Tetrahedron Vol. 45, No. 19, pp. 6203 to 6210, 1989
Printed in Great Britain.

0040-4020/89 $3.00+.00

A COMPLETELY STEREOSELECTIVE INTRAMOLECULAR DIELS-ALDER REACTION IN THE SUBSTITUTED CYCLOHEXANOL SERIES

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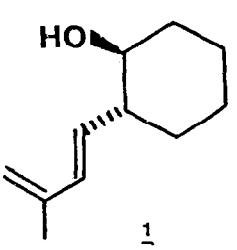
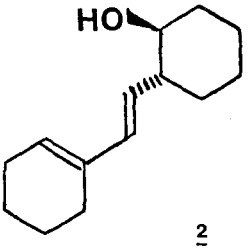
(*Received in Belgium* 27 *June* 1989)

Summary - *Subtituted dienyl cyclohexanols, obtained through opening of cyclohexene oxide by dienyl aluminum reagents, are easily esterified with acryloyl, crotonyl or methacryloyl chloride or with maleic anhydride. These esters undergo a completely stereoselective Lewis acid catalyzed Diels-Alder reaction. The obtained product were characterized by X-ray crystallography.*

In the preceding article[1] we have efficiently prepared homoallylic dienols such as 1 and 2

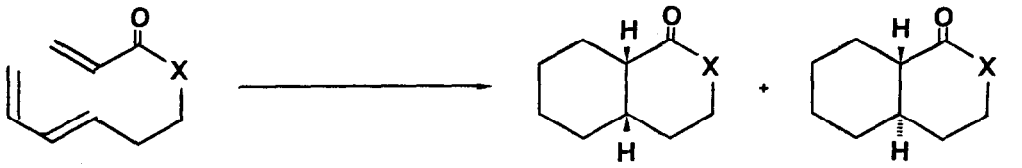


1



2

As part of our program on natural product synthesis, we were interested in their use in intramolecular Diels-Alder reaction, after esterification with acrylic acid derivatives. This reaction, and particularly its intramolecular version[2], is a powerful tool in organic synthesis. However, inspection of litterature data[2-5] reveals that incorporation of an ester linkage in the chain has an adverse effect on the reaction :

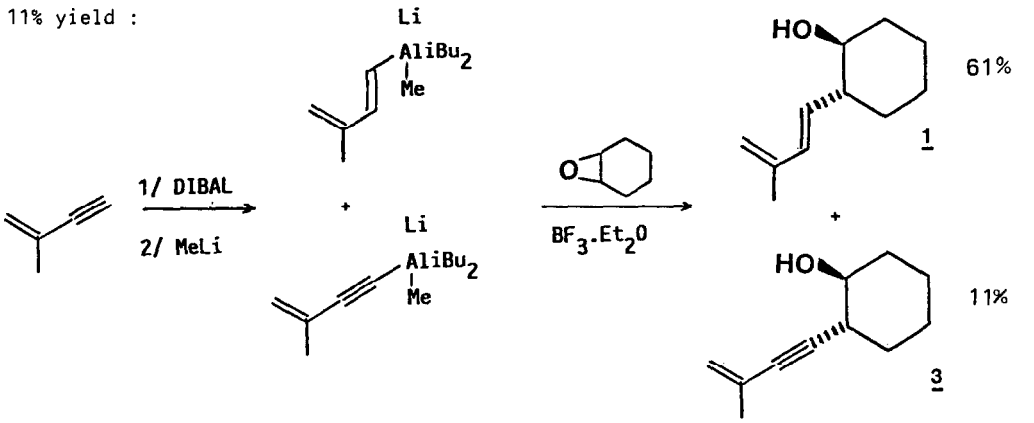


X = $-CH_2-$	0°C/1h	78%	100	0	ref. 3
-NMe-	80°C/2h	83%	8	1	ref. 4
-NH-	85°C/10h	71%	7	1	ref. 4
-O-	210°C/5h	42%	9	1	ref. 4

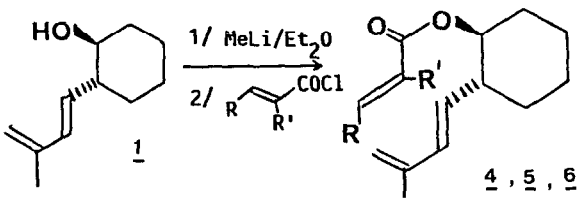
The poor reactivity of esters has been attributed to preference for the transoid form and a relatively high barrier for interconversion of the two rotamers, or, perhaps, to loss of ester resonance in the transition state[5].

In the case of the acrylic derivatives of 1 and 2, it was hoped that the trans-diequatorial relationship of the diene and the dienophile would facilitate the reaction. This is indeed the case as shown by the results reported herein.

As described in the preceding article[1], compound 1 was accompanied by the parent enynol 3 in 11% yield :

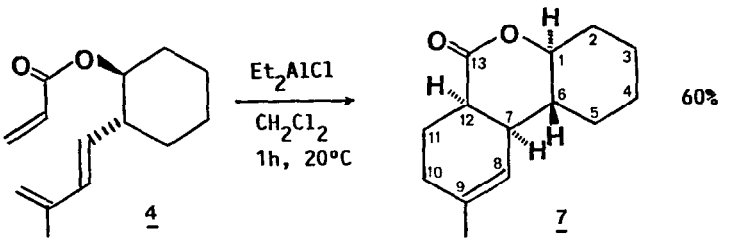


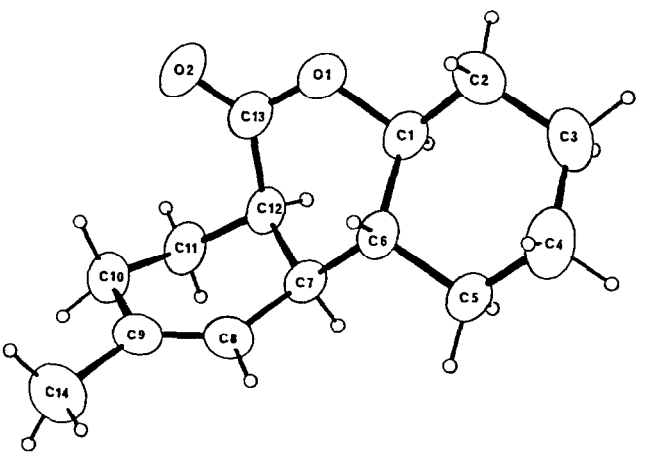
This inseparable mixture was esterified according to modified Kaiser's method[6] with acryloyl chloride, crotonyl chloride or methacryloyl chloride. In all these cases the esters of the corresponding enynols were also formed and again they could not be removed. However since they do not undergo the Diels-Alder reaction they will be ommited in the next schemes.



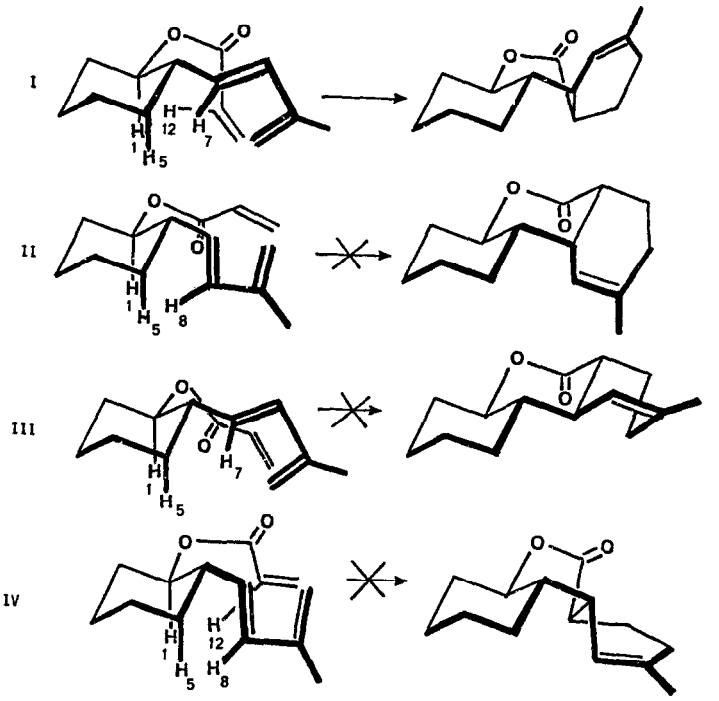
4	R = H ;	R' = H :	67%
5	R = CH_3 ;	R' = H :	65%
6	R - H ;	R' = CH_3 :	60%

Compounds 4, 5, 6 are stable at room temperature, even after several weeks. The Diels-Alder reaction was first attempted with ester 4 ; no cyclisation occured in refluxing toluene after several hours, and in refluxing xylenes, decomposition products were formed. However, in the presence of a Lewis acid, Et_2AlCl, the reaction proceeds rapidly (1 h) at room temperature. Analysis of the crude product by G.C. on capillary glass column, shows a single adduct, 7, which was isolated in 60% yield. The structure of compound 7 was fully characterized by X-ray crystallography .

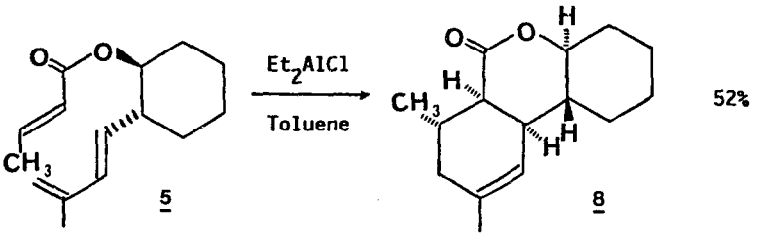




The ester 4 may adopt four possible conformations (I-IV) leading to a Diels-Alder adduct. Conformations III and IV correspond to an "exo" process and are, thus, disfavoured[2]. The "endo" process in conformations I and II explains the cis relationship between H_7 and H_{12}. The formation of a single product indicates that there is a strong difference between conformations I and II. This difference is probably due to the presence of the Lewis acid. Complexation of the Lewis acid by the carbonyl group on conformation II is quite hindered by the axial protons H_1 and H_5, whereas this is not the case with conformation I. This effect could therefore explain the trans relationship between H_6 and H_7.



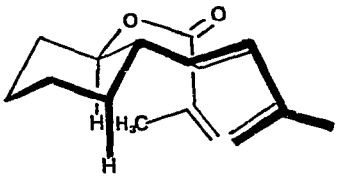
The cycloaddition of ester 5, having a crotonyl ester, is more difficult and requires heating and the presence of a Lewis acid. The presence of the additional methyl group may interfere sterically. In addition, by its electron-donating ability it reduces thediennophilicity of the enoate moiety. Both effects contribute to lower the reactivity of ester 5. Here again only one stereoisomer can be detected by G.C. on capillary glass column and the product 8 is isolated in 52% yield.



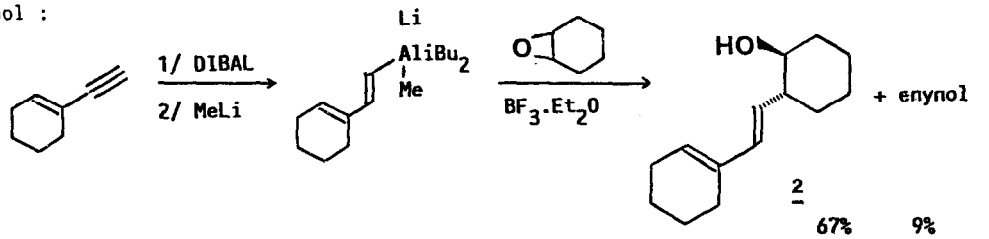
The structure of 8 was determined by analogy with 7 and by NMR decoupling and NOE experiments.

Finally, the cycloaddition of the methacryloyl ester 6 was also attempted. However no reaction took place under a variety of conditions (heat, Et_2AlCl, $BF_3.Et_2O$, $TiCl_4$ ....) ;

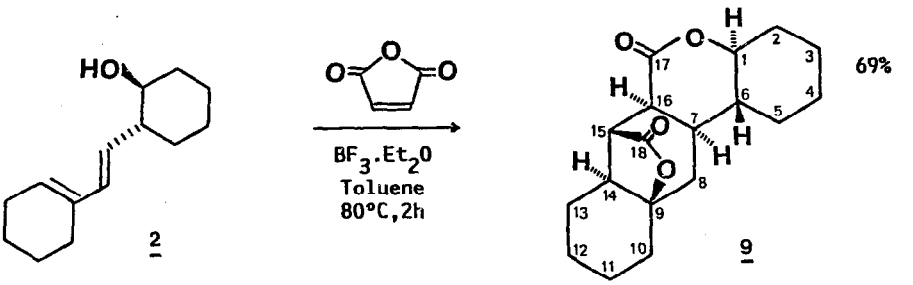
under forcing conditions only tars were obtained. This is not really surprising since the most favorable conformation I is, now, a sterically demanding one :

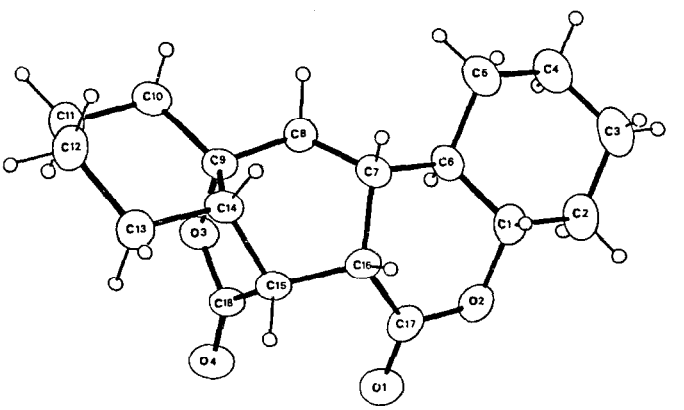


Dienol 2 was prepared in the same manner as 1 and therefore it is also accompanied by some enynol :

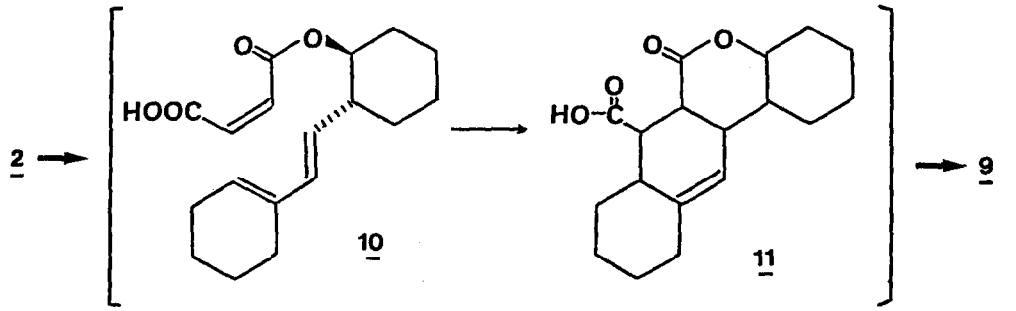


The cycloaddition reaction was performed with a maleic ester derivative. In our first attempt to esterify 2 with maleic anhydride, in the presence of $BF_3.Et_2O$[7], we obtained directly the cycloadduct 9 in 69% yield, as a single isomer ! Its structure was completely elucidated by X-ray crystallography :





The formation of 9 is easily rationalised through the following steps : esterification to 10 ; cycloaddition to 11 and finally acid catalysed lactonisation to 9 :



That the Diels-Alder reaction was an intramolecular process was shown by the fact that the acetate of 2 did not undergo such an intermolecular reaction with maleic anhydride ; nor did compound 2 with dimethyl fumarate. On the other hand, compound 10 could be prepared in 91% isolated yield in the absence of any Lewis acid[8]. 10 was stable at room temperature but polymerises upon heating. In the presence of $BF_3.Et_2O$, 9 is formed in low yield among many unidentified products. In the above one-pot procedure, where heating is necessary for the esterification step, 10 cyclises as soon as it is formed and, thus, its polymerisation is avoided to a great extend.

The stereochemistry of the cycloadduct 9 results again from the same considerations as the ones described above. The reaction takes place through the most favourable conformation I. As for the lactonisation step, it is easily understood since the free acid is locked in a proximal position to the trisubstituted double bond.

The role of the cyclohexane ring is essential for the success of the above Diels-Alder reactions, since by the trans diequatorial position of the substituants it locks the cycloaddition partners in a close enough position. Moreover, a rigorous stereocontrol of the reaction is, thus, achieved.

EXPERIMENTAL PART

NMR spectra were recorded on a Brucker AC 250 apparatus ($CDCl_3$; δ ppm from TMS).
IR spectra were obtained on a Perkin Elmer model 457 spectrometer (neat, cm^{-1}).
GLPC analyses were performed on a Carlo Erba chromatograph model G1 and 2150 using a 3m glass column (10% SE30 on silanized chromosorb G 80/100 mesh or carbowax 20M) and 25m capillary glass column (OV 101).
The gas chromatograph was coupled to an integrator Hitachi D2000.

Esterification of dienol 1
To a stirred solution of dienol 1 (3.9 g ; 20 mmol) in Et_2O (50 ml) are added, at -30°C, MeLi.LiBr (1.5 M solution in Et_2O ; 14.6 ml ; 22 mmol). After 5 min acryloyl chloride (5 ml ; 62 mmol) or crotonyl chloride (6 ml ; 63 mmol) or methacryloyl chloride (6 ml ; 61 mmol) is added at -10°C. The solution is stirred at room temperature until completion (30 min). It is then carefully hydrolyzed, at 0°C, with aqueous Na_2CO_3. The organic layer is dried over $MgSO_4$, concentrated in vacuo, and the residue flash chromatographied on SiO_2 (eluent : cyclohexane/ethyl acetate : 95/5). In all the cases, the ester of dienol 1 would not be separeted from the ester of enynol 3.

Ester 4 : viscous oil
I.R. : 3010, 1710, 1620, 965
^{1}H NMR : 6.86 (dd, 1H), 6.12 (d, 1H), 5.75 (m, 2H), 5.45 (dd, 1H), 4.81 (s, 2H), 4.64 (m, 1H), 1.75 (s, 3H), 2.3-1.1 (m, 9H).
^{13}C NMR : 165.5, 141.9, 133.6, 131.5, 129.8, 129.0, 114.9, 75.7, 46.7, 31.6, 24.9, 24.5, 18.5

Ester 5 : viscous oil

I.R. : 3010, 1710, 1670, 965

^{1}H NMR : 6.26 (dq, 1H), 6.08 (d, 1H), 5.76 (d, 1H), 5.45 (dd, 1H), 4.82 (s, 2H), 4.68 (m, 1H), 1.75 (s, 6H), 2.3-1.0 (m, 9H)

^{13}C NMR : 165.8, 143.5, 141.9, 133.4, 131.7, 123.3, 114.8, 75.2, 46.7, 31.6, 25.0, 24.6, 18.5, 17.8

Ester 6 : viscous oil

I.R. : 3010, 1710, 1640, 965

^{1}H NMR : 6.10 (d, 1H), 5.75 (d, 2H), 5.45 (dd, 1H), 4.82 (s, 2H), 4.72 (m, 1H), 1.98 (s, 3H), 1.75 (s, 3H), 2.3-1.1 (m, 9H)

^{13}C NMR : 166.5, 141.9, 137.0, 133.7, 131.6, 124.3, 114.8, 75.8, 47.0, 31.5, 25.0, 24.6, 18.5, 18.3

Cycloaddition of ester 4

To a stirred solution of ester 4 (1.04 g ; 4 mmol) in methylene chloride (200 ml) is added, at -40°C, a solution of Et_2AlCl (7 ml of 1 M sol. in hexane). The solution is warmed up to room temperature, stirred for 1 h. whereupon all of the starting material was consumed.

The mixture is hydrolyzed with aqueous Na_2CO_3. The organic phase is dried over $MgSO_4$ and concentrated under atmospheric pressure (the product sublimizes readily !). The residue is recrystallized in pentane. The cycloadduct 7 crystallizes as thin needles ; m.p. 134°C.

I.R. : 1720, 810.

^{1}H NMR : 5.29 (dq, 1H), 3.90 (ddd, 1H), 2.74 (ddd, 1H), 2.35-1.70 (m, 9H), 1.66 (d, 3H), 1.45-1.05 (5H).

^{13}C NMR : 174.4, 134.9, 121.1, 80.4, 44.7, 38.0, 37.8, 32.1, 29.6, 27.6, 25.4, 24.2, 23.7, 23.3.

Cycloaddition of ester 5

To a solution of ester 5 (0.83 g, 3 mmol) in anhydrous toluene (100 ml) is added, at room temperature, a solution of Et_2AlCl (6 ml of 1 M sol. in hexane). The solution is refluxed (110°C) for 18 h whereupon the starting material is consumed. The mixture is hydrolyzed with aqueous Na_2CO_3. The organic phase is dried over $MgSO_4$ and most of the solvent is removed at atmospheric pressure. The last traces of toluene are azeotropically removed with 30 ml MeOH, then 20 ml CH_2Cl_2. The crude cycloadduct 8 is recrystallized in pentane (needles). m.p. 102°C. Anal. calcd. for $C_{15}H_{22}O_2$: C, 76-88 ; H, 9.46. Found : 6,76-71 ; H, 9.52.

I.R.: 1720, 810.

^{1}H NMR : 5.25 (s, 1H), 3.93 (ddd, 1H), 2.47 (m, 1H), 2.43 (m, 2H), 2.30 (m, 1H), 2.10 (m, 2H), 1.85 (m, 1H), 1.75 (m, 1H), 1.64 (s, 3H), 1.65-1.50 (m, 1H), 1.4-1.1 (m, 5H), 1.00 (d, 3H).

^{13}C NMR : 174.2, 132.3, 120.6, 78.7, 45.2, 35.2, 33.8, 31.9, 30.4, 26.2, 25.4, 24.0, 23.9, 19.1. NOESY spectrum is available upon request.

Esterification of dienol 2

Dienol 2 (0.84 g, 4 mmol) and maleic anhydride (0.78 g, 8 mmol) are dissolved in Et_2O (10 ml). N-Methyl morpholine (0.81 g, 8 mmol) is added, at room temperature, and the mixture is stirred overnight, whereupon the reaction is completed. The mixture is poured onto a solution of AcOH (7 ml of 0.5 M sol. in water). The aqueous phase is extracted twice with Et_2O (2 x 50 ml), the ethereal extracts are dried over $MgSO_4$ and the solvents are removed in vacuo. The crude product is purified by column chromatography on silica gel (eluent = cyclohexane/ethyl acetate = 90/10). The ester of the enynol could not be separated.

IR : 3100, 3000, 1740, 1730

^{1}H : 6.43 (d, 1H), 6.26 (d, 1H), 5.96 (d, 1H), 5.58 (m, 1H), 5.16 (dd, 1H), 4.70 (m, 1H), 2.2-1.0 (m, 17H).

^{13}C NMR : 167.2, 165.6, 142.8, 135.6, 135.1, 130.2, 128.7, 126.7, 79.2, 47.0, 31.8, 31.2, 26.0, 24.9, 24.7, 24.5, 22.7, 22.6.

One-pot obtention of cycloadduct 9

To a solution of dienol 2 (0.53 g, 2.5 mmol) and maleic anhydride (0.5 g, 5 mmol) in hot (80°C) toluene (30 ml) is aded $BF_3.Et_2O$ (0.32 ml, 2.5 mmol). The mixture is stirred 2 h at 80°C, and after cooling to room temperature, hydrolyzed with aqueous $NaHCO_3$. The organic phase is dried over $MgSO_4$ and concentrated in vacuo. The residue is purified by flash column chromatography through SiO_2 (eluent : cyclohexane/ethyl acetate : 50/50). The cycloadduct is recrystallized in CH_2Cl_2/Et_2O : m.p. 202°C.

I.R. : 1770.

^{1}H NMR : 3.85 (ddd, 1H), 3.18 (dd, 1H), 2.92 (d, 1H), 2.25-0.9 (m, 21 H).

^{13}C **NMR** : 177.2, 170.2, 84.7, 84.2, 50.6, 46.6, 43.1, 40.0, 35.9, 34.1, 32.5, 32.2, 28.6, 26.4, 24.9, 24.1, 23.6, 20.2.

Crystallographic study of the compound 7

$C_{14}H_{20}O_2$, Mr = 220.3, monoclinic, $P2_1/c$, a = 5.318(4), b = 12.600(6), c = 17.627(6) A, = 90.18(4)°, V = 1196.2(5) A^{-3}, Z = 4, Dx = 1.22Mg.m^{-3}, (MoK) = 0.71073 A, = 0.74 cm^{-1}, F_{000} = 480, T = 296K, final R = 0.042 for 1267 observations.

The sample (prism 0.25 0.25 0.15) is studied on an automatic ENRAF-NONIUS diffractometer. The cell parameters are determined by least-square refinement of a set of 25 high-theta reflections. The crystal gives 2289 reflections (2 $_{max}$ = 52°) with 1267 independent (R_{int} = 0.016; I (I)) ; range of HKL : H 0,6 K 0,15 L -20,20, scan /2 = 1, t_{max} = 45s, intensity controls without appreciable decay.

The structure is solved with Direct Methods (Main and al, 1982) which reveal all the non-hydrogene atoms. After isotropic (R = 0.12) then anisotropic (R = 0.10) refinements of the molecule, the hydrogene atoms are located with a Fourier Difference between 0.051 and 0.026.

The best full-matrix least-square refinement (F magnitude, x, y, z, ij for the non-hydrogene atoms, x, y, z for the hydrogene atoms) of the structure gives :

R = 0.045 R = 0.042 S = 1.12 e = 0.20e.A^{-3}

Atomic scattering factors from International Tables for X-ray Crystallography (1974). All the calculations were performed on a Digital PDP 11/60 computer with the SDP package (Frenz, 1985).

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Crystallographic study of the compound 9.

$C_{18}H_{24}O_4$, Mr = 304.4, monoclinic, $P2_1/c$, a = 21.902(3), b = 6.700(3), c = 10.316(9) A, = 95.94(3)°, V = 1506(1) A^{-3}, Z = 4, DX = 1.27Mg.m^{-3}, (MoK) = 0.71073 A, = 0.87 cm^{-1}, F_{000} = 656, T = 296 K, final R = 0.044 for 1685 observations.

The sample (prism shaped 0.35 0.35 0.55) is studied on an automatic ENRAF-NONIUS diffractometer. The cell parameters are determined by least-square refinement of a set of 25 high-theta reflections. The crystal gives 2907 reflections (2 $_{max}$ = 50°) with 1685 independent (R_{int} = 0.023, I (I)) ; range of HKL : H 0,12 K 0,7 L -25,25, scan /2 = 1, t_{max} = 60s, intensity controls without appreciable decay.

The structure is solved with Direct Methods which reveal all the non-hydrogene atoms. After isotropic (R = 0.117) then anisotropic (R = 0.096) refinements of the molecule, the hydrogene atoms are located with a Fourier Difference between 0.048 and 0.031.

The best full-matrix least-square refinement of the structure (F magnitude, x, y, z, ij for the non-hydrogene atoms, x; y, z for the hydrogene atoms) gives :

R = 0.056 R = 0.044 S = 2.01 e = 0.22 e.A^{-3}

Lists of structure factors, coordinates, bonds and angles tables, anisotropic thermal parameters for the two X-ray analysis have been deposited with the British Document Supply Centre as Supplementary Publication No SUP_____. Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Acknowledgements : The authors thank Professor J.F. Normant for fruitful discussions and the CNRS (U.A. 473) for financial support.

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