CHIRALITY 23:245–249 (2011)

Synthesis of Enantiopure *Trans*-*N*-Boc-3-Aminobicyclo[2.2.2]octane-2-carboxylic acids and Their Bicyclic 1,3-Amino alcohol Derivatives via the [4+2] Cycloaddition of 1,3-Cyclohexadiene to a Chiral β-Nitroacrylate

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ABSTRACT The chiral β-nitroacrylate **2** derived from the (*R*)- or (*S*)-4-(3-hydroxy-4,4-dimethyl-2-oxopyrrolidin-1-yl) benzoic acid **1** acts as a reactive dienophile in a diastereoselective Diels-Alder reaction with 1,3-cyclohexadiene. The major cycloadducts have been isolated and transformed into enantiopure *trans*(2*S*,3*S*)- or (2*R*,3*R*)-*N*-Boc-3-aminobicyclic[2,2,2]octane-2-carboxylic acids **5.** The *trans*-(2*S*,3*S*)- or (2*R*,3*R*)-*N*-Boc 3-(hydoxymethyl)-2-aminobicyclic[2,2,2] octane **6** derivatives were also obtained. *Chirality 23:245–249, 2011.*

KEY WORDS: asymmetric synthesis; Diels-Alder reactions; bicyclic β-amino acids; bicyclic-1,3-amino alcohol; chiral β-nitroacrylate

INTRODUCTION

Nitroalkenes are versatile building blocks in the synthesis of many pharmaceutically interesting compounds.[1] In particular, β-nitroacrylates have proved to be useful in Diels-Alder reactions.[1] They act as electron deficient alkenes and react with different dienes to yield cyclic constrained β-amino acids after reduction of the nitro group.[2–5] Concerning asymmetric Diels-Alder syntheses, it is surprising that only a few methods involving the use of a chiral β-nitroacrylate have been reported so far.[6,7] Indeed, chiral cyclic β-amino acids are an important class of compounds as they are constituents of natural products such as alkaloids, peptides, and β-lactam antibiotics.[8–13] Furthermore, their incorporation into peptides or peptidomimetics induces conformational restriction and provides significant structural effects that can be used for structural and biomechanistic investigations.[14–17] Apart from this, enantiopure cyclic β-amino acids also play a significant role in the synthesis of various cyclic structures.[18] In particular, their simple reduction allowed the preparation of chiral cyclic 1,3-amino alcohols that can be used as ligands in asymmetric reactions[19–21] or as convenient starting materials for the synthesis of various 1,3-heterocycles.[22–24]

In this context, synthesis of new sterically constrained enantiomerically pure cyclic amino acids is particularly attractive. We have previously found that the chiral nitroacrylate (*S*)- or (*S*)-**2** was an efficient dienophile to prepare enantiopure *trans*-β-norbornane amino acids by reacting with cyclopentadiene.[7] In connection with an enlarged use of the new chiral β-nitroacrylate **2** in synthesis, we have focused our attention on the synthesis of chiral bicyclic amino acids possessing a bicyclo[2.2.2]octane structure. They were obtained by a Diels-Alder reaction of this acrylate with 1,3-cyclohexadiene (Scheme 1). We have also investigated the preparation of their enantiopure bicyclic 1,3-amino alcohol derivatives (Scheme 2).

The interest in amino acid possessing a bicyclo[2.2.2]octane structure is highlighted by several investigations.[25–37] Some of these synthetic derivatives exhibit noticeable biological activities. As an example, 2-aminobicyclo[2.2.2]octane-2-carboxylic acids selectively disturb levels of neutral amino acids in the cerebral cortex,[25–33] while dihydroxylated 1-aminobicyclo[2.2.2]octane-4-carboxylic acids have been used as scaffolds for antiviral agents.[34] A series of cyclic β-amino acid derivatives has also been investigated as VLA-4 antagonists implicated in several inflammatory and autoimmune disease states.[35]

The current route to obtain racemic 3-aminobicyclo[2.2.2]octane-2-carboxylic acid derivatives uses a Diels-Alder reaction involving often a β-nitroacrylate.[26,27,31,36,37] To the best of our knowledge there is no example of the asymmetric version of this cycloaddition reaction. One attempt to obtain enantiopure compounds using N-3,5-dichlorobenzenesulfonyl-(L)-proline as chiral resolving agent, provided unseparable diastereoisomers by column chromatography.[36]

MATERIALS AND METHODS

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. ^{1}H or ^{13}C NMR spectra (DEPT, $^{1}H/^{13}C$ 2D-correlations) were recorded with a Bruker A DRX 400 spectrometer using the solvent as 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 were performed with a Waters model 510 instrument or a Beckman System Gold 126 instru-

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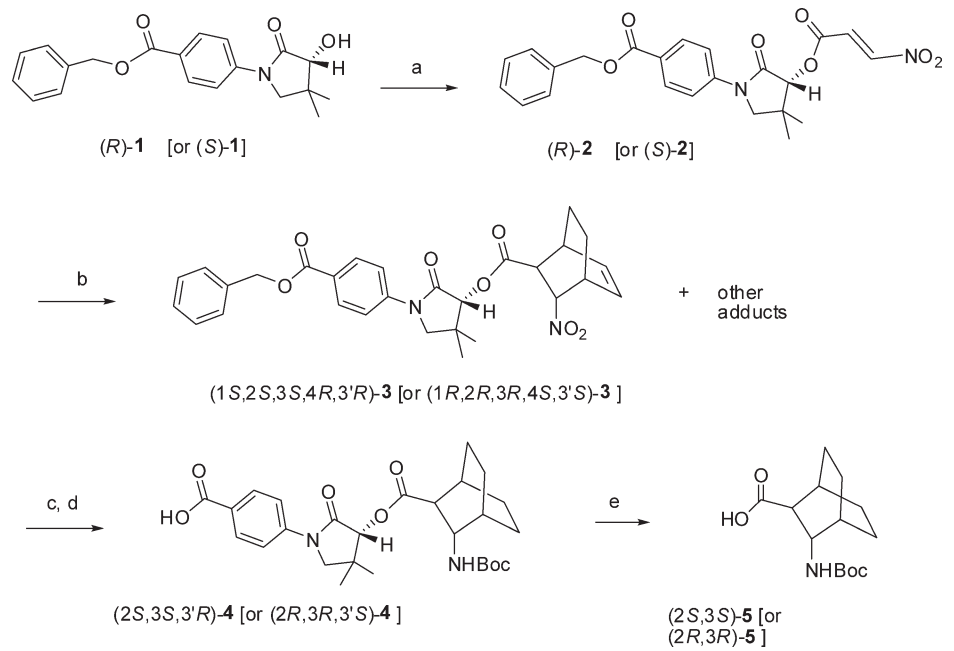
Received for publication 7 December 2009; Accepted 22 June 2010
DOI: 10.1002/chir.20906
Published online 6 October 2010 in Wiley Online Library (wileyonlinelibrary.com).



(*R*)-**1** [or (*S*)-**1**] (*R*)-**2** [or (*S*)-**2**]

(1*S*,2*S*,3*S*,4*R*,3′*R*)-**3** [or (1*R*,2*R*,3*R*,4*S*,3′*S*)-**3**]

(2*S*,3*S*,3′*R*)-**4** [or (2*R*,3*R*,3′*S*)-**4**] (2*S*,3*S*)-**5** [or (2*R*,3*R*)-**5**]

Scheme 1. Reagents: (**a**) see Ref. 7: 4 steps 52% overall; (**b**) cyclohexadiene, 10 equiv, −20°C, 72 h (92%); (**c**) column chromatography (21%); (**d**) H_2/Pd-C/CH_3OH/Boc_2O/NEt_3, 20 h (65%); (**e**) LiOH, H_2O, THF, rt, 5 h (58%).

ment with variable detector using: column A: SymmetryShield™ C_{18}, 3.5 μ, (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, hexane:2-propanol: 60/40; Microwave activation was performed with a Biotage initiator 2.0 instrument.

Preparation of the Nitro β-Acrylate (R)-*2*

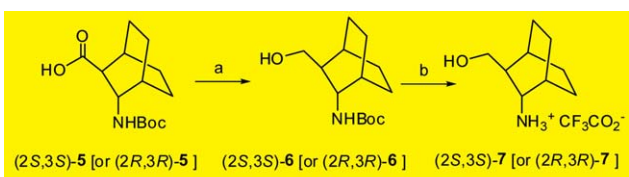
The enantiopure chiral auxiliary (*R*)-Benzyl 4-(3-hydroxy-4,4-dimethyl-2-oxopyrrolidin-1-yl) benzoate (*R*)-**1** and the corresponding nitro acrylate (*R*)-Benzyl-4-(3-(3-nitroacryloyloxy)-4,4-dimethyl-2-oxopyrrolidin-1-yl)-benzoate (*R*)-**2** were prepared as previously described.[7,38–40]

Diels-Alder reaction of the 1,3-Cyclohexadiene with the Nitroacrylate (R)-*2*[a]

1.3-Cyclohexadiene (4.4 ml, 10 equiv, 46 mmol) was added to a solution of the nitroacrylate **(***R***)-2** (2.00 g, 4.6 mmol) in CH_2Cl_2 (4 ml) at −20°C. [The nitroacrylate (*R*)-**2** contains about 5–7% of the OMesyl derivative of the compound (*R*)-**1** (HPLC analyse) as ineluctable hydrolysis of the ester bond during the Henry reaction, that was transformed in OMesyl derivative in the following step]. The reaction mixture was stirred for 24–48 h at the same temperature (monitored by HPLC, column A). Removal of the 1,3-cyclohexadiene excess and of the CH_2Cl_2 in vacuo afforded in good yield (2.26 g, 4.4 mmol, 95% yield) a mixture of the four expected cycloadducts **3** (two endo-nitro isomers and two exo-nitro isomers) in a 60/26/10/4 ratio [(t_R (HPLC, column B) 15.8 min (60%), 18.6 min (10%), 26.3 min (4%), and 29.2 min (26%)]. Some significant differences of the resonance signals on the ^1H and ^{13}C spectra were also observed for the differents cycloadducts **3**. For example 3-*H* chemical shifts were, respectively: [4.83 ppm (m)] (10%), [4.87 ppm (m)] (4%), [5.05 ppm (dd)] (60%), and [5.08 ppm (dd)] (26%). Crude adducts were submitted to two consecutive flash column chromatography using first cyclohexane/ethyl acetate (8/2) and then cyclohexane/dichloromethane/ethyl acetate (7/2/1) as eluents to yield the enantiopure endo-nitro major adduct (1*S*,2*S*,3*S*,4*R*,3′*R*)-[*N*-(4-Benzyloxycarbonylphenyl)-4,4-Dimethyl-2-oxopyrrolidin-3-yl]-1-(3-nitrobicyclo[2.2.2]oct-5-ene-2-carboxylate [(1*S*,2*S*,3*S*,4*R*,3′*R*)-**3**] (0.50 g, 0.97 mmol, 21 % yield, 99 de) as a white solid; m.p. 115°C; $[\alpha]_D^{20}$ = + 73 (*c* = 1.2 in CH_2Cl_2); t_R (HPLC, column A) 12.5 min; t_R (HPLC, column B) 15.8 min; MS (ESI) *m/z*: 519.2 [$(M+H)^+$]; ^1H NMR ($CDCl_3$) δ 1.12 (s, 3H, C*H*$_3$), 1.17 (m, 1H, *H*-CH), 1.27 (s, 3H, C*H*$_3$), 1.38 (tt, $J_1 = J_2$ = 12.2, and $J_3 = J_4$ =3.9, 1H, *H*-CH), 1.63 (tdd, $J_1 = J_2$ = 9.6, J_3= 4.4, and J_4 =2.1, 1H, *H*-CH), 1.75 (tdd, $J_1 = J_2$ = 9.6, J_3= 3.6, and J_4 =2.7, 1H, *H*-CH), 3.17 (m, 1H, 4-*H*), 3.29 (m, 1H, 2-*H*), 3.41 (m, 1H, 1-*H*), 3.51 (d, *J* = 9.6, 1H, 5′-*H*), 3.60 (d, *J* = 9.6, 1H, 5′-*H*), 5.05 (dd, J_1 = 2.8 and J_2 = 4.3, 1H, 3-*H*), 5.28 (s, 2H, C*H*$_2$-C_6H_5); 5.40 (s, 1H, 3′-*H*), 6.12 (t, $J_1 = J_2$ = 7.0, 1H, 6-*H*), 6.42 (t, $J_1 = J_2$ = 7.0, 1H, 5-*H*), 7.31 (m, 5H, *H*-arom), 7.65 (d, *J* = 9.4, 2H, *H*-arom), 8.01 (d, *J* = 9.4, 2H, *H*-arom); ^{13}C NMR ($CDCl_3$) 19.5 (*C*-8), 21.2 (*C*H$_3$), 22.0 (*C*-7), 24.6 (*C*H$_3$), 33.0 (*C*-4), 34.1 (*C*-1), 37.2 (*C*-4′), 47.8 (*C*-2), 57.4 (*C*-5′), 66.7 (O*C*H$_2$C$_6$H$_5$), 78.9 (*C*-3′), 85.5 (*C*-3), 118.4 (*C*H-arom), 126.2 (*C*-arom), 128.2, 128.3, and 128.6 (*C*H-arom), 130.3 (*C*H=), 130.8 (*C*H-arom), 135.1 (*C*H=), 136.0 (*C*-arom), 142.9 (*C*-arom), 165.8, 169.0, and 171.4 (*C*O); HRMS (FAB) Calcd for $C_{29}H_{31}N_2O_7$ (MH^+) 519.2131, found 519.2112.

(2S,3S,3′R)-[N-(4-Carboxyphenyl)-4,4-Dimethyl-2-oxopyrrolidin-3-yl]-1-(3-tert-butoxycarbonylaminobicyclo[2.2.2]octane-2-carboxylate [(2S,3S,3′R)-4]

To a solution of compound (1*S*,2*S*,3*S*,4*R*,3′*R*)-**3** (500 mg, 0.96 mmol) in methanol (25 ml) at room temperature, atmospheric pressure, and under argon was added NEt_3 (202 μl, 1.45 mmol, 1.5 equiv), $(Boc)_2O$ (377 mg, 1.72 mmol, 1.8 equiv) and by portionwise palladium on carbon (10% Pd/C, 500mg). This mixture was stirred vigorously under 1 atm of H_2 for 20 h at the same temperature (controlled by HPLC, column A). The suspension was filtered through Celite and the filtrate was concentred in vacuo. After removal of the solvent, the residue was dissolved in water (15 ml) and this 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, concentrated in vacuo to yield



(2*S*,3*S*)-**5** [or (2*R*,3*R*)-**5**] (2*S*,3*S*)-**6** [or (2*R*,3*R*)-**6**] (2*S*,3*S*)-**7** [or (2*R*,3*R*)-**7**]

Scheme 2. Reagents: (**a**) BOP/DIPEA/$NaBH_4$/THF (67%); (**b**) TFA/CH_2Cl_2 3/7 (quantitative yield). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com]

TABLE 1. Diels-Alder reaction of the 1,3-cyclohexadiene with the nitroacrylate (*R*)-2[a]

Entry	*T* (°C)	Solvent	Additive (equiv)	Time (h)	Conversion (%)[b]	Cycloadducts ratio[c]
1	−78	CH_2Cl_2	–	24	0	–
2	RT	CH_2Cl_2	–	5/24	10/90	52/28/13/7
3	−20	CH_2Cl_2	–	48	>99	60/26/10/4
4	MW 60	CH_2Cl_2	–	0.5	>99	53/27/13/7
5	RT	–	–	5/24	55[d]	68/17/12/3
6	RT	CH_2Cl_2	$ZnCl_2$ (1)	5/24	70/>99	52/31/11/6
7	−20	CH_2Cl_2	$ZnCl_2$ (1)	20	10	–

[a]In CH_2Cl_2 using 10 equivalents of 1,3-cyclohexadiene, 0.5*M* acrylate concentration or in solvent free condition using 20 equivalents of cyclohexadiene.
[b]Determined by HPLC analysis and based on acrylate disappearance.
[c]Determined by ^{1}H NMR, HPLC (achiral and chiral), and LC/MS analysis.[13,14]
[d]Incomplete solubility of the nitroacrylate in solvent-free conditions.

the expected compound (2*S*,3*S*,3′*R*)-**4** (310 mg, 0.62 mmol, 65 % yield) as a white solid; m.p. 123°C; $[\alpha]_D^{20} = -10$ (*c* = 0.9 in CH_2Cl_2); t_R (HPLC, column A) 9.8 min; MS (ESI) *m/z*: 501.3 [(M+H)$^+$], 445.3, 401.3; ^{1}H NMR ($CDCl_3$) δ 1.00–1.80 (m + s, 2(C*H*$_3$), C(C*H*$_3$)$_3$, 4(C*H*$_2$), C*H*), 2.04 (br s, 1H, C*H*), 2.37, and 2.55 (br s, 1H, C*H*), 3.49 (d, *J* = 9.5, 1H, 5′-*H*), 3.57 (d, *J* = 9.5, 1H, 5′-*H*), 3.98 (br s, 1H, C*H*), 4.64 (br s, 1H, N*H*), 5.40 (s, 1H, 3′-*H*), 7.60 (d, *J* = 8.5, 2H, *H*-arom), 7.90 (d, *J* = 8.5, 2H, *H*-arom); ^{13}C NMR ($CDCl_3$) 19.6 (*C*H$_2$), 20.2 (*C*H$_3$), 23.2 (*C*H$_2$), 23.6 (*C*H$_3$), 24.84 (*C*H$_2$), 27.4 (*C*H), 27.5 (C(*C*H$_3$)$_3$), 28.2 (*C*H), 28.4 (*C*H$_2$), 36.4 (*C*-4′), 49.9 (*C*-2 and *C*-3), 56.5 (*C*-5′), 77.1 (*C*-3′), 81.18 (*C*(CH$_3$)$_3$), 117.3 (*C*H-arom), 124.4 (*C*-arom), 130.2 (*C*H-arom), 142.5 (*C*-arom), 155.8, 168.7, 169.5, and 172.6 (*C*O); HRMS (FAB) Calcd for $C_{27}H_{37}N_2O_7$ (MH$^+$) 501.2601, found 501.2602.

(2S,3S)-3-tert-Butoxycarbonylaminobicyclo[2.2.2]octane-2-carboxylic acid [(2S,3S)-5]

A solution of LiOH, H_2O (55 mg, 1.32 mmol, 2.2 equiv) in water was added dropwise to a solution of compound (2*S*,3*S*,3′*R*)-**4** (300 mg, 0.6 mmol) in THF/H_2O (2/1) (18 ml) and the mixture was stirred at room temperature till completion of the hydrolysis (˜ 6 h) (monitored by HPLC, column A). The organic solvent was removed in vacuo, the residue was taken up in ethyl acetate/H2O (10/5 ml), the aqueous phase was acidified (pH 3) and extracted with ethyl acetate. The residue obtained after evaporation of the ethyl acetate phase was submitted to a 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 (2*S*,3*S*)-**5** (94 mg, 0.35 mmol, 58% yield) as a white solid; m.p. 142°C; $[\alpha]_D^{20} = +9$ (*c* = 1.2 in CH_2Cl_2); MS (ESI) *m/z*: 270.3 [(M+H)$^+$], 214.2 and 170.2; ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 9H, C(C*H*$_3$)$_3$), 1.40–1.58 (m, 8H, C*H*$_2$), 1.62(br s, 1H, 4-*H*), 1.76 (br m, 1H, HC*H*), 2.02 (br s, 1H, 1-*H*), 2.29 (br s, 1H, 2-*H*), 3.78 (br m, 1H, 3-*H*), 4.97 (br s, 1H, N*H*); ^{13}C NMR ($CDCl_3$) 18.1 (*C*H$_2$), 19.3 (*C*H$_2$), 23.3 (*C*H$_2$), 24.6 (*C*H$_2$), 26.1 (*C*-1), 27.3 (C(*C*H$_3$)$_3$), 28.1 (*C*-4), 50.1 (*C*-3), 51.0 (*C*-2), 79.9(*C*(CH$_3$)$_3$), 155.9, and 175.3 (*C*O); HRMS (FAB) Calcd for $C_{14}H_{24}NO_4$ (MH$^+$) 270.1705, found 270.1709.

Trans-(2S,3S)-N-Boc 3-(hydroxymethyl)-2-aminobicyclic[2,2,2]octane [(2S,3S)-6]

To a stirred solution of the amino acid (2*S*,3*S*)-**5** (90 mg, 0.33 mmol) in THF (3 ml) was added at room temperature benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP reagent) (148 mg, 0.33 mmol, 1 equiv) and N,N-Diisopropylethylamine (DIEA) (86 mg, 0.49 mmol, 1.5 equiv). The resulting solution was stirred for 10 min, then $NaBH_4$ (38 mg, 1 mmol, 3 equiv) was added by portionwise at 0°C. After stirring 40 min at room temperature, the solvent was evaporated and the residue was dissolved in ethyl acetate (20 ml). This organic phase was washed with 0.1N HCl (2 × 5 ml), dried over Na_2SO_4 and concentrated in vacuo. The residue obtained was submitted to a column chromatography on silica gel, using ethyl acetate/cyclohexane (1/1) as eluent to yield the expected compound (2*S*,3*S*)-**6** as a white solid (56 mg, 0.22 mmol, 67% yield); m.p. 117°C; $[\alpha]_D^{20} = -47$ (*c* = 1.3 in CH_2Cl_2); MS (ESI) *m/z*: 256.3 [(M+H)$^+$], 200.2 and 156.2; ^{1}H NMR ($CDCl_3$) δ 1.35–1.60 (m, 11H, C*H*$_2$, 1-*H*, 4-*H*, 2-*H*), 1.38 (s, 9H, C(C*H*$_3$)$_3$), 3.27 (br s, 1H, 3-*H*), 3.46 (dd, *J* = 5.1 and 10.8, 1H, HC*H*-OH), 3.60 (t, *J* = 10.8, 1H, HC*H*-OH), 4.05 (br s, 1H, O*H*), 4.87 (br s, 1H, N*H*); ^{13}C NMR ($CDCl_3$) 18.0 (*C*H$_2$), 18.7 (*C*H$_2$), 23.4 (*C*H$_2$), 25.0 (*C*H$_2$), 25.4 (*C*-1 or *C*-4), 26.9 (C(*C*H$_3$)$_3$), 28.2 (*C*-1 or *C*-4), 48.5 (*C*-2), 51.8 (*C*-3), 64.8 (*C*H$_2$OH), 78.4 (*C*(CH$_3$)$_3$), 154.9 (*C*O); HRMS (FAB) Calcd for $C_{14}H_{26}NO_3$ (MH$^+$) 256.1913 , found 256.1906.

Trans-(2S,3S)-3-(Hydroxymethyl)-2-aminobicyclic[2,2,2]octanic acid-Trifluoroacetic acid salt [(2S,3S)-7]

Trifluoroacetic acid (450 μl) was added at 0°C and under argon to a stirred solution of the *N*-Boc bicyclic 1,3-amino alcohol (2*S*,3*S*)-**6** (56 mg, 0.22 mmol) in CH_2Cl_2 (1.5 ml). After stirring 30 min at room temperature, the reaction mixture was diluted with cyclohexane (5 ml) and concentrated in vacuo to give the deprotected compound **7** (59 mg, quantitative yield) as a colorless oil; $[\alpha]_D^{20} = -41$ (*c* = 0.7 in CH_2Cl_2); MS (ESI) *m/z*: 156.1 [(M+H)$^+$]; ^{1}H NMR ($CDCl_3$) δ 1.12–1.90 (m, 10H, C*H*$_2$, 1-*H*, 4-*H*), 2.31 (m, 1H, 2-*H*), 3.12 (br s, 1H, O*H*), 3.38 (t, *J* = 9.6, 1H, 3-*H*), 3.50 (dd, *J* = 6.5 and 4.5, 1H, HC*H*-OH), 3.86 (t, *J* = 6.5, 1H, HC*H*-OH), ^{13}C NMR ($CDCl_3$) 23.7 (*C*-1 or *C*-4), 25.2 (*C*H$_2$), 25.4 (*C*-1 or *C*-4), 27.8 (*C*H$_2$), 28.2 (*C*H$_2$), 30.1 (*C*H$_2$), 61.1 (*C*H$_2$OH), 62.8 (*C*-2), 63.2 (*C*-3); HRMS (FAB) Calcd for $C_9H_{18}NO$ (MH$^+$) 156.1388, found 156.1391. **The same synthetic route could be achieved using the chiral auxiliary (*R*)-1**

RESULTS AND DISCUSSION

The asymmetric Diels-Alder cycloaddition (Scheme 1) was first carried out using the optimized conditions previously defined, when using cyclopentadiene as diene[7] i.e., without catalyst in dry CH_2Cl_2 at −78°C for 20 h (Table 1, Entry 1). In these conditions no Diels-Alder adduct formation was detected and the starting nitroacrylate was recovered. However, the reaction was successfully carried out at room temperature for 24 h to yield a mixture of the four expected cycloadducts with one predominant diastereoisomer (Table 1, Entry 2).

We also observed total consumption of the nitroacrylate (*R*)-**2** with formation of the cycloadducts within 0.5 h using microwave irradiation at 60°C without modification of the diastereoisomeric ratios (Table 1, Entry 4). A moderate enhancement of the stereoselectivity could be achieved by carrying out the reaction in dry CH_2Cl_2 at −20°C (Table 1, Entry 3) or in solvent-free conditions using 20 equivalents of cyclohexadiene at room temperature (Table 1, Entry 5). However, the latter conditions were not really usable because of the incomplete solubility of the nitroacrylate in cyclohexadiene that limits yield whatever is the reaction time. The addition of $ZnCl_2$ as a Lewis acid catalyst enhanced

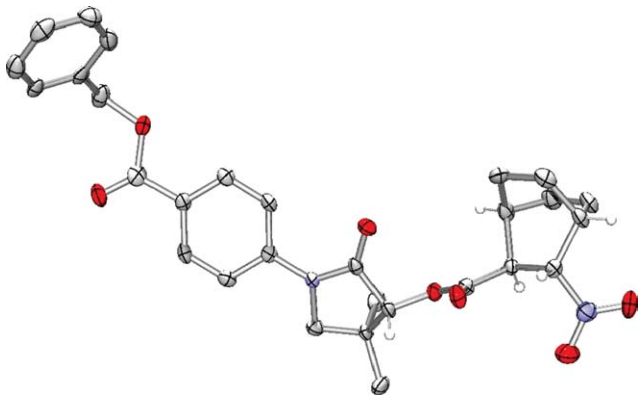


Fig. 1. ORTEP drawing of the adduct (1*S*,2*S*,3*S*,4*R*,3′*R*)-**3**. Crystal data for (1*S*,2*S*,3*S*,4*R*,3′*R*)-3: Molecular formula $C_{29}H30N_2O_7$ M = 518.2, triclinic, space group $P1$, a = 10.0377(5) Å, b =10.5374(5) Å, c = 13.5760(7) Å, α = 89.667(4)°, β = 76.192(4)°, γ = 68.204(4)°, V= 1289.3(1) Å^3, Z = 2, D_c= 1.336 g cm^{-3}. X-Ray diffraction data were collected at low temperature with MoKα radiation using the Oxford Diffraction Excalibur system. The structure was solved using direct methods and the model was refined by full-matrix least-squares procedures on F^2. 16450 reflections measured, 4485 unique, R_1 [$I > 2\sigma(I)$] = 0.046, wR_2 (all data) = 0.077 for 686 parameters, GooF = 0.94, residual density (max./min.) = 0. 235/−0.196 e A^{-3}. Details of the crystal structure (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 753006. 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]. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com]

the reaction rate of the cycloaddition at room temperature but had no positive effect on the stereoselectivity (Table 1, Entry 6). When the temperature was lowered to −20°C and in the presence of the Lewis acid, only 10% of the cycloadduct was formed after 20 h (Table 1, Entry 7).

Under the best conditions i.e., using 10 equivalents of 1,3-cyclohexadiene without catalyst in CH_2Cl_2 at −20°C, the main Diels-Alder adduct **3** could be isolated in enantiopure form in moderate yield after two consecutive flash column chromatography on silica gel. This compound was then recrystallized from isopropanol/diethyl ether and the absolute configuration of the newly generated stereocenters was assigned on the basis of a X-ray crystal structure determination (Fig. 1). From the known *R* configuration of the chiral auxiliary, it was determined that the main cycloadduct **3** had the (1*S*,2*S*,3*S*,4*R*,3′*R*) configuration that resulted from an endo nitro selectivity on the Cα/Cβ Si face. Attemps to isolate the three minor adducts **3** in pure form by column chromatography failed, so their configuration could not be unambiguously assigned. However, it could be assume that the two separated peaks (t_R (HPLC, column A) 12.3 min (30%) and 12.5 min (70%)) obtained by HPLC analysis of the crude mixture **3** (Table 1, Entry 3) by using an achiral stationary phase, correspond to the exo/endo mixture. By the same way, as the four cycloadducts **3** could be totally separated by using a chiral stationary phase (t_R (HPLC, column B) 15.8 min (60%), 18.6 min (10%), 26.3 min (4%), and 29.2 min (26%) the facial selectivity (72%) could be presumed.

Hydrogenation at room temperature and atmospheric pressure of the isolated enantiopure cycloadduct (1*S*,2*S*,3*S*,4*R*,3′*R*)-**3** with palladium on charcoal in methanol in the presence of Boc_2O and NEt_3 gave—by reduction of the nitro group and direct *N*-Boc protection of the obtained amino group, concomitant with hydrogenation of the double bond and hydrogenolysis of the benzyl ester—the compound (2*S*,3*S*,3′*R*)-**4.** Finally, LiOH hydrolysis at room temperature of the compound (2*S*,3*S*,3′*R*)-**4** afforded the expected enantiopure *trans*-3-*tert*-butyloxycarbonyl aminobicyclo[2.2.2]oct-5-ene-2-carboxylic acid (2*S*,3*S*)-**5** after elimination of the chiral auxiliary by column chromatography.

The *trans*-3-nitrobicyclo[2.2.2]oct-5-ene-2-carboxylate (1*R*,2*R*,3*R*,4*S*,3′*S*)-**3** and the *trans*-3-*tert*-butyloxy carbonyl aminobicyclo[2.2.2]oct-5-ene-2-carboxylic acid (2*R*,3*R*)-**5** could be obtained by the same synthetic route by using the chiral auxiliairy (*S*)-**1**.

The *N*-Boc bicyclic β-amino acid (2*S*,3*S*)-**5** [or (2*R*,3*R*)-**5]** has been converted into the corresponding *N*-Boc bicyclic 1,3-amino alcohol (2*S*,3*S*)-**6** [or (2*R*,3*R*)-**6**] using the method developped by McGreary.[41] Treatment with BOP/DIEA to transform the carboxylic acid into an activated derivative, which can be rapidly reduced using a mild reductant as $NaBH_4$ provided the alcohol derivative **6** in good yield. Deprotection of the amino group of compound 6 with trifluoroacetic acid in dichloromethane at room temperature yielded 3-(hydroxymethyl)-2-aminobicyclic[2,2,2]octane (2*S*,3*S*)-**7** [or (2*R*,3*R*)-**7**].

In conclusion, the enantiopure preparation of the (2*S*,3*S*)- or (2*R*,3*R*)-*trans*-3-*tert*-butyloxycarbonylaminobicyclo[2.2.2]octane-2-carboxylic acids **5** and their bicyclic 1,3-amino alcohol derivatives **6** has been developed from the chiral nitroacrylate (*R*)- or (*S*)-**2**. These syntheses constitute the first preparation of such compounds and further studies concerning their application are currently in progress.

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