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A STEREOSPECIFIC TOTAL SYNTHESIS OF WABURGANAL

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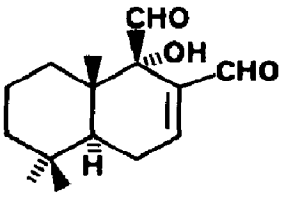
ABSTRACT: A stereospecific, efficient synthesis of the potent insect antifeedant, waburganal, 1, is described.

Several sesquiterpenes of the drimane class have been found to possess significant antifeedant activity[1]. Among the most potent of these is the unsaturated hydroxy-dialdehyde waburganal, 1[2]. Isolated from the bark of Waburgia ugandensis and W. stuhlmanii, waburganal shows specific antifeedant activity against the African army worm, Spodoptera exempta. Waburganal also exhibits heliocidal and cytotoxic activity as well as being an active constituent of an East African folk remedy and spice.

As a result of its intriguing biological properties great interest has been elicited in the synthesis of 1, and total syntheses have been published from several laboratories[3a,b,c,d]. In this report we describe an efficient, short, and stereospecific synthesis of (±)-waburganal.



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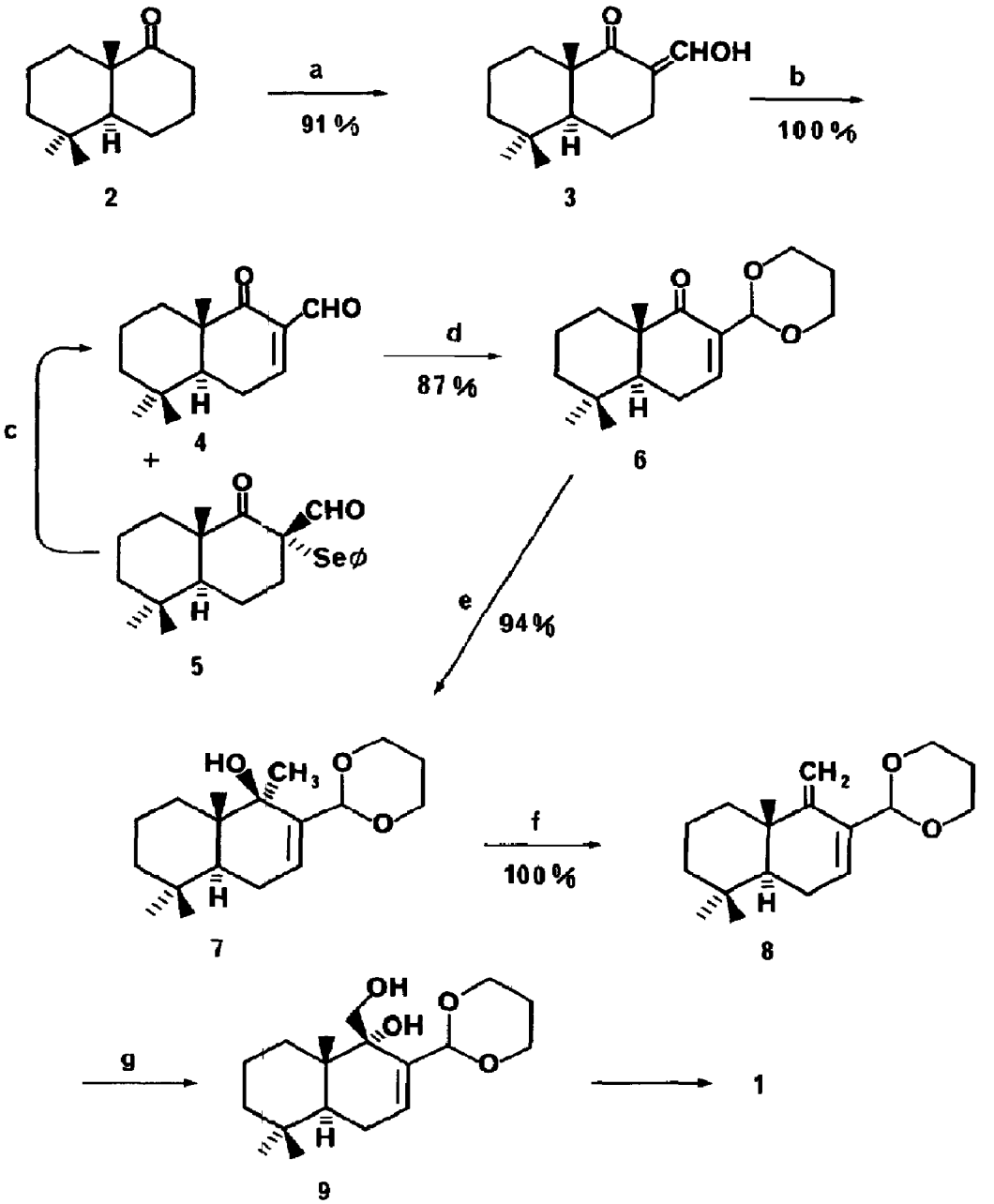
As shown in Scheme I, formylation of the readily available ketone 2[4] gave the α-hydroxymethylene ketone 3[5]. Dehydrogenation of 3 using a selenation-deselenation procedure afforded the unsaturated ketoaldehyde 4 quantitatively, in contrast to the modest yields of 4 obtainable from the reaction of 3 with DDQ[5,3d]. Interestingly, in the reaction of 3 with C_6H_5SeCl in pyridine a mixture of 4 and the equatorial phenylselenenyl ketone 5 is first obtained[6]. Hydrogen peroxide oxidation of the crude reaction product and elimination of the resulting selenoxide suffice, however, to convert the mixture entirely to 4.

Selective acetal formation with 4 may be achieved with either ethylene glycol or propane-1,3-diol. In the case reported here the propylene acetal 6 was employed. While Wittig reagents

Scheme I



(a) NaH, HCO_2Et, C_6H_6, 0 °C → rm.t., 10h; (b) PhSeCl, pyridine, $CHCl_3$, 0 °C; (c) 30% H_2O_2, 0 °C, 45 min; (d) $HOCH_2CH_2CH_2OH$, C_6H_6, p-TsOH, reflux, 10h; (e) CH_3Li, THF, HMPA, -78 °C → rm.t., 8h; (f) MeO_2CNSO_2NEt, Et_3N, THF, reflux, 2.5h; (g) OsO_4, pyridine, Et_2O, rm.t., 20h.

do not react with the hindered carbonyl group of 6, methyl lithium readily adds to afford tertiary alcohol 7. No rigorous proof of the stereochemistry of 7 has been obtained, but consideration of the accessibility of either face of the carbonyl group suggests that addition of a nucleophile should occur preferentially from the α-side[7,8]. Smooth and quantitative dehydration of 7 to diene 8 was then effected employing the Burgess reagent, $MeO_2CNSO_2NEt_3$[9].

At this stage we anticipated that reaction at the exomethylene group of 8 would occur, in similar fashion to the formation of 7, from the less hindered α-face of the double bond. Specifically, when 7 was treated with osmium tetroxide it yielded the known diol 9[3b]. This reaction while affording a by-product of as yet unknown constitution, does not give any of the diol epimeric at C-9, and is thus specific for the waburganal stereochemistry. Without extensive purification diol 9 was carried forward by reported procedures[3a,b] for oxidation and hydrolysis directly to (±)-waburganal, mp 99.5 - 101°C with an overall yield for the synthesis of 15%[10]. In a comparison of its spectral and thin-layer chromatographic properties the synthetic material proved identical in all respects to an authentic sample of natural waburganal.

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References and Notes

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2. I. Kubo, Y.-W. Lee, M. J. Pettei, F. Pilkiewicz, and K. Nakanishi, J. Chem. Soc., Chem. Commun., 1013 (1976).

3. (a) S. P. Tanis and K. Nakanishi, J. Am. Chem. Soc., 101, 4398 (1979); (b) T. Nakata, H. Akita, T. Naito, and T. Oishi, J. Am. Chem. Soc., 101, 4400 (1979); (c) A. Ohsuka and A. Matsukawa, Chem. Lett., 635 (1979); (d) A. S. Kende and T. J. Blacklock, Tetrahedron Lett., 0000 (1980).

4. Several preparations of this compound have been reported, the most recent being described by D. L. Snitman, M.-Y. Tsai, D. S. Watt, C. L. Edwards and P. L. Stotter, J. Org. Chem., 44, 2838 (1979). Our material was prepared by (a) Wolff-Kishener reduction, (b) oxidation of 4,4,10β-trimethyl-9β-hydroxy-trans-3-decalone (J. S. Dutcher, J. G. Macmillan and C. H. Heathcock, J. Org. Chem., 41, 2663 (1976).

5. N. Ototani, T. Kato and Y. Kitahara, Bull. Chem. Soc., Japan, 40, 1730 (1967).

6. Monocyclic β-ketoesters and aldehydes bearing axial substituents have been found to give directly the α,β-unsaturated ketoesters and aldehydes when treated with phenylselenenyl chloride and pyridine; Personal Communication from Professor D. Liotta, Emory University.

7. A monocyclic model system for the waburganal hydroxydialdehyde system has been prepared (A. J. G. M. Peterse, J. H. Roskam and Ae. de Groot, Recl. Trav. Chim. Pays-Bas, 97, 277 (1978)) by the addition of lithiodithane to 6,6-dimethylcyclohex-2-enone-2-carboxaldehyde dimethylacetal and subsequent hydrolysis. This procedure would be expected to yield epi-waburganal[3d] when applied to 6 or related acetals.

8. Satisfactory elemental analyses have been obtained for all new compounds reported herein.

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10. The crude yield of waburganal from diene 8 is approximately 50%. Efforts to effect a more efficient purification of 1 will be reported in the full paper.

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