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A NOVEL SYNTHESIS OF THE CIS-FUSED 2-OXA-3-DECALONE SYSTEM PRESENT IN VERNOLEPIN.

F. Zutterman, P. De Clercq and M. Vandewalle*
State University of Ghent, Department of Organic Chemistry,
Laboratory of Organic Synthesis,
Krijgslaan, 271 (S.4), B-9000 Gent (Belgium).

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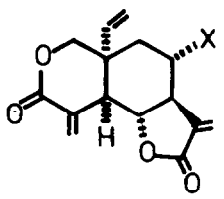
Since the isolation and structural elucidation[1] of vernolepin 1 and vernomenin 2, a substantial amount of research[2-5] has been performed, aimed at the synthesis of these novel elemanolide dilactones. This recently culminated in their total synthesis[2d,3e] and in the synthesis of 8-desoxyvernolepin[2e] 3. Both vernolepin 1 and 8-desoxyvernolepin 3 show antitumor activity.

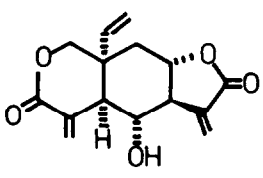
Several groups have focused their efforts on the synthesis of a functionalised cis-fused 2-oxa-3-decalone system, most approaches use rather long sequences involving as a rule cleavage of carbon-carbon bonds in a carbocyclic precursor. We therefore studied a novel approach which could lead directly to the key-compound 9 from which 2-oxa-3-decalones would easily be generated.
A recent publication[6] describing the synthesis of an analogous key-compound constructed however along different lines, prompts us to disclose our results concerning a direct stereoselective synthesis of appropriately functionalised cis-fused 2-oxa-3-decalones 10 and 11.

Reaction of the readily available[7] cyclohexadiene carboxylic acid 4 and chloromethyl methyl ether in THF-HMPT with lithium diisopropylamide as base gave product 5. The crude acid was reduced with lithium aluminum hydride affording the alcohol 6 in an overall yield of 60 %. |$\delta(CCl_4)$ 5.75 (2H, m), 5.50 (2H, m), 3.35 (2H, s), 3.22 (3H, s), 3.19 (2H,s), 2.60 (2H, m); $(M-31)^+$ at m/e 123|. Compound 5 could also be obtained, although in a somewhat lower overall yield, upon directly trapping of the dianion, produced during Birch reduction of benzoic acid.

Treatment of alcohol 6 with methyl malonylchloride and pyridine in ether gave malonic ester 7 (75 %) |ν(neat); 1750 cm^{-1}, $M^{+\cdot}$ at m/e 254|. Subsequent reaction[8] with p.tosylazide and triethylamine in acetonitrile produced diazomalonic ester 8 (91 %) |ν (neat) 1695, 1740, 1760, 2150 cm^{-1}; $\delta(CDCl_3)$ 5.92 (2H, m), 5.63 (2H,m), 4.16 (2H,s), 3.82 (3H, s), 3.31 (3H, s), 3.28 (2H, s), 2.68 (2H, m)|.



1 (X = OH)
3 (X = H)



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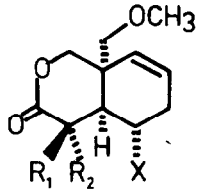
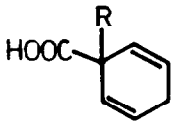
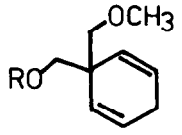


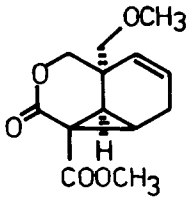
10 (X = OAc, R_1, R_2 = H)
11 (X = SPh, R_1 = $COOCH_3$, R_2 = H)



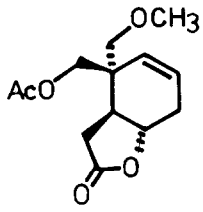
4 (R = H)
5 (R = CH_2OCH_3)



6 (R = H)
7 (R = $COCH_2COOCH_3$)
8 (R = $COCN_2COOCH_3$)



9



12

Reflux of 8 in toluene with cupric acetyl acetonate as catalyst for 30 min yielded (71 %) the tricyclic compound 9 |m.p. 112°C; V 1750 cm^{-1} (brd); δ($CDCl_3$) 5.82 (1H, m), 5.37 (1H, m), 4.38 and 3.88 (2H, dd, J10.5 Hz), 3.71 (3H, s), 3.42 (2H, s), 3.36 (3H, s); $M^{+\cdot}$ at m/e 252|.

A crucial step in our approach involved the cyclopropane ring opening in 9, with formation of a third chiral center on the carbocyclic ring. Solvolysis of 9 with acetic acid and a catalytic amount of sulphuric acid at 90°C for 3 h yielded the cis-fused 2-oxa-3-decalone 10 with three of the 5 chiral centers of vernolepin in a correct set-up |V (neat) 1740, 1240 cm^{-1}; δ($CDCl_3$) 5.84 (1H, m), 5.50 (1H, m), 4.29 and 3.99 (2H, dd, J11.4 Hz), 4.84 (1H, m), 3.34 and 3.25 (2H, dd, J9.0 Hz), 3.35 (3H, s), 2.06 (3H, s); $(M-15)^{+\cdot}$ at m/e 239|. Under the described conditions about 70 % conversion of the starting material 9 has occurred. Traces of 12,

formed by subsequent transesterifications, were detected on TLC. The compounds 9 and 10 are separable by column chromatography (SiO_2 with ether:iso-octane 2:1 as eluent), allowing 9 to be recycled. Longer reaction times or reflux led to the γ-lactone 12 as major product (ν (neat) 1780, 1740 cm^{-1}; δ($CDCl_3$) 5.83 (1H, m), 5.57 (1H, m), 4.45 (1H, m), 3.53 and 3.60 (2H, dd), 3.36 (3H,s), 3.27 and 3.40 (2H, dd), 2.10 (3H, s); $(M-HOAc)^{+\cdot}$ at m/e 194|.

During this solvolysis the methyl ester was cleaved and decarboxylation occurred. Since an α-methoxycarbonyl group on the δ-lactone will afford facile introduction of an α-methylene group present in vernolepin, this approach should prove in total synthesis to be most advantageous.

Opening of the cyclopropane ring by nucleophilic attack with sodium thiophenolate in methanol at reflux for 4 h yielded exclusively 11 (80 %) |ν (neat) 1750, 1580 cm^{-1}; δ($CDCl_3$) 7.4 (5H, m), 5.95 (1H, m), 5.65 (1H, m), 4.35 and 4.05 (2H, dd, 11.4 Hz), 3.89 (3H, s), 3.75 (1H, d, 6.9 Hz), 3.38 (3H, s), 3.37 (2H, s); $M^{+\cdot}$ at m/e 362; m.p. 132-134°C|.

In summary we have achieved, with this model study, the formation of the desired cis-fused 2-oxa-3-decalone system in a 7 step synthesis. The yields quoted are of isolated and purified products, although not optimalised.

The total synthesis of vernolepin 1, using the concept described in the present paper, is currently explored.

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