Synthesis of Glycidol- and Sugar-Derived Bicyclic β- and γ/δ-Amino Acids for Peptidomimetic Design

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Constrained bicyclic β- and γ/δ-amino acids using glycidol and sugar derivatives were developed. The synthetic strategies involved epoxide ring opening of a glycidol derivative, and subsequent coupling with sugar-derived amines, leading to di- or trisubstitued bicyclic scaffolds after cyclisation with trifluoroacetic acid. Achievement of β- or γ/δ-amino acids was accomplished by changing the protecting group strategy of the starting materials. Compatibility of the scaffold with solid-phase peptide synthesis was assessed by preparing model peptidomimetics using acid- and base-labile resins, thus giving a new tool for peptidomimetic design.

Introduction

The development of new therapeutics based on bioactive peptides is a valid tool for drug discovery, but it has been generally limited due to several pharmacological problems, including poor absorption, rapid metabolism and low oral bioavailability. Thus, considerable attention has been dedicated to the generation of peptidomimetics,[1] which are able to preserve peptide-like activity and to enhance resistance towards proteases. In the context of this research area, unnatural amino acids are of great interest in drug discovery, and their use as new building blocks for the development of peptidomimetics with high diversity level and possessing high-ordered structures is of special interest. In particular, medicinal chemistry has taken advantage of the use of amino acid homologues to introduce elements of diversity for the generation of new molecules as drug candidates. β-Amino acids gathered interest in the so-called "peptidomimetic approach", where a peptide lead is processed into a new non-peptide molecule in a hierarchical approach.[2] They also proved to be of great interest in the field of foldamers, as the corresponding β-peptides demonstrated exceptional capabilities to generate stable secondary structures such as β-turns, β-sheets and α-helices,[3] as well as showing great stability towards proteolysis.[4] Recently, γ- and δ-amino acids gathered the same interest. In particular, the folding properties of γ-[5] and δ-peptides[6] have been investigated, as they proved to generate stable secondary structures. β-Amino acids are found in many naturally occurring peptides as key components,[7] and also exhibit pharmacological properties as single compounds.[8] Many synthetic approaches to the creation of β-amino acids have been published, giving a great variety of β-amino acids as a tool for medicinal chemistry,[9] and some examples include bicyclic β-amino acids, which are thought to mimic a rigidified β-proline.[10] In particular, (3*S*)-carboxypyrrolidine,[11] and β^2- and β^3-homoprolines[12] have been reported as β-proline analogues, and it has been demonstrated that the corresponding oligomers are capable of forming rigid secondary structures. During the last years we have been developing new bicyclic amino acids based on the 6,8-dioxa-3-azabicyclo[3.2.1]octane skeleton, which derives from the combination of amino acids and tartaric acid or sugar derivatives,[13] and selected compounds were applied as peptidomimetics and reverse-turn inducers.[14] The synthetic strategy followed a general concept consisting in two basic reactions, namely coupling and cyclisation by a *trans*-acetalisation process, involving a diol species carrying an electrophile and an amino carbonyl derivative having both nucleophilic and electrophilic moieties. Coupling reaction occurs in the first step, followed by acetalisation of the diol species on the carbonyl moiety. Following the concept of formal COOH

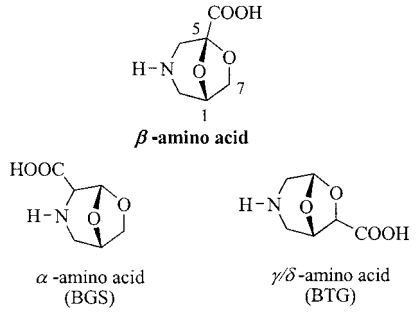

Figure 1. Formal COOH shift of BTAa scaffolds.

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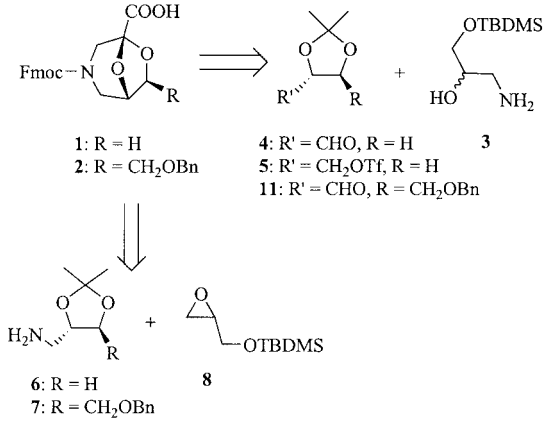
shift (Figure 1), we planned to design and synthesise a new scaffold having the carboxylic function in position 5, in order to generate a β-amino acid, which would be isomeric to α-amino acid BGS (*B*icycle from *G*lyceraldehyde and *S*erine),[14b] and γ/δ-amino acid BTG (*B*icycle from *T*artaric acid and *G*lycine) compounds.[13a,14a]

Results and Discussion

The new bicyclic β-amino acid was specifically designed to be introduced into peptides as a β-proline analogue by means of solid-phase peptide synthesis according to the Fmoc protocol. The retrosynthetic approach for **1** (Scheme 1) considered the combination of glyceraldehyde and 3-amino-1,2-propanediol derivatives to obtain the key adduct for the preparation of the title scaffold, in analogy with the synthesis of BGS compounds.[14b] In particular, racemic **3** was chosen as starting material for the synthetic route, and reactions with either protected glyceraldehyde **4**[15] by reductive amination, or with isopropylidene-glycerol triflate **5**[16] by S_N2 reaction were taken into account. Moreover, a second synthetic strategy involved epoxide ring opening of **8** by (2,2-dimethyl-1,3-dioxolan-4-yl)methanamines **6** and **7** deriving from sugars (Scheme 1).

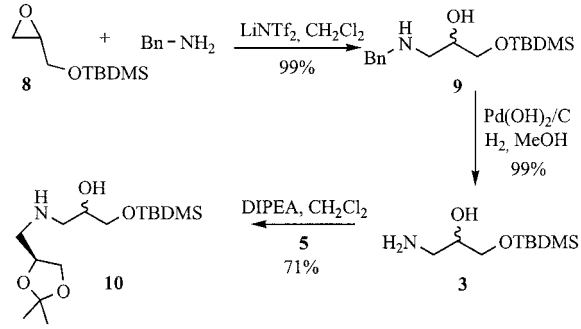


Scheme 1.

Compound **3** was obtained with excellent purity and yield after a two-step procedure involving reaction of benzylamine with **8**[17] in anhydrous CH_2Cl_2 for 16 h, and subsequent hydrogenation of the benzylic group (Scheme 2). $LiNTf_2$ was used as Lewis acid promoter for ring opening of **8**, as described by Cossy et al.[18]

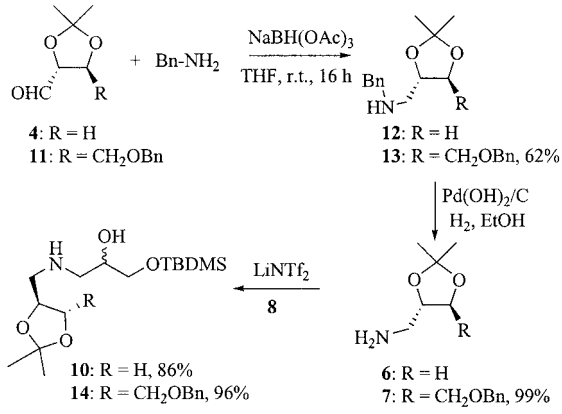
Reaction of **3** with isopropylidene-glycerol triflate **5** afforded a diastereomeric mixture of **10** in 71% yield and with good purity to be used as crude material for the next step. As an alternative coupling method, attempted reductive amination of isopropylidene-glyceraldehyde **4** with **3** and $NaBH(OAc)_3$ failed.[19]

Furthermore, sugar component **6**, obtained from amination of protected sugar derivative **4**, was taken into account to accomplish the epoxide ring opening of **8** (Scheme 3),[20] and, in order to expand the possibility of generating scaffolds with higher molecular diversity, it was developed a trisubsti-

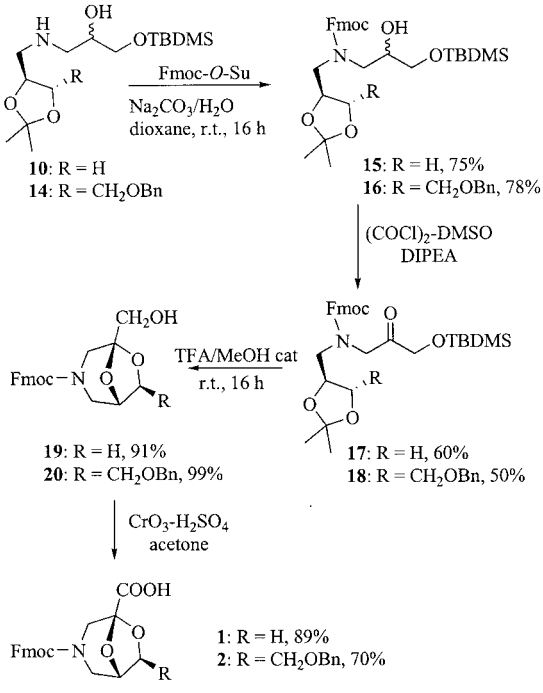


Scheme 2.

tuted β-amino acid, starting from a sugar of the tetrose family. Thus, protected L-threose derivative **11** was prepared as reported[21] and used as sugar component, providing a hydroxymethyl functionality in 7-*exo* position of the scaffold.



Scheme 3.



Scheme 4.

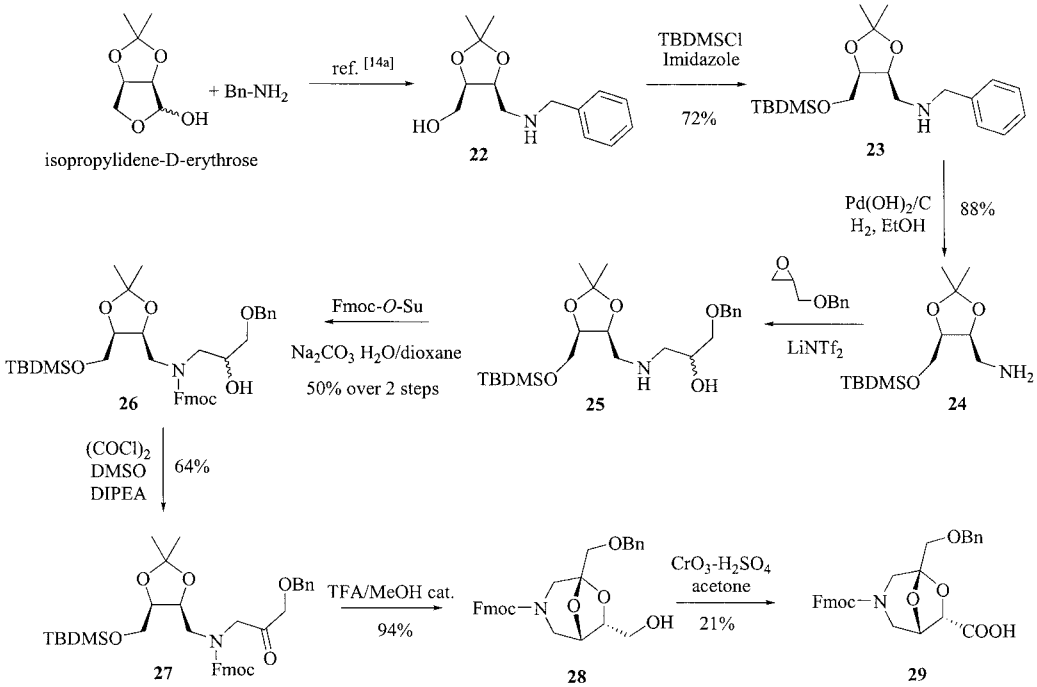
Reductive amination with benzylamine produced the amine **13** (Scheme 3), which after catalytic hydrogenolysis afforded free amine **7** in quantitative yield and in almost pure form. Subsequent reaction of **6** and **7** with **8** and $LiNTF_2$, in analogy with the previous procedure (see Scheme 2), gave the adducts **10** and **14**, respectively, in good yield and purity, which were further manipulated to give the corresponding bicyclic scaffolds. The amine function was thus protected to facilitate subsequent ring closure, and Fmoc-urethane was taken into account, giving **15** (75%) and **16** (78%) after purification (Scheme 4). Oxidation of the secondary alcohol was achieved by Swern reaction to obtain **17** and **18** as single stereoisomers, due to the loss of the stereogenic center at the carbon atom bearing the hydroxy group. The cyclisation step was initially carried out in methanol with TFA (4 equiv.), according to reported procedures for the synthesis of sialic analogues bearing a bicyclic acetal,[22] but a complex mixture of compounds was obtained, probably related with monocyclic species. On the contrary, cyclisation with 95% TFA, in analogy with other bicyclic compounds yet developed by our group,[13c,14a–14b] afforded the desired products **19** and **20** in >90% yield and with good purity, and having the hydroxymethyl moiety at C-5 deprotected from the acid-labile TBDMS group. Although showing complete compatibility with aqueous acid/base treatments, compounds **19** and **20** displayed marked instability during chromatographic purification on silica gel, giving pure products in poor yields.[23] Consequently, it was required to use the scaffolds as crude material for subsequent transformations. Bicyclic amino alcohols **19** and **20** showed full compatibility with Jones' method for alcohol oxidation to the carboxylic function, in contrast to BTKa (*B*icycles from *T*artaric acid and *K*eto *a*mine) scaffolds bearing a phenyl ring on C-5.[13c] Thus, final β-amino acids **1** and **2** were obtained with good purity in 89% and 70% yields, and showed higher chemical stability with respect to scaffolds **19** and **20**.

The inversion of the protecting group strategy with respect to the sugar and glycidol components allowed to generate a γ/δ-amino acid (Scheme 5). Specifically, the acid-labile TBDMS protecting group on the glycidol hydroxy function was replaced with an *O*-benzyl moiety, and a silylated sugar component was used instead of the *O*-benzylated sugar derivative **11**, thus giving a free hydroxymethyl group at C-7 after acid cyclisation.

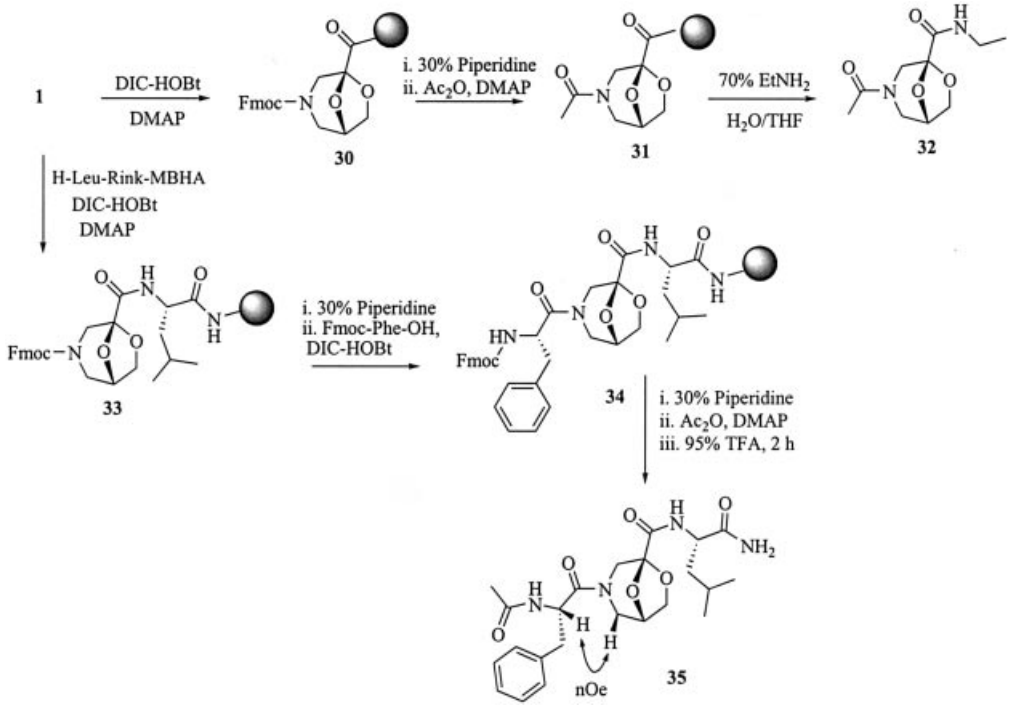
The hydroxy group of erythrose derivative **22**, prepared as reported,[14a] was protected with the acid-labile TBDMS group, and successively the resulting amino alcohol was debenzylated. Compound **24** was allowed to react with *O*-benzyl glycidyl ether to give the adduct **25**, which showed the protection scheme totally reversed with respect to **14**. Further amine protection with the Fmoc group, Swern oxidation of the secondary alcohol, and acid cyclisation produced the bicyclic compound **28**, which upon oxidation gave access to γ/δ-amino acid **29**, having a protected hydroxymethyl group in position 5 of the scaffold. It is worth noting that such compound, having the COOH group in 7-*endo* configuration, is suitable for generating reverse-turn peptides, and moreover such structure may act as a new bicyclic Ser–Xaa dipeptide isoster.[13b]

Finally, the bicyclic β-amino acid **1** was anchored to the base-labile HMBA resin with the aim of evaluating the compatibility of this new compound with solid-phase peptide synthesis.

The ester linkage was achieved by DIC/HOBt-mediated coupling, and after Fmoc deprotection with 30% piperidine in DMF, the amine was acetylated by acetic anhydride. The



Scheme 5.



Scheme 6.

resulting peptidomimetic compound **31** was cleaved off the resin as ethylamide by treatment with excess of ethylamine in water/THF at room temperature and for 18 h to give **32** in 70% overall yield (Scheme 6). The NMR spectra of **32** showed a mixture of two rotamers due to *cis*/*trans* isomerisation at the tertiary amide bond, in a 1:3 ratio. Successively, a tripeptidomimetic containing L-Phe and L-Leu at the amino and carboxy termini of the scaffold, respectively, was prepared using the acid-labile Rink-amide-MBHA resin, with the aim to assess full compatibility with common acid-labile resins (Scheme 6). Peptide couplings on both functionalities of the bicyclic amino acid proved to be slow, and complete conversion was achieved after repeated coupling cycles. Cleavage of the peptidomimetic from the resin using 95% TFA gave the title compound **35** in 41% overall yield, showing complete stability of the bicyclic acetal moiety under strong acid conditions. NMR analysis of **35** in [D_6] DMSO as solvent showed a mixture of *cis*/*trans*-amides in a 1:4 ratio, still due to slow interconversion at the C–N amide bond of the scaffold. NOESY analysis assessed the major rotamer as the *trans*-amide, as evinced from the strong NOESY peak between Phe H-α and H-2_{exo} of the scaffold (Scheme 6).

Conclusions

In conclusion, we have developed new Fmoc-protected bicyclic amino acids starting from glycidol and sugar derivatives, using a simple and efficient synthetic route. In particular, two convergent synthetic methods were taken into account for the β-amino acid, thus enabling the generation of a more general class of trisubstituted bicyclic scaffolds. Moreover, change of the protecting group strategy on both glycidol and sugar derivatives allowed to generate Fmoc-protected γ/δ-amino acids using the same reaction pathway. Finally, the compatibility with solid-phase peptide chemistry was demonstrated using both acid- and base-labile resins, thus giving a new tool for peptidomimetic design of constrained peptide sequences. Further applications of these bicyclic β-amino acids as peptidomimetic scaffolds in reverse-turn and cyclic peptides will be reported in due course.

Experimental Section

General Remarks: Chromatographic separations were performed on silica gel using flash-column techniques; R_f values refer to TLC carried out on 25 mm silica gel plates (Merck F_{254}) with the same eluent indicated for column chromatography. CH_2Cl_2 was distilled from CaH_2. All reactions requiring anhydrous conditions were performed in oven-dried glassware. All the solid-phase reactions were carried out on a shaker, using solvents of HPLC quality. Peptide **35** was purified with an HPLC system equipped with a semipreparative C18 10 μm, 250×4.6 mm, reverse-phase column. ^1H and ^{13}C NMR spectra were recorded with NMR instruments operating at 200 MHz and 400 MHz for ^1H and 50.33 and 100.66 for ^{13}C, respectively, and using $CDCl_3$ solutions unless otherwise stated. EI mass spectra were carried out at 70 eV ionizing voltage. Peptide **35** was characterised by 2D NMR, HPLC and ESI-MS. FT-IR spectra were recorded in $CHCl_3$ solutions.

(*R*/*S*)-1-Benzylamino-3-(*tert*-butyldimethylsilyloxy)propan-2-ol (9): To a solution of *tert*-butyldimethylsilyl glycidyl ether (**8**) (1 g, 5.31 mmol) and benzylamine (597 μL, 5.47 mmol) in anhydrous CH_2Cl_2 (2 mL) was added $LiNTf_2$ (762 mg, 2.65 mmol). The reaction mixture was stirred under nitrogen and at room temperature

for 12 h, then the mixture was diluted with diethyl ether (60 mL), quenched with a saturated aqueous solution of $NaHCO_3$ (3 × 30 mL) and extracted with CH_2Cl_2 (2 × 40 mL). The combined organic layers were dried with Na_2SO_4 and concentrated in vacuo to give **9** (1.44 g, 99%) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.26 (m, 5 H), 4.28–4.11 (m, 2 H), 3.80 (s, 2 H), 3.51 (m, 1 H), 2.85 [d, 1 H, ^3J(H,H) = 12 Hz], 2.79 (dd, 1 H, $^3J_{H,H}$ = 12, 12 Hz), 0.82 (s, 9 H), 0.04 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 133.4 (s, 1 C), 128.8 (d, 2 C), 128.7 (d, 2 C), 128.5 (d, 1 C), 68.0 (d, 1 C), 64.8 (t, 1 C), 52.3 (t, 1 C), 50.2 (t, 1 C), 25.5 (q, 3 C), 17.9 (s, 1 C), –5.8 (q, 2 C) ppm. MS: *m*/*z* (%) = 295 (0.5) [M^+], 238 (7), 204 (1), 91 (100). IR ($CHCl_3$): $\tilde{\nu}$ = 3523, 2937, 1603, 1463 cm^{-1}.

(*R*/*S*)-1-Amino-3-(*tert*-butyldimethylsilyloxy)propan-2-ol (3): Compound **9** (1.7 g, 5.75 mmol) was dissolved in MeOH (190 mL), and 20% $Pd(OH)_2$/C (430 mg) was added; the resulting suspension was stirred under hydrogen and at room temperature overnight. The catalyst was then removed by careful filtration through Celite, washed with MeOH, and the resulting solution was passed through a column filled with Amberlyst A-21 resin to give after solvent evaporation pure **3** (1.17 g, 99%) as a yellow oil. ^1H NMR (200 MHz, $CDCl_3$): δ = 4.60 (br. s, 2 H), 3.74–3.71 (m, 1 H), 3.58–3.40 (m, 2 H), 2.92–2.79 (m, 2 H), 2.46 (br. s, 2 H), 0.86 (s, 9 H), 0.04 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 68.2 (t, 1 C), 64.9 (d, 1 C), 43.1 (t, 1 C), 25.7 (q, 3 C), 18.2 (s, 1 C), –5.7 (q, 2 C) ppm. MS: *m*/*z* (%) = 205 (7) [M^+], 175 (11), 131 (13). IR ($CHCl_3$): $\tilde{\nu}$ = 3308, 2931, 1586 cm^{-1}. $C_9H_{23}NO_2Si$ (205.4): calcd. C 52.63, H 11.29, N 6.82; found C 52.60, H 11.21, N 6.87.

(2*R*/2*S*)-1-(*tert*-Butyldimethylsilyloxy)-3-{[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-ylmethyl]amino}propan-2-ol (10): To a solution of **3** (1.4 g, 6.85 mmol) and diisopropylethylamine (2.02 mL, 11.83 mmol) in anhydrous CH_2Cl_2 (15 mL) was added dropwise, at 0 °C and under nitrogen, a solution of D-1,2-*O*-isopropylidene-glycerol triflate **5** (1.65 g, 6.22 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was stirred at 0 °C for 30 min, and then at room temperature for 16 h. The mixture was then quenched with 5% $NaHCO_3$ solution (15 mL), and the organic layer was separated, washed with H_2O (3 × 10 mL) and dried with Na_2SO_4 to give after solvent evaporation compound **10** as an oil (1.41 g, 71%), sufficiently pure for the next step. Alternatively, compound **10** was obtained starting from (*tert*-butyldimethylsilyl)glycidyl ether (**8**) (1.40 g, 7.4 mmol) and (4*S*)-(2,2-dimethyl-1,3-dioxolan-4-yl)methanamine (**6**) (1.16 g, 7.7 mmol). To a solution of these reagents in anhydrous CH_2Cl_2 (2.5 mL), $LiNTf_2$ (1.07 g, 7.4 mmol) was added. The reaction mixture was stirred under nitrogen and at room temperature for 12 h, then it was diluted with diethyl ether (75 mL), washed with a saturated aqueous solution of $NaHCO_3$ (3 × 35 mL) and the aqueous phase extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried with Na_2SO_4 and concentrated in vacuo to afford **10** (2.03 g, 86%) as a colorless oil and as a 1:1 mixture of two diastereomers, sufficiently pure for the next step. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.62 (br. s, 2 H), 4.29 (m, 1 H), 4.05 (m, 2 H), 3.87 (m, 1 H), 3.58 (m, 2 H), 3.03 (m, 2 H), 2.92 (m, 1 H), 2.83 (m, 1 H), 1.37 (s, 3 H), 1.28 (s, 3 H), 0.83 (s, 9 H), 0.00 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 111.0 (s, 1 C), 73.1 (t, diast. A, 1 C), 72.8 (t, diast. B, 1 C), 68.5 (t, diast. A, 1 C), 68.4 (t, diast. B, 1 C), 67.6 (t, 1 C), 66.2 (t, diast. A, 1 C), 65.8 (t, diast. B, 1 C), 52.7 (d, 1 C), 52.4 (d, diast. A, 1 C), 52.1 (d, diast. B, 1 C), 27.4 (q, 1 C), 26.4 (q, 3 C), 25.7 (q, 1 C), 18.9 (s, 1 C), –4.9 (s, 2 C) ppm. MS: *m*/*z* (%) = 319 (0.3) [M^+], 304 (2), 218 (7), 204 (8), 69 (100). IR ($CHCl_3$): $\tilde{\nu}$ = 2930, 2248, 1710 cm^{-1}. $C_{15}H_{33}NO_4Si$ (319.5): calcd. C 56.39, H 10.41, N 4.38; found C 56.31, H 10.35, N 4.29.

(2*R*/2*S*)-1-(*tert*-Butyldimethylsilyloxy)-3-[{[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}(fluoren-9-ylmethoxycarbonyl)amino]propan-2-ol (15): To a solution of **10** (1.10 g, 3.44 mmol), in dioxane (22 mL) was added at 0 °C a solution of $Na_2CO_3 \cdot H_2O$ (364 mg, 3.44 mmol) in H_2O (22 mL), and then Fmoc-*O*-Su (1.17 g, 3.47 mmol). The mixture was stirred at room temperature overnight, then the organic solvent was evaporated in vacuo, the aqueous layer was saturated with NaCl and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried with anhydrous Na_2SO_4 to give a crude oil, which was purified by flash chromatography (EtOAc/petroleum ether, 1:3; R_f = 0.21), thus affording compound **15** (1.40 g, 75%) as a mixture of diastereomers (colorless oil). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.72 (d, 2 H, $^3J_{H,H}$ = 7.6 Hz), 7.53 (m, 2 H), 7.36 (m, 2 H), 7.29 (m, 2 H), 4.60 (m, 1 H, diast. A), 4.51 (m, 1 H, diast. B), 4.18 (s, 2 H), 3.98 (m, 1 H), 3.78–3.30 (m, 5 H), 3.27–2.80 (m, 4 H), 1.90 (br. s, 1 H), 1.36 (s, 3 H), 1.20 (s, 3 H), 0.91 (s, 9 H), 0.01 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 158.0 (s, 1 C, diast. A), 156.9 (s, 1 C, diast. B), 143.5 (s, 2 C), 141.2 (s, 2 C), 127.6 (d, 2 C), 126.9 (d, 2 C), 124.3 (d, 2 C), 119.9 (d, 2 C), 109.1 (s, 1 C), 74.8 (d, 1 C), 71.0 (d, 1 C, diast. A), 70.3 (d, 1 C, diast. B), 66.9 (t, 1 C, diast. A), 66.3 (t, 1 C, diast. B), 64.6 (t, 1 C, diast. A), 64.0 (t, 1 C, diast. B), 60.3 (t, 1 C), 52.3 (t, 1 C, diast. A), 51.8 (t, 1 C, diast. B), 51.4 (t, 1 C, diast. A), 51.3 (t, 1 C, diast. B), 47.0 (d, 1 C), 26.5 (q, 1 C), 25.7 (q, 3 C), 25.1 (q, 1 C), 18.0 (s, 1 C), –5.7 (q, 2 C) ppm. MS: *m*/*z* (%) = 288 (4) [M^+ – Fmoc – $(CH_3)_2$], 248 (17), 178 (100). IR ($CHCl_3$): $\tilde{\nu}$ = 3447, 2955, 2857, 1698 cm^{-1}. $C_{30}H_{43}NO_6Si$ (541.7): calcd. C 66.51, H 8.00, N 2.59; found C 66.07, H 7.82, N 2.30.

1-(*tert*-Butyldimethylsilyloxy)-3-[{[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}(fluoren-9-ylmethoxycarbonyl)amino]propan-2-one (17): A solution of $(COCl)_2$ (506 μL, 5.98 mmol) in dry CH_2Cl_2 (16 mL) under nitrogen was cooled to –60 °C, then anhydrous DMSO (990 μL, 13.96 mmol) in dry CH_2Cl_2 (7 mL) was slowly added in order to keep the temperature constant. After 10 min, a solution of **15** (2.7 g, 4.99 mmol) in CH_2Cl_2 (12 mL) was added dropwise, still maintaining the temperature at –60 °C. The mixture was stirred for 30 min, then DIPEA (4.2 mL, 24.9 mmol) was added and, after 10 min, the reaction mixture was left to warm to room temperature, and to react for an additional 1.5 h. Successively, 5% $KHSO_4$ (40 mL) and Et_2O (60 mL) were added, the organic phase was separated and washed with a saturated aqueous solution of $NaHCO_3$ (3 × 60 mL), H_2O (3 × 60 mL), brine (3 × 60 mL), and dried with Na_2SO_4. Solvent evaporation afforded a crude yellow oil which was purified by flash chromatography (EtOAc/petroleum ether, 1:4; R_f = 0.30) to give **17** (1.62 g, 60%) as a yellow oil. $[\alpha]_D^{22}$ = +2.0 (*c* = 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$; 1.2:1 mixture of two rotamers): δ = 7.76 (d, 2 H, $^3J_{H,H}$ = 7.6 Hz, rot. A), 7.74 (d, 2 H, $^3J_{H,H}$ = 7.8 Hz, rot. B), 7.57 (d, 2 H, $^3J_{H,H}$ = 7.4 Hz, rot. A), 7.51 (d, 2 H, $^3J_{H,H}$ = 7.4 Hz, rot. B), 7.39 (m, 2 H), 7.32 (m, 2 H), 4.57 (AB system, 2 H, rot. A), 4.47 (AB system, 2 H, rot. B), 4.39 (d, 2 H, $^3J_{H,H}$ = 9.6 Hz, rot. A), 4.30 (d, 2 H, $^3J_{H,H}$ = 4.0 Hz, rot. B), 4.24 (m, 1 H, rot A), 4.20 (m, 2 H, rot A), 4.20–4.16 (m, 1 H) 4.02 (dd, 1 H, $^3J_{H,H}$ = 8.4, 6.4 Hz, rot. A), 3.99 (s, 2 H, rot B), 3.81 (m, 1 H, rot. B), 3.72 (dd, 1 H, $^3J_{H,H}$ = 14.8, 3.6 Hz, rot. A), 3.68 (dd, 1 H, $^3J_{H,H}$ = 8.4, 6.4 Hz, rot. B), 3.56 (dd, 1 H, $^3J_{H,H}$ = 8.4, 7.2 Hz, rot. A), 3.35 (dd, 1 H, $^3J_{H,H}$ = 14.8, 3.6 Hz, rot. B), 3.28 (dd, 1 H, $^3J_{H,H}$ = 8.4, 7.2 Hz, rot. B), 3.12 (dd, 1 H, $^3J_{H,H}$ = 14.8, 6.8 Hz, rot. A), 2.94 (dd, 1 H, $^3J_{H,H}$ = 14.8, 6.4 Hz, rot. B), 1.36 (s, 3 H, rot. A), 1.32 (s, 3 H, rot. B), 1.30 (s, 3 H, rot. A), 1.26 (s, 3 H, rot. B), 0.93 (s, 9 H, rot. A), 0.91 (s, 9 H, rot. B), 0.08 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 206.3 (s, 1 C, rot. A), 206.0 (s, 1 C, rot. B), 156.3 (s, 1 C, rot. A), 156.0 (s, 1 C, rot. B), 143.7 (s, 2 C), 141.4 (s, 2 C), 127.7 (d, 2 C), 127.2 (d, 2 C), 124.7 (d, 2 C), 120.0 (d, 2

C), 109.2 (s, 1 C), 75.3 (d, 1 C, rot. A), 74.9 (d, 1 C, rot. B), 68.4 (t, 1 C, rot. A), 68.0 (t, 1 C, rot. B), 67.1 (t, 1 C, rot. A), 66.9 (t, 1 C), 66.6 (t, 1 C, rot. B), 55.4 (t, 1 C, rot. A), 55.3 (t, 1 C, rot. B), 50.7 (t, 1 C, rot. A), 50.0 (t, 1 C, rot. B), 47.2 (d, 1 C), 26.9 (q, 1 C), 25.7 (q, 3 C), 25.4 (q, 1 C), 18.0 (s, 1 C), –5.7 (q, 2 C) ppm. MS: *m*/*z* (%) = 482 (75) [M^+ – *t*Bu], 424 (88), 394 (6), 366 (4), 246 (100), 178 (30). IR ($CHCl_3$): $\tilde{\nu}$ = 2932, 2858, 1738, 1702, 1452 cm^{-1}. $C_{30}H_{41}NO_6Si$ (539.7): calcd. C 66.76,H 7.66, N 2.60; found C 66.56, H 7.59, N 2.47.

(1*S*,5*S*)-3-(Fluoren-9-ylmethoxycarbonyl)-5-(hydroxymethyl)-6,8-dioxa-3-azabicyclo[3.2.1]octane (19): Compound **17** (1.3 g, 2.41 mmol) was dissolved in trifluoroacetic acid (5 mL) and MeOH (50 μL), and was stirred overnight at room temperature. After TFA evaporation, the crude oil was dissolved in EtOAc, washed with saturated $NaHCO_3$, brine, and dried with anhydrous Na_2SO_4. After solvent evaporation, compound **19** was obtained as a pale yellow foam (880 mg, 91%). An analytical sample of **19** was obtained by flash chromatography (EtOAc/petroleum ether, 1:2; R_f = 0.57) in 35% yield after purification on silica gel. $[\alpha]_D^{22}$ = –1.3 (*c* = 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$; 1:1.5 mixture of two rotamers): δ = 7.77 (d, 2 H, $^3J_{H,H}$ = 7.5 Hz), 7.53 (m, 2 H), 7.41–7.25 (m, 4 H), 4.78 (m, 1 H, rot. A), 4.58–4.49 (m, 1 H), 4.48 (s, 2 H), 4.38 (m, 1 H, rot. A), 4.24 (m, 1 H), 3.99–3.76 (m, 3 H), 3.73 (s, 2 H), 3.60 (m, 1 H, rot. A), 3.24 (m, 1 H, rot. B), 3.07 (d, 1 H, $^3J_{H,H}$ = 12.6 Hz, rot. A), 2.98 (m, 1 H, rot. B), 1.74 (br. s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 155.9 (s, 1 C), 143.7 (s, 2 C), 141.3 (s, 2 C), 127.7 (d, 2 C), 127.0 (d, 2 C), 124.8 (d, 2 C), 120.0 (d, 2 C), 102.2 (s, 1 C), 73.5 (d, 1 C, rot. A), 73.0 (d, 1 C, rot. B), 68.6 (t, 1 C), 67.7 (t, 1 C, rot. A), 67.3 (t, 1 C, rot. B), 66.4 (t, 1 C), 48.5 (t, 1 C, rot. A), 48.2 (t, 1 C, rot. B), 47.2 (d, 1 C), 46.8 (t, 1 C, rot. A), 46.5 (t, 1 C, rot. B) ppm. MS: *m*/*z* (%) = 367 (1) [M^+], 178 (100). IR ($CHCl_3$): $\tilde{\nu}$ = 2930, 2880, 2248, 1792, 1451 cm^{-1}. $C_{21}H_{21}NO_5$ (367.4): calcd. C 68.65, H 5.76, N 3.81; found C 68.61, H 5.57, N 3.72.

(1*S*,5*S*)-3-(Fluoren-9-ylmethoxycarbonyl)-6,8-dioxa-3-azabicyclo-[3.2.1]octane-5-carboxylic Acid (1): To a solution of **19** (505 mg, 1.37 mmol) in acetone (27 mL) was added Jones' reagent at 0 °C [preparated by slow addition of H_2SO_4 (1 mL) to a solution of CrO_3 (549 mg, 5.49 mmol) in H_2O (6 mL) at 0 °C] and the mixture was stirred at room temperature overnight. 2-Propanol was then added until the color of the solution turned deep green/blue, then the mixture was filtered through Celite and the solvents were evaporated. The crude product was dissolved in EtOAc (20 mL), and treated twice with 5% Na_2CO_3 solution (2 × 15 mL). The organic products were extracted with diethyl ether, then the aqueous phase was acidified to pH = 1 with concd. HCl, and extracted with EtOAc (3 × 15 mL). The organic phase was washed with brine, dried with anhydrous Na_2SO_4, filtered, and concentrated to give **1** (469 mg, 89%) as a pale yellow solid. An analytical sample of **1** (192 mg, 41%) was obtained by flash chromatography (EtOAc/petroleum ether, 2:1 with 0.1% TFA; R_f = 0.28). $[\alpha]_D^{25}$ = +6.2 (*c* = 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$; 1:1 mixture of two rotamers): δ = 8.10 (br. s, 1 H), 7.79 (d, 2 H, $^3J_{H,H}$ = 7.4 Hz), 7.76 (m, 2 H), 7.74–7.30 (m, 4 H), 4.77 (m, 1 H, rot. A), 4.62 (m, 1 H, rot. B), 4.58–4.38 (m, 2 H), 4.27 (m, 1 H), 4.17 (m, 2 H, rot. A), 4.09 (m, 2 H, rot. A), 4.03 (m, 1 H, rot. A), 3.90 (m, 1 H, rot. B), 3.76 (m, 1 H, rot. B), 3.55 (d, 1 H, $^3J_{H,H}$ = 13.6 Hz, rot. A), 3.35 (d, 1 H, $^3J_{H,H}$ = 13.2 Hz, rot. B), 3.32 (d, 1 H, $^3J_{H,H}$ = 9.2 Hz, rot. B), 3.25 (d, 1 H, $^3J_{H,H}$ = 13.2 Hz, rot. B), 3.19 (d, 1 H, $^3J_{H,H}$ = 12.8 Hz, rot. B) ppm. ^{13}C NMR ($CDCl_3$): δ = 168.0 (s, 1 C), 156.2 (s, 1 C, rot. A), 156.1 (s, 1 C, rot. B), 143.6 (s, 2 C), 141.3 (s, 2 C), 127.8 (d, 2 C), 127.1 (d, 2 C), 124.9 (d, 2 C), 120.0 (d, 2 C), 101.2 (d, 1 C, rot. A), 100.7 (d, 1 C, rot. B), 73.8 (d, 1 C, rot. A), 73.2 (d, 1 C, rot. B), 68.7 (t, 1 C), 68.2 (t, 1 C, rot. A), 67.5 (t, 1 C, rot. B), 48.7 (t, 1 C, rot. A), 48.4 (t, 1 C, rot. B), 47.0 (d, 1 C), 46.6 (t, 1 C, rot. A), 46.4 (t, 1 C, rot. B) ppm. MS: *m*/*z* (%) = 381 (0.14) [M^+], 336 (1), 178 (100). IR ($CHCl_3$): $\tilde{\nu}$ = 3440, 3028, 1703 cm^{-1}. $C_{21}H_{19}NO_6$ (381.4): calcd. C 66.13, H 5.02, N 3.67; found C 65.96, H 5.07, N 3.37.

Benzyl{[(4*S*,5*S*)-5-(benzyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}amine (13): Benzylamine (0.961 mL, 8.8 mmol) was added to a solution of **11** (2 g, 8 mmol) in THF (40 mL), under nitrogen, and then $NaBH(OAc)_3$ (2.54 g, 12 mmol) portionwise and at 0 °C. The mixture was stirred at room temperature overnight, then saturated $NaHCO_3$ was added, and organic products were extracted with EtOAc (3 × 40 mL). The organic phase was dried with Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/petroleum ether, 1:1; R_f = 0.6) to give **13** (1.70 g, 62%) as a colorless oil. $[\alpha]_D^{21}$ = –12.7 (*c* = 0.58, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 7.33 (m, 5 H), 7.31 (m, 5 H), 4.58 (s, 2 H), 4.02 (m, 2 H), 3.82 (s, 2 H), 3.61 (AB system, 2 H), 2.82 (AB system, 2 H), 1.88 (br. s, 1 H), 1.43 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 140.0 (s, 1 C), 137.8 (s, 1 C), 128.2 (d, 3 C), 127.9 (d, 2 C), 127.5 (d, 3 C), 126.8 (d, 2 C), 109.0 (s, 1 C), 78.2 (d, 1 C), 78.0 (d, 1 C), 73.4 (t, 1 C), 70.6 (t, 1 C), 53.9 (t, 1 C), 51.1 (t, 1 C), 27.2 (q, 1 C), 26.9 (q, 1 C) ppm. MS: *m*/*z* (%) = 342 (0.45) [M^+ + H], 327 (1), 250 (4), 234 (4), 120 (74), 91 (100). IR ($CHCl_3$): $\tilde{\nu}$ = 3012, 2867, 1603, 1454, 1372, 1229 cm^{-1}. $C_{21}H_{27}NO_3$ (341.4): calcd. C 73.87, H 7.97, N 4.10; found C 73.67, H 8.07, N 4.00.

{[(4*S*,5*S*)-5-(Benzyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}amine (7): To a suspension of 20% $Pd(OH)_2$/C (150 mg) in absolute ethanol (10 mL) under hydrogen was added a solution of **13** (612 mg, 1.79 mmol) in absolute ethanol (8 mL). The reaction mixture was vigorously stirred at room temperature overnight, then it was filtered through Celite, and the solvent evaporated in vacuo to give **7** (450 mg, 99%) as a pure yellow oil. $[\alpha]_D^{21}$ = –14.0 (*c* = 0.53, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 7.29 (m, 5 H), 4.54 (s, 2 H), 3.96–3.70 (m, 2 H), 3.55 (AB system, 2 H), 2.89 (dd, 1 H, $^3J_{H,H}$ = 13.2, 3.7 Hz), 2.76 (dd, 1 H, $^3J_{H,H}$ = 13.2, 5.8 Hz), 2.00 (br. s, 2 H), 1.37 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 137.6 (s, 1 C), 128.1 (d, 2 C), 127.4 (d, 3 C), 108.9 (s, 1 C), 80.2 (d, 1 C), 77.1 (d, 1 C), 73.4 (t, 1 C), 70.5 (t, 1 C), 43.9 (t, 1 C), 27.1 (q, 1 C), 26.8 (q, 1 C) ppm. MS: *m*/*z* (%) = 251 (2) [M^+], 237 (1), 221 (1), 143 (2), 121 (13), 91 (100). IR ($CHCl_3$): $\tilde{\nu}$ = 3387, 2990, 2868, 1601, 1372 cm^{-1}.

(*R*/*S*)-1-({[(4*S*,5*S*)-5-(Benzyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}amino)-3-(*tert*-butyldimethylsilyloxy)propan-2-ol (14): Compound **14** was obtained according to the same procedure as for **10**, starting from **7** (686 mg, 2.73 mmol) and *tert*-butyldimethylsilyl-glycidyl ether **8** (499 mg, 2.65 mmol), to afford a yellow oil (1.12 g, 96%), sufficiently pure for the next step. An analytical sample of compound **14** was obtained by flash chromatography (EtOAc/petroleum ether, 1:1; R_f = 0.3). ^1H NMR (200 MHz, $CDCl_3$; mixture of two diastereomers): δ = 7.33 (m, 5 H) 4.65 (br. s, 2 H), 4.56 (s, 2 H), 4.12–4.03 (m, 1 H), 3.94–3.84 (m, 2 H), 3.75–3.48 (m, 4 H), 3.18–2.97 (m, 4 H), 1.40 (s, 3 H), 1.38 (s, 3 H), 0.89 (s, 9 H), 0.08 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 137.0 (s, 1 C), 128.5 (d, 2 C), 128.2 (d, 3 C), 110.6 (s, 1 C), 78.0 (d, 1 C, diast. A), 77.9 (d, 1 C, diast. B), 75.8 (d, 1 C, diast. A), 75.6 (d, 1 C, diast. B) 73.9 (t, 1 C) 69.8 (t, 1 C, diast. A), 69.6 (t, 1 C, diast. B), 67.4 (t, 1 C, diast. A), 67.3 (d, 1 C, diast. B), 65.5 (t, 1 C, diast. A), 65.0 (t, 1 C, diast. B), 51.8 (t, 1 C, diast. A), 51.6 (t, 1 C, diast. B), 50.7 (t, 1 C), 26.7 (q, 1 C), 26.6 (q, 1 C), 25.7 (q, 3 C), 18.2 (s, 1 C), –5.7 (q, 2 C) ppm. MS: *m*/*z* (%) = 440 (1) [M^+ + H], 424 (1), 382

(3), 362 (1), 348 (1), 332 (2), 318 (2), 294 (1), 264 (5), 250 (1), 218 (5), 91 (100). IR ($CHCl_3$): $\tilde{\nu}$ = 3543, 2930, 1732 cm^{-1}. $C_{23}H_{41}NO_5Si$ (439.7): calcd. C 62.83, H 9.40, N 3.19; found C 62.76, H 9.33, N 3.12.

(*R*/*S*)-1-[{[(4*S*,5*S*)-5-(Benzyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}(fluoren-9-ylmethoxycarbonyl)amino]-3-(*tert*-butyldimethylsilyloxy)propan-2-ol (16): Compound **16** was obtained according to the same procedure as for **15**, starting from **14** (554 mg, 1.26 mmol), to afford a colorless oil (660 mg, 78%) after purification by flash column chromatography (EtOAc/petroleum ether, 1:4; R_f = 0.15). ^1H NMR (200 MHz, $CDCl_3$; 1:1 mixture of two diastereomers): δ = 7.74 (m, 2 H) 7.56 (m, 2 H), 7.35 (m, 4 H), 7.25 (s, 5 H), 4.58–4.48 (m, 4 H), 4.25–4.12 (m, 1 H), 3.83–3.23 (m, 11 H), 1.40 (s, 3 H), 1.37 (s, 3 H), 0.91 (s, 9 H), 0.07 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 156.0 (s, 1 C), 143.6 (s, 2 C), 141.0 (s, 2 C), 137.6 (s, 1 C), 128.0 (d, 2 C), 127.4 (d, 5 C), 126.8 (d, 2C), 124.4 (d, 2 C), 119.6 (d, 2 C), 109.2 (s, 1 C, diast. A), 109.1 (s, 1 C, diast. B), 77.9 (d, 1 C), 76.8 (d, 1 C), 73.2 (t, 1 C), 71.2 (d, 1 C, diast. A), 70.5 (d, 1 C, diast. B), 69.9 (t, 1 C), 66.7 (t, 1 C), 64.7 (t, 1 C, diast. A), 64.2 (t, 1 C, diast. B), 52.2 (t, 1 C, diast. A), 51.9 (t, 1 C, diast. B), 51.2 (t, 1 C, diast. A), 50.6 (t, 1 C, diast. B), 47.1 (d, 1 C), 26.8 (q, 2 C, diast A), 26.7 (q, 2 C, diast. B), 25.6 (q, 3 C), 18.0 (q, 3 C), –5.6 (q, 2 C) ppm. MS: *m*/*z* (%) = 604 (1)[M^+ – *t*Bu], 546 (1), 408 (1), 368 (4), 234 (1), 178 (49), 91 (100). IR ($CHCl_3$): $\tilde{\nu}$ = 3450, 2930, 2858, 2248, 1694 cm^{-1}. $C_{38}H_{51}NO_7Si$ (661.9): calcd. C 68.95, H 7.77, N 2.12; found C 68.59, H 7.37, N 1.90.

1-[{[(4*S*,5*S*)-5-(Benzyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}(fluoren-9-ylmethoxycarbonyl)amino]-3-(*tert*-butyldimethylsilyloxy)propan-2-one (18): Compound **18** was obtained according to the same procedure as for **17**, starting from **16** (660 mg, 1.00 mmol), to afford a colorless oil (332 mg, 50%) after purification by flash column chromatography (EtOAc/petroleum ether, 1:6; R_f = 0.27). $[\alpha]_D^{25}$ = –6.0 (*c* = 0.4, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$; 1:1 mixture of two rotamers): δ = 7.78 (d, 2 H, $^3J_{H,H}$ = 7.6 Hz, rot. A), 7.77 (d, 2 H, $^3J_{H,H}$ = 7.2 Hz, rot. B), 7.58 (d, 2 H, $^3J_{H,H}$ = 7.6 Hz, rot. A), 7.54 (d, 2 H, $^3J_{H,H}$ = 7.6 Hz, rot. B), 7.44–7.25 (m, 9 H), 4.62 (s, 2 H, rot. A), 4.51 (s, 2 H), 4.56–4.38 (m, 2 H), 4.35 (s, 2 H, rot. A), 4.26 (s, 2 H, rot. B), 4.21 (m, 1 H), 4.03 (s, 2 H, rot. B), 3.99 (m, 1 H), 3.89–3.85 (m, 1 H), 3.81–3.77 (m, 1 H), 3.70–3.62 (m, 1 H), 3.48 (dd, 1 H, $^3J_{H,H}$ = 10.4, 5.6 Hz, rot. A), 3.42 (dd, 1 H, $^3J_{H,H}$ = 10.4, 4.0 Hz, rot. A), 3.26 (dd, 1 H, $^3J_{H,H}$ = 15.2, 6.4 Hz, rot. B), 3.20 (dd, 1 H, $^3J_{H,H}$ = 15.2, 7.2 Hz, rot. B), 1.38 (s, 6 H), 0.96 (s, 9 H), 0.10 (s, 6 H, rot. A), 0.09 (s, 6 H, rot. B) ppm. ^{13}C NMR ($CDCl_3$): δ = 205.9 (s, 1 C), 156.4 (s, 1 C), 143.9 (s, 2 C), 141.3 (s, 2 C), 137.6 (s, 1 C), 128.3 (d, 2 C), 127.7 (d, 5 C), 127.1 (d, 2 C), 124.8 (d, 2 C), 119.9 (d, 2 C), 109.2 (s, 1 C), 77.9 (d, 1 C), 77.7 (d, 1 C), 73.5 (t, 1 C), 70.1 (t, 1 C, rot. A), 69.9 (t, 1 C, rot. B), 68.5 (t, 1 C, rot. A), 68.2 (t, 1 C, rot. B), 67.5 (t, 1 C, rot. A), 67.2 (t, 1 C, rot. B), 55.2 (t, 1 C), 49.5 (t, 1 C), 47.3 (d, 1 C), 27.1 (q, 1 C), 26.8 (q, 1 C), 25.7 (q, 3 C), 18.0 (s, 1 C), –5.6 (q, 2 C) ppm. MS: *m*/*z* (%) = 539 (1) [M^+ – CH_2OBn], 480 (1), 424 (1), 395 (1), 178 (12). IR ($CHCl_3$): $\tilde{\nu}$ = 2931, 2858, 1700 cm^{-1}. $C_{38}H_{49}NO_7Si$ (659.9): calcd. C 69.16, H 7.48, N 2.12; found C 68.96, H 7.24, N 2.02.

(1*S*,5*R*,7*S*)-7-*exo*-(Benzyloxymethyl)-3-(fluoren-9-ylmethoxycarbonyl)-5-(hydroxymethyl)-6,8-dioxa-3-azabicyclo[3.2.1]octane (20): Crude **20** (248 mg, 99%) was obtained according to the same procedure as for **19**, starting from **18** (332 mg, 0.5 mmol). Purification by flash chromatography (EtOAc/petroleum ether, 1:3; R_f = 0.43) gave pure **20** (90 mg, 37%) as a pale yellow oil. $[\alpha]_D^{25}$ = –5.2 (*c* = 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$; 1:1 mixture of two rotamers): δ = 7.68 (m, 2 H), 7.47 (m, 2 H), 7.34–7.22 (m, 9 H), 4.45 (m, 2 H), 4.48–4.31 (m, 3 H), 4.17 (m, 1 H), 4.16 (m, 1 H, rot. A), 4.00 (m, 1 H, rot. B), 3.90 (d, 1 H, $^3J_{H,H}$ = 13.2 Hz, rot. A), 3.81 (d, 1 H, $^3J_{H,H}$ = 13.2 Hz, rot. A), 3.76–3.70 (m, 1 H, rot. A), 3.65 (m, 2 H), 3.59–3.54 (m, 1 H), 3.39–3.31 (m, 2 H, rot. A), 3.26– 3.19 (m, 2 H, rot. B), 3.16 (m, 1 H, rot. B), 2.97 (d, 1 H, $^3J_{H,H}$ = 12.4 Hz, rot. B), 2.88 (m, 1 H, rot. B), 2.30 (br. s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 155.9 (s, 1 C), 143.7 (s, 2 C), 141.3 (s, 2 C), 137.6 (s, 1 C), 128.5 (d, 2 C), 127.8 (d, 5 C), 127.1 (d, 2 C), 124.8 (d, 2 C), 120.0 (d, 2 C), 103.2 (s, 1 C), 77.7 (d, 1 C, rot. A), 77.0 (d, 1 C, rot. B), 75.4 (d, 1 C, rot. A), 74.9 (d, 1 C, rot. B), 73.5 (t, 1 C), 70.1 (t, 1 C), 67.7 (t, 1 C), 66.0 (t, 1 C), 48.2 (t, 1 C, rot. A), 47.9 (t, 1 C, rot. B), 47.2 (d, 1 C), 46.5 (t, 1 C, rot. A), 46.1 (t, 1 C, rot. B) ppm. MS: *m*/*z* (%) = 487 (3) [M^+], 57 (100). IR ($CHCl_3$): $\tilde{\nu}$ = 2928, 2871, 2248, 1792, 1702, 1451, 1227 cm^{-1}. $C_{29}H_{29}NO_6$ (487.5): calcd. C 71.44, H 6.00, N 2.87; found C 71.36, H 5.87, N 2.83.

(1*S*,5*R*,7*S*)-7-*exo*-(Benzyloxymethyl)-3-(fluoren-9-ylmethoxycarbonyl)-6,8-dioxa-3-azabicyclo[3.2.1]octane-5-carboxylic Acid (2): Compound **2** was obtained according to the same procedure as for **1** starting from **20** (67 mg, 0.137 mmol) and using a different workup: the crude product was dissolved in EtOAc (5 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (2 × 5 mL); the aqueous phase was then acidified to pH = 1 with HCl and extracted with EtOAc (3 × 5 mL). The organic phase was then dried with anhydrous Na_2SO_4, filtered and concentrated to give **2** (48 mg, 70%). An analytical sample was obtained by flash chromatography (EtOAc/petroleum ether, 2:5; R_f = 0.65) to give pure **2** as a pale yellow oil. $[\alpha]_D^{25}$ = +3.2 (*c* = 0.25, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$; 3:2 mixture of two rotamers): δ = 7.76 (m, 2 H), 7.59 (m, 2 H), 7.40–7.26 (m, 9 H), 4.60–4.47 (m, 1 H), 4.55 (s, 2 H), 4.44–4.23 (m, 2 H), 4.14–4.07 (m, 2 H), 4.01 (d, 1 H, $^3J_{H,H}$ = 13.2 Hz, rot. A), 3.66 (d, 1 H, $^3J_{H,H}$ = 13.9 Hz, rot. B), 3.52 (m, 2 H), 3.41 (m, 1 H), 3.28 (d, 1 H, $^3J_{H,H}$ = 12.4 Hz), 3.13 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 171.2 (s, 1 C), 156.0 (s, 1 C), 143.8 (s, 1 C), 141.3 (s, 1 C), 137.8 (s, 1 C), 128.4 (d, 2 C), 127.7 (d, 5 C), 127.1 (d, 2 C), 125.0 (d, 2 C), 120.0 (d, 2 C), 101.5 (s, 1 C, rot. A), 102.0 (s, 1 C, rot. B), 77.8 (d, 1 C), 75.5 (d, 1 C, rot. A), 75.0 (d, 1 C, rot. B), 73.5 (t, 1 C), 70.4 (d, 1 C, rot. A), 70.0 (d, 1 C, rot. B), 67.8 (t, 1 C, rot. A), 67.4 (t, 1 C, rot. B), 48.7 (t, 1 C, rot. A), 48.3 (t, 1 C, rot. B), 47.1 (d, 1 C), 46.3 (t, 1 C, rot. A), 46.0 (t, 1 C, rot. B) ppm. MS: *m*/*z* (%) = 501 (1) [M^+], 178 (100). IR ($CHCl_3$): $\tilde{\nu}$ = 3440, 2928, 2871, 2248, 10706, 1451 cm^{-1}. $C_{29}H_{27}NO_7$ (501.5): calcd. C 69.45, H 5.43, N 2.79; found C 69.32, H 5.37, N 2.48.

Benzyl({(4*S*,5*R*)-5-[(*tert*-butyldimethylsilyloxy)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl}methyl)amine (23): To a solution of **22** (1.23 g, 5.04 mmol), prepared as reported,[14a] in dry CH_2Cl_2 (4 mL) was added at 0°, under nitrogen, imidazole (300 mg, 4.54 mmol) and *tert*-butyldimethylsilyl chloride (660 mg, 4.54 mmol). The mixture was stirred at 0 °C for 1 h, and at room temperature for 1.5 h. The solvent was evaporated, and the crude product was dissolved in EtOAc (20 mL) and washed with 1 N HCl, a saturated solution of $NaHCO_3$ and brine. The organic phase was then dried with anhydrous Na_2SO_4, filtered, and concentrated to give a crude oil that was purified by flash column chromatography (EtOAc/petroleum ether, 1:1; R_f = 0.60), to afford **23** as a colourless oil (1.33 g, 72%). $[\alpha]_D^{25}$ = –3.2 (*c* = 1, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 7.31 (m, 5 H), 4.41–4.32 (m, 1 H), 4.18–4.08 (m, 1 H), 3.83 (s, 2 H), 3.65–3.60 (m, 2 H), 2.92–2.73 (m, 2 H), 2.17 (br. s, 1 H), 1.39 (s, 3 H), 1.34 (s, 3 H), 0.85 (s, 9 H), 0.03 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 139.7 (s, 1 C), 128.0 (d, 2 C), 127.8 (d, 2 C), 126.6 (d, 1 C), 107.8 (s, 1 C), 77.3 (d, 1 C), 76.9 (d, 1 C), 61.5 (t, 1 C), 54.0 (t, 1 C) 48.2 (d, 1 C), 27.9 (q, 1 C), 25.7 (q, 3 C), 25.3 (q, 1 C), 18.1 (s, 1 C), –5.5 (q, 2 C) ppm. MS: *m*/*z* (%) = 365 (6) [M^+],

350 (21), 274 (5), 120 (100), 106 (20), 91 (91). IR ($CDCl_3$): $\tilde{\nu}$ = 3318, 2930, 2857, 2247, 1462, 1372, 1095 cm^{-1}. $C_{20}H_{35}NO_3Si$ (365.6): calcd. C 65.71, H 9.65, N 3.83; found C 64.30, H 9.01, N 3.62.

({(4*S*,5*R*)-5-[(*tert*-butyldimethylsilyloxy)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl}methyl)amine (24): Compound **24** was obtained according to the same procedure as for **7**, starting from **23** (1.28 g, 3.49 mmol), to afford a colourless oil (847 mg, 88%), sufficiently pure for the next step. $[\alpha]_D^{20}$ = –2.2 (*c* = 0.25, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 4.17–4.12 (m, 2 H), 3.67–3.60 (m, 2 H), 2.92–2.87 (m, 2 H), 1.44 (br. s, 2 H), 1.40 (s, 3 H), 1.34 (s, 3 H), 0.88 (s, 9 H), 0.06 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 107.7 (s, 1 C), 79.4 (d, 1 C), 77.0 (d, 1 C), 61.4 (t, 1 C), 41.3 (t, 1 C), 28.0 (q, 1 C), 25.8 (q, 3 C), 25.4 (q, 1 C), 18.1 (s, 1 C), –5.5 (q, 2 C) ppm. MS: *m*/*z* (%) = 275 (1)[M^+], 260 (5), 218 (16), 160 (18), 131 (38). IR ($CDCl_3$): $\tilde{\nu}$ = 3685, 2930, 2858, 2247, 1471, 1382, 1253, 1095 cm^{-1}. $C_{13}H_{29}NO_3Si$ (275.5): calcd. C 56.68, H 10.61, N 5.08; found C 56.52, H 10.45, N 4.91.

1-(Benzyloxy)-3-({[5-[(*tert*-butyldimethylsilyloxy)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl}methyl)amino}propan-2-ol (25): Compound **25** was obtained according toh the same procedure as for **10**, starting from **24** (827 mg, 3.02 mmol) and benzyl-glycidyl ether (446 μL, 2.93 mmol), to afford 1.29 g of a yellow oil, sufficiently pure for the next step. An analytical sample of compound **25** was obtained by flash chromatography (EtOAc/petroleum ether, 1:2; R_f = 0.1). ^1H NMR (200 MHz, $CDCl_3$; mixture of two diastereomers): δ = 7.32 (s, 5 H), 4.55 (s, 2 H), 4.31 (m, 1), 4.12 (m, 1 H), 3.88 (m, 1 H), 3.65–3.60 (m, 2 H), 3.50–3.46 (m, 2 H), 2.85–2.78 (m, 2 H), 2.74–2.63 (m, 2 H), 1.40 (s, 3 H), 1.33 (s, 3 H), 0.87 (s, 9 H), 0.05 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 138.5 (s, 1 C), 128.8 (d, 2 C), 128.1 (d, 3 C), 108.6 (s, 1 C), 77.4 (d, 1 C), 76.9 (d, 1 C), 74.0 (t, 1 C), 73.3 (t, 1 C), 69.1 (d, 1 C), 62.2 (t, 1 C), 52.9 (t, 1 C), 49.6 (t, 1 C), 28.7 (q, 1 C), 26.5 (q, 3 C), 26.1 (q, 1 C), 18.9 (s, 1 C), –4.7 (q, 2 C) ppm. MS: *m*/*z* (%) = 439 (1) [M^+], 424 (9), 382 (12), 348 (1), 324 (7), 318 (5), 288 (48), 194 (71), 91 (100). IR ($CDCl_3$): $\tilde{\nu}$ = 2930, 2858, 2247, 1471, 1257, 1097 cm^{-1}. $C_{23}H_{41}NO_5Si$ (439.7): calcd. C 62.83, H 9.40, N 3.19; found C 62.02, H 9.12, N 3.12.

(*R*/*S*)-3-(Benzyloxy)-1-[({(4*S*,5*R*)-5-[(*tert*-butyldimethylsilyloxy)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl}methyl)(fluoren-9-ylmethoxycarbonyl)amino]propan-2-ol (26): Compound **26** was obtained according to the same procedure as for **15**, starting from **25** (1.29 g, 2.93 mmol), to afford a colorless oil (967 mg, 50% over two steps) after purification by flash column chromatography (EtOAc/petroleum ether, 1:4; R_f = 0.29). ^1H NMR (200 MHz, $CDCl_3$; 1:1 mixture of two diastereomers): δ = 7.74 (m, 2 H), 7.57 (m, 2 H), 7.31 (m, 9 H), 4.65 (m, 1 H), 4.54 (m, 3 H), 4.24–4.00 (m, 3 H), 3.79–3.61 (m, 3 H), 3.49–3.43 (m, 3 H), 3.36–3.14 (m, 2 H), 3.08–2.93 (m, 1 H), 1.42 (s, 3 H, diast.A), 1.35 (s, 3 H, diast. B), 1.32 (s, 3 H, diast. A), 1.17 (s, 3 H, diast B), 0.88 (s, 9 H, diast A), 0.85 (s, 9 H, diast. B), 0.05 (s, 6 H, diast. A), 0.02 (s, 6 H, diast. B) ppm. ^{13}C NMR ($CDCl_3$): δ = 156.8 (s, 1 C), 143.9 (s, 2 C), 141.3 (s, 2 C), 138.1 (s, 1 C), 128.3 (d, 2 C), 127.7 (d, 5 C), 127.1 (d, 2 C), 124.7 (d, 2 C), 119.1 (d, 1 C), 108.4 (s, 1 C), 76.6 (d, 1 C), 76.1 (d, 1 C), 73.5 (t, 1 C, diast A), 73.4 (t, 1 C, diast B), 72.2 (t, 1 C), 70.3 (t, 1 C, diast A), 70.1 (t, 1 C, diast B), 67.0 (t, 1 C, diast A), 66.6 (t, 1 C, diast B), 61.6 (t, 1 C, diast A), 61.4 (t, 1 C, diast B), 54.5 (t, 1 C), 49.6 (t, 1 C, diast A), 49.0 (t, 1 C, diast B), 47.4 (d, 1 C), 27.8 (q, 1 C, diast A), 27.4 (q, 1 C, diast B), 26.0 (q, 3 C), 25.5 (q, 1 C, diast A), 25.3 (q, 1 C, diast B), 18.4 (s, 1 C), –5.2 (q, 2 C) ppm. MS: *m*/*z* (%) = 661 (1) [M^+], 604 (1), 546 (1), 408 (8), 178 (79), 91 (100). IR ($CDCl_3$): $\tilde{\nu}$ = 3442, 2930, 2858, 2247, 1694, 1451, 1251, 1103 cm^{-1}. $C_{38}H_{51}NO_7Si$ (661.9): calcd. C 68.95, H 7.77, N 2.12; found C 68.02, H 7.46, N 2.08.

3-(Benzyloxy)-1-[({(4*S*,5*R*)-5-[(*tert*-butyldimethylsilyloxy)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl}methyl)(fluoren-9-ylmethoxycarbonyl)amino]propan-2-one (27): Compound **27** was obtained according to the same procedure as for **17**, starting from **26** (950 mg, 1.44 mmol), to afford a colorless oil (654 mg, 64%) after purification by flash column chromatography (EtOAc/petroleum ether, 1:6; R_f = 0.38). $[\alpha]_D^{24}$ = –3.5 (*c* = 0.3, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$; 1:1 mixture of two rotamers): δ = 7.74 (m, 2 H), 7.64–7.49 (m, 2 H), 7.34 (m, 9 H), 4.58–4.40 (m, 4 H), 4.27–4.14 (m, 3 H), 4.10 (s, 2 H), 3.87 (s, 2 H), 3.87–3.80 (m, 1 H), 3.61–3.56 (m, 1 H), 3.47–3.41 (m, 1 H), 2.98–2.86 (m, 1 H), 1.35 (s, 3 H, rot A), 1.33 (s, 3 H, rot B), 1.24 (s, 3 H, rot A), 1.21 (s, 3 H, rot B), 0.88 (s, 9 H, rot A), 0.85 (s, 3 H, rot B), 0.05 (s, 6 H, rot A), 0.02 (s, 6 H, rot B) ppm. ^{13}C NMR ($CDCl_3$): δ = 203.2 (s, 1 C), 155.7 (s, 1 C), 143.6 (s, 2 C), 140.9 (s, 2 C), 136.8 (s, 1 C), 128.2 (d, 2 C), 127.4 (d, 5 C), 126.7 (d, 2 C), 124.4 (d, 2 C), 119.5 (d, 2 C), 108.0 (s, 1 C), 76.7 (d, 1 C), 76.4 (d, 1 C), 73.7 (t, 1 C, rot A), 73.2 (t, 1 C, rot B), 66.8 (t, 1 C), 61.3 (t, 1 C, rot A), 61.1 (t, 1 C, rot B), 55.3 (t, 1 C, rot A), 55.0 (t, 1 C, rot B), 48.2 (t, 1 C, rot A), 47.9 (t, 1 C, rot B), 47.0 (d, 1 C), 27.5 (q, 1 C), 25.6 (q, 3 C), 24.9 (q, 1 C), 20.6 (s, 1 C), –5.6 (q, 2 C) ppm. MS: *m*/*z* (%) = 659 (14) [M^+], 553 (3), 245 (12), 178 (21), 91 (37), 57 (100). IR ($CDCl_3$): $\tilde{\nu}$ = 2931, 2858, 2248, 1739, 1697, 1452, 1246, 1105 cm^{-1}. $C_{38}H_{49}NO_7Si$ (659.9): calcd. C 69.16, H 7.48, N 2.12; found C 68.77, H 7.31, N 2.16.

(1*S*,5*R*,7*R*)-5-(Benzyloxymethyl)-3-(fluoren-9-ylmethoxycarbonyl)-7-*endo*-(hydroxymethyl)-6,8-dioxa-3-azabicyclo[3.2.1]octane (28): Crude **28** was obtained according to the same procedure as for **1**, starting from **27** (300 mg, 0.455 mmol), to afford a pale yellow oil (210 mg, 94%) after purification by flash chromatography (EtOAc/petroleum ether, 1:4; R_f = 0.41). $[\alpha]_D^{25}$ = –2.8 (*c* = 0.70, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$; 1:1 mixture of two rotamers): δ = 7.86 (m, 2 H), 7.48 (m, 2 H), 7.31–7.21 (m, 9 H), 4.56–4.51 (m, 2 H), 4.40–4.26 (m, 3 H), 4.21–4.15 (m, 2 H), 3.91–3.87 (m, 1 H), 3.74 (s, 2 H), 3.58–3.52 (m, 1 H), 3.40–3.37 (m, 1 H), 3.19–3.13 (m, 1 H), 3.05–2.99 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 155.4 (s, 1 C), 143.7 (s, 2 C), 141.2 (s, 2 C), 137.4 (s, 1 C), 128.4 (d, 2 C), 127.7 (d, 5 C), 127.6 (d, 2 C), 124.8 (d, 2 C), 119.9 (d, 2 C), 114.0 (s, 1 C), 78.7 (d, 1 C), 76.4 (d, 1 C), 73.9 (t, 1 C), 71.5 (t, 1 C, rot A), 71.1 (t, 1 C, rot B), 67.8 (t, 1 C, rot A), 66.9 (t, 1 C, rot B), 61.2 (t, 1 C), 53.0 (d, 1 C), 48.7 (t, 1 C), 42.8 (d, 1 C) ppm. MS: *m*/*z* (%) = 487 (1) [M^+], 178 (100), 91 (67). IR ($CDCl_3$): $\tilde{\nu}$ = 3065, 2955, 2265, 1750, 1698, 1451, 1246 cm^{-1}. $C_{29}H_{29}NO_6$ (487.5): calcd. C 71.44, H 6.00, N 2.87; found C 70.45, H 5.61, N 2.70.

(1*S*,5*R*,7*S*)-5-(Benzyloxymethyl)-3-(fluoren-9-ylmethoxycarbonyl)-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-*endo*-carboxylic Acid (29): Compound **29** was obtained according to the same procedure as for **19**, starting from **28** (165 mg, 0.34 mmol), to afford a pale yellow oil (36 mg, 21%) after flash chromatography (EtOAc/petroleum ether, 2:7, TFA 0.1%; R_f = 0.1). $[\alpha]_D^{24}$ = –4.1 (*c* = 0.27, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$; 1:1 mixture of two rotamers): δ = 7.65 (m, 2 H), 7.46 (m, 2 H), 7.27 (m, 9 H), 6.21 (br. s, 1 H), 4.73–4.67 (m, 1 H), 4.57–4.45 (m, 3 H), 4.33 (m, 1 H), 4.12–4.02 (m, 3 H), 3.95–3.83 (m, 1 H), 3.64–3.58 (m, 2 H), 3.19–3.06 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 170.7 (s, 1 C), 155.9 (s, 1 C), 141.1 (s, 2 C), 137.1 (s, 2 C), 130.1 (s, 1 C), 128.4 (d, 2 C), 127.8 (d, 5 C), 127.6 (d, 2 C), 124.9 (d, 2 C), 119.9 (d, 2 C), 106.0 (s, 1 C), 76.7 (d, 1 C), 75.5 (d, 1 C), 73.9 (t, 1 C), 70.8 (t, 1 C), 68.3 (t, 1 C), 48.6 (t, 1 C), 47.0 (d, 1 C), 43.8 (t, 1 C) ppm. MS: *m*/*z* (%) = 501 (9) [M^+], 393 (3), 279 (20). IR ($CDCl_3$): $\tilde{\nu}$ = 3689, 2930, 2359, 1722, 1696, 1451, 1215 cm^{-1}. $C_{29}H_{27}NO_7$ (501.5): calcd. C 69.45, H 5.43, N 2.79; found C 68.74, H 5.48, N 2.50.

Ac-BGG-NHEt (32): HMBA-AM resin (100 mg, 0.08 mmol) was used as starting reagent. Coupling of **1** was performed using a threefold amino acid excess (91 mg, 0.24 mmol), a mixture of HOBt (54 mg, 0.40 mmol) and DIC (62 μL, 0.40 mmol) as coupling reagents, and catalytic DMAP (1 mg) as base, in DMF as solvent (2 mL), shaking the mixture for 12 h. Fmoc deprotection was performed twice with 30% piperidine in DMF for 10 min, followed by resin washing with DMF. After Fmoc deprotection, the resin-bound compound was treated with Ac_2O (76 μL, 0.8 mmol), and DMAP (1 mg) overnight. After resin washings with DMF and CH_2Cl_2, compound **32** was cleaved off the resin with a solution of 70% $EtNH_2$ in H_2O (1 mL) and THF (1 mL), and the mixture was stirred at room temperature for 12 h, then the solution was filtered and the solvents were evaporated. The resulting crude oil was purified by semi-preparative HPLC using 0–10% CH_3CN for 5 min, then 10–90% CH_3CN for 25 min as gradient (t_R = 13.9 min) to give a pure compound (14 mg, 70%) as a 3:1 mixture of two rotamers (white solid). ^1H NMR (400 MHz, $CDCl_3$; major rotamer): δ = 6.62 (br. s, 1 H), 4.75 (m, 1 H), 4.41 (d, 1 H, $^3J_{H,H}$ = 13.8 Hz), 4.04 (d, 1 H, $^3J_{H,H}$ = 10.1 Hz), 3.94 (m, 1 H), 3.84 (d, 1 H, $^3J_{H,H}$ = 13.0 Hz), 3.56 (d, 1 H, $^3J_{H,H}$ = 13.0 Hz), 3.38 (m, 2 H), 3.10 (d, 1 H, $^3J_{H,H}$ = 13.8 Hz), 2.75 (s, 3 H, rot. A), 1.11 (t, 3 H) ppm. ESI-MS: *m/z* = 229 [M^+ + H], 251 [M^+ + Na].

Ac-Phe-BGG-Leu-NH_2 (35): Rink-HMBA resin (200 mg, 0.13 mmol) was used as starting reagent. Fmoc deprotections were performed twice with 30% piperidine in DMF for 10 min, followed by resin washing with DMF. Coupling of leucine was performed using a fourfold Fmoc-amino acid excess (0.53 mmol), a mixture of HOBt (72 mg, 0.53 mmol) and DIC (83 μL, 0.53 mmol) as coupling reagents and DMAP (1 mg, 0.05 mmol) as base, in DMF (2 mL) as solvent, shaking the mixture for 12 h. After Fmoc deprotection, compound **1** was mounted on peptide resin using a twofold amino acid excess (99 mg, 0.26 mmol) and a mixture of HOBt (72 mg, 0.53 mmol) and DIC (83 μL, 0.53 mmol) in DMF (2 mL) for 16 h. After Fmoc deprotection, peptide bound to resin **33** was treated with an activating mixture containing HOBt (72 mg, 0.53 mmol), DIC (83 μL, 0.53 mmol) and Fmoc-Phe-OH (204 mg, 0.53 mmol) in DMF (2 mL), to obtain peptide **34**, that, after Fmoc deprotection, was treated with Ac_2O (145 μL, 1.32 mmol), and DMAP (1 mg, 0.01 mmol) overnight. After resin washing with DMF and CH_2Cl_2, the peptide was cleaved off the resin with a solution of 95% TFA/2.5% TIS/2.5% H_2O (2 mL, 1 × 5 min, 1 × 2 h) and then the solutions were filtered, combined and concentrated in vacuo to give crude peptide **35**. Semi-preparative HPLC using 0–10% CH_3CN for 5 min, then 10–90% CH_3CN for 25 min as gradient (t_R = 11.2 min) gave pure **35** (25 mg, 41%), as a white solid. ^1H NMR (400 MHz, [D_6]DMSO; mixture of two rotamers, 4:1; major rotamer): δ = 8.41 (d, 1 H, $^3J_{H,H}$ = 8.3 Hz), 7.89 (m, 1 H,), 7.48 (m, 1 H), 7.33 (m, 5 H), 7.17 (m, 1 H), 4.96 (m, 1 H), 4.86 (m, 1 H), 4.34 (m, 1 H), 4.17 (d, 1 H, $^3J_{H,H}$ = 13.7 Hz), 3.91 (d, 1 H, $^3J_{H,H}$ = 12.8 Hz), 3.70 (m, 1 H), 3.40 (m, 1 H), 3.01 (d, *J* = 12.8 Hz, 1 H), 2.98–2.77 (m, 2 H), 2.89 (d, 1 H, $^3J_{H,H}$ = 14 Hz), 1.83 (s, 3 H), 1.62–1.43 (m, 3 H), 0.93 (m, 6 H) ppm. ESI-MS: *m/z* = 461 [M^+ + H], 483 [M^+ + Na].

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