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EFFICIENT TOTAL SYNTHESES OF POLYGODIAL AND DRIMENIN.

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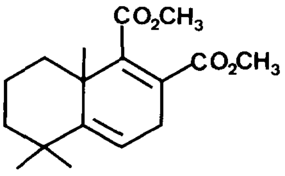
Abstract : A short and stereoselective total synthesis of (±) polygodial and drimenin is presented. The efficiency of the synthesis is due to the easy access to intermediate diol 4 and its successful direct oxidation into polygodial.

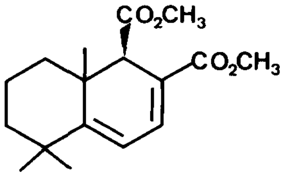
Various terpenoids [1-7] of the drimane family have been recently isolated and identified. Four compounds are of special interest : polygodial [5], warburganal [6], muzigadial [6b] and sacculatal [7]. They are all unsaturated dialdehydes which are efficient antifeedants ; warburganal exhibits in addition antitumor, antifungal and plant-growth regulatory activity. This important class of organic compounds stimulated organic synthetic chemists and several total synthesis were achieved recently [8-14].

We would like to report here a short, efficient and stereospecific total synthesis of racemic polygodial 5 and drimenin 7.

Our synthetic route starts with the diester 1 resulting of the Diels-Alder reaction of dimethyl acetylenedicarboxylate with 1-vinyl-2,6,6-trimethyl cyclohexene [8,15]. Treatment of diester 1 with $LiN(iC_3H_7)_2$ (THF, -78°) followed by kinetic protonation (H_2SO_4 1N, -78°) leads to conjugated diester 2. Isomerisation of 1 with tBuOK in tBuOH leads to a mixture of diesters 2 and 2', the thermodynamically more stable 9α isomer. A mixture of 2 and 2' after treatment



1



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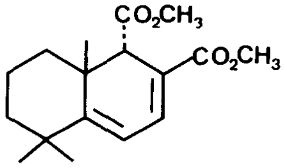
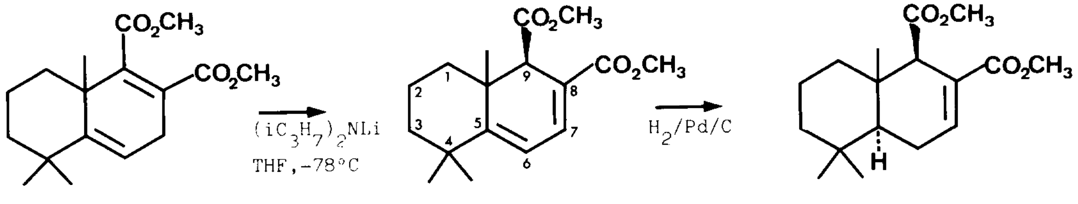


2'

with LDA and kinetically controlled protonation, as described above, leads to pure 2 isomer only. The structures of 2 and 2' are well established by ^{1}H NMR analysis at 250 MHz ($CDCl_3$) :

2 : 1.16 (3H, s) ; 1.18 (3H, s) ; 1.20 (3H, s) 3.36 (H_9, d, $JH_9 - H_7$ = 2.5Hz) ; 3.72 (6H,s); 6.08 (H_6, d, $JH_7 - H_6$ = 6Hz) 7.16 (H_7, dd) ppm.

2' : 1.20 (9H, s) ; 3.36 (H_9, $JH_7 - H_9 \simeq 0$) ; 3.66 (3H, s) ; 3.80 (3H, S) ; 6.10 (H_6, d, $JH_6 - H_7$ = 6Hz) ; 7.22 (H_7, d) ppm.

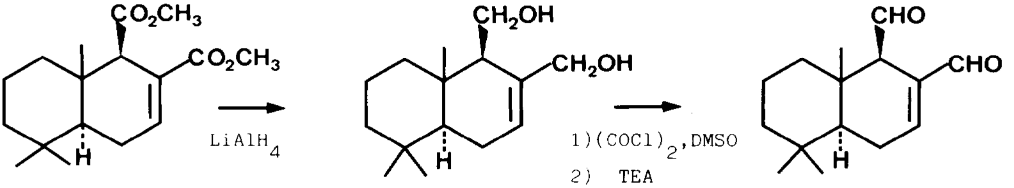


1 2 3

Catalytic hydrogenation (Pd/C, methanol, 1 atm.) of the dienic diester 2 provides as sole product the trans-fused dihydrodiester 3[8]. Hydrogenation of 1 and 2' leads to the corresponding cis-fused compounds only. The structure of 3 is established by comparison with a reference sample prepared according to Nakanishi [8] and by ^{1}H NMR analysis at 250 MHz : ($CDCl_3$) : 0.90 (3H, s) ; 0.92 (3H, s) ; 0.95 (3H,s) ; 3.22 (H_9, m) ; 3.70 (3H, s) ; 3.75 (3H, s) ; 7.40 (H_7, m). The purified diester 3 is obtained in 60% overall yield from diester 1

$LiAlH_4$ reduction of diester 3 gives diol 4 in 82% yield. ^{1}H NMR (250MHz, $CDCl_3$) : 0.75 (3H, s) ; 0.87 (6H, s). 9-CH_2OH : 3.65 (1H, dd, J= 11Hz, 8Hz) ; 3.80 (1H, dd, J = 11Hz, 1.5Hz). 8-CH_2OH : 3.95 (1H, d, J = 12Hz) ; 4.32 (1H, d, J = 12Hz). 5.76 (H_7, m) ppm.

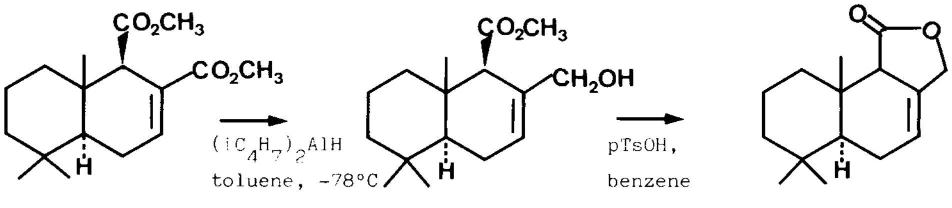
Despite the report of some recent unsuccessful or difficult attempts of direct oxidation of 1,4-diols to dialdehydes [8,9,16], we tried the Swern DMSO oxidation method [17].



3 4 5

Under Swern's conditions (oxalyl chloride - DMSO, -60°C, 15mn, in methylene chloride and triethylamine), diol 4 is transformed directly into polygodial 6 in 75% yield after purification, identical (NMR, 250MHz) to a sample extracted from *Polygonum hydropiper*. ^{1}H NMR at 250 MHz ($CDCl_3$) : 0.94 (3H, s) ; 0.96 (3H,s) : 0.98 (3H;s) ; 2.84 (H_9, m) ; 7.20 (H_7, m) ; 9.52 (1H,s) 9.60 (1H, d, J = 4.5Hz) ppm.

Partial reduction of diester 3 leads to drimenin 7 in two steps :



3 6 7

Diisobutylaluminium hydride reduction of diester 3 in toluene at -78°C provides intermediate 6 (pure[18] ; 70% yield). ^{1}H NMR analysis at 250 MHz : 0.88 (3H, s) ; 0.92 (5H,s) ; 0.94 (3H, s) ; 3.10 (H_9, m) ; 3.72 (3H, s) ; 3.98 (1H,s, J = 12Hz) ; 4.10 (1H, d; J = 12Hz) ; 5.90 H_7, m) ppm.

6 in benzenic solution is allowed to react 12 hours with a small amount of p-toluenesulfonic acid to give pure drimenin 7. ^{1}H NMR at 250MHz : 0.88 (3H,s) ; 0.90 (3H,s) ; 0.92 (3H,s) ; 2.80 (H_9, m) ; 4.68 (2H,m) ; 5.78 (H_7,m) ppm.

The efficiency of this synthesis is due first to the easy access to intermediate diol 4 through a two step stereoselective sequence from diester 1, and secondly to the successful direct oxidation of diol 4 into polygodial.

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18. Crude *6* is accompanied by small amounts of starting material and diol *4* which are easily separated by column chromatography.

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