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New enantiopure 7-azanorbornane β-substituted prolines by S_N2 displacements at the Cγ of the side chain

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Abstract—Continuing our work on building new β-substituted prolines in enantiomerically pure form as new surrogates to be incorporated into model peptides, we describe functional group conversions and carbon–carbon bond forming reactions by S_N2 displacements at the γ-position of the α-amino acid side chain of an azanorbornane derivative. This work extends efforts on the elaboration of the side arm at carbon C2 of the 7-azabicyclo[2.2.1]heptane core.

1. Introduction

Several β-substituted prolines have been synthesised to serve as amino acid chimeras, in which the functional groups of the amino acid side chain are combined with the conformational restrictions characteristic of the cyclic amino acid residue.[1] Replacement of the natural amino acids in peptides for such proline–α-amino acid chimeras has led to a better understanding of the bioactive conformations.[2–10] Additionally, β-alkylproline analogues have served for the development of enzyme inhibitors,[11,12] as well as peptidomimetics exhibiting improved bioactivity and greater metabolic stability.[5,12]

We are currently involved in a research project devoted to determining the conformational preferences of constrained analogues of proteinogenic amino acids when incorporated into a peptide chain. In this context, we have evaluated the relative stability of the βI- and βII-turn conformations in model peptides RCO-L-Pro-L-Phe-NHR′, in which phenylalanine has been replaced by different constrained derivatives.[13–15] Recently, we reported the first results on the structural consequences arising from the replacement of the proline residue in this sequence by an analogue of azanorbornane structure (Fig. 1).[16]

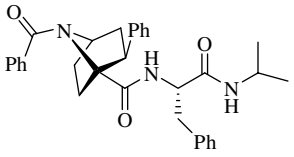

Figure 1. Structure of (1*S*,2*S*,4*R*)-*N*-benzoyl-2-phenyl-7-azabicyclo[2.2.1]heptane-1-carbonyl-(*S*)-*N*′-isopropylphenylalaninamide.

In this proline surrogate, the flexibility of the pyrrolidine ring was frozen by linking the α- and δ-carbons through an ethylene bridge, and an additional phenyl substituent, which can interact with the backbone both sterically and electronically, incorporated at the β-position. This result provides evidence that the bicyclic proline system exhibits a higher propensity for βI-folding than proline itself. Several factors contribute to the stabilisation of the type I β-turn observed in the crystalline structure of (1*S*,2*S*,4*R*)-*N*-benzoyl-2-phenyl-7-azabicyclo[2.2.1]-heptane-1-carbonyl-(*S*)-*N*′-isopropylphenylalaninamide (Fig. 1).[16]

Promising results in this area have focussed our interest on the synthesis of new 7-azanorbornane proline–α-amino acid chimeras as a source of surrogates for the study of structural peculiarities induced by their introduction in model peptides.

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2. Results and discussion

After optimisation of the procedure for the synthesis of the key intermediate methyl (1*S*,2*R*,4*R*)-*N*-benzoyl-2-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-7-azabicyclo[2.2.1]-heptane-1-carboxylate **2**,[17–19] we were able to scale up the process and proceed to undertake the preparation of this enantiomerically pure product on a 40 gram scale. This process involved seven stereocontrolled steps and gave an overall yield of 30% from a 95:5 mixture of the two geometric isomers (*Z*/*E*) of the chiral oxazolone **1**. From intermediate **2**, the transformation of the 1,3-dioxolane ring into a formyl group was easily achieved with aldehyde **3** being obtained in 88% yield by using periodic acid according to the procedure described in the literature (Scheme 1).[18] Subsequent reduction of aldehyde (1*S*,2*R*,4*R*)-**3** was simply carried out by treatment with $NaBH_4$ in a methanol/water mixture and provided the primary alcohol (1*S*,2*R*,4*R*)-**4** (Scheme 1) in almost quantitative yield (97%).

In order to explore the versatility of the S_N2 reaction at the γ-position, the transformation of the hydroxyl group into a good leaving group was initially tested and then the displacement by different nucleophiles attempted on the most suitable derivatives.

2.1. Introduction of leaving groups at the Cγ of the α-amino acid side chain

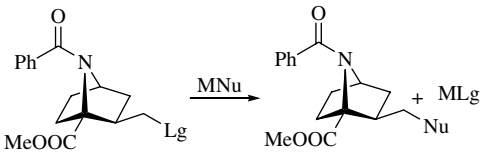
Treatment of alcohol (1*S*,2*R*,4*R*)-**4** with PCl_5/chloroform or $SOCl_2$/pyridine was tried, but chloride **5** could not be obtained under any of these reaction conditions. However, the use of triphenylphosphine and dry carbon tetrachloride as the halide source gave **5** in 96% yield (Scheme 1).

The introduction of bromide as a leaving group was achieved by treatment of (1*S*,2*R*,4*R*)-**4** with *N*-bromosuccinimide, which provided bromo derivative **6** in 85% yield. A higher efficiency was obtained by treatment of the alcohol with CBr_4 and triphenylphosphine (Scheme 1), which gave compound **6** in very good yield (92%).

Tosylate **7** was synthesised by treatment of the alcohol with tosyl chloride and triethylamine in dichloromethane and, in this way, derivative **7** (Scheme 1) was isolated in low yield (44%). A similar procedure, using mesyl chloride instead of tosyl chloride, readily led to isolated mesylate **8** (Scheme 1) in excellent yield (98%).

2.2. Functionalisation and carbon–carbon bond formation reactions at the Cγ of the α-amino acid side chain: study of S_N2 displacements

Given the ready availability of mesylate **8** and its generally good behaviour as a leaving group, we initially focussed our attention on a detailed study into S_N2 displacements of this compound (Scheme 2).

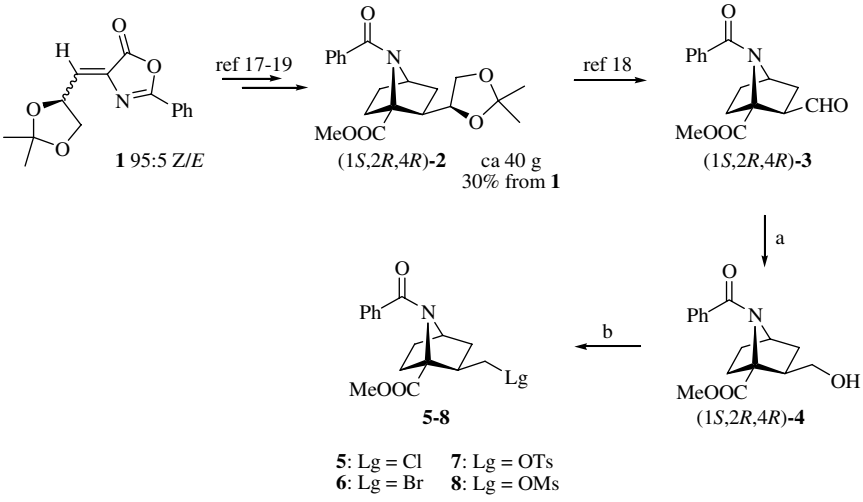


6: Lg = Br
7: Lg = OTs
8: Lg = OMs

9: Nu = H
10: Nu = SMe
11: Nu = SBn
12: Nu =CN
13: Nu = N_3

Scheme 2. S_N2 study.

The exchange of the leaving group for hydride was achieved from mesylate **8** by treatment with sodium borohydride in HMPA. This provided compound **9** in good yield (79%), although it should be noted that an additional portion of the hydride had to be added to achieve complete consumption of the starting material



5: Lg = Cl
6: Lg = Br
7: Lg = OTs
8: Lg = OMs

Scheme 1. Synthesis of the derivatives containing a Cγ leaving group, **5**–**8**. Reagents and conditions: (a) $NaBH_4$, MeOH/H_2O, 0 °C, 50 min (97%). (b) (i) PPh_3, CCl_4, reflux, 48 h (**5**, 96%); (ii) PPh_3, CBr_4, 35 °C, 24 h (**6**, 92%); (iii) TsCl, Et_3N, CH_2Cl_2, from 0 °C to reflux, 24 h (**7**, 44%); (iv) MsCl, Et_3N, CH_2Cl_2, from 0 °C to rt, 4 h (**8**, 98%).

(Table 1, entry 1). Nucleophilic substitution on mesylate **8** by the thiomethoxide ion was also achieved, but this reaction was not reproducible and the isolated yield of compound **10** (Table 1, entry 2) never surpassed 60%. The replacement of the mesylate by the benzylthiolate group was also successful and benzylthioether **11** (Table 1, entry 3) was isolated in 70% yield. This route provided a conveniently protected 7-azanorbornane cysteine analogue.

Table 1. Nucleophilic displacements on **6** and **8**

Entry	Lg	MNu (equiv)	Temp (°C)	Time	Compound	Yield[a]
1	OMs	$NaBH_4$ [12+8]	70	2 d	**9**	79
2	OMs	$NaSCH_3$ [3]	60	2 d	**10**	<60
3	OMs	NaSBn [2]	60	5 d	**11**	70
4	OMs	KCN [5][b]	90	1 d	**12**	<28
5	OMs	NaN_3 [2]	100	1 d	**13**	83
6	OMs	LiBr [4+4]	Reflux	6 d	**6**	75
7	Br	$NaBH_4$ [12]	70	12 h	**9**	87
8	Br	$NaSCH_3$ [3]	60	28 h	**10**	88
9	Br	NaSBn [2]	60	3 h	**11**	77
10	Br	KCN [5][c]	90	1 d	**12**	76
11	Br	NaN_3 [2]	90	5 h	**13**	92

The solvent used was dry DMF except for entries 1 and 7 where HMPA was the solvent of choice.
[a] Yield of isolated product.
[b] CsF (4 equiv) and 18-crown-6 ether (cat) were also used as additives.
[c] 18-Crown-6 ether (cat) was added.

On the other hand, reaction of mesylate **8** with the cyanide ion proved disappointing. The reaction with sodium cyanide led to complex mixtures that could not be characterised, even when using a phase transfer catalyst [$Bn(Et)_3NH_4Cl$] or in the presence of sodium iodide. In an attempt to promote carbon–carbon bond formation with cyanide ion, we systematically varied the solvent and additives such as crown ether and caesium fluoride.[20] The use of DMF as solvent, CsF and 18-crown-6 ether made the process slightly more favourable and the substitution product **12** (Scheme 2) was isolated for the first time—albeit in very poor yield (<28%) (Table 1, entry 4). The substitution product could not be detected when the solvent was changed from DMF to toluene, which has been described as the solvent of choice for other azabicyclic substrates.[20] Under these reaction conditions, the major product **14**, proceeding from the nucleophilic attack of the cyanide ion on the methyl ester and subsequent cyclisation by substitution of the mesylate, could be isolated and its structure undeniably determined by X-ray analysis (Fig. 2).

Substitution by cyanide on tosylate **7** was also tested and gave rise to very low yields (<28%). However, introduction of the azide ion into mesylate **8** was acceptably achieved by treatment with sodium azide in DMF to give azide **13** in good yield (83%) (Table 1, entry 5).

In addition, the mesylate leaving group was exchanged for bromide in moderate yield by treatment of **8** with lithium bromide and, in this way, bromide **6** was obtained in 75% yield (Table 1, entry 6).

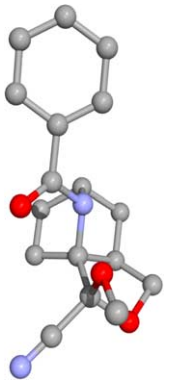


Figure 2. Structure of **14**.

The substitution with mesylate **8** did not produce completely satisfactory results due to low yields, long reaction times and, in some cases, lack of reproducibility. For these reasons, the study was repeated on bromo derivative **6**. This compound, which contained a bromide that is considered a good leaving group, could also be obtained in very high yield from alcohol (1*S*,2*R*,4*R*)-**4**.

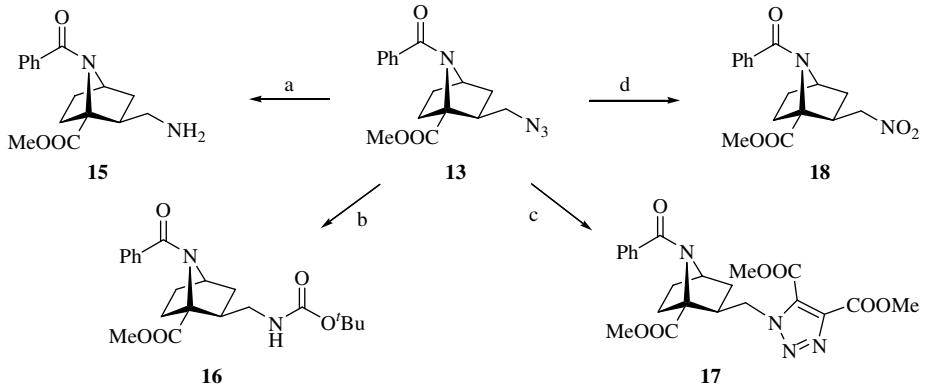
Fortunately, displacements on bromide **6** were much better in all cases than the corresponding reactions with **8**. Substitution by hydride (Table 1, entry 7) was more easily achieved on the bromide, with a shorter reaction time and lower reagent/starting material ratio required, while the reaction gave derivative **9** in higher yield (87%). Substitutions on bromide derivative **6** also allowed the isolation of derivatives **10** and **11** in better yields (88% and 77%, respectively) and much shorter reaction times (Table 1, entries 8 and 9) than the same substitutions on mesylate **8**. Displacement of the bromide group on **6** by the cyanide ion also proceeded much more efficiently and, in the absence of the two aforementioned additives, gave cyano derivate **12** in 61% yield. Addition of a catalytic amount of 18-crown-6 ether led to the best result and this modification provided, from bromide **6**, cyano derivative **12** in good yield (76%) (Table 1, entry 10). Once again, a better result was obtained in the substitution of azide on bromide **6** and this allowed the isolation of azide **13** in excellent yield (92%) with a marked decrease in the reaction time (Table 1, entry 11).

2.3. Transformations of substitution products

The introduction of different functional groups containing nitrogen at the Cγ was also investigated. We decided to take advantage of the availability of azide **13**, obtained as an S_N2 substitution product, and explore its potential reactivity.

Simple hydrogenation of **13** using Pd/C at 30 °C and atmospheric pressure, cleanly yielded an unstable amine derivative **15** (Scheme 3).

Given the lack of stability of amine **15**, and with the aim of facilitating the preparation and isolation of a stable



Scheme 3. Transformations on the azide **13**. Reaction conditions: (a) 10% Pd/C, H_2, MeOH, 30 °C, 3 h. (b) 10% Pd/C, H_2, Boc_2O, EtOAc, rt, 36 h (88%). (c) dimethylacetylenedicarboxylate, EtOH, reflux, 24 h (92%). (d) (i) 10% Pd/C, H_2, MeOH, 30 °C, 3 h; (ii) MCPBA, 1,2-dichloroethane, 75 °C, immediate (31%).

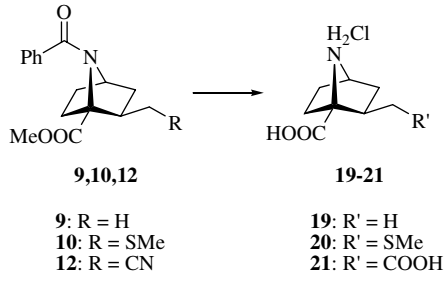
amine derivative for later manipulation, direct protection of the amine function with a suitable group, such as Boc, was tried from azide **13**. Both the reduction and protection steps could be performed with hydrogen-presaturated Pd/C[21] in the presence of di-*tert*-butyldicarbonate (Boc_2O). Under these conditions, derivative **16** (Scheme 3) was isolated in good yield (88%).

In addition, other one-pot conversions of azides into Boc-protected amines were assessed. For example, treatment of azide **13** with Et_3SiH (2.0 equiv), $Pd(OH)_2/C$ (10 mg/mmol) and Boc_2O (1.5 equiv) in EtOH[22] also led to the corresponding Boc-protected amine, albeit in low yield. On the other hand, the formation of a Staudinger intermediate (phosphazenes from azides and tertiary phosphines) shows it to be a convenient method for generating a nucleophilic amine from an azide.[23,24] In our case, according to the procedure described by Vilarrasa et al.,[25] the use of triphenylphosphine (1.1 equiv) and 2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile (Boc-ON, 1.1 equiv) enabled us to directly obtain the desired Boc-amine **16** in moderate yield from azide **13** (68%).

In order to demonstrate the synthetic versatility of the azide group in this 7-azanorbornane skeleton, we proceeded to carry out transformations into other interesting functional groups. For example, derivative **13** was treated with dimethylacetylenedicarboxylate.[26] The azide underwent 1,3-dipolar cycloaddition very readily to give triazol derivative **17** (Scheme 3) in excellent yield (92%).

The transformation of the azide function into a nitro group was also achieved by means of a simple two-step procedure.[27] Reduction of the azide to the amine by simple hydrogenation with Pd/C at 30 °C was followed by the addition of MCPBA to the amine solution. This simple procedure supplied the nitro derivative **18** in 31% yield (Scheme 3).

Finally, other compounds proceeding from the S_N2 displacements, such as **9**, **10** and **12**, were treated with aqueous 6 M HCl under reflux to provide enantiomerically pure proline–α-amino acid chimeras in quantitative or nearly quantitative yields (Scheme 4). The resulting amino acids **19**–**21**, which can also be considered as (2*S*,3*R*)-3-methylproline, (2*S*,3*R*)-3-methylthiomethylproline and (2*S*,3*S*)-3-carboxymethylproline analogues, respectively, were fully characterised. These amino acids can also be considered as a combination of proline with L-valine, L-methionine and L-glutamic acid with a 7-azanorbornane skeleton.



Scheme 4. Synthetic route to enantiomerically pure 7-azanorbornane proline–α-amino acid chimeras, **19**–**21**. Reaction conditions: 6 M HCl, reflux, 24 h (**19**), 30 h (**20**), or 48 h (**21**).

3. Conclusion

Manipulation of the dioxolane moiety in the key intermediate methyl (1*S*,2*R*,4*R*)-*N*-benzoyl-2-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-7-azabicyclo[2.2.1]heptane-1-carboxylate has made it possible to introduce a β-hydroxymethyl group. This functionalisation generates a huge range of possibilities for the preparation of a very special type of amino acid where the rigidity provided by the azabicyclic skeleton is combined with the presence of a β-substituent, which mimics the α-amino acid side chain. Further studies on the structural consequences arising from the replacement of the proline residue by analogues of bicyclic structure into model peptides are currently underway

and the results of this study will be published in due course.

4. Experimental section

4.1. General methods

Melting points were determined using a Büchi SMP-20 apparatus. IR spectra were registered on a Mattson Genesis FTIR spectrophotometer; ν_{max} is given for the main absorption bands. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity-300 or a Bruker ARX-300 apparatus at room temperature, using the residual solvent signal as the internal standard; chemical shifts (δ) are quoted in ppm, and coupling constants (J) measured in Hertz. Optical rotations were measured in a cell with a 10 cm path length at 25 °C using a JASCO P-1020 polarimeter. Elemental analyses were carried out on a Perkin–Elmer 200 C, H, N, S analyser. TLC was performed on Polygram® sil G/UV254 precoated silica gel polyester plates and the products were visualised under UV light (254 nm), ninhydrin, anisaldehyde or phosphomolybdic acid developers. Column chromatography was performed using silica gel (Kieselgel 60). (1*S*,2*R*,4*R*)-*N*-Benzoyl-2-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-7-azabicyclo[2.2.1]-heptane-1-carboxylate **2** was obtained according to the literature procedure.[17,19]

4.2. X-ray diffraction

The X-ray diffraction data were collected at room temperature on a Bruker Smartapex CCD Area diffractometer, using graphite-monochromated Mo-Kα radiation ($\lambda = 0.71073$ Å). The structure was solved by direct methods using SHELXS 97[28] and refinement was performed using SHELXL 97[29] by the full-matrix least-squares technique with anisotropic thermal factors for heavy atoms.

Colourless single crystals of **14** were obtained by slow evaporation from an ether solution. Reflections were measured in the $\omega/2\theta$-scan mode in the 2θ range 2.02–25.03°. Hydrogen atoms were located by calculation and affected by an isotropic thermal factor fixed to 1.2 times the U_{eq} of the carrier atom (1.5 for the methyl protons). Crystallographic data: orthorhombic, $P2_12_12_1$; $a = 7.0710(2)$ Å; $b = 12.3060(3)$ Å, $c = 17.6070(4)$ Å; $Z = 4$; d (calcd) $= 1.293$ g cm^{-3}; reflections collected/independent: 8880/2689 [R(int) = 0.0414]; data/parameters: 2698/201; final R indices [$I > 2\sigma(I)$]: $R_1 = 0.0370$, $wR_2 = 0.0801$; final R indices (all data): $R_1 = 0.0470$, $wR_2 = 0.0848$.

Crystallographic data (excluding structure factors) for the structure of compound **14** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 279067. Copies of the data can be obtained, free of charge, via www.ccdc.cam.ac.uk/conts/retrieving.html or on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.3. Methyl (1*S*,2*R*,4*R*)-*N*-benzoyl-2-hydroxymethyl-7-azabicyclo[2.2.1]heptane-1-carboxylate, 4

Over a solution of methyl (1*S*,2*R*,4*R*)-*N*-benzyl-2-formyl-7-azabicyclo[2.2.1]heptane-1-carboxylate **3** (3 g, 10.4 mmol) in methanol (240 mL) at 0 °C, a suspension of $NaBH_4$ (195 mg, 5 mmol) in water (36 mL) was slowly added. When the reaction was finished, after 50 min under stirring at the same temperature, the resulting mixture was neutralised by an aqueous solution of 0.5 M hydrochloric acid and the methanol was evaporated under vacuum. Then, water was added (100 mL) and the crude extracted with dichloromethane (3×100 mL). The organic layers were combined, dried over anhydrous magnesium sulfate, filtered and evaporated under vacuum. The resulting mixture was purified by column chromatography, using 9:1 ether/ethanol mixture as an eluent. In this way, compound **4** was obtained as a white solid in 97% yield (2.91 g, 10 mmol). Mp 91–93 °C. $[\alpha]_D = -40.7$ (c 1.0, $CHCl_3$) {lit.[30] Mp 91–93 °C. $[\alpha]_D = -40.7$ (c 1.0, $CHCl_3$)}.

4.4. Methyl (1*S*,2*R*,4*R*)-*N*-benzoyl-2-chloromethyl-7-azabicyclo[2.2.1]heptane-1-carboxylate, 5

To a solution of (1*S*,2*R*,4*R*)-*N*-benzoyl-2-hydroxymethyl-7-azabicyclo[2.2.1]heptane-1-carboxylate (100 mg, 0.35 mmol) in dry carbon tetrachloride **4** (10 mL) was added triphenylphosphine (183 mg, 0.7 mmol). The reaction mixture was refluxed for two days under argon atmosphere. The solvent was then evaporated under vacuum and the resulting mixture was chromatographed. The column chromatography (hexane/ethyl acetate, 1:1) provided the product in 96% yield (103 mg, 0.33 mmol). Colourless oil. $[\alpha]_D = -84.2$ (c 1.0, $CHCl_3$). IR (neat) ν (cm^{-1}): 3650–3461, 1741, 1657, 1644; ^{1}H NMR ($CDCl_3$) δ (ppm): 7.71–7.68 (m, 2H), 7.53–7.48 (m, 1H), 7.43–7.39 (m, 2H), 4.24 (dd, 1H, $J = 4.8$ Hz, $J = 4.8$ Hz), 3.95 (dd, 1H, $J = 10.9$ Hz, $J = 5.5$ Hz), 3.80 (s, 3H), 3.44 (dd, 1H, $J = 10.6$ Hz, $J = 10.4$ Hz), 2.48–2.39 (m, 2H), 1.93–1.72 (m, 4H), 1.58–1.51 (m, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 173.6, 169.9, 134.3, 131.9, 128.8, 128.4, 69.7, 61.7, 52.3, 48.7, 47.5, 37.3, 31.7, 30.3.

4.5. Methyl (1*S*,2*R*,4*R*)-*N*-benzoyl-2-bromomethyl-7-azabicyclo[2.2.1]heptane-1-carboxylate, 6

Triphenylphosphine (1.1 g, 4.14 mmol) was slowly added, under argon atmosphere, over a 0 °C chilled solution of (1*S*,2*R*,4*R*)-*N*-benzoyl-2-hydroxymethyl-7-azabicyclo[2.2.1]heptane-1-carboxylate **4** (400 mg, 1.38 mmol) and carbon tetrabromide (1.4 g, 4.14 mmol) in dry dichloromethane (20 mL). After the addition, the reaction mixture was allowed to warm up to room temperature followed by heating at 35 °C for one day. Then, the mixture was chilled at room temperature and the solid filtered and washed with dichloromethane.

The filtrate was concentrated under vacuum and the residue purified by column chromatography, using 7:3 mixture of hexane/ethyl acetate as an eluent, which allowed the isolation of compound **6** in 92% yield (447 mg, 1.27 mmol). Colourless oil. $[\alpha]_D = -92.3$ (*c* 1.0, $CHCl_3$). IR (neat) *v* (cm^{-1}): 1744, 1658, 1642; ^1H NMR ($CDCl_3$) δ (ppm): 7.69–7.66 (m, 2H), 7.50–7.46 (m, 1H), 7.42–7.37 (m, 2H), 4.21 (dd, 1H, $J = 4.8$ Hz, $J = 4.5$ Hz), 3.84 (dd, 1H, $J = 9.8$ Hz, $J = 4.8$ Hz), 3.77 (s, 3H), 3.30 (dd, 1H, $J = 10.6$ Hz, $J = 9.8$ Hz), 2.55–2.47 (m, 1H), 2.44–2.35 (m, 1H), 1.90 (dd, 1H, $J = 12.1$ Hz, $J = 8.3$ Hz), 1.83–1.73 (m, 3H), 1.55–1.48 (m, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 173.5, 169.7, 134.3, 131.8, 128.7, 128.4, 70.3, 61.7, 52.2, 48.7, 38.8, 37.1, 32.0, 30.2.

4.6. Methyl (1*S*,2*R*,4*R*)-*N*-benzoyl-2-(4-methylphenyl)sulfonyloxymethyl-7-azabicyclo[2.2.1]heptane-1-carboxylate, 7

Over a solution of methyl (1*S*,2*R*,4*R*)-*N*-benzoyl-2-hydroxymethyl-7-azabicyclo[2.2.1]heptane-1-carboxylate **4** (50 mg, 0.17 mmol) in dry dichloromethane (5 mL) at 0 °C and under argon atmosphere was added triethylamine (35.5 mg, 0.35 mmol) followed by *p*-toluenesulfonyl chloride (66.5 mg, 0.35 mmol). The reaction mixture was allowed to warm up to room temperature and stirred for an additional 24 h under reflux. The solvent was evaporated under vacuum and the resulting residue was redissolved in dichloromethane (10 mL) and washed with water (3×5 mL). The organic layer was dried with anhydrous magnesium sulfate, filtered and evaporated under vacuum. The resulting oil was purified by column chromatography, using 1:1 ethyl acetate/hexane mixture as an eluent. This procedure provided product **7** in 44% yield (33.14 mg, 0.07 mmol). White solid. Mp 49 °C. $[\alpha]_D = -6.7$ (*c* 0.4, $CHCl_3$). IR (nujol) *v* (cm^{-1}): 1737, 1651; ^1H NMR ($CDCl_3$) δ (ppm): 7.78 (d, 2H, $J = 8.1$ Hz), 7.61 (d, 2H, $J = 7.0$ Hz), 7.52–7.43 (m, 1H), 7.42–7.29 (m, 4H), 4.39 (dd, 1H, $J = 9.6$ Hz, $J = 7.3$ Hz), 4.17 (dd, 1H, $J = 4.4$ Hz, $J = 4.4$ Hz), 3.95 (dd, 1H, $J = 9.6$ Hz, $J = 8.8$ Hz), 3.72 (s, 3H), 2.51–2.28 (m, 5H), 1.86–1.43 (m, 5H); ^{13}C NMR ($CDCl_3$) δ (ppm): 173.4, 169.6, 144.8, 134.2, 132.9, 131.9, 129.9, 128.7, 128.4, 127.9, 71.2, 68.6, 61.5, 52.3, 45.1, 35.0, 31.7, 30.2, 21.7.

4.7. Methyl (1*S*,2*R*,4*R*)-*N*-benzoyl-2-methylsulfonyloxymethyl-7-azabicyclo[2.2.1]heptane-1-carboxylate, 8

Over a solution of methyl (1*S*,2*R*,4*R*)-*N*-benzoyl-2-hydroxymethyl-7-azabicyclo[2.2.1]heptane-1-carboxylate **4** (1.34 g, 4.65 mmol) in dry dichloromethane (50 mL) under argon at 0 °C was added triethylamine (941.3 mL, 9.32 mmol) followed by methanesulfonyl chloride (1.06 g, 9.32 mmol). The reaction mixture was allowed to warm up to room temperature and stirred for an additional 4 h until the total consumption of the starting material. Then, the solvent was evaporated under vacuum and the resulting residue redissolved in dichloromethane (100 mL) and extracted with water (3×50 mL). The combined organic layers were dried with anhydrous magnesium sulfate and filtered. The oil resulting from the complete evaporation of the solvent under vacuum was purified by column chromatography, using 8:2 ether/dichloromethane mixture as an eluent. This procedure provided product **8** in 98% yield (1.66 g, 4.52 mmol). Colourless oil. $[\alpha]_D = -32.4$ (*c* 0.5, $CHCl_3$). IR (neat) *v* (cm^{-1}): 1737, 1651; ^1H NMR ($CDCl_3$) δ (ppm): 7.72–7.67 (m, 2H), 7.55–7.48 (m, 1H), 7.46–7.38 (m, 2H), 4.53 (dd, 1H, $J = 10.1$ Hz, $J = 7.6$ Hz), 4.24 (dd, 1H, $J = 4.8$ Hz, $J = 4.5$ Hz), 4.16 (dd, 1H, $J = 9.8$ Hz, $J = 7.1$ Hz), 3.81 (s, 3H), 3.03 (s, 3H), 2.59–2.38 (m, 2H), 1.92–1.68 (m, 4H), 1.64–1.51 (m, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 173.6, 169.8, 134.1, 131.9, 128.7, 128.4, 70.6, 68.5, 61.4, 52.4, 45.4, 37.3, 34.6, 31.3, 30.4.

4.8. Methyl (1*S*,2*R*,4*R*)-*N*-benzoyl-2-methyl-7-azabicyclo[2.2.1]heptane-1-carboxylate, 9

A solution of methyl (1*S*,2*R*,4*R*)-*N*-benzoyl-2-bromomethyl-7-azabicyclo[2.2.1]heptane-1-carboxylate **6** (100 mg, 0.28 mmol) and $NaBH_4$ (31.8 mg, 0.84 mmol) in HMPA (4 mL) was heated at 70 °C for 12 h. Then, the solution was allowed to cool down to room temperature and the resulting mixture diluted with water (20 mL). The mixture was extracted with dichloromethane (3×10 mL). The combined organic layers were washed with water (10 mL), dried over anhydrous magnesium sulfate, filtered and the solvent was removed under vacuum. Finally, the residue was chromatographed, using 9:1 dichloromethane/ethyl acetate as an eluent. Compound **9** was isolated in 87% yield (66.5 mg, 0.24 mmol). White solid. Mp 86 °C. $[\alpha]_D = -94.1$ (*c* 1.0, $CHCl_3$). IR (nujol) *v* (cm^{-1}): 1746, 1647; ^1H NMR ($CDCl_3$) δ (ppm): 7.74–7.70 (m, 2H), 7.52–7.46 (m, 1H), 7.43–7.37 (m, 2H), 4.17 (dd, 1H, $J = 4.8$ Hz, $J = 4.8$ Hz), 3.78 (s, 3H), 2.40 (ddd, 1H, $J = 12.1$ Hz, $J = 12.1$ Hz, $J = 4.4$ Hz), 2.22–2.10 (m, 1H), 1.89–1.75 (m, 2H), 1.70–1.44 (m, 3H), 1.09 (d, 3H, $J = 6.9$ Hz); ^{13}C NMR ($CDCl_3$) δ (ppm): 174.1, 170.9, 134.9, 131.6, 128.8, 128.2, 70.3, 62.2, 51.7, 41.6, 39.5, 30.7, 30.6, 19.9. Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.48; H, 6.92; N, 4.98.

4.9. Methyl (1*S*,2*R*,4*R*)-*N*-benzoyl-2-methylthiomethyl-7-azabicyclo[2.2.1]heptane-1-carboxylate, 10

Over a solution of methyl (1*S*,2*R*,4*R*)-*N*-benzoyl-2-bromomethyl-7-azabicyclo[2.2.1]heptane-1-carboxylate **6** (100 mg, 0.27 mmol) in dry DMF (8 mL), $NaSCH_3$ (57.0 mg, 0.81 mmol) was added under an argon atmosphere. The resulting solution was heated at 60 °C for 18 h. Then, the reaction mixture was allowed to cool down to room temperature and the solvent was evaporated under vacuum. The resulting crude mixture was dissolved in a water/dichloromethane mixture. The aqueous layer was washed with dichloromethane (3×10 mL), the combined organic layers were dried over anhydrous magnesium sulfate, filtered and the solvent was removed under vacuum. A column chromatography, using a 6:4 mixture of hexane/ethyl acetate, provided the thioether derivative **10** in 88% yield

(76.6 mg, 0.24 mmol). Colourless oil. $[\alpha]_D = -90.0$ (*c* 0.4, $CHCl_3$). IR (neat) *v* (cm^{-1}): 1738, 1651; ^1H NMR ($CDCl_3$) δ (ppm): 7.71–7.65 (m, 2H), 7.45–7.44 (m, 1H), 7.42–7.34 (m, 2H), 4.18 (dd, 1H, $J = 4.4$ Hz, $J = 4.4$ Hz), 3.76 (s, 3H), 2.87 (dd, 1H, $J = 12.9$ Hz, $J = 5.2$ Hz), 2.51–2.34 (m, 2H), 2.29–2.18 (m, 1H), 2.06 (s, 3H), 1.89–1.70 (m, 4H), 1.54–1.43 (m, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 173.9, 170.3, 134.5, 131.7, 128.8, 128.3, 70.2, 62.0, 52.1, 45.7, 38.5, 37.8, 31.3, 30.4, 15.4.

4.10. Methyl (1*S*,2*R*,4*R*)-*N*-benzoyl-2-benzylthiomethyl-7-azabicyclo[2.2.1]heptane-1-carboxylate, 11

Over a suspension of NaH (13.0 mg, 0.54 mmol) in dry DMF (5 mL) under argon atmosphere was slowly added benzylmercaptane (67.0 mg, 0.54 mmol) and the mixture stirred at room temperature for one hour. Then, a solution of methyl (1*S*,2*R*,4*R*)-*N*-benzoyl-2-bromomethyl-7-azabicyclo[2.2.1]heptane-1-carboxylate **6** (100 mg, 0.27 mmol) in dry DMF (2 mL) was added and the resulting solution heated at 60 °C for 3 h under an argon atmosphere. Then, the reaction mixture was allowed to cool down to room temperature and the solvent evaporated under vacuum. The resulting crude mixture was dissolved in a water/dichloromethane mixture. The aqueous layer was washed with dichloromethane (3×10 mL), the combined organic layers were dried over anhydrous magnesium sulfate, filtered and the solvent was removed under vacuum. A column chromatography, using a 7:3 mixture of hexane/ethyl acetate, provided the thioether derivative **11** in 77% yield (85.2 mg, 0.22 mmol). Colourless oil. $[\alpha]_D = -75.1$ (*c* 0.5, $CHCl_3$). IR (neat) *v* (cm^{-1}): 3059–2874, 1737, 1656; ^1H NMR ($CDCl_3$) δ (ppm): 7.60–7.57 (m, 2H), 7.43–7.39 (m, 1H), 7.33–7.30 (m, 2H), 7.27–7.20 (m, 4H), 7.19–7.15 (m, 1H), 4.07 (dd, 1H, $J = 4.8$ Hz, $J = 4.5$ Hz), 3.66 (s, 3H), 3.62 (s, 2H), 2.77 (dd, 1H, $J = 12.8$ Hz, $J = 5.2$ Hz), 2.36–2.28 (m, 2H), 2.02–2.01 (m, 1H), 1.74–1.53 (m, 4H), 1.42–1.35 (m, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 173.8, 170.1, 138.3, 134.4, 131.6, 128.8, 128.7, 128.4, 128.2, 126.9, 70.1, 62.0, 51.9, 45.9, 37.7, 36.3, 35.7, 31.0, 30.3.

4.11. Methyl (1*S*,2*S*,4*R*)-*N*-benzoyl-2-cyanomethyl-7-azabicyclo[2.2.1]heptane-1-carboxylate, 12

To a suspension of potassium cyanide (91.2 mg, 1.4 mmol) and a catalytic quantity of 18-crown-6 ether in dry DMF (2 mL) under argon atmosphere, a solution of methyl (1*S*,2*R*,4*R*)-*N*-benzoyl-2-bromomethyl-7-azabicyclo[2.2.1]heptane-1-carboxylate **6** (100 mg, 0.28 mmol) in dry DMF (2 mL) was added. The mixture was heated at 80 °C for one day and, then, it was allowed to cool down to room temperature and the solvent was evaporated under vacuum. The resulting crude mixture was dissolved in a water/dichloromethane mixture. The aqueous layer was washed with dichloromethane (3×10 mL), the combined organic layers dried over anhydrous magnesium sulfate, filtered and the solvent was removed under vacuum. The column chromatography of the resulting oil, using a 1:1 mixture of hexane/ethyl acetate as an eluent, supplied the cyanomethyl derivative **12** in 76% yield (63.0 mg, 0.22 mmol). Colourless oil. $[\alpha]_D = -60.2$ (*c* 0.3, $CHCl_3$). IR (nujol) *v* (cm^{-1}): 3060–2854, 2246, 1745, 1648; ^1H NMR ($CDCl_3$) δ (ppm): 7.70–7.68 (m, 2H), 7.54–7.49 (m, 1H), 7.44–7.40 (m, 2H), 4.28 (dd, 1H, $J = 4.8$ Hz, $J = 4.8$ Hz), 3.81 (s, 3H), 2.96 (dd, 1H, $J = 16.2$ Hz, $J = 4.8$ Hz), 2.54–2.40 (m, 3H), 2.01 (dd, 1H, $J = 12.7$ Hz, $J = 8.2$ Hz), 1.88–1.72 (m, 3H), 1.59–1.52 (m, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm): 173.3, 169.6, 134.0, 132.0, 128.7, 128.5, 118.7, 69.1, 61.6, 52.4, 42.1, 38.0, 32.1, 30.1, 22.1.

4.12. Methyl (1*S*,2*S*,4*R*)-*N*-benzoyl-2-azidomethyl-7-azabicyclo[2.2.1]heptane-1-carboxylate, 13

Sodium azide (36.4 mg, 0.56 mmol) was added over a solution of methyl (1*S*,2*R*,4*R*)-*N*-benzoyl-2-bromomethyl-7-azabicyclo[2.2.1]heptane-1-carboxylate **6** (100 mg, 0.28 mmol) in dry DMF (5 mL) under an argon atmosphere and the mixture heated at 90 °C for 5 h. Then, the solvent was evaporated under vacuum, the residue redissolved in dichloromethane (100 mL), and washed with water (3×50 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and the solvent eliminated under vacuum. The residue was purified by column chromatography (eluent: 6:4 hexane/ethyl acetate). The product was obtained in this way as a white solid in 92% yield (81.0 mg, 0.26 mmol). White solid. Mp 115 °C. $[\alpha]_D = -62.3$ (*c* 0.5, $CHCl_3$). IR (nujol) *v* (cm^{-1}): 2093, 1737, 1646; ^1H NMR ($CDCl_3$) δ (ppm): 7.74–7.66 (m, 2H), 7.55–7.36 (m, 3H), 4.22 (dd, 1H, $J = 4.8$ Hz, $J = 4.4$ Hz), 3.83 (s, 3H), 3.78–3.70 (m, 1H), 3.27 (dd, 1H, $J = 12.5$ Hz, $J = 8.1$ Hz), 2.50–2.36 (m, 1H), 2.33–2.19 (m, 1H), 1.90–1.66 (m, 4H), 1.59–1.47 (m, 1H). ^{13}C NMR ($CDCl_3$) δ (ppm): 173.7, 169.9, 134.2, 131.8, 128.7, 128.3, 77.2, 68.9, 61.7, 54.0, 52.3, 45.8, 35.8, 31.1, 30.3. Anal. Calcd for $C_{16}H_{18}N_4O_3$: C, 61.13; H, 5.77; N, 17.82. Found: C, 61.20; H, 5.68; N, 17.67.

4.13. Methyl (1*S*,2*S*,4*R*)-*N*-benzoyl-2-aminomethyl-7-azabicyclo[2.2.1]heptane-1-carboxylate, 15

To a solution of methyl (1*S*,2*S*,4*R*)-*N*-benzoyl-2-azidomethyl-7-azabicyclo[2.2.1]heptane-1-carboxylate **13** (100 mg, 0.32 mmol) in dry methanol (10 mL), 10% Pd/C (20 mg) was added and the resulting suspension heated at 30 °C under hydrogen atmosphere for 3 h. The catalyst was then filtered off through a Celite pad, which was washed with dichloromethane. The solvent was evaporated under vacuum until dryness. This procedure supplied the unstable amino derivative in pure NMR spectroscopic form. ^1H NMR ($CDCl_3$) δ (ppm): 7.77–7.67 (m, 2H), 7.50–7.44 (m, 1H), 7.41–7.35 (m, 2H), 4.17 (dd, 1H, $J = 4.8$ Hz, $J = 4.4$ Hz), 3.78 (s, 3H), 2.94 (dd, 1H, $J = 12.9$ Hz, $J = 6.2$ Hz), 2.65 (dd, 1H, $J = 12.9$ Hz, $J = 6.6$ Hz), 2.40 (ddd, 1H, $J = 12.5$ Hz, $J = 12.1$ Hz, $J = 4.6$ Hz), 2.14–2.03 (m, 1H), 1.86–1.59 (m, 4H), 1.54–1.45 (m, 3H). ^{13}C NMR ($CDCl_3$) δ (ppm): 173.7, 170.8, 134.7, 131.6, 128.8, 128.3, 69.5, 62.0, 51.9, 50.1, 44.8, 35.1, 31.1, 30.6.

4.14. Methyl (1*S*,2*S*,4*R*)-*N*-benzoyl-2-*tert*-butoxy carbonylaminomethyl-7-azabicyclo[2.2.1]heptane-1-carboxylate, 16

Over a suspension of 10% Pd/C (10 mg) in ethyl acetate (5 mL) under hydrogen atmosphere were added methyl (1*S*,2*S*,4*R*)-*N*-benzoyl-2-azidomethyl-7-azabicyclo[2.2.1]-heptane-1-carboxylate **13** (100 mg, 0.32 mmol) and di-*tert*-butyldicarbonate (104.8 mg, 0.48 mmol). The mixture was vigorously stirred at room temperature until complete consumption of the starting material (36 h). The catalyst was then filtered off by means of a Celite pad and the solvent eliminated under vacuum. The residue was purified by column chromatography (eluent: 1:1 hexane/ethyl acetate) and the compound obtained in 88% yield (109 mg, 0.28 mmol). White solid. Mp 59–60 °C. $[\alpha]_D = -68.1$ (*c* 1.0, $CHCl_3$). IR (nujol) *v* (cm^{-1}): 1737, 1709, 1654; ^1H NMR ($CDCl_3$) δ (ppm): 7.70–7.68 (m, 2H), 7.50–7.47 (m, 1H), 7.41–7.37 (m, 2H), 5.34–5.28 (m, 1H), 4.15 (dd, 1H, $J = 4.5$ Hz, $J = 4.5$ Hz), 3.82 (s, 3H), 3.42–3.35 (m, 1H), 3.14 (ddd, 1H, $J = 14.2$ Hz, $J = 3.7$ Hz, $J = 3.7$ Hz), 2.41 (ddd, 1H, $J = 12.4$ Hz, $J = 12.4$ Hz, $J = 4.2$ Hz), 2.32–2.22 (m, 1H), 1.86–1.60 (m, 4H), 1.55–1.48 (m, 1H), 1.44 (s, 9H). ^{13}C NMR ($CDCl_3$) δ (ppm): 173.5, 171.0, 134.5, 131.8, 128.8, 128.3, 79.0, 77.3, 69.3, 61.8, 52.4, 46.8, 42.5, 34.1, 30.8, 28.5. Anal. Calcd for $C_{21}H_{28}N_2O_5$: C, 64.93; H, 7.27; N, 7.21. Found: C, 64.82; H, 7.39; N, 7.10.

4.15. Methyl (1*S*,2*S*,4*R*)-*N*-benzoyl-2-(4,5-dimethoxy-carbonyl-1,2,3-triazol-1-yl)methyl-7-azabicyclo[2.2.1] heptane-1-carboxylate, 17

Dimethylacetylenedicarboxylate (59.7 mg, 0.42 mmol) was added to a solution of (1*S*,2*S*,4*R*)-*N*-benzoyl-2-azidomethyl-7-azabicyclo[2.2.1]heptane-1-carboxylate **13** (100 mg, 0.32 mmol) in ethanol (10 mL) and the mixture refluxed for one day. Then, the mixture was allowed to cool down to room temperature and the solvent removed under vacuum. The resulting residue was purified by column chromatography (eluent: 6:4 hexane/ethyl acetate) and the compound was obtained in 92% yield (134 mg, 0.29 mmol). White solid. Mp 60–62 °C. $[\alpha]_D = -72.4$ (*c* 1.0, $CHCl_3$). IR (nujol) *v* (cm^{-1}): 3059–2850, 1743, 1648, 1600, 1578; ^1H NMR ($CDCl_3$) δ (ppm): 7.71–7.69 (m, 2H), 7.49–7.45 (m, 1H), 7.41–7.37 (m, 2H), 5.08 (dd, 1H, $J = 13.9$ Hz, $J = 5.0$ Hz), 4.57 (dd, 1H, $J = 13.6$ Hz, $J = 10.9$ Hz), 4.23 (dd, 1H, $J = 4.8$ Hz, $J = 4.5$ Hz), 3.98 (s, 3H), 3.90 (s, 3H), 3.75 (s, 3H), 2.95–2.87 (m, 1H), 2.44–2.37 (m, 1H), 1.92–1.82 (m, 2H), 1.75–1.69 (m, 1H), 1.51–1.46 (m, 2H). ^{13}C NMR ($CDCl_3$) δ (ppm): 173.1, 169.8, 160.5, 159.0, 139.6, 134.2, 131.9, 130.8, 128.8, 128.4, 68.9, 61.5, 53.5, 52.8, 52.6, 52.3, 45.0, 35.6, 33.1, 30.1. Anal. Calcd for $C_{22}H_{24}N_4O_7$: C, 57.89; H, 5.30; N, 12.27. Found: C, 57.55; H, 5.21; N, 12.03.

4.16. Methyl (1*S*,2*S*,4*R*)-*N*-benzoyl-2-nitromethyl-7-azabicyclo[2.2.1]heptane-1-carboxylate, 18

To a solution of (1*S*,2*S*,4*R*)-*N*-benzoyl-2-azidomethyl-7-azabicyclo[2.2.1]heptane-1-carboxylate **13** (100 mg, 0.32 mmol) in dry methanol (6 mL) was added 10% Pd/C (20 mg) and the resulting suspension heated at 30 °C under a hydrogen atmosphere for 3 h. The reaction mixture was filtered through Celite and the solvent evaporated to dryness. Then, over a solution of the resulting residue in 1,2-dichloroethane (6 mL), heated at 75 °C, was added a solution of MCPBA (358 mg, 2.08 mmol) in 1,2-dichloroethane (4 mL). The reaction went to completion immediately and the solvent evaporated under vacuum. A column chromatography, using a 1:1 mixture of hexane/ethyl acetate, provided the compound as a white solid in 31% yield (32 mg, 0.1 mmol). Mp 134–135 °C. $[\alpha]_D = -34.0$ (*c* 0.6, $CHCl_3$). IR (neat) *v* (cm^{-1}): 1737, 1709, 1737; ^1H NMR ($CDCl_3$) δ (ppm): 7.69–7.67 (m, 2H), 7.54–7.51 (m, 1H), 7.45–7.41 (m, 2H), 5.07 (dd, 1H, $J = 14.2$ Hz, $J = 6.3$ Hz), 4.34 (dd, 1H, $J = 14.3$ Hz, $J = 9.0$ Hz), 4.31–4.28 (m, 1H), 3.77 (s, 3H), 3.02–2.95 (m, 1H), 2.51–2.44 (m, 1H), 1.97–1.86 (m, 3H), 1.69–1.57 (m, 2H). ^{13}C NMR ($CDCl_3$) δ (ppm): 173.2, 169.6, 133.9, 132.1, 128.7, 128.5, 77.7, 68.5, 61.3, 52.5, 42.9, 36.3, 32.5, 30.1. Anal. Calcd for $C_{16}H_{18}N_2O_5$: C, 60.37; H, 5.70; N, 8.80. Found: C, 60.56; H, 6.02; N, 8.55.

4.17. General procedure for the hydrolysis of compounds 9, 10 and 12

Aqueous 6 M HCl (15 mL) was added to the amido esters **9**, **10** or **12** (100 mg) and the mixture heated under reflux for 24, 30 or 48 h, respectively. After the reaction was complete, the solvent was evaporated under vacuum and the residue dissolved in water (30 mL). The solution was extracted with chloroform (3×20 mL) and the separated aqueous phase evaporated to dryness. Total removal of water was achieved by final lyophilisation. In this way the amino acid hydrochlorides **19**–**21** were obtained.

(1*S*,2*R*,4*R*)-2-Methyl-7-azabicyclo[2.2.1]heptane-1-carboxylic acid hydrochloride, **19**. Quantitative yield. White solid. Mp dec. $[\alpha]_D = -34.1$ (*c* 0.4, H_2O). IR (nujol) *v* (cm^{-1}): 3200–2522, 1726; ^1H NMR (D_2O) δ (ppm): 4.11 (dd, 1H, $J = 4.7$ Hz, $J = 4.1$ Hz), 2.40–2.28 (m, 1H), 2.16–1.97 (m, 4H), 1.81–1.70 (m, 1H), 1.58–1.49 (m, 1H), 0.93 (d, 3H, $J = 7.3$ Hz); ^{13}C NMR (D_2O) δ (ppm): 171.7, 75.9, 58.4, 37.5, 36.7, 30.5, 26.6, 17.0.

(1*S*,2*R*,4*R*)-2-Methylthiomethyl-7-azabicyclo[2.2.1]heptane-1-carboxylic acid hydrochloride, **20**. White solid containing a small amount of impurity. IR (nujol) *v* (cm^{-1}): 3500–3300, 1640; ^1H NMR (D_2O) δ (ppm): 4.16 (dd, 1H, $J = 4.0$ Hz, $J = 4.0$ Hz), 2.88 (d, 1H, $J = 6.3$ Hz), 2.68 (dd, 1H, $J = 12.9$ Hz, $J = 4.8$ Hz), 2.60–2.42 (m, 1H), 2.37–2.27 (m, 1H), 2.19–1.94 (m, 7H), 1.85–1.71 (m, 3H); ^{13}C NMR (D_2O) δ (ppm): 173.6, 77.9, 60.8, 44.2, 37.7, 37.4, 33.4, 29.0, 28.9, 16.6.

(1*S*,2*S*,4*R*)-2-Carboxymethyl-7-azabicyclo[2.2.1]heptane-1-carboxylic acid hydrochloride, **21**. Quantitative yield. Mp dec. $[\alpha]_D = -25.5$ (*c* 0.4, H_2O). IR (nujol) *v* (cm^{-1}): 3600–2800, 1723; ^1H NMR (D_2O) δ (ppm): 4.16 (dd, 1H, $J = 4.4$ Hz, $J = 4.4$ Hz), 2.71–2.53 (m,

2H), 2.51 (d, 1H, $J = 5.2$ Hz), 2.41 (dd, 1H, $J = 16.6$ Hz, $J = 8.5$ Hz), 2.18 (dd, 1H, $J = 13.6$ Hz, $J = 8.8$ Hz), 2.13–1.96 (m, 3H), 1.84–1.64 (m, 2H); ^{13}C NMR (D_2O) δ (ppm): 177.8, 173.4, 77.1, 60.8, 41.2, 38.6, 37.4, 33.6, 29.0.

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References

1. See: Sharma, R.; Lubell, W. D. *J. Org. Chem.* **1996**, *61*, 202–209, and Refs. 1–7 cited therein.
2. Holladay, M. W.; Lin, C. W.; May, C. S.; Garvey, D. S.; White, D. G.; Miller, T. R.; Wolfram, C. A.; Nadzan, A. M. *J. Med. Chem.* **1991**, *34*, 455–457.
3. Tilley, J. W.; Danho, W.; Madison, V.; Fry, D.; Swistok, J.; Makofske, R.; Michalewsky, J.; Schwartz, A.; Weatherford, S.; Triscari, J.; Nelson, D. *J. Med. Chem.* **1992**, *35*, 4249–4252.
4. Kolodziej, S. A.; Nikiforovich, G. V.; Skeean, R.; Lignon, M. F.; Martinez, J.; Marshall, G. R. *J. Med. Chem.* **1995**, *38*, 137–149.
5. Marshall, G. R. *Tetrahedron* **1993**, *49*, 3547–3558.
6. Plucinska, K.; Kataoka, T.; Yodo, M.; Cody, W. L.; He, J. X.; Humblet, C.; Lu, G. H.; Lunney, E.; Major, T. C.; Panek, R. L.; Schelkun, P.; Skeean, R.; Marshall, G. R. *J. Med. Chem.* **1993**, *36*, 1902–1913.
7. Kaczmarek, K.; Li, K. M.; Sheean, R.; Dooley, D.; Humblet, C.; Lunney, E.; Marshall, G. R. In *Peptides: Chemistry, Structure and Biology*; Hodges, R. S., Smith, J. A., Eds.; ESCOM Science Publishers B.V.: Leiden, The Netherlands, 1994; p 687.
8. Mosberg, H. I.; Kroona, H. B. *J. Med. Chem.* **1992**, *35*, 4498–4500.
9. Mosberg, H. I.; Lomize, A. L.; Wang, C.; Kroona, H.; Heyl, D. L.; Sobczyk-Kojiro, K.; Ma, W.; Mousigian, C.; Porreca, F. *J. Med. Chem.* **1994**, *37*, 4371–4383.
10. Nelson, R. D.; Gottlieb, D. I.; Balasubramanian, T. M.; Marshall, G. R. In *Opioid Peptides: Medicinal Chemistry; NIDA Research Monograph 69*; Rapaka, R. S., Banett, G., Hawks, R. L., Eds.; U.S. Dept. of Health and Human Services, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute on Drug Abuse, Rockville (MD), U.S.A.; For sale by the Supt. of Docs., U.S. Government Printing Office, Washington (DC), U.S.A., 1986; p. 204.
11. Ghose, A. K.; Logan, M. E.; Treasurywala, A. M.; Wang, H.; Wahl, R. C.; Tomczuk, B. E.; Gowravaram, M. R.; Jaeger, E. P.; Wendoloski, J. J. *J. Am. Chem. Soc.* **1995**, *117*, 4671–4682.
12. Hutton, J. J., Jr.; Marglin, A.; Witkop, B.; Kurtz, J.; Berger, A.; Undenfrien, S. *Arch. Biochem. Biophys.* **1968**, *125*, 779–785.
13. Jiménez, A. I.; Cativiela, C.; Aubry, A.; Marraud, M. *J. Am. Chem. Soc.* **1998**, *120*, 9452–9459.
14. Jiménez, A. I.; Cativiela, C.; Gómez-Catalán, J.; Pérez, J. J.; Aubry, A.; París, M.; Marraud, M. *J. Am. Chem. Soc.* **2000**, *122*, 5811–5821.
15. Jiménez, A. I.; Cativiela, C.; Marraud, M. *Tetrahedron Lett.* **2000**, *41*, 5353–5356.
16. Gil, A. M.; Buñuel, E.; Jiménez, A. I.; Cativiela, C. *Tetrahedron Lett.* **2003**, *44*, 5999–6002.
17. Buñuel, E.; Gil, A. M.; Díaz-de-Villegas, M. D.; Cativiela, C. *Tetrahedron* **2001**, *57*, 6417–6427.
18. Gil, A. M.; Buñuel, E.; Díaz-de-Villegas, M. D.; Cativiela, C. *Tetrahedron: Asymmetry* **2003**, *14*, 1479–1488.
19. Orús, E., Master of Science Thesis, 2003. University of Zaragoza.
20. Schrake, O.; Franz, M. H.; Wartchow, R.; Hoffmann, H. M. R. *Tetrahedron* **2000**, *56*, 4453–4465.
21. Woltering, T. J.; Weiz-Schmidt, G.; Wong, C. H. *Tetrahedron Lett.* **1996**, *37*, 9033–9036.
22. Kotsuki, H.; Ohishi, T.; Araki, T. *Tetrahedron Lett.* **1997**, *38*, 2129–2132.
23. Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 635–646.
24. Gololobov, Yu. G.; Kasukhin, L. F. *Tetrahedron* **1992**, *48*, 1353–1406.
25. Ariza, X.; Urpí, F.; Viladomat, C.; Vilarrasa, J. *Tetrahedron Lett.* **1998**, *39*, 9101–9102.
26. Abu-Orabi, S. T.; Atfah, M. A.; Sibril, I.; Mari'I, F. M.; Ali, A. A. *J. Heterocycl. Chem.* **1989**, *26*, 1461–1468.
27. Maguire, M. R.; Feldman, P. L.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 948–955.
28. Sheldrick, G. M. SHELXS 97. Program for the solution of crystal structures; University of Göttingen: Germany, 1997.
29. Sheldrick, G. M. SHELXL 97. Program for the refinement of crystal structures; University of Göttingen: Germany, 1997.
30. Gil, A. M.; Buñuel, E.; López, P.; Cativiela, C. *Tetrahedron: Asymmetry* **2004**, *15*, 811–819.