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Olefination of methyl (1*S*,2*R*,4*R*)-*N*-benzoyl-2-formyl-7-azabicyclo[2.2.1]heptane-1-carboxylate, a synthetic approach to new conformationally constrained prolines

Ana M. Gil,[a] Elena Buñuel,[b] María D. Díaz-de-Villegas[a] and Carlos Cativiela[a,*]

[a]*Departamento de Química Orgánica, ICMA, Universidad de Zaragoza-CSIC, 50009 Zaragoza, Spain*
[b]*Departamento de Química Orgánica, Universidad Autónoma de Madrid, 28049 Madrid, Spain*

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Abstract—Wittig olefinations of methyl (1*S*,2*R*,4*R*)-*N*-benzoyl-2-formyl-7-azabicyclo[2.2.1]heptane-1-carboxylate with several phosphoranes and the Horner–Wittig reaction, using methyl diethylphosphonoacetate, have been tested in order to evaluate their utility in the synthesis of β-substituted conformationally constrained prolines. Subsequent elaboration of the resulting alkenes has provided proline–amino acid chimeras [combinations of proline with other α-amino acids, such as L-norvaline, L-norleucine, L-α-(3-phenylpropyl)glycine or L-homoglutamic acid] with the 7-azabicyclo[2.2.1]heptane skeleton in an enantiomerically pure form.

1. Introduction

The introduction of conformationally constrained amino acid analogues in place of natural α-amino acids in parent peptide can generate structurally defined peptides that serve a dual role as conformational probes and bioactive peptidomimetics.[1–4] The suitability of cyclic amino acids in this area has translated into the development of the different stereoselective synthetic methods that supply them.[5,6]

Incorporation of proline-related residues, where the nitrogen forms part of the ring, constitutes one way to strongly decrease the conformational freedom of peptides. Several detailed studies concerning α-alkylprolines[7–9] initially indicated the potential importance of introducing an extra conformational restriction by connecting the α-carbon with another proline ring carbon. In this context, the first results regarding the benefits of proline analogues containing the 7-azabicyclo[2.2.1]heptane skeleton have unquestionably contributed to the increased interest shown in this kind of amino acid.[10,11]

Since the discovery of epibatidine by Daly et al. in 1992,[12] we have witnessed a proliferation of synthetic methods to create azabicyclic systems.[13] However, few procedures have been described on the asymmetric synthesis of proline analogues containing the 7-azabicyclo[2.2.1]heptane skeleton.[14–18]

We recently proposed a practical route to methyl (1*S*,2*R*,4*R*)-*N*-benzoyl-2-formyl-7-azabicyclo[2.2.1]heptane-1-carboxylate **3** (Scheme 1). Our strategy is based on the preparation of the azabicyclic intermediate **2** from the chiral oxazolone **1*Z*** through seven fully stereocontrolled steps that proceed with an overall yield of 57%.[18]

Substrate **2** is a valuable intermediate since it possesses an acetal moiety in the β-position, which can be easily transformed into a wide variety of functional groups such as the formyl group in **3**. β-Substituted prolines can be considered as amino acid chimeras in which the functional groups of the amino acid side-chain are combined with the conformational restrictions specific to the cyclic amino acid residue. Thus, several chimeras based on proline bodies have been synthesised and used to provide a better understanding of the relationship between the side-chain geometry and the bioactive conformations.[19,20]

* Corresponding author. Tel./fax: +34-976-761210; e-mail: cativiela@unizar.es

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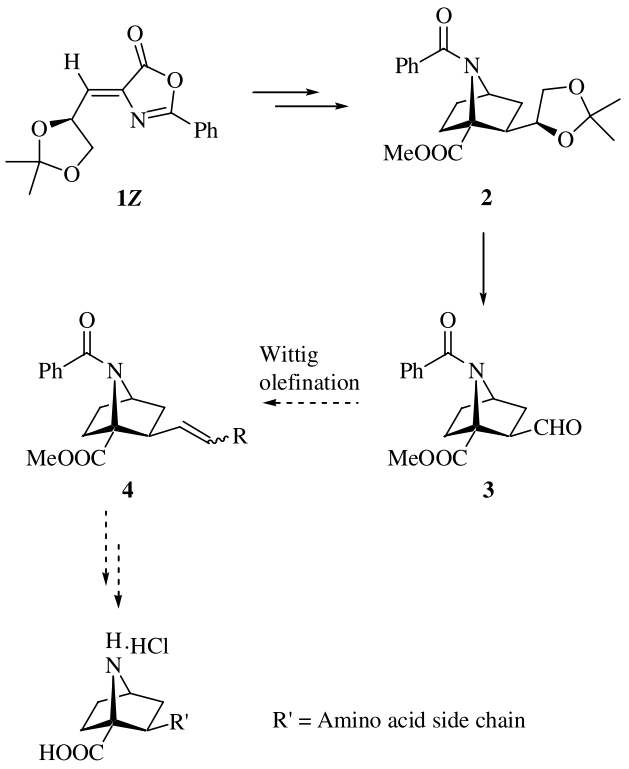


Scheme 1. Suggested route to 7-azabicyclo[2.2.1]heptane amino acids.

Wittig olefination is widely recognised as one of the most useful ways to create C–C bonds from aldehydes and so we studied the behaviour of compound **3** with several phosphoranes. This study was performed in order to evaluate the versatility of this approach as a synthetic route to new enantiopure conformationally restricted β-substituted prolines via the corresponding Wittig adducts **4** (Scheme 1).

2. Results and discussion

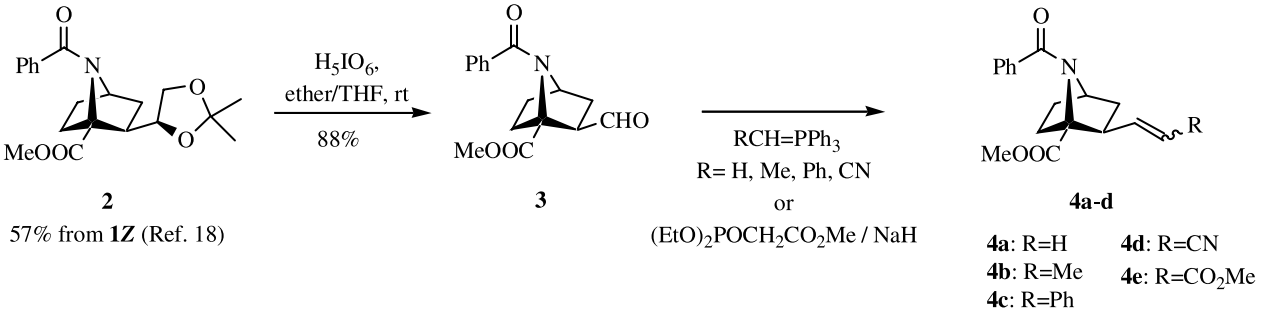
The excellent results obtained in an initial study aimed at exploring the behaviour of methyl (1*S*,2*R*,4*R*)-*N*-benzoyl-2-formyl-7-azabicyclo[2.2.1]heptane-1-carboxylate **3** in the Wittig reaction[18] prompted us to extend this olefination study.

As described recently, the preparation of compound **3** can be achieved in 60% yield through a two-step process that involves hydrolysis of the acetal in intermediate **2** and oxidation of the resulting diol. The moderate yield of this procedure was mainly caused by the formation of an undesired side product identified as a six-membered lactone, which was formed by cyclisation of the methyl ester with the corresponding hydroxy group.[18] At this point in our investigation, a re-examination of this synthetic procedure seemed appropriate in order to obtain compound **3** in a more efficient manner.

A highly effective synthesis of **3** was achieved by direct transformation of the acetal moiety into the formyl group (Scheme 2). Treatment of 1.0 g of compound **2** with H_5IO_6[21] gave product **3** in 88% yield through a one-step procedure, with no evidence for the formation of any lactonisation product. This synthesis therefore represents a marked improvement on the methodology previously reported. The behaviour of **3** in reaction with several triphenylphosphonium ylides was then evaluated (Scheme 2).

The reaction of **3** with methylenetriphenylphosphorane involved treatment of methyltriphenylphosphonium iodide with *n*-BuLi in THF and subsequent addition of the carbonyl compound to the reaction mixture. This procedure gave the desired methyl (1*S*,2*S*,4*R*)-*N*-benzoyl-2-vinyl-7-azabicyclo[2.2.1]heptane-1-carboxylate **4a**, which was isolated in 75% yield under the optimum reaction conditions (see Table 1, entry 1).

In order to compare the efficacy of the Wittig procedure to obtain the vinyl product we also explored an alternative method (Scheme 3). Diol **5**, obtained from hydrolysis of the acetal in key intermediate **2**,[18] was converted into the vinyl azabicyclic product **4a** through the two-step Corey–Winter procedure to obtain olefins from 1,2-diols via a thionocarbonate intermediate.[22–24] This method was carried out using *N*,*N*′-thiocarbonyldiimidazole (TCDI) under reflux in toluene, as in the original protocol,[22] instead of thiophosgene/DMAP.[24] The procedure gave thionocarbonate **6** in good yield (83%) and treatment of this compound with trimethylphosphite afforded **4a** in 72% yield. When 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine (DMP-DAP)[24] was used instead of trimethylphosphite, the yield of **4a** increased to 86%. In summary, this proce-

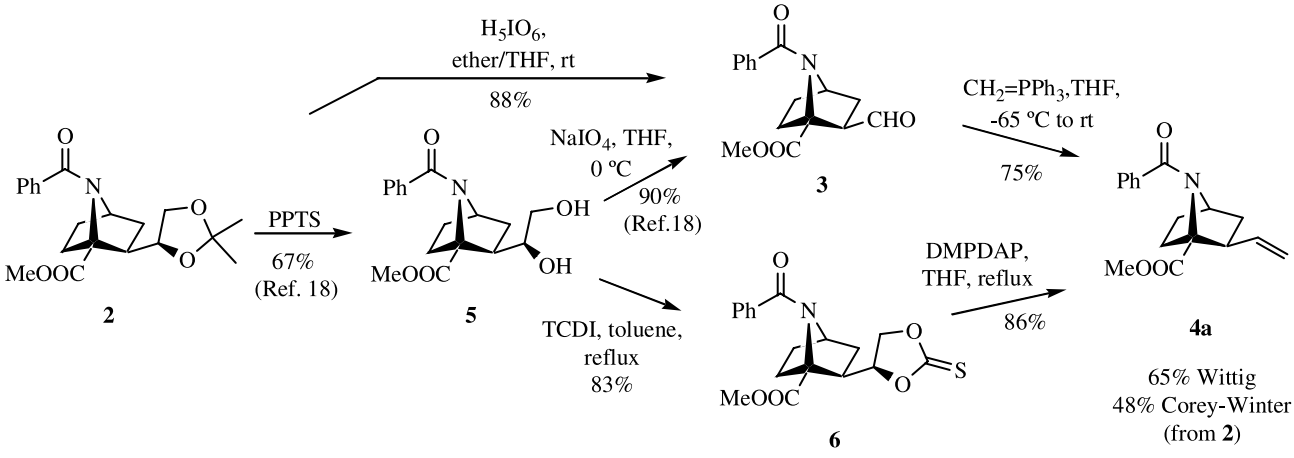


Scheme 2. Wittig and Horner–Wittig olefination of compound **3**.

Table 1. The best results in Wittig and Horner–Wittig olefination of compound **3**

Entry	R′	Reagent	Base[a]	Time and temperature	Yield[b] (%)	Z/E[c]
1	H	Ph_3PMeI	*n*-BuLi	10 min at −65°C, then 45 min at rt	75	
2	Me	Ph_3PEtBr	*n*-BuLi	Immediate at −65°C	90	71/29
3	Ph	Ph_3PCH_2PhCl	*n*-BuLi	5 h at −40°C	85	6/94
4	CO_2Me	$Ph_3PCH_2CO_2MeCl$	*n*-BuLi	10 min at 0°C, then 20 min at rt	–[d]	
5	CO_2Me	$Ph_3PCH_2CO_2MeCl$	Propylene oxide	1 day at rt	–[e]	
6	CN	Ph_3PCH_2CNCl	Propylene oxide	3 days under reflux	99	52/48
7	CO_2Me	$(EtO)_2POCH_2CO_2Me$	NaH	45 min at rt	95	12/88

[a] Reactions using *n*-BuLi or NaH were carried out in dry THF.
[b] After isolation of the isomeric mixtures by column chromatography.
[c] Determined by integration of the ^1H NMR spectra of the reaction mixtures.
[d] Complete disappearance of **3** was observed but no Wittig adducts were detected.
[e] Mixtures of products were obtained due to partial epimerization at C-2.



Scheme 3. Wittig and Corey–Winter procedures to obtain **4a**.

dure gave 48% overall yield from the key intermediate **2** through a three-step transformation. No improvement was observed in comparison to the Wittig procedure, which also provided **4a** in 66% yield from **2** through a two-step process beginning with the direct transformation of the acetal moiety into a formyl group (Scheme 3).

The Wittig reaction of **3** with ethylidenetriphenylphosphorane (Scheme 2) under previously reported conditions[18]—represented here in Table 1, entry 2—provided methyl (1*S*,2*S*,4*R*)-*N*-benzoyl-2-(1-propenyl)-7-azabicyclo[2.2.1]heptane-1-carboxylate **4b** as a 71/29 mixture of the *Z* and *E* isomers in excellent yield (90%). The determination of the Z/E ratio was carried out by integration of the appropriate signals in the ^1H NMR spectrum of the crude reaction mixture and was possible thanks to the partial separation of the isomers by HPLC, which afforded a pure analytical sample of the major isomer. The double bond stereochemistry of each isomer was elucidated by ^1H NMR experiments. Thus, irradiation of the olefinic methyl signal in the ^1H NMR spectrum of the pure isolated isomer of **4b** gave a spectrum where the coupling constant between the olefinic protons could be clearly measured ($J=11.0$ Hz), allowing the assignment of the *Z* configuration for the double bond in the major product. A similar experiment on the mixture enriched with the minor isomer, by irradiation of the olefinic methyl signals of both isomers, revealed a coupling constant ($J=15.0$ Hz) consistent with an *E* stereochemistry for the double bond of the minor reaction product.

The reaction of **3** with the semi-stabilised ylide benzylidenetriphenylphosphorane led to a 6/94 mixture of (Z/E)-methyl (1*S*,2*S*,4*R*)-*N*-benzoyl-2-(2-phenylvinyl)-7-azabicyclo[2.2.1]heptane-1-carboxylate **4c** (Scheme 2) in 85% yield under the reaction conditions given in Table 1 (entry 3). The major product was fully characterised and analysis of the single-crystal X-ray data unequivocally confirmed the stereochemistry (Fig. 1). The coupling constants between the olefinic protons were determined from the ^1H NMR spectra obtained from benzene-d_6 solutions ($J=11.4$ Hz and $J=15.4$ Hz for the *Z* and *E* isomers, respectively).

As far as the stabilised ylides are concerned, reaction of **3** with carbomethoxymethylenetriphenylphosphorane did not give acceptable yields of the corresponding Wittig adducts under any of the reaction conditions tested. Treatment of carbomethoxymethyltriphenylphosphonium chloride with an aqueous solution of sodium hydroxide and reaction of the carbonyl compound **3** with the isolated ylide gave only a very

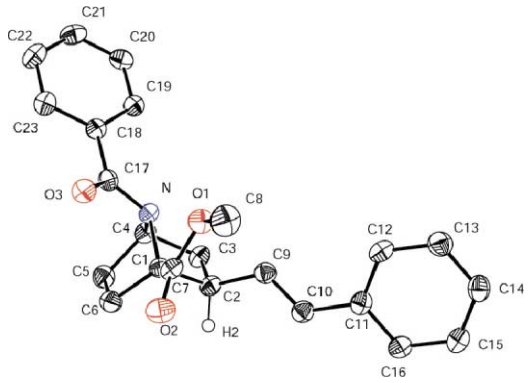


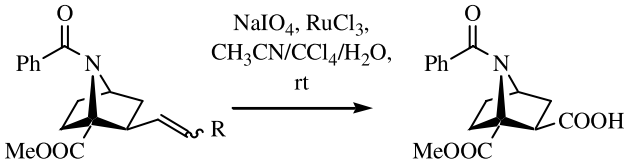
Figure 1. ORTEP drawing of compound (*E*)-**4c**. The C-2 hydrogen is represented by a sphere of arbitrary size, the rest of the hydrogen atoms have been omitted for clarity. Non-hydrogen atoms are represented by ellipsoids corresponding to 50% probability.

low conversion into products. The use of strong bases, such as *n*-BuLi or MeONa, to generate the ylide under anhydrous conditions did not improve the results. Thus, starting material **3** was completely consumed upon addition to the phosphorane generated with *n*-BuLi, but Wittig adducts were not detected (Table 1, entry 4). On using MeONa the conversion of **3** was total at room temperature after only 20 min, but a complex mixture of products was obtained due to partial epimerization at C-2. Formation of the ylide in situ using propylene oxide also led to a mixture of C-2 epimeric products (Table 1, entry 5).

As an alternative, we explored the reactivity of **3** with cyanomethylenetriphenylphosphorane, which would also allow access to a carboxylic acid function by hydrolysis of the cyano group. The method involving cyanomethyltriphenylphosphonium chloride and *n*-BuLi in THF proved to be unsuitable due to a lack of reproducibility in these experiments. After numerous trial reactions, generation of the ylide—from the freshly prepared phosphonium halide—with an excess of propylene oxide in the presence of the carbonyl compound **3** cleanly led to a 52/48 *Z*/*E* mixture of methyl (1*S*,2*S*,4*R*)-*N*-benzoyl-2-(2-cyanovinyl)-7-azabicyclo-[2.2.1]heptane-1-carboxylate **4d** (Table 1, entry 6). Although this process required 3 days for total conversion, the isomers were isolated by column chromatography in excellent yield (99%) and were separated for full characterisation. The assignment of the double bond stereochemistry for each isomer was made according to the coupling constants between the olefinic proton signals in the ^{1}H NMR spectra of the isolated products (J=11.0 Hz and J=16.2 Hz for the *Z* and *E* isomers, respectively).

The results obtained with the stabilised ylides were not completely satisfactory due to the formation of epimeric mixtures of isomers and the long reaction times required to achieve total conversion of **3**. Therefore, in order to improve the efficiency of this methodology, the reaction of **3** with a phosphonate was tested (Scheme 2). The Horner–Wittig reaction, using methyl diethylphosphonoacetate and NaH in dry THF at room temperature, cleanly provided a 12/88 *Z*/*E* mixture of **4e** in excellent yield (95%) after only 45 min (Table 1, entry 7). For characterisation purposes, the isomers were separated by column chromatography and measurement of the coupling constants for the olefinic proton signals in the ^{1}H NMR spectra allowed the double bond stereochemistry to be assigned (J=12.0 Hz and J=15.0 Hz for the *Z* and *E* isomers, respectively).

Bearing in mind the possible epimerization problem detected at C-2 and in order to verify the *exo* stereochemistry of the isolated Wittig adducts, oxidative cleavage of the double bond under Sharpless conditions[25] was carried out on **4a** and the isomeric mixtures (*Z*/*E*)-**4b**–**e**. This procedure transformed all the products into the carboxy derivative **7** (Scheme 4). The stereochemistry at C-2 of these Wittig adducts was therefore confirmed, since we had already reported the synthesis of **7** through two consecutive stereocontrolled processes that involved acetal hydrolysis of the key intermediate **2** and subsequent oxidative cleavage of the resulting diol.[18]



4a-e **7**

Scheme 4. Oxidative cleavage of **4a**–**e**.

Moreover, an additional and rigorous proof of the assignment of the stereochemistry at C-2 was provided by single-crystal X-ray analysis of **7**, the direct precursor of the 7-azabicyclo[2.2.1]heptane L-aspartic acid analogue, as shown in Fig. 2. These data unquestionably demonstrate the *exo* configuration at the β-position.

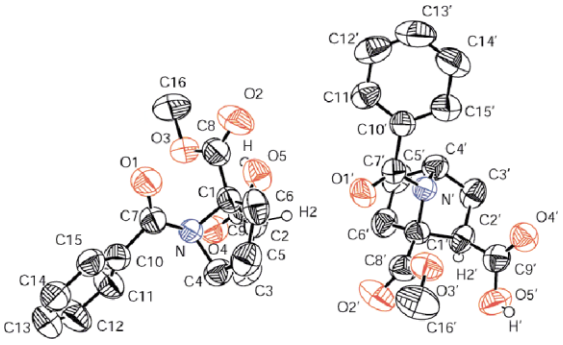


Figure 2. ORTEP drawing of compound **7**. This picture shows the molecules comprised in the asymmetric unit cell. Non-hydrogen atoms are represented by ellipsoids corresponding to 30% probability. The acidic and C-2 hydrogens are represented by spheres of arbitrary size, the rest of the hydrogen atoms have been omitted for clarity.

The next stage of our investigation involved the elaboration of these systems to give azabicyclic amino acids (Scheme 5). The first step involved hydrogenation of the double bond and the use of a catalytic amount of palladium hydroxide at room temperature and atmospheric pressure cleanly afforded the corresponding saturated compounds **8a–e** in excellent yields ($\geq$91%). Final hydrolysis of compounds **8a–e** with 6N hydrochloric acid under reflux gave the desired products in very good yields (94% for **9a**, 97% for **9b**,[18] 85% for **9c** and quantitative yield for **9d** from **8d** or **8e**). Compounds **9a–d** are (2*S*,3*R*)-3-ethylproline, (2*S*,3*R*)-3-propylproline, (2*S*,3*R*)-3-(2-phenylethyl)proline and (2*S*,3*R*)-3-(2-carboxyethyl)proline analogues, respectively. These products can also be considered as proline–L-norvaline **9a**, proline–L-norleucine **9b**, proline–L-α-(3-phenylpropyl)glycine **9c** and proline–L-homoglutamic acid **9d** chimeras with a 7-azabicyclo[2.2.1]heptane skeleton.

3. Conclusions

Wittig olefination of compound **3** has been shown to be an efficient way of introducing amino acid side chains via the corresponding non-stabilised and semi-stabilised triphenylphosphonium ylides. In this way, (2*S*,3*R*)-3-ethylproline **9a**, (2*S*,3*R*)-3-propylproline **9b** and (2*S*,3*R*)-3-(2-phenylethyl)proline **9c** analogues, which actually consist of combinations of proline with L-norvaline, L-norleucine and L-α-(3-phenylpropyl)glycine containing a 7-azabicyclo[2.2.1]heptane structure, have been obtained in enantiopure form in 35, 41 and 34% overall yield, respectively, from oxazolone **1*Z***.

The use of the Horner–Wittig variation leads to an improvement in the results obtained in comparison to the Wittig procedure with stabilised phosphoranes and provides excellent conditions for the synthesis of the enantiomerically pure (2*S*,3*R*)-3-(2-carboxyethyl)-proline analogue **9d** with a 7-azabicyclo[2.2.1]heptane skeleton. The product, a combination of proline with L-homoglutamic acid, was obtained in 48% overall yield from **1*Z***.

4. Experimental

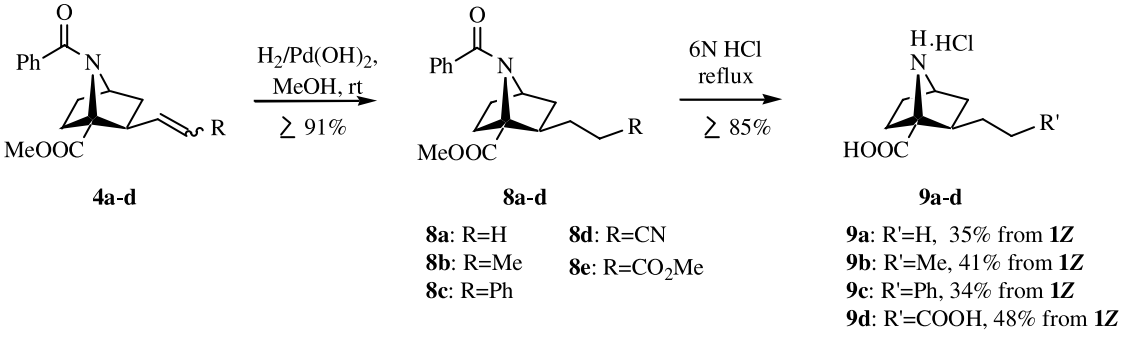
4.1. General

Melting points were determined using a Gallenkamp apparatus and are uncorrected. 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 rt, using the residual solvent signal as the internal standard; chemical shifts (δ) are quoted in ppm, and coupling constants (J) are measured in hertz. Optical rotations were measured in a cell with a 10 cm pathlength at 25°C using a JASCO P-1020 polarimeter. Elemental analyses were carried out on a Perkin–Elmer 200 C, H, N, S analyser. High resolution mass spectral data (HRMS) were obtained on a VG AutoSpec spectrometer. TLC was performed on Polygram® sil G/UV$_{254}$ precoated silica gel polyester plates and products were visualised under UV light (254 nm) or using ninhydrin, anisaldehyde or phosphomolybdic acid developers. Column chromatography was performed using silica gel (Kieselgel 60). HPLC was carried out on a system equipped with a Waters 600-E pump and a Waters 2487 dual absorbance detector and the solvents used as mobile phases were of spectral grade. 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**[18] and cyanomethyltriphenylphosphonium chloride[26] were obtained according to the literature procedures.

4.2. X-Ray diffraction

The X-ray diffraction data were collected at rt on a Bruker Smartapex CCD Area diffractometer, using graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å). The structure was solved by direct methods using SHELXS-97[27] and refinement was performed using SHELXL-97[28] by the full-matrix least-squares technique with anisotropic thermal factors for heavy atoms.

Colourless single crystals of (*E*)-**4c** were obtained by slow evaporation from an ether solution. Reflections



4a-d **8a-d** **9a-d**

8a: R=H
8b: R=Me
8c: R=Ph
8d: R=CN
8e: R=CO_2Me

9a: R'=H, 35% from **1*Z***
9b: R'=Me, 41% from **1*Z***
9c: R'=Ph, 34% from **1*Z***
9d: R'=COOH, 48% from **1*Z***

Scheme 5. Elaboration to the azabicyclic amino acids.

were measured in the $\omega/2\theta$-scan mode in the θ range 2–28°. Hydrogen atoms were located by calculation and affected by an isotropic thermal factor fixed to 1.2 times the U_{eq} value of the carrier atom (1.5 for the methyl protons). Crystallographic data: orthorhombic, $P2_12_12_1$; $a=9.7030(8)$ Å; $b=12.6509(11)$ Å, $c=15.5470(13)$ Å; $Z=4$; $d_{calcd}=1.258$ g cm^{-3}; reflections collected/independent: 12310/4404 [R(int) = 0.0388]; data/parameters: 4404/244; final R indices [$I>2\sigma(I)$]: $R_1=0.037$, $wR_2=0.069$; final R indices (all data): $R_1=0.050$, $wR_2=0.072$.

Colourless single crystals of **7** were obtained by slow evaporation from a dichloromethane/*n*-hexane solution. Reflections were measured in the $\omega/2\theta$-scan mode in the θ range 2–25°. Hydrogen atoms were located by calculation (with the exception of the acidic proton, which was found on the E-map) and affected by an isotropic thermal factor fixed to 1.2 times the U_{eq} value of the carrier atom (1.5 for the methyl protons). Crystallographic data: triclinic, $P3_1$; $a=b=11.0492(17)$ Å, $c=21.961(5)$ Å; $Z=6$; $d_{calcd}=1.301$ g cm^{-3}; reflections collected/independent: 12723/5427 [R(int) = 0.0558]; data/parameters: 5427/404; final R indices [$I>2\sigma(I)$]: $R_1=0.042$, $wR_2=0.071$; final R indices (all data): $R_1=0.084$, $wR_2=0.080$.

Crystallographic data (excluding structure factors) for the structures of compounds **4c** and **7** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 200457 and 200458, respectively. Copies of the data can be obtained, free of charge, via http://www.ccdc.cam.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. Synthesis of methyl (1*S*,2*R*,4*R*)-*N*-benzoyl-2-formyl-7-azabicyclo[2.2.1]heptane-1-carboxylate, 3

A mixture of 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** (1.0 g, 2.8 mmol) and H_5IO_6 (1.3 g, 5.6 mmol) in a 1/1 ether/THF mixture (100 mL) was stirred at rt for 8 h. The resulting mixture was filtered and the solvent was evaporated under vacuum. Dichloromethane was added and the organic phase was washed with water and brine. The organic layer was dried over anhydrous $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. Compound **3** was isolated from the crude mixture by flash chromatography (eluent: 1/1 ethyl acetate/*n*-hexane) as a white solid in 88% yield (702 mg, 2.4 mmol). Mp = 110°C. $[\alpha]_D=-7.6$ (c 1, $CHCl_3$). [lit.[18] mp = 108°C. $[\alpha]_D=-6.7$ (c 1, $CHCl_3$)].

4.4. General procedures for the Wittig olefination of methyl (1*S*,2*R*,4*R*)-*N*-benzoyl-2-formyl-7-azabicyclo-[2.2.1]heptane-1-carboxylate, 3

Method a. To a suspension of the corresponding phosphonium halide (1.2 mmol) in dry THF (9 mL) was added a solution of *n*-BuLi (0.75 mL, 1.6 M in *n*-hexane, 1.2 mmol) at rt and the mixture was stirred at this temperature for 30 min. The mixture was cooled (see Table 1) and a solution of aldehyde **3** (300 mg, 1.0 mmol) in dry THF (6 mL) was added. The mixture was stirred at the temperature indicated in Table 1. When the reaction was complete (see Table 1), it was quenched by addition of saturated aqueous NH_4Cl. The resulting mixture was stirred for 5 min at rt. The solution was concentrated under vacuum and the aqueous residue was extracted with dichloromethane (3×10 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The resulting residues were analysed by ^{1}H NMR spectroscopy. Where appropriate, the Z/E ratios were determined by integration of the signals in the ^{1}H NMR spectrum of the crude product and the Wittig adducts were purified by column chromatography.

Method b. The corresponding phosphonium halide (2.0 mmol) was added to a solution of aldehyde **3** (100 mg, 0.35 mmol) in propylene oxide (20 mL) at rt and the mixture was stirred (see Table 1 for temperature and reaction time). When the reaction was complete the solvent was evaporated under reduced pressure and the residue dissolved in dichloromethane. The organic layer was washed with water, dried over $MgSO_4$ and concentrated under vacuum. The reaction residues were analysed by ^{1}H NMR spectroscopy. Where appropriate, the Z/E ratios were determined by integration of the signals in the ^{1}H NMR spectrum of the crude product and the resulting adducts were purified by column chromatography.

4.4.1. Methyl (1*S*,2*S*,4*R*)-*N*-benzoyl-2-vinyl-7-azabicyclo[2.2.1]heptane-1-carboxylate, 4a. According to *method a*, the use of methyltriphenylphosphonium iodide as the reagent and flash chromatography (eluent: 9/1 dichloromethane/ethyl acetate) as the purification technique afforded compound **4a** as an oil in 75% yield. $[\alpha]_D=-53.6$ (c 1, $CHCl_3$). IR (neat) ν (cm^{-1}): 3070–2873, 1737, 1657. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.48–1.57 (m, 1H), 1.60–1.72 (m, 1H), 1.81–1.95 (m, 3H), 2.42 (ddd, 1H, $J=4.6$ Hz, $J=12.7$ Hz, $J=12.7$ Hz), 2.61–2.69 (m, 1H), 3.72 (s, 3H), 4.22 (dd, 1H, $J=4.6$ Hz, $J=4.6$ Hz), 4.93 (m, 2H), 5.93 (ddd, 1H, $J=9.8$ Hz, $J=10.6$ Hz, $J=16.5$ Hz), 7.38–7.44 (m, 2H), 7.71–7.75 (m, 1H), 7.69–7.72 (m, 2H). ^{13}C NMR ($CDCl_3$) δ (ppm): 30.3, 30.6, 37.9, 51.6, 51.8, 62.1, 71.4, 114.1, 128.3, 128.8, 131.7, 134.6, 139.9, 170.1, 173.9.

4.4.2. (*Z*/*E*)-Methyl (1*S*,2*S*,4*R*)-*N*-benzoyl-2-(1-propenyl)-7-azabicyclo[2.2.1]heptane-1-carboxylate, 4b. Following *method a*, with ethyltriphenylphosphonium bromide as the reagent and flash chromatography (eluent: 6/4 ethyl acetate/*n*-hexane) as purification technique, a 71/29 mixture of (*Z*/*E*)-**4b** was obtained in 93% yield. This compound was used in the next step without purification. However, the separation of (*Z*)- and (*E*)-**4b** was carried out for characterisation purposes.

High performance liquid chromatography. HPLC was performed using a non-commercial polysaccharide-derived support, consisting of mixed 10-undecenoate/4-methylbenzoate of cellulose covalently bonded to allylsilica gel, as the chiral stationary phase.[29,30] The separation of (*Z*/*E*)-**4b** was carried out by successive injections of 2.5 μL (*c* 100 mg mL^{-1} in dichloromethane) on a 150×4.6 mm ID column using as eluent a 98/2 mixture of *n*-hexane/ethanol with a flow rate of 1 mL min^{-1} and UV monitoring at 280 nm. A total of 37 injections were required with an injection being performed every 8 min. Three separate fractions were collected. Evaporation of the first fraction provided an analytically pure sample (2.1 mg) of the major isomer. The second (2.0 mg) and third (2.5 mg) fractions contained (*Z*/*E*)-**4b** mixtures, the latter consisting of a mixture enriched with the minor isomer (23/77).

Assignment of the double bond stereochemistry. The double bond stereochemistry of the isomers was assigned by ^{1}H NMR experiments. Irradiation of the olefinic methyl signal in the ^{1}H NMR analysis of the first HPLC fraction, which contained a pure sample of the major isomer, provided a spectrum in which the olefinic proton signals at 5.44 ppm (d, 1H, J=11.0 Hz) and 5.53 ppm (dd, 1H, J=9.6 Hz, J=11.0 Hz) did not show any coupling with the olefinic methyl group. Therefore, the coupling constant between olefinic protons could be clearly measured (J=11.0 Hz), allowing a *Z* configuration to be assigned to the major product. A similar experiment was also performed on the spectrum of the third HPLC fraction, which was a mixture enriched with the minor isomer. In this case, irradiation of the olefinic methyl signals of both isomers revealed the signals corresponding to the olefinic protons for the minor reaction product at 5.36 ppm (d, 1H, J=15.0 Hz) and 5.51 ppm (dd, 1H, J=9.3 Hz, J=15.0 Hz). The observed coupling constant between them (J=15.0 Hz) confirmed an *E* stereochemistry for this isomer. Having assigned the stereochemistry of each isomer, the *Z*/*E* ratio of the reaction mixture was determined as 71/29 by integration of its ^{1}H NMR spectrum.

(*Z*)-**4b**: ^{1}H NMR ($CDCl_3$) δ (ppm): 1.50–1.62 (m, 6H), 1.86–1.96 (m, 2H), 2.43 (ddd, 1H, J=4.8 Hz, J=12.1 Hz, J=12.5 Hz), 3.02 (ddd, 1H, J=4.8 Hz, J=8.8 Hz, J=9.2 Hz), 3.72 (s, 3H), 4.22 (dd, 1H, J=4.4 Hz, J=4.8 Hz), 5.41–5.60 (m, 2H), 7.38–7.53 (m, 3H), 7.72–7.75 (m, 3H). Note: the small quantity of single pure isomer (the major *Z* isomer) only allowed its IR and ^{1}H NMR characterisation.

4.4.3. (*Z*/*E*)-Methyl (1*S*,2*S*,4*R*)-*N*-benzoyl-2-(2-phenylvinyl)-7-azabicyclo[2.2.1]heptane-1-carboxylate, 4c. Following *method a*, with benzyltriphenylphosphonium chloride as the reagent and flash chromatography (eluent: 6/4 ethyl acetate/*n*-hexane), as the purification technique gave a mixture 6/94 of (*Z*/*E*)-**4c** in 93% yield. This compound was used in the next step without further purification. The chromatographic purification also allowed the partial separation of the major *E* isomer.

(*E*)-**4c**: White solid. Mp=173°C. $[\alpha]_D$=−125.1 (*c* 0.5, $CHCl_3$). IR (Nujol) ν (cm^{-1}): 1734, 1648. ^{1}H NMR (benzene-d_6) δ (ppm): 0.98 (m, 1H), 1.24–1.36 (m, 2H), 1.53–1.62 (m, 1H), 1.76 (ddd, 1H, J=4.8 Hz, J=9.2 Hz, J=12.5 Hz), 2.51 (ddd, 1H, J=4.8 Hz, J=9.2 Hz, J=9.2 Hz), 2.70 (ddd, 1H, J=4.0 Hz, J=12.5 Hz, J=12.5 Hz), 3.43 (s, 3H), 3.75 (dd, 1H, J=4.8 Hz, J=4.8 Hz), 6.22 (d, 1H, J=15.8 Hz), 6.50 (dd, 1H, J=9.9 Hz, J=15.8 Hz), 7.01–7.15 (m, 6H), 7.33–7.36 (m, 2H), 7.78–7.82 (m, 2H). ^{13}C NMR ($CDCl_3$) δ (ppm): 30.1, 30.3, 38.2, 51.2, 51.7, 62.2, 71.8, 126.3, 127.2, 128.3, 128.5, 128.9, 129.4, 131.7, 131.9, 134.7, 137.2, 170.2, 174.0. Elemental analysis calcd for $C_{23}H_{23}NO_3$: C, 76.43; H, 6.41; N, 3.88. Found: C, 76.83; H, 6.61; N, 3.87.

4.4.4. (*Z*/*E*)-Methyl (1*S*,2*S*,4*R*)-*N*-benzoyl-2-(2-cyanovinyl)-7-azabicyclo[2.2.1]heptane-1-carboxylate, 4d. Following *method b*, using cyanomethyltriphenylphosphonium chloride as the reagent gave a 52/48 mixture of (*Z*/*E*)-**4d**. Purification of the crude reaction product by flash chromatography (eluent: 9/1 ether/*n*-hexane) provided the *Z* and *E* isomers in 99% yield and allowed their partial separation for characterisation purposes.

(*Z*)-**4d**: White solid. Mp=107°C. $[\alpha]_D$=+32.1 (*c* 1, $CHCl_3$). IR (Nujol) ν (cm^{-1}): 2214, 1728, 1644. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.58–1.73 (m, 2H), 1.85–2.01 (m, 2H), 2.08 (dd, 1H, J=8.8 Hz, J=12.9 Hz), 2.44 (ddd, 1H, J=5.1 Hz, J=13.2 Hz, J=13.2 Hz), 3.30 (m, 1H), 3.78 (s, 3H), 4.31 (dd, 1H, J=4.8 Hz, J=4.8 Hz), 5.26 (d, 1H, J=11.0 Hz), 6.81 (dd, 1H, J=11.0 Hz, J=11.0 Hz), 7.39–7.44 (m, 2H), 7.49–7.54 (m, 1H), 7.67–7.72 (m, 2H). ^{13}C NMR ($CDCl_3$) δ (ppm): 30.0, 32.2, 38.2, 47.5, 52.3, 61.5, 70.4, 97.5, 115.9, 128.4, 128.7, 131.9, 134.0, 155.7, 169.2, 172.9.

(*E*)-**4d**: White solid. Mp=137°C. $[\alpha]_D$=+4.8 (*c* 0.5, $CHCl_3$). IR (Nujol) ν (cm^{-1}): 2220, 1737, 1656. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.50–1.59 (m, 1H), 1.71–1.96 (m, 4H), 2.36–2.46 (m, 1H), 2.78 (ddd, 1H, J=4.4 Hz, J=8.8 Hz, J=9.9 Hz), 3.74 (s, 3H), 4.27 (dd, 1H, J=4.8 Hz, J=4.8 Hz), 5.23 (d, 1H, J=16.2 Hz), 6.84 (dd, 1H, J=10.3 Hz, J=16.2 Hz), 7.38–7.43 (m, 2H), 7.47–7.53 (m, 1H), 7.66–7.69 (m, 2H). ^{13}C NMR ($CDCl_3$) δ (ppm): 30.3, 31.3, 37.6, 50.0, 52.2, 61.7, 70.9, 98.6, 117.1, 128.5, 128.7, 132.1, 134.0, 155.9, 169.3, 173.3. Elemental analysis calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.65; H, 5.90; N, 9.04.

4.5. Procedure for the Horner–Wittig olefination of (1*S*,2*R*,4*R*)-*N*-benzoyl-2-formyl-7-azabicyclo[2.2.1]heptane-1-carboxylate, 3

To a suspension of NaH (33.6 mg, 1.4 mmol) in dry THF (6 mL) was added methyl diethylphosphonoacetate (294 mg, 1.4 mmol) and the mixture was stirred for 1 h. A solution of the carbonyl compound **3** (200 mg, 0.70 mmol) in THF (4 mL) was added at rt and the stirring was continued for 45 min. When the reaction was complete it was quenched by the addition of water

(10 mL). The solution was concentrated under vacuum and the aqueous residue was extracted with dichloromethane (3×20 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and the solvent was evaporated under vacuum. The ^1H NMR spectrum of the crude product revealed a 12/88 mixture of (*Z*/*E*)-methyl (1*S*,2*S*,4*R*)-*N*-benzoyl-2-(2-carbomethoxyvinyl)-7-azabicyclo[2.2.1]heptane-1-carboxylate **4e**. The geometric isomers were purified by column chromatography (eluent: 1/1 ethyl acetate/*n*-hexane), which afforded the two compounds in 95% yield (228 mg, 0.66 mmol). Moreover, the chromatographic separation supplied a small amount of the *Z* isomer (25 mg) and a mixture of the two isomers from which the *E* isomer was isolated in pure form by precipitation with ether.

(*Z*)-**4e**: Oil. $[\alpha]_D=-7.9$ (*c* 0.5, $CHCl_3$). IR (neat) *v* (cm^{-1}): 3056–2853, 1741, 1638, 1629, 1599, 1577. ^1H NMR ($CDCl_3$) δ (ppm): 1.53–1.70 (m, 2H), 1.72–1.85 (m, 1H), 1.89–1.97 (m, 1H), 2.08 (dd, 1H, $J=8.8$ Hz, $J=12.2$ Hz), 2.41 (ddd, 1H, $J=4.9$ Hz, $J=12.2$ Hz, $J=12.7$ Hz), 3.68 (s, 3H), 3.74 (s, 3H), 4.11 (ddd, 1H, $J=4.9$ Hz, $J=9.3$ Hz, $J=9.3$ Hz), 4.24 (dd, 1H, $J=4.9$ Hz, $J=4.9$ Hz), 5.71 (dd, 1H, $J=1.0$ Hz, $J=11.7$ Hz), 6.60 (dd, 1H, $J=10.2$ Hz, $J=11.7$ Hz), 7.36–7.42 (m, 2H), 7.45–7.51 (m, 1H), 7.67–7.69 (m, 2H). ^{13}C NMR ($CDCl_3$) δ (ppm): 30.4, 31.6, 38.5, 44.5, 51.1, 52.1, 61.7, 70.5, 117.1, 128.4, 128.7, 131.7, 134.5, 150.9, 166.7, 169.7, 174.1. HRMS *m*/*z* (EI) calcd for $C_{19}H_{21}NO_5$: 343.1420. Found: 343.1407.

(*E*)-**4e**: White solid. Mp = 145°C. $[\alpha]_D=-42.3$ (*c* 1, $CHCl_3$). IR (Nujol) *v* (cm^{-1}): 1728, 1712, 1652. ^1H NMR ($CDCl_3$) δ (ppm): 1.49–1.58 (m, 1H), 1.64–1.75 (m, 1H), 1.81–1.91 (m, 3H), 2.44 (ddd, 1H, $J=4.4$ Hz, $J=12.5$ Hz, $J=12.5$ Hz), 2.74–2.82 (m, 1H), 3.69 (s, 3H), 3.71 (s, 3H), 4.25 (dd, 1H, $J=3.7$ Hz, $J=3.7$ Hz), 5.70 (d, 1H, $J=15.4$ Hz), 7.02 (dd, 1H, $J=10.3$ Hz, $J=15.8$ Hz), 7.37–7.43 (m, 2H), 7.47–7.52 (m, 1H), 7.70–7.73 (m, 2H). ^{13}C NMR ($CDCl_3$) δ (ppm): 30.4, 30.5, 37.3, 49.5, 51.5, 51.8, 61.9, 71.1, 120.0, 128.4, 128.8, 131.8, 134.2, 149.1, 166.6, 169.6, 173.6. Elemental analysis calcd for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.16; N: 4.08. Found: C, 66.11; H, 6.28; N, 4.31.

4.6. Procedure for the Corey–Winter olefination of 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

4.6.1. Synthesis of methyl (1*S*,2*S*,4*R*)-*N*-benzoyl-2-[(*S*)-2-thionocarbonyl-1,3-dioxolan-4-yl]-7-azabicyclo[2.2.1]-heptane-1-carboxylate, 6. To a solution of diol **5** (100 mg, 0.31 mmol) in dry toluene (10 mL) was added *N*,*N*′-thiocarbonyldiimidazole (TCDI) (84 mg, 0.47 mmol). The mixture was kept under an argon atmosphere and heated under reflux for 1 h. The solution was concentrated under reduced pressure and the residue was purified by flash chromatography (eluent: 6/4 ethyl acetate/*n*-hexane). Thionocarbonate **6** was obtained in 83% yield (93 mg, 0.26 mmol) as a white solid. Mp = 97°C. $[\alpha]_D=-61.9$ (*c* 1, $CHCl_3$). IR (Nujol) *v* (cm^{-1}): 1730, 1650, 1335, 1299, 1276. ^1H NMR ($CDCl_3$) δ (ppm): 1.56–1.64 (m, 2H), 1.81–2.13 (m, 3H), 2.38–2.53 (m, 2H), 3.79 (s, 3H), 4.32 (dd, 1H, $J=4.8$ Hz, $J=4.8$ Hz), 4.47 (dd, 1H, $J=7.0$ Hz, $J=9.6$ Hz), 4.90 (dd, 1H, $J=7.7$ Hz, $J=9.6$ Hz), 5.23 (ddd, 1H, $J=7.0$ Hz, $J=7.7$ Hz, $J=10.3$ Hz), 7.41–7.47 (m, 2H), 7.51–7.57 (m, 1H), 7.66–7.69 (m, 2H). ^{13}C NMR ($CDCl_3$) δ (ppm): 29.7, 33.4, 35.6, 50.0, 52.8, 61.2, 69.0, 75.1, 83.74, 128.6, 128.7, 132.1, 133.6, 170.3, 172.9, 191.3. Elemental analysis calcd for $C_{18}H_{19}NO_5S$: C, 59.82; H, 5.30; N, 3.88. Found: C, 60.15; H, 5.09; N, 3.73.

4.6.2. Synthesis of methyl (1*S*,2*S*,4*R*)-*N*-benzoyl-2-vinyl-7-azabicyclo[2.2.1]heptane-1-carboxylate, 4a. 1,3-Dimethyl-2-phenyl-1,3,2-diazaphospholidine (DMPDAP) (91 μL, 0.49 mmol) was added to a solution of thionocarbonate **6** (59 mg, 0.16 mmol) in dry THF (1 mL). The mixture was heated under reflux under an argon atmosphere during 15 h. The solvent was evaporated under vacuum and the residue was purified by flash chromatography (eluent: 8/2 *n*-hexane/ethyl acetate). This procedure provided **4a** in 86% yield (39 mg, 0.14 mmol).

4.7. General procedure for the oxidative cleavage of 4a and the *Z*/*E* mixtures of 4b–e

$NaIO_4$ (1.44 mmol) was added to a solution of compound **4a** or the *Z*/*E* mixtures of **4b**–**e** (0.18 mmol) in a 1/1/1.2 carbon tetrachloride/acetonitrile/water mixture (1.6 mL). The biphasic solution was treated with $RuCl_3$ (2 mg, 0.01 mmol) and the mixture was vigorously stirred for 12 h at rt. Dichloromethane (5 mL) was added, the organic phase was separated and the aqueous phase extracted with dichloromethane (3×5 mL). The organic extracts were dried over $MgSO_4$ and concentrated under vacuum. The residue was analysed by ^1H NMR spectroscopy and, in all cases, carboxylic acid **7** was the only compound detected.[18]

4.8. General procedure for the hydrogenation of 4a and the alkene mixtures 4b–e

Compound **4a** or the corresponding *Z*/*E* mixtures of **4b**–**e** (100 mg) were dissolved in methanol (10 mL) and hydrogenated at atmospheric pressure and rt using palladium hydroxide (10 mg) as a catalyst. After 1 day the catalyst was filtered off through a Celite pad and the solvent was removed under vacuum to provide the corresponding saturated compound **8a**–**e**.

4.8.1. Methyl (1*S*,2*R*,4*R*)-*N*-benzoyl-2-ethyl-7-azabicyclo[2.2.1]heptane-1-carboxylate, 8a. Oil, 98% yield. $[\alpha]_D=-111.5$ (*c* 1, $CHCl_3$). IR (neat) *v* (cm^{-1}): 3059–2874, 1733, 1656. ^1H NMR ($CDCl_3$) δ (ppm): 0.83 (t, 3H, $J=7.2$ Hz), 1.24–1.52 (m, 2H), 1.56–1.69 (m, 3H), 1.75–1.83 (m, 2H), 1.86–1.95 (m, 1H), 2.38 (ddd, 1H, $J=4.6$ Hz, $J=12.1$ Hz, $J=12.4$ Hz), 3.77 (s, 3H), 4.17 (dd, 1H, $J=4.6$ Hz, $J=4.6$ Hz), 7.36–7.42 (m, 2H), 7.45–7.51 (m, 1H), 7.69–7.73 (m, 2H). ^{13}C NMR ($CDCl_3$) δ (ppm): 11.1, 26.4, 30.5, 31.0, 37.1, 49.0, 51.7, 62.3, 70.5, 128.2, 128.8, 131.5, 134.8, 171.0, 174.1.

HRMS (EI) m/z calcd for $C_{17}H_{21}NO_3$: 287.1521. Found: 287.1527.

4.8.2. Methyl (1*S*,2*R*,4*R*)-*N*-benzoyl-2-*n*-propyl-7-azabicyclo[2.2.1]heptane-1-carboxylate, 8b. Obtained in 91% yield and completely characterised, as described previously in the literature.[18]

4.8.3. Methyl (1*S*,2*R*,4*R*)-*N*-benzoyl-2-(2-phenylethyl)-7-azabicyclo[2.2.1]heptane-1-carboxylate, 8c. Oil, 95% yield. $[\alpha]_D = +62.4$ (c 1, $CHCl_3$). IR (neat) ν (cm^{-1}): 3056–2855, 1739, 1726, 1657, 1639, 1600, 1579. ^1H NMR ($CDCl_3$) δ (ppm): 1.41–1.51 (m, 1H), 1.58–1.86 (m, 5H), 1.91–2.05 (m, 2H), 2.33–2.49 (m, 2H), 2.58–2.67 (m, 1H), 3.76 (s, 3H), 4.18 (dd, 1H, $J=4.4$ Hz, $J=4.8$ Hz), 7.14–7.19 (m, 3H), 7.24–7.29 (m, 2H), 7.37–7.42 (m, 3H), 7.45–7.50 (m, 2H). ^{13}C NMR ($CDCl_3$) δ (ppm): 30.4, 31.1, 32.9, 35.1, 37.7, 46.5, 51.8, 62.2, 70.4, 125.8, 128.3, 128.4, 128.4, 128.8, 131.6, 134.9, 141.7, 170.8, 174.1.

4.8.4. Methyl (1*S*,2*R*,4*R*)-*N*-benzoyl-2-(2-cyanoethyl)-7-azabicyclo[2.2.1]heptane-1-carboxylate, 8d. White solid, 98% yield. Mp = 108°C. $[\alpha]_D = -66.8$ (c 0.5, $CHCl_3$). IR (neat) ν (cm^{-1}): 2245, 1743, 1667, 1602, 1578. ^1H NMR ($CDCl_3$) δ (ppm): 1.47–1.91 (m, 7H), 2.07–2.45 (m, 4H), 3.78 (s, 3H), 4.21 (dd, 1H, $J=4.4$ Hz, $J=4.8$ Hz), 7.36–7.42 (m, 2H), 7.46–7.52 (m, 1H), 7.65–7.69 (m, 2H). ^{13}C NMR ($CDCl_3$) δ (ppm): 14.7, 29.1, 30.2, 31.7, 37.2, 45.2, 52.2, 61.9, 70.0, 119.3, 128.4, 128.8, 131.9, 134.4, 170.3, 173.7. Elemental analysis calcd for $C_{18}H_{22}N_2O_3$: C, 69.21; H, 6.45; N, 8.97. Found: C, 69.10; H, 6.05; N, 8.39.

4.8.5. Methyl (1*S*,2*R*,4*R*)-*N*-benzoyl-2-(2-carbomethoxyethyl)-7-azabicyclo[2.2.1]heptane-1-carboxylate, 8e. Oil, quantitative yield. $[\alpha]_D = -76.3$ (c 1, $CHCl_3$). IR (neat) ν (cm^{-1}): 3059–2850, 1743, 1648, 1600, 1578. ^1H NMR ($CDCl_3$) δ (ppm): 1.40–1.51 (m, 1H), 1.59–1.83 (m, 5H), 1.93–2.06 (m, 2H), 2.13–2.44 (m, 3H), 3.66 (s, 3H), 3.78 (s, 3H), 4.17 (dd, 1H, $J=4.8$ Hz, $J=4.8$ Hz), 7.36–7.41 (m, 2H), 7.45–7.50 (m, 1H), 7.67–7.71 (m, 2H). ^{13}C NMR ($CDCl_3$) δ (ppm): 28.9, 30.4, 31.0, 31.4, 37.2, 46.2, 51.7, 52.0, 62.1, 70.3, 128.3, 128.8, 131.7, 134.6, 170.6, 173.6, 174.1. HRMS (EI) m/z calcd for $C_{19}H_{23}NO_5$: 345.1576. Found: 345.1577.

4.9. General procedure for the hydrolysis of compounds 8a–d

Aqueous 6N HCl (15 mL) was added to the amido esters **8a**–**e** (100 mg) and the mixture was heated under reflux for 24 h. 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 was evaporated to dryness. Total removal of water was achieved by final lyophilization. This procedure gave the amino acid hydrochlorides **9a**–**e**.

4.9.1. (1*S*,2*R*,4*R*)-2-Ethyl-7-azabicyclo[2.2.1]heptane-1-carboxylic acid hydrochloride, 9a. White solid, 94% yield. Mp = dec. $[\alpha]_D = -48.3$ (c 1, H_2O). IR (Nujol) ν (cm^{-1}): 3700–2000, 1728. ^1H NMR (D_2O) δ (ppm): 0.72 (t, 3H, $J=7.3$ Hz), 0.95–1.10 (m, 1H), 1.38–1.48 (m, 1H), 1.54–1.63 (m, 1H), 1.69–1.80 (m, 1H), 1.91–2.14 (m, 5H), 4.08 (dd, 1H, $J=4.4$ Hz, $J=4.8$ Hz). ^{13}C NMR (D_2O) δ (ppm): 9.9, 24.5, 26.6, 30.9, 34.5, 44.5, 58.4, 76.1, 172.2.

4.9.2. (1*S*,2*R*,4*R*)-2-Propyl-7-azabicyclo[2.2.1]heptane-1-carboxylic acid hydrochloride, 9b. Prepared in 97% yield according to the procedure reported previously.[18]

4.9.3. (1*S*,2*R*,4*R*)-2-(2-Phenylethyl)-7-azabicyclo[2.2.1]-heptane-1-carboxylic acid hydrochloride, 9c. White solid, 86% yield. Mp = dec. $[\alpha]_D = -48.5$ (c 0.5, H_2O). IR (Nujol) ν (cm^{-1}): 3500–3200, 1725. ^1H NMR (D_2O) δ (ppm): 1.32–1.45 (m, 1H), 1.62–1.74 (m, 3H), 1.81–2.12 (m, 5H), 2.29–2.43 (m, 1H), 2.53–2.62 (m, 1H), 4.07 (dd, 1H, $J=3.3$ Hz, $J=4.0$ Hz), 7.10–7.13 (m, 3H), 7.18–7.23 (m, 2H). ^{13}C NMR (D_2O) δ (ppm): 26.5, 30.9, 31.4, 33.1, 34.8, 41.9, 58.4, 76.1, 126.3, 128.6, 128.7, 141.4, 171.9.

4.9.4. (1*S*,2*R*,4*R*)-2-(2-Carboxyethyl)-7-azabicyclo-[2.2.1]heptane-1-carboxylic acid hydrochloride, 9d. White solid, quantitative yield. Mp = dec. $[\alpha]_D = -44.5$ (c 0.5, H_2O): (from **8d**). [Pale brown solid, quantitative yield. Mp: dec. $[\alpha]_D$ (c 0.5, H_2O): −42.3 (from **8c**)]. IR (Nujol) ν (cm^{-1}): 3256–2558, 1732, 1600. ^1H NMR (D_2O) δ (ppm): 1.27–1.40 (m, 1H), 1.54–1.63 (m, 1H), 1.68–1.79 (m, 2H), 1.91–2.06 (m, 4H), 2.13–2.35 (m, 3H), 4.08 (dd, 1H, $J=4.4$ Hz, $J=4.4$ Hz). ^{13}C NMR (D_2O) δ (ppm): 26.5, 26.8, 30.5, 31.0, 34.6, 41.8, 58.2, 76.3, 172.1, 177.6.

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