Asymmetric Diels–Alder Reactions of Chiral (*E*)-2-Cyanocinnamates with Cyclopentadiene

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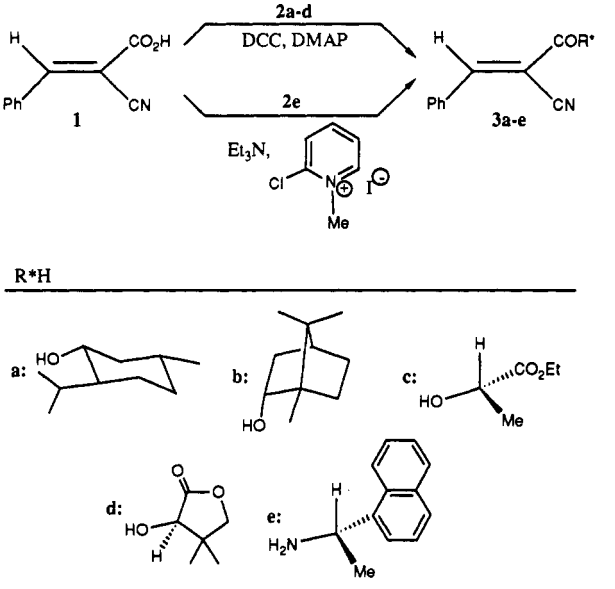
Several chiral derivatives of (*E*)-2-cyanocinnamic acid are used as trisubstituted dienophiles, and their asymmetric Diels–Alder reactions with cyclopentadiene are studied. The reactions of (*E*)-2-cyanocinnamates of (*S*)-ethyl lactate and (*R*)-pantolactone with cyclopentadiene, catalyzed by $TiCl_4$, allow the synthesis of enantiomerically pure cycloadducts whose absolute configurations are assigned by an X-ray diffraction study of enantiomerically pure (1*S*,2*S*,3*R*,4*R*,5*R*,6*R*)-iodolactone. The results obtained show that the α-cyano group influences asymmetric induction, probably through an influence on the s-cis/s-trans equilibrium of the enoate moiety of the chiral dienophile.

The Diels–Alder reaction is one of the most powerful tools available in organic synthesis and, as a consequence, the induction of asymmetry in this reaction has been profusely studied. High levels of diastereofacial selectivity have been achieved in reactions of prochiral 1,3-dienes with chiral unsaturated esters,[1] *N*-acyloxazolidinones,[2] *N*-acylsultams,[3] *O*-acylhydroxy acid derivatives,[4] and *N*-acylamino esters.[5] However, the aim of this earlier research was to study the effectiveness of the chiral auxiliary and only mono- or disubstituted dienophiles were used; there are relatively few studies on asymmetric Diels–Alder reactions with more substituted dienophiles. Recently, we have described[6] the reaction between the (*E*)-2-cyanocinnamate of (*S*)-ethyl lactate and cyclopentadiene, which was the first example of asymmetric Diels–Alder reaction with a chiral trisubstituted dienophile. The results obtained prompted us to study the reaction of cyclopentadiene with several chiral derivatives of the (*E*)-2-cyanocinnamic acid. An additional point of interest of these chiral dienophiles is that the cycloadducts obtained can easily be transformed into the 2-amino-3-phenylbicyclo[2.2.1]heptane-2-carboxylic acids,[7] opening up a route to the asymmetric synthesis of these cycloaliphatic amino acids.[8]

Scheme I



Scheme II

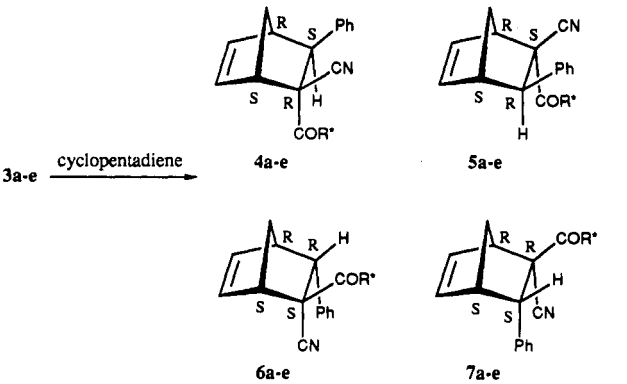


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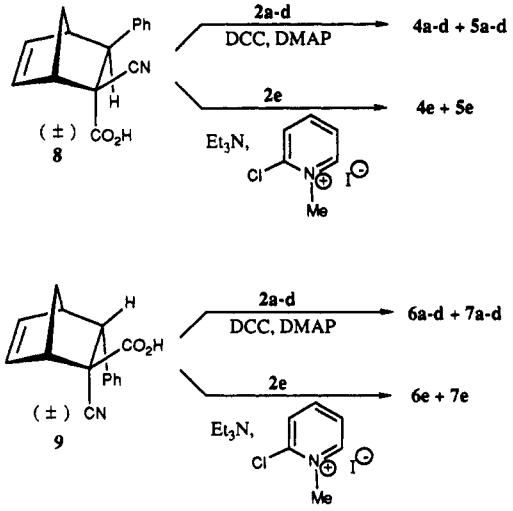
Table I. Results Obtained from the Diels–Alder Cycloadditions between Dienophiles 3a–e and Cyclopentadiene

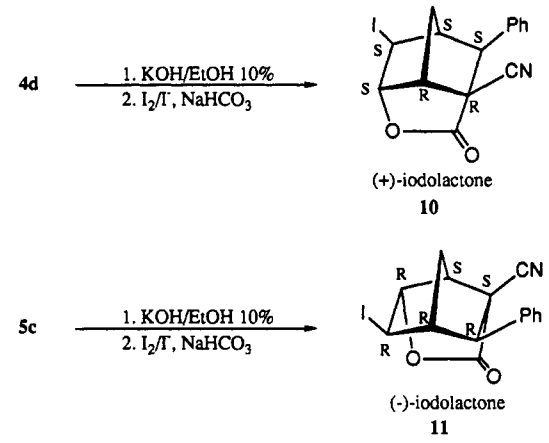
entry	dienophile[a]	diene	Lewis acid (equiv)	*T* (°C)	*t* (h)	convn[b] (%)	4 + 5:6 + 7[c]	4/5[c]
1	**3a**	3	$AlCl_3$ (0.75)	−40	24	90	80:20	36:64
2	**3b**	3	$AlCl_3$ (0.75)	−40	24	94	78:22	33:67
3	**3c**	10		20	120	99	51:49	70:30
4	**3c**	5	$AlCl_2Et$ (0.75)	20	6	86	48:52	53:47
5	**3c**	5	$AlCl_2Et$ (0.75)	0	6	98	59:41[d]	47:53[d]
6	**3c**	5	$AlCl_2Et$ (0.75)	−78	20	60	73:27	44:56
7	**3c**	5	$TiCl_4$ (0.30)	−40	44	43	88:12	15:85
8	**3c**	5	$TiCl_4$ (0.50)	−40	44	99	88:12	2:98
9	**3c**	5	$TiCl_4$ (0.75)	−40	44	97	89:11	4:96
10	**3c**	5	$TiCl_4$ (1.50)	−40	44	28	87:13	9:91
11	**3d**	10		20	48	100	66:34[d]	27:73[d]
12	**3d**	5	$AlCl_2Et$ (0.75)	−40	6	100	69:31	54:46
13	**3d**	5	$TiCl_4$ (0.75)	−40	5	94	85:15	99:1
14	**3e**	3	$TiCl_4$ (1.10)	−40	24			
15	**3e**	3	$TiCl_4$ (1.10)	20	100			

[a] All reactions were carried out in CH_2Cl_2 (c = 0.05 M). [b] Determined by HPLC using a Hypersil silica column (5 μm, 4.6-mm i.d. × 200 mm) and monitored, at 210 nm, using a diode array detector. [c] See ref 11. [d] Endo/exo ratio and diasteromeric excess (de) were ratified by integration of the ^{1}H-NMR signals for the H_6 vinylic protons.

Scheme III



Scheme IV



Chiral esters **3a–d** were prepared by the reaction of (*E*)-2-cyanocinnamic acid (**1**) and the corresponding chiral alcohol **2a–d** in the presence of DCC and DMAP.[9] The chiral amide **3e** was obtained by the reaction of the same acid **1** and (*S*)-1-(1-naphthyl)ethylamine (**2e**) in the presence of 2-chloro-1-methylpyridinium iodide and triethylamine[10] (Scheme I).

These chiral dienophiles **3a–e** were reacted with cyclopentadiene (Scheme II) and, in order to find suitable methods for determining the results of the reactions, the cycloadducts were prepared by alternative synthetic procedures. Endo cycloadducts **4a–e** and **5a–e** were obtained from the (±)-2-*exo*-cyano-3-*exo*-phenylbicyclo[2.2.1]-hept-5-ene-2-*endo*-carboxylic acid (**8**)[7] and the corresponding chiral auxiliary, following the same procedures described for the synthesis of the dienophiles. Starting from (±)-2-*endo*-cyano-3-*endo*-phenylbicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylic acid (**9**)[7], exo-cycloadducts **6a–e** and **7a–e** were obtained in the same way (Scheme III). The results of the reactions of cyclopentadiene with **3c**, **3d** and **3e** were determined by HPLC analysis of the crudes of the Diels-Alder reactions,[11] but in the reactions of cyclopentadiene with **3a** and **3b**, the direct HPLC analysis only allowed the determination of the percentage of conversion. In order to determine the endo/exo ratio and the diastereofacial selectivities of the latter reactions, the mixtures of cycloadducts afforded by them, **4a–7a**, **4b–7b**, were saponified and reacted with (*S*)-1-(1-naphthyl)ethylamine to yield mixtures of amides **4e–7e**, which were analyzed by HPLC.[11]

Table I shows the results obtained from the Diels–Alder reactions. As the absolute configurations of the cyclo-

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(11) Entries 1 and 2: The Diels–Alder reactions were quenched, saponified by addition of 10% KOH/EtOH, and purified by extraction. The oily mixture of acid exo and endo cycloadducts was derivatized with (*S*)-(−)-1-(1-naphthyl)ethylamine, following the same procedure for the synthesis of **4e**, **5e**, **6e**, and **7e** described in the Experimental Section. Endo/exo ratio and de (**4e**/**5e**) were determined by HPLC, using a hexane–^{i}PrOH mixture as the mobile phase. Linear gradient from 99:1 to 98:2 (v/v) in 3 min and other linear gradient from 98:2 to 95:5 in 0.5 min. Flow rate: 1.2 mL/min. Entries 3–10: Endo/exo ratio and de (**4c**/**5c**) were determined by HPLC using a 95:5 hexane–*tert*-butyl methyl ether mixture as mobile phase. Flow rate: 2.5 mL/min. Entries 11–13: Endo/exo ratio and de (**4d**/**5d**) were determined by HPLC using a hexane-*tert*-butyl methyl ether mixture as eluent. First 75:25 for 4 min and then lineal gradient for 0.5 min until 60:40. Flow rate 2 mL/min.

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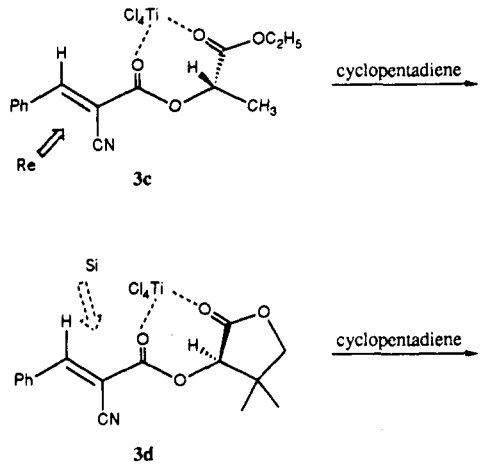
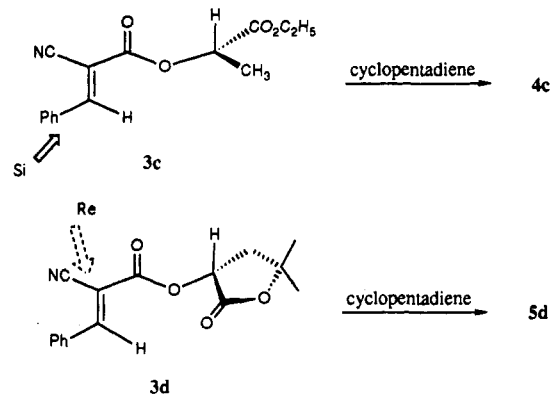
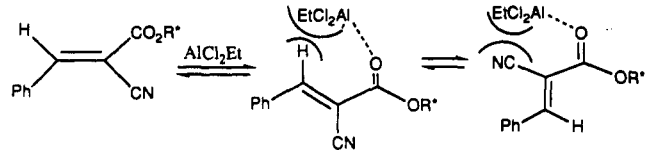
Scheme V



Scheme VI



Scheme VII



adducts are unknown, the mixtures afforded by the most selective reactions (entries 8 and 13) were saponified and transformed into the corresponding iodolactones **10** and **11** (Scheme IV), which were recrystallized until they had constant optical rotations. Polarimetric analysis[12-15] showed that both iodolactones displayed enantiomeric configurations, which were determined by X-ray analysis of **11**. Given that the results obtained from the Diels–Alder reactions of the other dienophiles were determined by HPLC analysis of the amides **4e–7e**, the mixtures resulting from the reactions used to obtain the iodolactones (entries 8 and 13) were transformed into the corresponding mixtures of amides **4e–7e** and analyzed by HPLC.[11] These analyses allowed us to determine the absolute configuration of the cycloadduct, preferably obtained from the reactions of **3a** and **3b** with cyclopentadiene.

The results summarized in Table I show that chiral (*E*)-2-cyanocinnamates are efficient dienophiles and high conversions can be obtained at room temperature or, in the presence of Lewis acids, even at lower temperatures. However, amides are worse dienophiles and no reaction is observed. The endo/exo ratio depends on the reaction conditions, in a such a way that high values are only afforded in the presence of Lewis acid and at low reaction temperatures. As expected, diastereofacial selectivity depends on both the chiral auxiliary and the reaction conditions. The best results are observed when chiral derivatives of α-hydroxy acids are used as chiral auxiliaries **3c, 3d**. The reactions of the latter dienophiles with cyclopentadiene take place with high diastereofacial selectivities when $TiCl_4$ is used as a catalyst. The direction of the asymmetric induction and the dependence of the results obtained on the amount of $TiCl_4$ agree with the model of dienophile–$TiCl_4$ chelate complex proposed by Helmchen[4] to explain the results in the reactions of acrylates of (*S*)-ethyl lactate and (*R*)-pantolactone with cyclopentadiene (Scheme V).

The noncatalyzed reactions of **3c** and **3d** with cyclopentadiene take place with moderate diastereofacial selectivities and, in comparison with $TiCl_4$-catalyzed reactions, with reversal induction. These results suggest that the approach of the diene takes place preferably on the s-trans conformation of the dienophile (Scheme VI).

Surprisingly, the $EtAlCl_2$-catalyzed reactions proceed with very low diastereofacial selectivities. In aluminum-catalyzed reactions of chiral acrylates, the coordination of the catalyst leads to a marked preference for the s-trans conformer of the dienophile. The presence of the α-cyano group may modify the s-cis/s-trans conformational equilibrium in such a way that there is no great preference for any conformer, which accounts for the low diastereofacial selectivities (Scheme VII).

The results obtained show that trisubstituted chiral propenoates possessing two activating substituents are efficient dienophiles in asymmetric Diels–Alder reactions. The results obtained with chiral acrylates cannot be directly extrapolated to these dienophiles, because the presence of a substituent geminal to the chiral alcoxycarbonyl group may modify asymmetric induction through a modification of the s-cis/s-trans equilibrium of the dienophile. However, the right choice of chiral auxiliary and reaction conditions permits the obtenting of enantiomerically pure cycloadducts.

Experimental Section

All manipulations with air-sensitive reagents were carried out under a dry argon atmosphere, using standard Schlenk techniques. Solvents were purified according to standard procedures. $EtAlCl_2$ (1 M solution in hexane), $TiCl_4$ (1 M solution in CH_2Cl_2), and other chemical reagents were purchased from the Aldrich Chemical Co. Organic solutions were dried over anhydrous Na_2SO_4 and, when necessary, were concentrated under reduced pressure with a rotary evaporator. Analytical TLC was performed by using Kieselgel 60 F_{254} plates. Column chromatography was performed by using Kieselgel 60 (230–400 mesh). ^1H and ^{13}C-NMR spectra were recorded in $CDCl_3$ with TMS as the internal standard (the chemical shifts are reported in ppm on the δ scale, coupling constants in Hz). Melting points are uncorrected. Optical rotations were measured in 1 dm cells of 1 ml capacity.

Preparation of Chiral Dienophiles. General Procedure. A solution of (*E*)-2-cyanocinnamic acid (**1**) (1.73 g, 10 mmol), alcohols **2a–d** (10 mmol), and DMAP (220 mg, 1.8 mmol), in CH_2Cl_2 (15 mL), was cooled at 0 °C. DCC (2.27 g, 11 mmol) was dissolved in CH_2Cl_2 (5 mL) and added dropwise to the previous solution. The mixture was stirred for 1 h at 0 °C, warmed to room temperature, and stirred for an additional 20 h. The separated *N,N'*-dicyclohexylurea was filtered off and washed with CH_2Cl_2. The combined filtrate and washings were evaporated, and Et_2O (20 mL) was added to the oil residue. The corresponding *N*-acylurea was filtered off and washed with Et_2O. The filtrate was concentrated in vacuo and the residue was purified by silica column chromatography or recrystallization.

(−)-(1*R*,2*S*,5*R*)-Menthyl (*E*)-2-Cyanocinnamate (3a). Purified by silica column chromatography (benzene/hexane (1:1)). Isolated yield, 2.89 g (93%) as an oil. ^1H-NMR: δ 0.75 (d, 3 H, J = 6.9, Me_2-C_7); 0.87 (d, 3 H, J = 7.0, Me_2-C_7); 0.88 (d, 3 H, J = 6.3, Me-C_5); 0.86–0.92 (m, 1 H, H_4), 0.95–1.14 (m, 2 H, H_6 and H_3); 1.41–1.55 (m, 2 H, H_2 and H_5); 1.62–1.68 (m, 2 H, H_3 and

H_4); 1.86–1.95 (m, 1 H, H_7); 2.02 (m, 1 H, H_6); 4.83 (td, 1 H, J_{ax-ax} = 10.8, J_{ax-eq} = 4.3, H_1); 7.40–7.51 (m, 3 H, $2H_m$ and H_p); 7.93 (m, 2 H, $2H_o$); 8.18 (s, 1 H, C*H*=C). ^{13}C-NMR: δ 16.5 (*Me*$_2$-C_7); 20.7 (*Me*$_2$-C_7); 22.0 (*Me*-C_5); 23.5 (C_3); 26.4 (C_7); 31.4 (C_5); 34.1 (C_4); 40.6 (C_6); 46.8 (C_2); 77.0 (C_1); 103.4 (PhC=*C*); 115.4 (*C*N); 129.3, 131.1 (o- and m-arom.); 131.6 (ipso-arom.); 133.2 (p-arom.); 154.7 (Ph*C*=C); 161.9 (*C*O). Anal. Calcd for $C_{20}H_{25}NO_2$: C, 77.14; H, 8.09; N, 4.50. Found: C, 77.15; H, 8.06; N, 4.52.

(–)-(1*S*,2*R*,4*S*)-Bornyl (*E*)-2-Cyanocinnamate (3b). Recrystallized from hexane. Isolated yield, 2.59 g (84%). Mp: 142–4 °C. ^{1}H-NMR: δ 0.92 (s, 6 H, $(CH_3)_2$C); 0.94 (s, 3 H, CH_3); 1.13 (dd, 1 H, J_{6x-5x} = 13.9, J_{6x-6n} = 3.4, H_{6x}); 1.29–1.44 (m, 2 H, H_{5x} and H_{5n}); 1.73–1.82 (m, 2 H, H_{6n} and H_{3n}); 2.09–2.19 (m, 1 H, H_4); 2.44 (m, 1 H, H_{3x}); 5.07 (dd, 1 H, J_{2x-3x} = 9.7, J_{2x-6x} = 3.0, H_{2x}); 7.69 (m, 3 H, $2H_m$ and H_p); 7.99 (m, 2 H, $2H_o$); 8.23 (s, 1 H, PhC*H*=C). ^{13}C-NMR: δ 13.6 (*Me*-C_7); 18.9 (*Me*-C_7); 19.8 (*Me*-C_1); 27.1 (C_6); 28.1 (C_5); 36.8 (C_3); 45.0 (C_4); 48.0 (C_7); 49.3 (C_1); 82.8 (C_2); 103.5 (PhC=*C*); 115.4 (*C*N); 129.3, 131.1 (o- and m-arom.); 131.6 (ipso-arom.); 133.3 (p-arom.); 154.7 (Ph*C*=C); 162.7 (*C*O). Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.62; H, 7.51; N, 4.50.

(*E*)-2-Cyanocinnamate of (*S*)-Ethyl Lactate (3c). Recrystallized from MeOH/H_2O. Isolated yield, 2.50 g (91%). Mp: 89–91 °C. ^{1}H-NMR: δ 1.26 (t, 3 H, *J* = 8.0, CH_2CH_3); 1.62 (d, 3 H, *J* = 6.7, $CHCH_3$); 4.20 (q, 2 H, *J* = 8.0, CH_2CH_3); 5.20 (q, 1 H, *J* = 6.7, *C*HCH_3); 7.30–7.70 (m, 3 H, $2H_m$ and H_p); 7.80–8.20 (m, 2 H, $2H_o$); 8.23 (s, 1 H, *H*C=C). ^{13}C-NMR: δ 14.1 (CH_2CH_3); 16.8 (CH*C*H$_3$); 61.7 (CH_2CH_3); 70.6 (*C*HCH$_3$); 102.3 (PhC=*C*); 115.1 (*C*N); 129.3; 131.2 (o,m-arom.); 131.4 (ipso-arom.); 133.6 (p-arom.); 155.8 (PhC=C); 162.0 (C=*C*O); 169.9 (CO_2Et). Anal. Calcd for $C_{15}H_{15}NO_4$C, 65.92; H, 5.53; N, 5.13. Found: C, 65.99; H, 5.51; N, 5.10.

(*E*)-2-Cyanocinnamate of (*R*)-Pantolactone (3d). Recrystallized from EtOH. Isolated yield 2.50 g (92%). Mp: 112–4 °C. ^{1}H-NMR: δ 1.27 (s, 3 H, CH_3); 1.29 (s, 3 H, CH_3); 4.10 (d, 1 H, *J* = 9.0, CH_2OCO); 4.15 (d, 1 H, *J* = 9.0, CH_2OCO); 5.49 (s, 1 H, CO_2CHCO_2); 7.50–7.64 (m, 3 H, $2H_m$ and H_p); 8.00–8.05 (m, 2 H, $2H_o$); 8.34 (s, 1 H, PhC*H*=C). ^{13}C-NMR: δ 19.8 (CH_3); 22.9 (CH_3); 40.3 (*C*(CH$_3$)$_2$); 76.3 (CH_2OCO); 76.9 (CO_2CHCO_2); 101.5 (PhC=*C*); 114.8 (*C*N); 129.4; 131.4 (o,m-arom.); 132.4 (ipso-arom.); 133.9 (p-arom.); 156.7 (Ph*C*=C); 161.6 (C=*C*CO); 171.3 (*C*O pantolactone). Anal. Calcd for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.39; H, 5.27; N, 4.93.

(*E*)-*N*-[(*S*)-(–)-1-(1-Naphthyl)ethyl]-2-cyanocinnamide (3e). A mixture of (*S*)-(–)-1-(1-naphthyl)ethylamine (**2e**) (205 mg, 1.2 mmol), 2-chloro-1-methylpyridinium iodide (306 mg, 1.2 mmol), triethylamine (243 mg, 2.4 mmol), and (*E*)-2-cyanocinnamic acid (**1**) (173 mg, 1.0 mmol) in CH_2Cl_2 (20 mL) was heated at reflux for 2 h and stirred for an additional 20 h at room temperature. The solvent was removed, and the oil residue was purified by silica column chromatography (cyclohexane/EtOAc (1:1)) to give 277 mg (85%) of **3e** as an oil: ^{1}H-NMR: δ 1.77 (d, 3 H, *J* = 8.0, *Me*CH); 6.08 (m, 1 H, C*H*Me); 6.61 (d, 1 H, *J* = 4.0, N*H*CH); 7.05–8.13 (m, 12 H, arom.); 8.38 (s, 1 H, PhC*H*=C). ^{13}C-NMR: δ 20.9 (*C*H$_3$); 76.5 (NH*C*HCH$_3$); 103.8 (PhC=*C*); 117.1 (*C*N); 122.7; 123.0; 125.3; 125.9; 126.7; 128.7; 129.0; 129.2; 130.6; 130.9; 131.8; 132.8; 134.0; 137.3 (arom.); 153.4 (PhC=C); 159.2 (C=*C*CO). Anal. Calcd for $C_{22}H_{18}N_2O$: C, 80.96; H, 5.56; N, 8.58. Found: C, 80.98; H, 5.51; N, 8.50.

Asymmetric Diels–Alder Cycloadditions without a Catalyst. General Procedure. Cyclopentadiene freshly distilled (330 mg, 5 mmol) was added to a solution of chiral dienophile (0.5 mmol) in CH_2Cl_2 (10 mL) at room temperature. The reactions were analyzed by HPLC or ^{1}H-NMR.

Asymmetric Diels–Alder Cycloadditions with a Catalyst. General Procedure. The catalyst was added, under an inert atmosphere, to a solution of chiral dienophile (0.5 mmol) in CH_2Cl_2 (10 mL). After being stirred 1 h at room temperature, the solution was cooled at reaction temperature (Table I) and freshly distilled cyclopentadiene (165 mg, 2.5 mmol) was added. The reaction was stirred for the time reported in Table I and quenched by the addition of Na_2CO_3·10H_2O. The mixture was filtered and the filtrate analyzed by HPLC or ^{1}H-NMR.

Alternative Synthesis of Endo Diels–Alder Cycloadducts. General Procedure. To a solution of (±)-2-*exo*-cyano-3-*exo*-phenylbicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic acid (**8**) (476 mg, 2 mmol) in CH_2Cl_2 (8 mL) were added alcohols **2a–d** (2 mmol), and DMAP (40 mg, 0.32 mmol). DCC (660 mg, 3.2 mmol) was dissolved in CH_2Cl_2 (2 mL) and added dropwise to the solution at 0 °C. After 1 h at 0 °C the mixture was warmed to room temperature and stirred for 20 h. The *N*,*N*′-dicyclohexylurea was filtered off and washed with CH_2Cl_2. The combined filtrate and washings were evaporated, and Et_2O (10 mL) was added to the oil residue. The precipitate was filtered off and washed with Et_2O, and the filtrate was concentrated in vacuo. The residue was purified by silica column chromatography or recrystallization.

(–)-(1′*R*,2′*S*,5′*R*)-Menthyl (1*S*,2*R*,3*S*,4*R*)- and (1*R*,2*S*,3*R*,4*S*)-2-*exo*-Cyano-3-*exo*-phenylbicyclo[2.2.1]-hept-5-ene-2-*endo*-carboxylate (4a + 5a). Purified by silica column chromatography (benzene/$CHCl_3$ (90:10)). Isolated yield, 447 mg (60%) as an oil. ^{1}H-NMR: δ 0.77 (d, 3 H, *J* = 7.0, *Me*$_2$-$C_{7'}$); 0.79 (d, 3 H, *J* = 7.0, *Me*$_2$-$C_{7'}$); 0.90 (d, 3 H, *J* = 7.0, *Me*$_2$-$C_{7'}$); 0.92 (d, 3 H, *J* = 7.0, *Me*$_2$-$C_{7'}$); 0.94 (d, 3 H, *J* = 6.3, *Me*-$C_{5'}$); 0.95 (d, 3 H, *J* = 6.3, *Me*-$C_{5'}$); 1.00–1.15 (m, 6 H, $2H_{3'}$, $2H_{4'}$ and $2H_{6'}$); 1.46–1.58 (m, 4 H, $2H_{2'}$ and $2H_{5'}$); 1.69–1.75 (m, 4 H, $2H_{3'}$ and $2H_{4'}$); 1.86–2.04 (m, 6 H, $2H_{6'}$, $2H_{7'}$ and $2H_{7s}$); 2.28–2.33 (m, 2 H, $2H_{7a}$); 3.28 (s broad, 2 H, $2H_4$); 3.60–3.65 (m, 4 H, $2H_1$ and $2H_{3n}$); 4.70–4.76 (m, 2 H, $2H_{1'}$); 6.05 (dd, 2 H, J_{6-5} = 5.6, J_{6-1} = 3.0, $2H_6$); 6.57 (dd, 2 H, J_{5-6} = 5.6, J_{5-4} = 3.0, $2H_5$); 7.25–7.42 (m, 10 H, arom.). ^{13}C-NMR: δ 16.0 (*Me*$_2$-$C_{7'}$); 20.8 (*Me*$_2$-$C_{7'}$); 22.0 (*Me*-$C_{5'}$); 23.2 ($C_{3'}$); 26.0 ($C_{7'}$); 31.4 ($C_{5'}$); 34.1 ($C_{4'}$); 40.1 ($C_{6'}$); 40.4 ($C_{6'}$); 46.7 (C_4); 46.8 ($C_{2'}$); 47.0 (C_4); 47.8 (C_7); 48.1 (C_7); 51.4 (C_3); 51.5 (C_3); 54.0 (C_1); 55.7 (C_2); 77.2 ($C_{1'}$); 77.4 ($C_{1'}$); 108.1 (*C*N); 127.3; 127.4; 128.0; 128.7; 139.3; 139.4 (arom.); 132.6 (C_6); 132.7 (C_6); 142.1 (C_5); 142.3 (C_5); 167.2 (*C*O). Anal. Calcd for $C_{25}H_{31}NO_2$C: 79.54; H, 8.28; N, 3.71. Found: C, 80.15; H, 7.98; N, 3.79.

(–)-(1′*S*,2′*R*,4′*S*)-Bornyl (1*S*,2*R*,3*S*,4*R*)- and (1*R*,2*S*,3*R*,4*S*)-2-*exo*-Cyano-3-*exo*-phenylbicyclo[2.2.1]-hept-5-ene-2-*endo*-carboxylate (4b + 5b). Purified by silica column chromatography (benzene/$CHCl_3$ (85.15)). Isolated yield, 518 mg (70%) as an oil. ^{1}H-NMR: δ 0.90 (s, 6 H, *Me*$_2$-$C_{7'}$); 0.92 (s, 3 H, *Me*-$C_{1'}$); 0.95–1.08 (m, 1 H, $H_{6'x}$); 1.28–1.37 (m, 2 H, $H_{5'x}$ and $H_{5'n}$); 1.74–1.89 (m, 2 H, $H_{6'n}$ and $H_{3'n}$); 1.93–1.98 (m, 2 H, H_{7s} and $H_{4'}$); 2.31–2.40 (m, 2 H, $H_{3'x}$ and H_{7a}); 3.29 (s broad, 1 H, H_4); 3.60 (d, 1 H, J_{3n-7s} = 2.4, H_{3n}); 3.68 (s broad, 1 H, H_1); 4.97 (m, 1 H, $H_{2'x}$); 6.08 (dd, 1 H, J_{6-5} = 5.5, J_{6-1} = 2.8, H_6); 6.55–6.59 (m, 1 H, H_5); 7.26–7.39 (m, 5 H, arom.). ^{13}C-NMR: δ 13.3 (*Me*$_2$-$C_{7'}$); 18.8 (*Me*$_2$-$C_{7'}$); 19.5 (*Me*-$C_{1'}$); 27.0 ($C_{6'}$); 27.1 ($C_{6'}$); 27.9 ($C_{5'}$); 38.7 ($C_{3'}$); 44.8 ($C_{4'}$); 46.8 (C_4); 47.9 (C_7 and $C_{7'}$); 49.2 ($C_{1'}$); 51.5 (C_3); 54.0 (C_1); 55.5 (C_2); 82.9 ($C_{2'}$); 118.2 (*C*N); 127.4; 128.1; 128.7; 138.6 (arom.); 132.7 (C_6); 132.8 (C_6); 142.1 (C_5); 142.2 (C_5); 167.2 (*C*O). Anal. Calcd for $C_{25}H_{29}NO_2$: C, 79.96; H, 7.78; N, 3.73. Found: C, 80.13; H, 7.47; N, 3.80.

(1*S*,2*R*,3*S*,4*R*)- and (1*R*,2*S*,3*R*,4*S*)-2-*exo*-Cyano-3-*exo*-phenylbicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylate of (*S*)-Ethyl Lactate (4c and 5c). The diastereomeric mixture was separated by silica column chromatography (hexane/EtOAc (80:20)). Isolated yield, 143 mg (21%) of **4c** as an oil. ^{1}H-NMR: δ 1.27 (t, 3 H, *J* = 7.1, CH_2CH_3); 1.56 (d, 3 H, *J* = 7.1, $CHCH_3$); 1.91 (dd, 1 H, J_{7s-7a} = 9.6, J_{7s-3n} = 1.8, H_{7s}); 2.32 (d, 1 H, J_{7a-7s} = 9.6, H_{7s}); 3.28 (s, 1 H, H_4); 3.62 (d, 1 H, J_{3n-7s} = 2.0, H_{3n}); 3.75 (s, 1 H, H_1); 4.22 (q, 2 H, *J* = 7.1, CH_2CH_3); 5.11 (q, 1 H, *J* = 7.1, *C*HCH_3); 6.24 (dd, 1 H, J_{6-5} = 5.6, J_{6-1} = 2.8, H_6); 6.54 (dd, 1 H, J_{5-6} = 5.6, J_{5-4} = 3.2, H_5); 7.24–7.39 (m, 5 H, arom.). ^{13}C-NMR: δ 14.2 (CH_2CH_3); 16.8 ($CHCH_3$); 47.0 (C_4); 48.1 (C_7); 51.7 (C_3); 54.8 (C_1); 55.4 (C_2); 61.7 (CH_2CH_3); 70.6 ($CHCH_3$); 118.8 (*C*N); 127.5; 128.2; 128.8; 139.3 (arom.); 133.2 (C_6); 141.7 (C_5); 167.3 (*C*O); 169.9 (CO_2Et). Anal. Calcd for $C_{20}H_{21}NO_4$: C, 79.78; H, 6.24; N, 4.13. Found: C, 79.82; H, 6.28; N, 4.16. Isolated yield, 160 mg (24%) of **5c** as an oil. ^{1}H-NMR: δ 1.27 (t, 3 H, *J* = 7.1, CH_2CH_3); 1.57 (d, 3 H, *J* = 7.1, $CHCH_3$); 1.91 (d, 1 H, J_{7s-7a} = 9.5, H_{7s}); 2.33 (d, 1 H, J_{7a-7s} = 9.5, H_{7a}); 3.28 (s, 1 H, H_4); 3.57 (d, 1 H, J_{3n-7s} = 1.8, H_{3n}); 3.65 (s, 1 H, H_1); 4.22 (m, 2 H, CH_2CH_3); 5.14 (q, 1 H, *J* = 7.1, *C*HCH_3); 6.14 (dd, 1 H, J_{6-5} = 5.5, J_{6-1} = 2.8, H_6); 6.54 (dd, 1 H, J_{5-6} = 5.5, J_{5-4} = 3.3, H_5); 7.25–7.38 (m, 5 H, arom.). ^{13}C-NMR: δ 14.1 (CH_2CH_3); 16.7 ($CHCH_3$); 46.9 (C_4); 47.9 (C_7); 52.7 (C_3); 53.5 (C_1); 55.5 (C_2); 61.7 (CH_2CH_3); 70.6 ($CHCH_3$); 118.5 (*C*N); 127.5; 128.2; 128.7; 139.1 (arom.); 133.4 (C_6); 141.6 (C_5); 167.3 (*C*O); 169.6 (CO_2Et). Anal. Calcd for $C_{20}H_{21}NO_4$: C, 79.78; H, 6.24; N, 4.13. Found: C, 79.80; H, 6.23; N, 4.10.

(1*S*,2*R*,3*S*,4*R*)- and (1*R*,2*S*,3*R*,4*S*)-2-*exo*-Cyano-3-*exo*-phenylbicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylate of

(*R*)-Pantolactone (4d and 5d). The diastereomeric mixture was separated by silica column chromatography, using (hexane/EtOAc (70:30)) as eluent. Isolated yield, 172 mg (25%) of **4d** as an oil. ^{1}H-NMR: δ 1.15 (s, 3 H, C(CH_3)$_2$); 1.23 (s, 3 H, C(CH_3)$_2$); 1.94 (dd, 1 H, J_{7s-7a} = 9.7, J_{7s-3n} = 1.8, H_{7s}); 2.38 (d, 1 H, J_{7a-7s} = 9.7, H_{7a}); 3.26 (s broad, 1 H, H_4); 3.49 (d, 1 H, J_{3n-7s} = 2.0, H_{3n}); 3.64 (s broad, 1 H, H_1); 4.07 (s, 2 H, Me_2CCH_2OCO); 5.37 (s, 1 H, CO_2CHCO_2); 6.24 (dd, 1 H, J_{6-5} = 5.5, J_{6-1} = 2.8, H_6); 6.57 (dd, 1 H, J_{5-6} = 5.5, J_{5-4} = 3.3, H_5); 7.29–7.39 (m, 5 H, arom.). ^{13}C-NMR: δ 19.9 (CH_3); 23.0 (CH_3); 40.4 (C(CH_3)$_2$); 47.4 (C_4); 47.9 (C_7); 53.0 (C_3); 54.1 (C_1); 55.7 (C_2); 76.2 (CH_2OCO); 76.7 (CO_2CHCO_2); 118.4 (*C*N); 127.7; 128.4; 128.7; 138.6 (arom.); 134.0 (C_6); 141.5 (C_5); 167.2 (*C*O); 171.2 (*C*O pantolactone). Anal. Calcd for $C_{21}H_{21}NO_4$: C, 71.78; H, 6.02; N, 3.99. Found: C, 71.80; H, 6.02; N, 4.03. Isolated yield, 151 mg (22%) of **5d** as an oil. ^{1}H-NMR: δ 1.19 (s, 3 H, C(CH_3)$_2$); 1.23 (s, 3 H, C(CH_3)$_2$); 1.93 (dd, 1 H, J_{7s-7a} = 9.6, J_{7s-3n} = 1.8, H_{7s}); 2.32 (d, 1 H, J_{7a-7s} = 9.6, H_{7a}); 3.31 (s broad, 1 H, H_4); 3.68 (d, 1 H, J_{3n-7s} = 2.0, H_{3n}); 3.74 (s broad, 1 H, H_1); 4.05 (s, 2 H, Me_2CCH_2OCO); 5.37 (s, 1 H, CO_2CHCO_2); 6.30 (dd, 1 H, J_{6-5} = 5.6, J_{6-1} = 2.8, H_6); 6.58 (dd, 1 H, J_{5-6} = 5.6, J_{5-4} = 3.2, H_5); 7.25–7.42 (m, 5 H, arom.). ^{13}C-NMR: δ 19.6 (CH_3); 22.8 (CH_3); 40.3 (C(CH_3)$_2$) 46.8 (C_4); 47.7 (C_7); 51.4 (C_3); 54.8 (C_1); 55.3 (C_2); 76.1 (CH_2OCO); 76.6 (CO_2CHCO_2); 118.4 (*C*N); 127.5; 128.0; 128.8; 138.9 (arom.); 132.9 (C_6); 142.2 (C_5); 166.9 (*C*O); 171.3 (*C*O pantolactone). Anal. Calcd for $C_{21}H_{21}NO_4$: C, 71.78; H, 6.02; N, 3.99. Found: C, 71.82; H, 6.06; N, 4.01.

(*N*)-[(*S*)-(−)-1-(1-Naphthyl)ethyl] (1*S*,2*R*,3*S*,4*R*)- and (1*R*,2*S*,3*R*,4*S*)-2-*exo*-Cyano-3-*exo*-phenylbicyclo[2.2.1]hept-5-ene-2-*endo*-carboxamide (4e and 5e). A mixture of (*S*)-(−)-1-(1-naphthyl)ethylamine (**2e**) (308 mg, 1.8 mmol), 2-chloro-1-methylpyridinium iodide (459 mg, 1.8 mmol), triethylamine (364 mg, 3.6 mmol), and carboxylic acid **8** (358 mg, 1.8 mmol) in CH_2Cl_2 (15 mL) was stirred at reflux for 2 h and 20 h at room temperature. The solvent was evaporated, and the oil diastereomeric mixture was separated by silica column chromatography (using hexane/EtOAc (70:30)) to give 170 mg (24%) of **4e** and 190 mg (27%) of **5e** as oils. **4e.** ^{1}H-NMR: δ 1.70 (d, 3 H, *J* = 6.9, CH_3CH); 1.80 (d, 1 H, J_{7a-7s} = 9.3, H_{7s}); 2.25 (d, 1 H, J_{7s-7a} = 9.3, H_{7a}); 3.23 (s broad, 1 H, H_4); 3.29 (s broad, 1 H, H_1); 3.83 (d, 1 H, J_{7s-3n} = 1.5, H_{3n}); 5.78 (dd, 1 H, J_{6-5} = 5.4, J_{6-1} = 2.7, H_6); 5.90 (m, 1 H, $CHCH_3$); 6.28 (d, 1 H, *J* = 7.2, NH); 6.52 (dd, 1 H, J_{5-6} = 5.4, J_{5-4} = 2.7, H_5); 7.08–8.05 (m, 12 H, arom.). ^{13}C-NMR: δ 20.2 (CH_3); 45.9 (C_4); 46.9 (C_7); 48.8 (C_3); 51.0 (C_1); 54.9 (C_2); 74.0 (*C*H); 120.9 (*C*N); 122.4; 122.9; 125.2; 125.9; 126.7; 127.3; 127.9; 128.6; 128.7; 128.9; 130.9; 134.0; 137.4; 139.6 (arom.); 131.7 (C_6); 141.6 (C_5); 164.9 (*C*O). Anal. Calcd for $C_{27}H_{24}N_2O$: C, 82.62; H, 6.16; N, 7.14. Found: C, 82.68; H, 6.14; N, 7.17. **5e.** ^{1}H-NMR: δ 1.68 (d, 3 H, *J* = 6.9, CH_3CH); 1.90 (d, 1 H, J_{7s-7a} = 9.6, H_{7s}); 2.31 (d, 1 H, J_{7a-7s} = 9.6, H_{7a}); 3.24 (s broad, 1 H, H_4); 3.50 (s broad, 1 H, H_1); 3.59 (s, 1 H, H_{3n}); 5.90 (m, 1 H, $CHCH_3$); 6.17 (dd, 1 H, J_{6-5} = 5.4, J_{6-1} = 2.7, H_6); 6.31 (d, 1 H, *J* = 7.2, NH); 6.56 (dd, 1 H, J_{5-6} = 5.4, J_{5-4} = 3.6, H_5); 7.09–8.06 (m, 12 H, arom). ^{13}C-NMR: δ 20.7 (CH_3); 46.1 (C_4); 47.1 (C_7); 48.8 (C_3); 52.6 (C_1); 54.5 (C_2); 74.0 (*C*H); 120.8 (*C*N); 122.4; 122.9; 125.2; 125.9; 126.7; 127.3; 127.9; 128.6; 128.7; 128.9; 130.9; 134.0; 137.5; 139.3 (arom.); 132.3 (C_6); 141.1 (C_5); 165.2 (*C*O). Anal. Calcd for $C_{27}H_{24}N_2O$: C, 82.62; H, 6.16; N, 7.14. Found: C, 82.66; H, 6.18; N, 7.19.

Alternative Synthesis of Exo Diels–Alder Cycloadducts. General Procedure. Compounds **6a–d** and **7a–d** were prepared in a similar way, starting from (±)-2-*endo*-cyano-3-*endo*-phenylbicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylic acid **9**.

(−)-(1′*R*,2′*S*,5′*R*)-Menthyl (1*S*,2*S*,3*R*,4*R*)- and (1*R*,2*R*,3*S*,4*S*)-2-*endo*-Cyano-3-*endo*-phenylbicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylate (6a + 7a). Purified by silica column chromatography, using benzene/$CHCl_3$ (90:10) as eluent. Isolated yield, 637 mg (85%) as an oil. ^{1}H-NMR: δ 0.80 (d, 3 H, *J* = 9.0, Me_2-$C_{7'}$); 0.90 (d, 3 H, *J* = 9.0, Me_2-$C_{7'}$); 0.95 (d, 3 H, *J* = 9.0, *Me*-$C_{5'}$); 0.95–1.34 (m, 3 H, $H_{3'}$, $H_{4'}$, and $H_{6'}$); 1.42–1.69 (m, 2 H, $H_{2'}$ and $H_{5'}$); 1.70–1.74 (m, 3 H, $H_{3'}$, $H_{4'}$, and $H_{6'}$); 1.88–1.93 (m, 3 H, $H_{7'}$, H_{7a}, and H_{7s}); 3.33 (s broad, 1 H, H_4); 3.50 (s broad, 1 H, H_1); 4.15 (d, 1 H, *J* = 2.9, H_{3x}); 4.78–4.88 (m, 1 H, $H_{1'}$); 6.50 (dd, 1 H, J_{6-5} = 5.6, J_{6-1} = 3.0, H_6); 6.67 (dd, 1 H, J_{5-6} = 5.6, J_{5-4} = 3.0, H_5); 7.26–7.33 (m, 5 H, arom.). ^{13}C-NMR: δ 16.0 (Me_2-$C_{7'}$); 20.8 (Me_2-$C_{7'}$); 22.0 (*Me*-$C_{5'}$); 23.0 ($C_{3'}$); 23.1 ($C_{3'}$); 26.0 ($C_{7'}$); 26.2 ($C_{7'}$); 31.4 ($C_{5'}$); 34.0 ($C_{4'}$); 40.3 ($C_{6'}$); 46.8 ($C_{2'}$); 47.6 (C_4); 48.1 (C_7); 48.2 (C_7); 53.3 (C_1); 53.6 (C_1); 55.0 (C_3); 55.2 (C_3); 55.5 ($C_{2'}$); 77.5 ($C_{1'}$); 117.8 (*C*N); 127.4; 128.3; 128.9; 138.1 (arom.); 135.6 (C_6); 139.0 (C_5); 168.7 (*C*O). Anal. Calcd for $C_{25}H_{31}NO_2$: C, 79.54; H, 8.28; N, 3.71. Found: C, 80.23; H, 7.89; N, 3.89.

(−)-(1′*S*,2′*R*,4′*S*)-Bornyl (1*S*,2*S*,3*R*,4*R*)- and (1*R*,2*R*,3*S*,4*S*)-2-*endo*-Cyano-3-*endo*-phenylbicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylate (6b + 7b). Purified by silica column chromatography (benzene/$CHCl_3$ (85:15)) and recrystallized from hexane. Isolated yield, 674 mg (91%). Mp: 97–9 °C. ^{1}H-NMR: δ 0.89 (s, 6 H, Me_2-$C_{7'}$); 0.90 (s, 6 H, Me_2-$C_{7'}$); 0.91 (s, 3 H, *Me*-$C_{1'}$); 0.94 (s, 3 H, *Me*-$C_{1'}$); 1.02–1.15 (m, 2 H, $2H_{6'x}$); 1.25–1.40 (m, 4 H, $2H_{5'x}$ and $2H_{5'n}$); 1.69–1.92 (m, 6 H, $2H_{7s}$, $2H_{6'n}$, and $2H_{3'n}$); 1.95–2.02 (m, 4 H, $2H_{7a}$ and $2H_{4'}$); 2.43–2.45 (m, 2 H, $2H_{3'x}$ 3.34 (s broad, 2 H, $2H_4$); 3.50 (m, 2 H, $2H_1$); 4.09 (d, 1 H, *J* = 2.7, $1H_{3x}$); 4.14 (d, 1 H, *J* = 2.7, $1H_{3x}$); 5.02–5.09 (m, 2 H, $2H_{2'x}$); 6.52 (dd, 2 H, J_{6-5} = 5.4, J_{6-1} = 2.9, $2H_6$); 6.68 (dd, 2 H, J_{5-6} = 5.4, J_{5-4} = 2.7, $2H_5$); 7.26–7.32 (m, 10 H, arom.). ^{13}C-NMR: δ 13.6 (Me_2-$C_{7'}$); 18.9 (Me_2-$C_{7'}$); 19.7 (*Me*-$C_{1'}$); 27.0 ($C_{8'}$); 27.1 ($C_{8'}$); 28.0 ($C_{5'}$); 36.6 ($C_{3'}$); 36.7 ($C_{3'}$); 44.8 ($C_{4'}$); 47.6 (C_4); 48.0 ($C_{7'}$); 48.2 (C_7); 48.3 (C_7); 49.2 ($C_{1'}$); 53.4 (C_1); 55.2 (C_3); 55.4 (C_3); 55.5 (C_2); 83.0 ($C_{2'}$); 83.1 ($C_{2'}$); 118.0 (*C*N); 118.4 (*C*N); 127.5; 128.3; 128.9; 138.0 (arom.); 135.6 (C_6); 135.7 (C_6); 139.0 (C_5); 169.5 (*C*O). Anal. Calcd for $C_{25}H_{29}NO_2$: C, 79.96; H, 7.78; N, 3.73. Found: C, 80.18; H, 7.53; N, 3.80.

(1*S*,2*S*,3*R*,4*R*)- and (1*R*,2*R*,3*S*,4*S*)-2-*endo*-Cyano-3-*endo*-phenylbicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylate of (*S*)-Ethyl Lactate (6c + 7c). Purified by silica column chromatography, using hexane/EtOAc (80:20) as eluent. Isolated yield, 577 mg (85%) as an oil. ^{1}H-NMR: δ 1.30 (t, 6 H, *J* = 7.1, $2CH_2CH_3$); 1.58 (d, 3 H, *J* = 7.1, $CHCH_3$); 1.60 (d, 3 H, *J* = 7.1, $CHCH_3$); 1.70 (d, 1 H, J_{7s-7a} = 9.6, H_{7s}); 1.74 (d, 1 H, J_{7s-7a} = 9.6, H_{7s}); 1.90 (d, 1 H, J_{7a-7s} = 9.6, H_{7a}); 1.95 (d, 1 H, J_{7s-7s} = 9.6, H_{7a}); 3.34 (s, 2 H, $2H_4$); 3.54 (s, 1 H, H_1); 3.71 (s, 1 H, H_1); 4.14 (d, 1 H, J_{3x-4} = 1.8, H_{3x}); 4.22 (d, 1 H, J_{3x-4} = 1.8, H_{3x}); 4.25 (q, 4 H, *J* = 7.1, $2CH_2CH_3$); 5.19 (q, 2 H, *J* = 7.1, $2CHCH_3$); 6.48 (dd, 1 H, J_{6-5} = 5.6, J_{6-1} = 2.8, H_6); 6.52 (dd, 1 H, J_{6-5} = 5.6, J_{6-1} = 2.8, H_6); 6.69 (dd, 2 H, J_{5-6} = 5.6, J_{5-4} = 2.8, $2H_5$); 7.23–7.38 (m, 10 H, arom.). ^{13}C-NMR: δ 14.1 (CH_2CH_3); 16.6 ($CHCH_3$); 47.6 (C_4); 47.9 (C_4); 48.0 (C_7); 48.7 (C_7); 52.5; 54.2; 54.5; 56.0 ($2C_1$ and $2C_3$); 54.7 (C_2); 55.5 (C_2); 61.8 (CH_2CH_3); 70.8 ($CHCH_3$); 118.0 (*C*N); 118.1 (*C*N); 127.5; 127.6; 128.3; 128.4; 129.0; 129.1; 137.9; 138.0 (arom.); 135.4 (C_6); 135.5 (C_6), 139.2 (C_5); 139.3 (C_5); 168.6 (*C*O); 169.0 (*C*O); 169.9 (CO_2Et). Anal. Calcd for $C_{20}H_{21}NO_4$: C, 79.78; H, 6.24; N, 4.13. Found: C, 79.81; H, 6.20; N, 4.15.

(1*S*,2*S*,3*R*,4*R*)- and (1*R*,2*R*,3*S*,4*S*)-2-*endo*-Cyano-3-*endo*-phenylbicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylate of (*R*)-Pantolactone (6d + 7d). Purified by silica column chromatography, using hexane/EtOAc (70:30) as eluent. Isolated yield, 597 mg (85%) as an oil. ^{1}H-NMR: δ 1.21 (s, 3 H, C(CH_3)$_2$); 1.26 (s, 3 H, C(CH_3)$_2$); 1.73 (dd, 1 H, J_{7s-7a} = 9.4, J_{7s-3x} = 1.5, H_{7s}); 1.93 (d, 1 H, J_{7a-7s} = 9.4, H_{7a}); 3.37 (s broad, 1 H, H_4); 3.70 (s broad, 1 H, H_1); 4.09 (s, 2 H, Me_2CCH_2OCO); 4.32 (d, 1 H, J_{3x-7s} = 2.8, H_{3x}); 5.44 (s, 1 H, CO_2CHCO_2); 6.54 (dd, 1 H, J_{6-5} = 5.6, J_{6-1} = 3.2, H_6); 6.71 (dd, 1 H, J_{5-6} = 5.6, J_{5-4} = 3.0, H_5); 7.23–7.34 (m, 5 H, arom.). ^{13}C-NMR: δ 19.8 (CH_3); 22.8 (CH_3); 40.3 (C(CH_3)$_2$) 48.0 (C_7); 48.1 (C_4); 54.5 (C_1); 54.7 (C_3); 55.6 (C_2); 76.3 (CH_2OCO); 77.0 (CO_2CHCO_2); 117.8 (*C*N); 127.6; 128.4; 128.9; 137.7 (arom.); 135.4 (C_6); 139.3 (C_5); 168.3 (*C*O); 171.3 (*C*O pantolactone). Anal. Calcd for $C_{21}H_{21}NO_4$: C, 71.78; H, 6.02; N, 3.99. Found: C, 71.81; H, 6.00; N, 4.05.

(*N*)-[(*S*)-(−)-1-(1-Naphthyl)ethyl] (1*S*,2*S*,3*R*,4*R*)- and (1*R*,2*R*,3*S*,4*S*)-2-*endo*-Cyano-3-*endo*-phenylbicyclo[2.2.1]hept-5-ene-2-*exo*-carboxamide (6e and 7e). Compounds **6e** and **7e** were prepared starting from (±)-carboxylic acid **9**, following the above-described procedure for **4e** and **5e**. The diastereomeric mixture was purified by silica column chromatography, using hexane/EtOAc (70:30) as eluent. Isolated yield, 201 mg (28%) of **6e** as an oil. ^{1}H-NMR: δ 1.67 (d, 4 H, *J* = 6.9, CH_3CH and H_{7s}); 2.29 (d, 1 H, *J* = 9.0, H_{7a}); 3.21 (s broad, 1 H, H_4); 3.39 (s broad, 1 H, H_1); 3.94 (d, 1 H, J_{3x-4} = 2.4, H_{3x}); 5.98 (m, 1 H, $CHCH_3$); 6.45 (m, 1 H, NH) 6.49 (dd, 1 H, J_{6-5} = 5.7, J_{6-1} = 3.3, H_6); 6.66 (dd, 1 H, J_{5-6} = 5.7, J_{5-4} = 3.0, H_5); 6.85–8.12 (m, 12 H, arom.). ^{13}C-NMR: δ 20.6 (CH_3); 45.8 (C_4); 47.5 (C_7); 48.8 (C_1); 53.3 (C_3); 56.1 (C_2); 74.0 (*C*H); 120.4 (*C*N); 122.5; 122.9; 125.3; 125.9; 126.7; 128.3; 128.6; 128.7; 128.9; 129.0; 130.9; 134.0; 137.6; 137.9 (arom.); 136.5 (C_6); 139.2 (C_5); 166.9 (*C*O). Anal. Calcd for $C_{27}H_{24}N_2O$: C, 82.62; H, 6.16; N, 7.14. Found: C, 82.60; H, 6.13;

N, 7.18. Isolated yield, 230 mg (33%) of **7e** as an oil. ^{1}H-NMR: δ 1.69 (d, 4 H, J = 6.8, CH_3CH and H_{7s}); 2.21 (d, 1 H, J_{7a-7s} = 9.3, H_{7a}); 3.15 (s broad, 1 H, H_4); 3.28 (s broad, 1 H, H_1); 4.33 (d, 1 H, J_{3x-4} = 2.7, H_{3x}); 5.96-6.06 (m, 1 H, $CHCH_3$); 6.36 (dd, 1 H, J_{6-5} = 7.6, J_{6-1} = 2.9, H_6); 6.48 (dd, 1 H, J_{5-6} = 7.6, J_{5-4} = 2.9, H_5); 6.63 (m, 1 H, NH); 6.83-8.13 (m, 12 H, arom.). ^{13}C-NMR: δ 20.6 (CH_3); 46.0 (C_4); 47.7 (C_7); 48.2 (C_1); 54.3 (C_3); 54.9 (C_2); 74.0 (CH); 120.4 (CN); 122.4; 122.9; 125.2; 125.9; 126.7; 127.3; 127.9; 128.6; 128.7; 128.9; 130.9; 134.0; 137.4; 139.6 (arom.); 137.3 (C_6); 138.1 (C_5); 166.5 (CO). Anal. Calcd for $C_{27}H_{24}N_2O$: C, 82.62; H, 6.16; N, 7.14. Found: C, 82.66; H, 6.15; N, 7.10.

Synthesis of Enantiomerically Pure (1*R*,2*R*,3*S*,4*S*,5*S*,6*S*)-(+)-Iodolactone. (10). In an inert atmosphere, $TiCl_4$ (3 mL, 3 mmol) was added to a solution of **3d** (1.14 g, 4 mmol) in CH_2Cl_2 (40 mL). The solution was stirred at room temperature for 1 h and then cooled to -40 °C, and freshly distilled cyclopentadiene (1.32 g, 20 mmol) was added. After being stirred for 24 h, the solution was quenched by the addition of $Na_2CO_3 \cdot 10H_2O$ and filtered and the filtrate evaporated in vacuo. The oily residue was saponified with 10% KOH/EtOH (150 mL) and refluxed for 4 h, and the EtOH was removed in vacuo. Water (50 mL) was added and extracted with Et_2O (3 × 10 mL). The aqueous layer was acidified with HCl (12 N) and extracted with Et_2O (3 × 10 mL). The organic solution was evaporated in vacuo to yield an oily mixture of exo and endo carboxylic cycloadducts. This residue was dissolved in MeOH (5 mL), and the pH was adjusted to 8 with 5% aqueous $NaHCO_3$. It was then treated with an excess of iodine stock solution (5 g of I_2, 10 g of KI, 30 mL of water) and allowed to stand for 1 h. The precipitate was collected by filtration, washed with 5% aqueous $Na_2S_2O_3$ solution (3 × 5 mL), and dried to afford 870 mg (77%) of **10**. The iodolactone was successively recrystallized from MeOH/H_2O until constant α. Mp: 194-6 °C. $[\alpha]^{25}_D$ (c = 1.00 × 10^{-2} g/mL, $CHCl_3$); +87.5 ± 0.2°. ^{1}H-NMR: δ 2.66-2.68 (m, 2 H, H_{7a} and H_{7s}); 3.21 (s, 1 H, H_4); 3.81 (s, 1 H, H_{3n}); 3.90 (d, 1 H, J_{1-6} = 5.1, H_1); 4.40 (d, 1 H, J_{5-7a} = 1.9, H_{5n}); 5.40 (d, 1 H, J_{6-1} = 5.1, H_{6x}); 7.31-7.42 (m, 5 H, arom.). ^{13}C-NMR: δ 27.2 (C_5); 36.7 (C_7); 50.0 (C_2); 50.8; 52.5; 56.0 (C_1, C_3 and C_4); 87.8 (C_6); 114.3 (CN); 127.7; 128.6; 129.1; 135.6 (arom.); 170.8 (CO). Anal. Calcd for $C_{15}H_{12}INO_2$: C, 49.34; H, 3.31; N, 3.84; I, 34.75. Found: C, 49.29; H, 3.24; N, 3.77; I, 34.61.

Synthesis of Enantiomerically Pure (1*S*,2*S*,3*R*,4*R*,5*R*,6*R*)-(-)-Iodolactone. (11). (-)-Iodolactone **11** was obtained in a similar way, starting from the (*E*)-2-cyanocinnamate of (*S*)-ethyl lactate **3c** (1.09 g, 4 mmol). Isolated yield, 983 mg (87%). $[\alpha]^{25}_D$ (c = 1.00 × 10^{-2} g/mL, $CHCl_3$): -87.5 ± 0.2°. Anal. Calcd for $C_{15}H_{12}INO_2$: C, 49.34; H, 3.31; N, 3.84; I, 34.75. Found: C, 49.26; H, 3.26; N, 3.71; I, 34.67.

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Supplementary Material Available: X-ray crystallographic and ORTEP data for **11**, Tables S1-S4 containing a summary of crystal data, structure determination details, and atom positional and thermal parameters, a full list of bond lengths, bond and torsional angles, and interatomic contacts (15 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Insertion of Nitrogen Oxide and Nitrosonium Ion into the Cyclopropane Ring: A New Route to 2-Isoxazolines and Its Mechanistic Studies

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The 9,10-dicyanoanthracene (DCA)-sensitized photoreaction of 1,2-diarylcyclopropanes **1a-d** in nitrogen oxide (NO)-saturated CH_3CN afforded 3,5-diaryl-2-isoxazolines **2a-d** in excellent yields. The reaction of **1a-d** with $NOBF_4$ or with a mixture of NO and O_2 in CH_3CN also afforded **2a-d** or **2a-b**. These reactions proceed via the attack of NO on the radical cation of **1**, which is formed by electron transfer from **1** to ^{1}DCA* or NO^+. The reaction of 1-alkyl-2-arylcyclopropanes with $NOBF_4$ afforded mixtures of 3-alkyl-5-aryl-2-isoxazolines and 4-alkyl-5-aryl-2-isoxazolines via the direct attack of NO^+ on the cyclopropane rings. The reaction of 1,1,2,2-tetraphenylcyclopropane with $NOBF_4$ afforded 2,3,5,5-tetraphenyl-2-isoxazolinium tetrafluoroborate via the migration of the phenyl group to nitrogen.

Introduction

Nitrogen oxide (NO) has a radical character and can be used as a radical trapping agent.[1] An elegant use of this property of NO in organic synthesis is the photolysis of alkyl nitrites, in which an unactivated C-H group is nitrosated regioselectively. This reaction occurs via the photolytic cleavage of an alkyl nitrite to generate an alkoxyl radical and NO. Intramolecular hydrogen abstraction from the alkyl group by the alkoxyl radical in a 1,5-hydrogen shift fashion, followed by the attack of NO on the resulting carbon radical, produces 4-nitroso 1-ols. The reaction has been utilized for the selective introduction of functionality into a steroid skeleton.[1b] However, no information is yet available about the reactivity of NO toward radical cation species generated from organic compounds.

Nitrosonium ion (NO^+), generated from nitrosonium salts such as $NOBF_4$ and $NOPF_6$, acts as an electrophilic nitrosation reagent[2] and also as a strong one-electron ox-

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