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# STEREOSELECTIVE TOTAL SYNTHESES OF (±)-WARBURGANAL AND (±)-ISOTADEONAL

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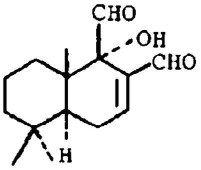
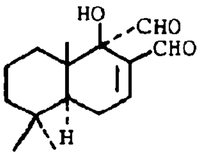
ABSTRACT: A short, stereoselective synthesis of (±)-warburganal (1), its C-9 epimer (2) and the related sesquiterpene dialdehyde (±)-isotadeonal is presented.

Warburganal (1),[1] a sesquiterpene dialdehyde isolated from the tree barks of Warburgia stuhlmanii and W. ugandensis, has been shown to possess strong antifeedant activity against the African army worms of the Spodoptera genus and also to have molluscicidal and antimicrobial properties. This compound and its congeners have recently received the intense attention of synthetic chemists, and within the past year three independent syntheses have been reported.[2a,b,c] We now describe a short and efficient total synthesis of (±)-1, of its C-9 epimer 2, and of the related sesquiterpene dialdehyde (±)-isotadeonal (3).[3]



1



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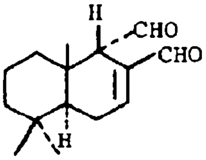
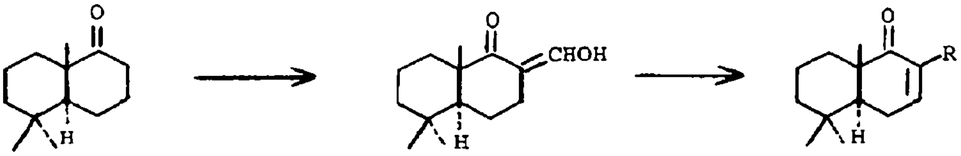


3

Reaction of 5,5,9-trimethyl-trans-1-decalone (4)[4] with ethyl formate and sodium hydride (THF, reflux, 4 hr) gave in 92% yield the 2-formyl derivative 5.[5] Mild dehydrogenation of 5 (DDQ, $C_6H_6$, 20°C, 15 min) followed by silica gel chromatography afforded 70% of the crystalline unsaturated ketoaldehyde 6, mp 74-76°C, previously obtained in lower yield by Kitahara et al.[5] The above ketoaldehyde was selectively and quantitatively protected (ethylene glycol, p-TSA, $C_6H_6$, Dean-Stark azeotrope) to yield monoacetal 7.[5]



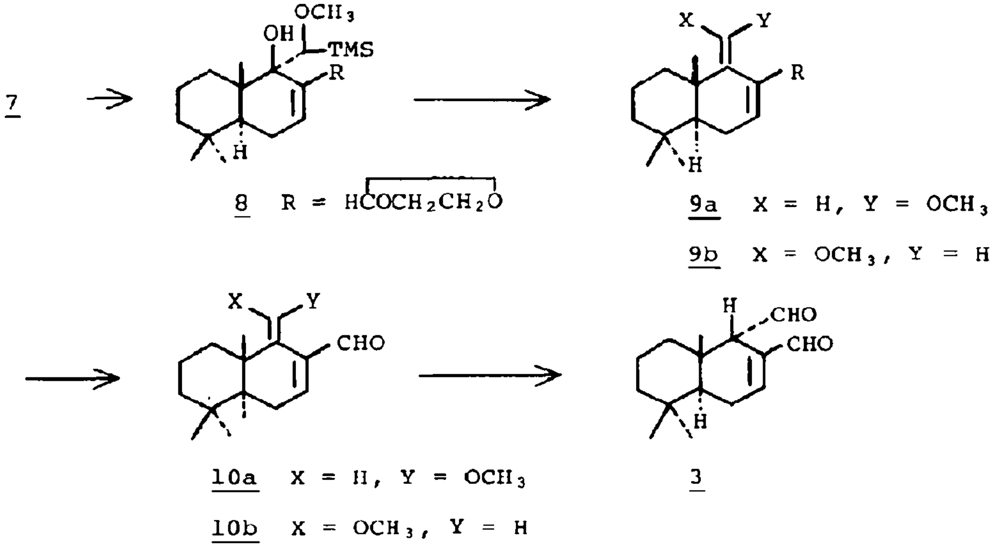
4

5

6 R = CHO

7 R = $\mathrm{HC\overline{OCH_2CH_2O}}$

The hindered ketone function in ketoacetal 7 did not react in satisfactory yield with $Ph_3P{=}CH_2$, $(EtO)_2POCHOCH_3$, $(EtO)_2POCHOCH_2CH_2OCH_3$, $(CH_3)_3SiCHCl$, or TosMIC.[6] Useful homologation was uniquely achieved by the addition of lithium methoxy(trimethylsilyl)methylide as described by Magnus and Roy[7] (-23°C, THF, 30 min) to give a diastereomeric mixture of alcohols 8 in 73% yield.[8] These alcohols, not readily separable by chromatography, underwent smooth elimination of $Me_3SiOH$ (KH, THF, 0°C, 20 min) to afford a 3:1 mixture of (Z)- and (E)-enol ether adducts 9a and 9b[8,9] in 85% yield. Hydrolysis of 9a and 9b (2% aqueous HCl in THF, r.t., 5 min) afforded the corresponding monoaldehydes 10a and 10b in quantitative yields. Continued hydrolysis under more vigorous conditions (1:1:2 $H_2O/H_2SO_4$/acetone, r.t., 10 min) transformed either isomer in high yield to a crystalline $C_{15}H_{22}O_2$ dialdehyde, mp 61-62°C, identified as (±)-isotadeonal (3) by careful comparison of its NMR spectrum with that reported by Ohsuka.[2a]



8 R = $HCOCH_2CH_2O$

9a X = H, Y = $OCH_3$

9b X = $OCH_3$, Y = H

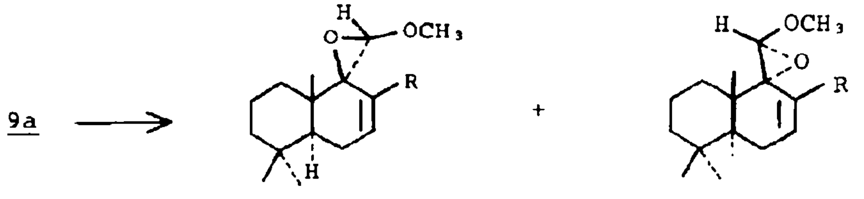
10a X = H, Y = $OCH_3$

10b X = $OCH_3$, Y = H

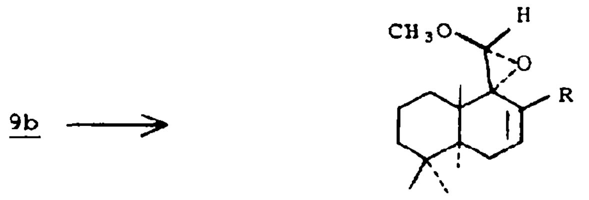
3

Epoxidation of enol ether 9a (m-CPBA, $CH_2Cl_2$, 0°C, $NaHCO_3$ buffer) produced a colorless oil which could be shown by NMR spectroscopy to contain a ca. 4:1 mixture of epoxy ether adducts 11a and 11b, respectively, while epoxidation of enol ether 9b under similar conditions produced only epoxy ether adduct 12a.[10] Mild acid hydrolysis of the mixture of epoxy ethers 11a and 11b produced a corresponding 4:1 mixture of epi-warburganal (2)[11] and

(±)-warburganal (1) in a 95% yield from 9a. In a similar fashion, hydrolysis of epoxy ether 12a produced only (±)-warburganal (1) in an 80% yield from 9b. The two epimeric $C_{15}H_{22}O_3$ dialdehydes were readily separated by silica gel chromatography to afford 1 and 2 in combined overall yield of 13.5% and 22.5%, respectively.



11a R = $\mathrm{HCOCH_2CH_2O}$    11b R = $\mathrm{HCOCH_2CH_2O}$



12a R = $\mathrm{HCOCH_2CH_2O}$

11a + 11b → 2 + 1

12a → 1

The synthetic warburganal obtained, mp 98-99°C, was identical by TLC and 100 MHz NMR with natural warburganal kindly provided by Professor Kubo.

Synthesis of (±)-1 was also achieved by stereospecific osmylation of enol ether 10a (1 eq $OsO_4$, 1:1 dioxane/$H_2O$, 0°C, 45 min) followed by reductive workup with $H_2S$. The yield however was only 37%.

The above syntheses of (±)-warburganal (1) and (±)-isotadeonal (2) proceed in only seven steps from decalone 4. Their brevity and yield thus compare favorably with alternative routes to these biologically active sesquiterpenes.

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## References:

1. I. Kubo, Y.-W. Lee, M. Pettei, F. Pilkiewicz and K. Nakanishi, J. Chem. Soc., Chem. Commun., 1013-1014 (1976).
2. (a) A. Ohsuka and A. Matsukawa, Chem. Let., 635-636 (1979); (b) S. P. Tanis and K. Nakanishi, J. Am. Chem. Soc., 101, 4398-4400 (1979); (c) T. Nakata, H. Akita, T. Naioto and T. Oishi, J. Am. Chem. Soc., 101, 4400-4401 (1979).
3. A. Ohsuka, Nippon Kagaku Zasshi, 84, 748 (1963).
4. Decalone 4 is available from 2-methyl-1,3-cyclohexanedione in 50% yield by the method of D. L. Snitman, M.-Y. Tsai, D. S. Watt, C. L. Edwards and P. L. Stotter, J. Org. Chem., 44, 2838-2842 (1979).
5. N. Ototani, T. Kato and Y. Kitahara, Bull. Chem. Soc., Japan, 40, 1730-1732 (1967).
6. While ylides such as those listed failed to react with ketoacetal 7 satisfactorily, it was found that 7 did readily undergo 1,2-addition with vinyl lithium, methyl lithium, and methyl magnesium bromide to afford high yields of the corresponding alcohols resulting exclusively from back side attack of the nucleophile.
7. P. Magnus and G. Roy, J. Chem. Soc., Chem. Commun., 822-823 (1979).
8. All new compounds gave satisfactory spectral and elemental analyses. Full experimental details will be presented in our forthcoming publication.
9. Stereochemical assignments of the enol ether adducts 9a and 9b and aldehydes 10a and 10b are provisional and based on the observation that the enol ether proton of aldehyde 10b ($\delta$7.32) shows a 1.4 ppm downfield shift relative to the enol ether proton of 10a ($\delta$5.92). Molecular models suggest that the enol ether proton of aldehyde 10b lies in the deshielding zone of the aldehyde carbonyl. This deshielding can only be present in adduct 10b. To further substantiate these stereochemical assignments, adduct 9b is currently undergoing single crystal X-ray structure determination.
10. For a discussion on the mechanism of a ring opening of an epoxy ether, see C. L. Stevens and S. J. Dykstra, J. Am. Chem. Soc., 75, 5975-5978 (1953).
11. NMR ($CDCl_3$, 100 MHz) $\delta$9.89 (s, 1H), 9.32 (s, 1H), 7.13 (dd, 1H, J = 3.5 and J = 4.5 Hz), 4.86 (s, 1H), 2.58-2.28 (m, 2H), 1.84-1.08 (m, 7H), 1.04 (s, 3H), 0.97 (s, 3H) and 0.92 (s, 3H); mass spectrum: m/e (% base): 250 ($M^+$, 3), 249 (2), 222 (19), 221 (base), 133 (29), 109 (76), 105 (38) and 95 (24).

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