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Synthesis of constrained prolines by Diels–Alder reaction using a chiral unsaturated oxazolone derived from (*R*)-glyceraldehyde as starting material

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Abstract—This report describes a new route for the asymmetric synthesis of enantiomerically pure 2-substituted 7-azabicyclo[2.2.1]-heptane-1-carboxylic acids, which are new conformationally constrained β-functionalised proline analogues. Our strategy is based on the preparation of a valuable azabicyclic intermediate by a key step that involves the intramolecular cyclisation of a derivative obtained from the transformation of the adducts provided by the asymmetric Diels–Alder reaction of a chiral oxazolone derived from (*R*)-glyceraldehyde with Danishefsky's diene. The application of this procedure to the synthesis of (1*S*,2*R*,4*R*)-7-azabicyclo[2.2.1]heptane-1,2-dicarboxylic acid and (1*S*,2*R*,4*R*)-2-propyl-7-azabicyclo[2.2.1]heptane-1-carboxylic acid hydrochlorides, which can be also considered as L-aspartic acid and L-norleucine analogues respectively, is useful to illustrate the versatility of our methodology.

1. Introduction

The discovery of new therapeutic agents based on non-proteinogenic amino acids has boosted the synthesis of conformationally constrained amino acids, particularly since their incorporation into peptides was undeniably recognised as a powerful approach for generating structurally defined peptides that could be used as conformational probes and bioactive compounds.[1–4]

Quaternary α-amino acids represent a remarkable type of conformationally restricted α-amino acid in which the conformational rigidity is generated by the introduction of a substituent at the α-carbon (Fig. 1). Among the numerous types of α-amino acids that constitute this group, the acyclic derivatives **I** have played a very important role in the design of peptides whose properties have been enhanced as a result of the conformational restrictions induced by the introduction of these residues into peptide chains.[5–7] The search for new approaches to the preparation of symmetric derivatives and their applications has been surpassed by the interest in chiral compounds, as evidenced by a recent compilation of their stereoselective syntheses.[8]

Another variety of quaternary α-amino acids comprises cyclic derivatives in which conformational restrictions are increased by the introduction of the amino acid moiety within a ring structure. α-Amino acids with a carbocyclic structure containing the quaternary α-carbon represent a significant part of this group. The symmetric carbocyclic derivatives **II** have been widely studied (Fig. 1).

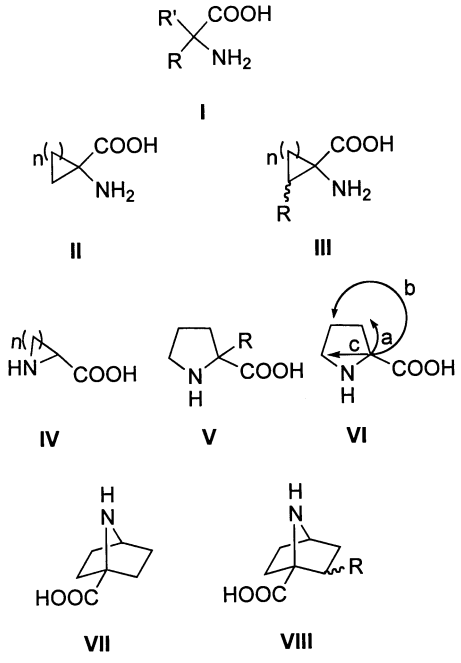

Figure 1.

Keywords: amino acids; constrained pralines; asymmetric synthesis; diastereoselective Diels–Alder reactions.

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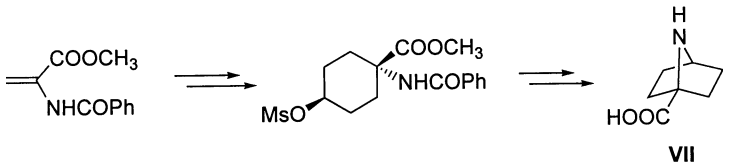


Scheme 1.

The introduction of an additional substituent in the β-position (**III**) is particularly attractive since it can turn these compounds into typical α-amino acids with a specific side chain restriction. The presence of a phenyl group at the β-carbon, for instance, gives rise to constrained phenylalanines. Some studies dealing with this subject have even explored the relationship between the absolute stereochemistry and the macroscopic properties of the model peptides containing these residues. In particular, we have conducted some surveys on 1-amino-2-phenylcyclopropanecarboxylic acid (c_3Phe), 1-amino-2-phenylcyclohexanecarboxylic acid (c_6Phe) and 1-amino-2,3-diphenylcyclopropanecarboxylic acid ($c_3$diPhe).[9–13] The significance of these conformationally restricted amino acids has translated into the development of different stereoselective synthetic methods, which have recently been reviewed.[14]

A very interesting way to decrease the conformational freedom of peptides involves the incorporation of residues **IV** where the nitrogen forms part of the ring (Fig. 1). This kind of amino acid constitutes a new family of compounds that can be considered as being related to prolines. Although there are very few references concerning the quaternary amino acids, and only a few α-alkylprolines **V** have been studied in detail,[15–17] their stereoselective synthesis has also been the subject of a review.[14]

Another possibility for the conformational restriction of α-alkylprolines involves connecting the α-carbon with another proline ring carbon, a process that entails the creation of diverse azabicyclic structures depending on the number of atoms involved in the formation of the new cycle **VI**. Several examples of proline analogues in which the α-carbon is linked to the β-**VIa**[18–23] or γ-carbon **VIb**[24–29] can be found in the literature.

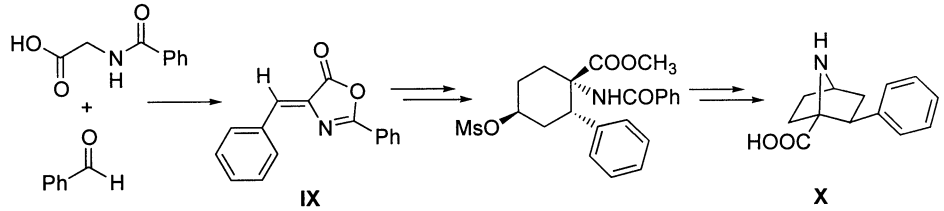
However, our attention here is focused on a third additional restriction to the proline ring that involves linking the α- and δ-carbons **VIc** through the construction of azabicyclo-[*n*.2.1]alkane skeletons.[30–43] In particular, we are interested in the connection through two carbons that leads to the creation of 7-azabicyclo[2.2.1]heptane rings **VII**.

Since the discovery of epibatidine by Daly and co-workers in 1992,[44] we have witnessed a proliferation of synthetic methods to construct this azabicyclic system.[45] The exceptional biological properties attributed to epibatidine and related analogues, as well as their possible clinical applications, have provided more than enough reasons to justify our interest. The first results regarding the benefits of proline analogues containing this structure as reasonable replacements for proline in the formation of a β-turn tripeptide mimetic[42] and as starting materials in the synthesis of a new class of HIV-1 protease inhibitor[39] have encouraged us to intensify our synthetic efforts.

In this context, and considering our experience in the use of α,β-didehydroamino acid derivatives as useful building blocks in synthetic organic chemistry, we have described a new procedure for the synthesis of the pattern compound 7-azabicyclo[2.2.1]heptane-1-carboxylic acid **VII**, which was prepared by Diels–Alder reaction of methyl 2-benzamidoacrylate (Scheme 1).[46]

Once again, the introduction of a substituent in the β-position **VIII** appears to be an interesting way to create a new 'chimera', a combination of α-amino acids and a constrained proline. To achieve this target, the application of the methodology described above to the corresponding trisubstituted α,β-didehydroamino acids was not feasible due to their very low reactivity as dienophiles in Diels–Alder reactions. Nevertheless, unsaturated oxazolones have proven to be a very valuable alternative since they show good reactivity in Diels–Alder cycloadditions[32,47–53] and have even allowed the synthesis of the desired compounds in their racemic form.[32] So, the preparation of exo-2-phenyl-7-azabicyclo[2.2.1]heptane-1-carboxylic acid **X** was carried out through a key step that involved the cycloaddition of (*Z*)-2-phenyl-4-benzylidene-5(4*H*)-oxazolone **IX** with Danishefsky's diene (Scheme 2).

More recently, and as a part of a study on the asymmetric Diels–Alder reaction, we reported the excellent behaviour of (*Z*)-2-phenyl-4-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-ylmethylene]-5(4*H*)-oxazolone, an unsaturated oxazolone derived from (*R*)-glyceraldehyde, as a dienophile towards several dienes.[54–59] This work enabled us to prepare enantiomerically pure carbocyclic quaternary α-amino acids.



Scheme 2.

We would like to report here the transformation of the cycloadducts derived from the reaction of this chiral oxazolone with Danishefsky's diene into the azabicyclic α-amino acids.

2. Results and discussion

According to the selected strategy we can divide our report into two different parts: the first covers the construction of the 7-azabicyclo[2.2.1]heptane structure and the second concerns the stereocontrolled manipulations of the 1,3-dioxolane ring. In this paper, we focus on the first part but, as an initial consideration of the vast diversity of potential transformations of the dioxolane moiety, we will also describe two examples of the preparation of enantiomerically pure α-amino acids.

2.1. Construction of the 7-azabicyclo[2.2.1]heptane system

We have already described the Diels–Alder reaction of (*Z*)-2-phenyl-4-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-ylmethylene]-5(4*H*)-oxazolone **1***Z*, derived from 1,2-*O*-isopropylidene-(*R*)-glyceraldehyde, and Danishefsky's diene.[58,59] The thermally induced reaction afforded a 1:1 mixture of cycloadducts **2a** and **2b** (Scheme 3). Hydrolysis of this mixture and subsequent elimination of the methoxy group and ring opening provided compound **4**.

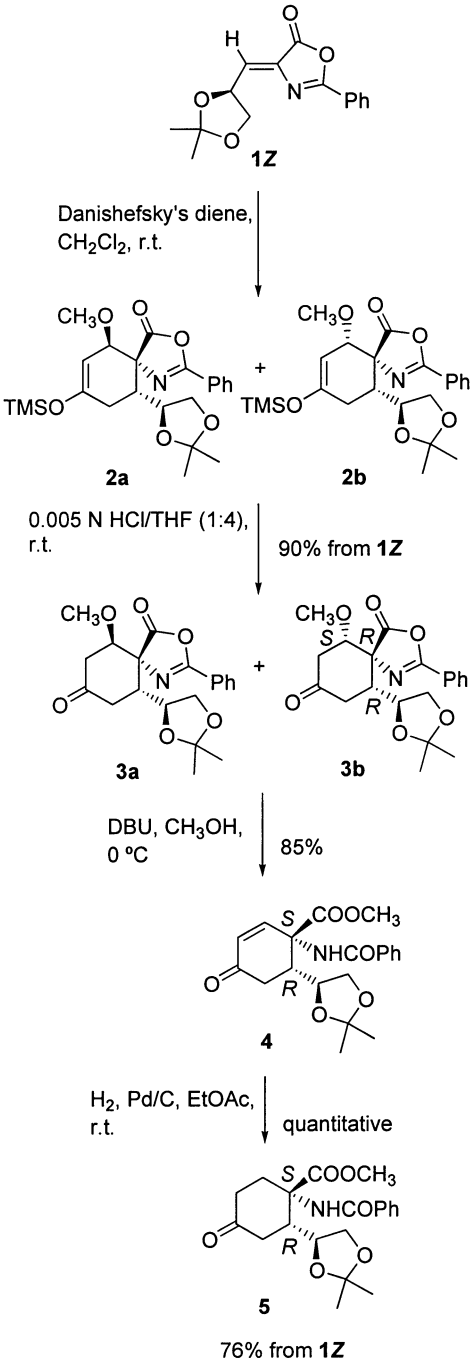
The absolute stereochemistry of the enone **4** and every preceding intermediate was confirmed by single crystal X-ray diffraction analysis of compound **3b**. From this result, we could confirm the attack of the diene at the $C_{\alpha\text{-Re}}$ face of the dienophile **1***Z* in accordance with the stereo-correlation model previously proposed for the attack of cyclopentadiene, cyclohexadiene and several open chain dienes on this oxazolone.[55,56]

Typical heterogeneous hydrogenation of the double bond of enone **4** afforded enantiomerically pure ketone **5** in nearly quantitative yield. Thus, starting from 8 g of oxazolone **1***Z*, this procedure supplied 8.26 g of ketone **5** in excellent overall yield (76%). Compound **5** is not only a valuable intermediate in the synthesis of a new conformationally constrained 4-oxo-1-aminocyclohexanecarboxylic acid in enantiomerically pure form, as we reported previously,[58,59] but a precursor of the aminocyclohexanol derivative that would allow us to achieve our current target.

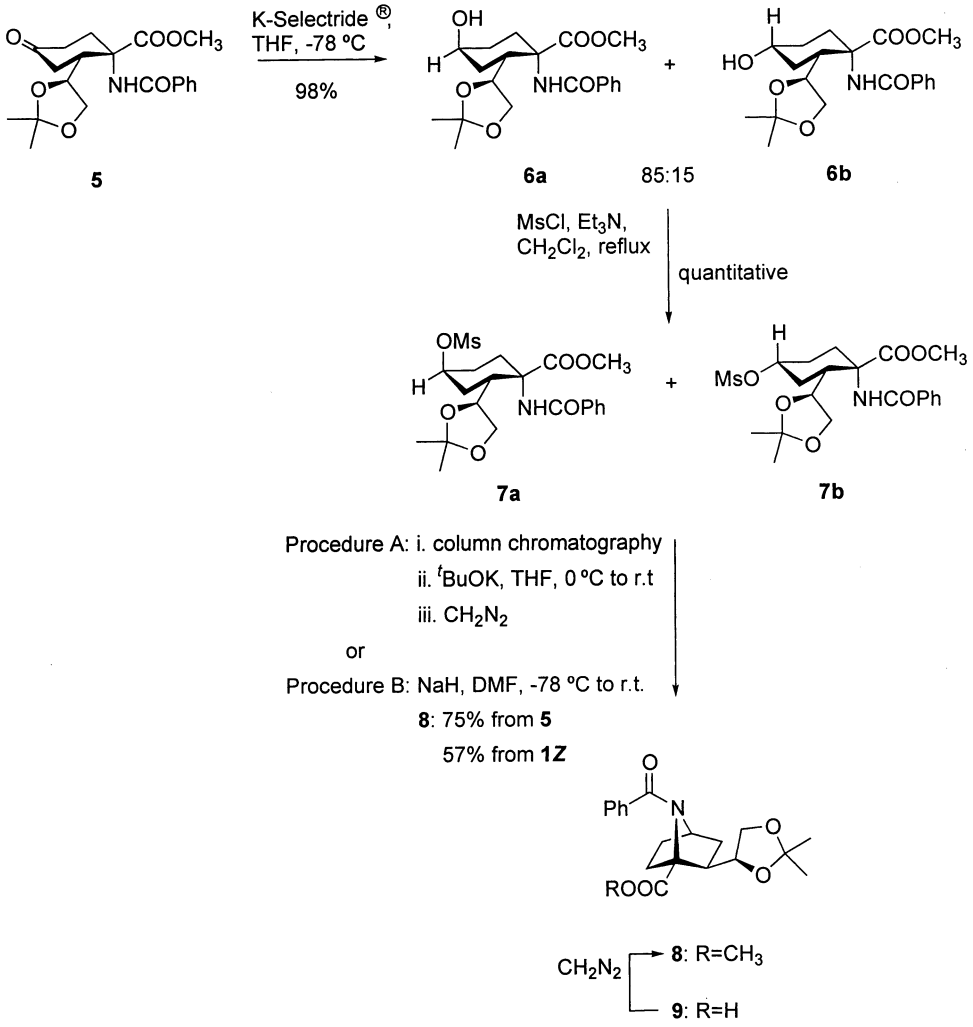
The preparation of the desired 4-hydroxyamino derivative involved the conversion of the ketone function on the cyclohexane ring into a hydroxy group (Scheme 4). Moreover, in order to make the subsequent cyclisation possible, hydroxy and benzamide groups on the cyclohexane skeleton were required to adopt axial positions, a situation that requires the synthesis of the kinetically controlled alcohol **6a**.

Several studies have demonstrated that the use of bulky reducing agents at low temperatures produces stereoselective processes that provide preferentially the kinetically controlled product. In accordance with these reports, and taking into account the highly favourable axial alcohol selectivity that lithium tri-*sec*-butylborohydride (L-selectride®) produced,[32,37] we decided to examine the influence of several hydride reagents on the course of the reaction.

As one might expect, L- and K-selectride® (lithium and potassium tri-*sec*-butylborohydride) provided preferentially the axial alcohol **6a** with a similar stereoselectivity (85:15). However, the use of $LiAlH(O^tBu)_3$ led to the thermodynamically controlled product **6b**, i.e. the equatorial alcohol, as a single isomer. The use of KS-selectride® (potassium trisiamylborohydride) did not lead to the desired products **6a** and **6b**.



Scheme 3.



Scheme 4.

All the reactions were performed at −78°C and the ratio of stereoisomers was determined from the crude reaction mixture by integration of the signals in the ^{1}H NMR spectra at 3.03 ppm (ddd, 1H, J=3.3, 3.3, 14.4 Hz) and 3.30 ppm (ddd, 1H, J=3.3, 3.3, 14.5 Hz) belonging to each isomer. The stereochemistry of the compound showing a signal at 3.03 ppm was assumed to correspond to the axial compound **6a**. Isolation of a small amount of compound **6a** allowed its characterisation and the subsequent cyclisation of its derivative allowed us to confirm the predicted stereochemistry.

From this study, we selected K-selectride® as the reducing agent of choice for the preparation of alcohol **6a** in the highest yield. Indeed, the reduction of cyclohexanone derivative **5** with K-selectride® in THF at −78°C gave an 85:15 mixture of axial and equatorial alcohols **6a** and **6b** in 98% yield.

The resulting mixture of the alcohols **6a** and **6b** was cleanly transformed into a mixture of the corresponding methanesulfonate derivatives **7a** and **7b** in nearly quantitative yield by treatment with methanesulfonyl chloride in triethylamine (Scheme 4). This mixture was purified by column chromatography and provided pure samples of both methanesulfonates, which were fully characterised.

The cyclisation of 4-aminocyclohexanol derivatives has become one of the most widely reported procedures to create 7-azabicyclo[2.2.1]heptane rings.[36,37,41,45] Base-promoted internal nucleophilic displacement of the methanesulfonate group had already been achieved by treatment with potassium *tert*-butoxide in THF.[32] The application of the same reaction conditions to the methanesulfonate **7a** produced a mixture of the ester derivative **8** and the carboxylic acid **9**, which could be transformed into compound **8** by addition of diazomethane. This combined treatment provided **8** in 65% yield, but the experiment could not be reproduced on a larger scale (several grams).

We therefore decided to carry out the intramolecular cyclisation of the methanesulfonate **7a** using sodium hydride (1.2 equiv.) with dry DMF as the solvent. These conditions, which had yet to be optimised, provided 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 (**8**) in good yield (76%).

Once again we optimised the conditions and were finally able to scale up the process. Thus, reduction of 5.05 g of ketone **5**, using K-selectride® under the aforementioned conditions, led to the alcohols **6a** and **6b** in an 85:15 ratio.

Treatment of this mixture with methanesulfonyl chloride and triethylamine in dry dichloromethane, followed by base-promoted internal nucleophilic displacement with sodium hydride (2.0 equiv.) in dry DMF, provided derivative **8** in 75% yield from ketone **5**.

In this way, the central goal of this investigation was achieved and we then undertook the first asymmetric synthesis of the enantiomerically pure product **8** on a scale of several grams. This process was achieved through seven fully stereocontrolled steps with an overall yield of 57% from oxazolone **1***Z*.

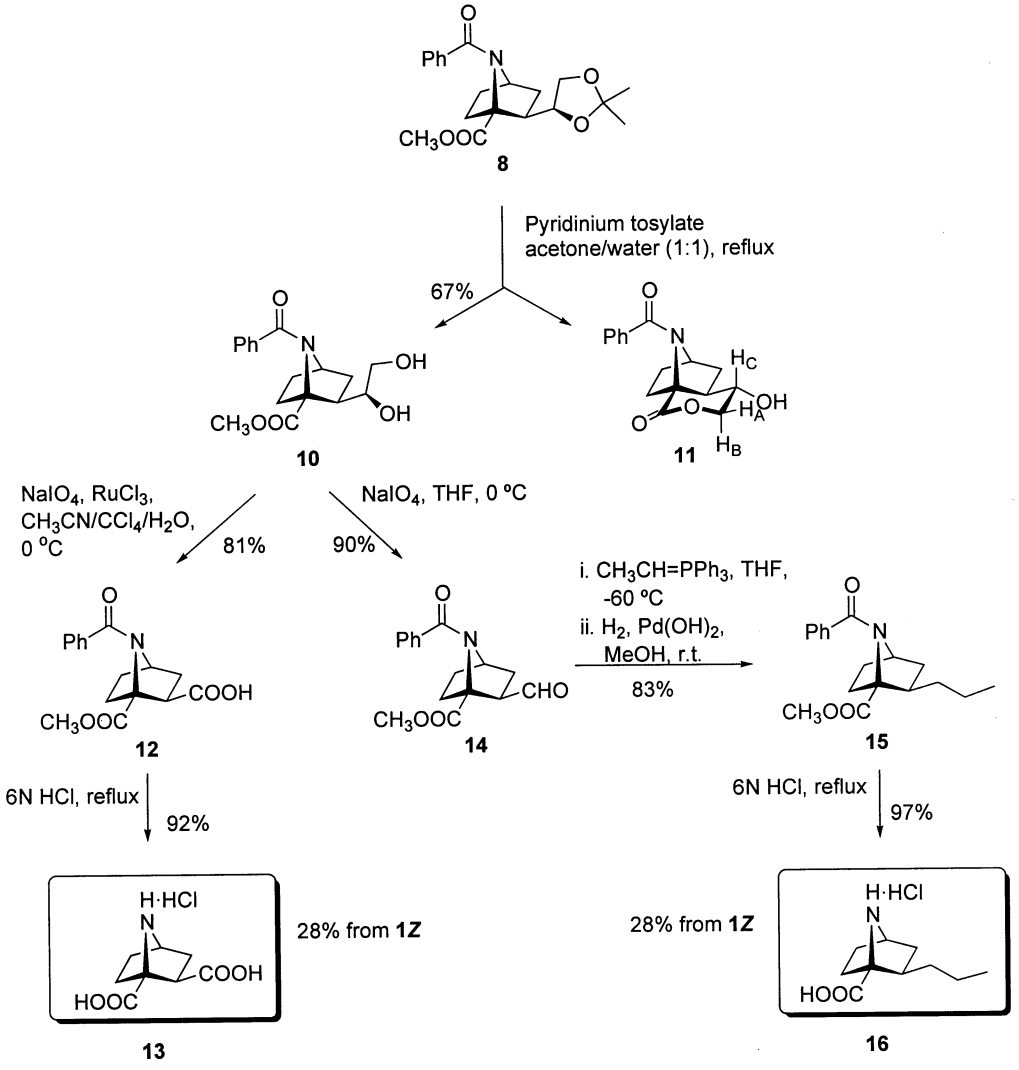
2.2. Transformation of the 1,3-dioxolane ring

After creating the 7-azabicyclo[2.2.1]heptane system, we undertook the manipulation of the 1,3-dioxolane ring in compound **8**. Some modifications have already been carried out, with high overall yields, on cyclopropane,[60–63] cyclohexane,[58] and bicyclic derivatives[57] arising from oxazolone **1***Z* and have given rise to analogues of several natural α-amino acids containing other cycloalkane skeletons in enantiomerically pure form.

The neurological effects that certain amino acids, such as glutamic and aspartic acid, induce in the mammalian central nervous system are well documented. A number of these compounds acts as excitatory neurotransmitters that activate the different receptors associated with a variety of physiological functions depending, sometimes, on their absolute configuration.[64–67] The introduction of conformational constraints into aspartic acid may provide useful information about conformational requirements for receptor binding and, at the same time, competitive antagonists of this type of excitatory amino acid. In addition, this approach may lead to new residues that can be considered in the design of conformationally constrained peptidomimetics with fascinating properties.

Taking into account the significance of these amino acids, we have undertaken a study of the asymmetric synthesis of L-aspartic acid analogues containing a cyclic skeleton.[57,58] As part of this study, we performed the stereocontrolled transformation of the dioxolane fragment of derivative **8** into an acid function (Scheme 5).

The hydrolysis of the acetal moiety was attempted using aqueous HCl according to the standard procedure that we



Scheme 5.

described previously.[57–59] However, this treatment did not lead to the desired diol **10** due to the formation of a lactonised derivative **11** (Scheme 5). The size of the lactone ring was elucidated by interpretation of a proton–proton COSY experiment performed on **11**. The resulting spectrum showed a clear coupling between the hydroxy proton [4.34 ppm (br s, 1H)] and proton H_C [3.80 ppm (m, 1H)]. In addition, coupling was not observed between the hydroxy proton and any of the other protons contained in the manipulated acetal moiety, i.e. H_A or H_B [4.56 ppm (1H, dd, J=11.4, 3.3 Hz); 4.14 ppm (1H, dd, J=11.4, 6.6 Hz)]. All these observations are completely consistent with the suggested structure **11**.

The amount of by-product **11** could be minimised by using pyridinium tosylate (PPTS). The lower acidity of PPTS, which was used in a refluxing mixture of acetone and water as the reaction solvent, afforded diol **10**. Compound **10** was purified by column chromatography (67%) and was fully characterised.

The direct oxidation of the diol moiety of **10** to the carboxylic acid was performed under similar conditions to those described previously.[57–59] Treatment of **10** with $NaIO_4$ in the presence of a catalytic amount of $RuCl_3$ at 0°C using a two-phase solvent mixture, $CH_3CN/CCl_4/H_2O$ (1:1:3), provided the β-carboxylic acid derivative **12** in 81% yield. Final hydrolysis of the benzamide and ester groups with 6N aqueous HCl under reflux led to (1*S*,2*R*,4*R*)-7-azabicyclo[2.2.1]heptane-1,2-dicarboxylic acid hydrochloride (**13**) in 92% yield.

In summary, compound **13**, which was obtained in enantiomerically pure form through 10 completely stereocontrolled steps in 28% overall yield from the oxazolone **1***Z*, comprises a combination of L-aspartic acid and (2*S*,3*R*)-3-carboxyproline analogues with a 7-azabicyclo[2.2.1]heptane skeleton.

The next step in our study was the preparation of the aldehyde derivative **14** and, with the aim of demonstrating its power as a synthetic tool, we carried out the conversion of the dioxolane ring into an alkyl chain by means of a Wittig reaction (Scheme 5). The introduction of a propyl group on the β-carbon can be considered as a way to reproduce the side chain of norleucine, a non-natural amino acid whose use has been extended to diverse areas. Definite applications have already been established for this system as an active ingredient in preservatives for cut flowers or in cosmetics related to hair care. Norleucine even proved to be an efficient instrument to explore recognition sites when it was used as a residue introduced into peptides that facilitated the mapping of the S1 binding pocket of human cathepsin G.[68] Its efficacy to probe the protein stability generated by the introduction of non-natural amino acids, e.g. as a replacement for methionine in human recombinant annexin V,[69] is another remarkable property. Potential applications derived from its ability to produce cell metabolism and composition changes without modifying cell growth,[70] or to cause metabolic alterations in rats fed diets containing it,[71–73] must be also considered when appreciating the significance of this amino acid.

Our methodology for the preparation of the β-alkylated derivative **16** employed the typical oxidation procedure for diol **10** with $NaIO_4$ (Scheme 5). In this way, the carbonyl compound **14** was obtained in 90% yield after isolation by column chromatography. The addition of ethyltriphenylphosphorane in THF at −60°C took place very quickly and resulted in a mixture of alkenes, which was hydrogenated using 20% palladium hydroxide on carbon powder to give the product **15** in 83% yield from carbonyl derivative **14**. Finally, hydrolysis of the ester and amide groups gave enantiomerically pure (1*S*,2*R*,4*R*)-2-propyl-7-azabicyclo[2.2.1]heptane-1-carboxylic acid hydrochloride (**16**) (97% yield).

In conclusion, compound **16**, which can be simultaneously considered an L-norleucine and (2*S*,3*R*)-3-propylproline analogue based on a 7-azabicyclo[2.2.1]heptane skeleton, was obtained as a single enantiomer in 28% overall yield from the oxazolone **1***Z* through 12 fully stereocontrolled steps.

Further studies on the conversion of the 1,3-dioxolane ring into different groups are currently underway with the aim of synthesising a wide variety of α-amino acids containing a 7-azabicyclo[2.2.1]heptane structure and performing the corresponding biological tests. The results of this study will be published in due course.

3. Conclusion

A versatile and efficient methodology for the synthesis of a new 'chimera', a combination of α-amino acids and a constrained proline, in enantiomerically pure form is reported.

The asymmetric reaction of (*Z*)-2-phenyl-4-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-ylmethylene]-5(4*H*)-oxazolone, a chiral unsaturated oxazolone derived from (*R*)-glyceraldehyde, and Danishefsky's diene opens the way to 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. The subsequent modification of the dioxolane moiety offers a huge range of possibilities and clear evidence about the unquestionable potential of our methodology is shown by the successful preparation of (1*S*,2*R*,4*R*)-7-azabicyclo[2.2.1]heptane-1,2-dicarboxylic acid and (1*S*,2*R*,4*R*)-2-propyl-7-azabicyclo[2.2.1]heptane-1-carboxylic acid hydrochlorides, two combinations of constrained prolines with L-aspartic acid and L-norleucine, respectively.

4. Experimental

Apparatus: Melting points were determined using a Büchi 510 capillary melting point apparatus and are uncorrected. Specific rotations were recorded using a Perkin–Elmer 241-C polarimeter with a thermally jacketed 10 cm cell at 25°C. IR spectra were obtained using a Perkin–Elmer 1600 FTIR infrared spectrophotometer. ^1H and ^{13}C NMR spectra were recorded in deuterochloroform or deuterated water and referenced with respect to the residual solvent signal using a Varian Unity 300 or a Bruker AMX300 spectrometer. All

chemical shifts are quoted in parts per million relative to tetramethylsilane (δ 0.00 ppm), and coupling constants (J) are measured in Hertz. Elemental analyses were performed using a Perkin–Elmer 200 C, H, N, S elemental analyser.

Chemicals: All reactions were carried out with magnetic stirring. All reagents were purchased from the Aldrich Chemical Co. and used as received. (*Z*)-2-Phenyl-4-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-ylmethylene]-5(4*H*)-oxazolone **1***Z* and methyl (1*S*,2*R*)-1-benzamido-2-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-oxocyclohexane-1-carboxylate **5** were obtained according to the literature procedure.[55,59] TLC was performed on pre-coated silica gel plates, which were visualised using UV light and ninhydrin, anisaldehyde or phosphomolybdic acid developers. Column chromatography was performed on silica gel.

4.1. Methyl 1-benzamido-2-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-hydroxycyclohexane-1-carboxylate 6a, 6b

General procedure for reduction study. Ketone **5** (50 mg, 0.13 mmol) was dissolved in dry THF (10 ml) and the reducing agent (0.13 ml of a 1 M solution in THF, 0.13 mmol) was added dropwise at −78°C under an inert atmosphere. After 2 h the reaction was complete and was quenched by the addition of a saturated aqueous NH_4Cl (2 ml). The resulting mixture was allowed to warm up to room temperature, the solution was concentrated under reduced pressure and extracted with dichloromethane (3×10 ml). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and the solvent was evaporated in vacuo. The ratio of alcohols was determined by integration of the ^{1}H NMR signals at 3.03 ppm (ddd, 1H, J=3.3, 3.3, 14.4 Hz) and 3.30 ppm (ddd, 1H, J=3.3, 3.3, 14.5 Hz) belonging to **6a** and **6b**, respectively. The residue was chromatographed on silica gel, eluting with hexane/ethyl acetate (2:8), to give the alcohols **6a** and **6b**. This chromatography allowed the purification of small amounts of each alcohol so that they could be fully characterised.

Larger scale procedure (*several grams*). Ketone **5** (5.05 g, 13.47 mmol) was dissolved in dry THF (203 ml) and K-selectride® (13.47 ml of 1 M solution in THF, 13.47 mmol) was added dropwise over a period of 10 min at −78°C under an inert atmosphere. After 1 h stirring at the same temperature, the reaction was quenched by the addition of a saturated aqueous NH_4Cl (100 ml) and allowed to warm up to room temperature. The solution was concentrated under reduced pressure and extracted with dichloromethane (3×100 ml). Drying over anhydrous $MgSO_4$, filtration and solvent evaporation in vacuo afforded an 85:15 mixture of **6a** and **6b**. The residue was chromatographed on silica gel, eluting with hexane/ethyl acetate (2:8), to give 4.98 g of a mixture of the two alcohols (98% yield).

4.1.1. Methyl (1*S*,2*R*,4*S*)-1-benzamido-2-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-hydroxycyclohexane-1-carboxylate 6a. Mp 139–140°C; $[\alpha]_D$ (c 1, $CHCl_3$)=−46.6; IR (nujol) ν (cm^{-1}): 3467, 3377, 1741, 1659; ^{1}H NMR ($CDCl_3$) δ (ppm): 1.35 (s, 3H), 1.49 (s, 3H), 1.52 (br s, 1H), 1.63–1.70 (m, 2H), 1.72–1.92 (m, 2H), 2.32–2.43 (m, 2H), 3.03 (ddd, 1H, J=3.3, 3.3, 14.4 Hz), 3.73 (dd, 1H, J=5.7, 8.7 Hz), 3.75 (s, 3H), 4.02 (dd, 1H, J=7.2, 8.7 Hz), 4.18–4.24 (m, 1H), 4.31 (dd, 1H, J=5.7, 7.2 Hz), 7.38–7.45 (m, 2H), 7.46–7.52 (m, 1H), 7.74 (br s, 1H), 7.80–7.84 (m, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm): 24.4, 24.7, 25.9, 26.8, 28.1, 38.5, 52.6, 64.7, 64.8, 67.1, 75.5, 110.0, 127.0, 128.5, 131.5, 135.0, 168.0, 173.4. Anal. calcd for $C_{20}H_{27}NO_6$: C: 63.64, H: 7.21, N: 3.71; found: C: 64.56, H: 7.12, N: 3.79.

4.1.2. Methyl (1*S*,2*R*,4*R*)-1-benzamido-2-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-hydroxycyclohexane-1-carboxylate 6b. Mp 162°C; $[\alpha]_D$ (c 1, $CHCl_3$)=−45.9; IR (nujol) ν (cm^{-1}): 3400–3000, 1745, 1659; ^{1}H NMR ($CDCl_3$) δ (ppm): 1.35 (s, 3H), 1.38–1.50 (m, 1H), 1.50 (s, 3H), 1.55–1.75 (m, 1H), 1.76–2.00 (m, 5H), 3.30 (ddd, 1H, J=3.3, 3.3, 14.5 Hz), 3.73 (dd, 1H, J=6.0, 8.7 Hz), 3.74 (s, 3H), 3.75–3.79 (m, 1H), 4.03 (dd, 1H, J=6.9, 8.7 Hz), 4.28 (dd, 1H, J=6.0, 6.9 Hz), 7.38–7.45 (m, 2H), 7.46–7.52 (m, 1H), 7.73 (br s, 1H), 7.80–7.84 (m, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm): 24.8, 25.9, 29.2, 29.3, 30.3, 43.9, 52.8, 63.7, 67.2, 69.6, 74.9, 110.2, 127.0, 128.5, 131.5, 134.8, 167.6, 173.6. Anal. calcd for $C_{20}H_{27}NO_6$: C: 63.64, H: 7.21, N: 3.71; found: C: 63.03, H: 7.21, N: 3.65.

4.2. Methyl 1-benzamido-2-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-methylsulfonyloxycyclohexane-1-carboxylate 7a, 7b

The mixture of alcohols **6a** and **6b** (4.98 g, 13.21 mmol), obtained from the reduction of ketone **5** with K-selectride®, was dissolved in dry dichloromethane (100 ml) under an inert atmosphere at 0°C. Triethylamine (2.67 g, 26.42 mmol) and methanesulfonyl chloride (3.03 g, 26.42 mmol) were added to this solution and the resulting mixture was heated under reflux. After 30 min the mixture was cooled down to room temperature and the solvent was removed in vacuo. The residue was dissolved in dichloromethane (200 ml) and washed with water (3×50 ml). The organic layer was dried over anhydrous $MgSO_4$ and filtered. Solvent removal under reduced pressure provided 6.0 g of a mixture of the two methanesulfonates **7a** and **7b** in nearly quantitative yield, and this mixture was used in the next step without further treatment. Additional purification of an analytical sample by column chromatography on silica gel, using hexane/ethyl acetate (2:8) as eluent, allowed the total characterisation of each product.

4.2.1. Methyl (1*S*,2*R*,4*S*)-1-benzamido-2-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-methylsulfonyloxycyclohexane-1-carboxylate 7a. Mp 160°C; $[\alpha]_D$ (c 1, $CHCl_3$)=−40.1; IR (nujol) ν (cm^{-1}): 3416, 1736, 1664; ^{1}H NMR ($CDCl_3$) δ (ppm): 1.35 (s, 3H), 1.48 (s, 3H), 1.68–1.80 (m, 1H), 1.90–2.02 (m, 2H), 2.09–2.18 (m, 1H), 2.25–2.38 (m, 2H), 3.04 (s, 3H), 3.15 (ddd, 1H, J=3.2, 3.2, 14.2 Hz), 3.74 (dd, 1H, J=5.9, 8.7 Hz), 3.76 (s, 3H), 4.04 (dd, 1H, J=7.2, 8.7 Hz), 4.32 (dd, 1H, J=5.9, 7.2 Hz), 5.08–5.14 (m, 1H), 7.40–7.48 (m, 2H), 7.48–7.53 (m, 1H), 7.76 (br s, 1H), 7.77–7.82 (m, 2H). ^{13}C NMR ($CDCl_3$) δ (ppm): 24.5, 24.9, 25.9, 26.1, 38.8, 39.0, 52.8, 64.1, 66.9, 74.9, 77.2, 110.2, 126.9, 128.5, 131.7, 134.7, 168.1, 172.9. Anal. calcd for $C_{21}H_{29}NO_8S$: C: 55.37, H: 6.42, N: 3.07, S: 7.04; found: C: 55.36, H: 6.42, N: 3.07, S: 6.94.

4.2.2. Methyl (1*S*,2*R*,4*R*)-1-benzamido-2-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-methylsulfonyloxycyclohexane-1-carboxylate 7b. Mp 163–164°C; $[\alpha]_D$ (*c* 0.9, $CHCl_3$)=−17.2; IR (nujol) ν (cm^{-1}): 3394, 1730, 1670; ^1H NMR ($CDCl_3$) δ (ppm): 1.34 (s, 3H), 1.52 (s, 3H), 1.69–1.79 (m, 1H), 1.88–2.16 (m, 5H), 3.00 (s, 3H), 3.35 (ddd, 1H, *J*=3.5, 3.5, 14.2 Hz), 3.74 (dd, 1H, *J*=5.8, 8.8 Hz), 3.75 (s, 3H), 4.05 (dd, 1H, *J*=7.2, 8.8 Hz), 4.29 (dd, 1H, *J*=5.8, 7.2 Hz), 4.71–4.80 (m, 1H), 7.40–7.48 (m, 2H), 7.48–7.52 (m, 1H), 7.77 (br s, 1H), 7.80–7.85 (m, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm): 24.6, 25.9, 27.0, 27.5, 29.0, 38.9, 44.0, 52.9, 63.2, 67.1, 74.6, 79.3, 110.4, 126.9, 128.5, 131.7, 134.5, 167.7, 172.9. Anal. calcd for $C_{21}H_{29}NO_8S$: C: 55.37, H: 6.42, N: 3.07, S: 7.04; found: C: 55.44; H: 6.32; N: 3.17; S: 6.89.

4.3. 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 8

Procedure A. To a solution of methanesulfonate **7a** (451 mg, 0.99 mmol) in dry THF (50 ml) at 0°C was added ^{t}BuOK (662 mg, 5.91 mmol). The reaction mixture was stirred at room temperature for 3 h. The mixture was filtered and the solvent was evaporated in vacuo. The residue was dissolved in dichloromethane (50 ml) and washed with water (3×30 ml). The organic layer was dried over anhydrous $MgSO_4$, filtered and the solvent was evaporated in vacuo to afford compound **8** (68 mg) as an oil. The aqueous layer was acidified by the addition of aqueous 2N HCl to pH=4–5 and extracted with dichloromethane (3×50 ml). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and the solvent was removed under vacuum to give acid **9**, which was immediately esterified. A solution of diazomethane in diethyl ether (prepared from *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine) was gradually added to a solution of the resulting acid **9** in diethyl ether (30 ml) at room temperature until a permanent yellow solution was obtained. (CAUTION! Diazomethane is a very harmful and hazardous reagent; it must be handled with caution and the preparation of a large amount is to be avoided.) $CaCl_2$ was added and stirring continued for 10 min to destroy the excess diazomethane. The resulting solution was filtered and the solvent was evaporated in vacuo. The residue was chromatographed, using a 2:1 hexane/ethyl acetate mixture as eluent, in order to separate compound **8** (162 mg). This treatment gave 230 mg of **8** (65% yield) as a pale yellow oil. $[\alpha]_D$ (*c* 1, $CHCl_3$)=−85.2; IR (neat) ν (cm^{-1}): 1738, 1659; ^1H NMR ($CDCl_3$) δ (ppm): 1.31 (s, 3H), 1.38 (s, 3H), 1.46–1.64 (m, 2H), 1.71–1.82 (m, 2H), 2.12–2.24 (m, 2H), 2.41 (ddd, 1H, *J*=4.5, 12.6, 12.6 Hz), 3.50 (dd, 1H, *J*=4.5, 8.7 Hz), 3.76 (s, 3H), 3.97 (dd, 1H, *J*=5.7, 8.7 Hz), 4.19 (dd, 1H, *J*=5.1, 5.1 Hz), 4.32 (ddd, 1H, *J*=4.5, 5.7, 10.2 Hz), 7.36–7.42 (m, 2H), 7.45–7.51 (m, 1H), 7.67–7.71 (m, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm): 24.9, 27.1, 30.6, 30.7, 34.6, 51.5, 52.2, 62.0, 68.8, 69.2, 77.0, 108.0, 128.3, 128.8, 131.8, 134.4, 170.5, 173.9.

Procedure B. A solution of the methanesulfonates **7a** and **7b** (6.0 g, 13.19 mmol) in dry DMF (50 ml) was added to a suspension of NaH (634 mg, 26.42 mmol) in dry DMF (80 ml) at −78°C under an argon atmosphere. After stirring at this temperature for 15 min, the mixture was allowed to warm up to room temperature and stirring was maintained at this temperature for an additional 2.5 h. Saturated aqueous NH_4Cl was added and, after stirring for a further 15 min, the solution was extracted with ethyl acetate (5×75 ml). The combined organic layers were washed with water (150 ml) and saturated brine (2×100 ml). The organic phase was dried over anhydrous $MgSO_4$, filtered and the solvent was evaporated in vacuo. Column chromatography of the resulting residue, using hexane/ethyl acetate (1:1), provided compound **8** (3.63 g) in 75% overall yield from ketone **5**.

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

Pyridinium tosylate (2.51 g, 10.00 mmol) was added to a previously prepared solution of azabicyclic compound **8** (3.63 g, 10.11 mmol) in acetone (88 ml) and water (88 ml). After refluxing the mixture for 6 h, the solvent was evaporated under vacuum and the residue was partitioned between water (100 ml) and dichloromethane (150 ml). The organic layer was separated and the aqueous layer was extracted with dichloromethane (3×50 ml). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under vacuum to afford diol **10**, which was purified by column chromatography using diethyl ether/ethanol (9:1) as eluent. In this way, product **10** was isolated as an oil (2.13 g) in 67% yield. A mixture (91 mg) containing diol **10** and the lactonised derivative **11** was also separated as well as the pure lactone **11** (307 mg).

4.4.1. Methyl (1*S*,2*R*,4*R*)-*N*-benzoyl-2-[(*S*)-1,2-dihydroxyethyl]-7-azabicyclo[2.2.1]heptane-1-carboxylate 10. $[\alpha]_D$ (*c* 1, $CHCl_3$)=−72.0; IR (neat) ν (cm^{-1}): 3600–3300, 1729, 1645; ^1H NMR ($CDCl_3$) δ (ppm): 1.49–1.57 (m, 2H), 1.66–1.82 (m, 2H), 2.08–2.14 (m, 2H), 2.30–2.46 (m, 2H), 3.36–3.51 (m, 3H), 3.86 (s, 3H), 4.08–4.12 (m, 1H), 4.22 (dd, 1H, *J*=4.5, 4.5 Hz), 7.36–7.42 (m, 2H), 7.45–7.51 (m, 1H), 7.65–7.69 (m, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm): 29.9, 30.6, 31.6, 48.1, 52.7, 61.9, 63.9, 70.0, 70.5, 128.4, 128.8, 131.9, 134.2, 171.1, 173.3.

4.4.2. Lactone 11. Mp 215°C; $[\alpha]_D$ (*c* 1, MeOH)=−9.9; IR (nujol) ν (cm^{-1}): 3396, 1717, 1654; ^1H NMR ($CDCl_3$) δ (ppm): 1.48 (ddd, 1H, *J*=5.1, 9.0, 12.3 Hz), 1.69 (m, 1H), 1.80 (ddd, 1H, *J*=3.6, 9.0, 12.3 Hz), 1.90–2.02 (m, 2H), 2.15–2.21 (m, 1H), 2.45 (ddd, 1H, *J*=5.1, 12.3, 12.3 Hz), 3.75–3.85 (m, 1H), 4.14 (dd, 1H, *J*=6.6, 11.4 Hz), 4.24 (dd, 1H, *J*=4.8, 4.8 Hz), 4.34 (br s, 1H), 4.56 (dd, 1H, *J*=3.3, 11.4 Hz), 7.30–7.37 (m, 2H), 7.38–7.45 (m, 1H), 7.46–7.51 (m, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm): 28.8, 33.4, 37.6, 48.5, 60.2, 64.5, 68.9, 71.2, 127.8, 128.3, 131.2, 134.4, 168.5, 169.6. Anal. calcd for $C_{16}H_{17}NO_4$: C: 66.89, H: 5.96, N: 4.88; found C: 66.52, H: 6.02, N: 4.93.

4.5. (1*S*,2*R*,4*R*)-*N*-Benzoyl-1-carbomethoxy-7-azabicyclo-[2.2.1]heptane-2-carboxylic acid 12

$NaIO_4$ (1.38 g, 6.45 mmol) was added to a stirred solution of the diol **10** (412 mg, 1.29 mmol) in 40 ml of a (1:1:3) mixture of acetonitrile/carbon tetrachloride/water cooled to 0°C. The resulting two-phase solution was treated with

$RuCl_3 \cdot H_2O$ (17 mg, 0.08 mmol) and stirred at this temperature for 1 day. Saturated aqueous $NaHCO_3$ was added until the pH was 8–9 and the mixture was stirred for an additional 5 min. The organic phase was separated and the aqueous phase was extracted with dichloromethane (2×20 ml). Dichloromethane was then added to the aqueous layer and the mixture was acidified by the addition of aqueous 6N hydrochloric acid until the pH was 1–2 and vigorously stirred for 5 min. The organic layer was separated and the aqueous phase extracted with dichloromethane (5×30 ml). The organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Purification of the residue by flash column chromatography using hexane/ethyl acetate (2:8) on silica gel (previously washed with aqueous HCl solution, ethanol, diethyl ether and finally dried in the oven before use) supplied the corresponding carboxylic acid **12** as a white solid (318 mg, 81% yield). Mp 171°C; $[\alpha]_D$ (*c* 1, $CHCl_3$)=+5.0; IR (nujol) ν (cm^{-1}): 3500–3300, 1746, 1721, 1645; ^1H NMR ($CDCl_3$) δ (ppm): 1.52–1.60 (m, 1H), 1.72–1.93 (m, 3H), 2.47 (ddd, 1H, *J*=4.8, 12.3, 12.3 Hz), 2.53–2.61 (m, 1H), 2.96 (dd, 1H, *J*=5.1, 8.5 Hz), 3.71 (s, 3H), 4.31 (dd, 1H, *J*=4.8, 4.8 Hz), 7.37–7.51 (m, 3H), 7.65–7.68 (m, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm): 30.3, 31.6, 33.6, 50.4, 52.4, 61.3, 70.9, 128.3, 128.6, 131.8, 133.9, 169.3, 172.5, 175.9. Anal. calcd for $C_{16}H_{17}NO_5$: C: 63.36, H: 5.65, N: 4.62; found C: 64.02, H: 5.56, N: 4.65.

4.6. (1*S*,2*R*,4*R*)-7-Azabicyclo[2.2.1]heptane-1,2-dicarboxylic acid hydrochloride 13

Treatment of the amido ester **12** (201 mg, 0.66 mmol) with aqueous 6N HCl (50 ml) under reflux for 30 h afforded, after solvent evaporation, a residue that was dissolved in water (40 ml) and extracted with chloroform (3×30 ml). The aqueous solution was concentrated in vacuo and the total removal of water was performed by the addition of acetone, followed by evaporation under vacuum and final freeze-drying. In this way, the amino acid hydrochloride **13** was obtained as a white solid (135 mg) in 92% yield. Mp dec; $[\alpha]_D$ (*c* 0.25, H_2O)=−46.5; IR (nujol) ν (cm^{-1}): 3512, 3413, 3300–2500, 1743, 1706; ^1H NMR (D_2O) δ (ppm): 1.75–1.90 (m, 1H), 2.00–2.18 (m, 4H), 2.29 (dd, 1H, *J*=9.9, 13.6 Hz), 3.20 (dd, 1H, *J*=5.4, 9.9 Hz), 4.19 (dd, 1H, *J*=4.2, 4.2 Hz); ^{13}C NMR (D_2O) δ (ppm): 26.4, 30.8, 33.7, 46.5, 57.8; 74.6, 171.6, 175.5. Anal. calcd for $C_8H_{12}NO_4Cl$: C: 43.35, H: 5.46, N: 6.32; found C: 43.58, H: 5.41, N: 6.43.

4.7. Methyl (1*S*,2*R*,4*R*)-*N*-benzoyl-2-formyl-7-azabicyclo-[2.2.1]heptane-1-carboxylate 14

A suspension of $NaIO_4$ (517 mg, 2.42 mmol) in water (2.7 ml) was added in small portions to a stirred solution of the diol **10** (812 mg, 2.54 mmol) in THF (81 ml) at 0°C. After 1 h stirring at this temperature and 4 h at room temperature, a further quantity of $NaIO_4$ (189 mg, 0.88 mmol) was added and the mixture was stirred at room temperature overnight. The resulting suspension was filtered. The solvent was evaporated under vacuum and the residue was dissolved in ethyl acetate (100 ml), washed with water (3×50 ml), dried over anhydrous $MgSO_4$ and filtered. Final evaporation of the solvent in vacuo afforded an oil that was chromatographed using hexane/ethyl acetate (1:1). This procedure provided the aldehyde **14** (656 mg) as a white solid in 90% yield. Mp 108°C; $[\alpha]_D$ (*c* 1, $CHCl_3$)=−6.7; IR (nujol) ν (cm^{-1}): 1733, 1708, 1643; ^1H NMR ($CDCl_3$) δ (ppm): 1.55–1.68 (m, 2H), 1.68–1.95 (m, 1H), 2.01–2.09 (m, 1H), 2.09–2.19 (m, 1H), 2.39 (ddd, 1H, *J*=4.5, 12.1, 12.1 Hz), 2.84 (ddd, 1H, *J*=3.0, 4.9, 8.4 Hz), 3.80 (s, 3H), 4.32 (dd, 1H, *J*=4.8, 4.8 Hz), 7.36–7.42 (m, 2H), 7.45–7.53 (m, 1H), 7.60–7.65 (m, 2H), 9.89 (d, 1H, *J*=3.0 Hz); ^{13}C NMR ($CDCl_3$) δ (ppm): 29.9, 31.1, 33.9, 52.6, 55.5, 61.2, 69.7, 128.4, 128.6, 131.8, 133.9, 169.6, 172.4, 199.5. Anal. calcd for $C_{16}H_{17}NO_4$: C: 66.89, H: 5.96, N: 4.88; found C: 67.17, H: 5.82, N: 4.93.

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

To a suspension of ethyltriphenylphosphonium bromide (232 mg, 0.62 mmol) in dry THF (3 ml) was added a solution of *n*-BuLi (0.5 ml, 1.6 M in hexane, 0.8 mmol) at room temperature and the mixture was stirred at this temperature for 30 min. The solution was then cooled down to −60°C and a solution of the aldehyde **14** (150 mg, 0.52 mmol) in dry THF (2 ml) was added. The reaction was complete immediately and was quenched by addition of saturated aqueous NH_4Cl (10 ml). The resulting mixture was stirred for 5 min at room temperature. The solution was concentrated under vacuum and the aqueous residue was extracted with dichloromethane (3×30 ml). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and the solvent was evaporated in vacuo. Flash chromatography using diethyl ether/ethanol (9:1) afforded a mixture of olefins (141 mg), which was dissolved in methanol (9 ml) and hydrogenated at atmospheric pressure and room temperature using 20% palladium hydroxide on carbon powder (35 mg) as a catalyst. After 1 day the catalyst was filtered off through a Celite pad and the solvent was removed in vacuo to provide the corresponding saturated compound **15** (129 mg) as an oil in 83% yield from formyl derivative **14**. $[\alpha]_D$ (*c* 0.88, $CHCl_3$)=−94.6; IR (neat) ν (cm^{-1}): 1732, 1659; ^1H NMR ($CDCl_3$) δ (ppm): 0.87 (t, 3H, *J*=7.2 Hz), 1.03–1.38 (m, 3H), 1.41–1.69 (m, 4H), 1.73–1.82 (m, 2H), 1.92–2.02 (m, 1H), 2.37 (ddd, 1H, *J*=4.8, 12.3, 12.3 Hz), 3.76 (s, 3H), 4.14 (dd, 1H, *J*=4.5, 4.5 Hz), 7.35–7.41 (m, 2H), 7.43–7.50 (m, 1H), 7.68–7.72 (m, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm): 14.1, 19.8, 30.5, 31.0, 35.7, 37.5, 47.0, 51.7, 62.3, 70.5, 128.2, 128.8, 131.6, 134.9, 171.0, 174.2.

4.9. (1*S*,2*R*,4*R*)-2-Propyl-7-azabicyclo[2.2.1]heptane-1-carboxylic acid hydrochloride 16

Aqueous 6N HCl (15 ml) was added to the amido ester **15** (100 mg, 0.33 mmol) and the mixture was heated under reflux for 24 h. After the reaction was complete the solvent was evaporated in vacuo and the residue dissolved in water (30 ml). The solution was extracted with chloroform (3×20 ml) and the separated aqueous phase was concentrated under vacuum. Total removal of water was achieved by adding acetone, followed by evaporation and final freeze-drying. In this way the amino acid hydrochloride **16** was obtained as a white solid (70 mg) in 97% yield. Mp dec; $[\alpha]_D$ (*c* 1, H_2O)=−62.4; IR (nujol) ν (cm^{-1}): 3300–3100, 1735; ^1H NMR (D_2O) δ (ppm): 0.73 (t, 3H,

J=6.9 Hz), 1.00–1.13 (m, 2H), 1.18–1.29 (m, 1H), 1.30–1.39 (m, 1H), 1.55–1.64 (m, 1H), 1.67–1.77 (m, 1H), 1.90–2.10 (m, 4H), 2.14–2.25 (m, 1H), 4.09 (dd, 1H, J=4.5, 4.5 Hz); ^{13}C NMR (D_2O) δ (ppm): 12.9, 18.7, 26.6, 30.9, 33.5, 34.8, 42.5, 58.5, 76.0, 172.1. Anal. calcd for $C_{10}H_{18}NO_2Cl$: C: 54.67, H: 8.26, N: 6.38; found C: 54.42, H: 8.32, N: 6.31.

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