DOI: 10.1002/ejoc.200700236

Asymmetric Diels–Alder Cycloaddition of 1-Aminocyclohexadiene to Chiral Acrylate: Synthesis of Enantiopure Bridgehead-Aminobicyclo[2.2.2]octane-2-carboxylic Acid Derivatives

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Keywords: Asymmetric synthesis / Diels–Alder reactions / Chiral auxiliaries / Bicyclic β-amino acids / Microwave activation

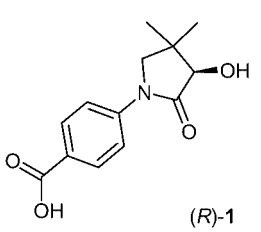
The acrylate derivative of the (*R*)-4-(3-hydroxy-4,4-dimethyl-2-oxopyrrolidin-1-yl)benzoic acid benzyl ester (*R*)-**2** reacted with 1-(benzyloxycarbonylamino)cyclohexadiene **3** under microwave irradation in solvent-free conditions to yield [4+2] cycloadducts in good yields (91 %). The reaction proceeded with moderate *endo* selectivity (67 %) and good facial selectivity (90 %). The major cycloadducts were isolated and transformed to afford three enantiopure bicyclic β-amino acids: (1*S*,2*R*,4*R*)-1-(benzyloxycarbonylamino)bicyclo[2.2.2]oct-5-ene-2-carboxylic acid [(1*S*,2*R*,4*R*)-**4**], (1*R*,2*R*,4*S*)-1-(benzyloxycarbonylamino)bicyclo[2.2.2]oct-5-ene-2-carboxylic acid [(1*R*,2*R*,4*S*)-**5**] and (*R*)-1-aminobicyclo[2.2.2]octane-2-carboxylic acid [(*R*)-**6**]. This work has led to the preparation of these enantiopure bicyclic β-amino acids and provides a rare example of an asymmetric Diels–Alder reaction by microwave activation.

Introduction

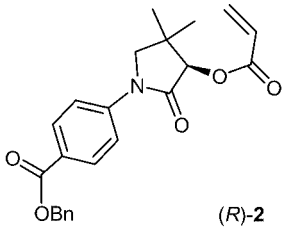
Conformationally constrained amino acids[1] are of great interest owing to their dominant role in both synthetic and medicinal chemistry. Incorporation of constrained cyclic amino acids into peptides or peptidomimetics induces conformational restriction and produces significant structural effects that can be used for structural and biomechanistic investigations.[2,3]

In this context, the synthesis of new sterically constrained cyclic amino acids in an enantiomerically pure form is particularly attractive. We have focused our attention on bicyclic amino acids possessing a bicyclo[2.2.2]-octane structure; the interest in these compounds is highlighted by the publication of several investigations in recent years.[4–7] Some of these synthetic derivatives exhibit noticeable biological activities; for example, 2-aminobicyclo-[2.2.2]octane-2-carboxylic acids selectively disturb levels of neutral amino acids in the cerebral cortex,[5] while dihydroxylated 1-aminobicyclo[2.2.2]octane-4-carboxylic acids have been used as scaffolds for antiviral agents.[6]

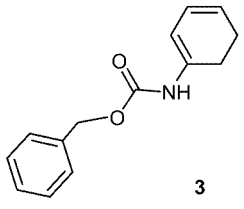
We have previously reported the preparation of a new chiral auxiliary, the (*R*)- or (*S*)-4-(3-hydroxy-4,4-dimethyl-2-oxopyrrolidin-1-yl)benzoic acid [(*S*)- or (*R*)-**1**], and have found that the acrylate derivative (*S*)- or (*R*)-**2** is an efficient chiral dienophile.[8]



(*R*)-**1**



(*R*)-**2**



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In the study herein reported, the asymmetric Diels–Alder cycloaddition of 1-(benzyloxycarbonylamino)cyclohexadiene **3** to the acrylate derivative (*R*)-**2** was examined with a view to preparing enantiopure bicyclic β-amino acids bearing an amino group at the bridgehead: 1-(benzyloxycarbonylamino)bicyclo[2.2.2]oct-5-ene-2-carboxylic acids (**4** and **5**) and 1-aminobicyclo[2.2.2]octane-2-carboxylic acid (**6**). These compounds combine the particular structural properties of constrained cyclic amino acids[1c,1d] and those of β-amino acids that are more resistant than α-amino acids to enzymatic degradation.[9]

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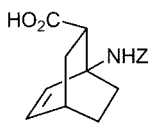

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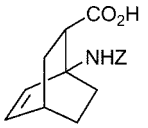

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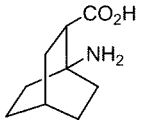

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Racemic *endo* and *exo* 1-aminobicyclo[2.2.2]oct-5-ene-2-carboxylic acid derivatives have previously been obtained by Diels–Alder reaction between protected 1-aminocyclohexadiene and dimethylacrylamide.[7] These compounds have been used as precursors to generate antibodies capable of catalysing Diels–Alder cycloaddition reactions and to control the stereochemistry of the reaction.[7]

To the best of our knowledge there is no example of the asymmetric version of this cycloaddition reaction.

Results and Discussion

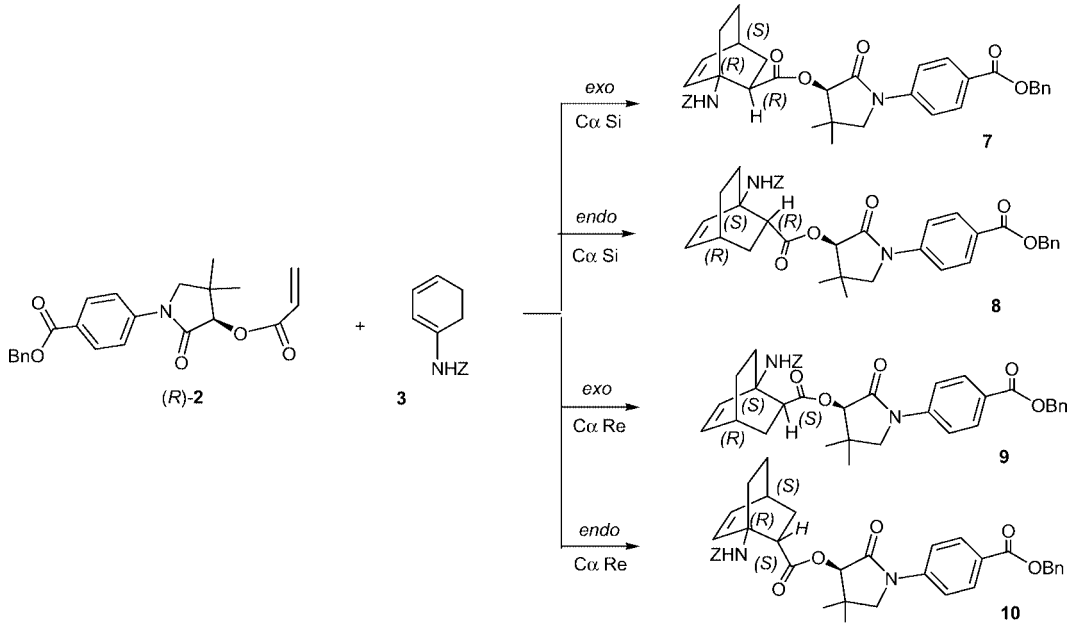
The 1-(benzyloxycarbonylamino)cyclohexadiene **3** was obtained from the cyclohexa-1,3-dienecarboxylic acid[10] via formation of the acyl azide followed by Curtius rearrangement at 110 °C and subsequent trapping with benzyl alcohol.[7] The enantiopure (*R*)-4-(3-hydroxy-4,4-dimethyl-2-oxopyrrolidin-1-yl)benzoic acid [(*R*)-**1**] and the corresponding acrylate benzyl ester (*R*)-**2** were prepared as described previously.[8b]

The results of the Diels–Alder reactions between (*R*)-**2** and **3** (Scheme 1) are summarized in Table 1 (entries 1–16).

When the acrylate derivative **2** reacted with the 1-(benzyloxycarbonylamino)cyclohexadiene **3** (4 equiv.) in toluene at room temperature, 80% of the starting material was consumed after 96 h and no residual diene was observed. Analysis of the crude reaction (HPLC and LC/MS) showed the formation of a mixture of the four expected cycloadducts, with the two diastereoisomers **7** (30%) and **8** (60%) predominating (Table 1, entry 1).

The following experiments (Table 1, entries 2–4) underlined both the low reactivity of the reacting partners and the instability of the aminodiene **3** under thermal conditions.

Although Lewis acid catalysts generally allow the Diels–Alder reactions to proceed with satisfactory yields and a high level of stereoselectivity,[11] the use of a variety of such catalysts ($TiCl_4$, $AlEtCl_2$, $[Sc(OTf)_3]$) was accompanied by diene decomposition (Table 1, entry 8).[12] To suppress this decomposition, we tested the simultaneous use of hindered bases to buffer the reaction medium. We examined the reaction of the acrylate (*R*)-**2** with the protected aminodiene **3** using ethylaluminium dichloride ($AlEtCl_2$) as catalyst and various quantities of di-*tert*-butylpyridine, present in the reaction mixture prior addition of the Lewis acid. The reaction with $AlEtCl_2$ and 0.5 equiv. of di-*tert*-butylpyridine resulted in decomposition of the diene with no formation of cycloadducts (Table 1, entry 9). On the other hand, adding a large excess of this base suppressed the decomposition of the aminodiene and led to the total consumption of the acrylate within 2 h with the formation of only the two diastereoisomers **8** and **10** (Table 1, entry 10). The dramatically increased rate of reaction and the different diastereoisomeric ratios observed with respect to our first experiment, pointed to both the beneficial effect of $AlEtCl_2$ and the ef-



Scheme 1. Diels–Alder reaction between the acrylate (*R*)-**2** and the (Z-amino)diene **3**.

Table 1. Diels–Alder reaction of the aminodiene **3** with the acrylate (*R*)-**2**.[a]

Entry	*T* [°C]	Additive (equiv.)	**3** (equiv.)	Solvent[a]	Time [h]	Conversion [%][b]	Ratio[c] of **7/8/9/10**
1	room temp.	–	4	toluene	96	80[d,e]	30:60:3:7
2	80	–	4	toluene	15	35[e,f]	30:60:3:7
3	80	–	4	CH_3CN	15	50[e,f]	30:60:3:7
4	110	–	4	toluene	15	50[d,e]	30:60:3:7
5	160	–	4	toluene	15	>99[d,e]	30:60:3:7
6	80	–	2	–	15	55[e,f]	30:60:3:7
7	room temp.	4 M $LiNTf_2$ (18)	4	acetone	96	40[d,e]	17:65:3:15
8	room temp.	$TiCl_4$ (0.1 or 1), $AlEtCl_2$ (1 or 2), $Sc(OTf)_3$ (0.1 or 1)	4	CH_2Cl_2	1	–[d]	–
9	room temp.	$AlEtCl_2$ (2), base (1)	4	CH_2Cl_2	2	–[d]	
10	room temp.	$AlEtCl_2$ (2), base (4)	4	CH_2Cl_2	2	>99[e,g]	0:78:0:22
11	room temp.	$[Eu(fod)_3]$ or $[Yb(fod)_3]$ (1)	4	CH_2Cl_2	96	75[d,e]	30:60:3:7
12	MW 80	–	4	CH_3CN	1.5	15	30:60:3:7
13	MW 110	–	4	CH_3CN	1.5	33	30:60:3:7
14	MW 160	–	4	CH_3CN	1.5	>99	24:50:8:18
15	MW 80	–	2	–	2	>99	30:60:3:7
16	MW 80	–	4	–	1.5	>99	30:60:3:7

[a] Acrylate concentration = 0.2 M. [b] Determined by HPLC analysis and based on acrylate disappearance. [c] See ref.[16] [d] No residual diene was observed. [e] Side-products were formed. [f] A little residual diene was detected. [g] The results were irreproducible.

fective role of a large excess of di-*tert*-butylpyridine which acted without interfering with the Lewis acid, as described previously.[13]

In an attempt to increase the stereoselectivity of the reaction, we investigated the use of mild Lewis acid catalysts such as the lanthanide complexes $[Eu(fod)_3]$ or $[Yb(fod)_3]$, which may be appropriate when the cycloaddition reaction involves acid-sensitive reagents.[11c,14] Under these conditions decomposition of the diene was avoided, but both the reaction rate and the diastereoisomeric ratio were comparable to those in the absence of Lewis acid catalyst (Table 1, entries 1 and 11).

Among various other conditions that have been reported to favour the Diels–Alder reaction,[11] we also tested the use of microwave activation (MW) and the use of a polar medium such as concentrated solutions of lithium trifluoromethanesulfonimide ($LiNTf_2$).

Several Diels–Alder cycloaddition reactions have been studied under the action of microwave irradiation, often affording reduced reaction times, increased yields and the suppression of side-product formation.[15] The microwave-assisted cycloaddition reaction between the chiral acrylate (*R*)-**2** and the aminodiene **3** at 160 °C in acetonitrile or at 80 °C in solvent-free conditions was significant (Table 1, entries 14–16). We observed total consumption of the acrylate with formation of the cycloadducts within 1.5 h (or 2 h when using 2 equiv. of the diene), whereas under classical thermal reaction conditions (Table 1, entries 2, 3 and 5) or in solvent-free conditions without microwave irradiation (Table 1, entry 6), moderate-to-good conversions were obtained after 15 h with considerable decomposition of the residual aminodiene making the final purification step difficult. When the reaction was carried out in acetonitrile at 80 or 110 °C instead of 160 °C (Table 1, entries 12 and 13), only a low yield was obtained within 1.5 h. On the other hand, lower selectivity was observed at 160 °C with microwave activation, whereas under classical thermal conditions at the same temperature no difference in the selectivity was observed (Table 1, entries 5 and 14). This underlines the dramatic effect of microwave activation in solvent-free conditions. Another important feature was the cleanness of the crude reaction medium which allowed easier purification and separation of the diastereomers obtained than is the case when the reaction is carried out at room temperature or under thermal or catalytic conditions.

Finally, even if we did not observe an enhancement of the Diels–Alder reaction in a concentrated lithium salt solution, which is the classic effect of this polar medium,[11c] we achieved a modification of the diastereoisomeric ratios, probably as a result of the Lewis acid character of the lithium ion which should favour the more polar transition state (Table 1, entry 7).

The two major Diels–Alder adducts **7** and **8** formed under microwave activation in solvent-free conditions were isolated in pure form after two consecutive column chromatographic runs on silica gel. When starting from the crude obtained at room temperature or under thermal conditions a smaller quantity of each diastereoisomer **7** and **8** was obtained, even after an additional chromatographic run. Attempts to isolate the pure minor adducts **9** and **10** by column chromatography failed, even for compound **10** when starting from the 78:22 mixture of **8** and **10** obtained when using $AlEtCl_2$/di-*tert*-butylpyridine (Table 1, entry 10).

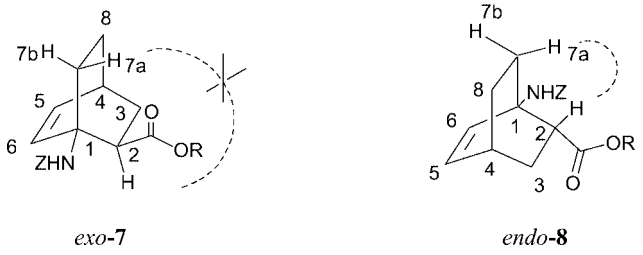
Notably, microwave irradiation in solvent-free conditions at 80 °C are the best experimental conditions for this Diels–Alder reaction, affording cleanly and in reproducible good yield, two separable optically pure cycloadducts.

Concerning the *endo*/*exo* or facial selectivity of the reaction, we first determined the relative stereochemistry of these two compounds on the basis of ^1H NMR analysis after assignment of the signals by H,H and C,H COSY spectroscopy.

There were some significant differences in the ^1H and ^{13}C NMR spectra of compounds **7** and **8** indicating that there

are different spatial interactions in these two compounds. This is particularly the case for the protons that interact with the CO_2R group. The 6-H signal of compound **8** is at 6.0 ppm, whereas it is at 6.5 ppm for compound **7**. The 7a-H signals are at 2.35 and 1.9 ppm, respectively. On the other hand, the 5-H signals of compounds **7** and **8** have similar chemical shifts.

We observed the presence of a NOE effect between the 2-H and 7a-H protons in compound **8** (Figure 1), indicating that these two atoms are in close proximity as a result of an *endo* cycloaddition reaction. Conversely, as no NOE effect was observed between the 2-H and 7a-H protons of compound **7**, it can be assumed that this compound results from *exo* selectivity.



exo-**7** *endo*-**8**

Figure 1. NOE relationships for compounds **7** and **8**.

The stereochemistry of the *endo* adduct **8** that crystallized from diethyl ether/petroleum ether was confirmed unambiguously by X-ray diffraction analysis (Figure 2).[17] Furthermore, from the known (*R*) configuration of the chiral auxiliary, the absolute configuration of the newly generated stereocentres was also determined and indicated that the major adduct **8** has the (3′*R*,1*S*,2*R*,4*R*) configuration resulting from *endo* selectivity at the Cα *Si* face. Unfortunately, compound **7**, could not be crystallized and was obtained as a colourless oil.

LiOH hydrolysis of compound (3′*R*,1*S*,2*R*,4*R*)-**8** at room temperature yielded the enantiopure (1*S*,2*R*,4*R*)-1-(benzyloxycarbonylamino)bicyclo[2.2.2]oct-5-ene-2-carboxylic acid [(1*S*,2*R*,4*R*)-**4**] (Scheme 2). To control the optical purity of **4** and to ensure that no epimerization had occurred during removal of the chiral auxiliary, we performed the Diels–Alder reaction with racemic acrylate (*SR*)-**2**. This afforded a racemic mixture; the HPLC profile of this mixture was

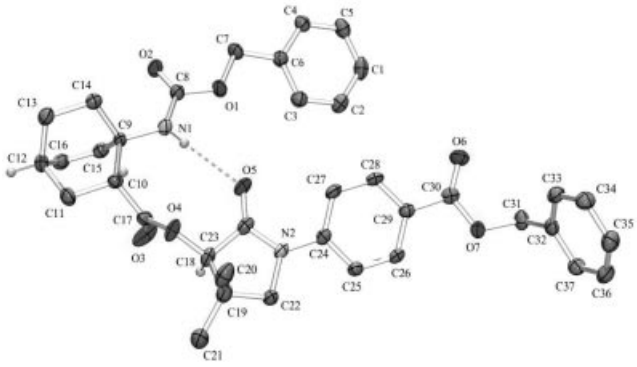


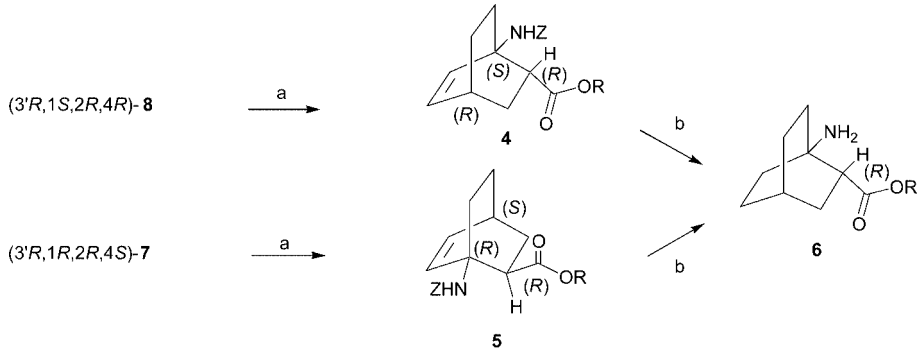
Figure 2. ORTEP drawing of adduct **8**.

compared with that obtained from the chiral experiment. The HPLC trace of the mixture of bicyclic β-amino acids **4** and **5** showed that all four stereoisomers were separable on the chiracel OD column.

Palladium-catalysed hydrogenation of the double bond concomitant with hydrogenolysis of the carbamate moiety of the acid (1*S*,2*R*,4*R*)-**4** yielded the bicyclic β-amino acid (*R*)-**6** with only one asymmetric carbon atom (Scheme 2).

To establish the absolute configuration of the pure compound **7** and to obtain the corresponding bicyclic β-amino acids, we followed the transformation route developed for the *endo* (3′*R*,1*S*,2*R*,4*R*)-**8** adduct. LiOH hydrolysis of compound **7** at room temperature (Scheme 2) yielded bicyclic β-amino acid **5** possessing different HPLC profile and NMR spectra to those of compound **4**. Palladium-catalysed hydrogenation of the acid **5** yielded the corresponding bicyclic β-amino acid which has the same specific rotation sign and value as that of compound (*R*)-**6** obtained from **8**, showing that the (*R*) enantiomer was also obtained. The stereochemistry of this bicyclic β-amino acid allowed us to establish the (1*R*,2*R*,4*S*) configuration for compound **5** and the (3′*R*,1*R*,2*R*,4*S*) configuration for compound **7** resulting from an *exo* selectivity, the reaction always occurring on the Cα *Si* face of the chiral dienophile.

These results show that despite the moderate *endo*/*exo* selectivity and due to a good facial selectivity induced by the chiral auxiliary (*R*)-**2**, when the only required compound was the bicyclic β-amino acid (*R*)-**6**, it could be obtained directly in good yield from a mixture of adducts **7**



Scheme 2. Synthesis of β-amino acid (*R*)-**6**. Reagents: (a) LiOH, H_2O, THF; (b) H_2, 10% Pd/C, CH_3OH.

and **8**. The enantiomer (*S*)-**6** was easily obtained by the same cycloaddition reaction by using the chiral auxiliary (*S*)-**2**.

Conclusions

In this study we have established strategies for the synthesis of some enantiopure bicyclic β-amino acids bearing an amino group at the bridgehead. We have demonstrated that benzyl (*R*)-4-(3-acryloyloxy-4,4-dimethyl-2-oxopyrrolidin-1-yl)benzoate [(*R*)-**2**] can be used as a chiral dienophile for the asymmetric synthesis of 1-aminobicyclo[2.2.2]octane-2-carboxylic acid derivatives. These syntheses constitute both the first preparation of these enantiopure bicyclic β-amino acids and a rare example of an asymmetric Diels–Alder reaction under microwave activation. Further studies concerning the transformation of these aminobicyclo[2.2.2]oct-5-ene and -octane derivatives are now in progress.

Experimental Section

General Remarks: 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 and ^{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 instrument with variable detector using one of two columns; column A: Nucleosil 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: Chiracel OD, flow: 1 mL/min, eluent I: hexane/2-propanol: 85:15; eluent II: hexane (0.1% TFA)/2-propanol (0.1% TFA) 90:10. Microwave activation was performed with a Biotage Initiator 2.0 instrument.

The racemic and enantiopure chiral auxiliaries (*RS*)- and (*R*)-4-(3-hydroxy-4,4-dimethyl-2-oxopyrrolidin-1-yl)benzoic acid [(*RS*)-**1** and (*R*)-**1**] and the corresponding benzyl acrylates, benzyl (*RS*)- and (*R*)-4-(3-acryloyloxy-4,4-dimethyl-2-oxopyrrolidin-1-yl)benzoates [(*RS*)-**2** and (*R*)-**2**], were prepared as described previously.[8]

1-(Benzyloxycarbonylamino)cyclohexa-1,3-diene (3): *N*,*N*-Diisopropylethylamine (9.7 mL, 0.056 mol, 1.2 equiv.) was added dropwise to a stirred solution of cyclohexa-1,3-diene-1-carboxylic acid[10] (5.76 g, 0.046 mol, 1.0 equiv.) in anhydrous acetone (30 mL) at room temperature under argon. After stirring for 10 min at 0 °C, a solution of ethyl chloroformate (5.6 mL, 0.059 mol; 1.3 equiv.) in anhydrous acetone (15.4 mL) was added over 30 min whilst maintaining the temperature below 0 °C. Stirring was continued for an additional 30 min at 0 °C and a solution of sodium azide (7.18 g, 0.110 mol, 2.4 equiv.) in water (17.5 mL) was added in several portions over 20 min whilst maintaining the temperature below 0 °C. Stirring was continued for an additional 20 min at 0 °C and the reaction mixture was diluted with ice/water (50 mL). The acyl azide was isolated by extraction with toluene (6 × 40 mL). The combined toluene extracts were dried with anhydrous magnesium sulfate and concentrated to a volume of 25 mL. ***Caution:*** Acyl azides are potentially explosive. The solution should not be evaporated to dryness and the rotary evaporator should be placed in a fume hood with the water bath at 40–50 °C. This acyl azide solution was then added over 20 min to a stirred solution of benzyl alcohol (4.7 mL; 0.046 mol, 1.0 equiv.) in refluxing dry toluene (20 mL). After refluxing for an additional 30 min, the toluene was removed in vacuo to afford a yellow oily residue. This was purified by chromatography on silica gel by using cyclohexane/acetone (9:1) as eluent (R_f = 0.4) to yield the pale yellow semi-solid diene **3** (6.3 g, 60% yield). t_R (HPLC column A) = 8.3 min. ^{1}H NMR (400 MHz, CD_3CN, 25 °C): δ = 2.15–2.35 (m, 4 H, CH_2), 5.12 (s, 2 H, OCH_2), 5.53–5.58 (dt, J = 9.3 Hz, 2.9 Hz, 1 H, 4-H), 5.92–5.97 (ddt, J = 9.3 Hz, 5.9 Hz, 1.7 Hz, 1 H, 3-H), 6.20 (d, J = 5.9 Hz, 1 H, 2–2), 7.10 (s, 1 H, NH), 7.30–7.50 (m, 5 H, H arom.) ppm. ^{13}C NMR (100 MHz, CD_3CN, 25 °C): δ = 22.6 (C-5), 25.7 (C-6), 65.7 (OCH_2), 104.2 (C-2), 120.1 (C-4), 124.5 (C-3), 127.8, 128.0, 128.5 (CH arom.), 134.0 (C-1), 136.6 (C arom.), 152.7 (CO) ppm.

(3′*R*,1*R*,2*R*,4*S*)- and (3′*R*,1*S*,2*R*,4*R*)-[*N*-(4-Benzyloxycarbonylphenyl)-4,4-dimethyl-2-oxopyrrolidin-3-yl] 1-(Benzyloxycarbonylamino)bicyclo[2.2.2]oct-5-ene-2-carboxylate [(3′*R*,1*R*,2*R*,4*S*)-7 and (3′*R*,1*S*,2*R*,4*R*)-8]: A mixture of 1-(benzyloxycarbonylamino)cyclohexa-1,3-diene (**3**) (3.89 g, 17.0 mmol, 2 equiv.) and benzyl (*R*)-4-(3-acryloyloxy-4,4-dimethyl-2-oxopyrrolidin-1-yl)benzoate [(*R*)-**2**] (3.32 g, 8.5 mmol, 1 equiv) was heated by microwave irradiation at 80 °C (initial power 300 W) for 2 h. After cooling, the crude product, which contained a 30:60:3:7 mixture of the four cycloadducts **7/8/9/10**, was obtained. This was purified by rapid column chromatography on silica gel using cyclohexane/ethyl acetate (7:3) as eluent to yield a pure mixture of the cycloadducts in 90.6% yield (4.81 g, 7.7 mmol). Diastereoisomers (3′*R*,1*R*,2*R*,4*S*)-**7** (0.94 g, 1.5 mmol, 19.5% yield, R_f = 0.32, 99% *de*) and (3′*R*,1*S*,2*R*,4*R*)-**8** (1.60 g, 2.6 mmol, 33.5% yield, R_f = 0.22, 99% *de*) were isolated after being subjected to flash column chromatography on silica gel twice using diethyl ether/petroleum ether (4:6) as eluent.

Crystallisation of an aliquot of compound (3′*R*,1*S*,2*R*,4*R*)-**8** from diethyl ether/petroleum ether yielded colourless crystals suitable for X-ray analysis.

(3′*R*,1*R*,2*R*,4*S*)-7: Colourless oil. $[\alpha]_D^{20}$ = –68 (c = 1.1, CH_2Cl_2); t_R (HPLC, column A) = 16.3 min; t_R (HPLC, column B, eluent I) = 24.9 min. IR (KBr): $\tilde{\nu}$ = 3334 (m), 1727 (s), 1710 (s), 1689 (s) cm^{-1}. MS (ESI): m/z = 623.2 [M + H]$^+$. ^{1}H NMR (400 MHz, CD_3CN, 25 °C): δ = 0.91 (s, 3 H, CH_3), 1.18 (s, 3 H, CH_3), 1.30 (m, 2 H, 7-H, 8-H), 1.55 (m, 1 H, 3-H), 1.72 (m, 1 H, 8-H), 1.86 (m, 1 H, 7-H), 2.06 (m, 1 H, 3-H), 2.54 (m, 1 H, 4-H), 3.23 (br. d, J = 10.9 Hz, 1 H, CHCO), 3.35 (d, J = 9.6 Hz, 1 H, 5′-H), 3.56 (d, J = 9.6 Hz, 1 H, 5′-H), 4.85 (d, J = 12.5 Hz, 1 H, OHC*H*C$_6$H$_5$), 5.04 (d, J = 12.5 Hz, 1 H, O*H*CHC$_6$H$_5$), 5.30 (s, 2 H, $OCH_2C_6H_5$), 5.49 (s, 1 H, 3′-H), 5.99 (s, 1 H, NH), 6.21 (t, J_1 = J_2 = 6.5 Hz, 1 H, CH=), 6.52 (d, J = 6.5 Hz, 1 H, CNCH=), 6.95–7.40 (m, 10 H, H arom.), 7.59 (d, J = 8.9 Hz, 2 H, H arom.), 7.99 (d, J = 8.9 Hz, 2 H, H arom.) ppm. ^{13}C NMR (100 MHz, CD_3CN, 25 °C): δ = 20.83 (CH_3), 23.97 (C-7), 24.31 (CH_3), 28.04 (C-8), 29.02 (C-4), 30.74 (C-3), 37.03 (C-4′), 43.58 (C-2), 55.71 (C-1), 57.62 (C-5′), 65.97 (OCH_2), 66.74 (OCH_2), 78.44 (C-3′), 118.59 (CH arom.), 126.20 (C arom.), 127.46, 127.68, 128.18, 128.26, 128.31, 128.65, 130.80 (CH arom.), 132.55 (C-5), 136.05 (C arom.), 136.33 (C-6), 136.48, 142.86 (C arom.), 155.71 (NH-CO-O), 165.83 (CO-OBn), 169.94 (CO-NC$_6$H$_4$-), 173.99 (O-CO-C) ppm. HRMS (FAB): calcd. for $C_{37}H_{39}N_2O_7$ [MH$^+$]: 623.2757; found 623.2773.

(3′*R*,1*S*,2*R*,4*R*)-8: M.p. 98 °C. $[\alpha]_D^{20}$ = –7.5 (c = 1.9, CH_2Cl_2); t_R (HPLC, column A) = 15.9 min; t_R (HPLC, column B, eluent I) =

29.6 min. IR (KBr): $\tilde{\nu}$ = 3340 (m), 1745 (s), 1705 (s), 1699 (s) cm^{-1}. MS (ESI): *m*/*z* = 623.2 $[M + H]^+$. ^1H NMR (400 MHz, CD_3CN, 25 °C): δ = 0.97 (s, 3 H, CH_3), 1.18 (s, 3 H, CH_3), 1.38 (m, 1 H, 8-H), 1.62 (m, 2 H, 7-H, 8-H), 1.79 (m, 2 H, 3-H), 2.34 (m, 1 H, 7-H), 2.60 (m, 1 H, 4-H), 3.35 (t, $J_1 = J_2$ = 6.9 Hz, 1 H, CHCO), 3.39 (d, *J* = 9.6 Hz, 1 H, 5′-H), 3.53 (d, *J* = 9.6 Hz, 1 H, 5′-H), 4.91 (d, *J* = 12.5 Hz, 1 H, O*H*CHC$_6$H$_5$), 5.03 (d, *J* = 12.5 Hz, 1 H, O*H*CHC$_6$H$_5$), 5.30 (s, 2 H, OCH_2C$_6$H$_5$), 5.37 (s, 1 H, 3′-H), 5.99 (d, *J* = 8.5 Hz, 1 H, CNCH=), 6.07 (s, 1 H, NH), 6.30 (dd, *J* = 6.7 Hz, 8.5 Hz, 1 H, CH=), 7.20 (m, 10 H, H arom.), 7.59 (d, *J* = 8.9 Hz, 2 H, H arom.), 7.99 (d, *J* = 8.9 Hz, 2 H, H arom.) ppm. ^{13}C NMR (100 MHz, CD_3CN, 25 °C): δ = 21.05, 24.48 (CH_3), 25.99 (C-8), 29.36 (C-4), 29.72 (C-3), 29.95 (C-7), 37.12 (C-4′), 45.18 (C-2), 56.68 (C-1), 57.49 (C-5′), 66.12 (OCH_2), 66.71 (OCH_2), 78.40 (C-3′), 118.42 (CH arom.), 126.07 (C arom.), 127.61, 127.73, 128.01, 128.15, 128.17, 128.24, 128.29, 128.32, 128.46, 128.57, 128.63, 130.78 (CH arom.), 132.39 (C-6), 134.07 (C-5), 136.07, 136.56, 142.95 (C arom.), 155.52 (NH-CO-O), 165.82 (CO-OBn), 169.69 (CO-NC$_6$H$_4$-), 173.39 (O-CO-C) ppm. HRMS (FAB): calcd. for $C_{37}H_{39}N_2O_7$ $[MH^+]$: 623.2757; found 623.2777.

(3′*R*,1*S*,2*S*,4*R*)-9:[18] t_R (HPLC, column A) = 15.8 min, t_R (HPLC, column B, eluent I) = 40.7 min.

(3′*R*,1*R*,2*S*,4*S*)-10:[18] t_R (HPLC, column A) = 15.8 min, t_R (HPLC, column B, eluent I) = 49.1 min.

***rac*-(3′*RS*,1*RS*,2*RS*,4*SR*)- and *rac*-(3′*RS*,1*SR*,2*RS*,4*RS*)-[*N*-(4-Benzyloxycarbonylphenyl)-4,4-dimethyl-2-oxopyrrolidin-3-yl] 1-(Benzyloxycarbonylamino)bicyclo[2.2.2]oct-5-ene-2-carboxylate [*rac*-(3′*RS*,1*RS*,2*RS*,4*SR*)-7 and *rac*-(3′*RS*,1*SR*,2*RS*,4*RS*)-8]:** A crude racemic mixture of the four cycloadducts was obtained as a colourless oil following the procedure described above by reaction of racemic acrylate (*RS*)-**2** with the diene **3**. Crystallisation of the residue from diethyl ether afforded directly a pure mixture of the *exo rac*-(3′*RS*,1*RS*,2*RS*,4*SR*)-**7** and *endo rac*-(3′*RS*,1*SR*,2*RS*,4*RS*)-**8** diastereoisomers which were easily isolated after flash column chromatography on silica gel using diethyl ether/petroleum ether (4:6) as eluent.

***rac*-(3′*RS*,1*RS*,2*RS*,4*SR*)-7:** M.p. 111 °C; t_R (HPLC, column A) = 16.3 min; t_R (HPLC, column B, eluent I) = 24.9 min [(3′*R*,1*R*,2*R*,4*S*)-**7** and (3′*S*,1*S*,2*S*,4*R*)-**7**]. The NMR spectroscopic data are identical to those of (3′*R*,1*S*,2*R*,4*R*) enantiomer.

***rac*-(3′*RS*,1*SR*,2*RS*,4*RS*)-8:** M.p. 127 °C; t_R (HPLC, column A) = 15.9 min; t_R (HPLC, column B, eluent I) = 29.6 [(3′*R*,1*S*,2*R*,4*R*)-**8**] and 40.7 min [(3′*S*,1*R*,2*S*,4*S*)-**8**]. The NMR spectroscopic data are identical to those of the (3′*R*,1*S*,2*R*,4*R*) enantiomer.

***rac*-(3′*RS*,1*SR*,2*SR*,4*RS*)-9**:[19] t_R (HPLC, column A) = 15.8 min; t_R (HPLC, column B, eluent I) = 40.7 min [(3′*R*,1*S*,2*S*,4*R*)-**9** and (3′*S*,1*R*,2*R*,4*S*)-**9**].

***rac*-(3′*RS*,1*RS*,2*SR*,4*SR*)-10:**[19] t_R (HPLC, column A) = 15.8 min; t_R (HPLC, column B, eluent I) = 49.1 [(3′*R*,1*R*,2*S*,4*S*)-**10**] and 78.4 min [(3′*S*,1*S*,2*R*,4*R*)-**10**].

(1*S*,2*R*,4*R*)- and (1*R*,2*R*,4*S*)-1-(Benzyloxycarbonylamino)bicyclo-[2.2.2]oct-5-ene-2-carboxylic Acid [(1*S*,2*R*,4*R*)-4 and (1*R*,2*R*,4*S*)-5]: A solution of LiOH·H_2O (1.2 equiv.) in water was added dropwise to a solution of compound (3′*R*,1*R*,2*R*,4*S*)-**7** or (3′*R*,1*S*,2*R*,4*R*)-**8** in THF and the mixture was stirred at room temperature until completion of the hydrolysis reaction (ca. 4 h) (monitored by HPLC, column A). The organic solvent was removed in vacuo, saturated aqueous $NaHCO_3$ was added and the mixture was extracted with ethyl acetate. The aqueous phase was acidified (pH = 2) and extracted with CH_2Cl_2 The combined organic phases were dried with anhydrous Na_2SO_4, concentrated in vacuo affording the expected acid (88–92% yield) along with about 5% of compound (*R*)-**1** (NMR analysis) as the saponification was not totally regioselective. This mixture was purified by column chromatography on silica gel using CH_2Cl_2/ethyl acetate (5:5) as eluent to yield the pure expected acid.

(1*S*,2*R*,4*R*)-4: Synthesized from compound (3′*R*,1*S*,2*R*,4*R*)-**8** (0.80 mg, 1.28 mmol) in THF (8 mL), the acid (1*S*,2*R*,4*R*)-**4** was obtained as a colourless oil (0.23 g, 0.76 mmol, 59% yield, >99% *ee*). $[\alpha]_D^{20}$ = –7 (*c* = 1, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 3360 (m), 3300–2900 (br), 1728 (s), 1658 (s) cm^{-1}. MS (ESI): *m*/*z* = 302.2 $[M + H]^+$. t_R (HPLC column A) = 8.9 min; t_R (HPLC, column B, eluent II) = 11.2 min. ^1H NMR (400 MHz, CD_3CN, 25 °C): δ = 1.32–1.41 (m, 1 H, 8-H), 1.52–1.70 (m, 3 H, 8-H, 7-H, 3-H), 1.92–1.99 (m, 1 H, 3-H), 2.10–2.19 (m, 1 H, 7-H), 2.62 (m, 1 H, 4-H), 3.23 (dd, *J* = 10.1 Hz, 5.2 Hz, 1 H, CHCOO), 5.07 (d, *J* = 12.7 Hz, 1 H, *H*CHO), 5.11 (d, *J* = 12.7 Hz, 1 H, *H*CHO), 5.98 (s, 1 H, NH), 6.15 (d, *J* = 8.6 Hz, 1 H, CNCH=), 6.30 (dd, *J* = 6.7 Hz, 8.6 Hz, 1 H, CH=), 7.31–7.42 (m, 5 H, H arom.) ppm. ^{13}C NMR (100 MHz, CD_3CN, 25 °C): δ = 24.93 (C-8), 29.36 (C-4), 30.46 (C-7), 31.07 (C-3), 45.10 (C-2), 55.81 (C-1), 65.54 (CH_2O), 127.55, 127.75, 128.41 (CH arom.), 132.76 (C-5), 133.13 (C-6), 137.51 (C arom.), 155.17 (NH-CO-O), 174.32 (COOH) ppm. HRMS (FAB): calcd. for $C_{17}H_{20}NO_4$ $[MH]^+$: 302.1392; found 302.1397.

(1*R*,2*R*,4*S*)-5: Synthesized from compound (3′*R*,1*R*,2*R*,4*S*)-**7** (0.50 g, 0.80 mmol) in THF (5 mL), the acid (1*R*,2*R*,4*S*)-**5** was obtained as a colourless oil (0.15 g, 0.49 mmol, 62% yield, >99% *ee*). $[\alpha]_D^{20}$ = –40 (*c* = 2, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 3408 (m), 3200–2500 (br), 1710 (s), 1697 (s) cm^{-1}. MS (ESI): *m*/*z* = 302.2 $[M + H]^+$. t_R (HPLC column A) = 9.1 min; t_R (HPLC, column B, eluent II) = 13.4 min. ^1H NMR (400 MHz, CD_3CN, 25 °C): δ = 1.25–1.40 (m, 2 H, 8-H, 7-H), 1.58–1.75 (m, 2 H, 7-H, 3-H), 1.88 (ddd, *J* = 12.6 Hz, 5.0 Hz, 2.3 Hz, 1 H, 3-H), 1.95–2.10 (m, 1 H, 8-H), 2.57 (m, 1 H, 4-H), 3.06 (dd, *J* = 11.3 Hz, 4.6 Hz, 1 H, CHCOO), 5.06 (d, *J* = 12.8 Hz, 1 H, *H*CHO), 5.13 (d, *J* = 12.8 Hz, 1 H, HC*H*O), 5.95 (s, 1 H, NH), 6.26 (dd, *J* = 6.6 Hz, 8.5 Hz, 1 H, CH=), 6.40 (d, *J* = 8.5 Hz, 1 H, CNCH=), 7.30–7.40 (m, 5 H, H arom.) ppm. ^{13}C NMR (100 MHz, CD_3CN, 25 °C): δ = 24.68 (C-7), 26.49 (C-8), 29.07 (C-4), 30.33 (C-3), 43.57 (C-2), 55.06 (C-1), 65.45 (CH_2O), 127.48, 127.77, 128.45 (CH arom.), 132.44 (C-5), 137.24 (C-6), 137.47 (C arom.), 155.19 (NH-CO-O), 175.30 (COOH) ppm. HRMS (FAB): calcd. for $C_{17}H_{20}NO_4$ $[MH]^+$: 302.1392; found 302.1408.

***rac*-(1*SR*,2*RS*,4*RS*)- and *rac*-(1*RS*,2*RS*,4*SR*)-1-(Benzyloxycarbonylamino)bicyclo[2.2.2]oct-5-ene-2-carboxylic Acid [*rac*-(1*SR*,2*RS*,4*RS*)-4 and *rac*-(1*RS*,2*RS*,4*SR*)-5]:** A racemic mixture of the two acids **4** and **5** was obtained as a colourless solid by saponification of a mixture of *rac*-**7** and *rac*-**8**, following the procedure described above.

***rac*-(1*SR*,2*RS*,4*RS*)-4:** M.p. 151 °C; t_R (HPLC, column A) = 8.9 min; t_R (HPLC, column B, eluent II) = 11.2 [(1*S*,2*R*,4*R*)-**4**] and 13.4 min [(1*R*,2*S*,4*S*)-**4**]. The NMR spectroscopic data are identical to those of the (1*S*,2*R*,4*R*) enantiomer.

***rac*-(1*RS*,2*RS*,4*SR*)-5:** M.p. 125 °C; t_R (HPLC, column A) = 9.1 min; t_R (HPLC, column B, eluent II) = 7.8 [(1*S*,2*S*,4*R*)-**5**] and 13.4 min [(1*R*,2*R*,4*S*)-**5**]. The NMR spectroscopic data are identical to those of the (1*R*,2*R*,4*S*) enantiomer.

(*R*)-1-Aminobicyclo[2.2.2]octane-2-carboxylic Acid [(*R*)-6]: 10% Pd/C (70 mg, 0.066 mmol, 0.2 equiv.) was added to a solution of compound (1*S*,2*R*,4*R*)-**4** or compound (1*R*,2*R*,4*S*)-**5** (100 mg, 0.33 mmol) in degassed methanol (9 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 concentrated in vacuo to give the expected β-amino acid (*R*)-**6** (55 mg, 0.32 mmol, 99% yield, >99% *ee*). M.p. >220 °C (decomp.). $[\alpha]_D^{20}$ = –50 (*c* = 1.3, CH_3OH). IR (KBr): $\tilde{\nu}$ = 3200–2500 (s), 2184 (s), 1653 (s), 1607 (s), 1530 (s) cm^{-1}. MS (ESI): *m/z* = 170.2 $[M + H]^+$. ^1H NMR (400 MHz, D_2O, 25 °C): δ = 1.44–1.70 (m, 8 H, 4-H, 5-H, 6-H, 7-H, 8-H), 1.84–1.95 (m, 3 H, 3-H, 6-H), 2.44 (br. t, $J_1 = J_2$ = 8.1 Hz, 1 H, 2-H) ppm. ^{13}C NMR (100 MHz, D_2O, 25 °C): δ = 23.61 (C-4), 24.87 (C-5), 24.90 (C-8), 25.86 (C-6), 30.19 (C-3), 30.72 (C-7), 44.48 (C-2), 52.38 (C-1), 181.67 (CO) ppm. HRMS (FAB): calcd. for $C_9H_{16}NO_2$ $[MH]^+$: 170.1181; found 170.1185.

(*RS*)-1-Aminobicyclo[2.2.2]octane-2-carboxylic Acid [(*RS*)-6]: A racemic mixture of the β-amino acid *rac*-**6** was obtained as a colourless solid by hydrogenation of *rac*-**4** or -**5** following the procedure described above. M.p. >220 °C (decomp.). The NMR spectroscopic data are identical to those of the (*R*) enantiomer.

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[16] Three of the four cycloadducts were separable using an achiral stationary phase and the ratio of the four cycloadducts was accurately determined by HPLC analyses using a chiracel OD column as a chiral stationary phase.

[17] Crystal data for ester (3′*R*,1*S*,2*R*,4*R*)-**8**: molecular formula $C_{37}H_{38}N_2O_7$, M = 622.69, monoclinic, space group $P2_1$, a = 11.3555(3), b = 18.0458(5), c = 16.0537(4) Å, β = 100.922(1)°, V = 3230.12(15) $Å^3$, Z = 4, D_c = 1.28 $Mg\,m^{-3}$. X-ray diffraction data were collected at room temperature using a Bruker AXS Kappa CCD system with Mo-K_α radiation. The structure was solved by direct methods and the model was refined by full-matrix least-squares procedures on F^2 to give values of R_1 = 0.0381 and of wR_2 = 0.0803 for reflections with $I > 2\sigma(I)$. CCDC-640598 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[18] HPLC data for the minor diastereoisomers **9** and **10** were deduced from a comparison of the HPLC profile of the crude diastereoisomeric mixtures with those of enantiopure compounds. It can be assumed that the *endo* approach at the Cα *Re* face of the dienophile was also favoured, which allowed us to assign the stereochemistry of compounds **9** and **10**. This was supported by the *rac*-**4**/*rac*-**5** ratio of 67:33 obtained after removal of the chiral auxiliary from a 30:60:3:7 mixture of compounds **7**/**8**/**9**/**10**.

[19] HPLC data for the minor diastereoisomers *rac*-**9** and *rac*-**10** were deduced from a comparison of the HPLC profile of racemic mixtures with those of diastereoisomeric mixtures.

Received: March 15, 2007
Published Online: May 25, 2007

