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Synthesis of all possible stereoisomers of polygodial

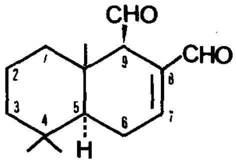
D. Guillerm, M. Delarue, M. Jalali-Naini, P. Lemaître and J.-Y. Lallemand*

Laboratoire de Chimie de l'Ecole Normale Supérieure, 24, rue Lhomond, 75231 PARIS Cedex 05.

Abstract : *The three possible isomers of polygodial, epimers at C-9, cis and trans fused, are described. Controlled kinetic and thermodynamic epimerizations allow preparation of all stereoisomers from the same key intermediate.*

In the course of our work concerning the total synthesis of polygodial 1 and drimenin, we were able to prepare some intermediate analogues with a cis ring linkage at the driman skeleton (1,2).

As isopolygodial 2 does not display any antifeeding activity it was interesting to test other modifications in the molecules. Our efforts were therefore directed toward the synthesis of the cis-fused dialdehydes 3 and 4.



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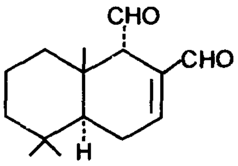

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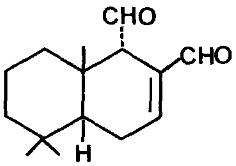

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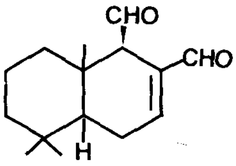

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Diester 5, the Diels-Alder adduct of dimethyl acetylenedicarboxylate with 1-vinyl-2,6,6-trimethyl cyclohexene and starting material for the synthesis of polygodial and warburganal from several laboratories (3-5) and ours (1,2), could be isomerized into conjugated diester 6 with potassium tertiobutylate in tertiobutanol (2) or, for large scale preparations, with 1,5 Diazabicyclo[5.4.0]undecene-5 (D.B.U). (refluxing toluene for two days). The preparative yield is 80 % after flash column chromatography and diester 6 is contaminated by 20 % of its C-9 epimer.

Catalytic hydrogenation (Pd/C/1 atm/methanol) followed by $LiAlH_4$ reduction gives diol 8 in 93 % yield. Cristallization (m.p. 82.83°) allows separation of 8 from the contaminating isomer. ^1H NMR (250 MHz, $CDCl_3$) : 0.85(3H,s) ; 1.14(3H,s) ; 1.23(3H,s) ; 9-$\underline{CH_2}OH$; 3.73(1H,dd,J=10Hz,7.5Hz) ; 3.94(1H,dd,J=10Hz,2Hz) ; 8-$\underline{CH_2}OH$ 4.02 and 4.3(2H,d,-J=12Hz) ; 5.8(1H,m).

The oxidation of diol 8 into the corresponding dialdehyde 3 was achieved using Swern oxidation (6) : the best results were obtained at -60° with trifluoroacetic anhydride, DMSO and triethylamine. The yield in crude material is estimated (NMR) to be 70 %, but dropped to 20 % after flash column chromatography. ^{1} H NMR (250 MHz, $CDCl_3$) : 0.66 (3H,s) ; 1.0(3H,s) , 1.20(3H,s) ; 2.15(1H,m) ; 2.55(2H,m) ; 3.1(H_9,m) ; 7.1(1H,t,d,J=5Hz, 5Hz and 1.5Hz) ; 9.52(1H,s) ; 9.75(1H,d,J=2.5Hz).

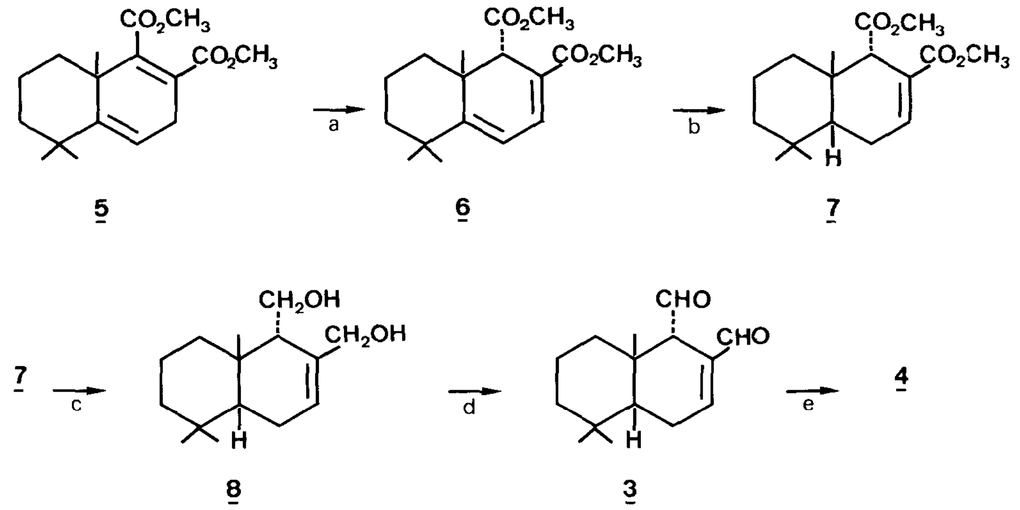
The main features of the NMR spectra of dialdehyde 3 confirm the presence of the cis ring linkage when compared with that of diester 7 whose structure has been unambiguously established by chemical correlations and careful study of the NMR data (2).

Dialdehyde 3, which does not display antifeeding activity on Mysus persicae (7), has been found (8) significantly deterrent at 0.01 % dry weight on Schistocerca gregaria and deterrent only at 0.1 % dry weight on Locusta migratoria.

Preparation of dialdehyde 4 was investigated by epimerization at carbon 9 on compound 3. This problem has been mentionned for polygodial and sacculatal (reverse epimerization). According to Kubo (9), polygodial 1 is transformed into isopolygodial 2 under basic conditions while sacculatal has been reported (10) to give isosacculatal when treated with concentrated sulfuric acid.

The direct conversion of dialdehyde 3 into the new dialdehyde 4 is observed instantly in C_6D_6 using one equivalent of 1,5 Diazabicyclo [4,3.0] nonene-5 (DBN) (11). ^1H NMR (250 MHz, $CDCl_3$) : 0.94(9H,s) ; 2.60(H_6 ,H_6 ,m) ; 3.60(H_9,m) ; 7.20(1H,m) ; 9.48 (1H,d,J=3.5Hz) ; 9.56(1H,s).

Further examination of the NMR spectra at 400 MHz in C_6D_6, and decoupling experiments, allow precise evaluation of the two H_5-H_6 coupling constants : $JH_5 - H_6$ = 1.5Hz and $JH_5 - H_6$ = 7Hz. These values corroborate the cis nature of the ring linkage in dialdehyde 4.



a) DBU, refluxing toluene ; b) H_2/Pd/C ; c) $LiAlH_4$; d) trifluoroacetic anhydride, DMSO, triethylamine -60° ; e) DBN in benzene.

Thus by a series of controlled kinetic and thermodynamic epimerizations it is possible to prepare polygodial and its three isomers from the same key intermediate. Activity of compound 4 is currently under investigation.

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7) We acknowledge Dr. J.D. Pickett (Rothamsted Experimental Station U.K.) for performing antifeeding activity tests

8) Tests kindly performed by Dr. E. Bernays at the Tropical Development and Research Institute (London U.K.)

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11) In the same conditions polygodial gives after 30 mn, a mixture of 65 % isopolygodial and 35 % polygodial, with no further evolution.

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