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CYCLOHEXANE ANALOGS OF POISON IVY AND POISON OAK DERIVATIVES. A TOTALLY STEREOSELECTIVE SYNTHESIS OF TRANS,TRANS-3-ALKYL-1,2-CYCLOHEXANEDIOLS.

Jean-Pierre LEPOITTEVIN and Claude BENEZRA*

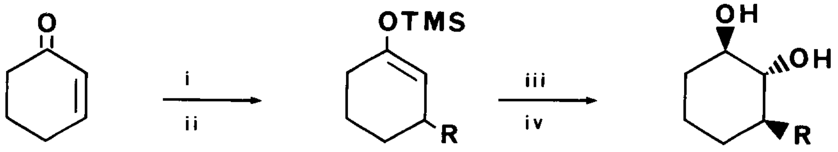
Laboratoire de Dermato-Chimie, Associé au CNRS (LA 31),
UNIVERSITE LOUIS PASTEUR, Clinique Dermatologique,
CHU de Strasbourg, 67091 STRASBOURG FRANCE.

Summary : Pure *trans,trans*-3-methyl-, 3-n-pentyl,3-n-decyl- and 3n-pentadecyl-1,2-cyclohexanediols have been prepared in two steps, in 55-70% overall yields from 2-cyclohexenone.

Allergic contact dermatitis (ACD) to pentadecyl, pentadecenyl-, pentadecadienyl- and pentadecatrienylcatechols and their C_{17} analogs (the constituents of urushiol, the sensitizing sap of poison ivy and poison oak) affects more than 80% of Americans[1]. The lipophilic character of these compounds apparently plays a major role in the intensity of the immunological reaction to poison ivy and poison oak. In order to assess the importance of lipophilic versus electrophilic properties in determining the sensitizing effect of an allergen, we have undertaken the synthesis of saturated (non electrophilic) analogs, namely 3-alkylcyclohexanediols.

To the best of our knowledge, the only synthesis of pure all *trans*-3-alkyl- (in this instance, 3-methyl)-cyclohexanediols was described by Klein and Dunkelblum[2]. The starting material they used, 3-methyl-2-cyclohexenone is the only easily accessible 3-akyl-derivative.

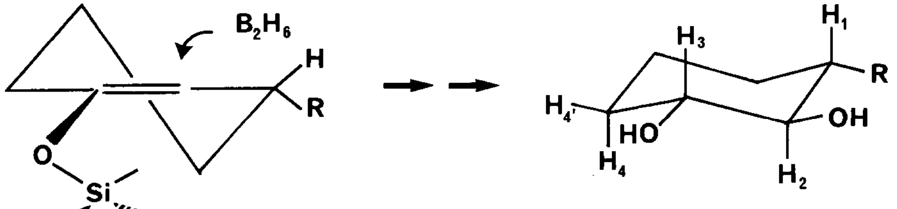
We have now devised a synthesis based on the Michael addition of R_2CuLi, on cyclohexenone 1 and quenching the resulting enolate with trimethylchlorosilane. The isolated trimethylsilane derivate 2 is then hydroborated[3,4] (Scheme I).



1 2 3

i) R_2CuLi ; ii) $ClSiMe_3$; iii) BH_3,Me_2S ; iv) H_2O_2,NaOH

Only one stereomer (the all-*trans*) derivative was obtained in every instance, as evidenced by GC and 200 MHz ^1H NMR : the 9.3 Hz J_{12} and J_{23} coupling constants are typical of a diaxial arrangement[5]. The presence of the bulky-OTMS group orients the attack of borane, increases the yield of the hydroboration reaction[6] and allows one to obtain only one isomer, the diborane attacking from the face opposite to both-OTMS and R groups as follows :



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EXPERIMENTAL : The general procedure was as follows. Cuprate R_2CuLi (2 equivalents) was reacted with 2-cyclohexenone in THF, at -40°C, under an argon atmosphere. After disappearance of the ketone (as shown by TLC), the process taking about 2 hours, the resulting enolate was trapped with $ClSiMe_3$ (2 equivalents, reacted for 15 minutes) ; copper salts were eliminated by a rapid filtration on a short (5 cm) silica gel column under pressure. Hydroboration was conducted under standard conditions (BH_3,Me_2S, followed by H_2O_2 alcaline oxidation).[4,7]

TABLE. 3-n-Alkyl-1,2-cyclohexanediols.

R	YIELDS[a] (%)	CHARACTERISTICAL NMR CHEMICAL SHIFTS (ppm)			
		^{1}H NMR (200 MHz)		^{13}C NMR[d]	
		H_2[b]	H_3[c]	C_2	C_3
CH_3	70	2.95	3.41	81.5	75.4
n-C_5H_{11}	65	3.00	3.38	80.5	75.5
n-$C_{10}H_{21}$	58	3.02	3.38	79.8	75.5
n-$C_{15}H_{31}$	55	3.01	3.38	80.0	75.5

[a] isolated compound ; yield calculated relative to the starting, 2-cyclohexenone

[b] triplet - $J_{12} = J_{23} = 9.3$ Hz

[c] multiplet - $J_{34} = 10.2$ Hz $J_{34'} = 4.6$ Hz

[d] relative to $CDCl_3$

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