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Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 15 (2004) 2515–2525

(*R*)- or (*S*)-4-(3-hydroxy-4,4-dimethyl-2-oxopyrrolidin-1-yl)benzoic acid as a new chiral auxiliary for solid phase asymmetric Diels–Alder reactions

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Received 2 June 2004; accepted 10 June 2004
Available online 23 July 2004

Abstract—The synthesis of enantiopure (*R*)- and (*S*)-4-(3-hydroxy-4,4-dimethyl-2-oxopyrrolidin-1-yl)benzoic acid is described and the corresponding supported chiral acrylate derivative has been used as a dienophile in solid phase asymmetric Diels–Alder reactions with different dienes. In all cases, the reaction gave the expected compound in good yield and with high regio or *endo* selectivity. Moreover, a high facial diastereoselectivity (86–99% de) was obtained using 2,3-dimethylbutadiene, cyclopentadiene or 1,3-cyclohexadiene. In contrast, low to moderate facial diastereoselectivity (40–76% de) was observed with isoprene depending on the polymer used.

1. Introduction

The Diels–Alder cycloaddition is a well known organic reaction, which is widely used to prepared a six-membered ring with several stereogenic centres in a regio and stereocontrolled way.[1–3] The development of asymmetric Diels–Alder reactions involves the use of either a chiral auxiliary[1,4,5] or a chiral catalyst.[6] Actually, among several possible combinations of chiral reactants, reactions between achiral dienes and chiral dienophiles such as acrylates or methacrylates of enantiomerically pure alcohols or amines have been extensively studied.[4,5,7]

In recent years a number of asymmetric organic reactions have been carried out with polymer-supported chiral reagents or catalysts.[8] On the other hand, stereoselective syntheses of complex molecules using a polymer-supported chiral auxiliary[9] are not always well developed. This is the case of solid phase Diels–Alder reactions whose syntheses mainly concern racemic preparations.[10,11] Only very few asymmetric examples have been reported so far.[11,12] Nevertheless, the usual advantages of the solid phase strategy, easy work-up, simple isolation of the desired compounds and facile separation and recovery of the chiral material, are now reliable.

We recently prepared and tested several *N*-substituted 3-hydroxy-4,4-dimethyl-2-pyrrolidinone acrylate derivatives as dienophiles in Diels–Alder reactions using isoprene and cyclopentadiene as dienes.[13] These experiments pointed out the difficulties associated with some of these compounds that failed to yield the corresponding cycloadduct. We found that the outcome of the reaction was dependent on the acrylate structure and that the 4-(3-hydroxy-4,4-dimethyl-2-oxopyrrolidin-1-yl)benzoic acid acrylate derivative was highly efficient to give the cycloadduct in good yield and with high regio or *endo* selectivity in both solution and solid phase reaction conditions. As part of our programme directed towards the development of asymmetric reactions on solid support,[14] we decided to convert the racemic 4-(3-hydroxy-4,4-dimethyl-2-oxopyrrolidin-1-yl)benzoic acid acrylate derivative into the corresponding enantiopure compound and to evaluate its possible use as a supported chiral auxiliary in asymmetric Diels–Alder reactions.

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doi:10.1016/j.tetasy.2004.06.012

2. Results and discussion

Racemic 4-(3-hydroxy-4,4-dimethyl-2-oxopyrrolidin-1-yl)benzoic acid (±)-**1** was prepared as previously described[15] in moderate yield under severe conditions by fusion of an excess of pantolactone **2** and the sodium salt of the 4-aminobenzoic acid at 190 °C (Scheme 1). The corresponding racemic benzyl ester **3** was obtained in high yield using benzyl alcohol, benzotriazolyloxy-tris-(dimethylamino)phosphonium hexafluorophosphate (BOP) and *N*,*N*-diisopropylethylamine (DIEA). Compound **3** was then transformed into a diastereoisomeric mixture of (1*S*,3′*S*)-**4** and (1*S*,3′*R*)-**4** using NEt_3/DMAP and (1*S*)-camphanic acid chloride. Enantiomerically pure compounds **4** were isolated by chromatographic separation of the mixture of the two diastereoisomers. (*S*)-**1** or (*R*)-**1** were finally obtained by saponification of the camphanyl ester followed by hydrogenolysis of the benzyl ester.

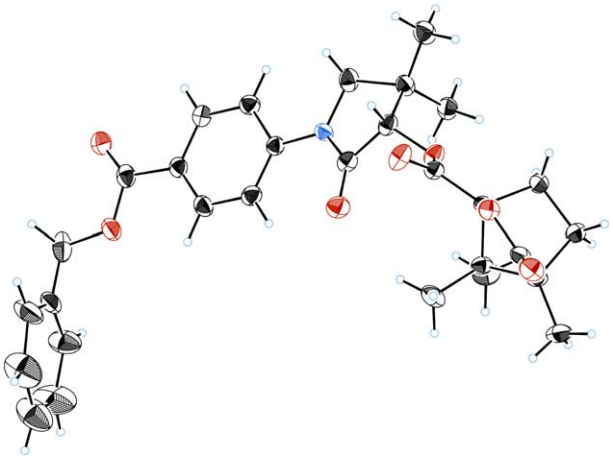


Figure 1. ORTEP drawing of ester (1*S*,3′*S*)-**4**.

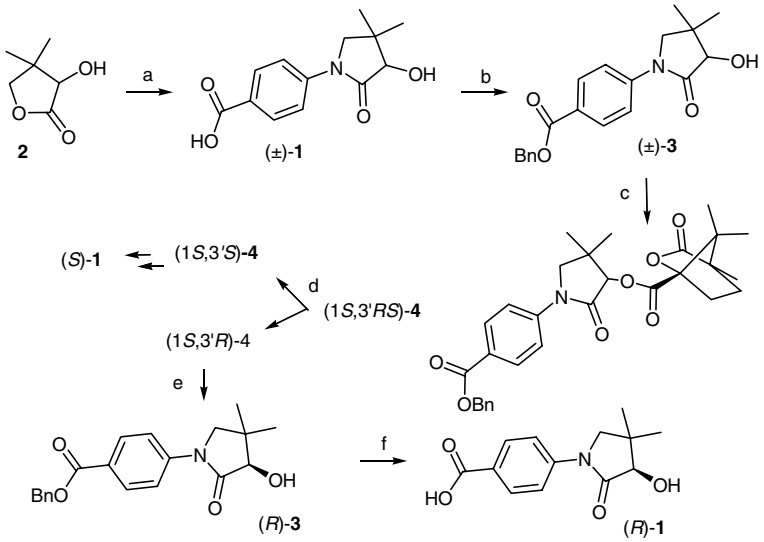
The structure of (1*S*,3′*R*)-**4** and (1*S*,3′*S*)-**4** were ascertained from the spectral data and the configuration of (1*S*,3′*S*)-**4** was assigned on the basis of an X-ray crystal structure determination (Fig. 1).[16] The stereochemistry of (1*S*,3′*S*)-**4** allowed us to establish that of compound (*S*)-**1**.

The polymer-supported (*R*)-4-(3-hydroxy-4,4-dimethyl-2-oxopyrrolidin-1-yl)benzoic acid (*R*)-**5** was obtained as previously described,[13,14] starting from a Fmoc Rink amide resin and the (*R*)-4-(3-hydroxy-4,4-dimethyl-2-oxopyrrolidin-1-yl)benzoic acid (*R*)-**1**. The corresponding supported acrylic ester **6** was prepared via reaction of the supported alcohol (*R*)-**5** with an excess of both acryloyl chloride and triethylamine in anhydrous CH_2Cl_2 at room temperature.

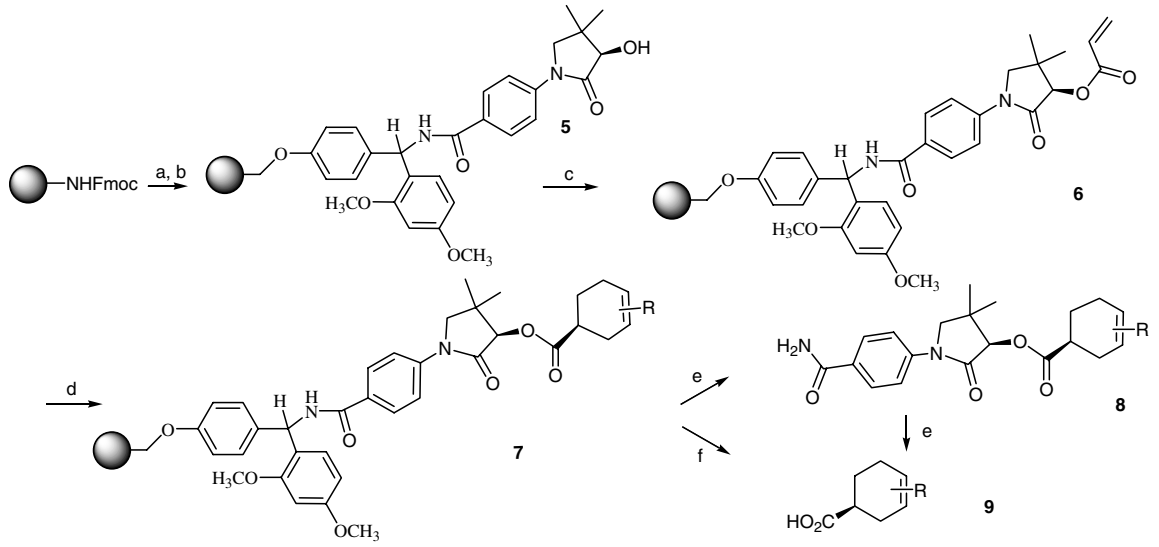
We used a Rink amide resin[14] because the benzhydrylamide bond created between the alcohol and the polymer remained stable under the reaction conditions and during the basic final hydrolysis of the ester bond (Scheme 2, step e). Furthermore, removal of compound **8** from the resin could be performed in acidic medium (5% TFA in CH_2Cl_2) (Scheme 2, step d). This strategy was of great help for the control of the different steps of the synthesis.

According to previous studies performed using the supported racemic acrylic ester (±)-**6**,[13] the supported Diels–Alder reaction was carried out under optimized reaction conditions that is, 6 equiv of diene in the presence of 1.1 equiv of $TiCl_4$ in anhydrous CH_2Cl_2 at 0 °C for 16 h.

The reaction of the supported acrylate ester (*R*)-**6** with isoprene, 2,3-dimethylbutadiene, cyclopentadiene and 1,3-cyclohexadiene,[17] gave in good yield (80–98%) the expected compound **8a**, **8b**, **8c** or **8d** after cleavage from



Scheme 1. Synthesis of (*R*)-**1** and (*S*)-**1**. Reagents and conditions: (a) 4-aminobenzoic acid sodium salt, 190 °C; (b) BnOH, BOP, DIEA, DMF; (c) (1*S*)-camphanic acid chloride, NEt_3, DMAP, CH_2Cl_2; (d) chromatographic separation; (e) LiOH, THF, H_2O; (f) H_2, $Pd(OH)_2$, AcOEt.



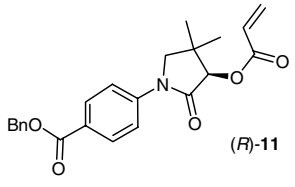
Scheme 2. Diels–Alder reaction with the supported-acrylate **6**. Reagents and conditions: (a) piperidine, DMF; (b) (*R*)-**1**, BOP, DIEA, DMF; (c) acryloyl chloride, NEt_3, CH_2Cl_2; (d) diene, $TiCl_4$, CH_2Cl_2; (e) TFA, CH_2Cl_2; (f) LiOH, THF, H_2O.

the resin under acidic conditions (Table 1). Concerning the determination of the regio, *endo* or facial selectivity of the reaction, we could not directly conclude even after several NMR and HPLC analyses. Indeed, no significant splitting of the resonance signals was observed on the ^1H and ^{13}C NMR spectra of compounds **8a**, **8b**, **8c** and **8d**. Whatever the conditions and chiral columns that were used, we only obtained one peak on the corresponding HPLC chromatograms. On the other hand, LiOH hydrolysis of compounds **8a**, **8c** and **8d** at room temperature yielded acids **9a**, **9c** and **9d** whose specific rotations allowed us to establish the (*S*)-configuration for the main newly generated stereogenic centre.[18] LiOH hydrolysis of **8b** at room temperature gave the acids (−)-**9b**, assumed to have an (*S*)-configuration. ^{13}C NMR spectrum showed that **9a** was mainly the *para*-compound (>99%)[19] and that **9c** and **9d** were mainly *endo* compounds (95% and 98%).[20] The accurate stereochemistry of (*S*)-**9a** (40% ee), (−)-**9b** (99% ee), (*S*)-**9c** (86% ee) and (*S*)-**9d** (85% ee), was determined by chiral HPLC analysis of the corresponding benzyl amide derivatives **10a**, **10b**, **10c** and **10d**[21] (Table 1).

Due to the low enantiomeric excess obtained with isoprene, new experiments were investigated. Acrylate derivative (*R*)-**11**, prepared from compound (*R*)-**3**, was first used in solution to examine the effect of the polymer matrix. In the solid phase, we either used a spacer introduced on the Rink amide resin to move the chiral auxiliary away from the polymer matrix or an aminomethylated resin to evaluate effects of the Rink linker.

The reaction of acrylate (*R*)-**11** with isoprene (2.0 equiv) in solution in the presence of 1 equiv of $TiCl_4$ at a temperature from −20 °C to 0 °C gave in 85% yield and with high diastereoisomeric excess (92%)[22] the desired cycloadduct (3′*R*,1*S*)-**12**, which consisted of only the corresponding *para*-adduct. The absence of the *meta* regioisomer was confirmed by ^{13}C NMR analysis of (*S*)-methyl cyclohex-3-ene carboxylic acid **9a**,[19] obtained after treatment of compound **12** with 2 equiv of lithium hydroxide monohydrate in THF/water for 4 h. The enantiomeric excess of (*S*)-**9a** (86%), determined by chiral HPLC analysis of the corresponding benzyl amide derivatives (*S*)-**10a**,[21] showed that slight racemization occurred during the saponification.

The spacer introduced on the Rink amide resin was 6-aminohexanoic acid as it allowed us to follow the same strategy while outlying the chiral auxiliary. Reaction of the corresponding supported acrylate (*R*)-**13** with isoprene carried out under previous optimized reaction conditions (6 equiv diene, 1.1 equiv $TiCl_4$, 0 °C 16 h), gave the expected compound **14** in good yield (77%) after acidic removal from the resin. The value of enantiomeric excess (70%) of the corresponding compound (*S*)-**9a** isolated after LiOH treatment, showed that the introduction of a spacer led to an increase of stereoselectivity.



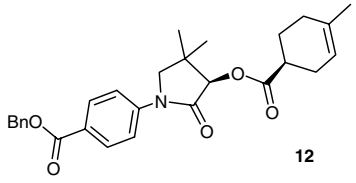
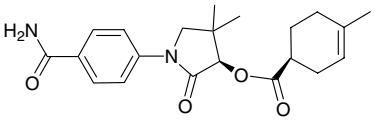
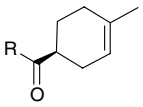
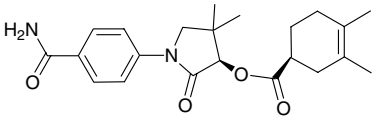
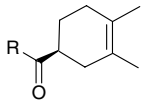
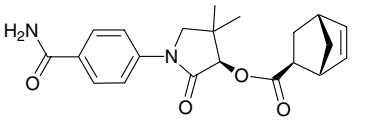
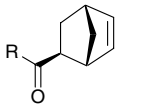
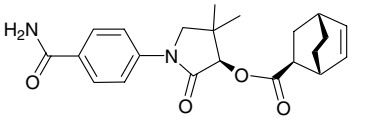
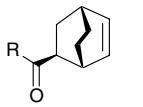
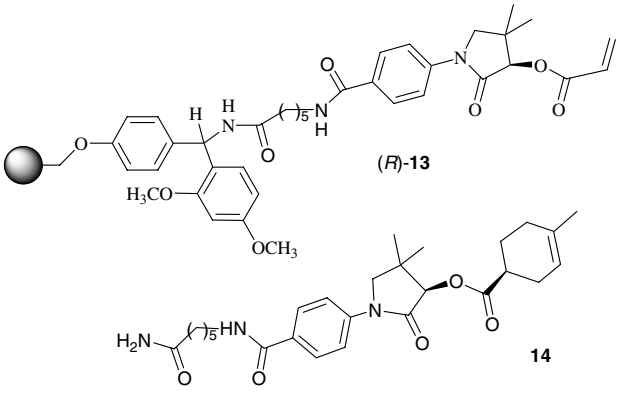
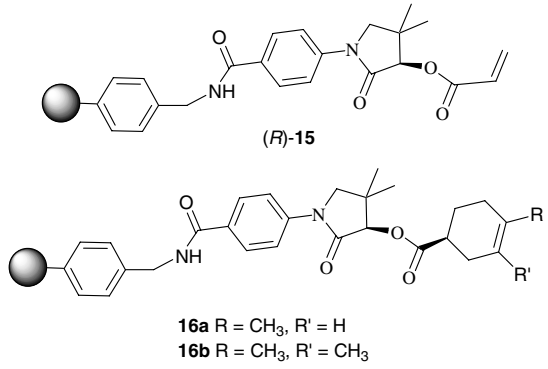


Table 1. $TiCl_4$-catalyzed Diels–Alder reactions of (*R*)-**6** with various dienes

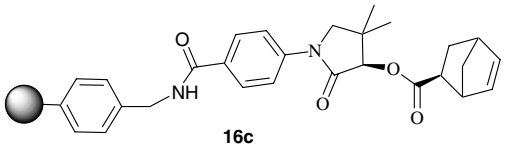
Dienes	Major products **8**		Major products **9** and **10**	
		**8a** 80% yield		**9a**: R = OH **10a**: R = NHBn *para* >99% Ee = 40%
		**8b** 95% yield		**9b**: R = OH **10b**: R = NHBn Ee = 99%
		**8c** 95% yield		**9c**: R = OH **10c**: R = NHBn *endo*/*exo* 95/5 Ee = 86%
		**8d** 98% yield		**9d**: R = OH **10d**: R = NHBn *endo*/*exo* 98/2 Ee = 85%





Finally, we used an aminomethylated resin to obtain the supported acrylate (*R*)-**15** by treatment of the corresponding supported alcohol with acryloyl chloride. The Diels–Alder reactions when carried out with (*R*)-**15** under various conditions always gave compound (*S*)-**9a** in moderate yield (10–50%) after direct saponification on polymer **16**. The best result was obtained using 1.1 equiv $TiCl_4$ and 6 equiv of isoprene at 0 °C for 16 h as in the case of the Rink amide resin. Moderate yields (40–50%) were also observed when a spacer was introduced on the aminomethylated resin to move away the chiral auxiliary. ^1H and ^{13}C NMR of compound (*S*)-**9a** and chiral HPLC of the corresponding benzyl amide derivatives **10a** showed the absence of the *meta* regioisomer and an increase of the stereoselectivity (76% ee) when compared to the Rink amide resin.

To complete our investigations, reactions of (*R*)-**15** with cyclopentadiene and 2,3-dimethylbutadiene were realized under the best conditions leading to resins **16b** and **16c**. After direct saponification on the polymer, compounds (−)-**9b** and (*S*)-**9c** were obtained in moderate yields (45% and 40%) and with good stereoselectivity (86% and 94%), respectively.



3. Conclusion

In conclusion, the supported chiral acrylate derivative of enantiopure (*R*)-4-(3-hydroxy-4,4-dimethyl-2-oxopyrrolidin-1-yl)benzoic acid reacted with different dienes under $TiCl_4$ catalysis with high regio or *endo* selectivity. A high facial diastereoselectivity was also observed using 2,3-dimethylbutadiene, cyclopentadiene or 1,3-cyclohexadiene as dienes. With the poor reactive iso-

prene, moderate results were obtained. It appeared that facial diastereoselectivity was dependent on the polymer used in this case.

4. Experimental section

4.1. General methods

All reagents were used as purchased from commercial suppliers without further purification, except for triethylamine (NEt_3), which was distilled from KOH and ninhydrin. Solvents were dried and purified by conventional methods prior to use; THF was freshly distilled under argon from sodium and benzophenone. Melting points were determined with a Büchi apparatus and are uncorrected. IR spectra were recorded with a FT-IR Perkin–Elmer 1000 spectrometer. ^1H or ^{13}C NMR spectra were recorded with a Bruker Advance 300 spectrometer or a Brucker A DRX 400 spectrometer using the solvent as the 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 a variable detector at 214 nm using: column A: a reverse phase Nucleosil C_{18}, 3.5μ, (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, 5μ, (250×10 mm), flow: 1 mL/min, eluent I: hexane/2-propanol 50/50; eluent II: hexane/2-propanol 98/2; column C: Chiracel OD-R, 5μ, (250×10 mm), flow: 1 mL/min, eluent: H_2O (0.1% TFA)/CH_3CN (0.1% TFA) 60/40; column D: (S,S)-Whelk 01, 5μ, (250×10 mm), flow: 1 mL/min, eluent I: hexane/2-propanol 90/10; eluent II: hexane/2-propanol 98/2.

(±)-4-(3-Hydroxy-4,4-dimethyl-2-oxopyrrolidin-1-yl)benzoic acid (±)-1 and (±)-benzyl 4-(3-hydroxy-4,4-dimethyl-2-oxopyrrolidin-1-yl)benzoate (±)-**3** were prepared as previously described.[13]

4.2. [1-(4-Benzyloxycarbonylphenyl)-4,4-dimethyl-2-oxopyrrolidin-3-yl]4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]-heptane-1-carboxylate 4

To a mixture of (±)-benzyl-4-(3-hydroxy-4,4-dimethyl-2-oxopyrrolidin-1-yl)benzoate (±)-**3** (3.10 g, 9.10 mmol) and (1*S*)-camphanic acid chloride (2.18 g, 10.0 mmol, 1.1 equiv) in 100 mL of dry CH_2Cl_2 were added 4-dimethylaminopyridine (1.70 g, 13.7 mmol, 1.5 equiv) and triethylamine (1.90 mL, 13.7 mmol, 1.5 equiv) at 0 °C. The mixture was then stirred at room temperature for 6 h (TLC: diethyl ether/hexane 7/3, indicated complete consumption of the starting material). The resulting mixture was filtered and washed successively with a 1 M HCl solution (80 mL), a saturated $NaHCO_3$ solution (80 mL) and water (80 mL), dried over Na_2SO_4 and concentrated in vacuo. Rapid column chromatography on silica gel, eluting with diethyl ether/hexane (7/3), afforded a pure mixture of (1*S*,3′*S*)/(1*S*,3′*R*) esters **4** in 95% yield (4.46 g, 8.64 mmol). Diastereoisomers (1*S*,3′*R*)-**4** (1.18 g, 25% yield, $R_f = 0.47$, 99% de) and (1*S*,3′*S*)-**4** (0.85 g, 18% yield, $R_f = 0.37$, 95% de) were isolated after flash column chromatography on silica gel, eluting with ether/hexane (7/3). Crystallization of an aliquot of compound (1*S*,3′*S*)-**4** from diethyl ether/hexane yielded colourless crystals suitable for X-ray analysis.

Compound (1*S*,3′*R*)-**4**: mp 105 °C; $[\alpha]_D^{20} = -6$ (*c* 2, acetone); t_R (HPLC, column A) 15.1 min; (HPLC, column B: eluent I) 10.8 min; MS (ESI) *m*/*z*: 520.1 [(M+H)$^+$]; ^1H NMR ($CDCl_3$) 1.02 (s, 3H, C*H*$_3$), 1.03 (s, 3H, C*H*$_3$), 1.05 (s, 3H, C*H*$_3$), 1.12 (s, 3H, C*H*$_3$), 1.25 (s, 3H, C*H*$_3$), 1.62 (ddd, $J = 13.2$, 9.2, 4.1, 1H, HC*H*-5′), 1.87 (ddd, $J = 13.2$, 10.7, 4.5, 1H, HC*H*-5′), 2.02 (ddd, $J = 13.6$, 9.2, 4.5, 1H, HC*H*-6′), 2.48 (ddd, $J = 13.6$, 10.7, 4.1, 1H, HC*H*-6′), 3.51 (d, $J = 9.6$, 1H, HC*H*-5), 3.57 (d, $J = 9.6$, 1H, HC*H*-5), 5.27 (s, 2H, C*H*$_2$C$_6$H$_5$), 5.43 (s, 1H, C*H*-3), 7.23–7.37 (m, 5H, *H*-arom), 7.63 (d, $J = 8.9$, 2H, *H*-arom), 7.99 (d, $J = 8.9$, 2H, *H*-arom); ^{13}C NMR ($CDCl_3$) 10.19, 17.05, 17.20, 21.67, 24.92 (*C*H$_3$), 29.17 (*C*H$_2$-5′), 31.09 (*C*H$_2$-6′), 37.40 (*C*-4), 54.99 (*C*-7′), 55.41 (*C*-4′), 57.77 (*C*H$_2$-5), 67.06 (CH$_2$C$_6$H$_5$), 79.47 (*C*H-3), 91.58 (*C*-1′), 118.79 (*C*H-arom), 126.54 (*C*-arom), 128.54, 128.65, 128.99, 131.16 (*C*H-arom), 136.43, 143.27 (*C*-arom), 166.14, 167.31, 168.81, 178.69 (*C*O). HRMS (FAB) calcd for $C_{30}H_{34}NO_7$ (MH$^+$) 520.2335, found 520.2318.

Compound (1*S*,3′*S*)-**4**: mp 40 °C; $[\alpha]_D^{20} = -15$ (*c* 2, CH_2Cl_2); t_R (HPLC, column A) 15.1 min; (HPLC, column B: eluent I) 15.6 min; MS (ESI) *m*/*z*: 520.1 [(M+H)$^+$]; ^1H NMR ($CDCl_3$) 1.02 (s, 3H, C*H*$_3$), 1.03 (s, 3H, C*H*$_3$), 1.05 (s, 3H, C*H*$_3$), 1.12 (s, 3H, C*H*$_3$), 1.24 (s, 3H, C*H*$_3$), 1.60 (ddd, $J = 13.2$, 9.2, 4.1, 1H, HC*H*-5′), 1.86 (ddd, $J = 13.2$, 10.7, 4.5, 1H, HC*H*-5′), 1.99 (ddd, $J = 13.6$, 9.2, 4.5, 1H, HC*H*-6′), 2.41 (ddd, $J = 13.6$, 10.7, 4.1, 1H, HC*H*-6′), 3.51 (d, $J = 9.6$, 1H, HC*H*-5), 3.57 (d, $J = 9.6$, 1H, HC*H*-5), 5.27 (s, 2H, C*H*$_2$C$_6$H$_5$), 5.46 (s, 1H, C*H*-3), 7.28–7.41 (m, 5H, *H*-arom), 7.64 (d, $J = 8.9$, 2H, *H*-arom), 8.00 (d, $J = 8.9$, 2H, *H*-arom); ^{13}C NMR ($CDCl_3$): δ 10.12, 16.84, 17.10, 21.68, 24.79 (*C*H$_3$), 29.44 (*C*H$_2$-5′), 31.12 (*C*H$_2$-6′), 37.41 (*C*-4), 55.06 (*C*-7′), 55.21 (*C*-4′), 57.51 (*C*H$_2$-5), 66.99 (CH$_2$C$_6$H$_5$), 79.15 (*C*H-3), 91.41 (*C*-1′), 118.78 (*C*H-arom), 126.42 (*C*-arom), 128.51, 128.64, 128.99, 131.10 (*C*H-arom), 136.46, 143.32 (*C*-arom), 166.08, 166.87, 168.86, 178.32 (*C*O). HRMS (FAB) calcd for $C_{30}H_{34}NO_7$ (MH$^+$) 520.2335, found 520.2341.

4.3. (*R*)-Benzyl 4-(3-hydroxy-4,4-dimethyl-2-oxopyrrolidin-1-yl)benzoate (*R*)-3

To a solution of the diastereoisomer (1*S*,3′*R*)-**4** (731 mg, 1.4 mmol) in THF (20 mL) was added dropwise a solution of LiOH, H_2O (60 mg, 1.4 mmol, 1.0 equiv) in water (15 mL) and the mixture was stirred at room temperature until completion of the hydrolysis (1.5 h) [the reaction was monitored by TLC (hexane/AcOEt/CH_2Cl_2 (5/4/1))]. The organic solvent was removed in vacuo,

saturated aqueous $NaHCO_3$ (10 mL) added and the mixture extracted with ethyl acetate (2×30 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated in vacuo to yield compound (*R*)-**3** as a white solid (467 mg, 1.38 mmol, 99%); mp 128 °C; $[\alpha]_D^{20} = +16$ (*c* 3, CH_2Cl_2); HPLC, MS, ^1H and ^{13}C NMR data are identical to those of the (±)-enantiomer.[13]

4.4. (*R*)-4-(3-Hydroxy-4,4-dimethyl-2-oxopyrrolidin-1-yl)benzoic acid (*R*)-1

A solution of (*R*)-benzyl-4-(3-hydroxy-4,4-dimethyl-2-oxopyrrolidin-1-yl)benzoate (*R*)-**3** (440 mg, 1.3 mmol) was added to a cooled solution (−20 °C) of 20% palladium hydroxide on charcoal in ethyl acetate (7 mL) under an argon atmosphere. The mixture was then stirred for 5 h at room temperature under H_2 (the reaction was monitored by TLC). After filtration through celite, concentration of the filtrate yielded compound (*R*)-**1** as a white solid (316 mg; 1.27 mmol, 98%): mp 223 °C; $[\alpha]_D^{20} = +13$ (*c* 1.5, acetone); HPLC, MS, ^1H and ^{13}C NMR data are identical to those of the (±)-enantiomer.[13]

4.5. Preparation of the supported alcohol (*R*)-5 and the acrylate derivative (*R*)-6

After deprotection of the Fmoc group of the Rink amide resin (2.0 g, 1.0 mmol) by the standard procedure (20% piperidine in DMF, 40 min), a solution of alcohol (*R*)-**1** (0.37 g, 1.5 mmol, 1.5 equiv), BOP (0.73 g, 1.65 mmol, 1.65 equiv) and DIEA (0.32 mL, 1.80 mmol, 1.8 equiv) in DMF (15 mL) was added to the resin. The suspension was stirred for 12 h at room temperature and the solution removed by filtration from the resin. The resin was washed with DMF (3×15 mL), CH_2Cl_2 (3×15 mL), CH_2Cl_2/CH_3OH (8/2) (3×15 mL), CH_2Cl_2 (3×15 mL) and diethyl ether (3×15 mL) and dried under reduced pressure. The reaction was monitored by the ninhydrin test. To this stirred and swollen resin (*R*)-**5** (1.0 mmol) in anhydrous CH_2Cl_2 (15 mL) was added 1.2 mL of triethylamine (8.5 mmol, 8.5 equiv) and then dropwise 0.4 mL of acryloyl chloride (5.0 mmol, 5 equiv) at room temperature. The suspension was stirred for 4–5 h at the same temperature and the solution removed from the resin by filtration. After washing with CH_2Cl_2 (3×20 mL), CH_2Cl_2/CH_3OH (8/2) (3×20 mL), CH_2Cl_2 (3×20 mL) and diethyl ether (3×20 mL), resin (*R*)-**6** was dried under reduced pressure.

4.6. Polymer-bound acrylate (*R*)-13

After deprotection of the Fmoc group of the Rink amide resin (2.0 g, 1.0 mmol) by the standard procedure (20% piperidine in DMF, 40 min), a solution of *N*-Fmoc-6-aminohexanoic acid (1.77 g, 5.0 mmol, 5 equiv), BOP (2.43 g, 5.5 mmol, 5.5 equiv) and DIEA (1.24 mL, 7.0 mmol, 7.0 equiv) in DMF (15 mL) was added. The suspension was stirred for 12 h at room temperature (monitored by the ninhydrin test) and the solution removed from the resin by filtration. The resin was washed with DMF (3×15 mL), CH_2Cl_2 (3×15 mL), CH_2Cl_2/CH_3OH (8/2) (3×20 mL), CH_2Cl_2 (3×20 mL) and diethyl ether (3×20 mL) and the resin dried under reduced pressure. From this stirred and swollen resin (1.0 mmol) in DMF (15 mL), the polymer-bound acrylate (*R*)-**13** was then obtained following the procedure described for the preparation of polymer (*R*)-**6**.

4.7. Polymer-bound acrylate (*R*)-15

Polymer-bound acrylate (*R*)-**15** was obtained following the procedure described for the preparation of polymer (*R*)-**6**, starting from an aminomethyl resin (2.0 g, 1.8 mmol) and avoiding the Fmoc deprotection step.

4.8. (*R*)-Benzyl-4-(3-acryloyloxy-4,4-dimethyl-2-oxopyrrolidin-1-yl)-benzoate (*R*)-11

Compound (*R*)-**11** was prepared as previously described[13] for the racemic mixture, starting from the (*R*)-benzyl-4-(3-hydroxy-4,4-dimethyl-2-oxopyrrolidin-1-yl)benzoate (*R*)-**3** (1.39 g, 4.1 mmol) by treatment with acryloyl chloride. Compound (*R*)-**11** was obtained as a colourless oil (1.32 g, 3.36 mmol, 82%); $[\alpha]_D^{20} = +20$ (*c* 1.4, EtOH); t_R (HPLC, column B: eluent I) (*R*)-**11**: 9.5 min and (*S*)-**11**: 11.6 min; IR, MS, ^1H and ^{13}C NMR data are identical to those of the (±)-enantiomer.[13]

4.9. General procedure for Diels–Alder reaction of the supported acrylate esters with dienes and for benzydrylamine hydrolysis

A solution of 1 M $TiCl_4$ in dry CH_2Cl_2 was added to the resin (0.6 mmol) swollen in dry CH_2Cl_2 (15 mL) at 0 °C and under argon atmosphere. The reaction mixture was stirred at the same temperature for 30 min. A solution of a diene was then added and the suspension stirred for 16 h at the same temperature. The solution was removed from the resin by filtration, the resin washed with CH_2Cl_2 (3×15 mL), CH_3OH (2×15 mL), CH_2Cl_2/CH_3OH (8/2) (3×15 mL), CH_2Cl_2 (3×15 mL) and ethyl ether (3×15 mL) and the resin dried under reduced pressure. To this resin swollen in dry CH_2Cl_2 was added 40 mL of a solution of 5% TFA in dry CH_2Cl_2 and the reaction mixture stirred for 40 min at room temperature. The solution was removed from the resin by filtration and the resin was washed with CH_2Cl_2 (3×15 mL), CH_2Cl_2/CH_3OH (8/2) (3×15 mL), CH_2Cl_2 (3×15 mL). Evaporation of the combined solvents in vacuo afforded the expected compound.

4.10. (3′*R*,1*S*)-[1-(4-Carbamoylphenyl)-4,4-dimethyl-2-oxopyrrolidin-3-yl]-4-methylcyclohex-3-ene-1-carboxylate (3′*R*,1*S*)-8a

Synthesized following the general procedure from resin (*R*)-**6** (0.6 mmol), $TiCl_4$ (1.1 equiv) and isoprene

(6 equiv). Compound **8a** was obtained as a colourless solid (177 mg, 0.48 mmol, 80% yield, 40% de);[24] t_R (HPLC column A) 11.43 min; IR, MS, ^{1}H and ^{13}C NMR data are identical to those of the previously obtained diastereoisomeric mixture.[13]

4.11. (−)-[1-(4-Carbamoylphenyl)-4,4-dimethyl-2-oxopyrrolidin-3-yl]-3,4-dimethylcyclohex-3-ene-1-carboxylate (−)-8b

Synthesized following the general procedure from resin (*R*)-**6** (0.6 mmol), $TiCl_4$ (1.1 equiv) and 2,3-dimethylbutadiene (6 equiv). Compound **8b** was obtained as a colourless solid (218 mg, 0.57 mmol, 95% yield, 99% de);[24] mp 75 °C; t_R (HPLC column A) 11.91 min; $[\alpha]_D^{20} = -4$ (*c* 1.7, EtOH); IR (KBr) 3415 (m), 3182 (m), 2939 (m), 1741 (s), 1706 (s), 1672 (s) 1607 (m) cm^{-1}; MS (ESI) *m*/*z*: 385.3 [(M+H)$^+$], 769.5; ^{1}H NMR ($CDCl_3$): δ 1.13 (s, 3H, C*H*$_3$), 1.29 (s, 3H, C*H*$_3$), 1.60 (s, 3H, C*H*$_3$), 1.63 (s, 3H, C*H*$_3$), 1.76 (m, 1H, HC*H*), 2.03 (m, 3H, HC*H* and C*H*$_2$), 2.17 (m, 2H, C*H*$_2$), 2.74 (m, 1H, C*H*CO), 3.54 (d, *J* = 9.6, 1H, HC*H*-5), 3.66 (d, *J* = 9.6, 1H, HC*H*-5), 5.44 (s, 1H, C*H*-3); 7.69 (d, *J* = 8.8, 2H, *H*-arom); 7.89 (d, *J* = 8.8, 2H, *H*-arom); ^{13}C NMR ($CDCl_3$) 18.80, 18.98, 21.04 and 21.41 (*C*H$_3$), 25.68, 30.51 and 33.68 (*C*H$_2$), 37.32 (*C*-4), 40.03 (*C*HCO), 57.42 (*C*-5), 78.18 (*C*-3), 118.81 (*C*H-arom), 123.50 and 125.56 (CH$_3$*C*═), 127.62 (*C*-arom), 128.91 (*C*H-arom), 142.56 (*C*-arom), 170.21, 170.83, 175.27 (*C*O); HRMS (FAB) Calcd for $C_{22}H_{29}N_2O_4$ (MH$^+$) 385.2127, found 385.2137.

4.12. (3′*R*,2*S*)-[1-(4-Carbamoylphenyl)-4,4-dimethyl-2-oxopyrrolidin-3-yl]bicyclo[2.2.1]hept-5-ene-2-carboxylate (3′*R*,2*S*)-8c

Synthesized following the general procedure from resin (*R*)-**6** (0.6 mmol), $TiCl_4$ (1.1 equiv) and cyclopentadiene (6 equiv). Compound **8c** was obtained as a colourless solid (210 mg, 0.57 mmol, 95% yield, 86% de);[24] mp 123–125 °C; $[\alpha]_D^{20} = -29$ (*c* 1.6, EtOH); t_R (HPLC column A) 10.48 min (95% endo), 10.78 min (5% *exo*); t_R (HPLC column A) 11.43 min; IR, MS, ^{1}H and ^{13}C NMR data are identical to those of the previously obtained diastereoisomeric mixture.[13]

4.13. (3′*R*,2*S*)-[1-(4-Carbamoylphenyl)-4,4-dimethyl-2-oxopyrrolidin-3-yl]bicyclo[2.2.2]hept-5-ene-2-carboxylate (3′*R*,2*S*)-8d

Synthesized following the general procedure from resin (*R*)-**6** (0.6 mmol), $TiCl_4$ (1.2 equiv) and cyclohexadiene (10 equiv). Compound **8d** was obtained as a colourless solid (223 mg, 0.59 mmol, 98% yield, 85% de);[24] mp 125–128 °C; $[\alpha]_D^{20} = -24$ (*c* 1.5, EtOH); t_R (HPLC, column A): 11.12 min (98% *endo*), 11.78 (2% *exo*); IR (KBr) 3440–3210 (m), 2940 (m), 1724 (s), 1702 (s), 1670 (s), 1607 (m) cm^{-1}; SM (ESI) *m*/*z*: 383.1 [(M+H)$^+$], 765.3; ^{1}H NMR (acetone-d_6) (*endo*) δ 1.17 (s, 3H, C*H*$_3$), 1.29 (s, 3H, C*H*$_3$), 1.51-1.59 (m, 2H, C*H*$_2$), 1.65–1.73 (m, 1H, C*H*$_2$), 1.8 (m, 2H, C*H*$_2$), 2.62 (m, 1H, C*H*), 2.86 (td, *J* = 7.2 and *J* = 2.2, 1H, C*H*-1′), 3.04 (m, 1H, C*H*), 3.68 (d, *J* = 9.7, 1H, *H*CH-5), 3.8 (d, *J* = 9.7, 1H, HC*H*-5), 5.48 (s, 1H, C*H*-3), 6.02 (t, *J* = 7.3, 1H, *H*C═), 6.19 (t, *J* = 7.8, 1H, *H*C═), 7.23 (s br, 1H, N*H*), 7.93 (s br, 1H, N*H*), 7.84 (d, *J* = 8.8, 2H, *H*-arom), 8.01 (d, *J* = 8.8, 2H, *H*-arom); ^{13}C NMR (acetone-d_6) (*endo*) 19.28 (*C*H$_3$), 22.98 (*C*H$_3$), 23.53 (*C*H$_2$), 24.14 (*C*H$_2$), 27.52 (*C*H$_2$), 29.05 (*C*H), 31.90 (*C*H), 36.35 (*C*-4), 41.66 (*C*H-1′), 57.99 (*C*-5), 76.97 (*C*-3), 117.65 (*C*-arom), 127.85 (*C*-arom), 128.01 (*C*-arom), 130.27 (H*C*═), 134.66 (H*C*═), 142.07 (*C*-arom), 168.45, 168.84, 173.14 (*C*O); HRMS (FAB) Calcd for $C_{22}H_{27}N_2O_4$ (MH$^+$) 383.1971, found 383.1976.

4.14. (3′*R*,1*S*)-[1-(4-(5-Carbamoylpentyl)carbamoylphenyl)-4,4-dimethyl-2- oxopyrrolidin-3-yl]-4-methylcyclohex-3-ene-1-carboxylate (3′*R*,1*S*)-14

Synthesized following the general procedure from resin (*R*)-**13** (0.6 mmol), $TiCl_4$ (1.1 equiv) and isoprene (6 equiv). Compound **14** was obtained as a colourless oil (223 mg, 0.46 mmol, 77% yield, 70 de);[24] t_R (HPLC column A) 11.06 min; MS (ESI) *m*/*z*: 484.2 [(M+H)$^+$]; ^{1}H NMR ($CDCl_3$): δ 1.13 and 1.28 (s, 3H, C*H*$_3$), 1.41 (m, 2H, C*H*$_2$), 1.55–1.63 (m, 4H, 2C*H*$_2$), 1.66 (s, 3H, C*H*$_3$), 1.80 (m, 2H, C*H*$_2$), 2.05 (m, 2H, C*H*$_2$), 2.20 (m, 2H, C*H*$_2$), 2.30 (m, 2H, C*H*$_2$), 2.70 (m, 1H, C*H*CO), 3.40 (dd, *J* = 12.8 and *J* = 6.5, 2H, C*H*$_2$), 3.53 (d, *J* = 9.5, 1H, HC*H*-5), 3.63 (d, *J* = 9.5, 1H, *H*CH-5), 5.38 (br, 1H, C*H*═), 5.41 (s, 1H, C*H*-3), 5.71 (br, 1H, N*H*), 6.00 (br, 1H, N*H*), 6.93 (br, 1H, N*H*), 7.66 (d, *J* = 8.38, 2H, *H*-arom), 7.82 (d, *J* = 8.38, 2H, *H*-arom); ^{13}C NMR ($CDCl_3$) 21.11, 22.51 and 23.44 (*C*H$_3$), 24.70, 24.80, 25.38, 26.69, 29.00, 29.09 and 35.45 (*C*H$_2$), 37.27 (*C*-4), 39.13 (*C*H-1′), 39.69 (*C*H$_2$), 57.50 (*C*-5), 77.70 (*C*-3), 118.97 (*C*-arom), 118.86 (*C*H═), 127.95 (*C*-arom), 130.66 (*C*-arom), 134.00 (CH$_3$*C*═), 141.52 (*C*-arom), 166.78, 169.46, 175.15 and 175.72 (*C*O).

4.15. (3′*R*,1*S*)-[1-(4-Benzyloxycarbonylphenyl)-4,4-dimethyl-2-oxopyrrolidin-3-yl]-4-methylcyclohex-3-ene-1-carboxylate (3′*R*,1*S*)-12

A solution of 1 M $TiCl_4$ (1 equiv) in dry CH_2Cl_2 was added to dienophile (*R*)-**11** (236 mg, 0.6 mmol) in dry CH_2Cl_2 (10 mL) at −20 °C and under an argon atmosphere. The mixture was stirred at the same temperature for 20 min and a solution of isoprene (123 μL, 1.2 mmol, 2 equiv) then added. The mixture was slowly warm up to 0 °C (5 h) and then stirred for 12 h at this temperature. Powdered $Na_2CO_3{\cdot}10H_2O$ was added to hydrolyze the $TiCl_4$ complexes, the mixture filtered and the filtrate concentrated in vacuo. The residue was submitted to column chromatography on silica gel, eluting with acetone/hexane (2/8) with compound **12** obtained as a colourless oil (235 mg, 0.51 mmol, 85% yield, 92% de);[22] t_R (HPLC column A) 14.90 min, (HPLC column B: eluent II) (3′*R*,1*S*)-**12**: 115.47 min and (3′*R*,1*R*)-**12**: 144.88 min; IR, MS, ^{1}H and ^{13}C NMR data are identical to those of the previously obtained diastereoisomeric mixtures.[13]

4.16. General procedure for the saponification of compounds 8a–d, 12 or 14

To a solution of compound **8a**–**d**, **12** or **14** (0.4 mmol) in THF or in DMF (6 mL) was added dropwise a solution of LiOH, H_2O (0.8 mmol, 2 equiv) in water (1 mL) and the mixture stirred at room temperature till completion of the hydrolysis (~5 h) (monitored by HPLC). The organic solvent was removed in vacuo, water (10 mL) and saturated aqueous $NaHCO_3$ (10 mL) then added and the mixture extracted with CH_2Cl_2 (2×20 mL). The aqueous phase was acidified (pH = 1) and extracted with a 98/2 mixture of *n*-pentane/CH_2Cl_2 (2×30 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated in vacuo to yield the expected acid **9a**–**d**.

4.17. General procedure for the saponification of the aminomethylated resin 16

To the aminomethylated resin **16** (0.6 mmol) swollen in dry DMF (10 mL) was added a solution of LiOH, H_2O (1.2 mmol, 2 equiv) in water (2 mL) and the reaction mixture stirred for 5 h at room temperature. The solution was removed from the resin by filtration and the resin washed with THF/H_2O (3×15 mL), THF/H_2O/$NaHCO_3$ saturated 8/1/1 (3×15 mL), THF (3×15 mL), CH_2Cl_2/CH_3OH (8/2) (3×15 mL) and CH_2Cl_2 (3×15 mL). After evaporation of the organic solvents in vacuo, the aqueous phase was acidified (pH = 1) and extracted with a 98/2 mixture of *n*-pentane/CH_2Cl_2 in the ratio of (3×20 mL). The combined organic phases were dried with anhydrous Na_2SO_4 and concentrated in vacuo to give the expected acids **9a**, **9b** and **9c** (40–50% yield).

4.18. (*S*)-4-Methylcyclohex-3-ene carboxylic acid (*S*)-9a[18]

Synthesized following the general procedure from compounds **8a**, **12** or **14** (0.4 mmol) in THF or in DMF, the expected acid (*S*)-**9a** was obtained (34–39 mg, 0.24–0.28 mmol, 60–70% yield, 40–86% ee);[24] t_R (HPLC column A) 9.23 min; ^{13}C NMR ($CDCl_3$): δ 23.73 (*C*H_3), 25.56, 27.76, 29.51 (*C*H_2), 39.46 (*C*HCO_2H), 119.46 (*C*H=), 134.02 (CH_3C=), 183.26 (*C*O).

4.19. (−)-3,4-Dimethyl cyclohex-3-ene carboxylic acid (−)-9b

Synthesized following the general procedure from compound **8b** (154 mg, 0.4 mmol) in DMF. The expected acid (−)-**9b** was obtained (37 mg, 0.24 mmol, 59% yield, 99% ee);[24] t_R (HPLC column A) 9.9 min; $[\alpha]_D^{20} = -85$ (*c* 1.8, EtOH); ^1H NMR ($CDCl_3$) 1.55 (s, 6H, 2CH_3), 1.62 (m, 1H, *H*CH), 1.88–1.95 (m, 3H, HC*H* and CH_2), 2.11 (m, 2H, CH_2), 2.50 (m, 1H, C*H*); ^{13}C NMR ($CDCl_3$) 18.83 and 18.95 (*C*H_3), 25.56, 30.83 and 33.4 (*C*H_2), 39.99 (*C*H-1), 123.71 and 125.36 (*C*=C), 182.51 (*C*O).

4.20. (2*S*)-*endo*-Bicyclo[2.2.1]hept-5-ene-2-carboxylic acid (2*S*)-9c

Synthesized following the general procedure from compound **8c** (147 mg, 0.4 mmol) in DMF. The expected acid (2*S*)-**9c** was obtained (32 mg, 0.23 mmol, 55% yield, 86% ee);[24] t_R (HPLC) 7.9 min (95% *endo*) and 8.5 min (5% *exo*); $[\alpha]_D^{20} = -139$ (*c* 0.8, EtOH); ^{13}C NMR ($CDCl_3$) (*endo*) 29.50 (*C*H_2), 42.94 (*C*H), 43.62 (*C*H_2), 46.07 (*C*H), 50.11 (*C*H-1), 132.82 (H*C*=CH), 138.29 (HC=*C*H), 181.42 (*C*O).

4.21. (2*S*)-*endo*-Bicyclo[2.2.2]hept-5-ene-2-carboxylic acid (2*S*)-9d

Synthesized following the general procedure from the compound **8d** (157 mg, 0.4 mmol) in DMF. The expected acid (2*S*)-**9d** was obtained (35 mg, 0.23 mmol, 57% yield, 85% ee);[24] t_R (HPLC) 8.9 min (98% *endo*) and 9.4 min (2% *exo*); ^1H NMR ($CDCl_3$) (*endo*): δ 1.18–1.38 (m, 2H, CH_2), 1.44–1.60 (m, 2H, CH_2), 1.62–1.82 (m, 2H, CH_2), 2.62 (m, 1H, C*H*CH_2), 2.68 (ddd, $J = 2.3$, $J = 5.5$, $J = 9.7$, 1H, C*H*-1), 2.98 (m, 1H, C*H*CH=), 6.19 (t, $J = J' = 7.4$, 1H, *H*C=), 6.33 (t, $J = J' = 7.4$, 1H, *H*C=); ^{13}C NMR ($CDCl_3$) (*endo*) 23.6 (*C*H_2), 24.63 (*C*H_2), 28.61 (*C*HCH=), 28.86 (*C*H_2), 31.64 (*C*HCH=) 41.98 (*C*HCO_2H), 130.67 (H*C*=), 134.62 (H*C*=), 181.34 (*C*O).

4.22. (±)-3-Methyl and (±)-4-methyl cyclohex-3-ene carboxylic acid mixture

The mixture of (±)-3-methyl and (±)-4-methyl cyclohex-3-ene carboxylic acids was obtained in 46% yield by the reaction at 120 °C of isoprene and acrylic acid following the method described by Kuehne et al.[23] t_R (HPLC) 9.2 min; ^{13}C NMR ($CDCl_3$): *rac*-4-Methyl cyclohex-3-ene carboxylic acid (main product) 23.73 (*C*H_3), 25.56, 27.76, 29.51 (*C*H_2), 39.46 (*C*HCO_2H), 119.46 (*C*H=), 134.02 (CH_3C=), 183.26 (*C*O); *rac*-3-Methyl cyclohex-3-ene carboxylic acid 23.81 (*C*H_3), 24.79, 25.03, 32.18 (*C*H_2), 40.07 (*C*HCO_2H), 121.04 (*C*H=), 132.39 (CH_3C=), 183.12 (*C*O).

4.23. (±)-3,4-Dimethyl cyclohex-3-ene carboxylic acid (±)-9b

Racemic sample of 3,4-dimethyl cyclohex-3-ene carboxylic acid (±)-**9b** was obtained by Diels–Alder reaction between the racemic supported acrylate ester (±)-**6** and 3,4-dimethylbutadiene, followed by saponification on polymer (40% yield). HPLC and NMR data are identical to those of the (−)-enantiomer.

4.24. (±)-Bicyclo[2.2.2]hept-5-ene-2-carboxylic acid (±)-9d

A racemic mixture of bicyclo[2.2.2]hept-5-ene-2-carboxylic acid benzyl ester was obtained as a colourless oil

in 44% yield (0.66 g, 2.7 mmol, 86/14 *endo*/*exo*) by reaction at 100 °C of cyclohexa-1,3-diene (1.8 mL, 18.7 mmol, 3 equiv) and benzyl acrylate (1.0 g, 6.2 mmol), followed by a column chromatography on silica gel, eluting with diethyl ether/hexane (1/9) ($R_f = 0.6$); t_R (HPLC, column A) 13.2 min; MS (ESI) m/z: 243.0 [(M+H)$^+$]; ^{1}H NMR ($CDCl_3$) (*endo*): δ 1.33 (m, 2H, CH_2), 1.58 (m, 2H, CH_2), 1.80 (m, 2H, CH_2), 2.65 (m, 1H, C*H*), 2.73 (td, $J = 7.5$ and $J = 2.3$, 1H, C*H*-1), 3.03 (m, 1H, C*H*), 5.10 (d, $J = 12.4$, 1H, HC*H*–C_6H_5), 5.17 (d, $J = 12.4$, 1H, HC*H*–C_6H_5), 6.20 (t, $J = J' = 7.8$, 1H, *H*C=), 6.37 (t, $J = J' = 7.8$, 1H, *H*C=), 7.38 (m, 5H, C_6H_5); ^{13}C NMR ($CDCl_3$) (endo) 23.84 and 24.68 (*C*H$_2$), 28.8 (*C*H), 29.1 (*C*H$_2$), 31.88 (*C*H), 42.16 (*C*H), 65.38 (O*C*H$_2$Ph), 127.35 (*C*-arom), 127.85 (*C*-arom), 130.69 (H*C*=), 134.58 (H*C*=), 135.81 (*C*-arom), 174.27 (*C*O).

To this benzyl ester in dioxane/water (4/1) was added NaOH (1.5 equiv) and the mixture stirred for 12 h at room temperature. After evaporation of the dioxane in vacuo, the aqueous solution was diluted with a 1 M solution of $NaHCO_3$ (20 mL) and washed with CH_2Cl_2 (2×20 mL). The aqueous phase was acidified (pH = 1) and extracted with CH_2Cl_2 (3×20 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated in vacuo to give the expected acid (±)-*endo*-**9d** (0.39 g, 2.6 mmol, 95% yield, 95% *endo*). HPLC and NMR data are identical to those of the (2*S*)-enantiomer.

4.25. General procedure for the preparation of benzyl amide derivatives 10a–d

The benzyl amide derivatives **10a**–**d** were obtained using the synthetic route describe by Sarakinos and Corey[25] starting from **9a**–**d**.

4.26. (*S*)-4-Methylcyclohex-3-ene carboxylic acid benzyl amide (*S*)-10a

Synthesized following the general procedure from compound (*S*)-**9a** (14 mg, 0.1 mmol). The benzyl amide derivative (*S*)-**10a** was obtained (23 mg, quantitative yield, 40–86% ee); t_R (HPLC column A) 12.1 min; t_R (HPLC column C) (*S*)-**10a**: 13.9 min, (*R*)-**10a**: 15.3 min;[26] SM (ESI) m/z: 230.2 [(M+H)$^+$]; ^{1}H NMR ($CDCl_3$) 1.65 (s, 3H, CH_3), 1.78 (m, 1H, *H*CH), 1.94–2.02 (m, 3H, HC*H* and CH_2), 2.18–2.38 (m, 3H, C*H* and CH_2), 4.46 (d, $J = 5.7$, 2H, C$H_2H_6C_5$), 5.40 (br, 1H, *H*C=), 5.78 (br, 1H, N*H*), 7.26–7.36 (m, 5H, *H*-arom).

4.27. (−)-3,4-Dimethylcyclohex-3-ene carboxylic acid benzyl amide (−)-10b

Synthesized following the general procedure from compound (−)-**9b** (15.4 mg, 0.1 mmol). The benzyl amide derivative (−)-**10b** was obtained (24 mg, quantitative yield, 99% ee); t_R (HPLC column A) 11.3 min; t_R (HPLC column C)[26] 19.9 min; SM (ESI) m/z: 244.2 [(M+H)$^+$]; $[\alpha]_D^{20} = -54$ (c 1.3, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) 1.30 (m, 1H, *H*CH), 1.57 (s, 6H, 2CH_3), 1.67 (m, 1H, *H*CH), 1.91 (m, 3H, HC*H* and CH_2), 2.20 (m, 2H, HC*H* and C*H*), 4.41 (d, $J = 5.7$, 2H, C$H_2C_6H_5$), 5.40 (br, 1H, *H*C=), 5.90 (br, 1H, N*H*), 7.26–7.36 (m, 5H, *H*-arom).

4.28. (±)-3,4-Dimethylcyclohex-3-ene carboxylic acid benzyl amide (±)-10b

Synthesized following the general procedure from compound (±)-**9b** (15.4 mg, 0.1 mmol). The benzyl amide derivative (±)-**10b** was obtained (24 mg, quantitative yield); t_R (HPLC column A) 11.3 min; t_R (HPLC column C)[25] (−)-**10b**: 19.9 min, (+)-**10b**: 22.5 min; HPLC and NMR data are identical to those of the (−)-enantiomer.

4.29. (2*S*)-Bicyclo[2.2.1]hept-5-ene-2-carboxylic acid benzyl amide (2*S*)-10c

Synthesized following the general procedure from compound (2*S*)-**9c** (13.8 mg, 0.1 mmol). The benzyl amide derivative (2*S*)-**10c** was obtained (22 mg, quantitative yield, 86% ee); t_R (HPLC column A) (*endo*): 10.1 min and (*exo*): 10.7 min; t_R (HPLC column D eluent I) (*exo*)-(*SR*)-**10c**: 21.8 min, (*endo*)-(*S*)-**10b**: 25.4 min and (*endo*)-(*R*)-**10b**: 27.4 min;[26] SM (ESI) m/z: 228.1 [(M+H)$^+$], 455.3; ^{1}H NMR ($CDCl_3$) (*endo*) 1.29–1.47 (m, 3H, *H*CH and CH_2), 1.38–2.00 (m, 1H, HC*H*), 2.92 (m, 2H, CH_2), 3.17 (br, 1H, C*H*-1), 4.38 (d, $J = 1.96$, 1H, HC*H*–C_6H_5), 4.41 (d, $J = 1.96$, 1H, HC*H*–C_6H_5), 5.98 (dd, $J = 3.0$ and $J = 5.7$, 1H, *H*C=), 6.24 (dd, $J = 3.0$ and $J = 5.7$, 1H, *H*C=), 7.23–7.37 (m, 5H, *H*-arom).

4.30. (2*S*)-Bicyclo[2.2.2]oct-5-ene-2-carboxylic acid benzyl amide (2*S*)-10d

Synthesized following the general procedure from compound (2*S*)-**9d** (15.2 mg, 0.1 mmol). The benzyl amide derivative (2*S*)-**10d** was obtained (24 mg, quantitative yield, 98% *endo*, 85% ee); t_R (HPLC column A) 10.8 min; t_R (HPLC column D eluent II) (2*S*)-**10b**: 117.5 min and (2*R*)-**10b**: 121.1 min;[26] SM (ESI) m/z: 242.0 [(M+H)$^+$], 483.3; ^{1}H NMR ($CDCl_3$) 1.27 (m, 2H, CH_2), 1.46–1.64 (m, 3H, HC*H* and CH_2), 1.88 (ddd, $J = 2.8$, $J = 10.1$, $J = 12.8$, 1H, HC*H*), 2.57–2.65 (m, 2H, 2C*H*), 2.83 (br, 1H, C*H*-1), 4.41 (2d, $J = 9.7$, 2H, CH_2–C_6H_5), 5.77 (br, 1H, N*H*), 6.25 (t, $J = J' = 7.2$, 1H, *H*C=), 6.4 (t, $J = J' = 7.2$, 1H, *H*C=), 7.24–7.37 (m, 5H, C_6H_5).

4.31. (±)-Bicyclo[2.2.2]oct-5-ene-2-carboxylic acid benzyl amide (±)-10d

Synthesized following the general procedure from compounds (±)-**9d** (15.2 mg, 0.1 mmol). The benzyl amide derivative (±)-**10d** was obtained (24 mg, quantitative

yield, 86/14 *endo*/*exo*); t_R (HPLC column A) 10.8 min (*endo*) and 11.4 min (*exo*); t_R (HPLC column D eluent II) (*exo*)-**10c**: 67.6 and 73.7 min, (*endo*)-(2*S*)-**10b**: 117.5 min and (*endo*)-(2*R*)-**10b**: 121.1 min;[26] NMR data are identical to those of the (2*S*)-enantiomer.

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21. Stereochemistry of compounds **10a**–**d** was deduced from the comparison of HPLC analysis of the corresponding racemic mixture prepared as described in the experimental part.
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