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The Use of 1-Amino-2-phenyl-1-cyclohexanecarboxylic Acids as Chiral Auxiliaries in Asymmetric Diels-Alder Reactions.

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Abstract: This report describes the behavior of four 1-amino-2-phenyl-1-cyclohexanecarboxylic acids, obtained in enantiomerically pure form starting from asymmetric Diels-Alder reactions between 1,3-butadiene and chiral (E)-2-cyanocinnamates, as chiral auxiliaries in the asymmetric Diels-Alder reactions of cyclopentadiene with chiral methyl N-acryloyl-1-amino-2-phenyl-1-cyclohexanecarboxylates. A model based on the formation of an intramolecular hydrogen bond accounts for the stereochemical outcome in the catalyzed reactions.

Interest in using amino acids as chiral auxiliaries in organic synthesis has notably increased in the last decade. Recent reviews demonstrate that amino acid derivatives behave as efficient chiral auxiliaries in a variety of organic reactions[1]. In this context, high levels of diastereoselectivity have been achieved in asymmetric Diels-Alder reactions of N-acryloyl-α-amino acids with several dienes when natural α-amino acids were used as chiral auxiliaries, in particular with L-proline[2]. In this case, the high diastereoselectivity observed could be explained by the models proposed by Helmchen[3] in the reactions of cyclopentadiene with acrylate of (S)-ethyl lactate catalyzed by $TiCl_4$ (a chelate complex dienophile-$TiCl_4$ with the acryloyl moiety in the syn conformation, in which a chlorine atom shields the *re* face of the dienophile) or $AlCl_3$ (a complex dienophile-$AlCl_3$ with an antiplanar enoate conformation, in which the ester group shields the *si* face of the double bond).

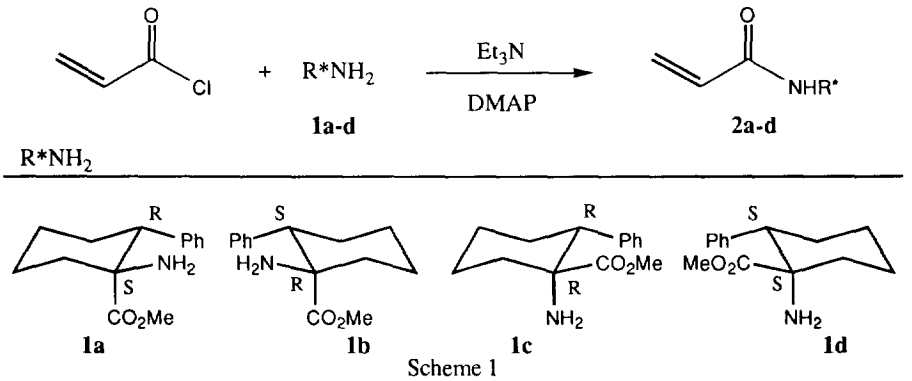
Nevertheless, when L-alanine or L-phenylalanine, both of which have a NH group, were used as chiral auxiliaries the reactions took place with moderate diastereoselectivities. The model proposed by us[2d] in explaining this behavior is founded on the preferential coordination of the Lewis acid ($TiCl_4$ or $AlCl_3$) with the amide group of the dienophile, which forces the formation of an intramolecular hydrogen bond that fixes the conformation of the amino acid, displaying the enoate moiety, in an antiplanar disposition. At this point, the methyl group (L-alanine) or the benzyl group (L-phenylalanine) shields the *re* face of the dienophile, favouring the diene attack on the *si* face.

In order to improve the results of the asymmetric Diels-Alder reactions when the α-amino acids used as chiral auxiliaries obey the behavior of the latter, we have decided to study the use of new synthetic α-amino acids, in particular conformationally constrained α,α-disubstituted-α-amino acids, as chiral auxiliaries, where

the presence of the substituents could prove definitive and responsible for the shielding of one face of the double bond.

We have recently reported the synthesis of all four 1-amino-2-phenyl-1-cyclohexanecarboxylic acids in enantiomerically pure form, starting from asymmetric Diels-Alder reactions of chiral (E)-2-cyanocinnamates[4] and now, we would like to report the results obtained when these constrained α-amino acids were used as chiral auxiliaries in the Diels-Alder reactions between chiral methyl N-acryloyl-1-amino-2-phenyl-1-cyclohexanecarboxylates and cyclopentadiene, taking into account that, if the model proposed is correct, the presence of the phenyl group, which must be placed in the equatorial position[5], should be responsible for the major diastereofacial selectivity showed in the stereoisomers in which the phenyl group and the double bond adopt a trans configuration (π-stacking).

The chiral dienophiles **2a-d** were prepared by condensation of the amino esters **1a-d**, prepared by the addition of diazomethane to α-amino acid chlorohydrates with acryloyl chloride in the presence of triethylamine and 4-dimethylaminopyridine[6] as the hypernucleophilic acylation catalyst[7] in dry CH_2Cl_2. (Scheme 1).

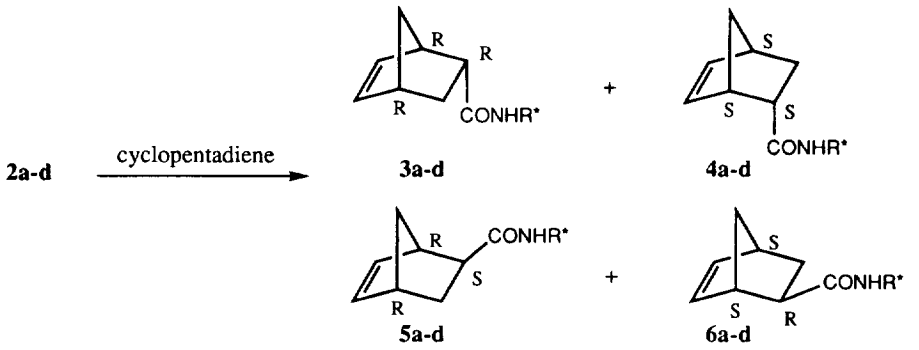


Scheme 1

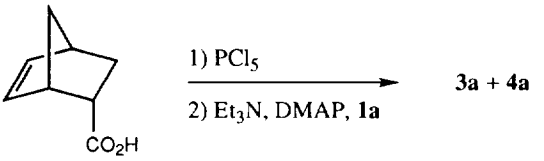
These chiral dienophiles were reacted with an excess of freshly distilled cyclopentadiene under several conditions (scheme 2). In order to find an appropriate method for determining the results of the Diels-Alder reactions, the *endo*-cycloadducts were prepared by an alternative procedure. The *endo*-cycloadducts (**3a** and **4a**) were obtained starting from the (±)-bicyclo[2.2.1]hept-5-en-2-*endo*-carboxylic acid **7** by treatment with PCl_5 and further addition of the corresponding chiral auxiliary, following the same synthetic procedure described above for the synthesis of the dienophiles **2a-d**. Following this, analytical samples of compounds **3a** and **4a** were separated by silica gel column chromatography (Scheme 3). The results of the reactions of cyclopentadiene with dienophiles **2a-d** were determined by direct HPLC analysis[8] of the crudes of the Diels-Alder reactions, the polymer of cyclopentadiene being previously eliminated with MeOH. The percentage of conversion, the *endo*/*exo* ratio and the diastereofacial selectivity **3**/**4** were ratified by integration of the ^{1}H-NMR signals[9] for the H_5 vinylic protons of the cycloadducts in the crudes of the cycloadditions. Neither HPLC analysis nor ^{1}H-NMR analysis were suitable methods to determine the diastereofacial selectivity in the *exo*-cycloadducts.

In order to verify the absolute configuration of the *endo*-cycloadduct preferentially obtained in the Diels-Alder cycloadditions, the crude of the reactions was treated with MeOH and the cycloadducts mixture was purified by silica gel column chromatography. Further hydrogenation of these mixtures using Pd/C as a catalyst at atmospheric pressure and room temperature, followed by hydrolysis with an aqueous 6N HCl solution under

reflux gave the corresponding bicyclo[2.2.1]heptane-2-*endo*-carboxylic acids whose specific optical rotations were compared with those given in the literature[10].



Scheme 2



Scheme 3

The experimental data obtained from the Diels-Alder reactions are summarized in Table 1 and show the influence of the reaction conditions on the conversion, *endo/exo* ratio and diastereoselectivity. In the catalyzed reactions, using $TiCl_4$ or $AlCl_2Et$, quantitative conversions could be obtained, working between 0 °C and -50 °C, but as the temperature decreases the cycloaddition rate falls simultaneously and at -78 °C, after 72 h, the conversion is very low. As expected, high values of *endo/exo* selectivities are only afforded in the presence of the Lewis acids. The non-catalyzed reaction takes place with moderate *endo/exo* selectivity and without diastereoselectivity of **3/4**. The diastereofacial selectivity of **3/4** depends on the nature of the chiral auxiliary. The best results were achieved in catalyzed reactions when chiral auxiliaries **1a** or **1b** were used and a great increase in the diastereoselectivity of **3/4** was not observed when working at lower temperatures.

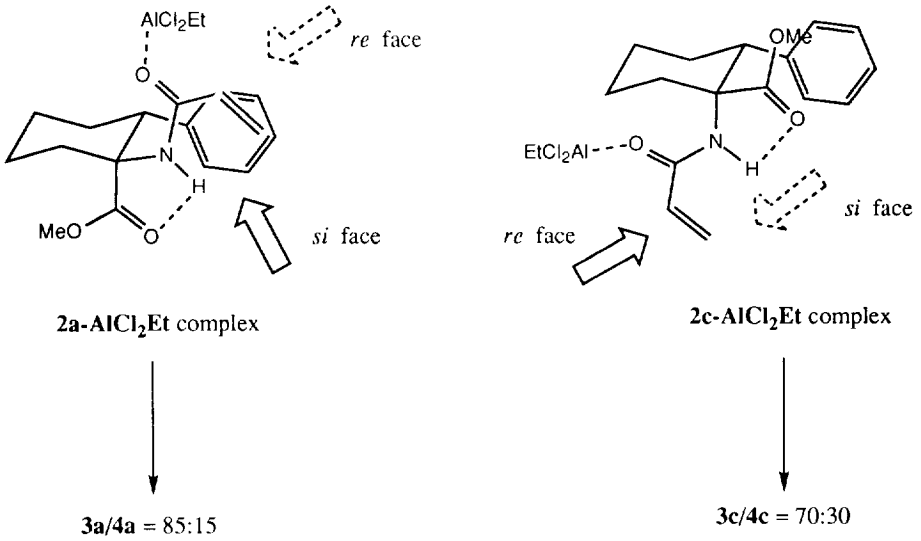
Table 1. Results Obtained from the Diels-Alder Cycloadditions between Dienophiles **2a-d** and Cyclopentadiene.

Entry	Dienophile[a]	Lewis Acid[b]	T(°C)	t(h)	convn(%)[c]	3+4/5+6[c]	3/4[c]
1	**2a**	$TiCl_4$	0	30	100	91:9	83:17
2	**2a**	$TiCl_4$	-30	48	100	93:7	82:18
3	**2a**	$AlCl_2Et$	-30	48	100	94:6	83:17
4	**2a**	$AlCl_2Et$	-54	52	100	98:2	85:15
5	**2a**	$AlCl_2Et$	-78	72	18	99:1	90:10
6	**2a**	-	100	20	50	59:41	50:50
7	**2b**	$TiCl_4$	0	30	100	91:9	17:83
8	**2b**	$AlCl_2Et$	-30	48	100	95:5	16:84
9	**2c**	$AlCl_2Et$	-30	22	100	94:6	70:30
10	**2d**	$AlCl_2Et$	-30	22	100	94:6	28:72

[a]All reactions were carried out with a diene/dienophile ratio of 7.0 and a dienophile concentration of 10 mg/mL in CH_2Cl_2 except for entry 6 which was carried out in 1,4-dioxane. [b]The Lewis acids were used in an equimolar ratio with the dienophile. [c]Determined by HPLC and ^{1}H-NMR, see ref. 8 and 9.

The sense of diastereoselectivity agrees with the intramolecular hydrogen bond model, previously reported by us, used to explain the results obtained in the reactions of cyclopentadiene with N-acryloyl-L-phenylalanine methyl ester and N-acryloyl-L-alanine methyl ester catalyzed by a Lewis acid[2d].

The catalyzed reaction of cyclopentadiene with **2a** led to **3a** as the major cycloadduct and with **2b** led to **4b** with a similar diastereoselectivity. The same reactions with **2c** and **2d** led to **3c** and **4d** as the major cycloadducts, respectively, with a similar diastereoselectivity but lower than for the above cases. This behavior can be explained in terms of the complexes formed between the dienophile and Lewis acid. In the model with **2a** as the chiral auxiliary, the reactive conformer adopts an antiplanar enoate conformation, in which the phenyl group attached to the cyclohexane ring should be ideally placed for inducing attractive interactions with the double bond (π-stacking)[11], shielding the *re* face of the dienophile. Thus, the approach of the cyclopentadiene was made on the *si* face to afford mainly cycloadduct **3a**. However, in the model with **2c** as the chiral auxiliary, the phenyl and the amide groups adopt equatorial and axial positions, respectively, in the cyclohexane ring, such that the acryloyl moiety, in an anti conformation, is a long way from the phenyl group, promoting a decrease in the diastereofacial selectivity. (Scheme 4).



2a-$AlCl_2Et$ complex

3a/4a = 85:15

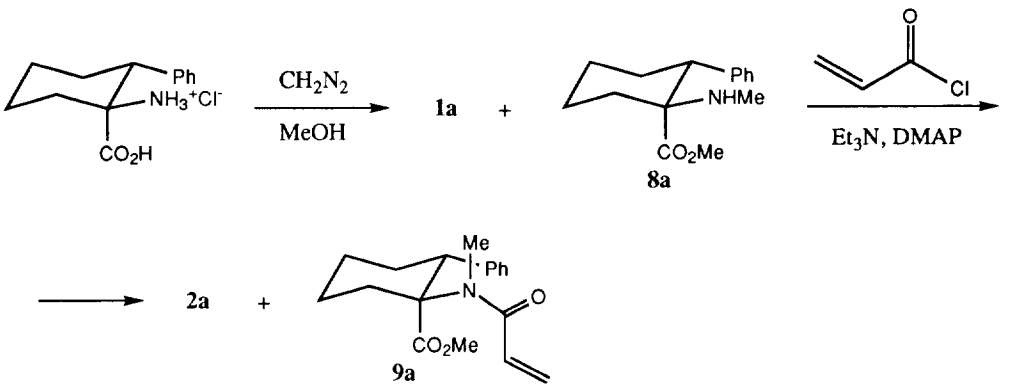
2c-$AlCl_2Et$ complex

3c/4c = 70:30

Scheme 4

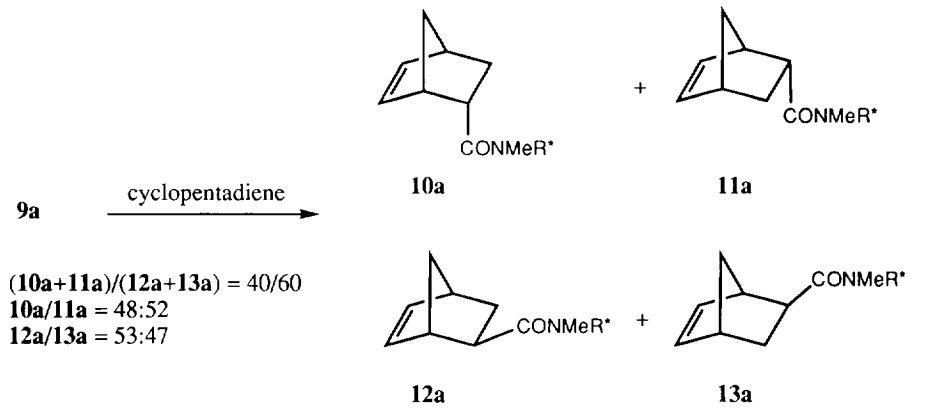
The results obtained from the Diels-Alder reactions with both catalysts ($TiCl_4$ and $AlCl_2Et$) account for the intramolecular hydrogen bond model; however, in order to confirm this model, an amino acid without an NH group was tested as a chiral auxiliary: methyl (1S, 2R)-N-methyl-1-amino-2-phenyl-1-cyclohexane-carboxylate **8a**. The new dienophile, methyl (1S, 2R)-N-acryloyl-N-methyl-1-amino-2-phenyl-1-cyclohexane-carboxylate **9a** was obtained as a byproduct in the synthesis of dienophile **2a**[12]. (Scheme 5).

When dienophile **9a** was reacted with an excess of cyclopentadiene using $TiCl_4$ as a catalyst in an equimolar ratio, at -30 °C, we observed poor *endo/exo* and diastereofacial selectivities. The reaction mixture was analyzed by ^1H-NMR, which showed that the peaks corresponding to the N-methyl protons can be used to determine the results obtained from the Diels-Alder reaction[13]. (Scheme 6).



Scheme 5

The poor diastereoselectivities observed in the reaction support the model proposed and reflect the importance of the intramolecular hydrogen bond in fixing a determined conformation.



Scheme 6

In conclusion, we have improved the results obtained in asymmetric Diels-Alder reactions, in which natural α-amino acids with NH groups were used as chiral auxiliaries by means of employing of synthetic α,α-disubstituted-α-amino acids, in particular (1S, 2R)-1-amino-2-phenyl-1-cyclohexanecarboxylic acid and its enantiomer.

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EXPERIMENTAL SECTION

Solvents were purified according to standard procedures. Analytical TLC was performed by using Polychrom SI F_{254} plates. Column chromatography was performed by using Silica gel 60 (230-400 mesh). ^1H and ^{13}C-NMR spectra were recorded on a Bruker ARX-300. Deuterated chloroform was used as a solvent with tetramethylsilane as the internal standard (the chemical shifts are reported in ppm on the δ scale, coupling constants in Hz). The assignment of all separate signals in the ^1H-NMR spectra was made on the basis of coupling constants, selective proton-proton homonuclear decoupling experiments and proton-proton COSY experiments. Microanalyses were carried out on a Perkin-Elmer 240-C analyser and were in good agreement with the calculated values. Optical rotations were measured in 1 and 0.5 dm cells of 1 and 3.4 mL capacity, respectively.

Synthesis of Chiral Dienophiles. General Procedure.

An ethereal diazomethane solution was added dropwise to a solution of a 1-amino-2-phenyl-1-cyclohexanecarboxylic acid chlorohydrate derivative (255 mg, 1.0 mmol) in MeOH (10 mL) and the reaction mixture was then stirred at room temperature. After 5 min, the solvents were eliminated *in vacuo* to yield an oily mixture of two products in a 90/10 ratio corresponding to methyl 1-amino-2-phenyl-1-cyclohexanecarboxylate **1** and methyl N-methyl-1-amino-2-phenyl-1-cyclohexanecarboxylate **8**, respectively[14]. This mixture was dissolved in dry CH_2Cl_2 (20 mL) and then 4-dimethylaminopyridine (19 mg, 0.16 mmol), triethylamine (121 mg, 1.20 mmol) and acryloyl chloride (99 mg, 1.10 mmol) were added at 0 °C, in an inert atmosphere. After stirring for 12 h at room temperature, the solution was washed with an aqueous 5% $NaHCO_3$ solution (2 x 10 mL), water (2 x 10 mL) and brine (2 x 10 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated to give a residue, which was purified by silica gel column chromatography using hexane-ethyl acetate (70:30) as eluent, yielding the methyl N-acryloyl-1-amino-2-phenyl-1-cyclohexanecarboxylate **2** in 83-87% yield.

2a: $[\alpha]^{25}_D$(c = 1.65, $CHCl_3$) = +102.7°.

^1H-NMR($CDCl_3$): δ: 1.55-2.02(m, 6H, H_{3e}, H_{4a}, H_{4e}, H_{5a}, H_{5e}, H_{6e}); 2.29('q'd, 1H, $J_{3a\text{-}3e}$~$J_{3a\text{-}2a}$~$J_{3a\text{-}4a}$=12.9, $J_{3a\text{-}4e}$=3.0, H_{3a}); 2.82('t'd, 1H, $J_{6a\text{-}6e}$~$J_{6a\text{-}5a}$=13.8, $J_{6a\text{-}5e}$=4.2, H_{6a}); 3.76(s, 3H, COOMe); 3.94(dd, 1H, $J_{2a\text{-}3a}$=12.9, $J_{2a\text{-}3e}$=3.9, H_{2a}); 5.61(dd, 1H, $J_{trans\text{-}gem}$=9.9, $J_{trans\text{-}cis}$=1.5, H_{trans}); 6.04(dd, 1H, $J_{gem\text{-}trans}$=9.9, $J_{gem\text{-}cis}$=16.8, H_{gem}); 6.26(dd, 1H, $J_{cis\text{-}gem}$=16.8, $J_{cis\text{-}trans}$=1.5, H_{cis}); 6.52(brs, 1H, NH); 7.03-7.26(m, 5H, Arom).

^{13}C-NMR($CDCl_3$): δ: 22.7, 25.0, 28.2, 31.7(C_3, C_4, C_5, C_6); 45.4, 52.3, 64.9(C_1, C_2, COOMe); 126.1, 127.1, 128.1, 128.2, 132.0, 141.2(Arom, CH_2=CH); 164.5(CONH); 173.4(COOMe).

Anal. calcd. for $C_{17}H_{21}NO_3$: C 71.04, H 7.37, N 4.88 found: C 71.20, H 7.48, N 5.01.

2b: $[\alpha]^{25}_D$(c = 1.65, $CHCl_3$) = -101.4°.

Anal. calcd. for $C_{17}H_{21}NO_3$: C 71.04, H 7.37, N 4.88 found: C 71.20, H 7.43, N 4.90.

2c: $[\alpha]^{25}_D$(c = 1.50, $CHCl_3$) = +12.3°.

^1H-NMR($CDCl_3$): δ: 1.39-1.97(m, 6H, H_{3e}, H_{4a}, H_{4e}, H_{5a}, H_{5e}, H_{6a}); 2.06('q'd, 1H, $J_{3a\text{-}3e}$~$J_{3a\text{-}2a}$~$J_{3a\text{-}4a}$=13.2, $J_{3a\text{-}4e}$=3.6, H_{3a}); 3.11-3.22(m, 2H, H_{2a}, H_{6e}); 3.50(s, 3H, COOMe); 5.60(dd, 1H, $J_{trans\text{-}gem}$=9.3, $J_{trans\text{-}cis}$=2.1, H_{trans}); 5.64(brs, 1H, NH); 6.09(dd, 1H, $J_{gem\text{-}trans}$=9.3, $J_{gem\text{-}cis}$=16.8, H_{gem}); 6.18(dd, 1H, $J_{cis\text{-}gem}$=16.8, $J_{cis\text{-}trans}$=2.1, H_{cis}); 7.12-7.37(m, 5H, Arom).

^{13}C-NMR($CDCl_3$): δ: 20.7, 25.7, 26.6, 31.0(C_3, C_4, C_5, C_6); 49.5, 51.9, 64.2(C_1, C_2, COOMe); 126.3, 127.5, 127.8, 128.8, 131.4, 140.0(Arom, CH_2=CH); 165.9(CONH); 173.2(COOMe).
Anal. calcd. for $C_{17}H_{21}NO_3$: C 71.04, H 7.37, N 4.88 found: C 71.13, H 7.47, N 4.96.
2d: $[\alpha]^{25}_D$(c = 1.50, $CHCl_3$) = -12.8°.
Anal. calcd. for $C_{17}H_{21}NO_3$: C 71.04, H 7.37, N 4.88 found: C 71.18, H 7.41, N 4.99.

Non-catalyzed Asymmetric Diels-Alder Cycloadditions. General Procedure.
Freshly distilled cyclopentadiene (165 mg, 2.50 mmol) was added to a solution of chiral dienophile **2a-d** (71 mg, 0.25 mmol) in dry 1,4-dioxane (7 mL) at room temperature, and then was heated to the reaction temperature. The reaction was analyzed by HPLC and ^{1}H-NMR.

Catalyzed Asymmetric Diels-Alder Cycloadditions. General Procedure.
The catalyst was added, under an inert atmosphere, to a solution of chiral dienophile **2a-d** (71 mg, 0.25 mmol) in dry CH_2Cl_2 (5 mL). After being stirred for 1 h at room temperature, the solution was cooled to the reaction temperature (Table 1) and freshly distilled cyclopentadiene (115 mg, 1.75 mmol) in CH_2Cl_2 (2 mL) was added. The reaction was stirred for the time reported in Table 1 and then quenched by the addition of solid $Na_2CO_3 \cdot 10H_2O$. The mixture was filtered and the filtrate analyzed by HPLC and ^{1}H-NMR.

Alternative Synthesis of *Endo*-Cycloadducts. 3a and 4a.
PCl_5 (114 mg, 0.55 mmol) was added to a solution of (±)-bicyclo[2.2.1]hept-5-en-2-*endo*-carboxylic acid **7** (69 mg, 0.50 mmol) in Et_2O (10 mL) and the reaction mixture was stirred at room temperature for 1 h. The solvent and most of the PCl_5 was removed under reduced pressure. The oily residue was dissolved in toluene (5 mL) and the solvent and the residual PCl_5 distilled off *in vacuo*. This operation was repeated to ensure complete removal of the PCl_5. The (±)-bicyclo[2.2.1]hept-5-en-2-*endo*-carbonyl chloride was dissolved in dry CH_2Cl_2 (2 mL) and then was added to a solution of 4-dimethylaminopyridine (10 mg, 0.08 mmol), triethylamine (61 mg, 0.60 mmol) and methyl (1S, 2R)-1-amino-2-phenyl-1-cyclohexanecarboxylate **1a** (106 mg, 0.45 mmol) in CH_2Cl_2 (10 mL) at 0 °C. After stirring for 12 h at room temperature, the solution was washed with an aqueous 5% $NaHCO_3$ solution (2 x 10 mL), water (2 x 10 mL) and brine (2 x 10 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated to give a residue, which was purified by silica gel column chromatography eluting with hexane-ethyl acetate (70:30) to afford 144 mg (92%) of the mixture of methyl N-[(1'R, 2'R, 4'R)-bicyclo[2.2.1]hept-5'-en-2'-ylcarbonyl]-(1S, 2R)-1-amino-2-phenyl-1-cyclohexanecarboxylate **3a** and methyl N-[(1'S, 2'S, 4'S)-bicyclo[2.2.1]hept-5'-en-2'-ylcarbonyl]-(1S, 2R)-1-amino-2-phenyl-1-cyclohexanecarboxylate **4a**. Analytical samples could be separated in order to determine their physical properties.
3a: ^{1}H-NMR($CDCl_3$): δ: 1.15-2.04(m, 10H, H_{3c}, H_{4a}, H_{4c}, H_{5a}, H_{5c}, H_{6c}, H_{3n}, H_{3x}, H_{7a}, H_{7s}); 2.23('q'd, 1H, $J_{3a\text{-}3e}$~$J_{3a\text{-}2a}$~$J_{3a\text{-}4a}$=12.9, $J_{3a\text{-}4c}$=3.3, H_{3a}); 2.54('t'd, 1H, $J_{6a\text{-}6c}$~$J_{6a\text{-}5a}$=13.5, $J_{6a\text{-}5e}$=4.8, H_{6a}); 2.80(m, 1H, H_{2x}); 2.87(brs, 1H, H_4); 3.05(brs, 1H, H_1); 3.69-3.74(m, 4H, H_{2a}, COOMe); 5.83(dd, 1H, $J_{5\text{-}6}$=5.7, $J_{5\text{-}4}$=2.7, H_5); 6.18(dd, 1H, $J_{6\text{-}5}$=5.7, $J_{6\text{-}1}$=3.0, H_6); 6.31(brs, 1H, NH); 7.03-7.30(m, 5H, Arom).
^{13}C-NMR($CDCl_3$): δ: 22.7, 25.1, 28.6, 30.4, 32.4(C_3, C_4, C_5, C_6, $C_{3'}$); 42.7, 46.1, 46.2, 46.5, 50.1, 52.0, 64.3(C_1, C_2, COOMe, $C_{1'}$, $C_{2'}$, $C_{4'}$, $C_{7'}$); 127.1, 128.0, 128.4, 132.5, 137.5, 141.3(Arom, $C_{5'}$, $C_{6'}$); 173.6,

173.8(COOMe, CONH). Anal. calcd. for $C_{22}H_{27}NO_3$: C 74.74, H 7.70, N 3.96 found: C 74.80, H 7.83, N 4.05.

4a: ^{1}H-NMR($CDCl_3$): δ: 1.23-2.02(m, 10H, H_{3e}, H_{4a}, H_{4e}, H_{5a}, H_{5e}, H_{6e}, H_{3n}, H_{3x}, H_{7a}, H_{7s}); 2.24('q'd, 1H, J_{3a-3e}~J_{3a-2a}~J_{3a-4a}=12.9, J_{3a-4e}=3.3, H_{3a}); 2.62('t'd, 1H, J_{6a-6e}~J_{6a-5a}=13.5, J_{6a-5e}=4.8, H_{6a}); 2.80-2.87(m, 2H, H_{2x}, H_4); 3.05(brs, 1H, H_1); 3.73(s, 3H, COOMe); 3.82(dd, 1H, J_{2a-3a}=12.9, J_{2a-3e}=3.9, H_{2a}); 5.76(dd, 1H, J_{5-6}=5.7, J_{5-4}=2.7, H_5); 6.20(dd, 1H, J_{6-5}=5.7, J_{6-1}=3.0, H_6); 6.35(brs, 1H, NH); 7.02-7.28(m, 5H, Arom).

^{13}C-NMR($CDCl_3$): δ: 22.7, 25.0, 28.3, 29.9, 32.1(C_3, C_4, C_5, C_6, $C_{3'}$); 42.7, 45.8, 45.9, 46.1, 49.9, 52.1, 64.5(C_1, C_2, COOMe, $C_{1'}$, $C_{2'}$, $C_{4'}$, $C_{7'}$); 127.0, 128.0, 128.3, 132.5, 137.5, 141.4(Arom, $C_{5'}$, $C_{6'}$); 173.5, 173.6(COOMe, CONH). Anal. calcd. for $C_{22}H_{27}NO_3$: C 74.74, H 7.70, N 3.96 found: C 74.82, H 7.81, N 4.02.

Procedure for Determining the Absolute Configuration.

The Diels-Alder reactions (entries 3, 8, 9 and 10 in Table 1) were quenched by the addition of solid $Na_2CO_3 \cdot 10H_2O$ and the mixtures were filtered and the filtrates evaporated *in vacuo*. The oily residues were chromatographed on silica gel using hexane-ethyl acetate (70:30) as eluent to purify the major cycloadducts. These cycloadducts were dissolved in CH_2Cl_2 (5 mL) and were hydrogenated at room temperature and atmospheric pressure for 12 h with 10% palladium-carbon as a catalyst. Removal of the solvent and the catalyst gave quantitatively the saturated cycloadducts which were hydrolyzed by refluxing for 48 h with 6N HCl solution (10 mL). The aqueous solutions were extracted with Et_2O (3 x 10 mL), the organic phases were dried over anhydrous Na_2SO_4 and the solvent evaporated *in vacuo* to afford (+) or (-)-bicyclo[2.2.1]heptane-2-*endo*-carboxylic acids, whose optical rotations agreed with the value given in the literature: $[\alpha]^{25}_D$(c = 2.5, EtOH 95%) = - and +27.8°.

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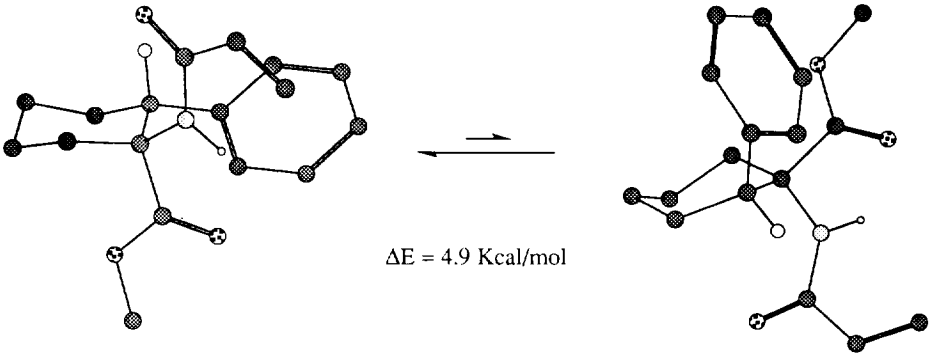
5. The most favorable conformer of **2a** was the chair conformation, where the phenyl and acrylamido groups adopted equatorial positions. This feature was demonstrated on the basis of the ^{1}H-NMR data of the H_2 proton (coupling constants) and molecular mechanics, using the Chem3D Plus™ program and MM2 force field: Burkert, H.; Allinger, N. L. *Molecular Mechanics*; American Chemical Society: Washington DC. 1982.



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8. HPLC analysis using a Hypersil® Silica column (5 μm, 4.6 mm i. d. x 250 mm) and monitored, at 200 nm, using a diode array detector. Mobile phase: hexane-^{t}butylmethyl ether (80:20). Flow rate: 2.0 mL/min. Retention times:
   (**2a** or **2b**) = 6.83 min, (**3a** or **4b**) = 5.49 min, (**4a** or **3b**) = 4.57 min, (**5a** + **6a** or **5b** + **6b**) = 2.85 min.
   (**2c** or **2d**) = 6.86 min, (**3c** or **4d**) = 5.52 min, (**4c** or **3d**) = 4.61 min, (**5c** + **6c** or **5d** + **6d**) = 2.90 min.
9. ^{1}H-NMR, H_5 vinylic protons (δ, ppm):
   5.83 (**3a** or **4b**), 5.76 (**4a** or **3b**), 6.06 (**5a** + **6a** or **5b** + **6b**).
   5.72 (**3c** or **4d**), 5.76 (**4c** or **3d**), 6.04 (**5c** + **6c** or **5d** + **6d**).
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12. Compound **9a**: ^{1}H-NMR($CDCl_3$): δ: 1.55-2.02(m, 6H, H_{3e}, H_{4a}, H_{4e}, H_{5a}, H_{5e}, H_{6e}); 2.78-2.99(m, 3H, H_{2a}, H_{3a}, H_{6a}); 3.08(s, 3H, N-Me); 3.62(s, 3H, COOMe); 5.43(dd, 1H, $J_{trans\text{-}gem}$=9.0, $J_{trans\text{-}cis}$=3.0, H_{trans}); 5.67(dd, 1H, $J_{cis\text{-}gem}$=15.0, $J_{cis\text{-}trans}$=3.0, H_{cis}); 6.34(dd, 1H, $J_{gem\text{-}trans}$=9.0, $J_{gem\text{-}cis}$=15.0, H_{gem}); 7.12-7.35(m, 5H, Arom).
   ^{13}C-NMR($CDCl_3$): δ: 22.7, 26.3, 28.4, 31.5(C_3, C_4, C_5, C_6); 35.7(N-Me); 48.7, 51.5(C_2, COOMe); 67.6(C_1); 126.1, 126.5, 127.4, 129.6, 132.0, 141.6(Arom, CH_2=CH); 166.7(CONMe); 170.8(COOMe).
   Anal. calcd. for $C_{18}H_{23}NO_3$: C 71.72, H 7.70, N 4.65 found: C 71.85, H 7.77, N 4.60.

13. Determined by integration of the N-methyl protons in the ^{1}H-NMR spectra (δ, ppm):
    3.04 and 3.05 (**12a** and **13a**).
    3.11 and 3.12 (**10a** and **11a**).
14. Determined by integration of the H_{2a} and methyl ester protons in the ^{1}H-NMR spectra (δ, ppm):
    (**1a** or **1b**): 2.62(dd, 1H, $J_{2a\text{-}3a}$=12.9, $J_{2a\text{-}3e}$=3.6, H_{2a}); 3.59(s, 3H, COOMe).
    (**8a** or **8b**): 2.74(dd, 1H, $J_{2a\text{-}3a}$=12.3, $J_{2a\text{-}3e}$=3.3, H_{2a}); 3.52(s, 3H, COOMe).
    (**1c** or **1d**): 3.16(dd, 1H, $J_{2a\text{-}3a}$=12.9, $J_{2a\text{-}3e}$=3.6, H_{2a}); 3.60(s, 3H, COOMe).
    (**8c** or **8d**): 2.99(dd, 1H, $J_{2a\text{-}3a}$=12.3, $J_{2a\text{-}3e}$=3.3, H_{2a}); 3.51(s, 3H, COOMe).

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