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**Diastereoselective Synthesis of (1*S*,2*S*,3*R*,4*R*) and (1*R*,2*S*,3*R*,4*S*)
-Bicyclo[2.2.1]hept-2-amino-2,3-dicarboxylic Acids: New Conformationally-
Constrained (*S*)-Aspartic Acid Analogues**

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Abstract: The title compounds were prepared from key intermediates readily obtained by the stereoselective Diels-Alder reaction of (*Z*)-2-phenyl-4-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-ylmethylene]-5(4*H*)-oxazolone, a chiral az-lactone derived from (*R*)-glyceraldehyde and cyclopentadiene. Copyright © 1996 Elsevier Science Ltd

The neurobiological effects that certain amino acids, such as glutamate and aspartate, induce in the mammalian central nervous system are well-documented. A number of these compounds act as excitatory neurotransmitters activating the different receptors that are associated with a variety of physiological functions.¹

One of the several types of the excitatory amino acids known at present is the group of compounds which have a particular affinity for *N*-methyl-*D*-aspartic acid (NMDA),² and these have been the most intensively investigated. The stereoselectivity of the NMDA receptor is surprising³, for glutamate the receptor prefers the *L*-configuration, whereas in the case of the shorter homologue (aspartate) the NMDA receptor does not differentiate between *L*-Asp and *D*-Asp. *N*-Methylation of aspartate changes the affinity for the receptor of both enantiomers, with the preference of the receptor being much greater for the compound with the (*R*)-configuration.

Moreover, there is currently growing interest in the development of rational approaches to the design of peptide and protein ligands with specific physical, chemical and biological properties.⁴ In this field, conformational constraints play an important role in the achievement of this goal and various systematic approaches have been attempted. One example of particular interest involves the use of cyclic amino acid analogues to obtain constrained amino acid residues in a particular stabilised specific conformation.⁵ The development of new therapeutic agents has stimulated great interest in the synthesis of unusual and non-naturally occurring amino acids⁶ since, when they are incorporated into peptides of interest, they can be used to address or even remedy unfavourable solubility, bioavailability, biodegradation or bioselectivity properties of the peptide and improve its biological activity.⁷

The introduction of conformational constraints into aspartate may provide useful information regarding the conformational requirements for receptor binding and, at the same time, provide a potential competitive

antagonist 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 interesting properties.

On the basis of these considerations, and in connection with our studies on the asymmetric synthesis of non-proteinogenic amino acids, we have developed a synthetic route to new cyclic aspartate analogues in which the functional groups probably responsible for the binding are in well-defined positions as they are situated on a rigid molecular framework (Figure 1).

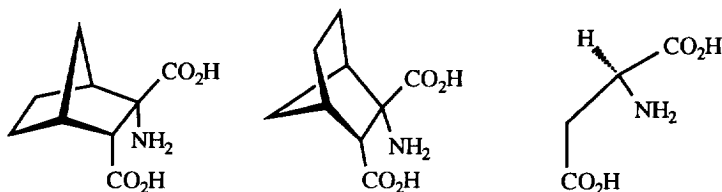
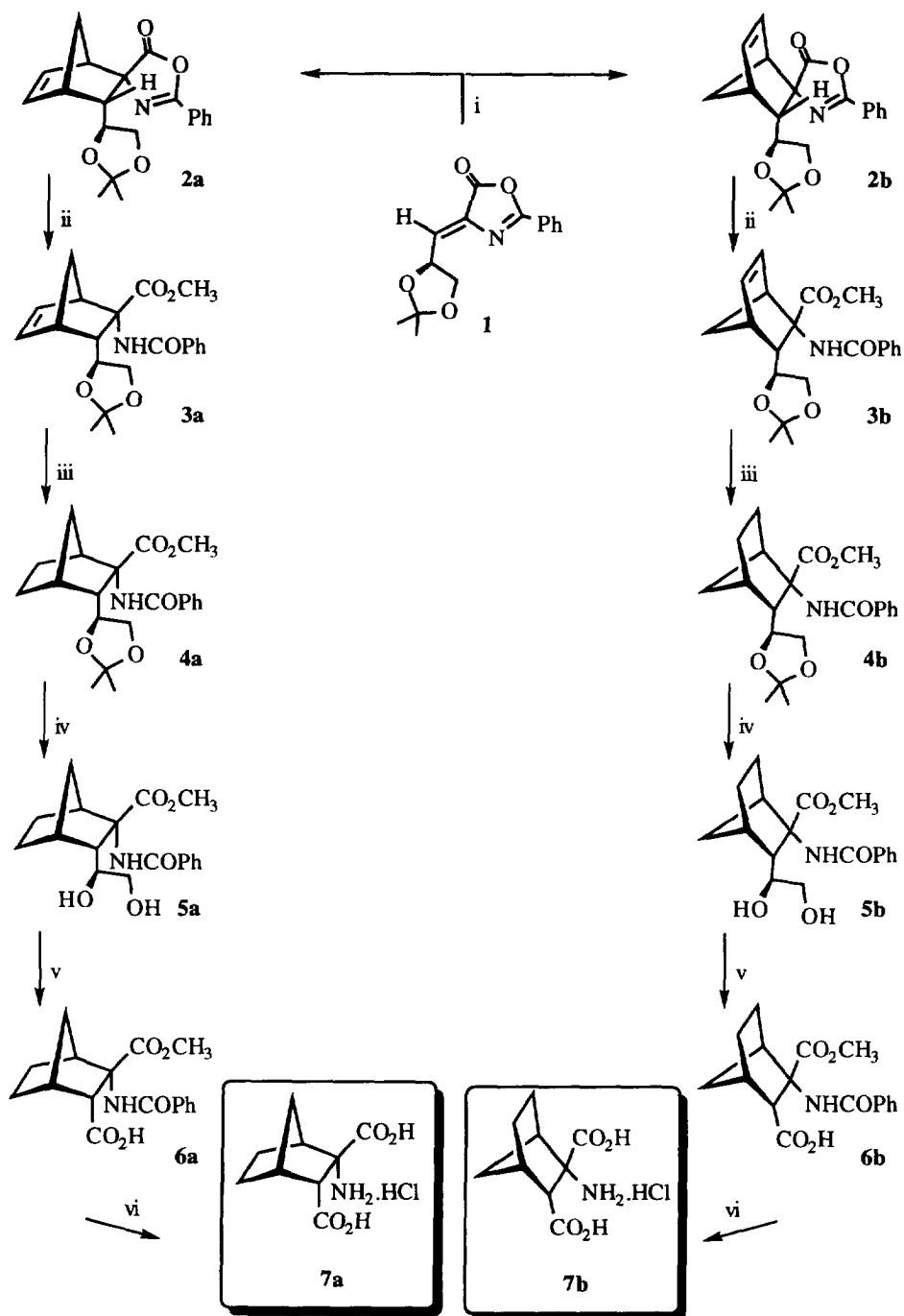


Figure 1

We have recently reported⁸ that the easily accessible chiral oxazolone **1** (see Scheme 1), derived from 1,2-*O*-isopropylidene-*D*-glyceraldehyde, readily gives (1*R*,2*S*,3*R*,4*S*)-3-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-bicyclo[2.2.1]hept-5-en-2-spiro-{4[2'-phenyl-5'(4*H*)-oxazolone]} **2a** and (1*S*,2*S*,3*R*,4*R*)-3-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-bicyclo[2.2.1]hept-5-en-2-spiro-{4[2'-phenyl-5'(4*H*)-oxazolone]} **2b** with high "exo" preference (**2a/2b** = 70/30) in a Diels-Alder reaction with cyclopentadiene in hexane at room temperature. These compounds, obtained in a high diastereomeric ratio (96/4 for **2a** and 96/4 for **2b**), can be easily isolated in diastereomerically pure form and provide useful key intermediates in the synthesis of new conformationally-constrained amino acids. These compounds were therefore chosen as substrates in the study reported here.

In order to develop an efficient route to amino acid **7a**, the substituent at C₃ in the *endo* position must be transformed into a carboxylic acid. This may be achieved by acid hydrolysis of the acetal moiety followed by oxidative cleavage of the resulting diol. However, acid treatment of the chiral spirooxazolone **2a** afforded mixtures of unidentified compounds due to the presence of the double bond at C₅-C₆. In order to obviate this problem, compound **2a** was first converted to the saturated *N*-benzoylmethyl ester **4a** in nearly quantitative yield by methanolysis with sodium methoxide in methanol for 0.5 h at room temperature followed by hydrogenation of the alkene moiety in the presence of a catalytic amount of 10 % palladium on activated carbon. Subsequent treatment of **4a** with 3*N* hydrochloric acid in methanol cleanly afforded methyl (1*S*,2*S*,3*R*,4*R*)-bicyclo[2.2.1]hept-2-benzamido-3-[(*S*)-1,2-dihydroxyethyl]-2-carboxylate **5a** in nearly quantitative yield. The next step in the synthesis involved the transformation of the 1,2-diol moiety into a carboxylic group, which can be easily performed by treatment of the 1,2-diol **5a** with an excess of sodium periodate in the presence of ruthenium trichloride. Hydrolysis of the resulting compound **6a** with 6*N* hydrochloric acid under reflux conditions gave enantiomerically pure (1*S*,2*S*,3*R*,4*R*)-bicyclo[2.2.1]hept-2-amino-2,3-dicarboxylic acid hydrochloride **7a** after elution through a silica-gel column eluting with isopropanol.

Similar results to those described above were obtained when the same protocol was applied to compound **2b** in order to elaborate conveniently the substituent at C₃ in the *exo* position. In some cases different behaviour has been observed between the same functional group situated in the *endo* or *exo* position.⁹



i) cyclopentadiene, hexane, and column chromatography; ii) CH_3ONa , CH_3OH ; iii) $\text{H}_2/\text{Pd-C}$; iv) HCl , CH_3OH ; v) NaIO_4 , $\text{RuCl}_3 \cdot \text{H}_2\text{O}$; vi) 6N HCl

Scheme 1

In conclusion, we have developed simple methodologies, starting from easily available chiral Diels-Alder adducts of oxazolone derived from *D*-glyderaldehyde and cyclopentadiene, which lead to the synthesis of the enantiomerically pure aspartate analogue amino acids **7a** and **7b** by standard transformations in five steps and with an overall yield of about 65 %. These compounds can be used as mechanistic probes to study the affinity of bioreceptors towards certain spatial arrangements. Further studies on the incorporation of these amino acids into peptides, changes induced in the peptide properties due to its conformational constraint and the specific properties of this aspartate analogue are being undertaken and will be published in due course.

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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 NMR and ¹³C NMR spectra were recorded in deuteriochloroform, deuterated dimethylsulphoxide 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. (1*R*,2*S*,3*R*,4*S*)-3-[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-bicyclo[2.2.1]hept-5-en-2-spiro-{4'[2'-phenyl-5'(4'H)-oxazolone]} **2a** and (1*S*,2*S*,3*R*,4*R*)-3-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-bicyclo[2.2.1]hept-5-en-2-spiro-{4'[2'-phenyl-5'(4'H)-oxazolone]} **2b** were prepared following the method described in the literature.^{8b} TLC was performed on precoated silica-gel plates which were visualised using UV light and ninhydrin. Flash column chromatography was performed on silica gel (Kieselgel 60).

General procedure for methanolysis of spirooxazolones **2a** and **2b**

A suspension of the spirooxazolone **2** (2.9 g, 10 mmol) in a solution of sodium methoxide (0.02 g) in absolute methanol (80 ml) was stirred at room temperature for 30 min. After the reaction was complete, the solution was concentrated *in vacuo* and the residue was dissolved in ethylacetate, washed with water, dried over MgSO₄ and concentrated *in vacuo* to afford the corresponding methyl ester **3** in nearly quantitative yield.

Methyl (1*R*,2*S*,3*R*,4*S*)-bicyclo[2.2.1]hept-5-en-2-benzamido-3-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-carboxylate **3a**.

M.p. = 156°C. $[\alpha]_D^{25} = +38.8$ (*c* = 1 in CHCl₃); IR (nujol) $\nu = 3401, 1737, 1669$ cm⁻¹. ¹H-NMR δ 1.36 (s, 3H), 1.44 (s, 3H), 1.60-1.64 (m, 1H), 1.74 (d, 1H, *J* = 9.3 Hz), 2.63 (dd, 1H, *J* = 3.1 Hz, *J* = 3.1 Hz), 3.00 (brs, 1H), 3.72 (brs, 1H), 3.75 (s, 3H), 3.78 (dd, 1H, *J* = 8.5 Hz, *J* = 8.5 Hz), 4.06 (dd, 1H, *J* = 8.5 Hz, *J* = 6.2 Hz), 4.34 (ddd, 1H, *J* = 8.5 Hz, *J* = 6.2 Hz, *J* = 3.1 Hz), 5.96 (dd, 1H, *J* = 5.4 Hz, *J* = 3.1 Hz), 6.40

(dd, 1H, $J = 5.4$ Hz, $J = 3.1$ Hz), 7.32 (brs, 1H), 7.36-7.42 (m, 2H), 7.44-7.52 (m, 1H), 7.66-7.74 (m, 2H). ^{13}C NMR δ 25.7, 26.5, 43.6, 48.6, 50.2, 52.0, 52.6, 66.4, 68.3, 74.4, 109.5, 127.0, 128.5, 131.6, 132.7, 133.6, 139.4, 166.5, 173.8. Anal. Calcd. for $\text{C}_{21}\text{H}_{25}\text{NO}_5$: C, 67.91; H, 6.78; N, 3.77. Found C, 67.97; H, 6.81; N, 3.63.

Methyl (1*S*,2*S*,3*R*,4*R*)-bicyclo[2.2.1]hept-5-en-2-benzamido-3-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-carboxylate **3b**.

M.p. = 124°C. $[\alpha]_{\text{D}}^{25} = -71.0$ ($c = 1$ in CHCl_3); IR (nujol) $\nu = 3351, 3325, 1729, 1637$ cm^{-1} . $^1\text{H-NMR}$ δ 1.39 (s, 3H), 1.45 (s, 3H), 1.56 (d, 1H, $J = 9$ Hz), 1.96 (d, 1H, $J = 9$ Hz), 2.00-2.03 (m, 1H), 2.85 (brs, 1H), 3.27 (brs, 1H), 3.66 (s, 3H), 3.80 (dd, 1H, $J = 8.1$ Hz, $J = 8.1$ Hz), 4.16 (dd, 1H, $J = 8.1$ Hz, $J = 8.1$ Hz), 4.65-4.71 (m, 1H), 6.26 (dd, 1H, $J = 5.1$ Hz, $J = 3.3$ Hz), 6.34 (dd, 1H, $J = 5.1$ Hz, $J = 3.3$ Hz), 7.36-7.42 (m, 2H), 7.44-7.54 (m, 1H), 7.74-7.82 (m, 2H), 7.90 (brs, 1H). ^{13}C NMR δ 25.3, 26.2, 42.1, 47.2, 50.4, 51.1, 52.2, 66.8, 68.6, 73.8, 109.9, 127.0, 128.5, 131.6, 134.0, 137.0, 138.6, 166.4, 172.8. Anal. Calcd. for $\text{C}_{21}\text{H}_{25}\text{NO}_5$: C, 67.91; H, 6.78; N, 3.77. Found C, 67.82; H, 6.67; N, 3.59.

General procedure for hydrogenation of alkenes **3a** and **3b**

A solution of olefin **3** (2.76 g, 7.5 mmol) in ethyl acetate (100 ml) was hydrogenated at atmospheric pressure in the presence of 10 % palladium on charcoal (80 mg) for 4 h. After the reaction was complete, the catalyst was filtered off using a celite pad and the solvent was removed *in vacuo* to afford the corresponding saturated compound **4** in nearly quantitative yield.

Methyl (1*S*,2*S*,3*R*,4*R*)-bicyclo[2.2.1]heptane-2-benzamido-3-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-carboxylate **4a**.

M.p. = 141°C. $[\alpha]_{\text{D}}^{25} = +16.4$ ($c = 1$ in CHCl_3); IR (nujol) $\nu = 3389, 1746, 1663$ cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ 1.45 (s, 3H), 1.49 (s, 3H), 1.35-1.52 (m, 4H), 1.75-1.80 (m, 1H), 2.08-2.18 (m, 2H), 2.41 (brs, 1H), 3.25 (brs, 1H), 3.69 (s, 3H), 3.78 (dd, 1H, $J = 8.8$ Hz, $J = 8.3$ Hz), 4.07 (dd, 1H, $J = 8.3$ Hz, $J = 6.0$ Hz), 4.56 (ddd, 1H, $J = 8.8$ Hz, $J = 6.0$ Hz, $J = 3.0$ Hz), 7.38-7.46 (m, 2H), 7.46-7.53 (m, 1H), 7.76-7.82 (m, 2H), 8.15 (brs, 1H). ^{13}C NMR (CDCl_3) δ 22.3, 23.6, 25.9, 26.4, 37.9, 39.4, 44.6, 49.1, 52.4, 64.7, 68.2, 75.0, 109.8, 127.0, 128.5, 131.6, 133.7, 166.7, 173.8. Anal. Calcd. for $\text{C}_{21}\text{H}_{27}\text{NO}_5$: C, 67.54; H, 7.29; N, 3.75. Found C, 67.47; H, 7.17; N, 3.63.

Methyl (1*R*,2*S*,3*R*,4*S*)-bicyclo[2.2.1]heptane-2-benzamido-3-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-carboxylate **4b**.

M.p. = 139°C. $[\alpha]_{\text{D}}^{25} = -109.2$ ($c = 1$ in CHCl_3); IR (nujol) $\nu = 3357, 3313, 1725, 1638$ cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ 1.07 (s, 3H), 1.23-1.35 (m, 2H), 1.37 (s, 3H), 1.49-1.63 (m, 3H), 2.05 (d, 1H, $J = 10.2$ Hz), 2.40 (brs, 1H), 2.49 (brs, 1H), 2.58 (s, 1H), 3.63 (dd, 1H, $J = 7.8$ Hz, $J = 7.8$ Hz), 3.74 (s, 3H), 4.00 (dd, 1H, $J = 7.8$ Hz, $J = 6.9$ Hz), 4.28-4.37 (m, 1H), 6.74 (brs, 1H), 7.36-7.44 (m, 2H), 7.45-7.51 (m, 1H), 7.70-7.78 (m, 2H). ^{13}C NMR (CDCl_3) δ 23.9, 25.0, 26.4, 28.8, 37.6, 37.6, 46.5, 51.4, 52.4, 68.6, 69.1, 74.4, 108.9, 127.0, 128.4, 131.5, 134.2, 167.0, 172.3. Anal. Calcd. for $\text{C}_{21}\text{H}_{27}\text{NO}_5$: C, 67.54; H, 7.29; N, 3.75. Found C, 67.50; H, 7.32; N, 3.81.

General procedure for hydrolysis of acetals **4a** and **4b**

3 N Hydrochloric acid (4 ml) was added to a solution of compound **4** (2 g, 5.4 mmol) in methanol (80 ml) at room temperature and the mixture was stirred for 24 h. After the reaction was complete, the solution was treated

with a saturated solution of NaHCO_3 and concentrated *in vacuo*. The residue was dissolved in ethylacetate (100 ml), washed with water, dried over MgSO_4 and concentrated *in vacuo*. Purification of the residue by flash chromatography on a silica gel column (eluent; ethyl acetate) afforded 2 g (85 % yield) of the corresponding diol **5** as a colourless solid.

Methyl (1*S*,2*S*,3*R*,4*R*)-bicyclo[2.2.1]heptane-2-benzamido-3-[(*S*)-1,2-dihydroxyethyl]-2-carboxylate **5a**.

95 % yield. M.p. = 149°C. $[\alpha]_{\text{D}}^{25} = +59.2$ ($c = 0.5$ in CHCl_3); IR (nujol) $\nu = 3296, 1734, 1639 \text{ cm}^{-1}$. $^1\text{H-NMR}$ (CDCl_3) δ 1.35-1.58 (m, 4H), 1.72-1.82 (m, 2H), 2.12-2.20 (m, 1H), 2.30 (brs, 1H), 2.54 (m, 1H), 3.26 (brs, 1H), 3.40 (s, 1H), 3.67 (s, 3H), 3.65-3.72 (m, 2H), 4.28-4.40 (m, 1H), 7.32-7.40 (m, 2H), 7.42-7.48 (m, 1H), 7.78-7.84 (m, 2H), 9.20 (brs, 1H). $^{13}\text{C NMR}$ (CDCl_3) δ 22.8, 23.4, 38.2, 39.5, 44.0, 49.5, 52.4, 65.4, 66.2, 72.2, 127.1, 128.5, 131.6, 133.5, 167.1, 174.5. Anal. Calcd. for $\text{C}_{18}\text{H}_{23}\text{NO}_5$: C, 64.85; H, 6.96; N, 4.20. Found C, 64.92; H, 6.89; N, 4.13.

Methyl (1*R*,2*S*,3*R*,4*S*)-bicyclo[2.2.1]heptane-2-benzamido-3-[(*S*)-1,2-dihydroxyethyl]-2-carboxylate **5b**.

96 % yield. M.p. = 125°C. $[\alpha]_{\text{D}}^{25} = -61.0$ ($c = 1$ in CHCl_3); IR (nujol) $\nu = 3318, 1732, 1643 \text{ cm}^{-1}$. $^1\text{H-NMR}$ (CDCl_3) δ 1.20-1.27 (m, 1H), 1.32 (d, 1H, $J = 10.5 \text{ Hz}$), 1.48-1.70 (m, 3H), 2.04-2.10 (brs, 1H), 2.08 (d, 1H, $J = 10.5 \text{ Hz}$), 2.26 (s, 1H), 2.39 (brs, 1H), 2.54 (brs, 1H), 2.60-2.80 (brs, 1H), 3.48-3.60 (m, 1H), 3.60-3.70 (m, 1H), 3.71 (s, 3H), 3.98-4.05 (m, 1H), 7.31 (brs, 1H), 7.34-7.42 (m, 2H), 7.44-7.50 (m, 1H), 7.72-7.78 (m, 2H). $^{13}\text{C NMR}$ (CDCl_3) δ 23.7, 29.4, 37.7, 37.9, 45.9, 50.7, 52.3, 66.4, 69.6, 71.0, 127.1, 128.6, 131.6, 133.9, 167.0, 172.6. Anal. Calcd. for $\text{C}_{18}\text{H}_{23}\text{NO}_5$: C, 64.85; H, 6.96; N, 4.20. Found C, 64.78; H, 6.95; N, 4.25.

General procedure for oxidation of diols **5a** and **5b**

NaIO_4 (1.52 g, 8 mmol) was added to a stirred solution of the corresponding diol **5** (0.5 g, 1.5 mmol) in acetonitrile-carbon tetrachloride-water (1:1:3) (50 ml). The biphasic solution was then treated with $\text{RuCl}_3 \cdot \text{H}_2\text{O}$ (20 mg, 0.088 mmol) and was vigorously stirred for 24h at room temperature. 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 extracted with dichloromethane (3 x 30 ml). Dichloromethane was then added to the aqueous layer and the mixture was acidified by the addition of 6N hydrochloric acid until the pH was 1-2 and vigorously stirred for 5 min. The organic phase was separated and the aqueous phase extracted with dichloromethane (3 x 30 ml). The organic extracts were dried over MgSO_4 , filtered and concentrated *in vacuo*. Purification of the the residue by flash column chromatography (silica gel treated with 12 N hydrochloric acid) (eluent hexane/ethyl acetate, 3:7) afforded the corresponding carboxylic acid **6** as a colourless solid.

(1*S*,2*S*,3*R*,4*R*)-Bicyclo[2.2.1]heptane-2-benzamido-2-carbomethoxy -3-carboxylic acid **6a**.

85 % yield. M.p. = 200°C. $[\alpha]_{\text{D}}^{25} = +32.4$ ($c = 0.5$ in CH_3OH); IR (nujol) $\nu = 3289, 1734, 1706, 1639 \text{ cm}^{-1}$. $^1\text{H-NMR}$ (DMSO-d_6) δ 1.34-1.44 (m, 4H), 1.46-1.54 (m, 1H), 1.73-1.82 (m, 1H), 2.51 (brs, 1H), 2.96 (brs, 1H), 3.00 (d, 1H, $J = 3.7 \text{ Hz}$), 3.53 (s, 3H), 7.42-7.60 (m, 3H), 7.72-7.80 (m, 2H), 9.73 (brs, 1H). $^{13}\text{C NMR}$ (DMSO-d_6) δ 22.7, 22.8, 36.7, 43.9, 49.0, 52.2, 63.3, 126.8, 128.7, 131.7, 133.6, 165.7, 173.0, 174.7. Anal. Calcd. for $\text{C}_{17}\text{H}_{19}\text{NO}_5$: C, 64.34; H, 6.04; N, 4.41. Found C, 64.27; H, 6.11; N, 4.32.

(1*R*,2*S*,3 ,4*S*)-Bicyclo[2.2.1]heptane-2-benzamido-2-carbomethoxy -3-carboxylic acid **6b**.

87 % yield. M.p. = 227°C. $[\alpha]_{\text{D}}^{25} = -103.3$ ($c = 0.45$ in CH_3OH); IR (nujol) $\nu = 3294, 1725, 1714, 1614 \text{ cm}^{-1}$. $^1\text{H-NMR}$ (DMSO-d_6) δ 1.00-1.58 (m, 6H), 2.31 (d, 1H, $J = 2.75 \text{ Hz}$), 2.44 (d, 1H, $J = 10.3 \text{ Hz}$), 3.41 (s,

1H), 3.57 (s, 3H), 7.38-7.44 (m, 2H), 7.46-7.54 (m, 1H), 7.72-7.78 (m, 2H), 8.68 (brs, 1H), 11.64 (brs, 1H). ¹³C NMR (DMSO-d₆) δ 23.6, 27.6, 37.6, 42.0, 45.0, 52.0, 53.4, 68.5, 127.8, 127.9, 131.1, 134.0, 166.4, 172.1, 173.1. Anal. Calcd. for C₁₇H₁₉NO₅: C, 64.34; H, 6.04; N, 4.41. Found C, 64.44; H, 5.92; N, 4.53.

General procedure for hydrolysis of amidoesters 6a and 6b

6 N Hydrochloric acid (55 ml) was added to of the corresponding amido ester **6** (258 mg, 0.8 mmol) and the mixture was heated under reflux for 48 h. After the reaction was complete the solvent was evaporated *in vacuo* and the residue dissolved in water. The solution was extracted with chloroform to eliminate the benzoic acid and the aqueous layer was evaporated *in vacuo*. The residue was purified by column chromatography (silica gel treated with 12 N hydrochloric acid, eluent isopropanol). After removal of the solvent the corresponding amino acid hydrochloride **7** was obtained as a colourless solid.

(1S,2S,3R,4R)-Bicyclo[2.2.1]heptane-2-amino-2,3-dicarboxylic acid hydrochloride **7a**.

85 % yield. M.p. 215°C (dec). $[\alpha]_D^{25} = -21.4$ (c = 0.7 in H₂O); IR (nujol) $\nu = 3600-2300, 1715 \text{ cm}^{-1}$. ¹H-NMR (D₂O) δ 1.30-1.40 (m, 2H), 1.40-1.60 (m, 3H), 1.82 (d, 1H, J = 10.8 Hz), 2.56 (brs, 1H), 2.60 (brs, 1H), 3.47 (d, 1H, J = 3.6 Hz). ¹³C NMR (D₂O) δ 20.6, 20.8, 34.7, 38.7, 45.0, 47.3, 62.3, 172.7, 173.0. Anal. Calcd. for C₉H₁₄ClNO₄: C, 45.86; H, 5.99; N, 5.97. Found C, 45.93; H, 6.05; N, 5.80.

(1R,2S,3R,4S)-Bicyclo[2.2.1]heptane-2-amino-2,3-dicarboxylic acid hydrochloride **7b**.

80 % yield. M.p. 194°C (dec). $[\alpha]_D^{25} = -49.4$ (c = 0.75 in H₂O); IR (nujol) $\nu = 3600-2400, 1722, 1716 \text{ cm}^{-1}$. ¹H-NMR (D₂O) δ 1.20-1.30 (m, 2H), 1.35-1.60 (m, 3H), 1.85 (d, 1H, J = 11.6 Hz), 2.43 (brs, 1H), 2.55 (brs, 1H), 3.28 (s, 1H). ¹³C NMR (D₂O) δ 22.1, 25.5, 35.0, 41.1, 45.1, 50.5, 66.5, 170.5, 173.3. Anal. Calcd. for C₉H₁₄ClNO₄: C, 45.86; H, 5.99; N, 5.97. Found C, 45.80; H, 6.10; N, 6.03.

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