Toward Diels−Alder Reactions on a Solid Support Using Polymer Bound *N*-Substituted 3-Hydroxy-4,4-dimethyl-2-pyrrolidinone Acrylate Derivatives

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Keywords: Diels−Alder reaction / Solid-phase synthesis / Pyrrolidinone acrylate derivatives

Several *N*-substituted 3-hydroxy-4,4-dimethyl-2-pyrrolidinone acrylate derivatives, selected to allow their attachment to a polymer, have been prepared and tested as dienophiles in the Diels–Alder reaction. The experiments, performed under $TiCl_4$ catalysis in solution or the solid phase with isoprene and cyclopentadiene as dienes, pointed out the difficulties associated with some of these compounds that failed to give the corresponding cycloadduct. ^{13}C NMR studies provided some evidence regarding the nature of the interactions between the acrylate compounds and $TiCl_4$. It appears that the outcome of the reaction is dependent on the acrylate structure and that the 4-(3-hydroxy-4,4-dimethyl-2-oxopyrrolidin-1-yl)benzoic acid acrylate derivatives are highly efficient to give the cycloadduct in good yield and with high regio- or endoselectivity in both solution and solid-phase reaction conditions.

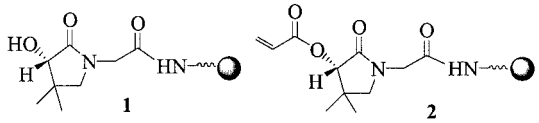
Introduction

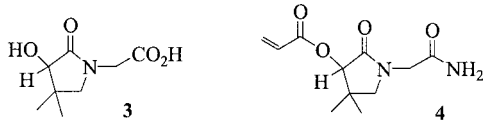
The Diels−Alder reaction can be considered as one of the most powerful transformations in synthetic organic chemistry.[1,2] The stereospecific creation of several stereogenic centers in a single step makes this reaction suitable for the preparation of complex molecules.[3] The development of asymmetric Diels−Alder reactions involves the use of 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] although 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 preparation.[10,11] Only a very few asymmetric examples have been reported so far.[11,12] Nevertheless, the usual advantages of the solid-phase strategy — easy workup, simple isolation of the desired compounds and facile separation and recovery of the chiral material — are now reliable.

We have recently described the preparation of a new insoluble polymer-supported chiral alcohol **1** and its use for the asymmetric transformation, via ketene formation, of both racemic aryl propionic acids and β^2-homoarylglycines.[13] As part of our program directed towards the development of asymmetric solid-phase reactions, we planned to examine the asymmetric solid-phase Diels−Alder reaction using the corresponding acrylate **2** of the polymer-supported chiral alcohol **1** as chiral dienophile.

In an initial approach we decided to investigate the Diels−Alder reaction on a solid support using the racemic dienophile (±)-**2**.





Results and Discussion

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

We used a Rink amide resin[14] since the benzhydrylamine bond created between the alcohol and the polymer is stable

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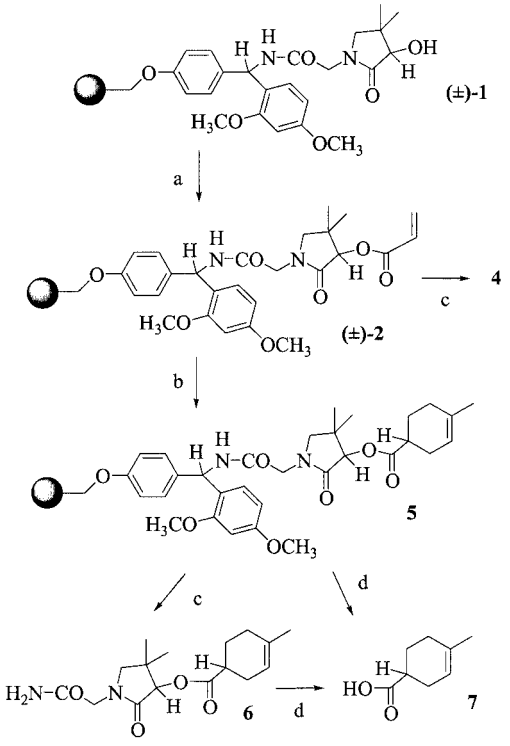
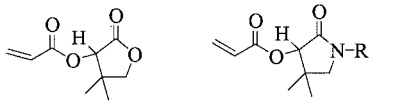
under the reaction conditions and during the basic final cleavage of the ester bond (Scheme 1, step d). The benzhydrylamine bond could be selectively cleaved in acidic medium (5% TFA in CH_2Cl_2) allowing an easier control of the different steps of the synthesis (Scheme 1, step c). The quantitative formation of the supported acrylate (±)-**2** was deduced from HPLC analysis of compound **4**, which was the only detectable product isolated after acid cleavage.



Scheme 1. Reagents: (a) acryloyl chloride, NEt_3, CH_2Cl_2; (b) CH_2Cl_2, $TiCl_4$, isoprene; (c) TFA, CH_2Cl_2; (d) LiOH, H_2O, THF

Isoprene and cyclopentadiene were chosen as representative dienes. According to previous studies performed in solution with both pantolactone acrylate **8**[7a−7c,15] or with 4,4-dimethyl-2-oxo-1-phenylpyrrolidin-3-yl acrylate (**9a**),[16] the supported Diels−Alder reaction was carried out under $TiCl_4$ catalysis in anhydrous CH_2Cl_2.



8 **9a:** R = C_6H_5 **9b:** R = CH_3

From the reaction of the supported acrylate ester (±)-**2** with isoprene (2.0 equiv.; Scheme 1) in the presence of 0.5 equivalents of $TiCl_4$ in a temperature ranging from −20 °C to 10 °C for 16 h, no cycloadduct **6** was isolated (Table 1, Entry 1). Only the acrylate ester **4** was obtained after acid cleavage of the benzhydrylamine bond.

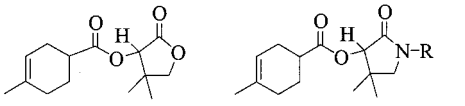
No improvement was observed under more drastic conditions: 1 to 10 equivalents of $TiCl_4$, 5 to 10 equivalents of diene, longer reaction time (24 to 92 h) and various temperatures (Table 1, Entry 1). The supported acrylate ester (±)-**2** also failed to react under similar experimental conditions with the more reactive cyclopentadiene (Table 1, Entry 2).

However, the acrylate **8** or **9a** reacted with isoprene in solution under $TiCl_4$ catalysis affording the corresponding *para*-cycloadducts **11** and **12a** in high yield.[15,16] Similarly, we observed that reaction between the acrylate ester (±)-**9b**, bearing an alkyl group on the lactam function, and isoprene under the same experimental conditions yielded the cycloadduct **12b** in good yield (76%; Table 1, Entry 3).

Table 1. Diels−Alder reaction using the *N*-substituted 3-hydroxy-4,4-dimethyl-2-pyrrolidinones as acrylate derivatives

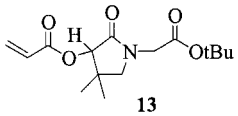
Entry	Dienophiles	Dienes (equiv.)	Lewis acids (equiv.)	T_1 [a]	T_2 [b] (reaction time)	Yields (%)
1	**2**	isoprene (2 to 10)	$TiCl_4$ (0.5−10)	−20 °C	−20 °C → 10 °C (16 to 92 h)	−
2	**2**	cyclopentadiene (2 to 10)	$TiCl_4$ (1.5−5)	−10 °C or room temp.	−20 °C → 0 °C (12 to 20 h)	−
3	**9b**	isoprene (2)	$TiCl_4$ (0.5)	−20 °C	−20 °C → 0 °C (25 h)	76 (**12b**)
4	**13**	isoprene (2)	$TiCl_4$ (0.5 −1)	−20 °C	−20 °C → 0 °C (25 h)	−
5	**13**	isoprene (2)	−	−	room temp., CH_2Cl_2 or reflux, C_6H_5 (72 h)	−
6	**14**	isoprene (2−4)	$TiCl_4$ (0.5−2)	room temp. or -20 °C	−20 °C → 10 °C (16 to 70 h)	−
7	**14**	isoprene (2)	Et_2AlCl	−20 °C	−20 °C → 0 °C (5 h) and 0 °C (12 h) and 10 °C (24 h)	−
8	**14**	isoprene (2)	$Zn(CF_3SO_3)_2$ (1) $Sm(CF_3SO_3)_2$ (1) $Sc(CF_3SO_3)_2$ (1)	−20 °C	−20 °C → 0 °C (5 h) and 0 °C (12 h) and 10 °C (24 h)	−
9	**15a**	isoprene (2)	$TiCl_4$ (1)	−20 °C	−20 °C → 0 °C (5 h) and 0 °C (12 h)	90 (**26a**)
10	**15b**	isoprene (6)	$TiCl_4$ (1.1)	0 °C	0 °C (16h)	80 (**26b**)
11	**15b**	cyclopentadiene (6)	$TiCl_4$ (1.1)	0 °C	0 °C (16h)	95 (**29**)
12	**16**	isoprene (2)	$TiCl_4$ (1)	−20 °C	−20 °C → 0 °C (5 h) and 0 °C (36 h)	90 (**27**)

[a] T_1: Temperature of the formation of the acrylate/Lewis acid complexes. [b] T_2: Temperature of the cycloaddition reaction.



11 **12a:** R = C_6H_5 **12b:** R = CH_3

It can be assumed that lack of reactivity of the supported Lewis acid coordinated-dienophile (±)-**2** might be due to the steric hindrance induced by the backbone of the insoluble polymer. However, no cycloadduct was formed in solution under similar conditions from the reaction of isoprene and the acrylate ester derivative **13** (which is the *tert*-butyl ester equivalent of **2**) (Table 1, Entry 4), suggesting that the resin alone does not influence the outcome of the reaction.



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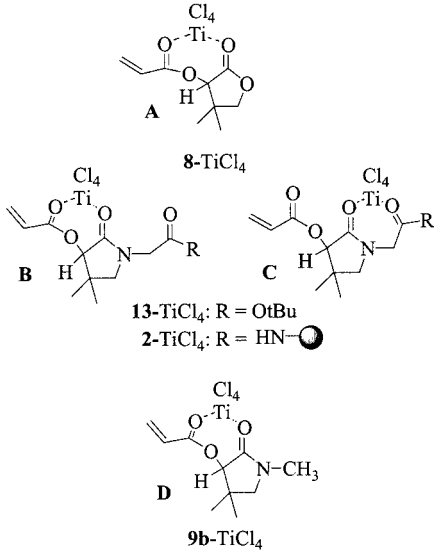
The formation of a doubly coordinated complex **A** (**8**-$TiCl_4$) between $TiCl_4$ and the dienophile derived from (*R*)-pantolactone has been proposed by Helmchen.[7a,7b,17] This coordination increases the reactivity of the dienophile and also improves the regio- and stereoselectivity relative to uncatalyzed Diels−Alder reactions. The results obtained recently by Camps[16] and Cativiela[18] with the 4,4-dimethyl-2-oxo-1-phenylpyrrolidin-3-yl acrylate **9a** and the (*R*)-pantolactone acrylate **8**, respectively, are in good agreement with this model.

We expected that a similar seven-membered chelate complex **B** between $TiCl_4$ and both the acrylate ester **13** and the supported acrylate **2** could be formed to lead to an activated dienophile. However, besides complex **B** other species could be present, like the doubly coordinated complex **C** for compounds **2** and **13**, for instance.



A

8-$TiCl_4$

B **C**

13-$TiCl_4$: R = OtBu

2-$TiCl_4$: R = HN–

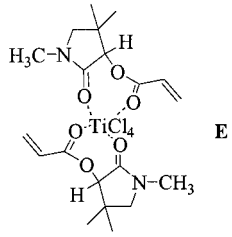
D

9b-$TiCl_4$

To investigate the question of the acrylate/Lewis acid complexes, an NMR spectroscopic study (HMQC and HMBC experiments) was performed. We recorded the spectrum of the acrylates **9b** and **13** alone or in the presence of $TiCl_4$ in CD_2Cl_2 at room temperature. Addition of increasing amounts of $TiCl_4$ (0.1−0.5 equiv.) to a CD_2Cl_2 solution of the acrylate **9b** resulted in progressive chemical-shift variations of most of the ^{13}C NMR resonance signals. For instance, a large downfield shift of the ^{13}C NMR resonance of the two carbonyl carbon signals of the acryloyl and lactam moieties was observed in the presence of 0.5 equiv. of $TiCl_4$ (Table 2), indicating the existence of complex **D**, which promotes the Diels−Alder reactions. Subsequently, when 0.5−1.0 equiv. of $TiCl_4$ were added, the variation in the chemical shifts of the carbon signals remained unchanged, suggesting that a 2:1 complex **E** was present in which two molecules of the acrylate were coordinated to one molecule of the Lewis acid.

Table 2. ^{13}C NMR chemical shifts of free and $TiCl_4$-complexed substrates (0.5 equiv. $TiCl_4$)

Carbon atoms	**9b** δ (ppm)	**9b**-$TiCl_4$ δ (ppm)	**13** δ (ppm)	**13**-$TiCl_4$ δ (ppm)
−O−*C*O−C_2H_3	165.6	172.0	165.5	164.6-165.6
−*C*O−O*t*Bu	/	/	167.7	174.8-175.2
−*C*O−N(*R*)-	169.6	175.2	170.2	176.9-177.5
−CH=*C*H_2	131.9	142.7	132.1	133.2-132.5
−*C*H=CH_2	128.1	125.1	128.1	127.2-127.9



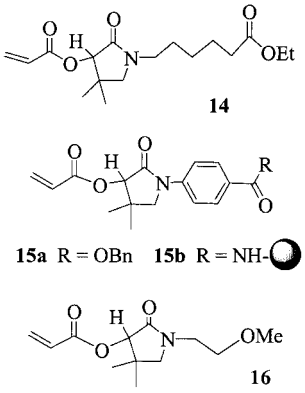
E

Addition of 0.5 equiv. of $TiCl_4$ to the acrylate **13** resulted in a splitting of most of the ^{13}C NMR resonance signals and in a large downfield shift of the ^{13}C NMR resonance signals associated with the two carbonyl carbons of the *tert*-butyl ester and lactam moieties (Table 2). In contrast, a lesser upfield shift was observed for the carbonyl carbon of the acryloyl moiety suggesting the presence in this case of the complex C. This latter complex leads to a poorly activated dienophile that is probably also sterically hindered, thus restricting the approach of the diene.[5] This could explain why no reaction occurred when using compounds **13** even under drastic thermal reaction conditions (excess of isoprene in refluxing benzene for 72 h; Table 1, Entry 5).

For the chemical shifts of the two vinyl carbons we observed significant chemical-shift changes for the **9b**-$TiCl_4$ complex (131.9 → 142.7) and (128.1 → 125.0) and, in contrast, lower values for the **13**-$TiCl_4$ complex (132.1 → 132.2−132.5) and (128.1 → 127.2−127.9) (Table 2), in agreement with the results obtained above.

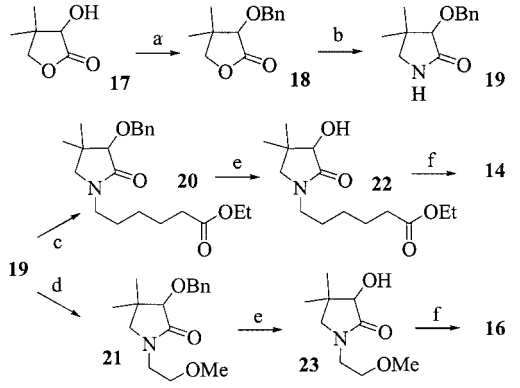
According to these results, we decided to synthesize and test several new acrylate ester derivatives of the 3-hydroxy-4,4-dimethyl-2-oxopyrrolidine type. Reactions were first carried out in solution with the racemic dienophiles **14**, **15a**

and **16**. The use of compounds **14** or **15a** should make it possible to eliminate or minimize the risks of competitive complexation of the $TiCl_4$ with the carbonyl group of the nitrogen substituent. Indeed, the increase in the length of the functionalised arm on the lactam nitrogen in compounds **14** or its rigidification in compounds **15a** should mainly favour the complexation of the $TiCl_4$ with the carbonyl function of the acrylate. Moreover, it can be assumed that a similar result should be obtained by using the acrylate **16**, which does not contain a third carbonyl group.

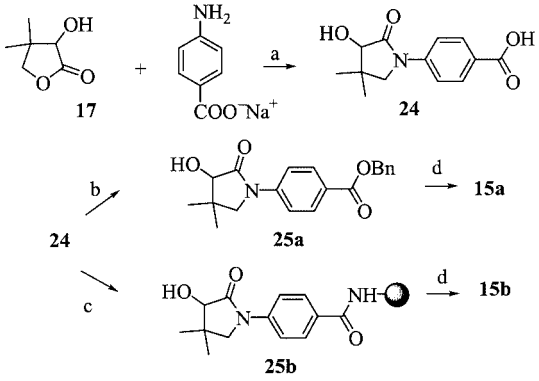


To prepare **14** and **16**, the commercially available pantolactone **17** was transformed into the corresponding benzyl ether as described recently (Scheme 2).[19] Then, the racemic 3-benzyloxy-4,4-dimethyl-yrrolidin-2-one (**19**) was formed at 230 °C in a sealed tube by reaction with an excess of aqueous ammonia solution. Alkylation of the lactam nitrogen with ethyl 6-bromohexanoate or with 2-bromoethyl methyl ether gave racemic compounds **20** and **21**, respectively. The benzyl ether was easily cleaved by hydrogenolysis affording the corresponding racemic alcohols **22** and **23**. The acrylate derivatives **14** and **16** were prepared by reaction of **22** and **23** with acryloyl chloride and triethylamine in anhydrous CH_2Cl_2 at −20 °C.

The racemic 1-(4-carboxyphenyl)-3-hydroxy-4,4-dimethyl-2-pyrrolidinone (**24**) was prepared in moderate yield, as described previously,[20] by fusion of a mixture of an excess of the lactone **17** with the sodium salt of 4-aminobenzoic acid at 190 °C (Scheme 3). The corresponding racemic benzyl ester **25a** was obtained in high yield upon reaction with (benzotriazolyloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP) and diisopropylethylamine (DIEA). Finally, the acrylic ester derivative **15a** was prepared as described above from acryloyl chloride.



Scheme 2. Reagents: (a) BnBr, Cs_2CO_3, DMF; (b) NH_3 aq., 230 °C; (c) NaH, $Br(CH_2)_5CO_2Et$, DMF; (d) NaH, $Br(CH_2)_2OMe$, DMF; (e) H_2, $Pd(OH)_2$, EtOAc; (f) acryloyl chloride, NEt_3, CH_2Cl_2



Scheme 3. Reagents: (a) 190 °C, 72 h; (b) BnOH, BOP/DIEA, DMF; (c) polymer-NH_2; BOP/DIEA, DMF; (d) acryloyl chloride, NEt_3, CH_2Cl_2

A second NMR spectroscopic study, at room temperature in CD_2Cl_2, of the acrylates **14**, **15a** and **16** alone or in the presence of $TiCl_4$ was realized. In each case a large downfield shift of the ^{13}C NMR resonance of the acryloyl and lactam carbonyl carbons was observed in the Lewis acid coordinated-acrylate, indicating a favourable complexation for the Diels−Alder reaction (Table 3).

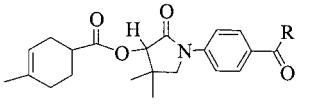
No cycloadduct was isolated from the reaction of the acrylate ester **14** with isoprene (2.0 equiv.) in the presence of 0.5 equivalents of $TiCl_4$ in a temperature range from −20 °C to 10 °C for 16 h, (Table 1, Entry 6). No improvement was observed under more drastic conditions — 1−2 equivalents of $TiCl_4$, 2−4 equivalents of diene, longer reaction

Table 3. ^{13}C NMR chemical shifts of free and $TiCl_4$-complexed substrates (0.5 equiv. $TiCl_4$)

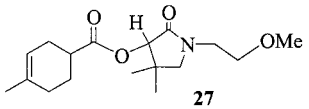
Carbon atoms	**14** δ (ppm)	**14**-$TiCl_4$ δ (ppm)	**15a** δ (ppm)	**15a**-$TiCl_4$ δ (ppm)	**16** δ (ppm)	**16**-$TiCl_4$ δ (ppm)
$-O-CO-C_2H_3$	165.6	172.6	165.5	174.8	165.6	173.1
$-CO-OR$	173.6	174.0	166.0	164.5	–	–
$-CO-N(R')-$	169.5	177.6	169.7	171.1	169.7	174.1
$-CH=CH_2$	131.9	141.6	132.5	142.6	131.9	141.0
$-CH=CH_2$	128.2	125.3	127.9	124.3	128.2	125.8

time (24−70 h) and different temperatures (Table 1, Entry 6).

Reaction of acrylates **15a** and **16** with isoprene (2.0 equiv.) in the presence of one equivalent of $TiCl_4$ at a temperature between −20 and 0 °C gave the desired compound, which consisted only of the corresponding *para* adducts **26a** and **27** (Table 1, Entry 9 and 12), in 90% yield. The absence of the *meta* regioisomer was confirmed by ^{13}C NMR analysis of the methylcyclohex-3-enecarboxylic acid obtained after LiOH hydrolysis of each cycloadduct.



26a R = OBn **26b** R = NH_2



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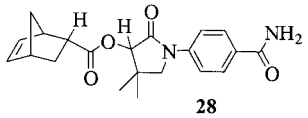
A possible explanation for the absence of reaction in the case of **14** could be the significance of the steric hindrance of the complexed molecule related to the nitrogen substituent and the Lewis acid. To complete this study we decided to test other Lewis acid catalysts [Et_2AlCl, $Zn(CF_3SO_3)_2$, $Sm(CF_3SO_3)_2$, $Sc(CF_3SO_3)_2$] with **14** and isoprene, but again no reaction occurred (Table 1, Entry 7 and 8).

Returning to the initial strategy, and considering the results obtained in solution with the acrylate **15a** (i.e. important yield and favourable $TiCl_4$ complexation), we decided to perform the solid-phase experiments using the supported acrylate **15b**. The supported acrylate **15b**, anchored on a Rink amide resin, was easily obtained, as described previously in the case of the acrylic ester **2**, by acryloyl chloride treatment of the corresponding supported alcohol **25b** (Scheme 3). As expected, using the optimized reaction conditions, the reaction of **15b** with six equivalents of isoprene or cyclopentadiene in the presence of 1.1 equivalents of $TiCl_4$ at 0 °C for 16 h yielded the *para*-compound **26b** (Table 1, Entry 10) and the *endo*-compound **28**, respectively, in good yield (Table 1, Entry 11) after removal from the resin by acidic cleavage of the benzhydrylamine bond. LiOH hydrolysis of these compounds afforded the expected racemic 4-methylcyclohex-3-enecarboxylic acid (**7**) or the racemic bicyclo[2,2,1]hept-5-ene-2-carboxylic acid (**29**).



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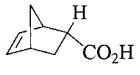

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Conclusions

In conclusion, several new acrylate compounds have been prepared starting from N-substituted 3-hydroxy-4,4-dimethyl-2-pyrrolidinones and tested as dienophiles in solution or solid-phase Diels−Alder reaction. We have demonstrated, by NMR spectroscopy, that the outcome of the Diels−Alder reaction is dependent on the pyrrolidinone structure. Good results, high yield and regio- or endoselectivity were obtained using the 4-(3-hydroxy-4,4-dimethyl-2-oxo-pyrrolidin-1-yl) benzoic acid derivatives in solution or solid phase Diels−Alder reaction. Studies are now in progress to convert this racemic compound into the corresponding enantiopure compound and to evaluate its possible use as a supported chiral auxiliary in the asymmetric Diels−Alder reaction.

Experimental Section

General Remarks: All reagents were used as purchased from commercial suppliers without further purification, except triethylamine, 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 (DEPT, HMQC, HMBC experiments) were recorded with a Bruker Advance 300 spectrometer or a Bruker A DRX 400 spectrometer using the solvent as internal reference. Data are reported as follows: chemical shifts (δ) in ppm, coupling constants (*J*) in Hz. The ESI mass spectra were recorded with a platform II quadrupole mass spectrometer (Micromass, Manchester, UK) fitted with an electrospray source. HPLC analysis were performed with a Waters model 510 instrument with variable detector at 214 nm using a reversed-phase Nucleosil C_{18} column, 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).

(±)-(3-Hydroxy-4,4-dimethyl-2-oxopyrrolidin-1-yl)acetic Acid (3): Racemic *tert*-butyl (3-hydroxy-4,4-dimethyl-2-oxopyrrolidin-1-yl)acetate (2 g, 8 mmol), obtained in 71% yield as described previously[13a], was treated with TFA (30 mL) in CH_2Cl_2 (140 mL). After standing for 1 h at room temperature, the volatile products were evaporated under reduced pressure and co-evaporated with cyclohexane and diethyl ether to afford the expected racemic compound **3** as a white solid (1.45 g, 100% yield). m.p. 168.5 °C; HPLC, NMR and MS (ESI) physical data are identical to those of the optically pure compounds.[13a]

Preparation of the Supported (±)-(3-Hydroxy-4,4-dimethyl-2-oxopyrrolidin-1-yl)acetic Acid (±)-1: 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 the alcohol **3** (0.28 g, 1.5 mmol, 1.5 equiv.), BOP (0.73 g, 1.65 mmol, 1.65 equiv.) and DIEA (0.31 mL, 1.8 mmol, 1.8 equiv.) in DMF (15 mL) was added to the resin. The suspension was stirred at room temperature for 12 h and the solution was 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 × 15 mL), CH_2Cl_2 (3 × 15 mL) and diethyl ether (3 × 15 mL), and then dried under reduced pressure. Reaction was monitored by the ninhydrin test.

General Procedure for the Preparation of Compounds 20 and 21: Racemic 3-benzyloxy-4,4-dimethylpyrrolidin-2-one (**19**) was obtained in 75% yield (two steps) starting from the commercially available pantolactone as described previously.[13a] Sodium hydride

(614 mg, 15.3 mmol, 60% in paraffin, 1.7 equiv.) was slowly added at 0 °C to a solution of racemic 3-benzyloxy-4,4-dimethylpyrrolidin-2-one (1.97 g, 9.0 mmol) in 100 mL of dry DMF under argon. After 15 min stirring at room temperature, ethyl 6-bromohexanoate or 2-bromoethyl methyl ether (9.9 mmol, 1.10 equiv.) was added dropwise and stirring was continued for 12 h at the same temperature until TLC indicated complete consumption of the starting material. The reaction mixture was then neutralized with 1 N HCl and the DMF was concentrated in vacuo. The residue was diluted with a 1 N HCl solution (100 mL) and was extracted with ethyl acetate (2 × 100 mL). The combined organic layers were dried with anhydrous sodium sulfate and concentrated in vacuo.

(±)-Ethyl 6-(3-Benzyloxy-4,4-dimethyl-2-oxopyrrolidin-1-yl)hexanoate (20): Synthesised following the general procedure from benzyloxy-4,4-dimethylpyrrolidin-2-one (1.97 g, 9.0 mmol) and ethyl 6-bromohexanoate (1.5 mL, 9.9 mmol, 1.10 equiv.). Pure **20** was obtained as a colourless oil (2.27 g, 6.3 mmol, 70%) after column chromatography on silica gel, eluting with hexane/ethyl acetate (6:4); t_R (HPLC) = 12.03 min. IR (CH_2Cl_2): $\tilde{\nu}$ = 3054 (m), 2934 (m), 2866 (m), 1728 (s), 1693 (s), 1269 (s) cm^{-1}. MS (ESI): *m*/*z* = 362.2 $[M + H]^+$, 723.8. ^1H NMR ($CDCl_3$): δ = 1.09 (s, 3 H, CH_3), 1.10 (s, 3 H, CH_3), 1.25 (t, *J* = 7.1 Hz, 3 H, CH_3CH$_2$O), 1.33 (m, 2 H, CH_2), 1.51 (m, 2 H, CH_2), 1.65 (m, 2 H, CH_2), 2.29 (t, *J* = 7.4 Hz, 2 H, CH_2CO), 2.95 (d, *J* = 9.5 Hz, 1 H, NCH_AH$_B$), 3.05 (d, *J* = 9.5 Hz, 1 H, NCH$_A$$H_B$), 3.25 (m, 2 H, C$H_2$N), 3.60 (s, 1 H, CMe$_2$C*H*), 4.11 (q, *J* = 7.1 Hz, 2 H, CH$_3$CH_2O), 4.78 (d, *J* = 12.2 Hz, 1 H, OHC*H*C$_6$H$_5$), 5.05 (d, *J* = 12.2 Hz, 1 H, OHC*H*C$_6$H$_5$), 7.34 (m, 5 H, *H*-arom.) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.6 (*C*H$_3$CH$_2$O), 21.2 (*C*H$_3$), 25.0 (*C*H$_2$), 25.8 (*C*H$_3$), 26.7 (*C*H$_2$), 27.2 (*C*H$_2$), 34.5 (*C*H$_2$CO), 38.2 (*C*Me$_2$), 42.6 (*C*H$_2$N), 57.6 (N*C*H$_A$H$_B$), 60.6 (CH$_3$*C*H$_2$O), 72.8 (O*C*H$_2$C$_6$H$_5$), 84.0 (CMe$_2$*C*H), 127.9 (*C*H-arom.), 128.2 (*C*H-arom.), 128.7 (*C*H-arom.), 138.8 (*C*-arom.), 173.2 (*C*O), 173.9 (*C*O) ppm. HRMS (FAB) calcd. for $C_{21}H_{32}NO_4$ $[MH^+]$ 362.2331, found 362.2327.

(±)-3-Benzyloxy-1-(2-methoxyethyl)-4,4-dimethylpyrrolidin-2-one (21): Synthesised following the general procedure from benzyloxy-4,4-dimethylpyrrolidin-2-one (1.97 g, 9.0 mmol) and 2-bromoethyl methyl ether (0.93 mL, 9.9 mmol, 1.1 equiv.). Pure **21** was obtained as a colourless oil (2.17 g, 7.8 mmol, 87%) after column chromatography on silica gel, eluting with hexane/ethyl acetate (5:5); t_R (HPLC) = 10.08 min. IR (CH_2Cl_2): $\tilde{\nu}$ = 2929 (m), 1695 (s), 1119 (m) cm^{-1}. MS (ESI): *m*/*z* = 278.1 $[M + H]^+$, 555.2. ^1H NMR ($CDCl_3$): δ = 1.09 (s, 3 H, CH_3), 1.10 (s, 3 H, CH_3), 3.10 (d, *J* = 9.6 Hz, 1 H, NCH_AH$_B$), 3.16 (d, *J* = 9.6 Hz, 1 H, NCH$_A$$H_B$), 3.33 (s, 3 H, C$H_3$O), 3.46 (m, 4 H, C$H_2$N and C$H_2$O), 3.65 (s, 1 H, CMe$_2$C*H*), 4.79 (d, *J* = 12.2 Hz, 1 H, OHC*H*C$_6$H$_5$), 5.07 (d, *J* = 12.2 Hz, 1 H, OHC*H*C$_6$H$_5$), 7.33 (m, 5 H, H-arom.). ppm. ^{13}C NMR ($CDCl_3$): δ = 20.7 (*C*H$_3$), 25.2 (*C*H$_3$), 38.1 (*C*Me$_2$), 42.4 (*C*H$_2$N), 58.5 (N*C*H$_A$H$_B$), 58.7 (*C*H$_3$O), 70.7 (*C*H$_2$O), 72.5 (O*C*H$_2$C$_6$H$_5$), 83.5 (CMe$_2$*C*H), 127.6 (*C*H-arom.), 127.8 (*C*H-arom.), 128.3 (*C*H-arom.), 138.3 (*C*-arom.), 173.1 (*C*ON) ppm. HRMS (FAB) calcd. for $C_{16}H_{24}NO_3$ $[MH^+]$ 278.1756, found 278.1768.

(±)-Ethyl 6-(3-Hydroxy-4,4-dimethyl-2-oxopyrrolidin-1-yl)hexanoate (22): A solution of (±)-ethyl 6-(3-benzyloxy-4,4-dimethyl-2-oxopyrrolidin-1-yl)hexanoate (**20**, 2.06 g, 5.7 mmol) in ethyl acetate (35 mL) was added to a cooled solution (−20 °C) of 20% palladium hydroxide on charcoal in ethyl acetate (35 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 the expected compound **22** as a colourless oil (1.54 g, 5.7 mmol, 100%); t_R (HPLC) = 8.54 min. IR (CH_2Cl_2): $\tilde{\nu}$ = 3332 (br), 3055 (w), 2933 (m), 2866 (m), 1727 (s), 1682 (s), cm^{-1}. MS (ESI): *m*/*z* = 272.1 $[M + H]^+$, 543.4, 565.5. ^1H NMR ($CDCl_3$): δ = 0.86 (s, 3 H, CH_3), 1.03 (s, 3 H, CH_3), 1.08 (t, *J* = 7.1 Hz, 3 H, CH_3CH$_2$O), 1.15 (m, 2 H, CH_2), 1.35 (m, 2 H, CH_2), 1.47 (m, 2 H, CH_2), 2.12 (t, *J* = 7.4 Hz, 2 H, CH_2CO), 2.82 (d, *J* = 9.6 Hz, 1 H, NCH_AH$_B$), 2.90 (d, *J* = 9.6 Hz, 1 H, NCH$_A$$H_B$), 3.09 (t, *J* = 7.2 Hz, 2 H, CH_2N), 3.82 (s, 1 H, CMe$_2$C*H*), 3.94 (q, *J* = 7.1 Hz, 2 H, CH$_3$CH_2O), 5.02 (br., 1 H, OH) ppm. ^{13}C NMR ($CDCl_3$): δ = 12.7 (*C*H$_3$CH$_2$O), 18.8 (*C*H$_3$), 23.0 (*C*H$_2$), 23.4 (*C*H$_3$), 24.7 (*C*H$_2$), 25.2 (*C*H$_2$), 32.6 (*C*H$_2$CO), 36.9 (*C*Me$_2$), 41.0 (*C*H$_2$N), 55.6 (N*C*H$_A$H$_B$), 58.7 (CH$_3$*C*H$_2$O), 76.2 (CMe$_2$*C*H), 172.0 (*C*O), 173.5 (*C*O) ppm. HRMS (FAB) calcd. for $C_{14}H_{26}NO_4$ (MH^+) 272.1862, found 272.1857.

(±)-3-Hydroxy-1-(2-methoxyethyl)-4,4-dimethylpyrrolidin-2-one (23): A solution of (±)-3-benzyloxy-1-(2-methoxyethyl)-4,4-dimethylpyrrolidin-2-one **21** (1.53 g, 5.5 mmol) in ethyl acetate (25 mL) was added to a cooled solution (−20 °C) of 20% palladium hydroxide on charcoal in ethyl acetate (25 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 the expected compound **23** as a colourless oil (1.03 g, 5.5 mmol, 100%); t_R (HPLC) = 5.46 min. IR (CH_2Cl_2): $\tilde{\nu}$ = 3349 (br), 2960 (s), 2871 (s), 1686 (s), 1458 (s), 1119 (m) cm^{-1}. MS (ESI): *m*/*z* = 188.0 $[M + H]^+$, 375.2. ^1H NMR ($CDCl_3$): δ = 0.97 (s, 3 H, CH_3), 1.14 (s, 3 H, CH_3), 3.04 (d, *J* = 9.7 Hz, 1 H, NCH_AH$_B$), 3.13 (d, *J* = 9.7 Hz, 1 H, NCH$_A$$H_B$), 3.26 (s, 3 H, C$H_3$O), 3.39 (m, 4 H, C$H_2$N and C$H_2$O), 3.94 (s, 1 H, CMe$_2$C*H*), 4.74 (br., 1 H, OH) ppm. ^{13}C NMR ($CDCl_3$): δ = 18.3 (*C*H$_3$), 22.9 (*C*H$_3$), 37.1 (*C*Me$_2$), 40.8 (*C*H$_2$N), 56.6 (N*C*H$_A$H$_B$), 56.8 (*C*H$_3$O), 68.7 (*C*H$_2$O), 76.1 (CMe$_2$*C*H), 173.3 (*C*ON) ppm. HRMS (FAB) calcd. for $C_9H_{18}NO_3$ $[MH^+]$ 188.1287, found 188.1290.

(±)-4-(3-Hydroxy-4,4-dimethyl-2-oxo-pyrrolidin-1-yl)benzoic Acid 24:[20] Commercially available pantolactone (25 g, 192.0 mmol, 2.9 equiv.) was melted at 190 °C and then sodium 4-aminobenzoate (10.5 g, 65.9 mmol) was added in one go. The mixture was vigorously stirred for 72 h at the same temperature. The temperature was then reduced to 80 °C and the reaction mixture was dissolved by addition of ethyl acetate (200 mL), water (200 mL) and saturated $NaHCO_3$ (100 mL). The combined aqueous phase was washed with ethyl acetate (2 × 200 mL), acidified to pH 1 with concentrated HCl and then extracted with ethyl acetate (2 × 500 mL). The combined organic layers were dried with anhydrous sodium sulfate and concentrated in vacuo. The expected compound **24** was precipitated by addition of CH_2Cl_2, isolated by filtration and washed successively with CH_2Cl_2 and diethyl ether (7.37 g; 29.6 mmol, 45%): m.p. 222−223 °C; t_R (HPLC) = 7.64 min. IR (KBr): $\tilde{\nu}$ = 3438 (m), 2964−2667 (br), 1680 (s), 1606 (m) cm^{-1}. MS (ESI): *m*/*z* = 250.2 $[M + H]^+$, 499.1. ^1H NMR ([D$_6$]DMSO): δ = 0.94 (s, 3 H, CH_3), 1.18 (s, 3 H, CH_3), 3.49 (d, *J* = 9.6 Hz, 1 H, NCH_AH$_B$), 3.55 (d, *J* = 9.6 Hz, 1 H, NCH$_A$$H_B$), 4.03 (s, 1 H, CMe$_2$C*H*), 5.82 (br., 1 H, OH), 7.80 (d, *J* = 8.9 Hz, 2 H, *H*-arom.), 7.95 (d, *J* = 8.9 Hz, 2 H, *H*-arom.). ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 20.0 (*C*H$_3$), 23.9 (*C*H$_3$), 37.1 (*C*Me$_2$), 56.0 (N*C*H$_A$H$_B$), 77.4 (CMe$_2$*C*H), 118.0 (*C*H-arom.), 125.5 (*C*-arom.), 130.2 (*C*H-arom.), 143.4 (*C*-arom.), 166.8 (*C*O), 174.1 (*C*O) ppm. HRMS (FAB) calcd. for $C_{13}H_{16}NO_4$ $[MH^+]$ 250.1079, found 250.1081.

(±)-Benzyl 4-(3-Hydroxy-4,4-dimethyl-2-oxopyrrolidin-1-yl)benzoate (25a): 2.2 Equivalents of diisopropylethylamine (2.51 mL, 14.4 mmol) and 2.0 equivalents of BOP (5.80g, 13.1 mmol) were added to (±)-4-(3-hydroxy-4,4-dimethyl-2-oxopyrrolidin-1-yl) benzoic

acid **24** (1.63 g, 6.5 mmol) in dry DMF (20 mL). After 15 min stirring at room temperature, benzyl alcohol (1.36 mL, 13.1 mmol, 2 equiv.) was added dropwise and stirring was continued for 5 h at the same temperature. The DMF solution was concentrated in vacuo, the mixture diluted with ethyl acetate (200 mL) and then successively washed with a saturated aqueous $NaHCO_3$ solution (200 mL), a 1 M $KHSO_4$ solution (200 mL) and water (200 mL). The organic layer was dried with anhydrous Na_2SO_4 and concentrated in vacuo. Column chromatography on silica gel, eluting with hexane/ethyl acetate/CH_2Cl_2 (5:4:1), yielded the pure compound **25a** as a white solid (1.98 g, 5.8 mmol, 90%); m.p. 108.4 °C; t_R (HPLC) = 10.97 min. IR (KBr): $\tilde{\nu}$ = 2964 (s), 2879 (s), 1790 (s), 1719 (s) 1269 (s) cm^{-1}. MS (ESI): *m*/*z* = 340.0 $[M + H]^+$, 679.3. ^1H NMR ($CDCl_3$): δ = 1.01 (s, 3 H, CH_3), 1.24 (s, 3 H, CH_3), 3.40 (d, *J* = 9.6 Hz, 1 H, NCH_AH_B), 3.46 (d, *J* = 9.6 Hz, 1 H, NCH_AH_B), 3.80 (br., 1 H, OH), 4.07 (s, 1 H, CMe_2CH), 5.27 (s, 2 H, $OCH_2C_6H_5$), 7.3 (m, 5 H, *H*-arom.), 7.63 (d, *J* = 11.2 Hz, 2 H, *H*-arom.), 7.99 (d, *J* = 11.2 Hz, 2 H, *H*-arom.). ppm. ^{13}C NMR ($CDCl_3$): δ = 20.1 (CH_3), 24.6 (CH_3), 38.3 (CMe_2), 57.5 (NCH_AH_B), 66.8 ($OCH_2C_6H_5$), 78.5 (CMe_2CH), 118.5 (*C*H-arom.), 126.0 (*C*-arom.), 128.2 (*C*H-arom.), 128.3 (*C*H-arom.), 128.7 (*C*H-arom.), 130.8 (*C*H-arom.), 136.1 (*C*-arom.), 143.2 (*C*-arom.), 165.9 (*C*O), 174.8 (*C*O) ppm. HRMS (FAB) calcd. for $C_{20}H_{22}NO_4$ $[MH^+]$ 340.1549, found 340.1555.

Preparation of the Supported (±)-4-(3-Hydroxy-4,4-dimethyl-2-oxopyrrolidin-1-yl)benzoic Acid (25b): 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 the alcohol **24** (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 was 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 × 15 mL), CH_2Cl_2 (3 × 15 mL) and diethyl ether (3 × 15 mL), and then dried under reduced pressure. The reaction was monitored by the ninhydrin test.

Polymer-Bound Acrylates (±)-2 and 15b: Triethylamine (1.2 mL, 8.5 mmol, 8.5 equiv.) and then acryloyl chloride (0.4 mL, 5.0 mmol, 5 equiv.) were added dropwise to the stirred and swollen resin (±)-**1** or **25b** (1.0 mmol) in anhydrous CH_2Cl_2 (15 mL) at room temperature. The suspension was stirred for 4−5 h at the same temperature and the solution was 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), the expected resin (±)-**2** or **15b** was dried under reduced pressure.

General Procedure for the Preparation of the Acrylates 9b, 13, 14, 15a, 16: Acryloyl chloride (4.92 mmol, 1.2 equiv.) was added dropwise to a mixture of the racemic pyrrolidinone derivative (4.1 mmol) and triethylamine (8.2 mmol, 2 equiv.) in anhydrous CH_2Cl_2 (10 mL) at −20 °C. After 2 h at this temperature the mixture was washed with a 1 N HCl solution (2 × 10 mL) and saturated aqueous $NaHCO_3$ (2 × 10 mL). The organic layer was dried with anhydrous Na_2SO_4 and concentrated in vacuo. Column chromatography of the residue on silica gel yielded the pure acrylate derivative.

(±)-1,4,4-Trimethyl-2-oxopyrrolin-3-yl Acrylate 9b: (±)-3-Hydroxy-1,4,4-trimethyl-2-pyrrolidinone was obtained in 80% yield by reaction of the commercially available pantolactone and methylamine according to the method described by Ryan et al,[21] m.p. 70−72 °C; t_R (HPLC) = 3.30 min. IR (KBr): $\tilde{\nu}$ = 3300−2600 (br), 1966 (m), 1712 (s), 1456 (m) cm^{-1}. MS (ESI): *m*/*z* = 144.1 $[M + H]^+$, 287.0. ^1H NMR ($CDCl_3$): δ = 0.97 (s, 3 H, CH_3), 1.13 (s, 3 H, CH_3), 2.78 (s, 3 H, NCH_3), 2.91 (d, *J* = 9.7 Hz, 1 H, NCH_AH_B), 3.03 (d, *J* = 9.7 Hz, 1 H, NCH_AH_B), 4.08 (s, 1 H, CMe_2CH), 4.89 (br. s, 1 H, OH) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.6 (CH_3), 25.4 (CH_3), 30.4 (NCH_3), 38.8 (CMe_2), 59.9 (NCH_AH_B), 78.1 (CMe_2CH), 175.5 (*C*O) ppm. Following the general procedure, compound **9b** was obtained as a white solid from (±)-3-hydroxy-1,4,4-trimethyl-2-pyrrolidinone (0.58 g, 4.1 mmol) after column chromatography on silica gel, eluting with ethyl acetate/hexane (8:2) (0.53 g, 2.66 mmol, 65%); m.p. 58.6 °C; t_R (HPLC) = 7.36 min. IR (CH_2Cl_2): $\tilde{\nu}$ = 2967 (w), 2873 (w), 1732 (s), 1707 (s), cm^{-1}. MS (ESI): *m*/*z* = 197.9 $[M + H]^+$, 395.1. ^1H NMR (CD_2Cl_2): δ = 1.06 (s, 3 H, CH_3), 1.22 (s, 3 H, CH_3), 2.85 (s, 3 H, NCH_3), 3.06 (d, *J* = 9.6 Hz, 1 H, NCH_AH_B), 3.18 (d, *J* = 9.6 Hz, 1 H, NCH_AH_B), 5.24 (s, 1 H, CMe_2CH), 5.93 (dd, *J* = 1.5 and *J* = 10.4 Hz, 1 H, HC*H*=), 6.22 (dd, *J* = 10.4 and *J* = 17.3 Hz, 1 H, C*H*=), 6.48 (dd, *J* = 1.5 and *J* = 17.3 Hz, 1 H, HC*H*=) ppm. ^{13}C NMR (CD_2Cl_2): δ = 21.5 (CH_3), 25.4 (CH_3), 30.1 (NCH_3), 37.8 (CMe_2), 59.6 (NCH_AH_B), 78.2 (CMe_2CH), 128.1 (*C*H=), 131.9 (CH_2=), 165.6 ($COCH{=}CH_2$), 169.6 ($CONCH_3$) ppm. HRMS (FAB) calcd. for $C_{10}H_{16}NO_3$ $[MH^+]$ 198.1130, found 198.1132.

(±)-(1-*tert*-Butoxycarbonylmethyl-4,4-dimethyl-2-oxopyrrolidin-3-yl) Acrylate (13): Racemic *tert*-butyl (3-hydroxy-4,4-dimethyl-2-oxopyrrolidin-1-yl)acetate was obtained in 71% yield as described previously.[13a] Following the general procedure, compound **13** was obtained as a colourless oil from racemic *tert*-butyl (3-hydroxy-4,4-dimethyl-2-oxopyrrolidin-1-yl)acetate (0.99 g, 4.1 mmol) after column chromatography on silica gel, eluting with ethyl acetate/hexane (8:2) (0.91 g, 3.1 mmol, 75%); t_R (HPLC) = 10.39 min. IR (CH_2Cl_2): $\tilde{\nu}$ = 3054 (m), 2984 (m), 1738 (s), 1713 (s), 1264 (s) cm^{-1}. MS (ESI): *m*/*z* = 242.0, 297.9 $[M + H]^+$, 595.2. ^1H NMR (CD_2Cl_2): δ = 1.12 (s, 3 H, CH_3), 1.23 (s, 3 H, CH_3), 1.48 [s, 9 H, $OC(CH_3)_3$], 3.15 (d, *J* = 9.3 Hz, 1 H, NCH_AH_B), 3.29 (d, *J* = 9.3 Hz, 1 H, NCH_AH_B), 3.93 (s, 2 H, $N{-}CH_2{-}CO$), 5.30 (s, 1 H, CMe_2CH), 5.93 (dd, *J* = 1.5 Hz and *J* = 10.4 Hz, 1 H, HC*H*=), 6.22 (dd, *J* = 10.4 and *J* = 17.3 Hz, 1 H, C*H*=), 6.48 (dd, *J* = 1.5 and *J* = 17.3 Hz, 1 H, HC*H*=) ppm. ^{13}C NMR (CD_2Cl_2): δ = 21.3 (CH_3), 25.2 (CH_3), 28.3 [$OC(CH_3)_3$], 38.2 (CMe_2), 45.2 ($N{-}CH_2{-}CO$), 57.9 (NCH_AH_B), 77.8 (CMe_2CH), 82.4 [$OC(CH_3)_3$], 128.1 (*C*H=), 132.1 (CH_2=), 165.5 ($COCH{=}CH_2$), 167.7 (CO_2tBu), 170.2 (*C*ON) ppm. HRMS (FAB) calcd. for $C_{15}H_{24}NO_5$ $[MH^+]$ 298.1654, found 298.1650.

(±)-[1-(5-Ethoxycarbonylpentyl)-4,4-dimethyl-2-oxopyrrolidin-3-yl] Acrylate (14): Following the general procedure, compound **14** was obtained as a colourless oil from (±)-ethyl 6-(3-hydroxy-4,4-dimethyl-2-oxopyrrolidin-1-yl)hexanoate (**22**, 1.11 g, 4.1 mmol) after column chromatography on silica gel, eluting with ethyl acetate/hexane (6:4) (1.17 g, 3.6 mmol, 88%); t_R (HPLC) = 10.38 min. IR (CH_2Cl_2): $\tilde{\nu}$ = 2934 (m), 2866 (m), 1729 (s), 1703 (s), 1184 (s) cm^{-1}. MS (ESI): *m*/*z* = 326.1 $[M + H]^+$, 651.4. ^1H NMR (CD_2Cl_2): δ = 1.02 (s, 3 H, CH_3), 1.19 (s, 3 H, CH_3), 1.21 (t, *J* = 7.1 Hz, 3 H, CH_3CH_2O), 1.28 (m, 2 H, CH_2), 1.48 (m, 2 H, CH_2), 1.59 (m, 2 H, CH_2), 2.25 (t, *J* = 7.4 Hz, 2 H, CH_2CO), 3.02 (d, *J* = 9.6 Hz, 1 H, NCH_AH_B), 3.13 (d, *J* = 9.6 Hz, 1 H, NCH_AH_B), 3.22 (t, *J* = 7.1 Hz, 2 H, CH_2N), 4.05 (q, *J* = 7.1 Hz, 2 H, CH_3CH_2O), 5.21 (s, 1 H, CMe_2CH), 5.88 (dd, *J* = 1.5 and *J* = 10.3 Hz, 1 H, HC*H*=), 6.17 (dd, *J* = 10.3 and *J* = 17.6 Hz, 1 H, C*H*=), 6.42 (dd, *J* = 1.5 and *J* = 17.6 Hz, 1 H, HC*H*=) ppm. ^{13}C NMR (CD_2Cl_2): δ = 14.4 (CH_3CH_2O), 21.4 (CH_3), 24.9 (CH_2), 25.3 (CH_3), 26.6 (CH_2), 27.1 (CH_2), 34.4 (CH_2CO), 38.0 (CMe_2), 42.8 (CH_2N), 57.2 (NCH_AH_B), 60.4 (CH_3CH_2O), 78.4 (CMe_2CH), 128.2 (*C*H=),

131.9 (CH_2=), 165.6 (COCH=CH_2), 169.5 (CON), 173.6 ($CO_2C_2H_5$) ppm. HRMS (FAB) calcd. for $C_{17}H_{28}NO_5$ [MH^+] 326.1967, found 326.1964.

(±)-Benzyl 4-(3-Acryloyloxy-4,4-dimethyl-2-oxopyrrolidin-1-yl)benzoate (15a): Following the general procedure, compound **15a** was obtained as a colourless oil from (±)-benzyl 4-(3-hydroxy-4,4-dimethyl-2-oxopyrrolidin-1-yl)benzoate (**25a**, 1.39 g, 4.1 mmol) after column chromatography on silica gel, eluting with acetone/hexane (3:7) (1.32 g, 3.36 mmol, 82%); t_R (HPLC) = 13.01 min. IR (CH_2Cl_2): $\tilde{\nu}$ = 2928 (w), 1716 (s), 1606 (m), 1181 (s) cm^{-1}. MS (ESI): m/z = 394.3 [M + H]$^+$, 787.3. ^{1}H NMR (CD_2Cl_2): δ = 1.22 (s, 3 H, CH_3), 1.36 (s, 3 H, CH_3), 3.61 (d, J = 9.6 Hz, 1 H, NCH_AH$_B$), 3.67 (d, J = 9.6 Hz, 1 H, NCH$_A$$H_B$), 5.42 (s, 2 H, C$H_2$−$C_6H_5$), 5.56 (s, 1 H, CMe$_2CH$), 6.02 (d, J = 10.6 Hz, 1 H, HCH=), 6.34 (dd, J = 10.6 and J = 17.3 Hz, 1 H, CH=), 6.60 (d, J = 17.3 Hz, 1 H, HCH=), 7.46 (m, 5 H, H-arom.), 7.83 (d, J = 8.7 Hz, 2 H, H-arom.), 8.16 (d, J = 8.7 Hz, 2 H, H-arom.) ppm. ^{13}C NMR (CD_2Cl_2): δ = 21.3 (CH_3), 24.8 (CH_3), 37.6 (CMe$_2$), 57.6 (NCH$_A$H$_B$), 66.9 (OCH$_2$C$_6$H$_5$), 78.5 (CMe$_2$$C$H), 118.8 ($C$H-arom.), 126.3 ($C$-arom.), 127.9 ($C$H=), 128.5 ($C$H-arom.), 129.0 ($C$H-arom.), 130.9 ($C$H-arom.), 132.5 ($CH_2$=), 136.8 ($C$-arom.), 143.7 ($C$-arom.), 165.5 ($C$OCH=$CH_2$), 166.0 ($C$OOCH$_2C_6H_5$), 169.7 ($C$ON) ppm. HRMS (FAB) calcd. for $C_{23}H_{24}NO_5$ [MH^+] 394.1654, found 394.1639.

(±)-[1-(2-Methoxyethyl)-4,4-dimethyl-2-oxopyrrolidin-3-yl] Acrylate (16): Following the general procedure, compound **16** was obtained as a colourless oil from (±)-3-hydroxy-1-(2-methoxyethyl)-4,4-dimethylpyrrolidin-2-one (**23**, 0.76 g, 4.1 mmol) after column chromatography on silica gel, eluting with ethyl acetate (0.51 g, 2.1 mmol, 52%); t_R (HPLC) = 7.99 min. IR (CH_2Cl_2): $\tilde{\nu}$ = 3054 (w), 2984 (w), 2875 (w), 1731 (s), 1704 (s), 1266 (s) cm^{-1}. MS (ESI): m/z = 242.0 [M + H]$^+$, 483.3. ^{1}H NMR (CD_2Cl_2): δ = 1.08 (s, 3 H, CH_3), 1.21 (s, 3 H, CH_3), 3.17 (d, J = 9.7 Hz, 1 H, NCH_AH$_B$), 3.28 (d, J = 9.7 Hz, 1 H, NCH$_A$$H_B$), 3.34 (s, 3 H, C$H_3$O), 3.46 (m, 4 H, C$H_2$N and C$H_2$O), 5.29 (s, 1 H, CMe$_2CH$), 5.94 (dd, J = 1.4 and J = 10.4 Hz, 1 H, HCH=), 6.24 (dd, J = 10.4 and J = 17.3 Hz, 1 H, CH=), 6.48 (dd, J = 1.4 and J = 17.3 Hz, 1 H, HCH=) ppm. ^{13}C NMR (CD_2Cl_2): δ = 21.2 (CH_3), 25.1 (CH_3), 38.3 (CMe$_2$), 42.9 (CH$_2$N), 58.3 (NCH$_A$H$_B$), 58.8 (CH$_3$O), 70.6 (CH$_2$O), 78.3 (CMe$_2$$C$H), 128.2 ($C$H=), 131.9 ($CH_2$=), 165.6 ($C$OCH=$CH_2$), 169.7 ($C$ON) ppm. HRMS (FAB) calcd. for $C_{12}H_{20}NO_4$ [MH^+] 242.1392, found 242.1387.

General Procedure for Diels−Alder Reactions of the Acrylate Esters 9b, 13, 14, 15a, 16 with Isoprene: A 1 N solution of $TiCl_4$ (0.5 to 1 equiv.) in dry CH_2Cl_2 was added to the ester **9b, 13, 14, 15a** or **16** (0.6 mmol) in dry CH_2Cl_2 (10 mL) at the selected temperature (T_1, Table 1) under argon. The mixture was stirred at the same temperature for 20 min and then heated to the temperature T_2 (Table 1). A solution of isoprene (123 μL, 1.2 mmol, 2 equiv.) was added and the mixture was stirred for the specified time at the indicated temperature. Powdered Na_2CO_3·10H_2O was added to hydrolyse the $TiCl_4$ complexes, the mixture was filtered and the filtrate was concentrated in vacuo. The residue was then submitted to column chromatography on silica gel

(1,4,4-Trimethyl-2-oxopyrrolidin-3-yl) 4-Methylcyclohex-3-ene-1-carboxylate (12b): Synthesized following the general procedure from the dienophile **9b** (118 mg, 0.6 mmol) and isoprene. Compound **12b** was obtained as a white solid after column chromatography on silica gel, eluting with ethyl acetate/hexane (8:2) (119 mg, 0.45 mmol, 76%); m.p. 79.0 °C, t_R (HPLC) = 10.68 min. IR (CH_2Cl_2): $\tilde{\nu}$ = 3049 (w), 2965 (w), 1735 (s), 1706 (s), 1164 (m) cm^{-1}. MS (ESI): m/z = 265.9 [M + H]$^+$, 553.3. ^{1}H NMR ($CDCl_3$): δ = 0.96 (s, 3 H, CH_3), 1.12 (s, 3 H, CH_3), 1.57 (s, 3 H, CH_3), 1.71 (m, 1 H, HCH), 1.96 (m, 3 H, CH_2 and HCH), 2.20 (m, 2 H, CH_2), 2.58 (m, 1 H, CHCO), 2.80 (s, 3 H, NCH_3), 2.99 (d, J = 9.7 Hz, 1 H, NCH_AH$_B$), 3.10 (d, J = 9.7, 1 H, NCH$_A$$H_B$), 5.13 (s, 1 H, CMe$_2CH$), 5.30 (br. s, 1 H, C$H$=) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.3 ($CH_3$), 23.4 ($CH_3$), 25.2 ($CH_2$), 25.4 ($CH_3$), 27.8 ($CH_2$), 28.9 ($CH_2$), 30.0 (N$CH_3$), 37.4 ($C$HCO), 39.0 ($CMe_2$), 59.5 (N$CH_AH_B$), 77.3 (CMe$_2$$C$H), 118.9 ($C$H=), 133.9 (CH$_3$$C$=), 169.9 ($C$O), 175.2 ($C$O) ppm. HRMS (FAB) calcd. for $C_{15}H_{24}NO_3$ [MH^+] 266.1756, found 266.1753.

Benzyl 4-[4,4-Dimethyl-3-(4-methylcyclohex-3-enylcarbonyloxy)-2-oxopyrrolidin-1-yl]benzoate (26a): Synthesized following the general procedure from the dienophile **15a** (236 mg, 0.6 mmol) and isoprene. Compound **26a** was obtained as a white solid after column chromatography on silica gel, eluting with acetone/hexane (2:8) (249 mg, 0.54 mmol, 90%); m.p. 72−73 °C; t_R (HPLC) = 14.90 min. IR (CH_2Cl_2): $\tilde{\nu}$ = 3053 (m), 2933 (m), 1718 (s), 1268 (m) cm^{-1}. MS (ESI): m/z = 462.2 [M + H]$^+$, 923.1. ^{1}H NMR ([D$_6$]DMSO): δ = 1.03 (s, 3 H, CH_3), 1.19 (s, 3 H, CH_3), 1.64 (s, 3 H, CH_3), 1.70 (m, 2 H, CH_2), 1.97 (m, 2 H, CH_2), 2.23 (m, 2 H, CH_2), 2.66 (m, 1 H, CHCO), 3.59 (d, J = 9.6 Hz, 1 H, NCH_AH$_B$), 3.75 (d, J = 9.6 Hz, 1 H, NCH$_A$$H_B$), 5.34 (s, 2 H, OCH$_2C_6H_5$), 5.37 (br. s, 1 H, C$H$=), 5.52 (s, 1 H, CMe$_2CH$), 7.40 (m, 5 H, H-arom.), 7.81 (d, J = 8.8 Hz, 2 H, H-arom.), 8.02 (d, J = 8.8 Hz, 2 H, H-arom.) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 21.6 (CH_3), 24.2 (CH_3), 24.5 (CH_3), 25.8 (CH_2), 28.1 (CH_2), 29.2 (CH_2), 37.6 (CMe$_2$), 39.1 (CHCO), 57.1 (NCH$_A$H$_B$), 66.9 (OCH$_2$C$_6$H$_5$), 78.2 (CMe$_2$$C$H), 119.3 ($C$H-arom.), 119.8 ($C$H=), 125.7 ($C$-arom.), 128.8 ($C$H-arom.), 128.9 ($C$H-arom.), 129.4 ($C$H-arom.), 131.0 ($C$H-arom.), 134.2 (CH$_3$$C$=), 137.1 ($C$-arom.), 144.2 ($C$-arom.), 165.9 ($C$O), 170.3($C$O), 175.0 ($C$O) ppm. HRMS (FAB) calcd. for $C_{28}H_{32}NO_5$ [MH^+] 462.2280, found 462.2280.

[1-(2-Methoxyethyl)-4,4-dimethyl-2-oxopyrrolidin-3-yl] 4-Methylcyclohex-3-ene-1-carboxylate (27): Synthesized following the general procedure from the dienophile **16** (144 mg, 0.6 mmol) and isoprene. Compound **27** was obtained as a colourless oil after column chromatography on silica gel, eluting with hexane/ethyl acetate (4:6) (166 mg, 0.54 mmol, 90%); t_R (HPLC) = 11.00 min. IR (CH_2Cl_2): $\tilde{\nu}$ = 3054 (w), 2930 (m), 1738 (s), 1705 (s), 1166 (s) cm^{-1}. MS (ESI): m/z = 310.2 [M + H]$^+$, 619.2. ^{1}H NMR ($CDCl_3$): δ = 0.97 (s, 3 H, CH_3), 1.12 (s, 3 H, CH_3), 1.58 (s, 3 H, CH_3), 1.70 (m, 1 H, HCH), 1.97 (m, 3 H, CH_2 and HCH), 2.21 (m, 2 H, CH_2), 2.56 (m, 1 H, CHCO), 3.11 (d, J = 9.8 Hz, 1 H, NCH_AH$_B$), 3.22 (d, J = 9.8 Hz, 1 H, NCH$_A$$H_B$), 3.26 (s, 3 H, C$H_3$O), 3.30−3.50 (m, 4 H, C$H_2$N and C$H_2$O), 5.20 (s, 1 H, CMe$_2CH$), 5.30 (br. s, 1 H, C$H$=) ppm. ^{13}C NMR ($CDCl_3$): δ = 18.7 ($CH_3$), 21.0 ($CH_3$), 22.6 ($CH_3$), 22.8 ($CH_2$), 25.5 ($CH_2$), 26.6 ($CH_2$), 35.8 ($C$HCO), 36.7 ($CMe_2$), 40.4 ($CH_2$N), 56.2 (N$CH_AH_B$), 56.2 ($CH_3$O), 68.1 ($CH_2$O), 75.0 (CMe$_2$$C$H), 116.5 ($C$H=), 131.5 (CH$_3$$C$=), 168.1 ($C$O), 172.81 ($C$O) ppm. HRMS (FAB) calcd. for $C_{17}H_{28}NO_4$ [MH^+] 310.2018, found 310.2010.

General Procedure for Diels−Alder Reaction of the Supported Acrylate Esters with Isoprene or Cyclopentadiene and for Benzhydrylamine-Bond Hydrolysis: A 1 N solution of $TiCl_4$ (0.5 to 10 equiv.) in dry CH_2Cl_2 was added to the resin **15b** (0.6 mmol) swollen in dry CH_2Cl_2 (15 mL) at the selected temperature T_1 (Table 1) under argon. The suspension was stirred at the same temperature for 30 min and then cooled to the temperature T_2 (Table 1). A solution of isoprene (2−10 equiv.) was added and the suspension was stirred for the specified time at the indicated temperature. The solution was removed from the resin by filtration, the resin was 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 diethyl ether (3 × 15 mL), and then dried under reduced pressure. A solution of 5% TFA in dry CH_2Cl_2 (40 mL) was added to this resin swollen in dry CH_2Cl_2 and the suspension was stirred for 40 min. 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) and CH_2Cl_2 (3 × 15 mL). Evaporation of the combined solvents in vacuo afforded the expected compound.

(1-Carbamoylphenyl-4,4-dimethyl-2-oxopyrrolidin-3-yl) 4-Methylcyclohex-3-ene-1-carboxylate (26b): Synthesized following the general procedure from the resin **15b** (0.6 mmol) and isoprene (6 equiv.), $T_1 = T_2 = 0$ °C, reaction time: 16 h. The expected pure compound **26b** was obtained as a colourless solid after column chromatography on silica gel, eluting with ethyl acetate (177 mg, 0.48 mmol, 80%); m.p. 105 °C; t_R (HPLC) = 11.42 min. IR (KBr): $\tilde{\nu}$ = 3327−3219 (br), 2969 (s) 1742 (s), 1694 (s) cm^{-1}. MS (ESI): *m/z* = 371.1 $[M + H]^+$, 741.5. ^1H NMR ($CDCl_3$): δ = 1.05 and 1.06 (s, 3 H, CH_3), 1.20 and 1.21 (s, 3 H, CH_3), 1.57 and 1.59 (s, 3 H, CH_3), 1.71 (m, 1 H, HC*H*), 1.9−2.00 (m, 3 H, HC*H* and CH_2), 2.22 (m, 2 H, CH_2), 2.61 (m, 1 H, C*H*CO), 3.46 (d, *J* = 9.6 Hz, 1 H, NCH_AH_B), 3.57 (d, *J* = 9.6 Hz, 1 H, NCH$_A$$H_B$), 5.30 (C*H*=), 5.35 and 5.36 (s, 1 H, CMe$_2$C*H*), 7.61 (d, *J* = 8.5 Hz, 2 H, *H*-arom.), 7.81 (d, *J* = 8.5 Hz, 2 H, *H*-arom.) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.4 and 21.5 (*C*H_3), 23.8 and 23.9 (*C*H_3), 24.9 and 24.9 (*C*H_3), 25.7 and 26.0 (*C*H_2), 27.9 and 28.2 (*C*H_2), 29.3 and 29.5 (*C*H_2), 37.8 (*C*Me$_2$), 39.5 and 39.5 (*C*HCO), 57.9 (N*C*H$_A$H$_B$), 78.1 and 79.2 (CMe$_2$*C*H), 119.3 (*C*H-arom.), 119.2 and 119.4 (*C*H=), 128.0 (*C*-arom.), 129.3 (*C*H-arom.), 134.1 and 134.5 (CH$_3$*C*=), 143.0 (*C*-arom.), 170.6 and 170.7 (*C*O), 171.5 (*C*O), 175.6 and 175.8 (*C*O) ppm. HRMS (FAB) calcd. for $C_{21}H_{27}N_2O_4$ $[MH^+]$ 371.1971, found 371.1981.

[1-(4-Carbamoylphenyl)-4,4-dimethyl-2-oxopyrrolidin-3-yl] Bicyclo-[2.2.1]hept-5-ene-2-carboxylate (28): Synthesized following the general procedure from the resin **15b** (0.6 mmol) and cyclopentadiene (6 equiv.), $T_1 = T_2 = 0$ °C, reaction time: 16 h. The expected pure compound **28** (209 mg, 0.57 mmol, 95%), was obtained as a colourless solid; m.p. 132−134 °C; t_R (HPLC) = 10.4 min (95% *endo*), 10.78 (5% *exo*). IR (KBr): $\tilde{\nu}$ = 3404−3320 (br), 2975 (s) 1775 (s), 1695 (s) cm^{-1}. MS (ESI): *m/z* = 369.4 $[M + H]^+$, 737.5. ^1H NMR ($CDCl_3$): δ = 1.22 and 1.32 (s, 3 H, CH_3), 1.37 (m, 1 H, HC*H*), 1.53 (m, 2 H, *H*CH and HC*H*), 1.99 (ddd, *J* = 3.6, *J* = 9.1 and *J* = 12.5 Hz, 1 H, *H*CH), 2.98 (br. s, 1 H, C*H*), 3.21 (td, *J* = 9.1 and *J* = 3.9 Hz, 1 H, C*H*-1′), 3.31 (br. s, 1 H, C*H*), 3.6 (d, *J* = 9.6 Hz, 1 H, NCH_AH_B), 3.7 (d, *J* = 9.6 Hz, 1 H, NCH$_A$$H_B$), 5.45 (s, 1 H, CMe$_2$C*H*), 5.95 (dd, *J* = 2.7 and *J* = 5.6 Hz, 1 H, *H*C=), 6.3 (dd, *J* = 3.1 and *J* = 5.6 Hz, 1 H, *H*C=), 7.79 (d, *J* = 8.9 Hz, 2 H, *H*-arom.), 7.91 (d, *J* = 8.9 Hz, 2 H, *H*-arom.) ppm. ^{13}C NMR: ($CDCl_3$): δ = 21.3 and 24.6 (*C*H_3), 28.9 (*C*H_2), 37.6 (*C*Me$_2$), 42.5 (CH$_2$*C*H), 43.1 and 46.1 (*C*H) 49.9 (*C*H_2), 57.6 (N*C*H$_A$H$_B$), 77.7 (CMe$_2$*C*H), 119.2 (*C*H-arom.), 127.4 (*C*-arom.), 128.9 (*C*H-arom.), 131.5 and 138.7 (H*C*=), 142.8 (*C*-arom.), 170.8 (*C*O), 171.5 (*C*O), 174.2 (*C*O) ppm. HRMS (FAB) calcd. for $C_{21}H_{25}N_2O_4$ $[MH^+]$ 369.1814, found 369.1823.

General Procedure for the Hydrolysis of Compounds 12b, 26a, 26b, 27 and 28: A solution of $LiOH·H_2O$ (0.8 mmol, 2 equiv.) in water (1 mL) was added dropwise to a solution of the compound (0.4 mmol) in THF (5 mL) or DMF (6 mL) and the mixture was stirred at room temperature till completion of the hydrolysis (reaction monitored by HPLC). The organic solvent was then removed in vacuo, water (10 mL) and saturated aqueous $NaHCO_3$ (5 mL) were added and the mixture was extracted with CH_2Cl_2 (2 × 15 mL). The aqueous phase was acidified to pH 1 and was then extracted with a mixture of *n*-pentane and CH_2Cl_2 (98:2; 2 × 25 mL). The combined organic phases were dried with anhydrous Na_2SO_4 and concentrated in vacuo to give the expected acid.

(±)-4-Methylcyclohex-3-ene-1-carboxylic Acid (7): Following the general procedure the expected acid **7** (0.24−0.32 mmol, 60−80%) was obtained from the compound **12b**, **26a**, **26b** or **27** (0.4 mmol) in THF; t_R (HPLC) = 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$_2$H), 119.46 (*C*H=), 134.02 (CH$_3$*C*=), 183.26 (*C*O) ppm.

(±)-*endo*-Bicyclo[2.2.1]hept-5-ene-2-carboxylic Acid (29): Following the general procedure the expected acid **29** (0.23 mmol, 58%) was obtained from compound **28** (0.4 mmol) in DMF; t_R (HPLC) = 7.92 min (95% *endo*) and 8.54 min (5% *exo*). ^{13}C NMR ($CDCl_3$) (*endo*): δ = 29.5 (*C*H_2), 42.9 (*C*H), 43.6 (*C*H_2), 46.1 (*C*H), 50.1 (*C*H_2CH), 132.8 (*C*H=CH), 138.3 (CH=*C*H), 181.4 (*C*O) ppm.

(±)-4-Methylcyclohex-3-ene-1-carboxylic Acid (7) and (±)-3-Methyl Isomer: A mixture of (±)-3- and (±)-4-methylcyclohex-3-ene-1-carboxylic acids was obtained in 46% yield by reaction of isoprene and acrylic acid at 120 °C following the method described by Kuehne et al.[22] t_R (HPLC) = 9.23 min. ^{13}C NMR [$CDCl_3$ (±)-3-methylcyclohex-3-ene-1-carboxylic acid (minor product)]: δ = 23.8 (*C*H_3), 24.8 (*C*H_2), 25.0 (*C*H_2), 32.2 (*C*H_2), 40.1 (*C*HCO$_2$H), 121.0 (*C*H=), 132.4 (CH$_3$*C*=), 183.1 (*C*O) ppm.

NMR Spectroscopy of the Acrylate/$TiCl_4$ Complexes: A solution of $TiCl_4$ (100 μL, 0.2 mmol, 0.5 equiv.) in CD_2Cl_2 (1 mL) was added dropwise at room temperature and under argon to a stirred solution of the acrylate (0.4 mmol) in CD_2Cl_2 (1 mmol in 0.5 mL of CD_2Cl_2). After 5 min, the solution (0.6 mL) was transferred to a dry NMR tube and analysed by ^1H and ^{13}C NMR spectroscopy.

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