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The Stereoselective Alkylation of Cyclohexane-1,2-dicarboxylic acid mono-(-)-menthyl ester.

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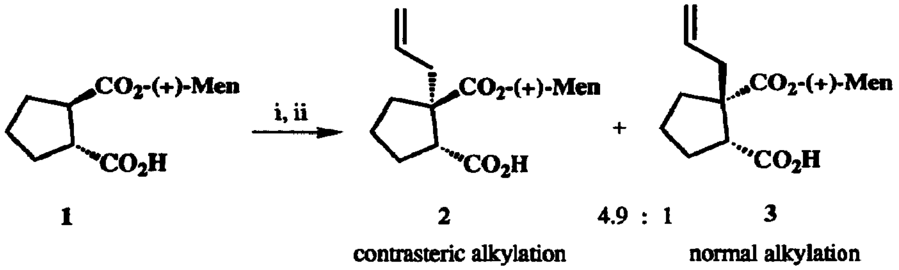
Abstract: The dianion of (1*R*),(2*S*)-cyclohexane-1,2-dicarboxylic acid mono-(-)-menthyl ester reacts with alkyl bromides and an iodide to give alkylation with selectivities ranging from 7:1 to 32:1, the configuration of one product has been proved by X-ray crystallography.

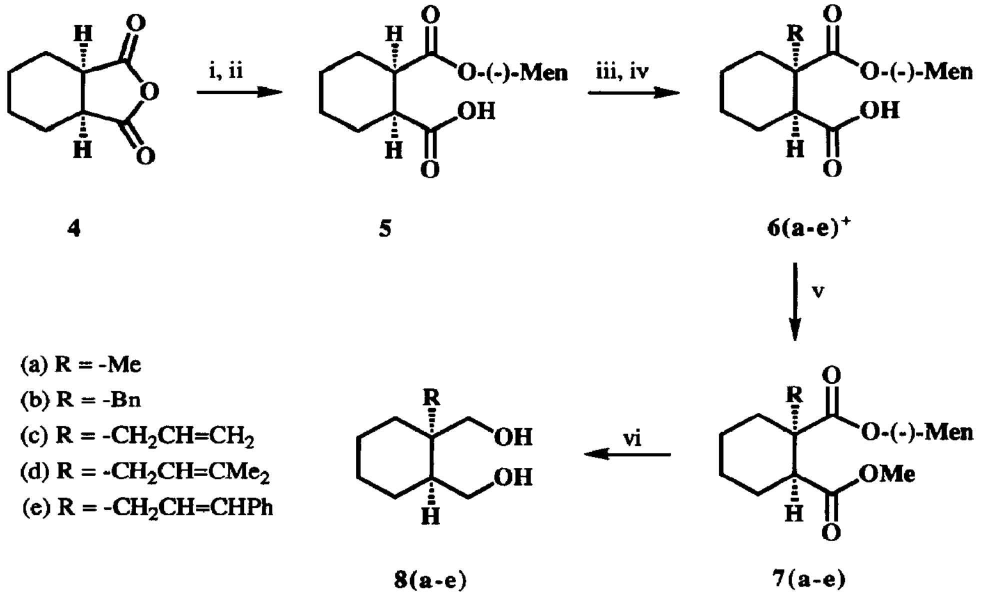
In 1991, Yamada *et al*[1] reported the contrasteric alkylation of a cyclopentane-1,2-dicarboxylic acid mono-(+)-menthyl ester (1) leading to acid esters (2) and (3), Scheme 1.



Scheme 1: i, LDA, THF, -25°C, 1h; ii, CH_2=$CHCH_2Cl$, -25 to +25°C, 3.7h, 96%.

As part of a synthetic venture we required a reliable route to homochiral, alkylated cyclohexane-1,2-dicarboxylic ester derivatives. The nearest results to our plan in a cyclohexane ring were reported by Corey and Su,[2] where 4-cyclohexene-1,2-dicarboxylic dimenthyl ester was deprotonated with LDA and subjected to a Claisen condensation with a substituted propargylic ester. No evidence for contrasteric alkylation was observed in this case and the stereoselectivity was very high. We decided it would be worthwhile to investigate the alkylation behaviour of cyclohexane-1,2-dicarboxylic acid mono-(-)-menthyl ester enolates.

In the cyclopentane studies[1] the starting material was prepared by a direct coupling of dimenthyl succinate with 1,3-dibromopropane,[3] whereas in the Corey work[2] the cyclohexane was prepared by Diels-Alder reaction of dimenthyl fumarate[4]. We chose simply to heat cyclohexane-1,2-dicarboxylic anhydride with (-)-menthol to give the acid ester (5) as a 2.4 :1 mixture of diasteroisomers. This rato was measured from the ^{1}H NMR of the methyl menthyl diester prepared by treatment of the crude product with diazomethane. Six recrystallisations from petroleum ether followed by methylation gave a product with a single methoxy signal in the ^{1}H NMR.



Scheme 2 : Reagents: i, (-)-menthol, 110°C, 16h, 100%; ii, 6 recrystallisations, petroleum ether, 9%; iii, LDA, THF, -25°C, 0.5h; iv, RX see table; v, CH_2N_2, Et_2O, 0°C, 0.5h, 93%; vi, 1M $LiAlH_4$ in THF, 25°C, 1h, 74-91%

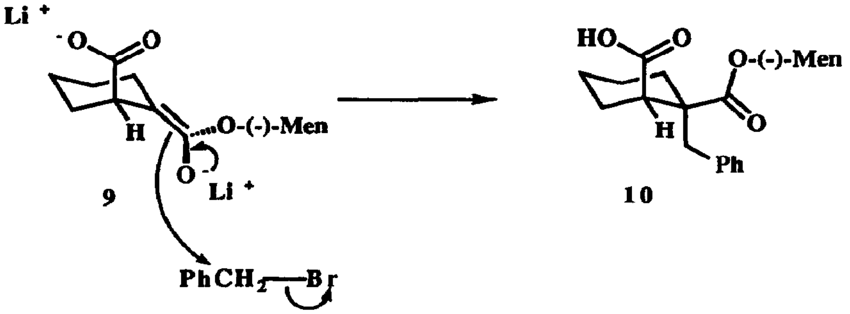
$^+$ The major isomer is shown, we assume that the configuration of compounds 6(a,c-e) are analogous to (6b), the structure of which was proved by X-ray crystallography.

Product	**Electrophile**	**Time**	**Yield**	**Diastereoisomer Ratio**	
				GC	**NMR***
6(a)	MeI	2h	91%	11.1 : 1	10.7 : 1
6(b)	BnBr	16h	88%	26.8 : 1	27.9 : 1
6(c)	$CH_2=CHCH_2Br$	16h	93%	7.2 : 1	7.6 : 1
6(d)	$Me_2C=CHCH_2Br$	48h	93%	-	13.4 : 1
6(e)	$PhCH=CHCH_2Br$	72h	98%	-	32.5 : 1

Table: The results of deprotonation and alkylation of acid ester (5) with a range of electrophiles.

* The diastereoisomer ratio was measured from the methoxy signal in the ^1H NMR spectrum of the crude methyl esters 7(a-e).

The results of deprotonation of mono ester (5) with LDA followed by alkylation are summarized in Scheme 2 and the table. The diastereoisomer ratio was measured by GC in 3 of the cases and the figures were very close to the ^1H NMR results. In the case of the benzyl compound the configuration of the product was proved by X-ray crystallography, the result is shown in Figure 1.[6] Interestingly, both the methyl ester group and the benzyl group are axial with the menthyl ester equatorial. A suggestion for the mechanism of the alkylation is shown by axial attack of the dianion (9) leading to the acid (10) after protonation, the structure of (10) being consistent with the X-ray crystal structure.



The acid esters 7(a-e) were reduced to the substituted 1,2-bismethanol derivatives 8(a-e). Both 1(*R*),2(*S*)-1-methyl (*cis*)-1,2-*bis*hydroxymethyl cyclohexane, $[\alpha]_D = +23.4^{\circ}$ and 1(*S*),2(*S*)-1-methyl (*trans*)-1,2-bishydroxymethyl cyclohexane, $[\alpha]_D = +1.2^{\circ}$ are known[5]. The observed rotation of the diol (8a) is $[\alpha]_D = +21.4^{\circ}$ which is consistent with an 11:1 mixture of *cis* and *trans* diols respectively.

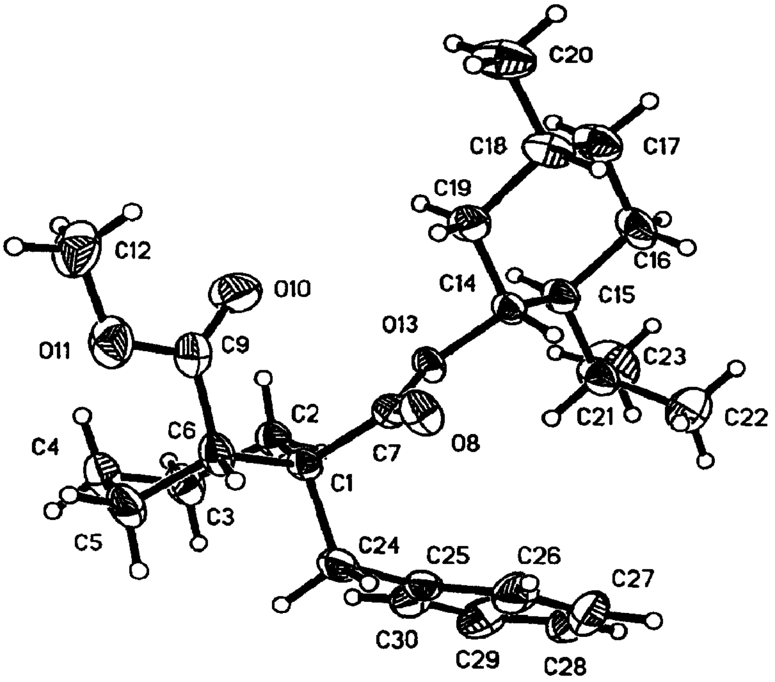


Figure 1. X-ray crystal structure of compound 6b

In conclusion we have observed good selectivity in the alkylation of the dianion of (5) which we believe will be of use in synthesis.

Acknowledgements

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References and Notes.

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6. *Crystal data* (for 6b): $C_{26}H_{38}O_4$; M = 414.6; orthorhombic, $P2_12_12_1$; a = 7.724(1), b = 16.920(1), c = 18.476(1) A; V = 2415(1) A^3; Z = 4; D_c = 1.14 g cm^{-3}; F(000) = 904; μ = 0.75 cm^{-1}.
   Accurate unit cell parameters were determined by least squares refinement of omega angles for 45 centered reflections with $9^o<2\theta<25^o$. Data were measured on a Siemens P4 diffractometer with graphite monochromated M_o-K_α radiation (λ = 0.7107A) at 293K using an omega scan technique. 2931 independent reflections were measured ($2\theta<52^o$), with 2100 having $I > 2\sigma(I)$ regarded as observed. The data were corrected for Lorentz and polarisation effects.
   The structure was solved by direct methods using the program SHELXTL - pc**. All hydrogen atoms were included in calculated positions (C-H = 0.96A). All other atoms were refined with anisotropic thermal parameters. Final cycles of refinement gave R = 0.0466 and R_w = 0.0600 [$w^{-1} = \sigma^2F + 0.0015 F^2$]. The maximum and minimum residual electron densities in the final ΔF map were 0.17 and -0.19eA respectively. The mean and maximum shift / error in the final refinement cycles were 0.002 and 0.013 respectively.
   ** Sheldrick G.M., SHELXTL - pc, (1991) Release 4.2 Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.
   Atomic coordinates, bond lengths and angles, and thermal parameters for compound 6b have been deposited at the Cambridge Crystallographic Data Centre.

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