Models for the Use of α-Amino Acids as Chiral Auxiliaries in Asymmetric Diels–Alder Reactions

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Three different models, depending on the Lewis acid used as a catalyst and the α-amino acid used as a chiral auxiliary, account for the diastereofacial selectivity obtained in reactions of cyclopentadiene with *N*-acryloyl derivatives of L-proline, L-phenylalanine, L-alanine, and *N*-methyl-L-alanine esters. For α-amino acids without an NH group and aluminum catalysts, a reactive conformer with antiplanar enoate conformation similar to those postulated for acrylates with only one center capable of coordination is proposed. These dienophiles form a chelate complex, where the acryloyl moiety is in syn conformation, with $TiCl_4$. For α-amino acids with an NH group, a reactive intermediate with an antiplanar disposition in the acryloyl moiety and the conformation of the amino ester fixed by an intramolecular hydrogen bond accounts for the results with both kinds of catalyst. These models seem to have general application for the use of α-amino acids as chiral auxiliaries in asymmetric Diels–Alder reactions.

High levels of diastereoselectivity have been achieved in asymmetric Diels–Alder reactions of prochiral 1,3-dienes with chiral unsaturated esters,[1] *N*-acyloxazolidones,[2] and *N*-acylsultams.[3] In particular, several derivatives of inexpensive chiral hydroxy acids are efficient chiral auxiliaries,[4] and this effectiveness is related to the formation of chelate complexes between the dienophile and the catalyst. Natural α-amino acids are also inexpensive chiral compounds, so it is interesting to test whether the latter compounds are also good chiral auxiliaries in asymmetric Diels–Alder reactions. In this context, reactions of prochiral 1,3-dienes with *N*-acryloyl L-phenylalanine methyl ester (**1c**)[5] and *N*-acryloyl-L-proline benzyl ester (**1b**)[6] have been studied. The results depend on the α-amino acid used as a chiral auxiliary, and they cannot be explained by the same model of dienophile–catalyst complex for both dienophiles. In order to clarify the behavior of α-amino acids as chiral auxiliaries in asymmetric Diels–Alder reactions, we have also studied the reaction of cyclopentadiene with the methyl esters of *N*-acryloyl-L-proline (**1a**), *N*-acryloyl-L-alanine (**1d**), and *N*-acryloyl-*N*-methyl-L-alanine (**1e**). The results obtained in the reaction of cyclopentadiene with **1a–e** showed a dependence on the nature of the α-amino acid and enabled us to propose two models which account for the diastereoselectivity obtained.

Chiral dienophiles were obtained by reaction of the amino acids with acryloyl chloride[7] followed by methylation with BF_3/MeOH complex, or by condensation of the methyl amino esters with acrylic acid in the presence of 2-chloro-1-methylpyridinium iodide. They were then reacted with cyclopentadiene in CH_2Cl_2 (Scheme I).

For determination of the absolute configuration of the endo product preferentially obtained, the mixture of cycloadducts was transformed into a mixture of the corresponding iodolactones by treatment with I_2 in H_2O/DME,[8] and the specific rotations were compared with those given in the literature.[9]

Table I shows the results obtained from the reactions of cyclopentadiene with **1a** and **1b**. These results suggest that the model proposed by Helmchen[4b] to explain the diastereofacial selectivity obtained in the reaction between the acrylate of (*S*)-ethyl lactate and cyclopentadiene can be used to explain the results obtained when *N*-acryloyl-L-proline esters are used as dienophiles (Figure 1).

In this model, the dienophile and $TiCl_4$ form a chelate complex with the acryloyl moiety in syn conformation (model 2). In this complex a chlorine atom of the Lewis acid shields the *re* face of the dienophile, and attack of the diene occurs preferentially on the *si* face. Accordingly, in the reactions of *N*-acryloyl-L-proline esters catalyzed by $TiCl_4$, **2a** and **2b** are preferentially obtained with a high level of diastereofacial selectivity regardless of the nature of the ester group.

With Lewis acids disposed to four coordination, like aluminum derivatives, a reactive conformer with an antiplanar enoate conformation, similar to those proposed for complexes of acrylates with only one center capable of coordination,[1,11] is preferred (model 1). In this intermediate, the ester group shields the *si* face of the double bond and **3a** and **3b** are obtained preferentially. The diastereofacial selectivity depends on the bulk of the ester group and is higher with a benzyl than with a methyl ester.

In view of these results, a question arises. Do other natural amino acids behave in the same way? Table II summarizes the results obtained from the reactions of cyclopentadiene with **1c** and **1d**.

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Table I. Results Obtained from the Reaction between 1a or 1b and Cyclopentadiene[a]

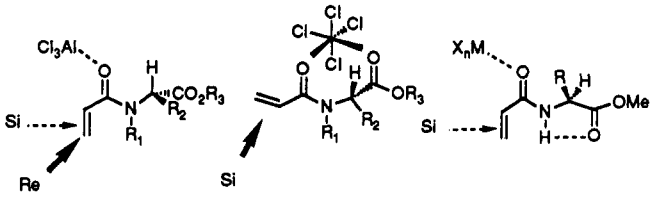
dienophile	Lewis acid (equiv)	T (°C)	time (h)	yield, %	(2 + 3):(4 + 5)[b]	2:3[b]
1a	$TiCl_4$ (0.75)	−20	120	99	11.3	91:9
1a	$TiCl_4$ (1.1)	−20	168	66	14.0	80:20
1a	$TiCl_4$ (0.5)	−20	120	100	18.0	65:35
1a	$TiCl_4$ (0.75)	−60	264	84	14.0	>95:5
1a	$TiCl_4$ (1.1)	−60	264	83	16.8	95:5
1a	$AlCl_3$ (1.1)	−20	120	100	5.5	25:75
1a	$AlCl_3$ (1.1)	−60	168	91	11.2	28:72
1a	$AlCl_3$ (2.2)	−60	168			
1b[c]	$EtAlCl_2$ (1.0)	0	20	96	11.5	10:90
1b[c]	$TiCl_4$ (0.75)	0	20	83	13.3	96:3:3.7

[a] In CH_2Cl_2 with a ratio dienophile:diene = 1:6. [b] For 1a determined by HPLC, column 5 μm silica Hypersil, eluent THF:*n*-hexane, gradient from 0 to 30% of THF in 12 min, flow rate 2.5 mL/min. [c] Reference 6.

Table II. Results Obtained from the Reaction between 1c or 1d and Cyclopentadiene[a]

dienophile	Lewis acid (equiv)	T (°C)	time (h)	yield, %[b]	(2 + 3):(4 + 5)[b]	2:3[b]
1d	$TiCl_4$ (0.75)	0	22	64	8.4	65:35
1d	$TiCl_4$ (0.5)	0	22	94	5.1	55:45
1d	$TiCl_4$ (1.1)	−20	100	5		
1d	$TiCl_4$ (0.75)	−20	100	12	10.6	68:32
1d	$TiCl_4$ (0.5)	−20	100	62	7.8	55:45
1d	$TiCl_4$ (0.75)	−40	168	42	12.1	74:26
1d	$AlCl_3$ (1.1)	0	69	89	15.3	52:48
1d	$AlCl_3$ (0.75)	0	69	90	18.0	52:48
1d	$AlCl_3$ (1.1)	−20	52	13	19.2	52:48
1d	$AlCl_3$ (0.75)	−20	52	36	21.5	52:48
1c	$TiCl_4$ (1.1)	25	72	77	9.5	77:23
1c	$TiCl_4$ (0.5)	−20	134	99	7.3	62:38
1c	$TiCl_4$ (0.75)	−60	168	77	20.4	82:18
1c	$AlCl_3$ (1.1)	25	5	99	7.3	60:40
1c	$AlCl_3$ (1.1)	0	20	80	15.9	70:30
1c	$AlCl_3$ (1.1)	−25	25	95	29.0	68:32
1c	$AlCl_3$ (1.1)	−40	50	93	31.3	71:29

[a] In CH_2Cl_2 with a ratio dienophile:diene = 1:6. [b] For 1c determined by HPLC, column 5 μm silica Hypersil, eluent ethanol:*n*-hexane, gradient from 1 to 5% of EtOH in 1 min, flow rate 2 mL/min; for 1d determined by HPLC, column 5 μm silica Hypersil, eluent ^{i}PrOH–hexane, gradient 5 to 10% of ^{i}PrOH in 5 min, flow rate 2 mL/min.



Dienophile	R_1	R_2	R_3
1a	-CH2-CH2-CH2-		CH_3-
1b	-CH2-CH2-CH2-		Ph-CH_2-
1c	H	Ph-CH_2-	CH_3-
1d	H	CH_3-	CH_3-
1e	CH_3-	CH_3-	CH_3-

Figure 1. Models explaining the diastereofacial selectivity obtained from the reactions between cyclopentadiene and *N*-acryloyl α-amino esters.

N-Acryloyl-L-alanine methyl ester (**1d**) is similar to the acrylate of (*S*)-ethyl lactate used by Helmchen,[4b] where preferential attack of the diene on the *re* face of the dienophile is observed in $AlCl_3$-catalyzed reactions. However, in the reactions between **1d** and cyclopentadiene, attack of the diene takes place preferentially on the *si* face, leading to **2d** with low selectivity, which cannot be explained by model 1. The dienophile–$TiCl_4$ chelate complex (model 2) would also account for the preferential formation of **2b** in $TiCl_4$-catalyzed reactions, but not for the low diastereofacial selectivity. So a new reactive intermediate must be proposed (Figure 1, model 3). In this model the enoate moiety displays an antiplanar disposition and the conformation of the amino acid is fixed by an intramolecular hydrogen bond.

Table III. IR spectra of 1c and Its $TiCl_4$ Complex in CH_2Cl_2 Solution

Lewis acid (equiv)	concn, M	ν (cm^{-1}) N—H	ν (cm^{-1}) —C(=O)—O	ν (cm^{-1}) —C(=O)—N
	0.1	3418.6	1742.5	1681.0
	0.05	3418.5	1741.4	1677.2
	0.033	3418.4	1742.0	1676.9
	0.025[a]	3418.9	1742.0	1676.8
	0.016	3418.4	1742.1	1676.9
	0.001	3418.2	1742.0	1676.7
$TiCl_4$ (0.75)	0.1	3367.8	1744.1	1639.9
$TiCl_4$ (0.75)	0.05	3367.5	1743.5	1639.6
$TiCl_4$ (0.75)	0.033	3365.4	1743.1	1639.5
$TiCl_4$ (0.75)	0.025[a]	3367.2	1743.0	1639.7
$TiCl_4$ (0.75)	0.016	3365.8	1742.5	1639.5
$TiCl_4$ (0.75)	0.01	3367.0	1742.6	1639.4

[a] Concentration used in the Diels–Alder reactions.

The reaction between **1c** and cyclopentadiene leads to **2c** as the major cycloadduct, resulting from attack of the diene on the *si* face of the dienophile. Though the three models account for the direction of asymmetric induction, the low diastereofacial selectivity obtained in $TiCl_4$-catalyzed reactions suggests that there is no formation of a dienophile–$TiCl_4$ chelate complex. In order to choose among the three models, the IR spectra of **1c** and its $TiCl_4$ complex were studied in several concentrations in CH_2Cl_2. The results obtained (Table III) show that the position of the ester carbonyl band is not changed by complexation

Scheme I

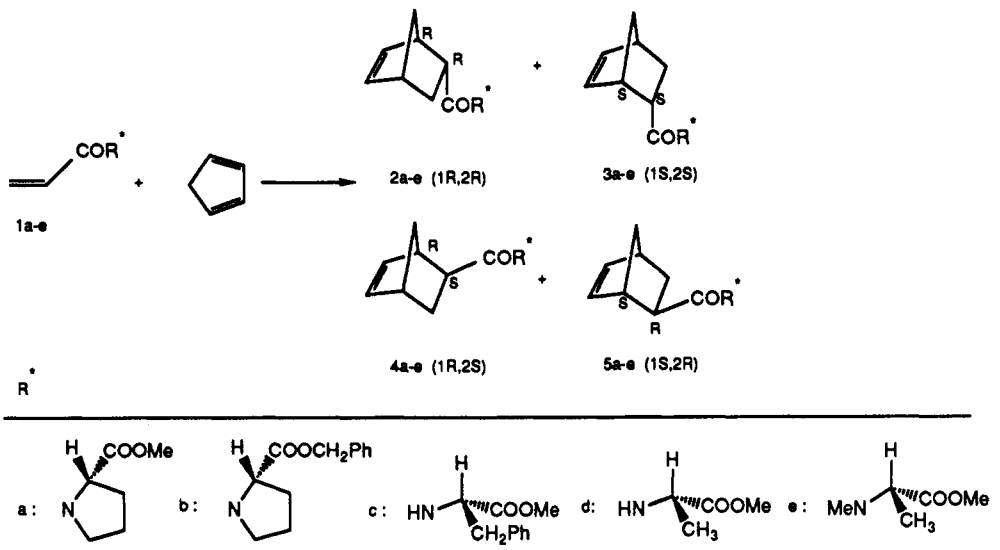


Table IV. Results Obtained from the Reaction between 1e and Cyclopentadiene[a]

entry	Lewis acid (equiv)	1e:diene	T (°C)	time (h)	yield, %[b]	(2 + 3):(4 + 5)[b]	2e:3e[b]	4e:5e[b]
1	$TiCl_4$ (0.75)	1:6	0	4	100	3.0:1.0	73:27	3:97
2	$TiCl_4$ (0.75)	1:6	0	16	100	3.0:1.0	66:34	10:90
3	$TiCl_4$ (0.5)	1:6	0	16	100	1.8:1.0	46:54	18:82
4	$TiCl_4$ (0.75)	1:6	25	69	100	1.0:1.5	26:74	36:64
5	$TiCl_4$ (0.5)	1:6	25	64	85	1.0:2.7	21:79	71:29
6	$TiCl_4$ (0.5)	1:6	−20	168	62	1.0:4.0	17:83	90:10
7	$AlCl_3$ (1.1)	1:12	25	15	100	4.9:1.0	24:76	67:33
8	$AlCl_3$ (1.1)	1:12	25	168	83	1.9:1.0	35:65	57:43

[a] In CH_2Cl_2. [b] Determined by ^1H NMR, CO_2CH_3 (δ, ppm): 3.721 (1e), 3.696 (2e), 3.677 (3e), 3.714 (4e), 3.705 (5e); NCH_3 (δ, ppm): 3.023 (1e), 3.041 (2e), 3.034 (3e), 2.965 (4e), 2.954 (5e).

with $TiCl_4$, whereas a noticeable shift of the corresponding band in the amide group is observed. These results indicate a preferential complexation of the catalyst with the amide group. Furthermore, the position of the NH stretching band is not modified by concentration in either the dienophile or in its $TiCl_4$ complex, which supports the intramolecular hydrogen bond and model 3.

Therefore, model 3 accounts for the results obtained with **1d** and **1c**. The higher selectivity obtained with the latter must reflect the fact that diastereofacial differentiation is caused by the differences between a hydrogen atom and the benzyl group which is bulkier with a possible electronic effect.[1,11]

In view of these results, a second question arises. Why L-phenylalanine and L-alanine not behave like L-proline? There are two possible reasons. On the one hand, the cyclic structure of the L-proline favors the formation of chelate intermediates. On the other hand, the intramolecular hydrogen bond can hinder, or even prevent, participation of the ester group in the coordination of the dienophile to the Lewis acid. An acyclic amino acid without an NH group, *N*-methyl-L-alanine, was tested as a chiral auxiliary in order to clarify this point. Table IV gathers the results obtained in the Diels–Alder reactions between cyclopentadiene and *N*-acryloyl-*N*-methyl-L-alanine methyl ester (**1e**).

In this case the results could not be determined by HPLC, so mixtures of endo (**2e** + **3e**) and exo (**4e** + **5e**) cycloadducts were obtained by passing a reaction mixture through a column of silica gel, using Et_2O:*n*-hexane = 1:1 as eluent. These mixtures were analyzed by ^1H NMR, which showed that the peaks corresponding to the methyls of the ester group and the amide group can be used to determine, by integration, the results obtained from the Diels–Alder reactions (Table IV).

The results obtained in this reaction (Table IV) were surprising because the endo/exo ratio and the configuration of the cycloadducts preferentially obtained are reversed as a function of the reaction conditions. These results can be explained by taking into account the reversibility of the reaction. When $TiCl_4$ is used as a catalyst and the reaction is carried out under kinetic conditions (0.75 equiv of catalyst and short reaction times, entries 1 and 2), endo cycloadducts are preferentially obtained and **2e** is the major product. With the same catalyst but under thermodynamic conditions (0.5 equiv of catalyst and long reaction times, entries 5 and 6), exo cycloadducts are preferentially obtained and **4e** is the major product. It can be concluded that **2e** is obtained through the more stable transition state and that **4e** forms the more stable cycloadduct–$TiCl_4$ complex. When $AlCl_3$ is used as a catalyst, a large excess of cyclopentadiene is needed (1:6 ratio gives no reaction), and under kinetic conditions (entry 7), **3e** and **4e** are preferentially obtained with endo adducts predominating over exo adducts.

Absolute configurations of **2e** and **3e** were determinated by the iodolactonization procedure. In order to assign the absolute configuration of exo cycloadducts, **4e**, separated from a reaction carried out under thermodynamic conditions (column chromatography on silicagel using AcOEt:*n*-hexane = 3:7 as eluent), was transformed into the corresponding *exo*-norbornane-2-carboxylic acid by hydrogenation and acid hydrolysis. The absolute configuration of this acid was determined by comparing its specific rotation with the values given in the literature.[12] In this way the ^1H NMR peaks were assigned to the corresponding cycloadducts.

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The results obtained under kinetic conditions must be considered in order to test the validity of the model proposed for the reactive intermediates. These results show an inversion of configuration of the cycloadducts preferentially obtained as a function of the Lewis acid used as a catalyst, which agrees with the results obtained with the acrylate of (*S*)-ethyl lactate[4d] and with L-proline derivatives **1a** and **1b** and can be explained by models 1 and 2 (Figure 1).

The differences observed between **1d** and **1e** indicate that the behavior of these dienophiles cannot be accounted for by the use of the same model and emphasizes the importance of the NH group.

It can be concluded that the models proposed by Helmchen to explain the results in the reaction between the acrylate of (*S*)-ethyl lactate and cyclopentadiene account for the results obtained when α-amino acids without an NH group are used as chiral auxiliaries. Nevertheless, for α-amino acids with the NH group, the participation of a reactive intermediate with an intramolecular hydrogen bond has to be considered.

Study of the reaction between **1e** and cyclopentadiene gave rise to another interesting result. Asymmetric Diels–Alder reactions of chiral derivatives of acrylic acid are generally carried out in the presence of a Lewis acid, which increases the diastereoselectivity by controlling the syn–anti conformational equilibrium of the enoate moiety.[1] As a consequence, high endo/exo ratios are obtained. So there is no method of preparing *exo*-norbornane-2-carboxylic acids asymmetrically. The results obtained in the reaction of cyclopentadiene with *N*-acryloyl-*N*-methyl-L-alanine methyl ester, with $TiCl_4$ and under thermodynamic conditions (Table 4, entries 5 and 6), show that this dienophile leads to exo cycloadducts with good yield and high diastereofacial selectivity.

Experimental Section

***N*-Acryloyl-L-phenylalanine.** To a solution of 1.815 g (11 mmol) of phenylalanine in 80 mL of 5% NaOH kept at 0 °C was added 0.905 g (10 mmol) of acryloyl chloride dropwise. The solution was acidified with HCl (12 *N*) and the solid was separated by filtration, washed with water, and recrystallized from EtOH to afford 1.52 g (70%) of *N*-acryloyl-L-phenylalanine, mp 126 °C: ^{1}H NMR (300 MHz, DMSO) δ 2.90 (m, 1 H), 3.10 (m, 1 H), 4.56 (m, 1 H), 5.56 (d, J = 10 Hz, 1 H), 6.10 (m, 1 H), 6.30 (m, 1 H), 7.24 (bs, 5 H), 8.40 (d, 1 H); ^{13}C NMR (75.4 MHz, DMSO) δ 36.9, 53.7, 125.9, 126.5, 128.3 (2 C), 129.1 (2 C), 131.3, 137.7, 164.6, 173.0. Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.62; H, 5.81; N, 6.55.

***N*-Acryloyl-L-alanine.** Following the above method and recrystallization from AcOEt, 0.858 g (60%) of *N*-acryloyl-L-alanine was obtained, mp 149 °C: ^{1}H NMR (300 MHz, DMSO) δ 1.25 (d, J = 7.2 Hz, 3 H), 4.22 (m, 1 H), 5.53 (d, J_1 = 9.9 Hz, 1 H), 6.04 (d, J_2 = 17.1 Hz, 1 H), 6.22 (dd, J_1 = 9.9 Hz, J_2 = 17.1 Hz, 1 H), 8.34 (d, 1 H); ^{13}C NMR (75.4 MHz, DMSO) δ 17.4, 47.9, 126.0, 131.5, 164.7, 174.4. Anal. Calcd for $C_6H_9NO_3$: C, 50.35; H, 6.34; N, 9.78. Found: C, 50.30; H, 6.57; N, 9.90.

***N*-Acryloyl-L-proline.** This product was prepared by the above method. The aqueous acid solution was extracted with AcOEt and dried over anhydrous Na_2SO_4, the solvent evaporated under reduced pressure, and the solid was recrystallized from AcOEt to afford 0.98 g (58%) of *N*-acryloyl-L-proline, mp 118–120 °C: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.80–1.93 (m, 3 H), 2.05–2.24 (m, 1 H), 3.37–3.67 (m, 2 H), 4.26 (dd, J_1 = 3.6 Hz, J_2 = 7.2 Hz, 1 H), 5.67 (dd, J_3 = 1.8 Hz, J_4 = 10.2 Hz, 1 H), 6.12 (dd, J_3 = 1.8 Hz, J_5 = 16.8 Hz, 1 H), 6.58 (dd, J_4 = 10.2 Hz, J_5 = 16.8 Hz, 1 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 24.5, 28.8, 46.7, 58.7, 127.5, 129.3, 163.4, 173.4. Anal. Calcd for $C_8H_{11}NO_3$: C, 56.80; H, 6.55; N, 8.28. Found: C, 56.87; H, 6.42; N, 8.05.

***N*-Acryloyl-*N*-methyl-L-alanine.** To a solution of 1.03 g (10 mmol) of *N*-methyl-L-alanine in 80 mL of 5% NaOH kept at 0 °C was added 1 g (11 mmol) of acryloyl chloride dropwise. The solution was acidified with 12 N HCl, extracted with AcOEt, and dried over anhydrous Na_2SO_4. The solvent was eliminated under reduced pressure and the solid recrystallized from AcOEt to afford 0.628 g (40%) of *N*-acryloyl-*N*-methyl-L-alanine, mp 78–80 °C: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47 (d, J_1 = 7.2 Hz, 3 H), 3.05 (s, 3 H), 5.23 (q, J_1 = 7.2 Hz, 1 H), 5.78 (dd, J_2 = 2 Hz, J_3 = 10.2 Hz, 1 H), 6.40 (dd, J_2 = 1.8 Hz, J_4 = 16.8 Hz, 1 H), 6.60 (dd, J_3 = 10.2 Hz, J_4 = 16.8 Hz, 1 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 14.0, 31.4, 51.9, 127.1, 128.2, 164.5, 173.0. Anal. Calcd for $C_7H_{11}NO_3$: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.60; H, 7.09; N, 8.70.

***N*-Acryloyl-L-phenylalanine Methyl Ester (1c).** BF_3·MeOH complex (22 mL) was added to 4.38 g (20 mmol) of *N*-acryloyl-L-phenylalanine. The solution was refluxed for 2 h and cooled, and 82 mL of a saturated solution of $NaHCO_3$ was added. The solid obtained was filtered, washed with water, and dried to afford 4.45 g (97%) of compound **1c**, mp 83 °C: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.12 (m, 2 H), 3.71 (s, 3 H), 4.95 (m, 1 H), 5.62 (d, J_1 = 9.1 Hz, 1 H), 6.10 (dd, J_1 = 9.1 Hz, J_2 = 16.4 Hz, 1 H), 6.27 (d, J_2 = 16.4 Hz, 1 H), 6.38 (bs, 1 H), 7.10 (bs, 2 H), 7.24 (bs, 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 37.7, 52.2, 53.1, 127.0, 127.1, 128.4 (2 C), 129.1 (2 C), 130.2, 135.7, 164.9, 171.9. Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.82; H, 6.63; N, 6.10.

***N*-Acryloyl-L-alanine Methyl Ester (1d).** Following the above method the solution obtained after the treatment with $NaHCO_3$ was extracted with Et_2O and dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude product was chromatographed on silica gel with AcOEt:*n*-hexane (1:1) as eluent to afford 2.826 g (90%) of amide **1d** as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39 (d, J = 7.2 Hz, 1 H), 3.70 (s, 1 H), 4.62 (m, 1 H), 5.62 (dd, J_1 = 10 Hz, J_2 = 1.7 Hz, 1 H), 6.08–6.17 (dd, J_1 = 9.9 Hz, J_3 = 17.1 Hz, 1 H), 6.23–6.30 (dd, J_2 = 1.8 Hz, J_3 = 17.1 Hz, 1 H), 6.63 (d, 1 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 18.2, 47.9, 52.3, 126.9, 130.3, 164.9, 173.4. Anal. Calcd for $C_7H_{11}NO_3$: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.40; H, 7.26; N, 8.76

***N*-Acryloyl-L-proline Methyl Ester (1a). Method A.** Following the procedure described for **1d**, 2.562 g (70%) of compound **1a** was obtained as an oil. **Method B.** Thionyl chloride (4 mL) was reacted with anhydrous MeOH (50 mL) in an ice bath for 1 h. Then 1.15 g (10 mmol) of L-proline was added and the solution was refluxed for 2 h. The solvent was evaporated under reduced pressure and the crude product dissolved in anhydrous CH_2Cl_2 (25 mL). Then 3 g (30 mmol) of NEt_3, 2.56 g (10 mmol) of 2-chloro-1-methylpyridinium iodide, and a solution of acrylic acid (0.72 g, 10 mmol) in anhydrous CH_2Cl_2 (25 mL) were added. The solution was refluxed for 3 h and extracted with 5% $NaHCO_3$ (2 × 30 mL), 2 N HCl (1 × 30 mL), and a saturated NaCl solution (2 × 30 mL). The organic phase was dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was chromatographed on silica gel with AcOEt:*n*-hexane (1:1) as eluent to afford 1.22 g (67%) of amide **1a** as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.80–2.02 (m, 3 H), 2.03–2.24 (m, 1 H), 3.50–3.60 (m, 2 H), 3.71 (s, 3 H), 4.42–4.50 (m, 1 H), 5.54–5.68 (dd, J_1 = 2.7 Hz, J_2 = 10 Hz, 1 H), 6.12–6.48 (m, 2 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 24.6, 29.0, 46.8, 52.0, 58.7, 127.9, 128.2, 164.4, 172.5. Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 59.22; H, 6.99; N, 7.92.

***N*-Acryloyl-*N*-methyl-L-alanine Methyl Ester (1e). Method A.** Following method A and using Et_2O:*n*-hexane (3:1) as eluent in column chromatography, 3.249 g (95%) of compound **1e** was obtained as an oil. **Method B.** Following the method described for **1a** and using Et_2O:*n*-hexane (3:1) as eluent in column chromatography, 1.23 g (72%) of compound **1e** was obtained as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (d, J_1 = 7.2 Hz, 3 H), 3.03 (s, 3 H), 3.71 (s, 3 H), 5.25 (q, J_1 = 7.2 Hz, 1 H), 5.75 (dd, J_2 = 1.8 Hz, J_3 = 10.2 Hz, 1 H), 6.34–6.40 (dd, J_2 = 1.8 Hz, J_4 = 16.8 Hz, 1 H), 6.57–6.66 (dd, J_3 = 10.1 Hz, J_4 = 16.9 Hz, 1 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 14.1, 31.5, 51.9, 52.0, 127.3, 128.3, 166.3, 171.9. Anal. Calcd for $C_8H_{13}NO_3$: C, 56.13; H, 7.65; N, 8.18. Found: C, 56.01; H, 7.86; N, 8.09.

Diels–Alder Reactions. In a typical experiment 1 mmol of dienophile **1** and the corresponding amount of catalyst (Tables I, II, and IV) were stirred in 20 mL of dry CH_2Cl_2 under argon at the appropriate temperature (Tables I, II, and IV) for 1 h. A solution of cyclopentadiene (6 or 12 mmol) in 5 mL of dry CH_2Cl_2

at the same temperature was then added. The mixture was stirred for an adequate time (Tables I, II, and IV), treated with $Na_2CO_3 \cdot 10H_2O$, filtered, and washed with water. The organic layer was then dried with anhydrous sodium sulfate, filtered, evaporated under reduced pressure, and analyzed by HPLC or ^1H NMR. In the case of *N*-acryloyl-L-proline methyl ester (**1a**) the cycloadducts were separated into *endo*-**2a**, *endo*-**3a**, and a mixture of *exo*-**4a** + *exo*-**5a** by column chromatography on silica gel with AcOEt:*n*-hexane (3:7) as eluent. In the case of *N*-acryloyl-*N*-methyl-L-alanine methyl ester (**1e**) the cycloadduct **2e** was purified from a reaction carried out under kinetic conditions, and **4e** from a reaction carried out under thermodynamic conditions, by using the same chromatographic method.

***N*-[(1*R*,2*R*,4*R*)-Bicyclo[2.2.1]hept-5-en-2-ylcarbonyl]-(*S*)-proline methyl ester (2a)**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.24–1.30 (m, 1 H), 1.39–1.54 (m, 2 H), 1.82–2.22 (m, 5 H), 2.91 (bs, 1 H), 3.02 (m, 1 H), 3.14 (bs, 1 H), 3.61–3.81 (m, 2 H), 3.69 (s, 3 H), 4.41 (m, 1 H), 5.95 (dd, J_1 = 5.4, J_2 = 3 Hz, 1 H), 6.18 (dd, J_1 = 5.4, J_3 = 2.7 Hz, 1 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 24.7, 28.8, 29.9, 42.4, 42.7, 44.8, 46.5, 49.6, 51.8, 58.6, 132.0, 136.8, 172.8, 172.9. Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.69; H, 7.60; N, 5.41.

***N*-[(1*S*,2*S*,4*S*)-Bicyclo[2.2.1]hept-5-en-2-ylcarbonyl]-(*S*)-proline methyl ester (3a)**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.24–1.30 (m, 1 H), 1.38–1.52 (m, 2 H), 1.82–2.22 (m, 5 H), 2.91 (bs, 1 H), 3.02 (m, 1 H), 3.23 (bs, 1 H), 3.61–3.81 (m, 2 H), 3.71 (s, 3 H), 4.44 (m, 1 H), 6.00 (dd, J_1 = 5.4, J_2 = 3 Hz, 1 H), 6.18 (dd, J_1 = 5.4, J_3 = 2.7 Hz, 1 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 24.8, 28.7, 29.5, 42.4, 42.8, 44.9, 46.5, 49.3, 51.8, 58.6, 132.3, 136.4, 172.8, 172.9. Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.20; H, 7.43; N, 5.80.

***N*-[(1*R*,2*R*,4*R*)-Bicyclo[2.2.1]hept-5-en-2-ylcarbonyl]-*N*-methyl-(*S*)-alanine methyl ester (2e)**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.28–1.31 (m, 1 H), 1.36 (d, J_1 = 7.2 Hz, 3 H), 1.40–1.48 (m, 2 H), 1.88–2.00 (m, 1 H), 2.88 (bs, 1 H), 3.04 (s, 3 H), 3.04–3.10 (m, 1 H), 3.11 (bs, 1 H), 3.70 (s, 3 H), 5.07 (q, J_1 = 7.2 Hz, 1 H), 5.95–6.01 (m, 1 H), 6.12–6.16 (m, 1 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 14.3, 30.6, 42.1, 42.4, 45.2, 49.2, 49.5, 52.0, 52.4, 132.5, 136.5, 172.3, 174.3. Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.77; H, 7.79; N, 6.06.

***N*-[(1*R*,2*S*,4*R*)-Bicyclo[2.2.1]hept-5-en-2-ylcarbonyl]-*N*-methyl-(*S*)-alanine methyl ester (4e)**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.39 (d, J_1 = 7.2 Hz, 3 H), 1.40–1.64 (m, 3 H), 1.78–1.86 (m, 1 H), 2.33–2.40 (m, 1 H), 2.91 (bs, 1 H), 2.97 (s, 3 H), 3.01 (bs, 1 H), 3.71 (s, 3 H), 5.19 (q, J_1 = 7.2 Hz, 1 H), 6.13–6.18 (m, 2 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 14.4, 30.8, 41.3, 41.5, 45.5, 46.3, 46.6, 52.0, 52.2, 135.9, 138.1, 172.5, 175.8. Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 66.00; H, 7.95; N, 5.80.

***N*-[(1*S*,2*S*,4*R*)-Bicyclo[2.2.1]heptan-2-ylcarbonyl]-*N*-methyl-(*S*)-alanine Methyl Ester (6e).** Compound **4e** was hydrogenated in methanol at room temperature and atmospheric pressure using 10% Pd/C as a catalyst until completion of the reaction (monitored by TLC): ^1H NMR (300 MHz, $CDCl_3$) δ 1.39 (d, J_1 = 7.2 Hz, 3 H), 1.45–1.59 (m, 7 H), 1.68–1.75 (m, 1 H), 2.28 (bs, 1 H), 2.41–2.46 (m, 2 H), 2.95 (s, 3 H), 3.69 (s, 3 H), 5.17 (q, J_1 = 7.2 Hz, 1 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 14.3, 28.8, 29.5, 34.6, 35.9, 36.4, 40.2, 44.4, 46.3, 51.9, 52.1, 172.6, 175.6. Anal. Calcd for $C_{13}H_{21}NO_3$: C, 65.25; H, 8.84; N, 5.85. Found: C, 65.02; H, 8.99; N, 5.57.

(1*S*,2*S*,4*R*)-Bicyclo[2.2.1]heptane-2-carboxylic Acid. Amide **6e** (70 mg, 0.3 mmol) was refluxed with 5 mL of HCl (6 N) for 2 days. The aqueous solution was extracted with Et_2O (6 × 7 mL), the organic phase was dried over anhydrous Na_2SO_4, and the solvent evaporated under reduced pressure. The crude product was chromatographed on silica gel with Et_2O:*n*-hexane (1:1) as eluent to afford 25 mg (60%) of this acid, whose rotation was determined and compared with the value given in the literature: $[\alpha]_D^{26}$ = +27.8° (*c* 2.5, EtOH 95%).

Iodolactonization Procedure. In a typical experiment 588 mg (2.2 mmol) of I_2 was added to a solution of the crude Diels–Alder product in 40 mL of DME:H_2O (1:1). The solution was stirred for 48 h at room temperature, diluted with AcOEt, and successively washed with a saturated solution of $Na_2S_2O_3$, 0.5 N HCl, a saturated solution of $NaHCO_3$, and a saturated solution of NaCl. The organic layer was dried over anhydrous Na_2SO_4, the solvent was evaporated under reduced pressure, and the iodolactone was purified by column chromatography on silica gel, using AcOEt:*n*-hexane (1:1) as eluent. The rotation of the iodolactone was determined and compared with the value described in the literature, $[\alpha]_D^{20}$ = −110.6° (*c* 1.0, $CHCl_3$), for the iodolactone obtained from the cycloadducts of configuration 1*R*,2*R*,4*R* (**2**).

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