# REACTION OF CYCLOPENTADIENE WITH (E)-2-CYANOCINNAMATE OF (S)-ETHYL LACTATE.

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**Abstract:** The model proposed by Helmchen explains the results obtained in the reaction of **1** with cyclopentadiene in the presence of $TiCl_4$ or in non-catalyzed reactions, but when $AlCl_2Et$ is used, the results are unexpected. A model based on the presence of the cyano group is proposed to explain the results obtained.

During the last few years we have been interested in the synthesis of cycloaliphatic α-aminoacids, compounds with biological properties related to the transport of ions through membranes.[1] So we have studied the reaction between N-acetyl and N-benzoyl-α,β-didehydroalanine esters and cyclopentadiene[2] and have developed a new synthesis of 2-amino-3-phenyl-2-norbornancarboxylic acids based on the reaction of methyl-(E)-2-cyanocinnamate and cyclopentadiene[3]. Recently, we have published[4] that the reaction between (-)-menthyl-α,β-didehydroalaninate and cyclopentadiene takes place with very high degree of asymmetric induction which allows an efficient asymmetric synthesis of 2-aminonorbornane-2-carboxylic acids.

Now, we want to describe our first results in the asymmetric Diels-Alder reactions of chiral (E)-2-cyanocinnamates and cyclopentadiene and the behaviour of (S)-ethyl lactate as a chiral auxiliary when incorporated into this dienophile. To the best of our knowledge this is the first example of asymmetric Diels-Alder reaction with a chiral trisubstituted dienophile.

Helmchen et al. have described[5] that acrylate of (S)-ethyl lactate behaves as an excellent chiral dienophile and a reversed diastereoselectivity is obtained by using an aluminium or titanium catalyst. This has been explained[6] by the formation of structurally different dienophile-catalyst complexes as a function of the Lewis acid used as a catalyst.

These results have been further explored by Helmchen[7], who has used (R)-pantolactone as a chiral auxiliary and by Waldmann[8], who has studied the reaction between N-acryloyl-L-proline benzyl ester and cyclopentadiene.

In view of these results, we have studied the reaction between (E)-2-cyanocinnamate of (S)-ethyl lactate (**1**) and cyclopentadiene which open a way to the asymmetric synthesis of the 2-amino-3-phenyl-2-norbornane carboxylic acids. The chiral dienophile (**1**) obtained by the reaction of (E)-2-cyanocinnamic acid and (S)-ethyl lactate in the presence of DCC and DMAP[9], was made to react with cyclopentadiene[10] under several conditions. (Table 1), (Figure 1).
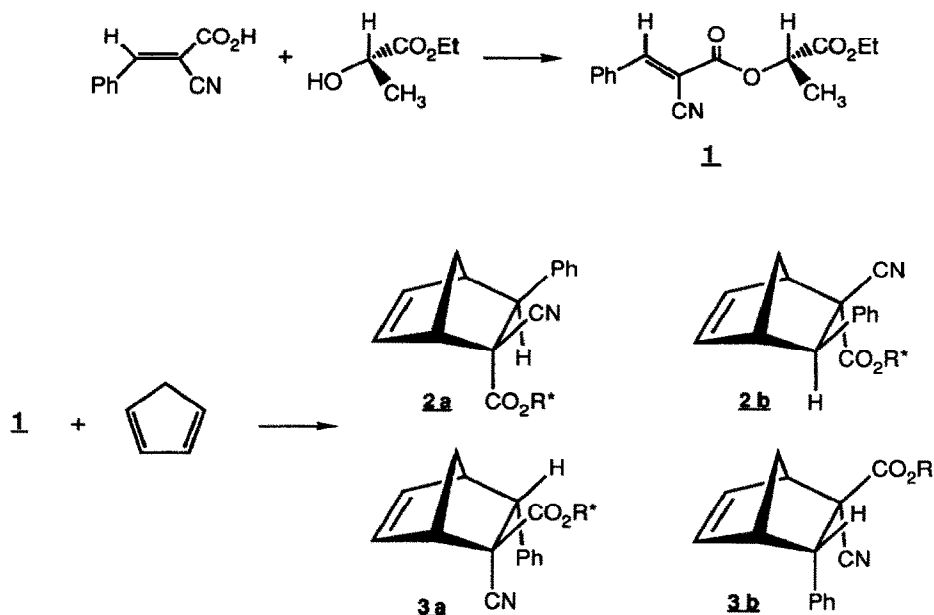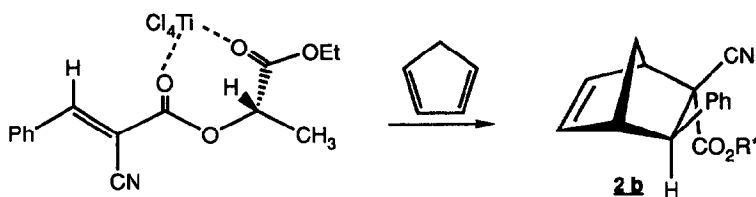
Figure 1

The results of the reactions were determined by hplc[11] and are collected in Table 1. In order to ensure peaks assignments, mixtures of **2a**+**2b** and **3a**+**3b** were prepared from the corresponding racemic acids and (S)-ethyl lactate in the presence of DCC and DMAP[9].

Table 1.- Results of the reaction between (E)-2-cyanocinnamate of (S)-ethyl lactate and cyclopentadiene.

| Lewis Acid (eq) | Diene/**1** | T (°C) | t (h) | % conversion | **2/3** | **2b/2a** |
|---|---|---|---|---|---|---|
| ---- | 10 | 20 | 120 | 99 | 51:49 | 30:70 |
| AlCl$_2$Et (0.75) | 5 | 20 | 6 | 86 | 48:52 | 47:53 |
| AlCl$_2$Et (0.75) | 5 | 0 | 6 | 98 | 59:41 | 53:47 |
| AlCl$_2$Et (0.75) | 5 | -78 | 20 | 60 | 73:27 | 56:44 |
| TiCl$_4$ (0.30) | 5 | -40 | 44 | 43 | 88:12 | 85:15 |
| TiCl$_4$ (0.50) | 5 | -40 | 44 | 99 | 88:12 | 98:2 |
| TiCl$_4$ (0.75) | 5 | -40 | 44 | 97 | 89:11 | 96:4 |
| TiCl$_4$ (1.50) | 5 | -40 | 44 | 28 | 87:13 | 91:9 |

As the absolute configuration of the cycloadducts and the corresponding α–aminoacids are not known, they were assigned accepting the model proposed by Helmchen in TiCl₄-catalyzed reactions (Figure 2).
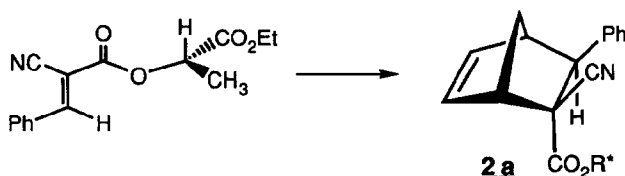


<u>Figure 2</u>

Surprisingly, the configuration of cycloadducts is not reversed when an aluminium or titanium catalyst is used. Unlike the situation with the acrylate of (S)-ethyl lactate , the cyano group leads the dienophile-AlCl₂Et complex to the S-cis conformation which explains why **2b** is preferably obtained. (Figure 3).
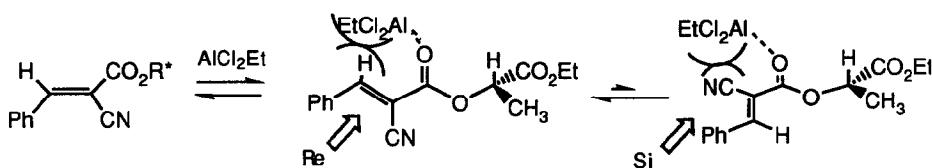


<u>Figure 3</u>

When TiCl₄ is used as a catalyst, the behaviour is similar to that described for the acrylate of (S)-ethyl lactate, though a slightly better diastereofacial selectivity is obtained in our case.

In non catalyzed reactions **2a** is preferably obtained so a reversal induction is observed. This result suggests that the approximation of the diene takes place preferably on the S-trans conformation. (Figure 4).



<u>Figure 4</u>

These results emphasize the importance of the S-cis/S-trans equilibrium of the enoate moiety on the asymmetric induction in Diels-Alder reactions of chiral propenoates and show that this equilibrium can be greatly modified by the presence of a substituent geminal to the carboxylic group.

Further studies in order to determine the complexes intermediates and the absolute configurations of cycloadducts are in progress.

### References and Notes

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10.- In a typical experiment, the catalyst was added to a solution of **1** (0.5 mmol) in dry dichloromethane (10 ml) under nitrogen. The solution was stirred during 1 h at room temperature and then cold at the corresponding reaction temperature. Freshly distilled cyclopentadiene (2.5 mmol) was added and the solution was stirred for the corresponding time and quenched by addition of $Na_2CO_3 \cdot 10\ H_2O$.

$^1H$ and $^{13}C$-NMR spectral data of products are the following: **1**: $^1H$-NMR ($CDCl_3$, 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, Arom.); 7.80-8.20(m, 2H, Arom.); 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; 131.4; 133.6(Arom.); 155.8(Ph$C$=C); 162.0(C=C-$CO$); 169.9($CO_2$Et). **2a**: $^1H$-NMR ($CDCl_3$, δ) = 1.27(t, 3H, J=7.1, $CH_2CH_3$); 1.56(d, 3H, J=7.1, $CHCH_3$); 1.91(dd, 1H, $J_{7s-7a}$=9.6, $J_{7s-3n}$=1.8, $H_{7s}$); 2.32(d, 1H, $J_{7a-7s}$=9.6, $H_{7a}$); 3.28(s, 1H, $H_4$); 3.62(d, 1H, J=2.0, $H_{3n}$); 3.75(s, 1H, $H_1$); 4.22(q, 2H, J=7.1, $CH_2CH_3$); 5.11(q, 1H, J=7.1, $CHCH_3$); 6.24(dd, 1H, $J_{5-6}$=5.6, $J_{5-4}$=2.8, $H_5$); 6.54(dd, 1H, $J_{6-5}$=5.6, $J_{6-1}$=3.2, $H_6$); 7.24-7.39(m, 5H, Arom.). $^{13}C$-NMR ($CDCl_3$, δ) = 14.2($CH_2CH_3$); 16.8($CHCH_3$); 47.0($C_3$); 48.1($C_7$); 51.7($C_1$); 54.8($C_4$); 55.4($C_2$); 61.7($CH_2CH_3$); 70.6($CHCH_3$); 118.8($CN$); 127.5; 128.2; 128.8; 139.3(Arom.); 133.2($C_6$); 141.7($C_5$); 167.3($CO$); 169.9($CO_2$Et). **2b**: $^1H$-NMR ($CDCl_3$, δ) = 1.27(t, 3H, J=7.1, $CH_2CH_3$); 1.57(d, 3H, J=7.1, $CHCH_3$); 1.91(d, 1H,$J_{7s-7a}$=9.5, $H_{7s}$); 2.33(d, 1H, $J_{7a-7s}$=9.5, $H_{7a}$); 3.28(s, 1H, $H_4$); 3.57(d, 1H, J=1.8, $H_{3n}$); 3.65(s, 1H, $H_1$); 4.22(m, 2H, $CH_2CH_3$); 5.14(q, 1H, J=7.1, $CHCH_3$); 6.14(dd, 1H, $J_{5-6}$=5.5, $J_{5-4}$=2.8, $H_5$); 6.54(dd, 1H, $J_{6-5}$=5.3, $J_{6-1}$=3.3, $H_6$); 7.25-7.38(m, 5H, Arom.). $^{13}C$-NMR ($CDCl_3$, δ) = 14.1($CH_2CH_3$); 16.7($CHCH_3$); 46.9($C_3$); 47.9($C_7$); 52.7($C_1$); 53.5($C_4$); 55.5($C_2$); 61.7($CH_2CH_3$); 70.6($CHCH_3$); 118.5($CN$); 127.5; 128.2; 128.7; 139.1(Arom.); 133.4($C_6$); 141.6($C_5$); 167.3($CO$); 169.6($CO_2$Et). **3a**: $^1H$-NMR ($CDCl_3$, δ) = 1.30(t, 3H, J=7.1, $CH_2CH_3$); 1.60(d, 3H, J=7.1, $CHCH_3$); 1.74(d, 1H, $J_{7s-7a}$=9.6, $H_{7s}$); 1.95(d, 1H, $J_{7a-7s}$=9.6, $H_{7a}$); 3.34(s, 1H, $H_4$); 3.71(s, 1H, $H_1$); 4.22(d, 1H, $J_{3x-7s}$=1.8, $H_{3x}$); 4.25(q, 2H, J=7.1, $CH_2CH_3$); 5.19(q, 1H, J=7.1, $CHCH_3$); 6.52(dd, 1H, $J_{5-6}$=5.6, $J_{5-4}$=2.8, $H_5$); 6.69(dd, 1H, $J_{6-5}$=5.6, $J_{6-1}$=2.8, $H_6$); 7.23-7.38(m, 5H, Arom.). $^{13}C$-NMR ($CDCl_3$, δ) = 14.1($CH_2CH_3$); 16.6($CHCH_3$); 47.9($C_3$); 48.0($C_7$); 52.5($C_1$); 54.3($C_4$); 55.5($C_2$); 61.8($CH_2CH_3$); 70.8($CHCH_3$); 118.1($CN$); 127.6; 128.4; 129.0; 138.0(Arom.); 135.5($C_6$); 139.3($C_5$); 168.6($CO$); 169.9($CO_2$Et). **3b**: $^1H$-NMR ($CDCl_3$, δ) = 1.30(t, 3H, J=7.1, $CH_2CH_3$); 1.58(d, 3H, J=7.1, $CHCH_3$); 1.70(d, 1H, $J_{7s-7a}$=9.6, $H_{7s}$); 1.90(d, 1H, $J_{7a-7s}$=9.6, $H_{7a}$); 3.34(s, 1H, $H_4$); 3.54(s, 1H, $H_1$); 4.14(d, 1H, $J_{3x-7s}$=2.8, $H_{3x}$); 4.25(q, 2H, J=7.1, $CH_2CH_3$); 5.19(q, 1H, J=7.1, $CHCH_3$); 6.48(dd, 1H, $J_{5-6}$=5.6, $J_{5-4}$= 2.8, $H_5$); 6.69(dd, 1H, $J_{6-5}$=5.6, $J_{6-1}$=2.8, $H_6$); 7.23-7.38(m, 5H, Arom.). $^{13}C$-NMR ($CDCl_3$, δ) = 14.1($CH_2CH_3$); 16.6($CHCH_3$); 47.6($C_3$); 48.7($C_7$); 54.2($C_4$); 54.7($C_2$); 56.0($C_1$); 61.8($CH_2CH_3$); 70.8($CHCH_3$); 118.0($CN$); 127.5; 128.3; 129.1; 137.9(Arom.); 135.4($C_6$); 139.2($C_5$); 169.0($CO$); 169.9($CO_2$Et).

11.- Reactions were analyzed by HPLC (Hewlett Packard 1090 M), using a Hypersil® Silica Column (5μm, 4,6 mm i.d. * 200 mm) and a Hexane-$^t$Butylmethyl ether mixture (95:5) as mobile phase. Flow rate: 2.5 ml/min. Detection UV at 210 nm, ratio of extinction coefficients at 210 nm: $ε_{2a}:ε_{2b}$: $ε_{3a+3b}$ = 1.01: 1.00: 1.36.