, the product was purified by flash chromatography (CH_2Cl_2–EtOAc, 2:1, R_f 0.26), thus affording pure **2c** as a white powder (11.06 g, 78%). Mp 39–42°C; $[\alpha]_D^{20}=-32.2$ (*c* 0.49, $CHCl_3$); ^{1}H NMR δ 7.77 (d, *J*=7.0 Hz, 2H), 7.57 (d, *J*=7.0 Hz, 2H), 7.38 (m, 4H), 5.51 (s, 1H), 4.92–2.95 (m, 12H); ^{13}C NMR mixture of rotamers δ 155.8 (s), 143.7 (s, 2C), 141.2 (s, 2C), 127.6 (d, 2C), 127.0 (d, 2C), 124.7 (d, 2C), 119.9 (d, 2C), 98.6 and 98.1 (d), 77.8 and 77.6 (d), 72.3 and 71.7 (d), 67.5 (t), 66.9 and 66.3 (t), 48.2 (t), 47.9 (t), 47.1 (d); MS *m*/*z* 367 (M^++1, 0.03), 178 (100); IR ($CHCl_3$) 3419, 1699 cm^{-1}. Anal. calcd for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76; N, 3.81. Found: C, 68.40; H, 5.61; N, 3.75.

4.1.4. (1*S*,5*S*,7*S*)-3-(9-Fluorenylmethoxycarbonyl)-6,8-dioxa-3-aza-bicyclo[3.2.1]octane-7-*endo*-carboxylic acid (4c). To a solution of **2c** (8.55 g, 23.3 mmol) in acetone (750 mL) was added Jones reagent at 0°C, [prepared by slow addition of H_2SO_4 (28.2 mL) to a solution of CrO_3 (15.5 g, 155 mmol) in H_2O (210 mL) at 0°C], and the mixture was stirred overnight at room temperature. Propan-2-ol was then added until the color of the solution turned deep green/blue, and the mixture was filtered through Celite and evaporated. The crude product was dissolved in EtOAc (450 mL) and washed with 10% aqueous $NaHCO_3$ solution (2×400 mL). The aqueous phase was then acidified to pH 1 with HCl and extracted with EtOAc (3×400 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and evaporated to give a deep yellow crude oil that was purified by chromatography (CH_2Cl_2–MeOH–TFA, 1000:30:1, R_f 0.53) affording pure **4c** as a white powder (6.66 g, 75%). Mp 79–82°C; $[\alpha]_D^{23}=-48.5$ (*c* 0.80, $CHCl_3$); ^{1}H NMR δ 7.75 (m, 2H), 7.53 (d, *J*=7.0 Hz, 2H), 7.38 (m, 4H), 5.56 (s,

1H), 4.74 (m, 1H), 4.60 (m, 1H), 4.45 (m, 1H), 4.18 (m, 3H), 3.95 (d, J=13.2 Hz, 1H), 3.25 (d, J=14.0 Hz, 1H), 3.16 (m, 1H); ^{13}C NMR δ 170.3 (s), 155.8 (s), 141.1 (s, 2C), 141.0 (s, 2C), 127.6 (d, 2C), 127.0 (d, 2C), 125.1 (d), 124.8 (d), 119.8 (d, 2C), 99.2 (d), 75.9 (d), 73.2 (d), 68.2 (t), 48.0 (t), 46.9 (d), 44.1 (t); MS m/z 381 (M^+, 0.2), 177 (100); IR ($CHCl_3$) 3445, 1701 cm^{-1}. Anal. calcd for $C_{21}H_{19}NO_6$: C, 66.13; H, 5.02; N, 3.67. Found: C, 66.21; H, 5.09; N, 3.59.

4.1.5. (1*S*,5*S*,7*S*)-3-*tert*-Butoxycarbonyl-6,8-dioxa-3-aza-bicyclo[3.2.1]octane-7-*endo*-carboxylic acid (4e). To a solution of **4c** (3.6 g, 9.45 mmol) in CH_2Cl_2 (10 mL) was added piperidine (2.81 mL, 28.35 mmol) and the mixture was stirred at room temperature for 4 h. The solution was then cooled to 0°C, and a solution of $(Boc)_2O$ (11.3 g, 47.3 mmol) in ethanol (6 mL) was added, and the mixture was stirred at room temperature overnight. The mixture was then diluted with CH_2Cl_2 (70 mL) and the organic products were extracted twice with 5% $NaHCO_3$ (35 mL). The aqueous phase was washed with CH_2Cl_2, then it was acidified with 0.1 M HCl to pH=5 and the organic product was extracted with CH_2Cl_2. Solvent evaporation afforded pure **4e** (1.52 g, 62%) as a foamy hygroscopic powder. $[\alpha]_D^{25}=-62.4$ (c 1.0, MeOH); ^{1}H NMR δ 7.63 (br, 1H), 5.56 (br, 1H), 4.71 (m, 1H), 4.57 (d, J=5.6 Hz, 1H), 4.12–3.87 (m, 2H), 3.19 (d, J=13.2 Hz, 1H), 3.05 (d, J=13.2 Hz, 1H), 1.42 (s, 9H); ^{13}C NMR δ 170.6 (s), 155.0 (s), 99.4 (d), 81.3 (s), 75.9 (d), 73.7 (d), 48.2 (t), 43.4 (t), 28.2 (q, 3C); MS m/z 158 (M^+-101, 46), 203 (73), 187 (10); IR ($CHCl_3$) 3443, 1774, 1710 cm^{-1}. Anal. calcd for $C_{11}H_{17}NO_6$: C, 50.96; H, 6.61; N, 5.40. Found: C, 50.90; H, 6.63; N, 5.35.

4.1.6. (4*R*,5*S*)-[5-(Benzylamino-methyl)-2,2-dimethyl-[1,3]dioxolan-4-yl]-methanol [(*R*,*S*)-14]. $NaBH(OAc)_3$ (87 g, 410 mmol) was added portionwise to a cooled (0°C), stirred solution of lactol **1** (41.0 g, 256 mmol) and benzylamine (42 mL, 384 mmol) in THF (1 L), and then the reaction mixture was allowed to warm to room temperature. After 16 h the mixture was concentrated under reduced pressure to give an oil that was partitioned between EtOAc and saturated $NaHCO_3$. The aqueous layer was extracted with EtOAc and the organic phase dried over Na_2SO_4, filtered and the solvent evaporated under reduced pressure. The residue was purified by chromatography on silica gel (EtOAc–petroleum ether, 2:1, R_f 0.1; then EtOAc–triethylamine, 100:1, R_f 0.36) to give (*R*,*S*)-**14** (26.7 g, 41%) as a clear oil. $[\alpha]_D^{24}=-9.1$ (c 1.0, $CHCl_3$); ^{1}H NMR δ 7.40–7.20 (m, 5H), 4.40–4.28 (m, 2H), 3.82 (s, 2H), 3.80–3.60 (m, 2H), 3.15–2.80 (m, 2H), 1.45 (s, 3H), 1.36 (s, 3H); ^{13}C NMR δ 137.9 (s), 128.5 (d, 2C), 128.2 (d, 2C), 127.4 (d), 107.9 (s), 77.3 (d), 75.4 (d), 60.2 (t), 53.6 (t), 47.7 (t), 27.3 (q), 24.8 (q); MS m/z 221 (7), 105 (100), 99 (99); IR ($CDCl_3$) 2989, 2936, 1454, 1383 cm^{-1}. Anal. calcd. for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57. Found: C, 66.88; H, 8.39; N, 5.53.

4.1.7. (4*R*,5*S*)-[5-(*N*-Benzyl-*N*-phenacyl-aminomethyl)-2,2-dimethyl-[1,3]dioxolan-4-yl]-methanol [(*R*,*S*)-15]. To a solution of alcohol (*R*,*S*)-**14** (47.75 g, 190 mmol) in CH_3CN (1.2 L) and H_2O (1.2 L) were added K_2CO_3 (39.4 g) and 2-bromoacetophenone (37.8 g, 190 mmol) and then stirred for 16 h. The reaction mixture was concentrated and the residue dissolved in $CHCl_3$. The solution was washed with brine and the combined aqueous phases treated with EtOAc. The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc–petroleum ether, 1:10, R_f 0.10, then EtOAc–petroleum ether, 1:2, R_f 0.18) to give (*R*,*S*)-**15** (36.3 g, 55%) as a yellow oil. $[\alpha]_D^{26}=+19.4$ (c 1.7, $CHCl_3$); ^{1}H NMR δ 7.88–7.82 (m, 2H), 7.60–7.25 (m, 10H), 4.48–4.30 (m, 2H), 4.02 (part A of AB system, J=12.8 Hz, 1H), 3.85 (part B of AB system, J=12.8 Hz, 1H) 3.80–3.60 (m, 2H) 3.20–2.90 (m, 2H), 1.41 (s, 3H), 1.35 (s, 3H); ^{13}C NMR δ 197.1 (s), 136.6 (s), 135.6 (s), 133.5 (d), 129.7 (d, 2C), 128.6 (d, 2C), 128.5 (d, 2C), 127.8 (d), 127.7 (d, 2C), 108.2 (s), 77.5 (d), 75.9 (d), 60.4 (t), 59.5 (t), 58.7 (t), 54.1 (t), 27.8 (q), 25.1 (q); MS m/z 263 (51), 246 (41), 106 (39), 104 (58), 91 (100); IR ($CDCl_3$) 2988, 2934, 1694 cm^{-1}. Anal. calcd. for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.68; H, 7.24; N, 3.80.

4.1.8. (1*S*,5*S*,7*R*)-3-Benzyl-5-phenyl-7-*endo*-hydroxymethyl-6,8-dioxa-3-aza-bicyclo[3.2.1]octane (3b). Ketone (*R*,*S*)-**15** (12.4 g, 34.7 mmol) was dissolved in a cooled 1:1 mixture of CH_2Cl_2–TFA (34 mL). The mixture was stirred at room temperature for 1 h and then concentrated under reduced pressure. The residue was dissolved in EtOAc (240 mL) and washed with saturated $NaHCO_3$. The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The alcohol **3b** (9.4 g, 87%) 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 (EtOAc–petroleum ether, 1:2, R_f 0.20). White powder: mp 78–80°C; $[\alpha]_D^{26}=-14.1$ (c 1.0, $CHCl_3$); ^{1}H NMR δ 7.60–7.50 (m, 2H), 7.41–7.20 (m, 8H), 4.58–4.56 (m, 1H), 4.34–4.32 (m, 1H), 4.26 (part A of AB system, J=12.1 Hz, 1H) 3.94 (part B of AB system, J=12.1 Hz, 1H), 3.80 (part A of AB system, J=12.5 Hz, 1H), 3.50 (part B of AB system, J=12.5 Hz, 1H), 3.18 (part A of AB system, J=11.5 Hz, 1H), 3.04 (part A of AB system, J=11.3 Hz, 1H), 2.82 (part B of AB system, J=11.5 Hz, 1H), 2.49 (part B of AB system, J=11.3 Hz, 1H); ^{13}C NMR δ 138.2 (s), 135.0 (s), 129.4 (d, 2C), 128.8 (d), 128.6 (d, 2C), 128.1 (d, 2C), 127.8 (d), 125.2 (d, 2C), 105.2 (s), 79.2 (d), 75.9 (d), 61.7 (t), 60.0 (t), 59.2 (t), 52.5 (t); MS m/z 311 (M^+, 6), 280 (2), 190 (100), 158 (48), 106 (33), 104 (61), 91 (100); IR ($CDCl_3$) 3011, 2927, 2828, cm^{-1}. Anal. calcd. For $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.21; H, 6.77; N, 4.59.

4.1.9. (1*S*,5*S*,7*R*)-5-Phenyl-7-*endo*-hydroxymethyl-6,8-dioxa-3-aza-bicyclo[3.2.1]octane (3a). To a degassed solution of benzyl amino alcohol **3b** (9.4 g, 30.2 mmol) in MeOH (300 mL) were added ammonium formate (8.8 g, 0.139 mmol), and 10% Pd/C (3.76 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 concentrated obtaining **3a** (6.56 g, 98%) as a white powder. Mp 125–127°C; $[\alpha]_D^{24}=-29.3$ (c 1.0, $CHCl_3$); ^{1}H NMR δ 7.65–7.58 (m, 2H), 7.50–7.35 (m, 3H), 4.60–4.50 (m, 1H), 4.42–4.22 (m, 2H), 4.04–3.96 (m, 1H), 3.40–3.16 (m, 4H); ^{13}C NMR

δ 138.5 (s), 128.8 (d), 128.2 (d, 2C), 125.1 (d, 2C), 105.7 (s), 79.3 (d), 76.6 (d), 59.3 (t), 53.0 (t) 44.8 (t); MS *m/z* 120 (58), 91 (100); IR ($CDCl_3$) 3064, 2892, 2849, 1602, 1451 cm^{-1}. Anal. calcd. for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 64.90; H, 6.95; N, 6.30.

4.1.10. (1*S*,5*S*,7*R*)-3-*tert*-Butoxycarbonyl-5-phenyl-7-*endo*-hydroxymethyl-6,8-dioxa-3-aza-bicyclo[3.2.1]octane (3e). Boc_2O (6.54 g, 29.6 mmol) was added portionwise to a solution of amine **3a** (6.56 g, 29.6 mmol) and DIPEA (6.1 mL, 29.6 mmol) in CH_2Cl_2–EtOH 3:1 (200 mL). The mixture was stirred at room temperature for 16 h and then concentrated under reduced pressure. The residue was partitioned between Et_2O–CH_2Cl_2 2:1 (260 mL) and 10% $NaHSO_4$ (160 mL). The aqueous layer was treated with Et_2O–CH_2Cl_2 2:1 (200 mL×3). The solvent was evaporated to give **3e** (6.95 g) as white powder in 98% yield and sufficiently pure to be used directly in the next step. A sample for elemental analysis was obtained by flash chromatography on silica gel (EtOAc–petroleum ether, 2:3, R_f 0.28). White powder. Mp 138–141°C; $[\alpha]_D^{25}=-4.6$ (*c* 0.65, $CHCl_3$); ^1H NMR δ 7.60–7.48 (m, 2H), 7.42–7.38 (m, 3H), 4.60–4.42 (m, 1H), 4.38–4.20 (m, 1H), 4.04–3.64 (m, 4H), 3.40–3.04 (m, 2H), 1.45 (s, 9H); ^{13}C NMR δ 155.1 (s), 137.8 (s), 129.0 (d), 128.3 (d, 2C), 125.3 (d, 2C), 105.0 (s), 80.6 (s), 78.8 (d), 74.1 (d), 61.2 (t),52.6 (t), 41.8 (t), 28.3 (q, 3C); MS *m/z* 265 (6), 240 (12), 105 (92), 57 (100); IR ($CDCl_3$) 3011, 2981, 2920, 1688, 1416 cm^{-1}. Anal. calcd. for $C_{17}H_{23}NO_5$: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.76; H, 7.27; N, 4.41.

4.1.11. (1*S*,5*S*,7*S*)-3-*tert*-Butoxycarbonyl-5-phenyl-6,8-dioxa-3-aza-bicyclo[3.2.1]octane-7-*endo*-carboxylic acid (5e). PDC (43.6 g, 116.0 mmol) was added portionwise to a solution of alcohol **3e** (7.47 g, 23.2 mmol) in anhydrous DMF (45 mL). The reaction mixture was stirred at room temperature for 2 days and then diluted with H_2O (125 mL) and extracted with Et_2O (6×125 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was taken with saturated $NaHCO_3$, washed with EtOAc (250 mL×4) and acidified with 20% HCl until pH 5 and extracted with EtOAc (250 mL×5). The combined organic phases were then dried over Na_2SO_4, filtered and concentrated under reduced pressure to give pure **5e** as a white powder (19.4 g, 50%). Mp 142–144°C; $[\alpha]_D^{26}=-39.1$ (*c* 1.02, $CHCl_3$); ^1H NMR δ 7.72–7.58 (m, 2H), 7.32–7.18 (m, 3H), 4.96 (br s, 1H), 4.80 (br s, 1H), 4.24–4.00 (m, 2H), 3.40–3.16 (m, 2H), 1.47 (s, 9H); ^{13}C NMR δ 170.5 (s), 154.9 (s), 136.8 (s), 130.0 (d), 128.2 (d, 2C), 125.3 (d, 2C), 106.2 (s), 81.3 (s), 75.3 (d), 52.6 (t), 42.7 (t), 28.3 (q, 3C); MS *m/z* 279 (9), 106 (40), 104 (62), 55 (100); IR ($CDCl_3$) 2980, 2926, 2866, 1693, 1417 cm^{-1}. Anal. calcd. for $C_{17}H_{21}NO_6$ (335.36): C, 60.89; H, 6.31; N, 4.18. Found: C, 60.68; H, 6.37; N, 4.42.

4.1.12. (4*S*,5*R*)-(5-[(2,2-Diethoxy-ethylamino)methyl]-2,2-dimethyl-[1,3]-dioxolan-4-yl(-methanol [(*S*,*R*)-12a]. Compound **6** (25.8 g, 161 mmol) was treated as described for the enantiomer, thus giving pure (*S*,*R*)-**12a** as an oil (26.8 g, 60%), with spectroscopic data as for the enantiomer. $[\alpha]_D^{20}=+9$ (*c* 0.29, $CHCl_3$). Anal. calcd for $C_{13}H_{27}NO_5$: C, 56.30; H, 9.81; N, 5.05. Found: C, 56.21; H, 9.75; N, 4.98.

4.1.13. (4*S*,5*R*)-{5-[*N*-(9-Fluorenylmethoxycarbonyl)-*N*-(2,2-diethoxy-ethyl)-aminomethyl]-2,2-dimethyl-[1,3]dioxolan-4-yl}-methanol [(*S*,*R*)-12c]. Compound (*S*,*R*)-**12a** (26.8 g, 96.6 mmol) was treated as described for the enantiomer, thus giving pure (*S*,*R*)-**12c** as an oil (33.3 g, 69%), with spectroscopic data as for the enantiomer. $[\alpha]_D^{20}=+35.1$ (*c* 0.69, MeOH). Anal. calcd for $C_{28}H_{37}NO_7$: C, 67.31; H, 7.46; N, 2.80. Found: C, 67.11; H, 7.38; N, 2.69.

4.1.14. (1*R*,5*R*,7*S*)-3-(9-Fluorenylmethoxycarbonyl)-7-*endo*-hydroxymethyl-6,8-dioxa-3-aza-bicyclo[3.2.1]octane (7c). Compound (*S*,*R*)-**12c** (33.3 g, 66.6 mmol) was treated as described for the enantiomer, thus giving pure **7c** as a white powder (18.3 g, 75%), with spectroscopic data as for the enantiomer. Mp 39–42°C; $[\alpha]_D^{20}=+30.1$ (*c* 1.62, $CHCl_3$). Anal. calcd for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76; N, 3.81. Found: C, 68.48; H, 5.69; N, 3.75.

4.1.15. (1*R*,5*R*,7*R*)-3-(9-Fluorenylmethoxycarbonyl)-6,8-dioxa-3-aza-bicyclo[3.2.1]octane-7-*endo*-carboxylic acid (9c). Compound **7c** (18.3 g, 49.8 mmol) was treated as described for the enantiomer, thus giving pure **9c** as a white powder (13.9 g, 73%), with spectroscopic data as for the enantiomer. Mp 71–81°C; $[\alpha]_D^{20}=+52.9$ (*c* 0.50, $CHCl_3$). Anal. calcd for $C_{21}H_{19}NO_6$: C, 66.13; H, 5.02; N, 3.67. Found: C, 66.17; H, 5.01; N, 3.70.

4.1.16. (1*R*,5*R*,7*R*)-3-*tert*-Butoxycarbonyl-6,8-dioxa-3-aza-bicyclo[3.2.1]octane-7-*endo*-carboxylic acid (9e). Compound **9c** (8.0 g, 20.98 mmol) was treated as described for the enantiomer, thus giving pure **9e** as a foamy hygroscopic powder (3.21 g, 59%), with spectroscopic data as for the enantiomer. $[\alpha]_D^{20}=+52.9$ (*c* 0.5, $CHCl_3$). Anal. calcd for $C_{11}H_{17}NO_6$: C, 50.96; H, 6.61; N, 5.40. Found: C, 50.81; H, 6.55; N, 5.36.

4.1.17. (4*S*,5*R*)-[5-(Benzylamino-methyl)-2,2-dimethyl-[1,3]dioxolan-4-yl]-methanol [(*S*,*R*)-14]. Compound **6** (31 g, 194 mmol) was treated as described for the enantiomer, thus giving (*S*,*R*)-**14** (47 g) as a clear oil, which was enough pure to be used in the next step, with spectroscopic data as for the enantiomer. A sample for elemental analysis was obtained by flash chromatography. $[\alpha]_D^{26}=+8.6$ (*c* 1.04, $CHCl_3$). Anal. calcd. for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57. Found: C, 66.78; H, 8.37; N, 5.59.

4.1.18. (4*S*,5*R*)-[5-(*N*-Benzyl-*N*-phenacyl-aminomethyl)-2,2-dimethyl-[1,3]dioxolan-4-yl]-methanol [(*S*,*R*)-15]. Crude ((*S*,*R*)-**14** (47 g) was treated as described for the enantiomer, thus giving (*S*,*R*)-**15** as a clear oil (36 g, 50% from **6**), with spectroscopic data as for the enantiomer. $[\alpha]_D^{24}=-20.2$ (*c* 1.0, $CHCl_3$). Anal. calcd. for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.59; H, 7.35; N, 3.68.

4.1.19. (1*R*,5*R*,7*S*)-3-Benzyl-5-phenyl-7-*endo*-hydroxymethyl-6,8-dioxa-3-aza-bicyclo[3.2.1]octane (8b). Compound (*S*,*R*)-**15** (36 g, 97.4 mmol) was treated as described for the enantiomer, thus giving **8b** as a white powder (28.1 g, 93%), with spectroscopic data as for the enantiomer. A sample for elemental analysis was obtained by flash chromatography. Mp 80–81°C, $[\alpha]_D^{26}=+14.9$ (*c* 1.0,

$CHCl_3$). Anal. calcd. for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.21; H, 6.77; N, 4.48.

4.1.20. (1*R*,5*R*,7*S*)-5-Phenyl-7-*endo*-hydroxymethyl-6,8-dioxa-3-aza-bicyclo[3.2.1]octane (8a). Compound **8b** (28.1 g, 90.5 mmol) was treated as described for the enantiomer, thus giving **8a** as a yellow oil (20.0 g, 100%), with spectroscopic data as for the enantiomer. $[\alpha]_D^{24}=+26.6$ (*c* 0.95, $CHCl_3$). Anal. calcd. for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.17; H, 6.79; N, 6.28.

4.1.21. (1*R*,5*R*,7*S*)-3-*tert*-Butoxycarbonyl-5-phenyl-7-*endo*-hydroxymethyl-6,8-dioxa-3-aza-bicyclo[3.2.1]octane (8e). Compound **8a** (20.0 g, 90.4 mmol) was treated as described for the enantiomer, thus giving **8e** as a white powder (21.3 g, 73%), with spectroscopic data as for the enantiomer. A sample for elemental analysis was obtained by flash chromatography (EtOAc–petroleum ether, 2:3, R_f 0.28). Mp 136–137°C. $[\alpha]_D^{26}=+4.0$ (*c* 0.98, $CHCl_3$). Anal. calcd. for $C_{17}H_{23}NO_5$: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.61; H, 7.26; N, 4.41.

4.1.22. (1*R*,5*R*,7*R*)-3-*tert*-Butoxycarbonyl-5-phenyl-6,8-dioxa-3-aza-bicyclo[3.2.1]octane-7-*endo*-carboxylic acid (10e). Crude **8e** (21.3 g, 66.3 mmol) was treated as described for the enantiomer, thus giving pure **10e** as a white powder (9 g, 41%), with spectroscopic data as for the enantiomer. Mp 141–142°C. $[\alpha]_D^{25}=+38.0$ (*c* 0.90, $CHCl_3$). Anal. calcd. for $C_{17}H_{21}NO_6$: C, 60.89; H, 6.31; N, 4.18. Found: C, 60.59; H, 6.61; N, 4.28.

4.1.23. (1*S*,5*S*,7*S*)-6,8-Dioxa-3-aza-bicyclo[3.2.1]octane-7-*endo*-carboxylic acid hydrochloride (4a). To a solution of **4c** (5.2 g, 13.7 mmol) in CH_2Cl_2 (80 mL) was added piperidine (4.1 mL, 41 mmol) and the mixture was stirred at room temperature for 4 h. The solution was then diluted with water and the aqueous phase was washed with EtOAc and passed through a column of Ambersep 900-OH. After resin washings with water and elution with 0.5 M HCl, solvent evaporation afforded the corresponding free amino acid **4a** (1.29 g, 48%) as a very hygroscopic salt: ^{1}H NMR (D_2O) δ 5.88 (s, 1H), 4.97 (s, 1H), 4.65 (m, 1H), 3.58 (d, *J*=12.9 Hz, 2H), 3.39 (d, *J*=15.4 Hz, 2H); MS *m*/*z* 158 (M^+-1, 7), 114 (13), 85 (69).

4.1.24. (4*R*,5*S*)-{5-[*N*-Benzyloxycarbonyl-*N*-(2,2-diethoxy-ethyl)-aminomethyl]-2,2-dimethyl-[1,3]dioxolan-4-yl}-methanol [(*R*,*S*)-12d]. To a solution of (*R*,*S*)-**12a** (25.2 g, 91 mmol) and triethylamine (38 mL, 273 mmol) in THF (400 mL) was dropwise added at 0°C Cbz-Cl (28.3 mL, 200 mmol), and the mixture was stirred 30 min at 0°C, and at room temperature overnight. Then diethyl ether was added and the organic phase was washed with water, giving 42 g of a crude oil which was purified by flash chromatography (CH_2Cl_2–MeOH, 20:1, R_f=0.27), thus giving pure (*R*,*S*)-**12d** (35 g, 94%) as an oil. $[\alpha]_D^{24}=-0.2$ (*c* 1.5, $CHCl_3$); ^{1}H NMR δ 7.34 (m, 5H), 5.15 (s, 2H), 4.58–4.08 (m, 4H), 3.84–3.29 (m, 10H), 1.39 (s, 3H), 1.24 (s, 3H), 1.09 (m, 6H); ^{13}C NMR mixture of rotamers δ 155.5 (s), 135.8 (s), 127.7 (d, 4C), 127.3 (d), 107.8 (s), 101.2 and 100.8 (d), 76.6 (d), 75.3 (d), 66.6 (t), 62.8 (t), 62.0 (t), 60.1 and 59.6 (t), 50.0 (t), 47.8 and 47.3 (t), 27.2 (q), 24.5 (q), 14.5 (q, 2C); MS *m*/*z* 276 (M^+–Cbz-1, 1), 350 (3), 308 (7), 91 (100); IR ($CHCl_3$) 3599, 2981, 1694 cm^{-1}. Anal. calcd for $C_{21}H_{33}NO_7$: C, 61.30; H, 8.08; N, 3.40. Found: C, 61.15; H, 7.91; N, 3.29.

4.1.25. (1*S*,5*S*,7*R*)-3-Benzyloxycarbonyl-7-*endo*-hydroxymethyl-6,8-dioxa-3-aza-bicyclo[3.2.1]octane (2d). Compound (*R*,*S*)-**12d** (34 g, 83 mmol) was treated with TFA (40 mL) as reported for (*R*,*S*)-**12c**, thus giving after flash chromatography (EtOAc–CH_2Cl_2, 1:2) **2d** (3.8 g, 16%) as an oil. ^{1}H NMR mixture of rotamers δ 7.36 (m, 5H), 5.56 and 5.50 (s, 1H), 5.16 (s, 2H), 4.44–4.34 (m, 1H), 4.12 (m, 1H), 4.00–3.63 (m, 2H), 3.35 (m, 1H), 3.13 (m, 1H); ^{13}C NMR mixture of rotamers δ 155.5 (s), 136.1 (s), 128.4 (d, 2C), 128.0 (d, 2C), 127.6 (d), 98.5 and 98.0 (d), 77.6 (d), 72.3 and 71.7 (d), 67.4 (t), 60.7 (t), 48.2 (t), 43.4 and 43.0 (t); MS *m*/*z* 279 (M^+, 0.1), 143 (2), 91 (70); IR ($CDCl_3$) 2925, 1786, 1701 cm^{-1}.

4.1.26. (1*S*,5*S*,7*R*) 3-(9-Fluorenylmethoxycarbonyl)-5-phenyl-7-*endo*-hydroxymethyl-6,8-dioxa-3-aza-bicyclo[3.2.1]octane (3c). Compound **3c** was obtained with the same procedure reported for (*R*,*S*)-**12c** starting from **3a** (190 mg, 0.86 mmol), giving after chromatography (CH_2Cl_2–EtOAc, 2:1 R_f 0.3) pure **3c** (42 mg, 11%) as a clear oil. $[\alpha]_D^{24}=-8.7$ (*c* 1.05, $CHCl_3$). ^{1}H NMR δ (mixture of rotamers) 7.84–7.65 (m, 2H), 7.62–7.48 (m, 4H), 7.46–7.22 (m, 7H), 4.80–4.50 (m, 2H), 4.48–3.82 (m, 6H), 3.78–3.50 (m, 1H), 3.39–3.15 (m, 2H); ^{13}C NMR δ mixture of rotamers 155.5 and 155.4 (s), 143.8 (s, 2C), 141.3 (s, 2C), 137.5 (s), 129.1 (d), 128.3 (d, 2C), 127.7 (d, 2C), 127.1 (d, 2C), 125.2 (d, 2C), 124.8 (d, 2C), 120.0 (d, 2C), 105.0 and 104.9 (s), 78.9 and 78.3 (d), 74.2 and 73.6 (d), 67.5 and 66.7 (t), 61.2 and 61.0 (t), 52.2 and 51.8 (t), 47.2 (t), 42.3 (d); MS *m*/*z* 443 (M^+, <1), 179 (80), 177 (100), 104 (60); IR ($CDCl_3$) 3064, 2925, 1698 cm^{-1}. Anal. calcd. for $C_{27}H_{25}NO_5$: C, 73.12; H, 5.68; N, 3.16. Found: C, 73.24; H, 5.71; N, 3.22.

4.1.27. (1*S*,5*S*,7*S*) 3-(9-Fluorenylmethoxycarbonyl)-5-phenyl-6,8-dioxa-3-aza-bicyclo[3.2.1]octane-7-*endo*-carboxylic acid (5c). Compound **3c** (15 mg, 0.034 mmol) was treated as described for **5e**, thus giving pure **5c** (10 mg, 66%) as a white powder: mp 69–70°C. $[\alpha]_D^{25}=-36.7$ (*c* 1.5, $CHCl_3$); ^{1}H NMR δ 7.77–7.10 (m, 13H), 5.00–4.90 (m, 1H), 4.84–4.74 (m, 1H), 4.62–4.32 (m, 3H), 4.28–4.08 (m, 2H), 3.40–3.16 (m, 2H); ^{13}C NMR δ 170.6 (s), 155.7 (s), 141.3 (s, 2C), 141.2 (s, 2C), 136.5 (s), 129.5 (d, 2C), 128.4 (d, 2C), 127.7 (d, 2C), 127.1 (d, 2C), 125.3 (d, 2C), 124.9 (d), 119.9 (d, 2C), 106.4 (s), 76.8 (d), 75.7 (d), 68.2 (t), 52.3 (t), 47.0 (t), 43.5 (d); MS *m*/*z* 279 (1), 180 (100); IR ($CDCl_3$) 1704 cm^{-1}. Anal. calcd. for $C_{27}H_{23}NO_6$: C, 70.89; H, 5.07; N, 3.06. Found: C, 70.69; H, 5.16; N, 3.24.

Acknowledgements

The authors thank COFIN 2000–2002 and Università degli Studi di Firenze for financial support. M. R. thanks CINMPIS-Università di Bari for financial grant. Dr Elisa Danieli is acknowledged for carrying out some experiments.

References

1. (a) Nagai, U.; Sato, K.; Nakamura, R.; Kato, R. *Tetrahedron* **1993**, *49*, 3577–3592. (b) Gardner, B.; Nakanishi, H.; Kahn,

M. *Tetrahedron* **1993**, *49*, 3433–3448. (c) Giannis, A.; Kolter, T. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1244–1267. (d) Lombart, H.-G.; Lubell, W. D. *J. Org. Chem.* **1994**, *59*, 6147. (e) Gante, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1699–1720. (f) Schneider, J. P.; Kelly, J. W. *Chem. Rev.* **1995**, *95*, 2169–2187. (g) Hanessian, S.; McNaughton-Smith, G.; Lombart, H.-G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789–12854. (h) Feng, Y.; Pattarawarapan, M.; Wang, Z.; Burgess, K. *Org. Lett.* **1999**, *1*, 121–124. (i) Gennari, C.; Mielgo, A.; Potenza, D.; Scolastico, C.; Piarulli, U.; Manzoni, L. *Eur. J. Org. Chem.* **1999**, 379–388. (j) Soth, M. J.; Nowick, J. S. *J. Org. Chem.* **1999**, *64*, 276–281. (k) Eguchi, M.; Lee, M. S.; Nakanishi, H.; Stasiak, M.; Lovell, S.; Kahn, M. *J. Am. Chem. Soc.* **1999**, *121*, 12204–12205. (l) Alonso, E.; López-Ortiz, F.; Del Pozo, C.; Peralta, E.; Macías, A.; González, J. *J. Org. Chem.* **2001**, *66*, 6333–6338.

2. Guarna, A.; Guidi, A.; Machetti, F.; Menchi, G.; Occhiato, E. G.; Scarpi, D.; Sisi, S.; Trabocchi, A. *J. Org. Chem.* **1999**, *64*, 7347–7364.
3. Guarna, A.; Bucelli, I.; Machetti, F.; Menchi, G.; Occhiato, E. G.; Scarpi, D.; Trabocchi, A. *Tetrahedron* **2002**, *58*, 9865–9870.
4. Scarpi, D.; Occhiato, E. G.; Trabocchi, A.; Leatherbarrow, R. J.; Brauer, A. B. E.; Nievo, M.; Guarna, A. *Bioorg. Med. Chem.* **2001**, *9*, 1625–1632.
5. Trabocchi, A.; Potenza, D.; Occhiato, E. G.; Guarna, A. *J. Org. Chem.* **2002**, *67*, 7483–7492.
6. (a) Mekki, B.; Singh, G.; Wightman, R. H. *Tetrahedron Lett.* **1991**, *32*, 5143–5146. (b) Williams, D. R.; Klingler, F. D. *J. Org. Chem.* **1988**, *53*, 2134–2136. (c) Pearson, W. H.; Hembre, E. J. *J. Org. Chem.* **1996**, *61*, 7217–7221.
7. (a) Kotsuki, H.; Miyazaki, A.; Ochi, M. *Chem. Lett.* **1992**, *1255*, 1258. (b) Batty, D.; Crich, D. *J. Chem. Soc. Perkin Trans. 1* **1992**, 3193–3204. (c) Schnurrenberger, P.; Hungerbuehler, E.; Seebach, D. *Liebigs Ann. Chem.* **1987**, 733–744. (d) Buchanan, J. G.; Edgar, A. R.; Hewitt, B. D. *J. Chem. Soc. Perkin. Trans. 1* **1987**, 2371–2376. (e) Hudlicky, J.; Luna, H.; Price, J. D.; Rulin, F. *J. Org. Chem.* **1990**, *55*, 4683–4687.
8. Thompson, D. K.; Hubert, C. N.; Wightman, R. H. *Tetrahedron* **1993**, *49*, 3827–3840.
9. Renard, A.; Lhomme, J.; Kotera, M. *J. Org. Chem.* **2002**, *67*, 1302–1307.
10. (a) Cicchi, S.; Corsi, M.; Brandi, A.; Goti, A. *J. Org. Chem.* **2002**, *67*, 1678–1681. (b) Buchanan, J. G.; Jigajinni, V. B.; Singh, G.; Wightman, R. H. *J. Chem. Soc. Perkin Trans. 1* **1987**, 2377–2384.
11. For a list of several multisteps syntheses, see Cohen, N.; Banner, B. L.; Lopresti, R. J.; Wong, F.; Rosemberger, M.; Liu, Y.-Y.; Thom, E.; Liebman, A. A. *J. Am. Chem. Soc.* **1983**, *105*, 3661–3672.
12. T series refers to amino acids **4** and **5** having the bicyclic structure with (1*S*,7*S*) configuration, while t series corresponds to (1*R*,7*R*) configuration of amino acids **9** and **10**.
13. All the procedures discussed for 7-*endo*-BTG **2** and **4** were also applied to the synthesis of the corresponding enantiomers 7-*endo*-BtG **7** and **9**.
14. Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849–3862.
15. Mitchell, A. R.; Merrifield, R. B. *J. Org. Chem.* **1976**, *41*, 2015–2019.
16. Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, *20*, 399–402.
17. Guidi, A.; Guarna, A.; Macherelli, M.; Menchi, G. *Arch. Pharm. Med. Chem.* **1997**, *330*, 201–202.