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Reaction of 2,3-Dimethyl-1,3-Butadiene with Chiral (E)-2-Cyanocinnamates.

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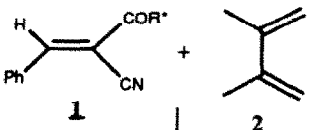
Abstract: The reactions of 2,3-dimethyl-1,3-butadiene with (E)-2-cyanocinnamates of (S)-ethyl lactate (**1a**) and (R)-pantolactone (**1b**), catalysed by $TiCl_4$, afford enantiomerically pure cycloadducts which are easily converted into the enantiomers (1R, 6S) and (1S, 6R) of the methyl 1-cyano-3,4-dimethyl-6-phenyl-3-cyclohexen-1-carboxylate. The reactions with $TiCl_4$ can be explained by the dienophile-$TiCl_4$ chelate model proposed by Helmchen. The non-catalysed reaction of (**1b**) with the same diene takes place at 100 °C, with a moderately high d.e. and reversal of selectivity.

Recently we have developed a new synthesis of 2-amino-3-phenyl-2-norbornanecarboxylic acids[1]. The key step in this synthetic procedure, the Diels-Alder reaction between cyclopentadiene and (E)-2-cyanocinnamates, can be carried out asymmetrically by using the (E)-2-cyanocinnamate of (S)-ethyl lactate as a dienophile[2]. This reaction constitutes the first useful example of an asymmetric Diels-Alder reaction with a chiral trisubstituted dienophile.

We now wish to report the reactivity of this kind of chiral trisubstituted dienophile with a less reactive diene. The reactions of (E)-2-cyanocinnamate of (S)-ethyl lactate (**1a**) and (E)-2-cyanocinnamate of (R)-pantolactone (**1b**) with 2,3-dimethyl-1,3-butadiene (**2**) are therefore used to obtain both enantiomers of methyl 1-cyano-3,4-dimethyl-6-phenyl-3-cyclohexen-1-carboxylate (**5,6**).

Chiral dienophiles (**1**) were obtained by the reaction of (E)-2-cyanocinnamic acid and the corresponding chiral alcohol in the presence of DCC and DMAP[3]. They were then reacted with 2,3-dimethyl-1,3-butadiene under several conditions. The major cycloadducts were purified by column chromatography through silica gel (AcOEt:n-hexane=7:3 for **3a**+**4a**; AcOEt:n-hexane=6:4 for **3b**+**4b**) and converted into enantiomerically pure methyl esters by saponification and methylation with diazomethane (Scheme 1). The results obtained from the asymmetric Diels-Alder reactions were determined by hplc and are collected in Table 1.



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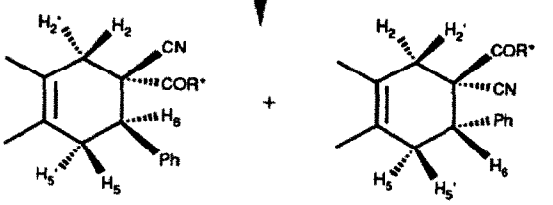
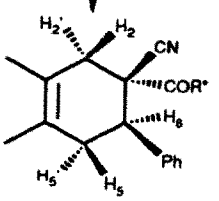


4 (1S, 6R) {**4a** (1S, 6R, S); **4b** (1S, 6R, R)} **3** (1R, 6S) {**3a** (1R, 6S, S); **3b** (1R, 6S, R)}

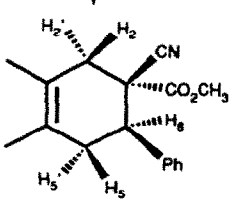
3a:**4a** = 5:95

column chromatography



4a (1S, 6R, S)

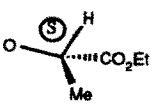
1) KOH/EtOH
2) CH_2N_2



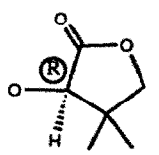
5 (1S, 6R)

R* =

a =

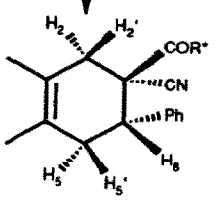


b =



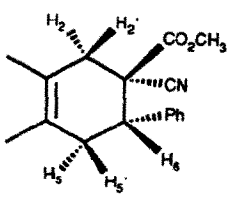
3b:**4b** = 96:4

column chromatography



3b (1R, 6S, R)

1) KOH/EtOH
2) CH_2N_2



6 (1R, 6S)

Scheme 1

Table 1.- Diels-Alder reactions of **1a** and **1b** with **2** in CH_2Cl_2.

Entry	Dienophile	Lewis acid (eq)	**2**:**1**	T(°C)	t(h)	% conversion[a]	**3**:**4**[a]
1	**1a**	---	10	40	120	60	53:47
2	**1a**[b,c]	---	10	100	---	---	---
3	**1a**	$AlCl_2Et$ (0.75)	5	-25	22	80	22:78
4	**1a**	$AlCl_2Et$ (1.40)	5	20	6	61	42:58
5	**1a**	$AlCl_2Et$ (1.40)	5	-50	21	0	---
6	**1a**	$TiCl_4$ (0.75)	5	-25	5	100	5:95
7	**1b**[b]	---	10	100	18	100	18:82
8	**1b**	$AlCl_2Et$ (0.75)	5	-25	24	100	66:34
9	**1b**	$TiCl_4$ (0.75)	5	-25	24	100	88:12
10	**1b**	$TiCl_4$ (0.75)	5	-40	24	91	96:4
11	**1b**	$TiCl_4$ (0.75)	5	-55	48	85	94:6

a. Determined by hplc. Column Hypersil® Silica (5µm, 4.6 mm id x 200 mm). Flow rate = 2 ml/min. Detection UV at 210 nm. Eluent for the reactions of **1a** Hexane:^{t}Butyl methyl ether (96:4) for 8 min, gradient 4 to 10% of ^{t}Butyl methyl ether in 0.5 min. Retention times: **3a** = 6.98 min, **4a** = 8.59 min. Eluent for the reactions of **1b** hexane:^{t}Butyl methyl ether (80:20). Retention times: **4b** = 4.44 min, **3b** = 5.29 min.

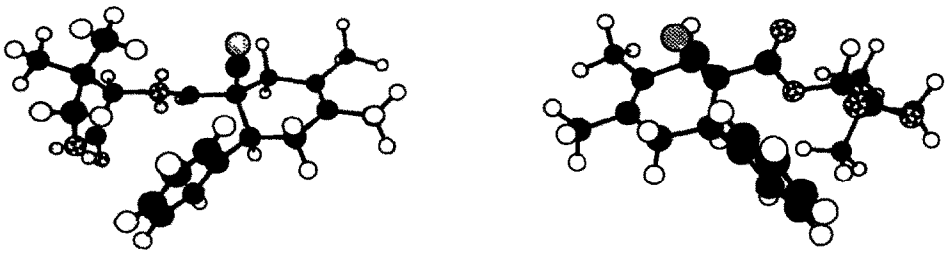
b. Reaction carried out in 1,4-dioxane.

c. Decomposition of the dienophile without formation of cycloadducts is observed.

Given that the cycloadducts obtained cannot easily be transformed into products of known absolute configuration, their absolute configurations were assigned on the basis of ^{1}H NMR data and MM2 energy minimization studies.

The results of the Diels-Alder reaction between cyclopentadiene and (E)-2-cyanocinnamate of (R)-pantolactone (entry 7) were analysed by ^{1}H NMR. An appreciable difference was observed in the chemical shifts of the methyl groups of the chiral auxiliary. In the ^{1}H NMR spectrum, the methyl signals of the major cycloadduct appear at a higher field (0.62 and 0.84 ppm) than those of the minor cycloadduct (0.91 and 0.92 ppm). Furthermore, the considerable large upfield shift ($\Delta\delta$: 0.22 ppm) shown by a methyl group of the major cycloadduct is noteworthy.

In order to explain these observations, the conformers of lowest energy of both cycloadducts were calculated by molecular mechanics, using the Chem 3D Plus™ program[4] and an MM2 force field[5]. The geometries of the most favorable conformers of (**3b**) and (**4b**) calculated by Chem 3D Plus™ program are depicted in Figure 1.

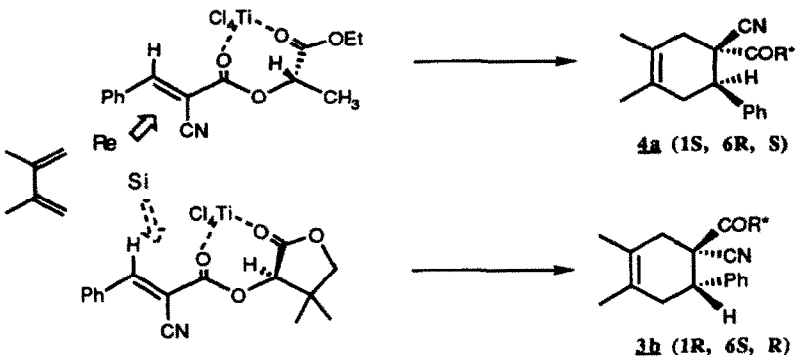


3b: (1R, 6S, R) **4b**: (1S, 6R, R)

Figure 1

Figure 1 shows a methyl group of the (1S, 6R, R) cycloadduct lying in the shielding region of the aromatic ring, providing the support required to explain the chemical shifts observed.

In conclusion, we have shown that, in non-catalysed reaction (entry 7), the (1S, 6R, R) cycloadduct is preferably obtained, in contrast to catalysed reactions (entries 8-11) where the (1R, 6S, R) cycloadduct is the predominant diastereoisomer. These results are in perfect agreement with the configurations of the cycloadducts deduced by the well established Helmchen model[6] (Figure 2), that has been successfully applied to other dienophiles[7].



4a (1S, 6R, S)

3b (1R, 6S, R)

Figure 2

Smaller diastereofacial selectivity is obtained when $AlCl_2Et$ is used as a catalyst, but the same cycloadducts are preferentially obtained with aluminium and titanium catalysts. This result indicates that the α-cyano group leads the dienophile-$AlCl_2Et$ complex to the s-cis conformation[2].

Non-catalysed reactions take place with reversal induction, but only the reaction of (E)-2-cyanocinnamate of (R)-pantolactone (**1b**) is interesting from a synthetic viewpoint. With this dienophile the non-catalysed reaction takes place with total conversion and a 64% preference of cycloadduct (**4b**).

It is difficult to account for the results obtained in a reaction carried out at 100 °C on the basis of conformational preferences, but the unexpectedly high diastereofacial selectivity obtained might be due to the interaction of the methyl groups of the diene with the chiral auxiliary in the endo approach.

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EXPERIMENTAL SECTION

(E)-2-cyanocinnamate of (S)-ethyl lactate (1a)

To a solution of (E)-2-cyanocinnamic acid (1.75 g, 10 mmol), (S)-ethyl lactate (1.18 g, 10 mmol) and N,N-dimethyl-4-aminopyridine (0.220 g, 1.8 mmol) in dry CH_2Cl_2 (15 ml), a solution of N,N'-dicyclohexylcarbodiimide (2.27 g, 11 mmol) in dry CH_2Cl_2 (5 ml) was added dropwise at 0 °C. The solution was kept at 0 °C for 1 h, then warmed at room temperature and stirred for an additional 20 h. The precipitate was filtered off and washed with CH_2Cl_2. The combined filtrate and washings were concentrated under vacuum and diethyl ether (20 ml) was added to the oily residue. The N-acylurea was filtered off and washed with diethyl ether. The filtrate and washings were combined and the solvent eliminated under reduced pressure to afford a residue that was recrystallized from MeOH/H_2O to give **1a** (2.50 g, 91.5%).

Found: C: 65.78, H: 5.69, N: 4.90.

Calc. for $C_{15}H_{15}NO_4$ C: 65.92, H: 5.53, N: 5.13

m. p.: 89-91 °C.

^{1}H-RMN ($CDCl_3$, δ): 1.26(t, 3H, J=8.0, CH_2CH_3); 1.62(d, 3H, J=6.7, $CHCH_3$); 4.20(q, 2H, J=8.0, CH_2CH_3); 5.20(q, 1H, J=6.7, $CHCH_3$); 7.30-7.70(m, 3H, H_m+H_p); 7.80-8.20(m, 2H, H_o); 8.23(s, 1H, HC=C).

^{13}C-NMR($CDCl_3$, δ): 14.1(CH_2CH_3); 16.8($CHCH_3$); 61.7(CH_2CH_3); 70.6($CHCH_3$); 102.3(PhC=C); 115.1(CN); 129.3; 131.2(C_{orto}+C_{meta}); 131.3(C_{ipso}); 133.6(C_{para}); 155.8(PhC=C); 162.0(C=C-CO); 169.8 (CO_2Et).

(E)-2-cyanocinnamate of (R)-pantolactone (1b)

This product was prepared by the above described procedure using EtOH as a recrystallisation solvent. Starting from (E)-2-cyanocinnamic acid (10 mmol) and (R)-pantolactone (10 mmol) 2.62 g (92%) of **1b** were obtained.

Found: C: 67.12, H: 5.22, N: 5.17

Calc. for $C_{16}H_{15}NO_4$ C: 67.36, H: 5.30, N: 4.91

m. p.: 112-4 °C.

^{1}H-RMN ($CDCl_3$, δ): 1.27(s, 3H, CH_3); 1.29(s, 3H, CH_3); 4.10(d, 1H, J=9.0, CH_2OCO); 4.15(d, 1H, J=9.0, CH_2OCO); 5.49(s, 1H, CO_2CHCO_2); 7.51-7.61(m, 3H, H_m+H_p); 8.03(d, 2H, J=7.5, H_o); 8.34(s, 1H, PhCH=C).

^{13}C-NMR($CDCl_3$,δ): 19.8(CH_3); 22.9(CH_3); 40.3($C(CH_3)_2$); 76.3(CH_2OCO); 76.9(CO_2CH); 101.5 (PhC=C); 114.8(CN); 129.4; 131.4(C_{orto}+C_{meta}); 132.4(C_{ipso}); 133.9(C_{para}); 156.7(PhC=C); 161.6(C=C-CO); 171.3(CO_2CH_2).

General procedures for Diels-Alder reactions

A) Without a catalyst: To a solution of chiral dienophile (0.5 mmol) in CH_2Cl_2 or 1,4-dioxane (10 ml) at the corresponding temperature (Table 1), 2,3-dimethyl-1,3-butadiene (410 mg, 5 mmol) was added and the reaction was stirred for the time reported in Table 1 and analyzed by hplc.

B) With a catalyst: The corresponding amount of an 1M solution of the catalyst ($AlCl_2Et$ in hexane or $TiCl_4$ in CH_2Cl_2) was added to a solution of the chiral dienophile (1 mmol) in dry CH_2Cl_2 (20 ml) kept under an inert atmosphere. After 1 h stirring at room temperature the solution was cold at reaction temperature (Table 1) and 2,3-dimethyl-1,3-butadiene (410 mg, 5 mmol) at the same temperature was added. The reaction was stirred for

the time reported in Table 1 and quenched by addition of $Na_2CO_3 \cdot 10H_2O$. The mixture was filtered and the filtrate analyzed by hplc.

(1S, 6R)-1-cyano-3,4-dimethyl-6-phenyl-3-cyclohexen-1-carboxylate of (S)-ethyl lactate (4a)

This compound was obtained from (E)-2-cyanocinnamate of (S)-ethyl lactate following the above described general procedure for a catalysed Diels-Alder reaction (0.75 eq $TiCl_4$, -25 °C, 5 h). The reaction mixture was treated with $Na_2CO_3 \cdot 10H_2O$, filtered and the solvent eliminated under reduced pressure. In order to purify the major cycloadduct, the oily residue was passed through a column of silicagel (n-hexane:AcOEt = 7:3 as an eluent). In this way **4a** is obtained in a 89% as an oil.

Found: C: 70.81, H: 6.89, N: 4.08

Calc. for $C_{21}H_{25}O_4N$ C: 70.96, H: 7.09, N: 3.94

^{1}H-RMN ($CDCl_3$, δ): 1.20(t, 3H, J=7.2, CH_2CH_3); 1.38(d, 3H, J=6.9, $CHCH_3$); 1.72(s, 6H, $2CH_3$); 2.29(dd, 1H, $J_{5'-5}$=17.7, $J_{5'-6}$=4.8, $H_{5'}$); 2.56(d, 1H, $J_{2-2'}$=17.1, H_2); 2.60-2.74(m, 1H, H_5); 2.98(d, 1H, $J_{2-2'}$=17.1, $H_{2'}$); 3.35(dd, 1H, J_{6-5}=12.0, $J_{6-5'}$=5.1, H_6); 4.10(m, 2H, CH_2CH_3); 4.91(q, 1H, J=6.9, $CHCH_3$); 7.27-7.35(m, 3H, H_m+H_p); 7.38-7.42(m, 2H, H_o).

^{13}C-NMR($CDCl_3$, δ): 13.9(CH_2CH_3); 16.5($CHCH_3$); 18.4; 18.7(C_3-CH_3, C_4-CH_3); 37.0(C_5); 41.0(C_2); 45.1(C_6); 50.5(C_1); 61.5(CH_2CH_3); 70.1($CHCH_3$); 118.2(CN); 121.0(C_3); 126.6(C_4); 127.8(C_{para}); 128.0; 128.5(C_{orto}+C_{meta}); 139.4 (C_{ipso}); 167.6(C_1-CO); 169.5(CO_2Et).

$[\alpha]_D^{25}\left(c = 2.33 \times 10^{-2}\text{g/ml}, CHCl_3\right) = -34.9 \pm 0.2$

(1R, 6S)-1-cyano-3,4-dimethyl-6-phenyl-3-cyclohexen-1-carboxylate of (R)-pantolactone (3b)

This compound was obtained from (E)-2-cyanocinnamate of (R)-pantolactone following the above described general procedure for a catalysed Diels-Alder reaction (0.75 eq $TiCl_4$, -40 °C, 24 h). The reaction mixture was treated with $Na_2CO_3 \cdot 10H_2O$, filtered and the solvent eliminated under reduced pressure. The residue was passed through a column of silicagel (n-hexane:AcOEt = 6:4 as an eluent). In this way **3b** is obtained in a 83% as an oil.

Found: C: 72.15, H: 6.97, N: 3.66

Calc. for $C_{22}H_{25}O_4N$ C: 71.91, H: 6.88, N: 3.81

^{1}H-RMN ($CDCl_3$, δ): 0.90(s, 3H, Me_2C); 0.91(s, 3H, Me_2C); 1.72(s, 6H, $2CH_3$); 2.34(dd, 1H, $J_{5'-5}$=18.6, $J_{5'-6}$=5.4, $H_{5'}$); 2.55-2.68(m, 2H, H_5 + H_2); 2.99(d, 1H, $J_{2'-2}$=18.0, $H_{2'}$); 3.35(dd, 1H, J_{6-5}=11.5, $J_{6-5'}$=5.5, H_6); 3.91(s, 2H, CH_2O); 5.12(s, 1H, CHO); 7.25-7.36(m, 3H, H_m+H_p); 7.41-7.44(m, 2H, H_o).

^{13}C-NMR($CDCl_3$, δ): 18.4; 18.6(C_3-CH_3, C_4-CH_3); 19.4; 22.4(Me_2C); 37.9(C_5); 39.9(Me_2C); 41.2(C_2); 45.4(C_6); 50.0(C_1); 76.0(CH_2O); 76.5(CHO); 118.0(CN); 121.0(C_3); 126.6(C_4); 127.8(C_{para}); 127.5; 128.8(C_{orto}+C_{meta}); 139.4(C_{ipso}); 167.7(C_1-CO); 170.6(CO_2CH_2).

$[\alpha]_D^{25}\left(c = 2.07 \times 10^{-2}\text{g/ml}, CHCl_3\right) = +22.5 \pm 0.2$

Methyl (1S, 6R)-1-cyano-3,4-dimethyl-6-phenyl-3-cyclohexen-1-carboxylate (5)

4a (335 mg, 1 mmol) was refluxed with 10% KOH/EtOH (40 ml) for 6 h. The solvent was eliminated under reduced pressure. The residue was diluted with water (20 ml) extracted with CH_2Cl_2 (3 x 10 ml), the aqueous layer acidified with HCl 12 N and extracted with CH_2Cl_2 (3 x 10 ml). The organic solution was dried over anhydrous Na_2SO_4 and the solvent evaporated under vacuum. The residue was dissolved in Et_2O and treated

with an ethereal solution of diazomethane until completion (monitored by TLC). The excess of diazomethane was destroyed with $CaCl_2$, the solution filtered, the solvent eliminated under reduced pressure and **5** purified by column chromatography on silicagel (n-hexane:AcOEt = 8:2 as an eluent) to afford 242 mg (90%) of **5** as a white solid.

Found: C: 75.99, H: 7.30, N: 4.98

Calc. for $C_{17}H_{19}O_2N$ C: 75.81, H: 7.11, N: 5.20

m.p.: 69-71 °C.

^{1}H-RMN ($CDCl_3$, δ): 1.70(s, 6H, $2CH_3$); 2.20-2.28(m, 1H, $H_{5'}$); 2.45(d, 1H, $J_{2-2'}$=17.1, H_2); 2.68-2.79(m, 1H, H_5); 2.91(d, 1H, $J_{2'-2}$=17.1, $H_{2'}$); 3.22(dd, 1H, J_{6-5}=12.3, $J_{6-5'}$=5.1, H_6); 3.44(s, 3H, CO_2CH_3); 7.27-7.34(m, 5H, Arom.).

^{13}C-NMR($CDCl_3$, δ): 18.4; 18.6(C_3-CH_3, C_4-CH_3); 36.0(C_5); 40.8(C_2); 46.1(C_6); 50.4(C_1); 53.0(CO_2CH_3) 118.5(CN); 120.9(C_3); 126.3(C_4); 127.9; 128.6(C_{orto}+C_{meta}+C_{para}); 139.0 (C_{ipso}); 169.1(CO).

$[\alpha]_D^{25}\left(c = 2.16 \times 10^{-2}\,g/ml, CHCl_3\right) = -60.4 \pm 0.2$

Methyl (1R, 6S)-1-cyano-3,4-dimethyl-6-phenyl-3-cyclohexen-1-carboxylate (6)

Starting from **3b** (367 mg, 1mmol) and following the above described saponification-methylation procedure, 245 mg (91%) of **6** were obtained as a white solid.

Found: C: 76.01, H: 7.00, N: 5.19

Calc. for $C_{17}H_{19}O_2N$ C: 75.81, H: 7.11, N: 5.20

m.p.: 69-71 °C.

$[\alpha]_D^{25}\left(c = 2.34 \times 10^{-2}\,g/ml, CHCl_3\right) = +63.2 \pm 0.2$

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