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Asymmetric Diels–Alder reaction using a new chiral β-nitroacrylate for enantiopure *trans*-β-norbornane amino acid preparation

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Abstract—The main nitronorbornene adduct derived from the asymmetric Diels–Alder reaction of (*S*)-benzyl-4-(3-(3-nitroacryloyloxy)-4,4-dimethyl-2-oxopyrrolidin-1-yl)benzoate (*S*)-**1** and cyclopentadiene was isolated and transformed to afford the enantiopure bicyclic β-amino acid (1*S*,2*R*,3*R*,4*R*)-*trans*-β-norbornane amino acid **9**. The enantiomer (1*R*,2*S*,3*S*,4*S*)-**9** could be obtained by the same synthetic route by using the chiral auxiliary (*R*)-**1**.

1. Introduction

In recent years, both the chemistry and the medicinal chemistry of β-amino acids have become the areas of intense research activity.[1,2] In particular, there has been a surge of interest with regards to the structure and the function of conformationally constrained β-amino acids and their oligomers. Indeed, the incorporation of constrained cyclic amino acids into peptides or peptidomimetics induces conformational restriction and provides significant structural effects that can be used for structural and biomechanistic investigations.[3]

Although a number of methods have been developed for the stereoselective preparation of cyclic β-amino acids, most of them focused on simple cyclic compounds and access to bicyclic structures has been less developed but remained attractive.[2] In connection with a project exploiting the use of a new chiral β-nitroacrylate in synthesis, we have focused our attention on β-amino acids possessing a bicyclo[2.2.1]heptane structure obtained by the Diels–Alder reaction of this acrylate with cyclopentadiene (Scheme 2).

Compounds containing the bicyclo[2.2.1]heptane structure are versatile building blocks often used in the synthesis of agonists or antagonists of biologically active substances, such as nucleosides[4] and prostanoids.[5] However, some β-amino acids possessing a bicyclo[2.2.1]heptane structure have been used as starting materials for the synthesis of compounds with medical applications. For example, among the number of thromboxane A2 (TXA2) receptor antagonists compound S-1452, a bicyclic sulfonylamide derivative salt prepared from one of the enantiomers of *trans-endo*/*exo*-3-aminobicyclo[2.2.1]heptane-2-carboxylic acid, has been found useful for the treatment of thrombotic disease.[6] Furthermore, the racemic form of this non-natural cyclic β-amino acid has recently been described as a precursor of a potent and bioavailable integrin VLA-4 antagonist.[7] Further applications of these constrained β-amino acids have been described, particularly in heterocyclic chemistry[8] and recently for the synthesis of foldamers.[9] In the latter case, it has been demonstrated that the oligomers of constrained *cis-diexo*-β-norbornene amino acid residues formed both right and left consecutive six-membered hydrogen-bonded β-strands for (2*S*,3*R*)- and (2*R*,3*S*)-enantiomers, respectively.

The current route to obtain enantiopure *cis*-3-aminobicyclo[2.2.1]heptane-2-carboxylic acids uses the enzyme-catalyzed enantioselective ring opening of the corresponding

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β-lactams.[10] The preparation of enantiopure *trans* derivatives is not so well described. To date and to the best of our knowledge only an elaborate synthesis, which was used in the synthesis of compound S-1452, has been reported.[6] This synthesis involved the enantioselective fission of the commercially available bicyclo[2.2.1]hept-5-ene-2,3-endo-dicarboxylic anhydride with lithium (*R*)-benzyl mandelate, followed by hydrogenation of the double bond, epimerisation of the ester and finally a Curtius rearrangement to introduce nitrogen.

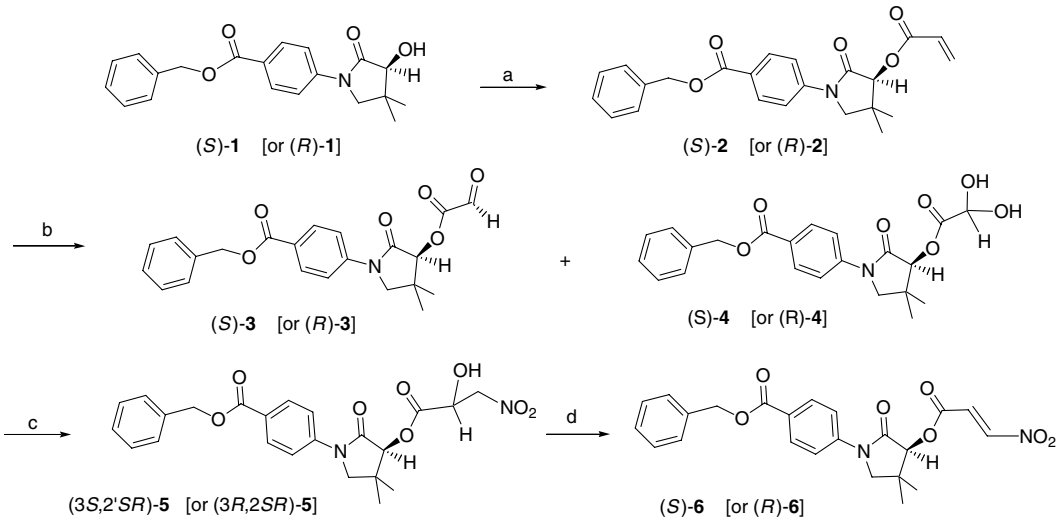
2. Results and discussion

We have previously reported the preparation of each enantiomer of a new chiral alcohol, the (*S*)- or (*R*)-4-(3-hydroxy-4,4-dimethyl-2-oxopyrrolidin-1-yl) benzoic acid (*S*)- or (*R*)-**1**, as well as the synthesis of its acrylate derivative (*S*)- or (*R*)-**2** and their use in asymmetric synthesis.[11]

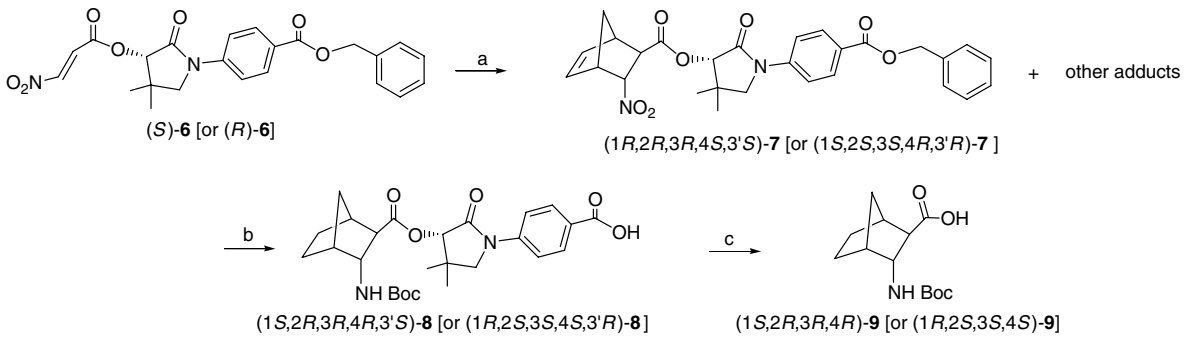
The nitroacrylate (*S*)- or (*R*)-**6** was prepared from the acrylate derivative (*S*)- or (*R*)-**2**. The synthesis consisted of (i) cleavage of the double bond under the classical Lemieux–Johnson conditions to afford a mixture (10/90) of the glyoxylate (*S*)- or (*R*)-**3** and the corresponding hydrate (*S*)- or (*R*)-**4**; (b) transformation via a Henry reaction in the presence of neutral alumina of the glyoxylate function into the corresponding 50/50 diastereoisomeric mixture of the alcohol **5**; (c) formation of the mesylate derivative which was spontaneously transformed into the required nitroacrylate (*S*)- or (*R*)-**6** (Scheme 1).[12]

The results of the following Diels–Alder reaction (Scheme 2) are summarized in Table 1 (entries 1–6).

The reaction between nitroacrylate (*S*)-**6** and cyclopentadiene (6 equiv) was first carried out without a catalyst in dry CH_2Cl_2 at room temperature to give after 8 h in 96% yield the corresponding Diels–Alder adducts (Table 1, entry 1). Analysis of the crude reaction by HPLC (achiral and chiral),[13] LC/MS and ^1H NMR,[14] showed the formation of a mixture of the four expected cycloadducts **7**, with one major diastereoisomer (Table 1, entry 1). An enhanced selectivity could be obtained by running the reaction at lower temperature, particularly at −78 °C to give in good yield a 81/13/5/1 mixture of adducts **7** (Table 1, entries 2 and 3). Under these conditions, the main Diels–Alder adduct **7** could be isolated in enantiopure form after flash



Scheme 1. Reagents and conditions: (a) acryloyl chloride, NEt_3, CH_2Cl_2, rt; (b) $NaIO_4$, OsO_4, H_2O–dioxane, rt; (c) CH_3NO_2, neutral alumine; (d) MsCl, NEt_3, CH_2Cl_2, 0 °C.



Scheme 2. Reagents and conditions: (a) cyclopentadiene, 6 equiv, CH_2Cl_2, −78 °C, 20 h; (b) H_2, 10% Pd–C, AcOH, rt, 15 h; (c) LiOH, H_2O, THF, rt, 5 h.

Table 1. Diels–Alder reaction of the cyclopentadiene with the nitroacrylate (*S*)-**6**[a]

Entry	*T* (°C)	Additive (equiv)	Time (h)	Conversion[b] (%)	Cycloadduct ratio[c]
1	rt	—	8	96	65/20/11/4
2	−20	—	15	95	70/17/10/3
3	−78	—	20	95	81/13/5/1
4	rt	$TiCl_4$ (1)	15	0	—
5	rt	$ZnCl_2$ (1)	5	96[d]	64/25/8/3
6	rt	Et_2AlCl (1)	5	95[d]	64/29/5/2

[a] In CH_2Cl_2 using 6 equiv of cyclopentadiene, 0.15 M acrylate concentration.
[b] Determined by HPLC analysis and based on acrylate disappearance.
[c] Determined by HPLC (achiral and chiral), LC/MS and ^1H NMR analysis.[13,14]
[d] Some non-identified side products were formed.

column chromatography on silica gel using ethyl acetate/cyclohexane (2/8) as an eluent. This compound was then recrystallized from acetonitrile, while the absolute configuration of the newly generated stereocenters was determined by X-ray diffraction analysis (Fig. 1).[15] From the known (*S*)-configuration of the chiral auxiliary, it was determined that the main cycloadduct **7** had a (1*R*,2*R*,3*R*,4*S*,3′*S*)-configuration which resulted from an *endo nitro* selectivity on the Cα/Cβ *ré* face. Attempts to isolate the three minor adducts **7** in their pure form by column chromatography failed, so their configuration could not be unambiguously assigned. However, it can be assumed by using HPLC (achiral and chiral), LC/MS and ^1H NMR analysis[13,14] as well as the determined configuration of the main diastereoisomer, that under the best conditions the reaction proceeded with moderate *endo*-nitro selectivity (84%) and good facial selectivity (94%).

In an attempt to increase the stereoselectivity of the reaction, we investigated the use of Lewis acid catalysts that generally allow the Diels–Alder reaction to proceed with satisfactory yields and a high level of stereoselectivity.[16] From the reaction of the nitroacrylate with cyclopentadiene in the presence of $TiCl_4$ at room temperature, no cycloadduct **7** was isolated (Table 1, entry 4). The addition of $ZnCl_2$ or Et_2AlCl enhanced the reaction rate of the cycloaddition but had no positive effect on the stereoselectivity. We also observed the formation of some side products particularly when using Et_2AlCl as a catalyst (Table 1, entries 5 and 6). It could be assumed that chelation by the Lewis acid involving the two oxygen atoms of the nitro group was responsible for the reaction rate acceleration, without favouring the stereoselectivity.

Hydrogenation of the nitro group concomitant with the hydrogenation of the double bond and hydrogenolysis of the benzyl ester, using palladium on carbon as a catalyst in acetic acid,[17] at room temperature and atmospheric pressure of the isolated enantiopure cycloadduct (1*R*,2*R*,3*R*,4*S*,3′*S*)-**7**, followed by Boc protection of the resulting free amine yielded compound (1*S*,2*R*,3*R*,4*R*,3′*S*)-**8**. Finally, LiOH hydrolysis of this compound at room temperature afforded the expected enantiopure *trans*-β-norbornane amino acid (1*S*,2*R*,3*R*,4*R*)-**9**.

The *trans*-β-norbornane amino acid (1*R*,2*S*,3*S*,4*S*)-**9** could be obtained by the same synthetic route by using the chiral auxiliary (*R*)-**1**.

3. Conclusion

In conclusion, we found that the chiral nitroacrylate (*S*)- or (*S*)-**6** was an efficient dienophile to prepare enantiopure *trans*-β-norbornane amino acids by reaction with cyclopentadiene. The Diels–Alder reaction proceeded in dry CH_2Cl_2 at −78 °C in good yield and good *endo-nitro* selectivity on the Cα/Cβ *ré* face. This study provides a rare example of an asymmetric *trans*-β-norbornane amino acid preparation.

4. Experimental

4.1. General

All reagents were used as purchased from commercial suppliers without further purification. Solvents were dried and purified by conventional methods prior to use. Melting points were determined with a Kofler Heizbank apparatus and are uncorrected. Optical rotations were measured with a Perkin Elmer 341 polarimeter. ^1H or ^{13}C NMR spectra (DEPT, $^1H/^{13}C$ 2D-correlations) were recorded with a Bruker A DRX 400 spectrometer using the solvent as an internal reference. Data are reported as follows: chemical shifts (δ) in parts per million, coupling constants (J) in hertz (Hz). The ESI mass spectra were recorded with a platform II quadrupole mass spectrometer (Micromass, Manchester, UK) fitted with an electrospray source. HPLC analyses

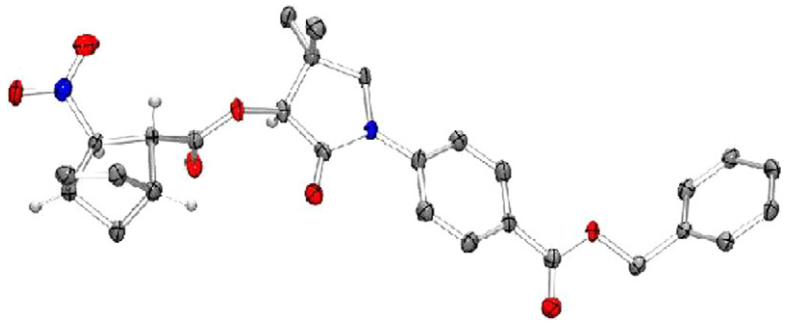


Figure 1. ORTEP drawing of the adduct (1*R*,2*R*,3*R*,4*S*,3′*S*)-**7**.

were performed with a Waters model 510 instrument or a Beckman System Gold 126 instrument with a variable detector using: column A: SymmetryShield™ C_{18}, 3.5 μm, (50 × 4.6 mm), flow: 1 ml/min, H_2O (0.1% TFA)/CH_3CN (0.1% TFA), gradient 0 → 100% (15 min) and 100% (4 min); column B: Whelk-01 (Pirkle), flow: 1 ml/min, eluent I: hexane/2-propanol: 60/40; eluent II: hexane (0.1% TFA)/2-propanol (0.1% TFA) 60/40. Microwave activation was performed with a Biotage initiator 2.0 instrument.

The enantiopure chiral auxiliary (*S*)-benzyl 4-(3-hydroxy-4,4-dimethyl-2-oxopyrrolidin-1-yl)benzoate (*S*)-**1**, and the corresponding acrylate (*S*)-benzyl-4-(3-acryloyloxy-4,4-dimethyl-2-oxopyrrolidin-1-yl)benzoate (*S*)-**2** were prepared as previously described.[11b]

4.1.1. (*S*)-Benzyl-4-[4,4-dimethyl-3-(2-oxoacetoxy)-2-oxopyrrolidin-1-yl]benzoate (*S*)-3 and (*S*)-benzyl-4-[3-(2.2-dihydroacetoxy)-4,4-dimethyl-2-oxopyrrolidin-1-yl]benzoate (*S*)-4. OsO_4 (20 mg, 0.07 mmol) was added at room temperature to a stirred solution of the (*S*)-benzyl-4-(3-acryloyloxy-4,4-dimethyl-2-oxopyrrolidin-1-yl)benzoate (*S*)-**2** (2.10 g, 6.2 mmol) in 26 ml of a H_2O/THF mixture (1/4). After 5 min, the reaction mixture turned brown, $NaIO_4$ (2.55 g, 11.9 mmol, 1.9 equiv) was slowly added portionwise over 10 min and stirring was continued for 2 h. The reaction mixture was diluted with brine (50 ml), organic solvent was removed in vacuo and the aqueous phase was extracted with diethyl ether (3 × 30 ml). The combined organic extracts were washed with water, 10% aqueous $NaHSO_3$ solution, dried over anhydrous sodium sulfate and concentrated in vacuo to yield a mixture of the glyoxylate (*S*)-**3** and its hydrate (*S*)-**4** (2.35 g, 5.7 mmol, 92% yield) in a 10/90 ratio as a colourless oil; t_R (HPLC, column A) 9.4 min; MS (ESI) *m*/*z*: 396.3 and 414.1 [(M+H)$^+$]; ^{1}H NMR (CD_3CN) δ 1.14 and 1.19 (s, 3H, C*H*$_3$), 1.28 and 1.30 (s, 3H, C*H*$_3$), 3.67 (m, 2H, 5-*H*), 5.29 (s, 0.9H, C*H*(OH)$_2$), 5.35 (s, 2H, C*H*$_2$–C$_6$H$_5$); 5.48 and 5.59 (s, 1H, 3-*H*), 7.44 (m, 5H, *H*-arom), 7.79 (d, *J* = 10.6, 2H, *H*-arom), 8.06 (d, *J* = 10.6, 2H, *H*-arom), 9.4 (s, 0.1H, CO–*H*) ^{13}C NMR (CD_3CN) δ 20.1 and 20.2 (*C*H$_3$), 23.3 and 23.5 (*C*H$_3$), 37.0 and 37.3 (*C*-4), 56.8 and 56.9 (*C*-5), 66.3 (O*C*H$_2$C$_6$H$_5$), 78.5 and 79.7 (*C*-3), 87.0 (*C*H(OH)$_2$), 177.3 (*C*-arom), 118.7 and 118.8 (*C*H-arom), 125.8 and 126.1 (*C*-arom), 128.0, 128.1, 128.6 and 130.3 (*C*H-arom), 136.6, 142.2 and 143.4 (*C*-arom), 158.6, 165.5, 168.4, 169.0, 169.8 and 183.7 (*C*O).

4.1.2. (3*S*,2′*RS*)-Benzyl-4-(3-(2-hydroxy-3-nitropropionyloxy)-4,4-dimethyl-2-oxopyrrolidin-1-yl)benzoate (3*S*,2′*RS*)-5. Neutral alumina[18] (2.4 g, 0.5 g/mmol) was added over a period of 10 min at 0 °C to a stirred solution of a mixture of the glyoxylate (*S*)-**3** and its hydrate (*S*)-**4** (2.00 g, 4.8 mmol, assuming all the material is the hydrate) in nitromethane (10 ml, 186 mmol). Stirring was continued for an additional 30 min at 0 °C and then 3 h at room temperature. To the resulting suspension was added CH_2Cl_2 (50 ml) and after filtration through Celite the filtrate was concentrated in vacuo. The crude was submitted to column chromatography on silica gel using cyclohexane/ethyl acetate as eluent (7/3) to yield a 50/50 diastereoisomeric mixture of the expected compound **5** (1.62 g, 3.55 mmol, 74% yield)[19] as a white solid; mp 48–50 °C; t_R (HPLC, column A) 10.4 and 10.5 min; MS (ESI) *m*/*z*: 457.2 [(M+H)$^+$]; ^{1}H NMR ($CDCl_3$) δ 1.05 and 1.11 (s, 3H, C*H*$_3$), 1.29 and 1.30 (s, 3H, C*H*$_3$), 3.49 and 3.51 (2d, *J* = 9.7, 1H, 5-*H*), 3.60 and 3.62 (2d, *J* = 9.7, 1H, 5-*H*), 4.79 (m, 2.5H, C*H*OH and C*H*$_2$NO$_2$), 4.89 (t, $J_1 = J_2 = 4.5$, 0.5H, C*H*OH), 5.29 (s, 2H, C*H*$_2$–C$_6$H$_5$); 5.44 and 5.51 (s, 1H, 3-*H*), 7.32 (m, 5H, *H*-arom); 7.63 (d, *J* = 9.4, 2H, *H*-arom); 8.02 (d, *J* = 9.4, 2H, *H*-arom); ^{13}C NMR ($CDCl_3$) δ 21.0 and 21.1 (*C*H$_3$), 24.3 and 24.5 (*C*H$_3$), 37.6 (*C*-4), 57.4 and 57.5 (*C*-5), 66.7 and 66.8 (O*C*H$_2$C$_6$H$_5$), 79.9 and 80.0 (*C*-3), 118.6 (*C*H-arom), 126.5 (*C*-arom), 128.2, 128.3, 128.6 and 130.8 (*C*H-arom), 136.0 and 142.6 (*C*-arom), 165.7 and 165.8 (*C*OCH=CH$_2$), 168.4, 168.5, 170.2 and 170.5 (*C*O); HRMS (FAB) Calcd for $C_{23}H_{25}N_2O_8$ (MH$^+$) 457.1611, found 457.1609.

4.1.3. (*S*)-Benzyl-4-(3-(3-nitroacryloyloxy)-4,4-dimethyl-2-oxopyrrolidin-1-yl)benzoate (*S*)-6. Mesylchloride (237 μl, 3.0 mmol, 1.05 equiv) was added dropwise at 0 °C and under argon to a stirred solution of compound **5** (1.33 g, 2.9 mmol) in dry CH_2Cl_2 (16 ml). Then, NEt_3 (1.62 ml, 11.6 mmol, 4 equiv) was added dropwise over 5 min with stirring at the same temperature. Stirring was continued for an additional 2 min at 0 °C. The reaction mixture diluted with diethyl ether (80 ml), was successively washed with a 0.1 M HCl solution (40 ml) and brine (40 ml), dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude nitro acrylate (*S*)-**6** (1.14 g, 2.6 mmol, 85% yield)[19] was used without further purification in the following step or could be purified by flash column chromatography using cyclohexane/ethyl acetate as eluent (7.5/2) to yield pure compound (*S*)-**6** as a colourless oil (1.00 g, 2.3 mmol, 75% yield); $[\alpha]_D^{20} = -17$ (*c* 1.7, CH_2Cl_2); t_R (HPLC, column A) 11.8 min; MS (ESI) *m*/*z*: 439.0 [(M+H)$^+$]; ^{1}H NMR ($CDCl_3$) δ 1.15 (s, 3H, C*H*$_3$), 1.28 (s, 3H, C*H*$_3$), 3.54 (d, *J* = 9.7, 1H, 5-*H*), 3.62 (d, *J* = 9.7, 1H, 5-*H*), 5.30 (s, 2H, C*H*$_2$–C$_6$H$_5$); 5.46 (s, 1H, 3-*H*), 7.15 (d, *J* = 13.5, 1H, CO–C*H*=), 7.32 (m, 5*H*, *H*-arom); 7.64 (d, *J* = 9.4, 2H, *H*-arom); 7.71 (d, *J* = 13.5, 1H, NO$_2$C*H*=), 8.03 (d, *J* = 9.4, 2H, *H*-arom); ^{13}C NMR ($CDCl_3$) δ 21.2 (*C*H$_3$), 24.7 (*C*H$_3$), 37.4 (*C*-4), 57.4 (*C*-5), 66.8 (O*C*H$_2$C$_6$H$_5$), 77.7 (*C*-3), 118.5 (*C*H-arom), 126.4 (*C*-arom), 126.5 (*C*H=), 128.2, 128.6 and 130.8 (*C*H-arom), 132.9 and 143.7 (*C*-arom), 149.8 (NO$_2$*C*H=), 162.8 (*C*OCH=CH$_2$), 165.7 and 168.1 (*C*O); HRMS (FAB) Calcd for $C_{23}H_{23}N_2O_7$ (MH$^+$) 439.1505, found 439.1512.

4.1.4. (1*R*,2*R*,3*R*,4*S*,3′*S*)-[*N*-(4-Benzyloxycarbonylphenyl)-4,4-dimethyl-2-oxopyrrolidin-3-yl] 3-nitrobicyclo[2.2.1]hept-5-ene-2-carboxylate (1*R*,2*R*,3*R*,4*S*,3′*S*)-7. Freshly-distilled cyclopentadiene (980 μl, 6 equiv, 13.8 mmol) was added to a solution of the nitroacrylate (*S*)-**6** (1.00 g, 2.3 mmol) in dry CH_2Cl_2 (100 ml) at −78 °C. The reaction mixture was stirred for 20 h at the same temperature. Removal of the solvent and of the cyclopentadiene excess in vacuo afforded in good yield (1.30 g, 2.2 mmol, 95% yield) a mixture of the four expected cycloadducts (two *endo-nitro* isomers and two *exo-nitro* isomers) in a 81/13/5/1 ratio. The crude adducts were submitted to flash column chromatography using cyclohexane/ethyl acetate as eluent (8/2) to yield the enantiopure *endo-nitro* major adduct

(1*R*,2*R*,3*R*,4*S*,3′*S*)-**7** (0.38 g, 0.76 mmol, 53.1% yield, 99 de) as a white solid; mp 119 °C; $[\alpha]_D^{20} = -102$ (*c* 0.9, CH_2Cl_2); t_R (HPLC, column A) 12.3 min; t_R (HPLC, column B, eluent I) 15.7 min; MS (ESI) *m*/*z*: 505.1 [$(M+H)^+$]; ^1H NMR ($CDCl_3$) δ 1.12 (s, 3H, C*H*$_3$), 1.26 (s, 3H, C*H*$_3$), 3.10 (dd, $J = 2.6$ and 3.1, 1H, 4-*H*), 3.38 (br s, 1H, 2-*H*), 3.51 (d, $J = 9.6$, 1H, 5′-*H*), 3.58 (br d, $J = 9.6$, 2H, 5′-*H* and 1-*H*), 5.28 (s, 2H, C*H*$_2$–C_6H_5); 5.39 (s, 1H, 3′-*H*), 5.41 (t, $J_1 = J_2 = 3.8$, 1H, 3-*H*), 6.05 (dd, $J = 2.7$ and 5.6, 1H, 6-*H*), 6.45 (dd, $J = 3.1$ and 5.6, 1H, 5-*H*), 7.32 (m, 5H, *H*-arom), 7.64 (d, $J = 7.0$, 2H, *H*-arom), 8.01 (d, $J = 7.0$, 2H, *H*-arom); ^{13}C NMR ($CDCl_3$) δ 21.2 (*C*H$_3$), 24.6 (*C*H$_3$), 37.1 (*C*-4′), 46.2 (*C*-7), 47.4 (*C*-1), 48.4 (*C*-2), 48.9 (*C*-4), 57.4 (*C*-5′), 66.7 (O*C*H$_2$C$_6$H$_5$), 78.9 (*C*-3), 87.8 (*C*-3′), 118.4 (*C*H-arom), 126.2 (*C*-arom), 128.2, 128.3, 128.4, 128.6 and 130.8 (*C*H-arom), 133.8 (*C*H=), 136.0 (*C*-arom), 139.4 (*C*H=), 142.9 (*C*-arom), 165.8, 169.2 and 171.8 (*C*O); HRMS (FAB) Calcd for $C_{28}H_{29}N_2O_7$ (MH^+) 505.1975, found 505.1981.

4.1.5. (1*S*,2*R*,3*R*,4*S*,3′*S*)-[*N*-(4-Carboxyphenyl)-4,4-dimethyl-2-oxopyrrolidin-3-yl] 3-*tert*-butoxycarbonylaminobicyclo[2.2.1]heptane-2-carboxylate (1*S*,2*R*,3*R*,4*S*,3′*S*)-8. Compound (1*R*,2*R*,3*R*,4*S*,3′*S*)-**7** (0.38 g, 0.76 mmol) in acetic acid (8 ml) was added to a suspension of 10% Pd/C (~20 mg) in acetic acid (2 ml). This mixture was stirred vigorously under 1 atm. of H_2 for 15 h at room temperature. The suspension was filtered through Celite and the filtrate was concentrated in vacuo. To the residue dissolved in ethyl alcohol (15 ml) was added DIEA (0.65 ml, 3.8 mmol, 5.0 equiv) and $(Boc)_2O$ (0.30 g, 1.37 mmol, 1.8 equiv). The resulting mixture was stirred for 15 h at room temperature (controlled by HPLC, column A). After the removal of the solvent, the residue was dissolved in aqueous 0.1 M NaOH (15 ml) and the aqueous phase was washed with ethyl ether (20 ml), acidified to pH 3 and extracted with diethyl acetate (3×20 ml). The organic layer was dried over Na_2SO_4, and concentrated in vacuo to yield the expected compound (1*S*,2*R*,3*R*,4*R*,3′*S*)-**8** (0.25 g, 0.51 mmol, 66% yield) as a white solid; mp 100 °C; $[\alpha]_D^{20} = -14$ (*c* 1.5, CH_2Cl_2); t_R (HPLC, column A) 10.5 min; t_R (HPLC, column B, eluent II) 6.2 min; MS (ESI) *m*/*z*: 487.0 [$(M+H)^+$], 430.9, 387.0; ^1H NMR ($CDCl_3$) δ 1.08 (s, 3H, C*H*$_3$), 1.25 (br m, 1H, HC*H*), 1.28 (s, 3H, C*H*$_3$), 1.36 (s, 9H, C(C*H*$_3$)$_3$), 1.40 (br m, 1H, HC*H*), 1.58 (br m, 1H, HC*H*), 1.75 (br d, $J = 10.0$, 1H, HC*H*), 2.00 (br s, 1H, 4-*H*), 2.37 (br s, 1H, 2-*H*), 2.56 (br s, 1H, 1-*H*), 3.49 (br d, $J = 9.6$, 1H, 5′-*H*), 3.57 (br d, $J = 9.6$, 1H, 5′-*H*), 4.07 (br s, 1H, 3-*H*), 5.39 (s, 1H, 3′-*H*), 7.68 (d, $J = 8.9$, 2H, *H*-arom), 8.03 (d, $J = 8.9$, 2H, *H*-arom); ^{13}C NMR ($CDCl_3$) δ 20.9 (*C*H$_2$), 21.0 (*C*H$_3$), 24.6 (*C*H$_3$), 28.4 (C(*C*H$_3$)$_3$), 29.7 (*C*H$_2$), 36.3 (*C*H$_2$), 37.4 (*C*-4′), 40.3 (*C*-2), 41.3 (*C*-1), 54.0 (*C*-4), 56.1 (*C*-3), 57.5 (*C*-5′), 77.8 (*C*-3′), 85.2 (*C*(CH$_3$)$_3$), 118.4 (*C*H-arom), 125.3 (*C*-arom), 131.3 (*C*H-arom), 143.6 (*C*-arom), 169.9, 170.6, 172.3 and 173.8 (*C*O); HRMS (FAB) Calcd for $C_{26}H_{35}N_2O_7$ (MH^+) 487.2444, found 487.2429.

4.1.6. (1*S*,2*R*,3*R*,4*R*)-3-*tert*-Butoxycarbonylaminobicyclo[2.2.1]heptane-2-carboxylic acid (1*S*,2*R*,3*R*,4*R*)-9. A solution of LiOH, H_2O (17.6 mg, 0.42 mmol, 2.1 equiv) in water was added dropwise to a solution of compound (1*S*,2*R*,3*R*,4*R*,3′*S*)-**8** (100 mg, 0.2 mmol) in THF/H_2O (2/1) (4 ml) and the mixture was stirred at room temperature until completion of the hydrolysis (~5 h) (monitored by HPLC, column A). The organic solvent was removed in vacuo and the aqueous phase was acidified (pH 3). The residue obtained after evaporation of the water was submitted to column chromatography on silica gel, using CH_2Cl_2/ethyl acetate/AcOH (9/1/0.01) as eluent to yield the expected pure β-amino acid (1*S*,2*R*,3*R*,4*R*)-**9** (35 mg, 0.14 mmol, 68% yield) as a white solid; mp 114–115 °C; $[\alpha]_D^{20} = -22$ (*c* 0.9, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.12–1.26 (m, 3H, C*H*$_2$ and HC*H*), 1.36–1.54 (m, 4H, C*H*$_2$), 1.40 (s, 9H, C(C*H*$_3$)$_3$), 1.62 (m, 1H, HC*H*), 2.07 (br s, 1H, 4-*H*), 2.33 (br s, 1H, 2-*H*), 2.77 (br d, $J = 3.8$, 1H, 1-*H*), 3.68 (br d, $J = 3.7$, 1H, 3-*H*), 5.06 (br s, 1H, N*H*); ^{13}C NMR ($CDCl_3$) δ 21.86 (*C*H$_2$), 28.3 (C(*C*H$_3$)$_3$), 29.7 (*C*H$_2$), 37.0 (*C*H$_2$), 39.7 (*C*-1), 40.2 (*C*-2), 56.1 (*C*-3), 56.5 (*C*-3), 82.1 (*C*(CH$_3$)$_3$), 158.6 and 174.1 (*C*O); HRMS (FAB) Calcd for $C_{13}H_{22}NO_4$ (MH^+) 256.1549, found 256.1554.

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14. Some significant differences of the resonance signals on the ^1H and ^{13}C spectra were observed for the different cycloadducts **7**. For example 6-*H* and 5-*H* chemical shifts were respectively: (6.05 and 6.20 ppm (dd)) (81%), (6.03 and 6.24 ppm (dd)) (13%), (6.46 and 6.48 ppm (dd)) (5%) and (6.46 and 6.48 ppm (dd)) (∼1%).
15. Crystal data for ester: (1*R*,2*R*,3*R*,4*S*,3′*S*)-**7**, Molecular formula $C_{28}H_{28}N_2O_7$ $M = 504.5$, orthorhombic, space group $P2_12_12_1$, $a = 6.1315(5)$ Å, $b = 9.3117(7)$ Å, $c = 43.314(3)$ Å, $V = 2473.0(3)$ Å^3, $Z = 4$, $D_c = 1.355$ Mg m^{-3}. X-ray diffraction data were collected at low temperature with Mo Kα radiation using the Bruker AXS Kappa CCD system. The structure was solved using direct methods and the model was refined by full-matrix least-square procedures on F^2 to values of $R_1 = 0.0593$ and of $Rw_2 = 0.1147$ for 2627 reflections with $I > 2\sigma(I)$. Details of the crystal structure (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 659166. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
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19. Compound **5** contains about 5–7% of the compound (*S*)-**1** (HPLC analysis) as inevitable hydrolysis of the ester bond during the Henry reaction, that was transformed in an OMesyl derivative in the following step providing the nitroacrylate (*S*)-**6**.