

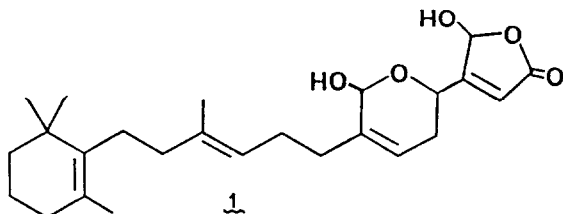
TOTAL SYNTHESIS OF MANOALIDE

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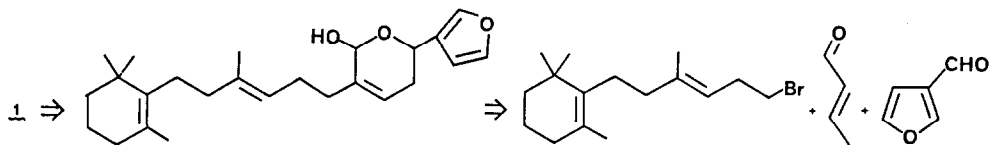
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Summary: An eight step synthesis of manoalide from β -ionone is reported.

Manoalide (**1**) was isolated by Scheuer¹ from *Luffariella variabilis* in 1979. Jacobs, *et al.*² have determined that manoalide inhibits phospholipase A₂ and possesses topical anti-inflammatory activity. Recently Katsumura, Fujiwara and Isoe³, reported a synthesis of manoalide. This report prompted us to disclose our related preparation of this compound.



Analysis of the structure of manoalide led to the following synthetic strategy. We felt that the sensitive hydroxybutenolide moiety could be constructed from a furan.⁴ This synthon for the butenolide should be stable during the course of the synthesis, could be unmasked under selective conditions, and would act as a building block for the pyran ring. The six-membered ring could be assembled by the use of Diels-Alder methods recently developed by Danishefsky,⁵ and the requisite aldehyde for this disconnection could arise from Wittig-type crotonaldehyde imine anion alkylation⁶ as modified by Schlessinger.⁷

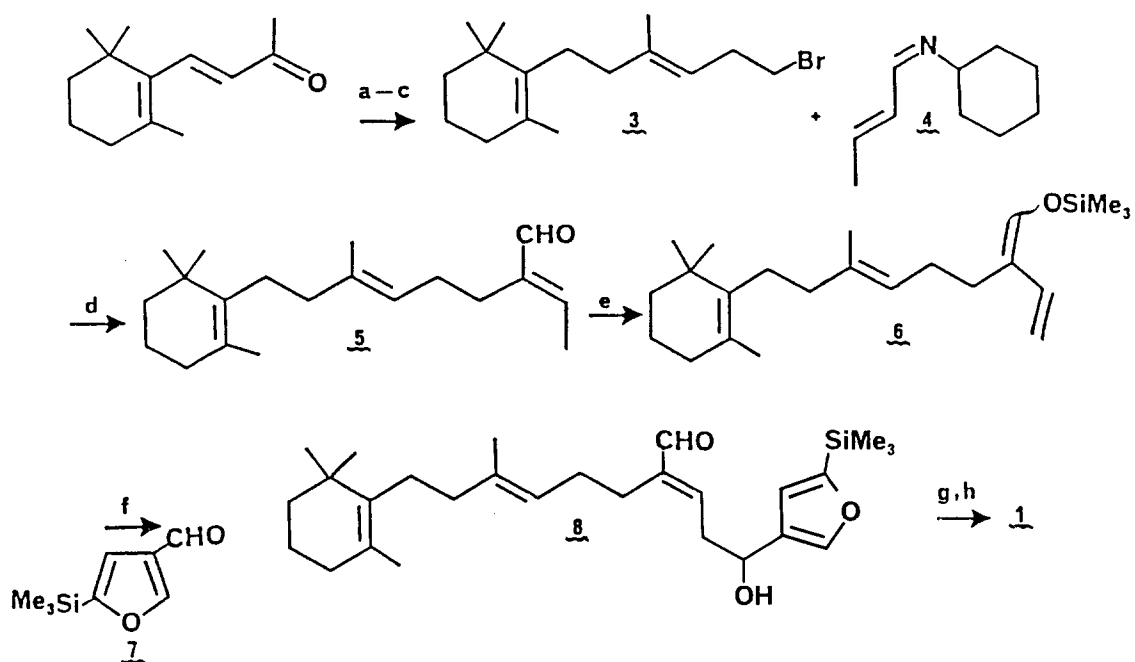


In fact execution of this synthesis proceeded with these moieties. The bromide **3** required for the Schlessinger alkylation was prepared from β -ionone in three steps. β -ionone was first converted into dihydro- β -ionone by reduction with triphenyltin hydride.^{8,9} Wittig condensation with 3-hydroxypropyltriphenyl phosphonium bromide afforded a 1:1 mixture of E- and Z-alcohols. Chromatographic separation afforded the E-alcohol in 29% yield from β -ionone.^{10,11} Bromide **3** was then prepared in 74% yield by treatment of the alcohol with tosyl chloride/pyridine, followed by lithium bromide/acetone. The alkylation of cyclohexylimine **4** was effected by anion formation with lithium diisopropyl amide/N,N'-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) complex, followed by the addition of bromide **3** at -60°C . Aqueous NH_4Cl hydrolysis after 20 hrs afforded aldehyde **5**.^{11,12} Aldehyde **5** was converted into its silyl enol ether **6** for the Diels Alder sequence.¹³ Despite numerous attempts we have been unable to affect a Diels-Alder cycloaddition between silyl ethers such as **6** and any furan aldehyde. However, γ -alkylation with **6** and furan aldehyde **7** occurs in 52% yield with boron trifluoride etherate catalysis at -55°C to provide hydroxyaldehyde **8**.

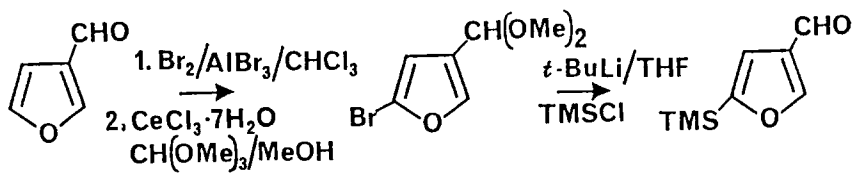
Furan aldehyde **7** was prepared from 3-furfural in three steps using the strategy outlined by Florentin, *et al.*^{14,15} Bromination of 3-furaldehyde with bromine and aluminum bromide in chloroform proceeded smoothly to provide 2-bromo-4-furaldehyde. Conversion of this crude, unstable bromide to the dimethyl acetal was effected by cerium chloride-timethylorthoformate-methanol in 85% yield for the two steps.¹⁶ Metal halogen exchange with t-butyl lithium in THF followed by quenching with TMSCl yielded aldehyde **7** in 44% yield.

Photochemical ring closure of hydroxyaldehyde **8** as detailed by Scheuer,¹ and photooxygenation of the resultant hemiacetal proceeded as expected to provide manoalide (**1**).¹⁷ Synthetic material exhibited spectral data identical to that of the natural substance (IR, ^1H NMR, ^{13}C NMR, MS).¹⁸

Scheme I



a. Ph_3SnH b. $\text{Ph}_3\text{P}^+(\text{CH}_2)_3\text{OH}^- \text{Br}^- / n\text{-BuLi} / \text{THF}$; separate c. TsCl / Py ;
 $\text{LiBr}, (\text{CH}_3)_3\text{CO}$ d. $\text{LiDA} / \text{DMPU} / \text{THF} / -78^\circ\text{C}$ e. $\text{TMSCl} / \text{Et}_3\text{N} / \text{PhH}$
 f. $\text{BF}_3\text{OEt}_2 / \text{CH}_2\text{Cl}_2 / -55^\circ\text{C}$ g. $300\text{nm} / \text{PhH}$ h. $^1\text{O}_2 / \text{CH}_3\text{OH}$



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17. In our hands, a directing group, such as trimethylsilyl, is necessary for regioselectivity. We are grateful to Professor S. Tanis (MSU) for continuing discussions on this and related issues.
18. We are grateful to Professor D. J. Faulkner (SIO) for this data and comments on this work.

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