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Synthesis of Methyl 2-exo-Cyano-3-exo-phenyl-5,6-endo (or exo)-epoxybicyclo[2.2.1]heptane-2-endo-carboxylates in Enantiomerically Pure Form.

C. Cativiela*

Department of Organic Chemistry. Instituto de Ciencia de Materiales de Aragón. Universidad de Zaragoza-C.S.I.C. 50009 Zaragoza. Spain.

A. Avenoza and J. M. Peregrina

Department of Chemistry (Organic Chemistry). Edificio Científico-Técnico. Sección Ciencias. Universidad de La Rioja. 26001 Logroño. Spain.

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Key Words: (E)-2-cyanocinnamic acid; Diels-Alder cycloaddition; iodolactones; endo and exo-epoxides.

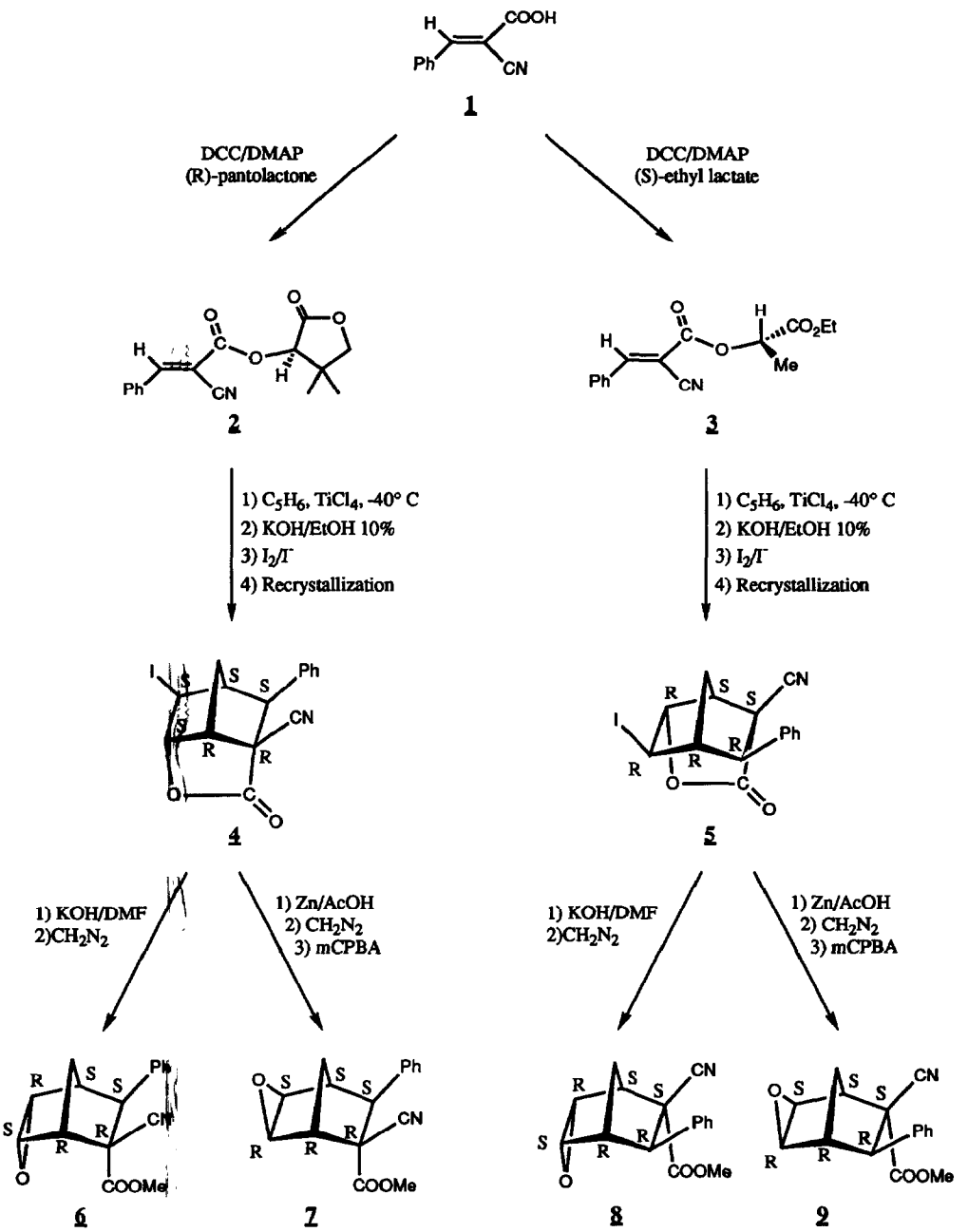
Abstract: *The enantiomers (1R, 2R, 3S, 4S, 5S, 6S) and (1S, 2S, 3R, 4R, 5R, 6R) of the 2-exo-cyano-6-endo-hydroxy-5-exo-iodo-3-exo-phenylbicyclo[2.2.1]heptane-2-endo-carboxylic acid lactone* **4** *and* **5**, *obtained starting from the endo-cycloadducts of the asymmetric Diels-Alder reactions between cyclopentadiene and (E)-2-cyanocinnamates of (R)-pantolactone* **2** *and (S)-ethyl lactate* **3**, *are converted into the methyl 2-exo-cyano-3-exo-phenyl-5,6-endo(and exo)-epoxybicyclo[2.2.1]heptane-2-endo-carboxylates* **6**, **7**, **8** *and* **9** *in enantiomerically pure form.*

The number of biologically active natural products containing quaternary carbon centres increases every day as does, the interest of researchers in synthesizing them in enantiomerically pure form. In the course of our research into the asymmetric synthesis of cycloaliphatic amino acids with a norbornane skeleton[1], we have studied the use of different chiral α,β-didehydroaminoacid derivatives and we have showed that the use of the Diels-Alder reaction between cyclopentadiene and (E)-2-cyanocinnamic chiral esters, using (R)-pantolactone and (S)-ethyl lactate as chiral auxiliaries, is the key step[2] to the enantioselective synthesis of the corresponding cycloadducts with a quaternary carbon centre. From these products and following a protocol with stereocontrolled transformations the desired α-amino acids with norbornane skeleton can be obtained in enantiomerically pure form.

The synthesis of new reactive intermediates, such as enantiomerically pure epoxide, allows the access to the stereocontrolled preparation of new chiral compounds. In our case, the synthesis of the stereoisomeric epoxides would allow us to obtain new valuable highly substituted norbornane systems with full stereocontrol at six chiral centres.

The synthesis of stereoisomeric chiral epoxides is gathered in scheme 1 as a stereodivergent synthesis from (E)-2-cyanocinnamic acid as starting material and using (R)-pantolactone and (S)-ethyl lactate as complementary chiral auxiliaries.

Scheme 1


1
DCC/DMAP
(R)-pantolactone
DCC/DMAP
(S)-ethyl lactate
2
3
1) C_5H_6, $TiCl_4$, -40° C
2) KOH/EtOH 10%
3) I_2/I^-
4) Recrystallization
1) C_5H_6, $TiCl_4$, -40° C
2) KOH/EtOH 10%
3) I_2/I^-
4) Recrystallization
4
5
1) KOH/DMF
2)CH_2N_2
1) Zn/AcOH
2) CH_2N_2
3) mCPBA
1) KOH/DMF
2)CH_2N_2
1) Zn/AcOH
2) CH_2N_2
3) mCPBA
6
7
8
9

So the easily available dienophiles **2** and **3** obtained from (E)-2-cyanocinnamic acid and (R)-pantolactone or (S)-ethyl lactate[3] were reacted with cyclopentadiene in the presence of titanium tetrachloride as a catalyst to give, after a typical iodolactonization procedure and recrystallization, the corresponding enantiomerically pure iodolactones **4** and **5**, whose absolute configuration were previously determined by X-ray diffraction[4].

Epoxides may be obtained by the action of base on halohydrins. The selectivity shown in these reactions is highly dependent on the solvent. Thus, in aqueous medium, the basic hydrolysis of halolactones with norbornane skeleton preferably yields the corresponding norbornanones[5], but the use of a polar aprotic medium favours the intramolecular attack of alkoxide ion on the carbon which the halogen is attached, to give the endo-epoxynorbornanes[6]. In our case, the endo-epoxides **6** and **8** were the sole compounds isolated by basic-catalysed hydrolysis, in dimethylformamide, of the corresponding enantiomerically pure iodolactones **4** and **5**, followed by methylation with diazomethane.

The epoxidation of norbornene derivatives with m-chloroperbenzoic acid in methylene chloride has been described in the literature[7], indicating a remarkable stereochemical preference of at least 100:1 for the exo epoxidation. So, the synthesis of the optically active exo-epoxides **7** and **9** was easily achieved by epoxidation with m-chloroperbenzoic acid of the enantiomerically pure cyano-esters, obtained by the zinc-acetic acid reduction, and further methylation with diazomethane of the iodolactones **4** and **5**.

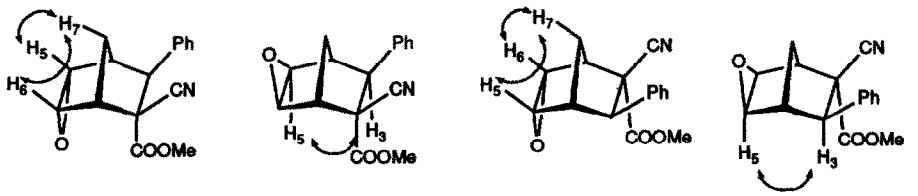
In norbornane derivatives, the chemical shifts of endo protons are generally found at a higher field than their exo counterparts[8]. Endo/exo stereochemistry of the oxirane ring in compounds **6**, **7**, **8** and **9** was assigned on the basis of their ^{1}H-NMR spectra. Endo epoxides **6** and **8** showed two typical triplet systems consistent with the exo position of H_5 and H_6 protons. The chemical shift to downfields of these signals (3.81 and 3.87 ppm) confirms the exo position of H_5 and H_6 protons, deshielded in comparison with the corresponding H_5 and H_6 protons in compounds **7** and **9**, whose chemical shifts remain practically unaffected by the presence of the epoxide ring[9] (two doublet of doublets resonances at δ 3.20 and 3.34 ppm).

Also, in these compounds the Karplus relationship[10] can be applied to elucidate the endo/exo stereochemistry at C_5 and C_6. In the well-documented norbornane derivatives the relationships $J_{5x\text{-}6x} > J_{5n\text{-}6n}$, $J_{6n\text{-}1}$ (0 - 2 Hz) < $J_{6x\text{-}1}$ (3 - 4.5 Hz) appear to be general[11]. In these epoxides, the value of the vicinal coupling constants ($J_{6n\text{-}1} = J_{5n\text{-}4} = 1.5$, $J_{6x\text{-}1} = J_{5x\text{-}4} = 3.9$, $J_{5n\text{-}6n} = 3.3$, $J_{5x\text{-}6x} = 3.9$ Hz) is in accordance with previous results of structurally related compounds[12].

Nevertheless, all of these correlations should be used with caution because the small differences between the chemical shifts of endo and exo protons may be of the same order of magnitude as the effects of more remote substituents on these chemical shifts[13].

Stereochemical confirmation of the oxirane ring was obtained from NOE experiments involving irradiation of the H_{7s} and H_{3n} hydrogens of both stereoisomers endo and exo. Indeed hydrogens H_5 and H_6 showed significant enhancement on presaturation of H_{7s} hydrogen when the oxirane ring has endo stereochemistry (compounds **6** and **8**) whereas when the oxirane ring has exo stereochemistry (compounds **7** and **9**) the hydrogen H_5 showed significant NOE enhancement on presaturation of the corresponding H_{3n} hydrogen. (Figure 1).

Figure 1



6 **7** **8** **2**

The configurational assignments of these compounds were deduced from the absolute configuration of iodolactones **4** and **5**.

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EXPERIMENTAL SECTION

^1H and ^{13}C-NMR spectra were recorded on a Varian UNITY 300. Deuterochloroform was used as a solvent with tetramethylsilane as the internal standard (the chemical shifts were reported in ppm on the δ scale, coupling constants in Hz). Melting points were determined on a Büchi SMP-20 and are uncorrected. Microanalyses were carried out on a Perkin-Elmer 240-C analyser and were in good agreement with the calculated values. Optical rotations were measured in 0.5 dm cells of 3.2 mL capacity using a Perkin-Elmer 241-C polarimeter.

Methyl (1R, 2R, 3S, 4S, 5R, 6S)-2-exo-cyano-3-exo-phenyl-5,6-endo-epoxybicyclo[2.2.1] heptane-2-endo-carboxylate. (6).

(+)-Iodolactone **4** (320 mg, 0.87 mmol) was added to a solution of 10% KOH in DMF (32 mL). After stirring at room temperature during 6 h, the solvent was evaporated. The residue was diluted in water (50 mL) and washed with Et_2O (3 x 15 mL). The aqueous layer was acidified with 2 N HCl and extracted with Et_2O (3 x 15 mL). After drying with Na_2SO_4, the organic solution was treated with an ethereal solution of diazomethane until completion (monitoring by TLC). The excess of diazomethane was destroyed with $CaCl_2$, the solution filtered, the solvent eliminated and **6** purified by silica column chromatography eluting with hexane-ethyl acetate (6:4). Isolated yield: 187 mg (79%). Mp: 92-4° C. $[\alpha]_D^{25}$(c=2.00 x 10^{-2} g/mL, $CHCl_3$): - 8.5 ±0.5 . ^1H-NMR($CDCl_3$): δ= 2.43(dq, 1H, $J_{7s\text{-}3n,1,4}$=1.8, $J_{7s\text{-}7a}$=10.8, H_{7s}); 2.54(d, 1H, $J_{7a\text{-}7s}$=10.8, H_{7a}); 2.88(bs, 1H, H_4); 3.18(bs, 1H, H_1); 3.81(t, 1H, $J_{5x\text{-}6x,4}$= 3.9, H_{5x}); 3.87(t, 1H, $J_{6x\text{-}5x,1}$= 3.9, H_{6x}); 3.91(s, 4H, H_{3n} + $CO_2\underline{Me}$); 7.24-7.40(m, 5H, Arom.). ^{13}C-NMR($CDCl_3$): δ= 41.2(C_7); 48.5, 49.6, 50.0(C_1, C_3, C_4); 53.8($CO_2\underline{Me}$); 56.2(C_2); 60.7, 62.7(C_5, C_6); 117.3(CN); 127.6(ipso-Ph); 128.1, 128.7(o,m-Ph); 139.0(p-Ph); 168.0(CO). Anal. Calc. for $C_{16}H_{15}NO_3$ C: 71.36, H: 5.61, N: 5.20; found C: 71.42, H: 5.71, N: 5.29.

Methyl (1S, 2S, 3R, 4R, 5S, 6R)-2-exo-cyano-3-exo-phenyl-5,6-endo-epoxybicyclo[2.2.1] heptane-2-endo-carboxylate. (8).

Compound **8** was obtained in a similar way, starting from the (-)-iodolactone **5** (260 mg, 0.71 mmol). Isolated yield: 154 mg (81%). $[\alpha]_D^{25}$ (c=2.00 x 10^{-2} g/mL, $CHCl_3$): + 8.5 ±0.5 . Anal. Calc. for $C_{16}H_{15}NO_3$ C: 71.36, H: 5.61, N: 5.20; found C: 71.31, H: 5.68, N: 5.32.

Methyl (1R, 2R, 3S, 4S, 5S, 6R)-2-exo-cyano-3-exo-phenyl-5,6-exo-epoxybicyclo[2.2.1] heptane-2-endo-carboxylate. (7).

Zinc dust (4 g) was slowly added to a solution of (+)-iodolactone **4** (250 mg, 0.68 mmol) in glacial acetic acid (35 mL). After 6 h, the mixture was filtered and the solid was washed with Et_2O (2 x 20 mL). The combined mother liquors and filtrate were evaporated to afford a residue, which was taken up in Et_2O (50 mL) and extracted with 5% $NaHCO_3$ solution (3 x 15 mL). After acidifying, the aqueous solution was extracted with ether (3 x 15 mL), dried over Na_2SO_4 and treated with a slight excess of a solution of diazomethane in ether. The evaporation of the solvent afforded methyl 2-exo-cyano-3-exo-phenylbicyclo[2.2.1]hept-5-ene-2-endo-carboxylate as a pure product. A solution of this compound (114 mg, 0.45 mmol) in CH_2Cl_2 (20 mL) under argon was treated with mCPBA (1.24 g, 7.20 mmol) at room temperature. After 5 h, the solution was evaporated and diluted with ether, washed with 1N NaOH and then dried over anhydrous $MgSO_4$. The solvent was removed in vacuum and the residue was purified by silica column chromatography, eluting with hexane-ethyl acetate (7:3). Isolated yield: 65 mg (36%). Mp: 96-8° C. $[\alpha]_D^{25}$ (c=1.12 x 10^{-2} g/mL, $CHCl_3$): - 70.0 ±0.5 . ^{1}H-NMR($CDCl_3$): δ= 1.78-1.81(m, 2H, H_{7s} + H_{7a}); 3.00(bs, 1H, H_4); 3.20(dd, 1H, J_{6n-1}= 1.5, J_{6n-5n}= 3.3, H_{6n}); 3.22(bs, 1H, H_1); 3.34(dd, 1H, J_{5n-4}= 1.5, J_{5n-6n}= 3.3, H_{5n}); 3.69(s, 1H, H_{3n}); 3.90(s, 3H, CO_2Me); 7.23-7.39(m, 5H, Arom.). ^{13}C-NMR($CDCl_3$): δ= 41.3(C_7); 48.3, 48.7, 50.0(C_1, C_3, C_4); 50.5(C_5, C_6); 54.0(CO_2Me); 57.4(C_2); 117.2(CN); 127.9(ipso-Ph); 128.0, 128.9(o,m-Ph); 138.2(p-Ph); 167.3(CO). Anal. Calc. for $C_{16}H_{15}NO_3$ C: 71.36, H: 5.61, N: 5.20; found C: 71.44, H: 5.69, N: 5.31.

Methyl (1S, 2S, 3R, 4R, 5R, 6S)-2-exo-cyano-3-exo-phenyl-5,6-exo-epoxybicyclo[2.2.1] heptane-2-endo-carboxylate. (9).

Compound **9** was obtained in a similar way, starting from the (-)-iodolactone **5** (250 mg, 0.68 mmol). Isolated yield: 67 mg (37%). $[\alpha]_D^{25}$ (c=1.14 x 10^{-2} g/mL, $CHCl_3$): + 70.0 ±0.5 . Anal. Calc. for $C_{16}H_{15}NO_3$ C: 71.36, H: 5.61, N: 5.20; found C: 71.41, H: 5.70, N: 5.27.

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