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(*R*)-(4-(Benzyloxycarbonylphenyl)-3-hydroxy-4,4-dimethyl-2-pyrrolidinone) acrylate derivative as a chiral dienophile for the synthesis of enantiopure 2-aminocyclohexane carboxylic acids

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Abstract—An asymmetric Diels–Alder reaction between the enantiopure (*R*)-benzyl-4-(3-acryloyloxy-4,4-dimethyl-2-oxopyrrolidin-1-yl)-benzoate (*R*)-**2** and the *N*-*Z*-aminodiene **3** proceeded with total *endo* diastereoselectivity and was facially controlled in favour of the (3′*R*,1*R*,2*S*)-adduct. The two adducts obtained, **4** (the main compound) and **5**, were isolated pure after column chromatography on silica gel. Their LiOH hydrolysis followed by palladium-catalyzed hydrogenation of the double bond concomitant with hydrogenolysis of the carbamate moiety yielded the enantiopure *cis*-2-aminocyclohexane carboxylic acids (1*R*,2*S*)-**8** and (1*S*,2*R*)-**8**.

1. Introduction

Cyclic β-amino acids are an important class of compounds, since they are constituents of natural products, such as alkaloids, peptides and β-lactam antibiotics.[1] These amino acids are often introduced into peptides to increase or modify their biological activities.[2] Furthermore, they have been used for structural and mechanistic investigations, since their incorporation into peptides or peptidomimetics induced conformational restrictions and provided important structural effects.[3] Cyclic β-amino acids also play an important role in the synthesis of various heterocyclic structures.[4]

A number of methods have been reported for the preparation of enantiopure 2-aminocyclohexane carboxylic acids,[4] many of which use an enzymatic or chemoselective resolution as a key step.[3b,4,5] Concerning asymmetric syntheses,[1c,6–9] the methods mainly involve a Michael addition of a chiral amine to α,β-unsaturated esters,[1c,4,7] diastereoselective reduction of chiral β-enamino esters[1c,8] or asymmetric Diels–Alder cycloadditions.[9]

This last reaction can be considered as one of the most powerful transformations in synthetic organic chemistry.[10] The stereoselective creation of several stereogenic centres in a single step makes the Diels–Alder reaction suitable for the preparation of complex molecules.[11]

2. Results and discussion

We have recently described the preparation of a new chiral auxiliary, the (*R*)- or (*S*)-4-(3-hydroxy-4,4-dimethyl-2-oxopyrrolidin-1-yl) benzoic acid (*R*)- or (*S*)-**1** and found that acrylate derivative **2** was an efficient chiral dienophile.[12] To extend our investigations concerning the efficiency of compound **1**, we examined an alternative route for the preparation of enantiopure 2-aminocyclohexane carboxylic acids using compound (*R*)-**2** as a chiral dienophile and the readily available *N*-*Z*-protected aminodiene **3**.[13] The stability of the benzyl carbamate function during basic final hydrolysis of the ester bond of adduct **4** or **5** and the ability to remove this group by catalytic hydrogenolysis increased interest for this protecting group. However, the main possible limitation concerning the carbamate moiety could be that it is reactive under some Lewis acid-catalyzed Diels–Alder conditions.[9c]

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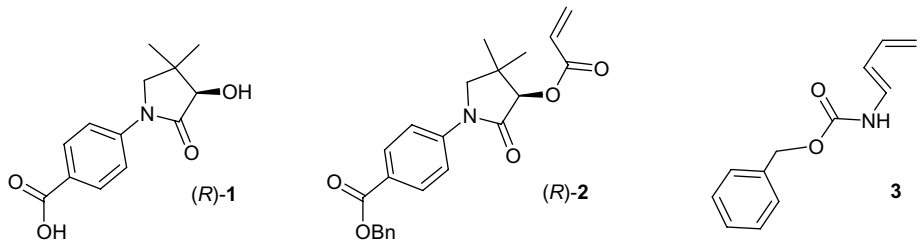
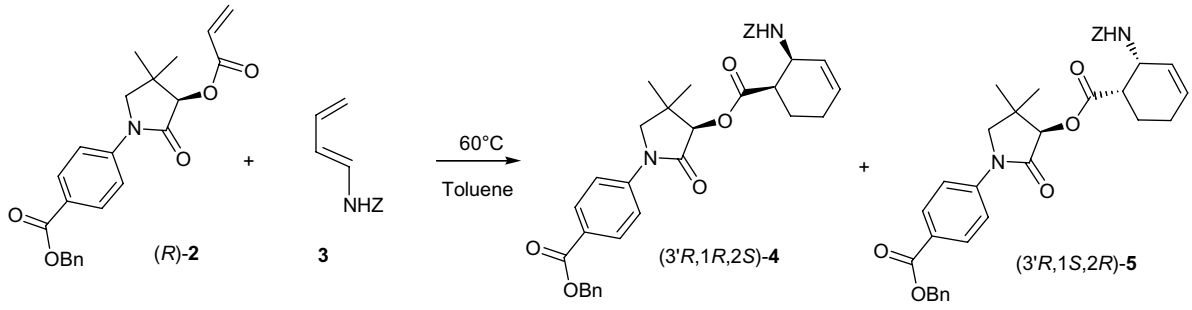


The enantiopure (*R*)-4-(3-hydroxy-4,4-dimethyl-2-oxo-pyrrolidin-1-yl) benzoic acid (*R*)-**1** and the corresponding acrylate benzyl ester (*R*)-**2** were prepared as previously described.[12b] The 1-(benzyloxycarbonyl-amino)butadiene **3** was obtained from the Curtius rearrangement of the 2,4-pentadienyl azide in benzyl alcohol according to the protocol described by Jessup et al.[13]

The asymmetric Diels–Alder cycloaddition between compound (*R*)-**2** and the *N*-*Z*-aminodiene **3** was carried out first without the catalyst in dry toluene at either room temperature (96 h) or at 60 °C (24 h), to produce in good yield a separable HPLC mixture of two diastereoisomeric Diels–Alder adducts[14] in a 85/15 ratio (Scheme 1). The reaction was completely regioselective, giving only the β-amino acid derivatives, since no trace of the γ-regioisomer was detected by ^{1}H NMR of the crude mixture. The two formed Diels–Alder adducts, **4** (main compound) and **5**, were isolated in pure form after column chromatography on silica gel.

Concerning the determination of the *endo*/*exo* or facial selectivity of the reaction, we could not directly conclude by NMR and HPLC analyses. Indeed, no significant differences of the resonance signals on the ^{1}H and ^{13}C NMR spectra of compounds **4** and **5**, as well as of the J_{H1-H2} coupling constant value[15] were observed. Furthermore, whatever the conditions and the chiral columns that were used, we only obtained one peak on their corresponding HPLC chromatograms. Compound **5** (minor adduct) was recrystallized from ethyl acetate/hexane, while the absolute configuration of the newly generated stereocentres was determined by X-ray diffraction analysis (Fig. 1).[16] From the known (*R*)-configuration of the chiral auxiliary, it was determined that the minor adduct **5** had a (3′*R*,1*S*,2*R*)-configuration, which resulted from an *endo* selectivity on the α face. Unfortunately, compound **4**, could not be crystallized and was obtained as an amorphous white solid.

LiOH hydrolysis of compounds (3′*R*,1*S*,2*R*)-**5** at room temperature yielded the *cis*-(1*S*,2*R*)-aminocyclohexene



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

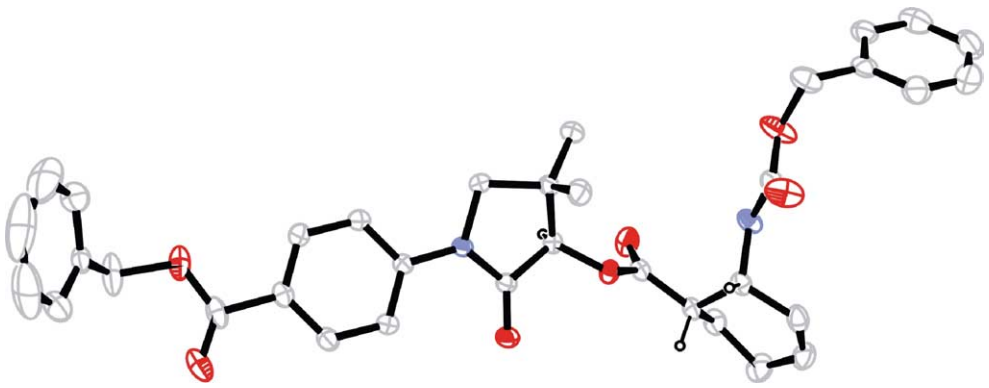
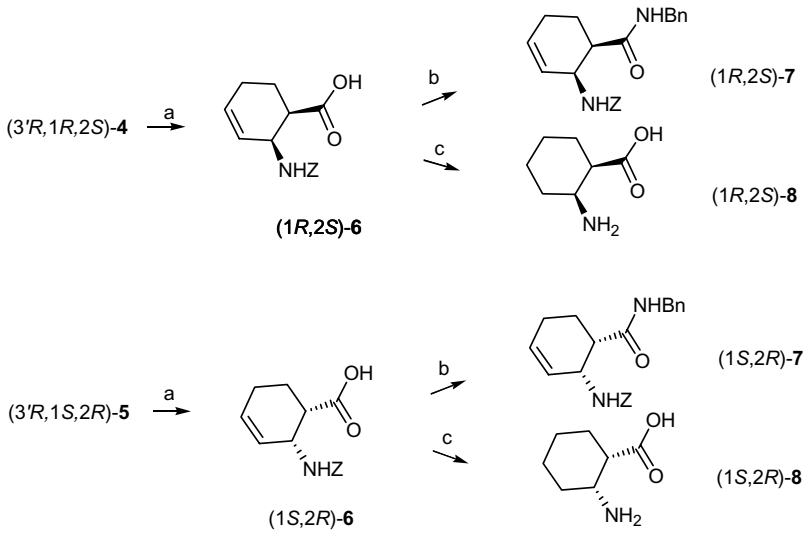


Figure 1. ORTEP drawing of the adduct **5**.



Scheme 2. Reagents: (a) LiOH, H_2O, THF; (b) $BnNH_2$, 2-chloro-1-methyl pyridinium iodide, NEt_3, CH_2Cl_2; (c) H_2, 10% Pd/C, CH_3OH.

carboxylic acid **6** (Scheme 2). It has been previously described that the *cis*- and *trans*-aminocyclohexene carboxylic acid derivatives, such as phenyl *cis*- and *trans*-6-carbomethoxy-2-cyclohexene-1-yl carbamates[17] or *cis*- and *trans*-3-(*N*-*p*-hydroxycarbonylbenzyloxycarbonyl amino)-1-cyclohexene-4-*N*,*N*-dimethylcarboxamides,[9c] have different ^1H and ^{13}C NMR spectra, as well as different J_{H1-H2} coupling constant values. Consequently, we then tried to assign the stereostructure of adduct **4** using comparisons between the NMR data of the two acids **6** obtained, respectively, from **4** and from (3′*R*,1*S*,2*R*)-**5**.

LiOH hydrolysis of compound **4** yielded acid **6** possessing both identical NMR spectra ($^1H/^{13}C$) and J_{H1-H2} coupling constant values ($J = 5.0$ Hz)[15] and an almost opposite specific rotation value to that of the acid *cis*-(1*S*,2*R*)-**6** obtained from compound **5**. Furthermore, the same ^1H NMR spectrum was obtained from the two corresponding benzyl amide derivatives **7** (Scheme 2).[18]

Considering the strong analogies between the ^1H NMR data of compounds **4** and **5**, of the two compounds **6** and of the two compounds **7**, it can be assumed that under the conditions used, both the two diastereoisomeric Diels–Alder adducts **4** and **5** resulted from an *endo*-selective cycloaddition process, that was facially controlled in favour of the (3′*R*,1*R*,2*S*)-**4** adduct when starting from the (*R*)-dienophile **2**. LiOH hydrolysis of compound (3′*R*,1*R*,2*S*)-**4** at room temperature yielded the *cis*-(1*R*,2*S*)-aminocyclohexene carboxylic acid **6** (Scheme 2).

The same reaction was performed at room temperature under the Lewis acid-catalyzed reaction conditions with $Eu(fod)_3$ (5 mol % or 1 equiv) and also yielded after 72 h the selective formation of the *endo* diastereoisomer without significant modification of the facial selectivity. When the temperature was lowered to 0 °C, no reaction was observed and the acrylate compound was totally recovered. Alternatively, the use of a catalytic amount of $Sc(Otf)_3$ as Lewis acid rapidly led to a complete degradation of the starting material even at 0 °C.

To complete our investigation and to obtain a racemic mixture for comparison of its HPLC profile with those obtained in the asymmetric synthesis experiment, we performed the Diels–Alder reaction using racemic acrylate (*RS*)-**2**. The HPLC trace of the obtained adducts showed that all four stereoisomers of the *endo* cycloaddition were separable on the Chiralcel OD column. Furthermore, the same HPLC chromatogram was obtained for the benzyl amide derivative obtained both from the major mixture assumed to be (3′*R*,1*R*,2*S*)/(3′*S*,1*S*,2*R*)-**4** or from the minor mixture (3′*R*,1*S*,2*R*)/(3′*S*,1*R*,2*S*)-**5**. This corresponded to the two HPLC traces of compounds (1*R*,2*S*)-**7** and (1*S*,2*R*)-**7** obtained in the chiral experiment confirming that only *endo* cycloaddition occurred.

Following the conditions described by Houk et al.,[9c] palladium-catalyzed hydrogenation of the double bond concomitant with the hydrogenolysis of the carbamate moiety of acids (1*R*,2*S*)-**6** and (1*S*,2*R*)-**6**, respectively, yielded β-amino acids (1*R*,2*S*)-**8** and (1*S*,2*R*)-**8**. Although the sign and the very small value of the specific rotation of compounds (1*R*,2*S*)-**8** and (1*S*,2*R*)-**8** were not really significant, a comparison with that previously reported,[7b,9c] supported our assignment of the absolute configuration of the new isolated compounds **4**–**6**.

3. Conclusion

In conclusion, we have demonstrated that the (*R*)-benzyl-4-(3-acryloyloxy-4,4-dimethyl-2-oxopyrrolidin-1-yl)-benzoate (*R*)-**2** can be used as a chiral dienophile for the preparation of the cis-enantiopure 2-aminocyclohexane carboxylic acid. The two stereogenic created centres on the cyclohexene ring resulted from an *endo*-selective cycloaddition process that was facially controlled in favour of the (1*R*,2*S*)-compound when starting from

the (*R*)-dienophile **2**. Studies are currently in progress to examine the solid supported version of this reaction and to evaluate its advantages and drawbacks compared to the solution approach.

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. ^{1}H or ^{13}C NMR spectra (^{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. 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 with variable detector at 214 nm using: column A: Nucleosil 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: Chiralcel OD-R, 5 μm, (250 × 10 mm), flow: 1 mL/min, eluent: H_2O (0.1% TFA)/CH_3CN (0.1% TFA) 40/60; column C: (*S*,*S*)-Whelk 01, 5 μm, (250 × 10 mm), flow: 1 mL/min, eluent: hexane–2-propanol 90/10; column D: Symmetry ShieldT^{MC} RP 18, 5 μm, (19 × 100 mm), flow: 20 mL/min, H_2O (0.1% TFA)/CH_3CN (0.1% TFA) gradient 95:5–85:15 for 5 min, 85:15–35:65 for 55 min and 35:65 for 5 min. The racemic and enantiopure chiral auxiliaries (*RS*)- and (*R*)-4-(3-hydroxy-4,4-dimethyl-2-oxopyrrolidin-1-yl) benzoic acids (*RS*)-**1** and (*R*)-**1**, the corresponding acrylate benzyl esters (*RS*)- and (*R*)-benzyl-4-(3-acryloyloxy-4,4-dimethyl-2-oxopyrrolidin-1-yl)-benzoates (*RS*)-**2** and (*R*)-**2** were prepared as previously described.[12] 1-(Benzyloxycarbonylamino)butadiene **3** was obtained from the Curtius rearrangement of pentadienolate in benzyl alcohol according to the protocol described by Jessup et al.[13]

4.2. [*N*-(4-Benzyloxycarbonylphenyl)-4,4-dimethyl-2-oxopyrrolidin-3-yl]-2-(benzyloxycarbonylamino)cyclohex-3-ene-1-carboxylate (3′*R*,1*R*,2*S*)-4 and (3′*R*,1*S*,2*R*)-5

A mixture of 1-(benzyloxycarbonylamino)butadiene **3** (1.58 g, 7.8 mmol, 1.2 equiv) and of (*R*)-benzyl-4-(3-acryloyloxy-4,4-dimethyl-2-oxopyrrolidin-1-yl)-benzoate (*R*)-**2** (1 equiv) (2.55 mg, 6.5 mmol) in dry toluene (8 mL) was stirred at 60 °C for 24 h. After concentration in vacuo, a crude product, which contained an 85/15 mixture of two cycloadducts, was obtained. This was submitted to column chromatography on silica gel, using hexane–ethyl acetate (7/3) as eluent to yield the pure minor diastereoisomer (3′*R*,1*S*,2*R*)-**5** (0.20 g, 0.33 mmol, 4.3% yield, R_f = 0.35, 99% de), a (88/12) mixture of the esters (3′*R*,1*R*,2*S*)-**4**/(3′*R*,1*S*,2*R*)-**5** (1.80 g, 3.0 mmol, 38.7% yield) and the pure major diastereoisomers (3′*R*,1*R*,2*S*)-**4** (0.74 g, 1.2 mmol, 15.9% yield, R_f = 0.25, 99% de). From the (88/12) mixture of the esters (3′*R*,1*R*,2*S*)-**4**/(3′*R*,1*S*,2*R*)-**5**, the minor diastereoisomer (3′*R*,1*S*,2*R*)-**5** was eliminated by filtration after treatment with hot ethyl acetate (minimum)/hexane to afford the pure major diastereoisomer (3′*R*,1*R*,2*S*)-**4** (1.4 g, 2.3 mmol, 30.1% yield, R_f = 0.25, 99% de).

Crystallization of an aliquot of compound (3′*R*,1*S*,2*R*)-**5** from ethyl acetate/hexane yielded colourless crystals suitable for X-ray analysis.

4.2.1. Compound (3′*R*,1*R*,2*S*)-4. Mp 55 °C; $[\alpha]_D^{20} = +65$ (*c* 0.5, CH_2Cl_2); t_R (HPLC, column A) 15.02 min, t_R (HPLC, column B) 31.46 min; MS (ESI) *m*/*z*: 597.2 [(M+H)$^+$]; ^{1}H NMR ($CDCl_3$): δ 1.05 (s, 3H, C*H*$_3$), 1.15 (s, 3H, C*H*$_3$), 2.02 (m, 4H, 2C*H*$_2$), 3.02 (br m, 1H, C*H*CO), 3.44 (d, J = 9.6, 1H, HC*H*-5), 3.52 (d, J = 9.6, 1H, HC*H*-5), 4.61 (br m, 1H, C*H*NH), 4.96 (d, J = 12.5, 1H, OHC*H*C$_6$H$_5$), 5.02 (d, J = 12.5, 1H, OHC*H*C$_6$H$_5$), 5.27 (s, 2H, OCH$_2$C$_6$H$_5$), 5.34 (s, 1H, C*H*-3), 5.62 (d br, J = 10.0, 1H, C*H*═), 5.65 (d, 1H, NH), 5.76 (br d, J = 10.0, 1H, C*H*═), 7.29 (m, 10H, *H*-arom), 7.64 (d, J = 9.5, 2H, *H*-arom), 8.00 (d, J = 9.5, 2H, *H*-arom); ^{13}C NMR ($CDCl_3$): δ 21.07 (*C*H$_3$), 22.10 (*C*H$_2$), 24.27 (*C*H$_3$), 37.20 (*C*-4), 43.54 (*C*HCO), 46.83 (CHNH), 57.41 (*C*-5), 66.66 (O*C*H$_2$C$_6$H$_5$), 66.71 (O*C*H$_2$C$_6$H$_5$), 78.10 (*C*-3), 118.34 (*C*H-arom), 126.01 (*C*-arom), 126.97 (*C*H═), 128.01, 128.05, 128.20, 128.29, 128.50, 128.63 (*C*H-arom), 129.54 (CH*C*═), 130.78 (*C*H-arom), 136.05, 136.54, 143.04 (*C*-arom), 155.91, 165.83, 169.62, 172.39 (*C*O); HRMS (FAB) Calcd for $C_{35}H_{37}N_2O_7$ (MH$^+$) 597.2601. Found 597.2587.

4.2.2. Compound (3′*R*,1*S*,2*R*)-5. Mp 160 °C; $[\alpha]_D^{20} = -35$ (*c* 0.35, CH_2Cl_2); t_R (HPLC, column A) 14.34 min, t_R (HPLC, column B) 37.74 min; MS (ESI) *m*/*z*: 597.2 [(M+H)$^+$]; ^{1}H NMR ($CDCl_3$): δ 1.05 (s, 3H, C*H*$_3$), 1.15 (s, 3H, C*H*$_3$), 2.02 (m, 4H, 2C*H*$_2$), 3.02 (br m, 1H, C*H*CO), 3.44 (d, J = 9.6, 1H, HC*H*-5), 3.52 (d, J = 9.6, 1H, HC*H*-5), 4.61 (br m, 1H, C*H*NH), 5.02 (s, 2H, OCH$_2$C$_6$H$_5$), 5.27 (s, 2H, OCH$_2$C$_6$H$_5$), 5.34 (s, 1H, C*H*-3), 5.42 (d, 1H, NH), 5.62 (br d, J = 10.0, 1H, C*H*═), 5.76 (br d, J = 10.0, 1H, C*H*═), 7.29 (m, 10H, *H*-arom), 7.64 (d, J = 9.5, 2H, *H*-arom), 8.00 (d, J = 9.5, 2H, *H*-arom); ^{13}C NMR ($CDCl_3$): δ 21.07 (*C*H$_3$), 22.10 (*C*H$_2$), 24.27 (*C*H$_3$), 37.20 (*C*-4), 43.54 (*C*HCO), 46.83 (*C*HNH), 57.41 (*C*-5), 66.71 (O*C*H$_2$C$_6$H$_5$), 78.10 (*C*-3), 118.34 (*C*H-arom), 126.01 (*C*-arom), 126.97 (*C*H═), 128.01, 128.05, 128.20, 128.29, 128.50, 128.63 (*C*H-arom), 129.54 (CH$_3$*C*═), 130.78 (*C*H-arom), 136.05, 136.54, 143.04 (*C*-arom), 155.91, 165.83, 169.62, 172.39 (*C*O); HRMS (FAB) Calcd for $C_{35}H_{37}N_2O_7$ (MH$^+$) 597.2601. Found 597.2601.

4.3. (1*R*,2*S*)/(1*S*,2*R*)-2-(Benzyloxycarbonylamino)cyclohex-3-ene-1-carboxylic acid 6

To a solution of compound **4** or **5** in THF was added dropwise a solution of LiOH, H_2O (1.2 equiv) in water

and the mixture stirred at room temperature until completion of the hydrolysis (~5 h) (monitored by HPLC column A). The organic solvent was removed in vacuo, after which saturated aqueous $NaHCO_3$ was added and the mixture extracted with CH_2Cl_2. The aqueous phase was acidified (pH 1) and then extracted with CH_2Cl_2. The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated in vacuo to afford the expected acid containing about 5% of the compound (*R*)-**1** as the saponification was not totally regioselective. A reverse-phase high performance liquid chromatography (column D) yielded the expected pure acid **6**.

4.3.1. Compound (1*R*,2*S*)-6. Synthesized from compound **4** (250 mg, 0.42 mmol) in THF (4 mL), the acid (1*R*,2*S*)-**6** was obtained as a colourless oil (49.6 mg, 0.18 mmol, 43% yield, >99% ee); $[\alpha]_D^{20} = +112$ (*c* 2.3, CH_2Cl_2); MS (ESI) *m*/*z*: 276.1 [$(M+H)^+$]; t_R (HPLC column A) 10.1 min; ^1H NMR ($CDCl_3$): δ 2.02 (m, 4H, 2CH_2), 2.73 and 2.82 (2br s (80/20), 1H, C*H*CO), 4.46 and 4.55 (2br s (80/20), 1H, C*H*NH), 4.96 (d, $J = 12.1$, 1H, OHC*H*C_6H_5), 5.03 (d, $J = 12.1$, 1H, OHC*H*C_6H_5), 5.36 (br d, $J = 9.3$, 1H, NH), 5.56 (br d, $J = 10.0$, 1H, C*H*═); 5.71 (br d, $J = 10.0$, 1H, C*H*═), 7.22 (m, 5H, *H*-arom); ^{13}C NMR ($CDCl_3$): δ 22.16, 23.02 (*C*H_2), 43.26 (*C*HCO), 46.98 (CHNH), 66.97 (O*C*$H_2C_6H_5$), 127.17 (*C*H═), 128.14, 128.36, 128.52 (*C*H-arom), 129.54 (CH*C*═), 136.33 (*C*-arom), 156.11, 178.14 (*C*O); HRMS (FAB) Calcd for $C_{15}H_{18}NO_4$ (MH^+) 276.1236. Found 276.1219.

4.3.2. Compound (1*S*,2*R*)-6. Synthesized from compound **5** (113 mg, 0.19 mmol) in THF (2 mL), the acid (1*S*,2*R*)-**6** was obtained as a colourless oil (28 mg, 0.102 mmol, 52% yield, 99% ee); $[\alpha]_D^{20} = -129$ (*c* 1.0, CH_2Cl_2); t_R (HPLC column A) 10.1 min; MS, ^1H and ^{13}C NMR data are identical to those of compound (1*R*,2*S*)-**6**.

4.4. (1*R*,2*S*)/(1*S*,2*R*)-2-(Benzyloxycarbonylamino)cyclohex-3-ene-1-benzylcarbamoyle 7

The benzyl amide derivatives (1*R*,2*S*)-**7** and (1*S*,2*R*)-**7** were obtained using the synthetic route described by Corey et al.[19] starting, respectively, from (1*R*,2*S*)-**6** and (1*S*,2*R*)-**6**.

4.4.1. Compound (1*R*,2*S*)-7. Synthesized from compound (1*R*,2*S*)-**6** (10 mg, 0.036 mmol). The benzyl amide derivative (1*R*,2*S*)-**7** was obtained as a colourless oil (12.3 mg, 0.034 mmol, 94% yield, 99% ee); t_R (HPLC column A) 11.7 min; t_R (HPLC column C) 17.2 min; SM (ESI) *m*/*z*: 365.3 [$(M+H)^+$]; ^1H NMR ($CDCl_3$): δ 1.59 (m, 1H, *H*CH), 1.89 (m, 2H, CH_2), 2.01 (m, 1H, *H*CH), 2.56 (br m, 1H, C*H*CO), 4.14 (dd, $J = 5.7$ and 14.8, 1H, HNHC*H*C_6H_5), 4.29 (dd, $J = 5.7$ and 14.8, 1H, HNHC*H*C_6H_5), 4.40 (br m, 1H, C*H*NH), 4.87 (d, $J = 12.3$, 1H, OHC*H*C_6H_5), 4.93 (d, $J = 12.3$, 1H, OHC*H*C_6H_5), 5.39 (d, $J = 9.3$, 1H, N*H*), 5.57 (m, 1H, *H*C═), 5.72 (br d, $J = 9.8$, 1H, *H*C═), 6.51 (br s, 1H, N*H*), 7.26 (m, 10H, *H*-arom); ^{13}C NMR ($CDCl_3$): δ 21.58, 23.87 (*C*H_2), 43.41 (HN*C*$H_2C_6H_5$), 44.24 (*C*HCO), 46.79 (*C*HNH), 66.74 (O*C*$H_2C_6H_5$), 126.73 (*C*H═), 127.38, 127.85, 127.99, 128.09, 128.51, 128.63 (*C*H-arom), 130.10 (*C*H═), 136.52, 138.56 (*C*-arom), 156.27, 172.52 (*C*O); HRMS (FAB) Calcd for $C_{22}H_{25}N_2O_3$ (MH^+) 365.1865. Found 365.1835.

4.4.2. Compound (1*S*,2*R*)-7. Synthesized from compound (1*S*,2*R*)-**6** (9.2 mg, 0.033 mmol). The benzyl amide derivative (1*S*,2*R*)-**7** was obtained as a colourless oil (11.7 mg, 0.32 mmol, 96% yield, 99% ee); t_R (HPLC column A) 11.7 min; t_R (HPLC column C) 21.4 min; MS, ^1H and ^{13}C NMR data are identical to those of compound (1*R*,2*S*)-**7**:

4.5. (1*R*,2*S*)/(1*S*,2*R*)-2-Aminocyclohexane-1-carboxylic acid 8

The *cis*-2-aminocyclohex-3-ene-1-carboxylic acids (1*R*,2*S*)-**8** and (1*S*,2*R*)-**8** were obtained by catalytic hydrogenation of the double bond and hydrogenolysis of the carbamate group, starting from, respectively (1*R*,2*S*)-**6** and (1*S*,2*R*)-**6**, using the synthetic route described by Houk et al.[9c]

The physical properties and chemical characteristics of 2-aminocyclohex-3-ene-1-carboxylic acids (1*R*,2*S*)-**8** and (1*S*,2*R*)-**8** are identical to those previously described.[7b,9c]

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16. Crystal data for ester (3′*R*,1*S*,2*R*)-**5**: Molecular formula $C_{35}H_{37}N_2O_7$, $M = 596.2$, monoclinic, space group $P2_1$, $a = 15.5190(5)$ Å, $b = 5.9620(2)$ Å, $c = 17.0943(7)$ Å, $\beta = 100.827(2)°$, $V = 1553.5(1)$ Å^3, $Z = 2$, $D_c = 1.276$ Mg m^{-3}. X-ray diffraction data were collected at room temperature with Mo K_α radiation using the Bruker AXS Kappa CCD system. The structure was solved using direct methods and the model was refined by full-matrix least-squares procedures on F^2 to values of $R_1 = 0.0591$ and of $Rw_2 = 0.1168$ for 2378 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 268576. 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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