Asymmetric Synthesis of 2-Amino-3-hydroxynorbornene-2-carboxylic Acid Derivatives

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The enantioselective synthesis of 2-amino-3-hydroxynorbornene-2-carboxylic acid derivatives (**5**) was studied using the Diels−Alder reaction between cyclopentadiene and different dienophiles, i.e., alkyl 5-oxo-2-phenyloxazol-4-methylenecarbonates (**1**) or 2-benzoylamino-3-alkoxycarbonyloxy-acrylates (**12**), operating with different Lewis acids and both with thermal and with ultrasound conditions. The enantioselective synthesis of the exo/endo compounds **5c**,**d** and **5′c**,**d** was achieved starting from the chiral menthyl acrylates **12b**,**c** using $Mg(ClO_4)_2$ as the catalyst and ultrasound. The cycloadducts were obtained in very good yield, in mild conditions, in short time, and in good diastereomeric excess (exo, 80%; endo, 87%). Finally, the use of alkylidene-oxazolones or acrylates and $EtAlCl_2$ or $Mg(ClO_4)_2$ as the catalyst allowed control of the cycloaddition reaction in favor of the exo or endo products.

Introduction

Recently,[1] we reported that 2-amino-3-hydroxynorbornane-2-carboxylic acids were synthesized through a Diels−Alder reaction, as a mixture of exo and endo adducts in a 70:30 ratio. As reported,[2] the skeleton of these constrained amino acids and their particular functionalization (i.e., the hydroxy group) make this class of amino acids particularly interesting for biological implications.

The possibility of finding an asymmetric synthesis of these amino acids attracted our attention considering that the biological activity of α-amino acids is often related to the substituent stereochemistry. Furthermore, it is known that constrained amino acids incorporated into bioactive peptides play an important role on the change of the conformation of the peptides with consequent change of their biological activity.[3]

As a part of our synthetic project on the preparation of constrained carbocyclic amino acids functionalized at the *β*-position with a heteroatom,[1,4−6] we have now developed a new asymmetric synthesis which affords 2-amino-3-hydroxynorbornene-2-carboxylic acid derivatives in very good yields and enantioselectivity. In fact, through the use of new chiral building blocks **12b**,**c**, it has been possible to obtain the diastereomeric derivatives *exo*- and *endo*-**5/5′c**,**d** with a good diastereomeric excess. The chiral moiety elimination will allow obtaining the enantiomeric 2-amino-3-hydroxynorbornenecarboxylic acids.

Furthermore, the possibility of finding reaction conditions to favor the formation of endo adduct with respect to the exo one was considered. Many efforts were made to attain these targets using the classical Diels−Alder reaction between cyclopentadiene and different dienophiles and changing the reaction conditions (catalyst, temperature). As known, different approaches to asymmetric syntheses can be carried out using either chiral catalysts or chiral starting materials. Both positive and negative results of these researches are given below.

Results

A first approach to the asymmetric synthesis of 2-amino-3-hydroxynorbornene-2-carboxylic acid derivatives was found starting from oxazolone **1a**, bearing the ethoxycarbonyl group on the methylene carbon, which was reacted with cyclopentadiene (**2**) in dichloromethane at 0 °C in the presence of chiral catalyst (*R*)-1,1′-binaphthalene-2,2′-diol-titaniodibromide (BINOL-$TiBr_2$) (25%). The ^1H NMR analysis of the crude reaction mixture revealed the formation of two cycloadducts, *exo*-**3a** and *endo*-**3a**, in a 64:36 ratio. Compounds **3a** were not isolated and were transformed, after solvent elimination,

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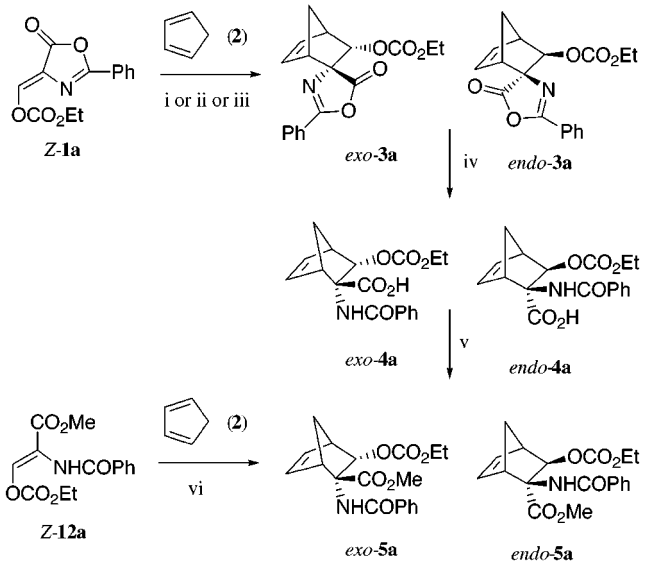
Scheme 1[a]



[a] Reagents and conditions: (i) CH_2Cl_2, $EtAlCl_2$; (ii) BINOL-$TiBr_2$, CH_2Cl_2, 0 °C; (iii) see Table 1; (iv) THF, HCl; (v) CH_2N_2, CH_2Cl_2; (vi) CH_2Cl_2, $EtAlCl_2$, 25 °C or CH_2Cl_2, $Mg(ClO_4)$, 95 °C.

Table 1. Diels–Alder Reaction of 1a with 2 in the Absence of Chiral Ligands

entry	catalyst[a]	mol equiv	*T* (°C)	*t* (h)	exo/endo[c]	yield (%)
1	A	0.2	40	2	70:30	60
2	A	0.2	25	3	70:30	74
3	A	0.2	−20	5	70:30	70
4	B	5	25	5	70:30	88
5	B	5	−20	18	70:30	88
6	C	0.2	25	1	70:30	90
7	D[b]	0.2	−20	5	85:15	50
8	D[b]	0.2	−50	8	82:18	64
9	D[b]	0.05	−50	18	75:25	25
10	D[b]	0.01	−20	48	69:31	78
11	E[b]	0.2	−20	48		
12	E[b]	0.2	25	18	68:32	79

[a] A = $EtAlCl_2$; B = $LiClO_4$; C = $Mg(ClO_4)_2$; D = $Ce(OTf)_4 \cdot H_2O$; E = $Yb(OTf)_4 \cdot H_2O$. [b] Molecular sieves. [c] Determined by ^1H NMR.

into the corresponding acids **4a** by treating the crude reaction mixture with acetic acid and a catalytic amount of HCl. After chromatography, the fraction containing the acid derivatives **4a** was dissolved in dichloromethane and treated with an excess of diazomethane, giving the corresponding methyl esters **5a** in 80% overall yield. The HPLC analysis using a chiral column did not show enantiomeric excess either in the couple of exo enantiomers or in that of endo enantiomers (Scheme 1).

An alternative approach involved catalyzing the cycloaddition reaction with a Lewis acid in the presence of chiral bis-oxazolines **6**–**9**. The use of these ligands requires a catalyst different from ethylaluminum dichloride, which is usually the best catalyst for the cycloaddition reactions involving alkylideneoxazolones. Accordingly, the reaction between oxazolone **1a** and cyclopentadiene (**2**) was studied with different Lewis acids. $LiClO_4$, $Mg(ClO_4)_2$, $Ce(OTf)_4$, and $Yb(OTf)_3$ were tested as catalysts in different reaction conditions (molar ratio, temperature, presence of molecular sieves) operating in dichloromethane as the solvent, and the results are reported in Table 1 in comparison with $EtAlCl_2$. The standard reaction in the presence of $EtAlCl_2$ (entries 1–3) gave the corresponding cycloadducts *exo*/*endo*-**3a** in a 70:30 ratio, and the best yield was observed at room temperature (entry 2). As shown in Table 1, the use of $LiClO_4$ (entries 4, 5) and $Mg(ClO_4)_2$ (entry 6) increased the reaction yield giving the *exo*/*endo*-**3a** adducts in the same 70:30 ratio. The best result was observed using $Mg(ClO_4)_2$ (entry 6). In fact, the reaction proceeded very quickly (1 h) using only 0.2 equiv of catalyst per mole of dienophile. The better efficiency of $Mg(ClO_4)_2$ with respect to $LiClO_4$ can be ascribed to the better solubility of the former. Interesting results were observed using $Ce(OTf)_4$, which proved to be a very efficient catalyst (entry 10) also at very low temperature. Furthermore, a different distribution of the exo/endo adducts was obtained by changing the amount of the catalyst (entries 7–10). In fact, greater amounts of catalyst favored the formation of the exo adduct. The use of $Yb(OTf)_3$ did not give relevant results.

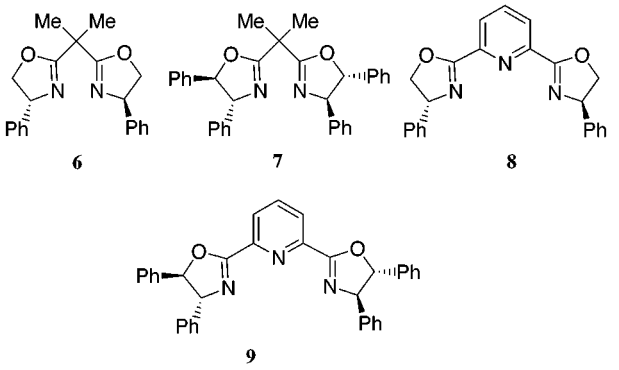


Figure 1.

Table 2. Diels–Alder Reactions of 1a with 2 and Chiral Ligands 6–9 at −20 °C

entry	catalyst[a]	ligand	*t* (h)	exo/endo[c]	endo ratio[d]	exo ratio[d]
1	A	6	48	75:25	43:57	50:50
2	A	7	24	80:20	47:53	43:57
3	A	8	100	70:30	50:50	50:50
4	A	9	24	75:25	56:44	66:34
5	B[b]	6	75	70:30	50:50	50:50
6	B[b]	8	150	75:25	50:50	50:50
7	B[b]	9	200	75:25	50:50	50:50

[a] A = $Mg(ClO_4)_2$; B = $Ce(OTf)_4 \cdot H_2O$. [b] Molecular sieves. [c] Determined by ^1H NMR. [d] Determined by HPLC.

Considering these data, we decided to test as catalysts in the cycloaddition reaction in the presence of chiral ligands the most efficient of the above, namely, $Mg(ClO_4)_2$ and $Ce(OTf)_4$. Four chiral ligands were tried to promote the asymmetric induction in the cycloaddition process, i.e., the monosubstituted bis-oxazolines **6** and **8** and the disubstituted bis-oxazolines **7** and **9**[7] (Figure 1). As shown (Table 2), the results in enantioselectivity were poor with the magnesium salt and negative with the cerium salt. Nevertheless, a reverted ratio in the formation of the exo enantiomers and endo enantiomers was observed using the magnesium salt when the ligands **7** and **9** (exo, entries 2, 4) and **6** and **9** (endo, entries 1, 4) were used.

In a second approach, chiral dienophiles were used. Two different methods were followed for the synthesis of these starting materials.

To introduce a stereocenter in the carbonate group of the oxazolone, the menthyl carbonate *Z*-**1b** was synthe-

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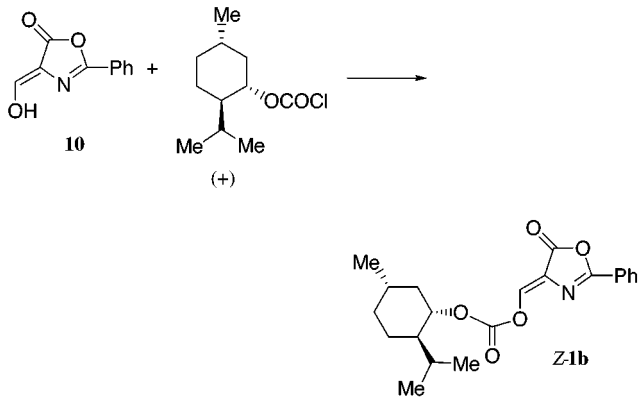
Scheme 2[a]



[a] Reagents and conditions: CH_2Cl_2, TEA, −5 °C.

sized by the same procedure as that used in the preparation of the corresponding ethyl carbonate **1a**. The chiral compound **1b** was obtained in good yield (78%) starting from 4-hydroxymethylene-5(4*H*)-oxazolone (**10**) and (+)-menthyl chloroformate at −5 °C in methylenechloride and in the presence of triethylamine (Scheme 2).

Oxazolone *Z*-**1b** was reacted with cyclopentadiene (**2**) in the presence of ethylaluminum dichloride at −20 °C. The mixture was quenched with EtOH, and a catalytic amount of AcOH/HBr was added. After chromatography, the ^{1}H NMR analysis of the fraction containing the mixture of esters **5b** and **5′b** demonstrated that four diastereomeric esters were formed. The exo/endo ratio was 60:40, and no significant diastereomeric excess was observed in each exo and endo couple (Scheme 3).

From these data, we can conclude that the bulky menthyl group increases the formation of the endo adduct as compared to the ethyl group but the effect of the chiral center on the diastereoselection is not relevant probably because of its distance from the reaction site.

The above results proved that oxazolones **1** probably are unsuitable starting materials for the enantioselective synthesis of 2-amino-3-hydroxynorbornene-2-carboxylic acids. Accordingly, our efforts were directed in the synthesis of different substrates, i.e., the chiral aminoacrylates **12b**,**c**, functionalized at C-3 with the ethyl carbonate group, which are the open-chain synthetic equivalents of oxazolones.

However, this synthetic approach suffered from a potential drawback. In fact, it is well-known that 3-substituted aminoacrylates do not react with dienes in the Diels−Alder reaction.[8] To verify the feasibility of this method and to ascertain the reactivity of the double bond, the achiral methyl 2-benzoylamino-3-ethoxycarbolyloxyacrylate **12a** was first synthesized. Many approaches were tried starting from oxazolone **1a**. Because oxazolones **1** can react with nucleophiles both at the lactone carbonyl group and at the carbonate group and also at the double bond by an addition−elimination mechanism, a mixture of compounds was obtained after reaction of methanol with **1a** in the presence of acidic or basic catalysts. Instead, the ester **12a** was successfully obtained by transforming oxazolone **1a** into the corresponding acrylic acid **11** (60%) with a catalytic amount of hydrochloric acid in THF. Compound **11** was then esterified to **12a** (95%) by reaction with diazomethane at 0 °C (Scheme 4).

The reactivity of compound **12a** with cyclopentadiene was tested with different Lewis acids ($EtAlCl_2$, $Mg(ClO_4)_2$, $Ce(OTf)_4$, and $Yb(OTf)_3$) and in different reaction conditions (amount of catalyst, temperature). Compounds **5a** were obtained (Scheme 1), but a low reactivity of the substituted acrylate double bond compared to that of oxazolones **1** was observed confirming the data reported in the literature. In fact, only $EtAlCl_2$ and $Mg(ClO_4)_2$ were efficient catalysts, but they worked only at higher temperatures and afforded lower reaction yields (see Experimental Section) compared to the corresponding reactions with oxazolone **1a** (see Table 1, entries 3, 6). However, an interesting observation was made. With the use of $EtAlCl_2$ as the catalyst, a reversed exo/endo ratio was obtained with respect to the corresponding reaction with oxazolone **1a**, which afforded (Table 1, entries 1−3) the exo/endo compounds in a 70:30 ratio. Instead, when acrylate **12a** was used as the dienophile, the exo/endo product ratio was 25:75. An explanation is given by considering that $EtAlCl_2$ coordinates the lactone group in alkylideneoxazolones, whereas in the case of amino acrylate derivatives, the coordination occurs at the amide carbonyl group.[9] The acrylate double bond is substituted at C-3, and both the cis-standing carbonate group and coordinated amido group (Scheme 5, intermediate **B**) increase the steric hindrance of this side favoring the approach of the diene from the other side so as to give preferably the endo adduct. This is not true in the case of the lactone (Scheme 5, intermediate **A**) in which the bulky catalyst hinders the opposite side. However, secondary interactions also may be of importance in explaining these results.[10]

In view of the positive results of the cycloaddition reaction of cyclopentadiene with acrylate **12a**, the synthesis of chiral acrylates **12b** and **12c**, i.e., (+)-menthyl and (−)-menthyl esters, respectively, was faced. Many problems were posed for the reasons reported above and for the lower reactivity of menthol compared to methanol. The difficulties were overcome by reacting hydroxyoxazolone **10** with (+)-menthol or (−)-menthol and bis-(dibutylchlorotin)oxide as catalyst.[11] The menthyl 3-hydroxyacrylates **13a** and **13b** were obtained in 85% yield and were reacted with ethyl choroformate in the presence of triethylamine giving the corresponding chiral compounds **12b** and **12c** (95%) (Scheme 4).

In principle, the cycloaddition reaction of cyclopentadiene with **12b** or **12c** can afford four diastereomers: two couples of adducts *exo*-**5c**, *exo*-**5′c**, *endo*-**5c**, and *endo*-**5′c** and two couples of adducts *exo*-**5d**, *exo*-**5′d**, *endo*-**5d**, and *endo*-**5′d**, respectively (Scheme 3).

The cycloaddition reaction was catalyzed both with $EtAlCl_2$ and with $Mg(ClO_4)_2$. The first catalyst was unsuccessful both at room temperature and at 45 °C; only decomposition products were found. In contrast, $Mg(ClO_4)_2$ was effective at 95 °C (Table 3, entries 2, 3), and the starting acrylates were partially transformed into the corresponding menthyl 2-phenyloxazol-4-ylcarboxylate.

A remarkable improvement in the yield of the above diastereomers was obtained when the cycloaddition reac-

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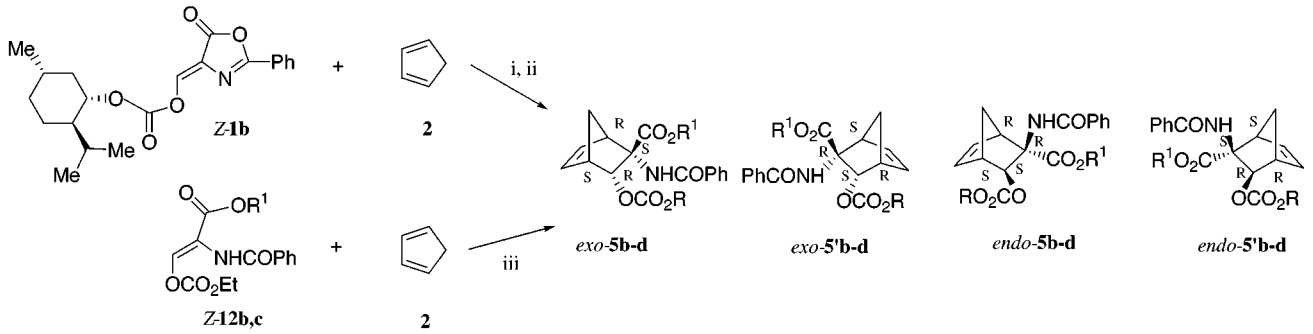
Scheme 3[a]



12b: R^1 = (+)-menthyl; **12c**: R^1 = (-)-menthyl

5b: R^1 = Et, R = (+)-menthyl; **5c,5'c**: R^1 = (+)-menthyl; R = Et; **5d,5'd**: R^1 = (-)-menthyl; R = Et

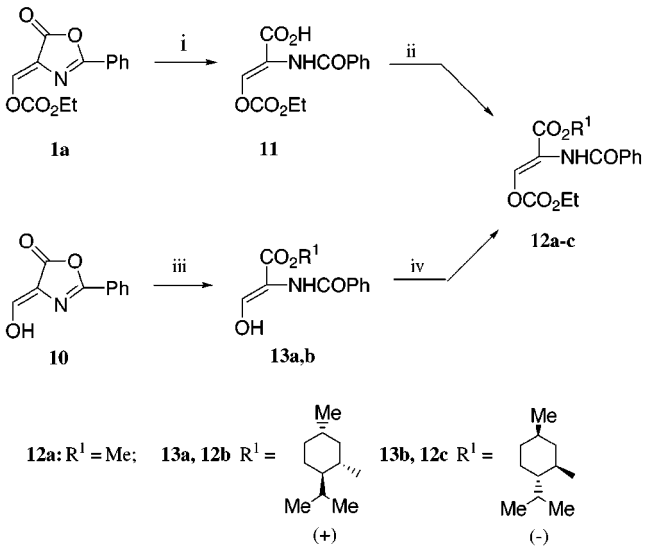
[a] Reagents and conditions: (i) CH_2Cl_2, $EtAlCl_2$, −20 °C; (ii) EtOH, AcOH/HBr; (iii) see Table 3.

Table 3. Diels−Alder Reactions of 2 with Chiral Acrylates 12b,c

entry	reagent	catalyst	method[a]	products	yield[b]	exo/endo[c]	*exo*-**5**/*exo*-**5′** (de)[d]	*endo*-**5**/*endo*-**5′** (de)[d]
1	**12c**	$EtAlCl_2$	)))	**5d/5′d**	36	70:30	23:77 (55)	87:13 (74)
2	**12b**	$Mg(ClO_4)_2$	Δ	**5c/5′c**	50	77:23	90:10 (79)	7:93 (87)
3	**12c**	$Mg(ClO_4)_2$	Δ	**5d/5′d**	50	77:23	10:90 (79)	93:7 (87)
4	**12b**	$Mg(ClO_4)_2$	)))	**5c/5′c**	90	78:22	89:11 (78)	7:93 (87)
5	**12c**	$Mg(ClO_4)_2$	)))	**5d/5′d**	90	77:23	10:90 (79)	92:8 (86)

[a] Δ: thermal reaction.))): ultrasound reaction. [b] Mixture of exo/endo isolated compounds. [c] Determined by ^{1}H NMR. [d] Determined by HPLC.

Scheme 4[a]

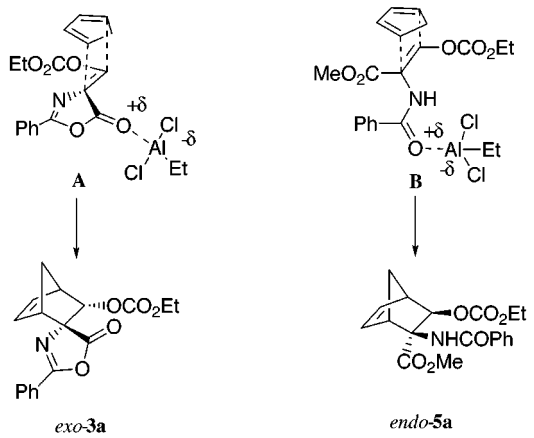


[a] Reagents and conditions: (i) THF/H_3O^+; (ii) CH_2Cl_2, CH_2N_2, 0 °C; (iii) C_6H_6, bis(dibutylchlorotin)oxyde, (+)- or (−)-menthol, reflux; (iv) CH_2Cl_2, $ClCO_2Et$, TEA.

tion was performed with ultrasound. Both $EtAlCl_2$ and $Mg(ClO_4)_2$ had a catalytic effect, but with the first catalyst, a long reaction time (48 h) and a relatively low yield (Table 3, entry 1) were observed. In contrast, excellent yields (Table 3, entries 4, 5) were achieved with the second catalyst. Furthermore, the reaction time was shorter (15 h) than that obtained by the thermal method (24 h).

The ^{1}H NMR and HPLC analyses of both the crude reaction mixtures obtained by the thermal method and those obtained by ultrasound showed analogous results, and in each exo and endo couple a different distribution existed (Table 3). Furthermore, an excess of one enantiomer with respect to the other was produced from the (+)-menthyl derivative **12b** (*exo*-**5c**, $[\alpha]^{25}_D$ +63; *endo*-**5c**, $[\alpha]^{25}_D$ +9) or from the (−)-menthyl derivative **12c** (*exo*-**5′d**, $[\alpha]^{25}_D$ −63; *endo*-**5′d**, $[\alpha]^{25}_D$ −9).

Scheme 5



The absolute configuration (1*S*,2*S*,3*R*,4*R*) of the major endo compound **5′c** was unequivocally determined by X-ray crystallography. Any attempt to prepare crystals of the exo adducts failed.

The configuration of the major endo adduct **5′c**, obtained from the (+)-menthyl ester **12b**, allows us to conclude that the isopropyl group of the menthyl substituent should have a shielding effect on the $C_{\alpha-Si}$ side of the double bond favoring the attack on the $C_{\alpha-Re}$ side (Figure S3, Supporting Information).

To support this, theoretical studies[12] to evaluate the conformational energy of **12b** were carried out through

(12) Calculations were done with the Hyperchem program (6.02 release), Hypercube, 1115 NW 4th Street, Gainesville, FL 32601, http://www.hyper.com.

a conformational search at the MM+ level;[13] the results show that most of the conformers with lower steric energy are characterized by the shielding of the isopropyl group on the Si face of the alkene **12b**. Moreover, the most representative structures were minimized using the AM1[14] semiempirical method and obtaining geometries and energy differences between distinct conformers in agreement with the data obtained at the MM+ level. In particular, the semiempirical calculations confirmed that the lowest energy conformer has a lower hindrance on the Re face and is energetically more stable by about 4 kJ mol^{-1} compared to the lower energy structure in which the isopropyl group shields the Re side.

The data reported in the literature[15] for the cycloaddition reactions of cyclopentadiene with (−)-menthyl esters of unsubstituted aminoacrylates showed that the H-1 and H-4 configurations of the norbornene ring are opposite in the exo and endo series for the major isomers, but for H-2, the same configuration holds. Furthermore, the crowded side of the olefin in compounds **12b**,**c** corresponds to the chiral acrylates of the literature.

In agreement with the above considerations and with theoretical results, we hypothesize for the major exo adduct of the (+)-menthyl series (compound **5c**) the 1*R*, 2*S*, 3*R*, 4*S* configuration.

In conclusion, many efforts were made to find an asymmetric synthesis of *exo*- and *endo*-2-amino-3-hydroxynorbornenecarboxylic acids, and this aim has been successfully attained.

As far as the stereoselectivity is concerned, some approaches were not positive, but in all cases, a lot of information was deduced in terms of catalyst choice and reaction conditions. $Mg(ClO_4)_2$ is the best catalyst, and the use of ultrasound allowed us to obtain the cycloadducts in very good yields, in mild conditions, and in a short time.

Finally, the use of alkylidene-oxazolones or acrylates and $EtAlCl_2$ or $Mg(ClO_4)_2$ as the catalysts allowed the control of the cycloaddition reaction in favor of the exo or endo products.

Experimental Section

General. Melting points are uncorrected. IR spectra of the Nujol method were measured using NaCl plates. ^1H and ^{13}C NMR were recorded in $CDCl_3$ at 200 and 50 MHz, respectively, with $CHCl_3$ as internal standard. Coupling constants (*J*) are given in hertz. Ethanol-free CH_2Cl_2 was used in all experiments. Oxazolones **1a**, **3a**, **4a**,[1] and **10**[16] are known compounds.

(*Z*)-(+)-Menthyl 5-Oxo-2-phenyloxazol-4-methylenecarbonate, 1b. Under nitrogen atmosphere, anhydrous oxazolone **10** (189 mg, 1 mmol) was suspended in anhydrous CH_2Cl_2 (5 mL). The solution was cooled at −5 °C, and menthyl chlorocarbonate (0.236 mL, 1.1 mmol) was added. A solution of triethylamine (TEA) (0.155 mL, 1.1 mmol) in CH_2Cl_2 (5 mL) was added dropwise. After 3 h, the organic layer was washed with HCl (10 mL, 10%) and dried over Na_2SO_4, and the solvent was evaporated. After crystallization of the crude reaction mixture with *i*-Pr_2O, the pure compound (*Z*)-**1b** (289 mg, 78%) was isolated: mp 98 °C. $[\alpha]^{25}_D$ +43. IR (Nujol): 1800, 1760, 1680 cm^{-1}. ^1H NMR: δ 8.20−7.40 (m, 5H), 8.10 (s, 1H, exch), 7.30 (s, 1H), 4.80−4.60 (m, 1H), 2.20−0.80 (m, 18H). Anal. Calcd: C, 67.89; H, 6.79; N, 3.77. Found: C, 67.80; H, 6.71; N, 3.72.

(*Z*)-2-Benzoylamino-3-ethoxycarbonyloxyacrylic Acid, 11. Oxazolone **1a** (700 mg, 2.7 mmol) was dissolved in THF (30 mL). H_2O (5 mL) and a catalytic amount of HCl (37%) were added, and the reaction mixture was stirred at room temperature for 30 min. The solvent was evaporated to dryness, and the crude reaction mixture was taken up with CH_2Cl_2. The pure acid **11** (430 mg, 60%) was separated as a solid and filtered: mp 160 C°, dec (EtOH). IR (Nujol): 3270, 1780, 1700, 1650 cm^{-1}. ^1H NMR: δ 9.68 (s, 1H, exch), 7.96−7.47 (m, 5H), 7.86 (s, 1H), 4.28 (q, J = 7.0, 2H), 1.26 (t, J = 7.0, 3H). Anal. Calcd: C, 55.90; H, 4.69; N, 5.02. Found: C, 55.78; H, 4.79; N, 4.93.

Methyl (*Z*)-2-Benzoylamino-3-ethoxycarbonyloxyacrylate, 12a. Acid **11** (340 mg, 1.22 mmol) was suspended in CH_2Cl_2 (10 mL). The reaction was cooled at 0 °C, and an excess of an ethereal solution of CH_2N_2 was added in small portions until the solid was dissolved. After solvent evaporation, the crude reaction mixture was chromatographed (CH_2Cl_2/Et_2O, 100:1 to 50:1). The ester **12a** was obtained in pure form (300 mg, 95%): mp 104 °C (CH_2Cl_2). IR (Nujol): 3270, 1770, 1730, 1660 cm^{-1}. ^1H NMR: δ 8.09 (s, 1H), 7.91−7.43 (m, 5H), 7.39 (s, 1H, exch), 4.33 (q, J = 7.1, 2H), 3.84 (s, 3H), 1.32 (t, J = 7.1, 3H). ^{13}C NMR: δ 165.2, 164.6, 151.3, 140.2, 133.5, 132.2, 128.7, 127.7, 113.4, 65.9, 52.6, 14.1. Anal. Calcd: C, 57.32; H, 5.16; N, 4.78. Found: C, 57.25; H, 5.10; N, 4.71.

(+)-Menthyl (*Z*)-2-Benzoylamino-3-hydroxyacrylate, 13a. Under nitrogen atmosphere, anhydrous oxazolone **10** (756 mg, 4 mmol) was suspended in anhydrous benzene (30 mL). (+)-Menthol (416 mg, 2.67 mmol) and bis(dibutylchlorotin)-oxide (243 mg, 0.44 mmol) were added, and the mixture was refluxed for 24 h, after which the starting reagents were dissolved. After solvent evaporation, the crude reaction mixture was chromatographed on silica gel (CH_2Cl_2) giving ester **13a** (800 mg, 85%) as an oil: $[\alpha]^{25}_D$ +51.

13a,b. IR (Nujol): 3350, 1710, 1660, 1640 cm^{-1}. ^1H NMR: δ 12.24 (d, J = 12.0, 1H, exch), 8.54 (s, 1H), 7.86−7.42 (m, 6H), 4.89−4.76 (m, 1H), 2.19−0.69 (m, 18H). Anal. Calcd: C, 69.53; H, 7.88; N, 4.06. Found: C, 69.45; H, 7.91; N, 3.96.

(+)-Menthyl (*Z*)-2-Benzoylamino-3-ethoxycarbonyloxyacrylate, 12b. Under nitrogen atmosphere, the ester **13a** (600 mg, 1.74 mmol) was dissolved in anhydrous CH_2Cl_2 (15 mL). The solution was cooled at −10 °C, and ethyl chlorocarbonate (0.195 mL, 2 mmol) was added. A solution of TEA (0.285 mL, 2 mmol) dissolved into CH_2Cl_2 (5 mL) was dropped in. After 3 h, the organic layer was washed with HCl (10 mL, 10%) and dried over Na_2SO_4, and the solvent was evaporated. After crystallization of the crude reaction mixture with *i*-Pr_2O/*n*-pentane, the pure compound **12b** (690 mg, 95%) was isolated: $[\alpha]^{25}_D$ +44. Mp 95 °C. IR (Nujol): 3300, 1770, 1730, 1655 cm^{-1}. ^1H NMR: δ 8.05 (s, 1H), 7.91−7.44 (m, 5H), 7.36 (s, 1H, exch), 4.92−4.79 (m, 1H), 4.35 (q, J = 7.0, 2H), 2.19−0.78 (m, 18H), 1.37 (t, J = 7.0, 3H). ^{13}C NMR: δ 165.0, 163.9, 151.5, 139.3, 133.8, 132.1, 128.7, 127.7, 113.7, 76.2, 65.8, 47.1, 40.8, 34.2, 31.5, 26.5, 23.6, 22.0, 15.5, 14.1. Anal. Calcd: C, 66.15; H, 7.49; N, 3.36. Found: C, 66.04; H, 7.41; N, 3.29.

General Procedures for the Diels Alder Reaction. Method a from 1a and BINOL-$TiBr_2$. Under argon atmosphere, anhydrous (*R*)-(+)-1,1′-binaphthole (143 mg, 0.5 mmol) was dissolved in anhydrous CH_2Cl_2 (15 mL) in the presence of molecular sieves (3 g, 4 Å, powdered). The (*i*-PrO)$_2TiBr_2$ (163 mg, 0.5 mmol) was added, and the solution was stirred at room temperature for 1 h. The solution was cooled at 0 °C, and cyclopentadiene (**2**) (528 mg, 8 mmol) and oxazolone *Z*-**1a** (524 mg, 4 mmol) were added. Stirring was continued for 24 h. The solution was evaporated, and the reaction mixture was taken up with THF (10 mL). A catalytic amount of HCl (36%) was added, and the mixture was stirred at room temperature for 4 h. After solvent elimination, the crude reaction mixture was chromatographed (CH_2Cl_2/MeOH, 1:0 to 0:1). The fraction corresponding to a mixture of the acids *exo*- and *endo*-**4a** was dissolved in CH_2Cl_2 (10 mL), and an excess of CH_2N_2 was added until the acids were transformed into the corresponding

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esters, *exo*- and *endo*-**5a** (4 h). The mixture of esters **5** was obtained in 80% overall yield (exo/endo, 64:36) and was analyzed by HPLC using an OD column (250 mm × 4.6 mm; *n*-hexane/*i*PrOH, 85:15; T = 30 °C; flow = 0.8 mL/min, λ = 254).

Method b from 1a and Different Lewis Acids. Oxazolone *Z*-**1a** (52.2 mg, 0.2 mmol) was dissolved in anhydrous CH_2Cl_2 (2 mL) under nitrogen atmosphere and under stirring. Diene **2** (15 mg, 0.22 mmol) and Lewis acid were added. Reaction conditions and results are given in Table 1. The crude reaction mixture was quickly filtered on silica gel using CH_2Cl_2 as the eluant, and the fraction corresponding to the exo/endo adducts **3a** was analyzed by ^{1}H NMR to calculate the exo/endo ratio. Yields and exo/endo ratio are given in Table 1.

Method c from 1a and Lewis Acids and Chiral Ligands 6−9. A solution of oxazolone *Z*-**1a** (52.2 mg, 0.2 mmol) dissolved in anhydrous CH_2Cl_2 (2 mL) was cooled at −20 °C under nitrogen atmosphere and under stirring. Diene **2** (15 mg, 0.22 mmol), $Mg(ClO_4)_2$ or $Ce(OTf)_4 \cdot H_2O$ (0.022 mmol), and the chiral ligand (**6**−**9**) (0.024 mmol) were added, and the reaction was stirred for the time indicated in Table 2. The reaction was monitored by ^{1}H NMR until consumption of the starting oxazolone **1a** was complete. The crude reaction mixture was filtered on a Supelclean LC-SI column (3 mL) and then analyzed by HPLC using a Chiralcel OF column (250 mm × 4 mm; *n*-hexane/*i*PrOH, 100:3; T = 30 °C; flow = 1 mL/min, λ = 254). The exo/endo ratio and the ratio of exo and endo enantiomers are given in Table 2.

Method d Starting from Oxazolone 1b. Oxazolone *Z*-**1b** (371 mg, 1 mmol) was dissolved in anhydrous CH_2Cl_2 (10 mL) under nitrogen atmosphere and stirring. The solution was cooled at −20 °C, and diene **2** (246 mg, 4 mmol) and $EtAlCl_2$ (225 μL, 1.8 M in toluene) were added. After 20 h, the solvent was evaporated, and EtOH (10 mL) and a mixture of AcOH/HBr (0.1 mL) were added. Stirring was continued for 5 h, after which the solvent was eliminated and the crude reaction mixture was chromatographed on silica gel (CH_2Cl_2/Et_2O, 1:0 to 10:1). A fraction containing the mixture of esters *exo*-**5b**, *exo*-**5′b** and *endo*-**5b**, *endo*-**5′b** was obtained (85%), which was analyzed by ^{1}H NMR from which the exo/endo ratio (60:40) and diastereomeric excess (de) (*exo*-**5b**/*exo*-**5′b**, 1:1; *endo*-**5b**/*endo*-**5′b**, 1:1) were determined.

Method e from Acrylate 12a and $EtAlCl_2$ or $Mg(ClO_4)_2$. Acrylate *Z*-**12a** (245 mg, 1 mmol) was suspended in anhydrous CH_2Cl_2 (5 mL) under nitrogen atmosphere and under stirring. Diene **2** (264 mg, 4 mmol) and Lewis acid were added ($EtAlCl_2$, 0.3 mmol, T = 25 °C, t = 3 h, 45%; $Mg(ClO_4)_2$, 1 mmol, T = 95 °C, t = 40 h, 50%). The crude reaction mixture was chromatographed on silica gel (*n*-pentane/AcOEt, 50:1 to 2:1), and the fraction corresponding to the exo/endo adducts **5a** was analyzed by ^{1}H NMR.

Method f: Thermal Method from Acrylates 12b,c and $Mg(ClO_4)_2$. Acrylate *Z*-**12b** or **12c** (500 mg, 1.2 mmol) and $Mg(ClO_4)_2$ (258 mg, 1.2 mmol) were suspended in anhydrous toluene (5 mL) under nitrogen and stirring. Diene **2** (948 mg, 5.3 mmol) was added, and the reaction mixture was warmed at 95 °C. After 24 h, the crude reaction mixture was chromatographed on silica gel (*n*-pentane/AcOEt, 50:1 to 2:1), and the fraction corresponding to the exo/endo adducts **5c**, **5′c** or **5d**, **5′d** was analyzed by ^{1}H NMR to calculate the exo/endo ratio. By HPLC with a Chiral OF column (250 mm × 4 mm; *n*-hexane/*i*PrOH, 85:15; T = 25 °C; flow = 0.8 mL/min, λ = 254), the diasteromeric excess was calculated. Yields, exo/endo ratio, and de are given in Table 3.

Method g: Ultrasound Method from Acrylates 12b,c and Lewis Acids. In a sealed tube, acrylate *Z*-**12b** or **12c** (500 mg, 1.2 mmol), the diene **2** (948 mg, 5.3 mmol), and a Lewis acid were suspended in anhydrous toluene (5 mL), and the solution was sonicated ($EtAlCl_2$, t = 48 h; $Mg(ClO_4)_2$, t = 15 h). The crude reaction mixture was chromatographed on silica gel, as described in method f, giving a mixture of exo/endo adducts **5c**, **5′c** (520 mg) or **5d**, **5′d** (525 mg), which was analyzed by ^{1}H NMR and by HPLC as reported above. Yields, exo/endo ratio, and de are given in Table 3.

It was possible to separate the diasteromeric compounds by column flash chromatography on silica gel (230−400 mesh ASTM; CH_2Cl_2/AcOEt, 50:1). In a typical procedure, a mixture of compounds *exo*-**5c**, **5′c** and *endo*-**5c**, **5′c** (500 mg) were separated (column, 3.5 mm × 25 cm; flow = 20 mL/min) giving four fractions containing *exo*-**5c** (200 mg), a mixture of *exo*-**5c**, **5′c** (150 mg), *endo*-**5′c** (120 mg), and a mixture of *endo*-**5c**, **5′c** (40 mg). The fractions were analyzed by HPLC using a silica Hipersil column (250 mm × 4.6 mm; CH_2Cl_2/AcOEt, 100:3; T = 30 °C, flow = 0.8 mL/min, λ = 254).

Methyl (1*R,2*S**,3*R**,4*S**)-2-Benzoylamino-3-ethoxycarbonyloxy-bicyclo[2.2.1]ept-5-ene-2-ylcarboxylate, *exo*-5a.** Mp 170 °C (CH_2Cl_2/*i*-Pr_2O). IR ν_{max}: 3350, 1730, 1700, 1640 cm^{-1}. ^{1}H NMR: δ 7.80−7.41 (m, 5H), 6.57 (s, 1H, exch), 6.40−6.27 (bs, 2H), 5.62 (d, J = 3.9, 1H), 4.22 (q, J = 7.0, 2H), 3.78 (s, 3H), 3.74 (bs, 1H), 3.27, (bs, 1H), 1.96, 1.75 (AB system, J = 10.2, 2H), 1.28 (t, J = 7.0, 3H). Anal. Calcd: C, 63.49; H, 5.89; N, 3.36. Found: C, 63.40; H, 5.92; N, 3.41.

Methyl (1*R,2*R**,3*S**,4*S**)-2-Benzoylamino-3-ethoxycarbonyloxy-bicyclo[2.2.1]ept-5-ene-2-ylcarboxylate, *endo*-5a.** Mp 138 °C (CH_2Cl_2/*i*-Pr_2O). IR ν_{max}: 3350, 1730, 1700, 1640 cm^{-1}. ^{1}H NMR: δ 7.83−7.41 (m, 5H), 6.98 (s, 1H, exch), 6.40−6.36, 6.23−6.18 (2 m, 2H), 5.17 (d, J = 1.8, 1H), 4.22 (q, J = 7.3, 2H), 3.70 (s, 3H), 3.35 (bs, 1H), 2.96 (bs, 1H), 2.04, 1.81 (AB system, J = 9.6, 2H), 1.28 (t, J = 7.1, 3H). Anal. Calcd: C, 63.49; H, 5.89; N, 3.36. Found: C, 63.43; H, 5.91; N, 3.40.

Ethyl 2-Benzoylamino-3-(+)-menthyloxycarbonyloxybicyclo[2.2.1]ept-5-ene-2-carboxylates, *exo*-5,5′b and *endo*-5,5′b. ^{1}H NMR (mixture of diastereomers): δ 7.80−7.40 (m, 5H), 6.94 (s, H_{endo}, exch), 6.90 (s, H_{endo}, exch), 6.53 (s, H_{exo}, exch), 6.51 (s, H_{exo}, exch), 6.35−6.15 (m, 2H), 5.64−5.23 (m, 1H), 4.56−4.47 (m, 1H), 4.28−4.11 (m, 2H), 3.70 (bs, H_{exo}), 3.30 (bs, H_{endo}), 3.20 (bs, H_{exo}), 2.91 (bs, H_{endo}), 2.80−0.62 (m, 23H).

(+)-Menthyl (1*R*,2*S*,3*R*,4*S*)-2-Benzoylamino-3-ethoxycarbonyloxybicyclo[2.2.1]ept-5-ene-2-carboxylate, *exo*-5c. Oil; $[\alpha]^{25}_D$ +63.

***exo*-5c/5′d.** IR (Nujol): 3400, 1756, 1729, 1667 cm^{-1}. ^{1}H NMR: δ 7.73−7.40 (m, 5H), 6.56 (s, 1H, exch), 6.38−6.32 (m, 2H), 5.56 (d, J = 3.7, 1H), 4.81−4.68 (m, 1H), 4.23 (q, J = 7.3, 2H), 3.77 (bs, 1H), 3.27 (bs, 1H), 2.20−2.05 (m, 1H), 1.93 (d, J = 10.3, 1H), 1.90−0.85 (m, 19H), 1.30 (t, J = 7.3, 3H). ^{13}C NMR: δ 171.5, 166.6, 153.8, 136.6, 136.2, 134.1, 131.6, 128.5, 127.0, 80.6, 75.7, 65.5, 64.5, 49.6, 47.1, 46.1, 43.9, 40.3, 34.3, 31.5, 25.8, 23.0, 22.1, 20.9, 15.8, 14.2. Anal. Calcd: C, 69.53; H, 7.72; N, 2.90. Found: C, 69.45; H, 7.68; N, 2.85.

***exo*-5′c/5d.** ^{1}H NMR: significative signals at δ 5.56 (d, 1H), 4.13 (q, 2H).

(+)-Menthyl (1*S*,2*S*,3*R*,4*R*)-2-Benzoylamino-3-ethoxycarbonyloxybicyclo[2.2.1]ept-5-ene-2-carboxylate, *endo*-5′c. Mp 150 °C (*i*Pr_2O). $[\alpha]^{25}_D$ +9.

***endo*-5′c/5d.** ^{1}H NMR: δ 7.81−7.40 (m, 5H), 6.90 (s, 1H, exch), 6.38−6.30, 6.20−6.17 (m, 2H), 5.12 (d, J = 2.2, 1H), 4.74−4.60 (m, 1H), 4.17 (q, J = 7.3, 2H), 3.38 (bs, 1H), 2.95 (bs, 1H), 2.10−2.00 (m, 1H), 2.04 (d, J = 9.2, 1H), 2.00−0.68 (m, 18H), 1.30 (t, J = 7.3, 3H). ^{13}C NMR: δ 171.1, 166.8, 153.8, 138.0, 134.3, 133.8, 131.6, 128.5, 127.0, 79.0, 75.4, 65.6, 64.4, 49.4, 47.9, 47.0, 45.8, 40.3, 34.3, 31.4, 25.7, 23.0, 22.0, 20.8, 15.8, 14.2. Anal. Calcd: C, 69.53; H, 7.72; N, 2.90. Found: C, 69.50; H, 7.74; N, 2.87.

***endo*-5c/5′d.** ^{1}H NMR: δ 7.81−7.43 (m, 5H), 6.80 (s, 1H, exch), 6.38−6.30, 6.23−6.18 (2 m, 2H), 5.19 (d, J = 1.9, 1H), 4.68−4.55 (m, 1H), 4.21 (q, J = 7.4, 2H), 3.33 (bs, 1H), 2.97 (bs, 1H), 2.10−0.70 (m, 20H), 1.27 (t, J = 7.4, 3H).

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Supporting Information Available: X-ray structure of compound *endo*-**5′c**, computational chemistry for compound **12b**, and specific rotation values for compounds **12c**, **13b**, *exo*-**5′d**, and *endo*-**5d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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