Divergent, stereoselective access to heterocyclic α,α-quaternary- and β\textsuperscript{2,3,3}-amino acid derivatives from a N-Pmp-protected Orn-derived β-lactam‡‡

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A suitably protected Orn-derived (35,4S)-β-lactam was used as common intermediate in the synthesis of conformationally constrained (35,4S)-2-oxoazepane α,α- and (25,3S)-2-oxopiperidine-β\textsuperscript{2,3,3},-amino acid derivatives. Compared to alternative procedures using an N-\textit{p}-methoxybenzyl group at the 2-azetidinone, the incorporation of a β-\textit{p}-methoxyphenyl moiety is crucial for the excellent stereochemical outcomes in the preparation of these heterocyclic amino acids. Chemoselective 7- or 6-exo-trig cyclization was achieved through alternative sequences of Pmp-deprotection/Boc-activation, followed by inter- and intramolecular β-lactam ring opening, respectively.

Introduction

In the design of peptidomimetics the incorporation of conformational constraints into bioactive peptides is a fundamental strategy to obtain information about their active conformation when interacting with therapeutic targets.\textsuperscript{1–3} Either global or local restrictions of the conformational space can be used to rigidify peptide-like molecules. Among the latter, the insertion of α,α-disubstituted amino acids has served to stabilize both β-turn and α-helix-type conformations, depending on the length of the peptide derivative and on the α-substituents.\textsuperscript{4}

While acyclic and different size carbocyclic α,α-quaternary α-amino acids have been thoroughly studied, only a few examples of heterocyclic derivatives have been described.\textsuperscript{5–8}

In the case of \textit{N}-containing heterocycles, the heteroatom could not only serve to interact with the environment, contributing to increase the solubility of the final peptide, but also as an anchoring point for substituents that could mimic important side-chains.\textsuperscript{9}

Although less studied, β-peptides, oligomers of β-amino acids, or mixed α,β-peptides can also adopt specific conformations, depending on the backbone carbon substituted (β\textsuperscript{2}, β\textsuperscript{3}, β\textsuperscript{2,2}, β\textsuperscript{2,3}, β\textsuperscript{3,2}, β\textsuperscript{3,3}) and on the relative configuration of the substituents.\textsuperscript{10–12} Again, only a few examples of β\textsuperscript{2,2}, or β\textsuperscript{3,3}-substituted amino acids bearing heterocyclic rings at 2 or 3 positions have been described in the literature.\textsuperscript{13–15} Among them, we can highlight some pyrrolidine and piperidine derivatives that constitute the central core of selective inhibitors of tumor necrosis factor-α.\textsuperscript{13,14}

The possibility that subtle changes in the structure of these α,α- and β-amino acids could result in different stabilization of peptide conformations has prompted a continuous interest in these restricted non-proteinogenic amino acids.\textsuperscript{16–23} Within this context, previous work in our group has led to the preparation of novel 2-oxoazepane (X = CO) and azepane (X = CH\textsubscript{3}) quaternary amino acid derivatives 2 that induce the adoption of β-turn conformations when incorporated into dipeptide derivatives.\textsuperscript{24,25} When amino acids 2 (X = CH\textsubscript{3}) were integrated in tripeptides, at any of the possible positions, we observed the preferential adoption of 3\textsubscript{10} helical structures, both in solution and in the solid state.\textsuperscript{25}

Compounds 2 (X = CO) were prepared in a simple and effective manner from enantiopure, Orn-derived \textit{N}-\textit{p}-methoxybenzyl-β-lactams 1, although partial epimerization at C3 (∼20%) was observed (Chart 1).\textsuperscript{24} Recently, we have also...
reported that both the acid or basic hydrolysis of the 4-carboxylic ester moiety in compounds 2 (X = CO) resulted in a fast and complete rearrangement to \( \beta \)2,3,4-amino acids 3, containing a piperidin-2-one ring at position 3.26

The epimerization at C3 in the Orn-derived \( \beta \)-lactams, occurring during the removal of the \( p \)-methoxybenzyl group (Pmb) from 1,24 decreased the stereochemical outcome of the whole 1→2→3 transformation process. To overcome the indicated limitations, we decided to search for alternative methods for the enantioselective preparation of these amino acids. We disclose herein highly stereoselective, divergent procedures, for the synthesis of these types of heterocycle-containing amino acids starting from a common \( \beta \)-lactam intermediate.

Results and discussion

Since the loss of stereochemical integrity occurred during formation of the \( N \)-unsubstituted azetidinone, because of the strong conditions used for the \( N \)-Pmb group removal (oxidation with \( K_2S_2O_8 \)), an easily detachable moiety at N1 is desirable. Among the described methods for the temporal protection of \( \beta \)-lactam-NH, some electron-rich phenyl moieties are within the most profusely exploited.27-29 These moieties, exemplified by the \( N-P \)-methoxyphenyl group (Pmp), can easily be removed by ceric ammonium nitrate (CAN) under relatively mild conditions.30-32 In addition, this oxidative cleavage is highly compatible with a large number of functional groups, making this protection/deprotection procedure a good option for our purposes.

Thus, the first step of the new synthetic sequence involved the attachment of the Pmp group into the suitable ornithine derivative 4 (Scheme 1). Although there are numerous reports on \( N \)-arylation reactions, using different palladium, copper and nickel based catalysts, most of them require high temperatures and strong bases.33,34 This could result in partial racemization in the case of amino acid derivatives. Therefore, to avoid this issue, we have applied a described method that requires copper(II) acetate and boronic acids, and proceeds under mild temperature conditions and weak bases.35 Compound 5 was obtained in moderate yield (47%) using these conditions. Then, the reaction with (2S)-chloropropionic acid, through the in situ generated acyl chloride, afforded acyl derivative 6. Upon cyclization with the phosphazene base tert-butylimino-tri(pyrrolidino)phosphorane (BTPP), compound 6 afforded the key \( \beta \)-lactam intermediate (35,4S)-7 in a totally stereoselective manner. As previously demonstrated for related analogues, the stereochemical course of the reaction is exclusively directed by the configuration of the 2-chloropropionyl moiety.36

Contrary to that observed for \( N \)-Pmb-N-2-chloropropionyl derivatives, no rotamers about the amide bond were found for compound 6 (only one pattern of signals in NMR spectra). The existing rotamer was assigned as \( Z \) by NOE experiments, since saturation of the H2 proton enhanced the intensity of protons at the ortho-position of the \( p \)-methoxyphenyl moiety (1.2%). This is in agreement with previous studies on \( N \)-methylacetanilides, in which the CO group and the phenyl ring are situated on opposite sides of the amide bond.37 This seems due to the steric hindrance between the two methyl groups present in the \( N \)-methylacetanilides and the electron repulsion between the CO lone pairs and the phenyl \( \pi \) electrons.37

As expected, removal of the \( p \)-methoxyphenyl group with CAN yielded the \( N \)-unprotected \( \beta \)-lactam 8 in excellent yield (87%), without appreciable signs of epimerization at position 3. Subsequently, to activate the \( \beta \)-lactam ring toward nucleophilic attacks, the reaction of 8 with di-\( t \)-butyl dicarbonate afforded the corresponding \( N \)-Boc-2-oxazetidine 9 (94%). Finally, removal of the Z protecting group promotes the intramolecular opening of the \( \beta \)-lactam ring by the free amino group of the side-chain, leading to the desired 2-oxazepane derivative 10 in high yield (90%). As expected by the stereochemistry of the starting \( \beta \)-lactam (3S,4S),24 only the 7-exo-trig-type cyclization to the 2-oxazepane was observed (Scheme 2).
The synthesis of compound 10 from 2-azetidinone 7 proceeded with high efficacy and total stereoselectivity. The overall yield for the three steps was 73%, much higher than that obtained when the corresponding N-Pmb-β-lactam was used as the starting material (47%). More importantly, the previously observed C3 epimerization was totally avoided by application of this new procedure.

The intermolecular nucleophilic ring opening of N-Boc-β-lactams has also been successfully applied to the synthesis of β-amino acids, β-amino-α-hydroxy acid and β,β-disubstituted-β-amino acid derived peptides. Based on these precedents, we envisaged a route for the preparation of conformationally restricted 2-piperidinone-containing β-amino acid derivatives, using again β-lactam 7 as the key precursor. Thus, removal of the Z protecting group from 7 by catalytic hydrogenation promoted the formation of the 3.5-spiro derivative 11 in good yield (84%), through a 6-exo-trig ring closure (Scheme 3).

To allow the selective manipulation of the CONH group of the β-lactam ring in an ulterior step, compound 11 was reacted with benzyl bromide to provide the 1-benzyl derivative 12 in almost quantitative yield. Treatment of compound 12 with CAN led to the removal of the p-methoxyphenyl group, yielding the N-deprotected spiro-β-lactam 13 (90%). As above, no epimerization at carbon 3 was observed, in contrast to what happened in the removal of the p-methoxybenzyl group from a related spiro-lactam. Finally, the synthetic sequence was completed by activation of position 1 with di-tert-butyl dicarbonate and subsequent intermolecular opening of the β-lactam ring by treatment with DBU/MeOH. The desired 2-oxopiperidino-β-amino ester 14 was obtained in excellent yield from 13 in this last one-pot, two-step procedure (97%). The notable overall yield (72%) for this 7→14 transformation was clearly superior to that obtained in the alternative method described by us, based on the use of the N-Pmb protecting group (15%). Again, in addition to the better yield, the main attractiveness of this approach is that the 3S,4S configuration in 7 is fully preserved along the synthetic sequence and transferred to the (2S,3S) β-amino ester 14.

As shown in Scheme 4, compound 14 can also be prepared in three steps from the 2-oxazepam derivative 10, involving N-benzylam, basic ester hydrolysis with concomitant rearrangement, and re-esterification in the presence of trimethylsilyl diazomethane. When we compare the two routes to 14 from 7, the sequence through the spiro-β-lactam 11 was shorter and more efficient than those involving 2-oxazepane derivatives as key intermediates.

**Conclusions**

In conclusion, the rapid and efficient construction of conformationally constrained (3S,4S)-2-oxazepam α,α-amino acids and 2-piperidinone-derived (2S,3S)β2,3,3-amino acids can be achieved through the chemoselective manipulation of the enantiopure Orn-derived β-lactam 7. The divergent, highly stereocontrolled processes rely essentially on the use of the easily removable Pmp protecting group, and on inter- and intramolecular β-lactam ring openings. Since different β-lactam derivatives can readily be synthesized, either with (3R,4R)-configuration or bearing other substituents at C-3, the preparation of diverse analogues of the α- and β-amino acids described here can easily be envisaged. Improvements in the incorporation of the Pmp group into the starting Orn derivative could result in higher total yield, and therefore, in better routes towards these conformationally restricted α- and β-amino acids.

**Experimental section**

**General experimental details**

All reagents were of commercial quality. Solvents were dried and purified by standard methods. 1H NMR spectra were
recording on a 300 MHz instrument and $^{13}$C NMR spectra were registered at 75 MHz. Analytical TLC was performed on aluminium sheets with a 0.2 mm layer of silica gel F254. Silica gel 60 (230–400 mesh) was used for column chromatography. Analytical HPLC was performed on a Eclipse Plus C18 (4.6 × 150 mm, 5 μm) column, with a flow rate of 1.5 mL min$^{-1}$, using a tuneable UV detector set at 220 nm. Mixtures of CH$_2$CN (solvent A) and 0.05% TFA in H$_2$O (solvent B) were used in the mobile phase. Electrospray mass spectra were recorded in the positive mode.

$N$-p-Methoxyphenyl-Orn(Z)-OMe (5). A mixture of $p$-methoxyphenylboronic acid (1.545 g, 10.77 mmol), and 4 Å molecular sieves (~0.800 g) in dry dichloromethane (120 mL), was successively treated with triethylamine (2.126 mL, 15.26 mmol), H-L-Orn(Z)-OMe·HCl (1.612 g, 5.09 mmol) and Cu(OAc)$_2$ (1.017 g, 5.60 mmol). The reaction was allowed to stir gently under argon atmosphere, and stirred at rt for 48 h. After evaporation of the solvent, the residue was partitioned between EtOAc and H$_2$O, and the phases were separated. The organic layer was dried over Na$_2$SO$_4$ and evaporated. The residue was purified on a silica gel column using EtOAc–hexane (2 : 1), affording compound (0.22 mmol) in 44% yield. $^{1}$H-NMR (300 MHz, CDCl$_3$): δ 1.65 (m, 2H, γ-H), 1.83 (m, 2H, β-H), 3.24 (m, 2H, δ-H), 3.69 (s, 3H, OCH$_3$), 3.76 (d, 2H, J = 8.9, 3-H and 5-H, Pmp), 6.76 (d, 2H, J = 8.9, 2-H and 6-H, Pmp), 7.35 (m, 5H, CH, Ph, Z). $^{13}$C-NMR (75 MHz, CDCl$_3$): δ 26.5 (γ-C), 30.5 (β-C), 40.8 (δ-C), 52.3 (OCH$_3$), 55.8 (p-OCH$_3$-Pmp), 57.7 (α-C), 66.8 (CH$_2$, Z), 115.1 (3-CH and 5-CH, Pmp), 115.4 (2-CH and 6-CH, Pmp), 128.2, 128.3 and 128.7 (CH, Ph, Z), 136.7 (1-C, Ph, Z), 140.9 (1-C, Pmp), 153.0 (4-C, Pmp), 156.5 (CO, Z), 174.8 (COO). (ESI) m/z = 387.0 [M + H]$^+$, 409.0 [M + Na]$^-$. Elemental analysis calcd (%) for C$_{21}$H$_{26}$N$_2$O$_5$: C 65.27, H 6.21, N 6.03.

$N$-[(S)-2-Chloropropionyl]-N-p-methoxyphenyl-$\epsilon$-Orn(Z)-OMe (6). PPh$_3$ (1.201 g, 4.58 mmol) was added to a solution of (S)-2-chloropropionic acid (0.299 mL, 3.44 mmol) and Cl$_2$CCN (0.459 mL, 4.38 mmol) in THF (10 mL) at 0 °C, and the reaction was stirred at rt for 30 min. Then, a solution of N-Pmp-$\epsilon$-Orn(Z)-OMe (0.884 g, 2.29 mmol) and propylene oxide (2.40 mL, 34.35 mmol) in THF (2 mL) was added dropwise to the reaction mixture. After stirring for 48 h at rt, the solvent was evaporated under vacuum and the residue was dissolved in cold Et$_2$O and filtered over Celite. The filtrate was concentrated under vacuum and purified by column chromatography on silica gel using EtOAc–hexane (1 : 2) as eluent, yielding 6 (0.480 g, 44%) as a syrup. $[\delta]_{D}^{20}$ = +24.1 (c 1.5, CHCl$_3$). HPLC $t_{R}$ = 16.54 min (gradient A/B from 5 : 95 to 80 : 20 over 20 min). $^{1}$H-NMR (300 MHz, CDCl$_3$): δ 1.55 (d, 3H, J = 6.7, 3-H), 1.59 (m, 2H, γ-H), 1.62 (m, 1H, β-H), 1.85 (m, 1H, β-H), 3.15 (m, 2H, δ-H), 3.74 (s, 3H, OCH$_3$), 3.82 (s, 3H, p-OCH$_3$-Pmp), 4.20 (q, 1H, J = 6.7, 2-H), 4.76 (t, 1H, J = 6.1, δ-H), 4.95 (m, 1H, α-H), 5.07 (s, 2H, CH$_2$, Z), 6.91 (d, 2H, J = 8.0, 3-H and 5-H, Pmp), 7.29 (d, 2H, J = 8.0, 2-H and 6-H, Pmp), 7.35 (s, 5H, CH, Ph, Z). $^{13}$C-NMR (75 MHz, CDCl$_3$): δ 21.2 (3-C), 26.6 (β-C), 27.1 (γ-C), 40.7 (δ-C), 50.3 (2-C), 52.5 (OCH$_3$), 55.6 (p-OCH$_3$-Pmp), 60.0 (α-C), 66.8 (CH$_2$, Z), 114.7 (3-CH and 5-CH, Pmp), 115.1 (2-CH and 6-CH, Pmp), 128.2, 128.7 and 130.1 (CH, Ph, Z), 131.1 (1-C, Pmp), 136.7 (1-C, Ph, Z), 156.5 (CO, Z), 160.0 (4-C, Pmp), 170.7 and 171.4 (CO). (ESI) $m/z$ = 477.0 [M + H]$^+$. Elemental analysis calcd (%) for C$_{24}$H$_{28}$N$_2$O$_6$: C 60.09, H 6.21, N 6.03. $^{13}$C-NMR (75 MHz, CDCl$_3$): δ 10.8 (3-CH$_2$), 25.8 (2-C$^-$), 34.2 (1-C$^-$), 40.7 (3-C$^-$), 52.6 (OCH$_3$), 55.6 (3-C$^-$), 64.1 (4-C$^-$), 71.0 (2-C$^-$), 76.5 (3-C$^-$), 79.3 (2-C$^-$), 120.7 (4-C$^-$), 156.4 (3-C, Pmp), 156.8 (CO, Z). (ESI) $m/z$ = 412.2 [M$^+$]$.^+$, 463.0 [M + Na]$^-$. Elemental analysis calcd (%) for C$_{25}$H$_{28}$N$_2$O$_6$: C 65.44, H 6.41, N 6.36. Found (%): C 65.19, H 6.22, N 6.28.

**General procedure for the removal of the p-methoxyphenyl group**

To a solution of the corresponding p-methoxyphenyl-substituted compound (0.22 mmol) in CH$_2$CN (2 mL) was added slowly a solution of CAN (0.106 g, 0.19 mmol) in H$_2$O (2 mL) at 0 °C. The addition of the CAN solution in H$_2$O was repeated twice, waiting 10 min between each addition. After stirring at 0 °C for another 10 min, the solvent was evaporated and the aqueous phase was extracted with EtOAc. The combined organic layer was washed with NaHCO$_3$ (10%), H$_2$O and brine, dried over Na$_2$SO$_4$ and evaporated. The resulting residue was purified on a silica gel column, using the appropriate solvent system.
3.26 (m, 2H, 7-H), 4.28 (d, 1H, 4-NH), 6.07 (s, 1H, 1-H), 7.29 (m, 5H, CH, Bn). 13C-NMR (75 MHz, CDCl3): δ 10.9 (3-CH3), 21.0 (8-C), 33.9 (9-C), 47.2 (7-C), 50.7 (6-CH2), 57.7 (3-C), 60.2 (4-C), 72.8, 128.5, 128.8 and 136.9 (1-C and CH, Bn), 168.4 and 170.3 (CO). [ESI] m/z = 259.1 (M + H)+, 359.3 (2M + Na)+. Elemental analysis calculated (%) for C17H22N2O5: C 61.07, H 6.63, N 8.38. Found (%): C 61.28, H 8.18, N 9.11.

(3AS,4S)-4-(1-Benzoxycarbonyl)aminopropyl-1,6-diaza-spiro[3.5]nonane-2,5-dione (13). A solution of the 1-NH oxoazetidine 8 (0.050 g, 0.15 mmol) in dry CH2Cl2 (4 mL) was successively treated with TEA (0.021 mL, 0.15 mmol), DMAP (0.002 g, 0.015 mmol) and di-tert-butyl dicarbonate (0.033 g, 0.15 mmol), and stirred for 3 h. Then, the solution was evaporated to dryness and the residue was purified on a silica gel column using EtOAc–hexane (1:1) as eluent, yielding 9 (0.061 g, 94%) as a syrup. [α]D 25 = −19.4 (c 1.3, CHCl3). HPLC tR = 15.59 min (gradient A/B from 5:95 to 80:20 over 20 min). 1H-NMR (300 MHz, CDCl3): δ 1.16 (d, 3H, J = 7.5, 3-CH3), 1.49 (s, 9H, CH3, Boc), 1.55 (m, 1H, 1-2H), 1.78 (m, 1H, 2-2H), 2.14 (m, 2H, 1-2H), 3.21 (q partially overlapped, 1H, J = 7.5, 3-H), 3.23 (m, 2H, 3-H), 3.78 (s, 3H, OCH3), 4.85 (s, 1H, 3-2NH), 5.09 (s, 9H, CH3, Boc), 7.35 (s, 5H, CH, Ph, Z). 13C-NMR (75 MHz, CDCl3): δ 9.4 (3-CH3), 24.6 (2-C), 28.1 (CH1, Boc), 30.4 (1-C), 41.0 (3-C), 52.3 (3-C), 52.6 (OCH3), 66.6 (4-C), 66.9 (CH2, Z), 83.9 (C, Boc), 128.3, 128.3 and 128.7 (CH, Ph, Z), 136.6 (1-C, Ph, Z), 147.6 (CO, Boc), 156.5 (CO, Z), 166.5 (2-CO), 170.3 (COO). [ESI] m/z = 457.2 (M + Na)+. Elemental analysis calculated (%) for C28H34N2O5: C 62.80, H 6.96, N 6.45. Found (%): C 62.70, H 6.77, N 6.32.

(3AS,4S)-4-(1-Benzoxycarbonyl)aminopropyl-1,6-diaza-spiro[3.5]nonane-2,5-dione (14). A solution of 13 (0.030 g, 0.12 mmol) in dry CH2Cl2 (5 mL) was treated with triethylamine (0.016 mL, 0.116 mmol), DMAP (0.021 mL, 0.15 mmol), DMAP (0.002 g, 0.015 mmol) and di-tert-butyl dicarbonate (0.033 g, 0.15 mmol), and stirred for 3 h. Then, the solution was evaporated to dryness and the residue was purified on a silica gel column using EtOAc–hexane (1:1) as eluent, yielding 12 (0.025 g, 98%) as a syrup. [α]D 25 = −50.0 (c 0.5, CHCl3). HPLC tR = 15.59 min (gradient A/B from 5:95 to 80:20 over 20 min). 1H-NMR (300 MHz, CDCl3): δ 1.37 (d, 3H, J = 7.4, 3-CH3), 1.89 (m, 1H, 2-2H), 2.04 (m, 1H, 1-2H), 2.51 (td, 1H, J = 13.0 and 3.9, 9-H), 3.13 (q, 1H, J = 7.4, 3-H), 3.78 (s, 1H, p-OCH3), 4.51 (d, 1H, J = 14.3, 6-CH2), 4.84 (d, 1H, J = 14.3, 6-CH2), 6.83 (d, 2H, J = 9.1, 3-H and 5-H, Pmp), 7.24 (d, 2H, J = 9.1, 2-2H and 6-H, Pmp), 7.33 (m, 5H, CH, Bn). 13C-NMR (75 MHz, CDCl3): δ 10.4 (3-CH3), 20.7 (8-C), 31.3 (9-C), 47.3 (7-C), 50.9 (6-CH2), 55.7 (OCH2), 75.2 (3-C), 64.7 (4-C), 114.5 (3-CH and 5-CH), 120.2 (2-CH and 6-CH, Pmp), 127.9, 128.8 and 128.9 (CH, Bn), 130.2 (1-C, Pmp), 137.1 (1-C, Bn), 156.4 (4-C, Pmp), 166.4 and 167.0 (CO). [ESI] m/z = 365.1 (M + H)+, 387.1 (M + Na)+. Elemental analysis calculated (%) for C28H34N2O5: C 72.50, H 6.70, N 7.48. Found (%): C 72.58, H 6.70, N 7.48.

Methyl (25S,3S)-3-tert-butoxycarbonylamino-2-methyl-3-(1-benzyl-2'-oxopiperidin-3'-yl)propanoate (15). A solution of compound 13 (0.030 g, 0.12 mmol) in dry CH2Cl2 (5 mL) was treated with triethylamine (0.016 mL, 0.116 mmol), DMAP (0.021 mL, 0.15 mmol), DMAP (0.002 g, 0.015 mmol) and di-tert-butyl dicarbonate (0.033 g, 0.15 mmol), and stirred for 3 h. Then, the solution was evaporated to dryness and the residue was purified on a silica gel column using EtOAc–hexane (1:1) as eluent, yielding 12 (0.025 g, 98%) as a syrup. [α]D 25 = −50.0 (c 0.5, CHCl3). HPLC tR = 15.59 min (gradient A/B from 5:95 to 80:20 over 20 min). 1H-NMR (300 MHz, CDCl3): δ 1.37 (d, 3H, J = 7.4, 3-CH3), 1.89 (m, 1H, 2-2H), 2.04 (m, 1H, 1-2H), 2.51 (td, 1H, J = 13.0 and 3.9, 9-H), 3.13 (q, 1H, J = 7.4, 3-H), 3.78 (s, 1H, p-OCH3), 4.51 (d, 1H, J = 14.3, 6-CH2), 4.84 (d, 1H, J = 14.3, 6-CH2), 6.83 (d, 2H, J = 9.1, 3-H and 5-H, Pmp), 7.24 (d, 2H, J = 9.1, 2-2H and 6-H, Pmp), 7.33 (m, 5H, CH, Bn). 13C-NMR (75 MHz, CDCl3): δ 10.4 (3-CH3), 20.7 (8-C), 31.3 (9-C), 47.3 (7-C), 50.9 (6-CH2), 55.7 (OCH2), 75.2 (3-C), 64.7 (4-C), 114.5 (3-CH and 5-CH), 120.2 (2-CH and 6-CH, Pmp), 127.9, 128.8 and 128.9 (CH, Bn), 130.2 (1-C, Pmp), 137.1 (1-C, Bn), 156.4 (4-C, Pmp), 166.4 and 167.0 (CO). [ESI] m/z = 365.1 (M + H)+, 387.1 (M + Na)+. Elemental analysis calculated (%) for C28H34N2O5: C 72.50, H 6.70, N 7.48. Found (%): C 72.58, H 6.70, N 7.48.
(0.002 g, 0.01 mmol) and Boc₂O (0.028 g, 0.13 mmol). After stirring at rt for 4 h, the solvent was removed under vacuum and the residue was dissolved in MeOH (3 ml). DBU (0.017 ml, 0.12 mmol) was added and the solution was stirred 1 h at rt. After evaporation of the solvent, the residue was purified on a silica gel column using EtOAc–hexane (1 : 3) as eluent to yield 14 (0.044 g, 97%) as a syrup. [α]D sp = +20.1 (c 1.1, CHCl₃). HPLC tR = 16.52 min (gradient A/B from 5 : 95 to 80 : 20 over 20 min). 1H-NMR (300 MHz, CDCl₃): δ 1.27 (d, 3H, J = 7.3, 2-CH₃), 1.87 (s, 9H, CH₃, Boc), 3.15 (q, 1H, J = 7.3, 2-H), 3.24 (m, 2H, 6'-H), 4.36 (s, 9H, OCH₃), 4.41 (d, 1H, J = 14.7, 1'-CH₃), 4.71 (d, 1H, J = 14.7, 1'-CH₂), 7.24-7.30 (m, 5H, CH, Bn). 13C-NMR (75 MHz, CDCl₃): δ 12.4 (2-CH₃), 19.7 (5'-C), 28.5 (CH₃, Boc), 52.1 (OCH₃), 60.0 (3-C), 79.6 (C, Boc), 127.5, 128.3, 128.7 and 137.2 (1-C and CH, Bn), 154.8 (CO, Boc), 169.8 (2'-CO), 174.2 (1'-CO). MS (ESI) m/z = 413.3 (M + Na)+, 803.5 (2M + Na)+. Elemental analysis calcd (%) for C₂₁H₃₀N₂O₅: C 64.59, H 7.17, N 7.17. Found (%): C 64.48, H 7.65, N 7.20.

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Notes and references


