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THE OLEFIN METATHESIS/TRANSANNULAR ENE SEQUENCE: A METHOD FOR THE STEREOCONTROLLED SYNTHESIS OF TRANS-DECALIN DERIVATIVES. 3. TOTAL SYNTHESIS OF (±)-WARBURGANAL[1,2]

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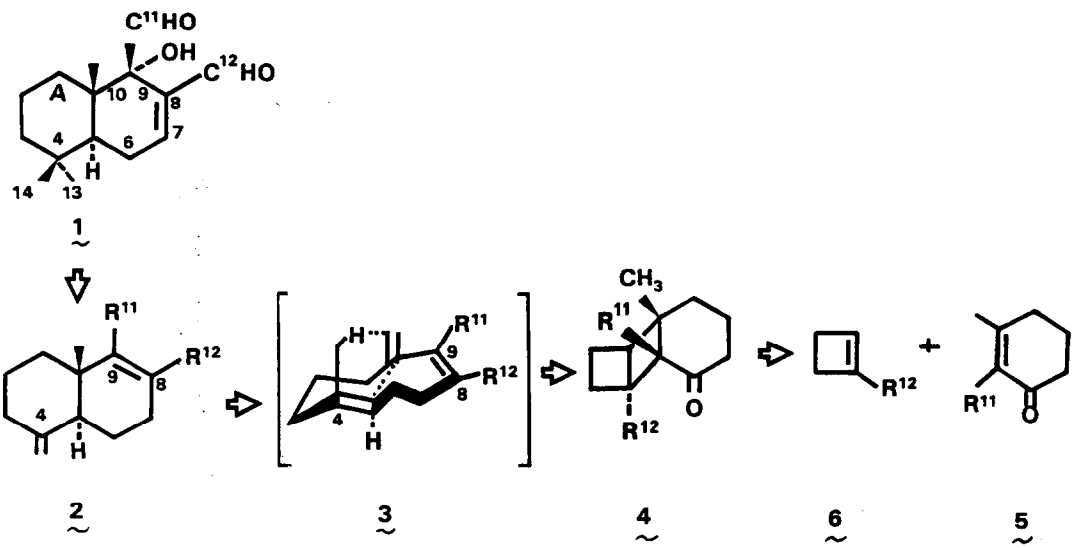
Abstract: A total synthesis of the potent antifeedant warburganal is described.

Studies initiated at the International Centre of Insect Physiology and Ecology in Nairobi have led to the isolation of several active constituents of African medicinal plants.[4] Among the most potent of these compounds, warburganal (1) was shown to exhibit antifeedant activity against African army worms (Spodoptera exempta) at concentrations of as low as 0.1 ppm. This drimane was also reported to possess significant helicocidal, antifungal, plant growth regulatory, and cytotoxic activities. A total synthesis of warburganal is described herein based on a topologically unique approach[5] to its trans-fused nucleus (5→6→4→3→2) in which the ring junction stereochemistry is completely and unambiguously determined by conformational restrictions imposed on a transannular ene reaction (3 →2). The methodology utilized for elaboration of the ene product (2) provides the basis for the crucial extension of this olefin metathesis/transannular ene sequence to the large class of trans-fused decalin derivatives and related polycyclics bearing an A-ring quaternary center.[6]

Initially, the title sequence was directed at the preparation of 2 with R^{11} = R^{12} = CHO or its equivalent since quaternization of this intermediate at C4 and oxidative transposition of its



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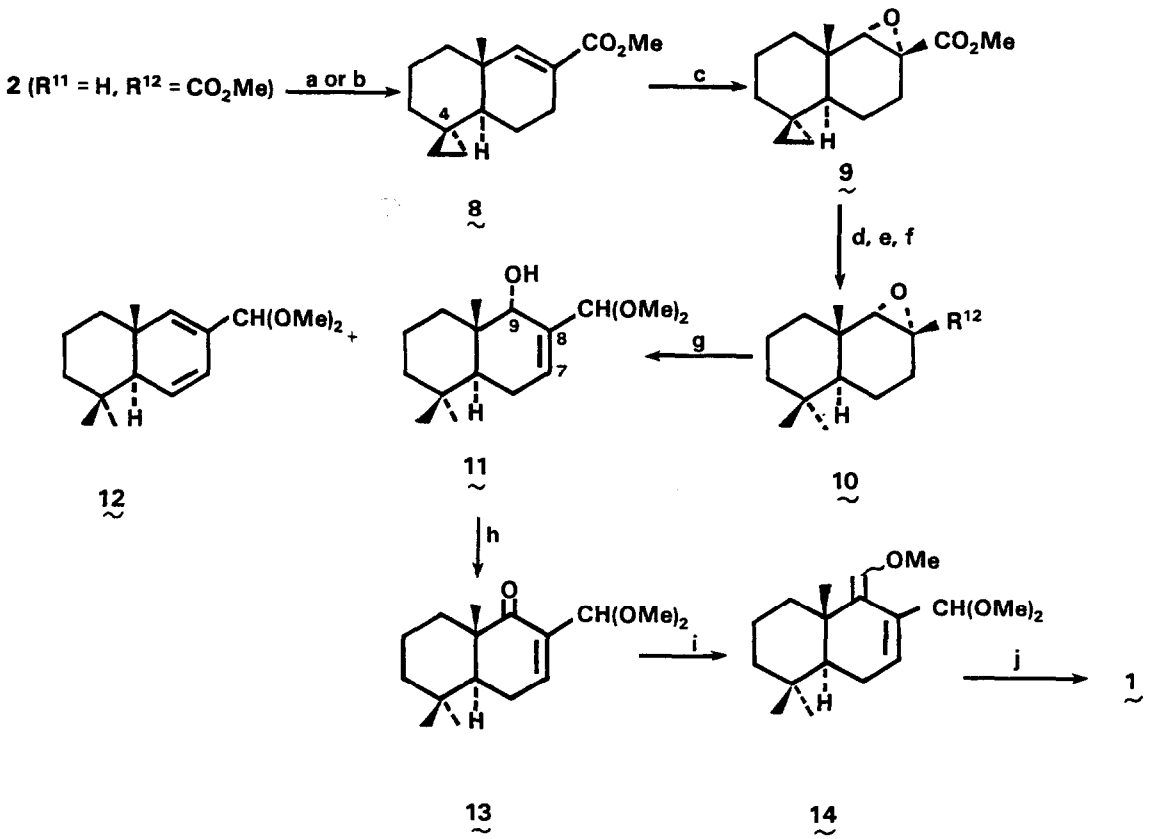

a) Zn/Cu, CH_2I_2, Et_2O, Δ; b) $[Cp(CO)_2FeCH_2S(CH_3)_2]^+ FSO_3^-$; 7;

c) 3,5 - $(NO_2)_2C_6H_3CO_3H$, CH_2Cl_2, Na_2HPO_4, 3-t-butyl-4-hydroxy-5-methylphenyl sulfide, 23°; d) H_2, PtO_2, HOAc, 23°; e) DIBAL, ϕCH_3, -80°; f) $HC(OMe)_3$, MeOH, HCl, 23°, g) MICA, THF, 45°; h) PDC, 3Å molecular sieve powder, CH_2Cl_2;
i) $\phi_2PCHLiOMe$, THF, -90°; then CH_3I, CH_3OH, 23°; j) OsO_4, Et_2O, 0°; H_2S; then HCl/H_2O/acetone

C8-C9 double bond would provide, overall, a simple route to the target. However, the reluctance of 2-substituted enones (e.g., 5:R^{11}=CO_2Me,Me,Br or Cl) to undergo the requisite [2+2] photocycloaddition with 6 (R^{12}=CO_2Me) necessitated the use of 5 (R^{11}=H) which as previously described,[2] provides 2 (R^{11}=H,R^{12}=CO_2Me) in 50% overall yield on a preparative (multi-gram) scale.

Quaternization of 2 at C4 was successfully accomplished via the following cyclopropanation-hydrogenolysis sequence. Reaction of 2 (R^{11}=H, R^{12}=CO_2Me) with a zinc copper couple and diiodomethane[7,8] (3.5 equiv. added over 7 h) in ether (0.7 ml/mmole) at reflux for 10 h provided the cyclopropane 8 (bp 105-106° @ 0.002mm) in 84% yield. Alternatively, when 2 (R^{11}=H,R^{12}=CO_2Me) was treated according to the procedure of Helquist and Brandt with the methylene transfer reagent 7,[9] cyclopropane 8 was obtained in 86% yield. Epoxidation of 8 with 3,5-dinitroperoxybenzoic acid[10] (2 equiv.) and a trace of 3-t-butyl-4-hydroxy-5-methylphenylsulfide[11] provided 9 (mp 56.5-57.5°) after 4 h in 93% yield. Finally, hydrogenolysis of 9 with Pt_2O catalyst in acetic acid at 23° under 1 atmosphere of hydrogen gave, in quantitative yield, epoxyester 10 (R=CO_2Me; mp 47-49°), the product resulting from reductive cleavage of the sterically most accessible cyclopropane bond of 9[12].

At this stage, the oxidation level at C12 was adjusted and protected by initial treatment of 10 (R^{12}=CO_2Me) with diisobutylaluminum hydride (1.5 equiv.) in toluene (5.6 ml/mmole) at -80° and reaction of the resultant aldehyde 10 (R^{12}=CHO) with excess trimethylorthoformate in methanolic hydrogen chloride at 23°. In this fashion, acetal 10 (R^{12}=$CH(OMe)_2$) was obtained in quantitative overall yield. The C7-C8 double bond of the target was introduced next by reaction of this acetal in THF (21 ml/mmole) at 45° with magnesium bromide isopropylcyclohexyl amide[13] (MICA; 27 equiv.) for 30 hours from which allylic alcohol 11 was obtained in 62% yield along with recovered acetal (16%) and diene acetal 12 (10%). Longer reaction times and higher temperatures favored the formation of dieneacetal 12 which is presumably derived from the alkoxide precursor of 11 via a 1,4 elimination process since reaction of 11 with MICA in THF at 66° for 24h gave 12 in 89% yield.

Introduction of the C9 substituents of the target was effected at this point through a variation of an olefination/oxidation tact which has since seen service in other warburganal syntheses[5c,d]. Thus, 11 was first oxidized with pyridinium dichromate[14] (2.6 equiv.) as a slurry with molecular sieve powder (2.6g/mmole, 3Å, 600 mesh) in dichloromethane (23 ml/mmole) to give enone 13 (85% yield). Treatment of this enone with lithio methoxymethyldiphenylphosphine[15] (10 equiv.) at -90° in THF (60 ml/mmole) and subsequent addition of excess methanol and iodomethane at 23° gave enol ether 14 in 82% yield. The α-C9 hydroxyl group was introduced by reaction of 14 with osmium tetroxide (1 equiv.) in ether (18 ml/mmole) at 0°, followed by addition of hydrogen sulfide. Hydrolysis of the resulting aldehyde acetal intermediate (aqueous HCl in acetone) gave (±)-warburganal[16] in 61% yield from 14. Thus, from 3-methylcyclohexenone, (±)-warburganal (1) was prepared in 13% overall yield and in 12 steps.

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7. All new compounds gave satisfactory nmr, ir and mass spectra. Combustion analyses were in agreement with theoretical values. Selected spectral data are as follows: 8, nmr (δ,$CDCl_3$) 6.66(t,J=1Hz,1H), 3.71 (s,3H), 2.5-0.75 (m,11H), 1.04 (s,3H), 0.55--0.25 (m,4H), ir (CCl_4) 1720; 9,nmr (δ,$CDCl_3$) 3.73 (s,3H), 3.00 (d,J=0.5 Hz,1H), 2.81-2.49 (ddd,1H), 2.05-1.80 (m,8H), 1.15-0.5 (m,2H), 1.05(s,3H), 0.40--0.25 (m,4H), ir (CCl_4) 1735; 11,nmr (δ,$CDCl_3$) 5.92 (dd,J=1.1 Hz,1H), 4.58 (s,1H), 3.37 (s,3H), 3.31 (s,3H), 2.42 (d,J=2.7 Hz,1H), 2.15-1.0 (m, 10H), 0.91, 0.90, 0.79 (s,3H), ir (CCl_4) 3550, 2920, 1680; 13, nmr (δ,$CDCl_3$) 7.06 (dd, J=2, 0.9 Hz, 1H), 5.13 (d, J=0.9 Hz, 1H), 3.35 (s,3H), 3.29 (s,3H), 2.35-2.29 (dd,2H), 2.95-1.05 (m, 7H), 1.04, 0.97, 0.89 (s,3H), ir (CCl_4) 1680; 14, nmr (δ,$CDCl_3$) 6.10-6.07 (m,1H), 5.82 (d,J=0.7 Hz,1H),5.42 (d,J=1 Hz,1H), 3.59, 3.42, 3.23 (s,3H), 2.25-2.15 (m,2H), 1.9-1.0 (m,7H), 1.00, 0.90, 0.84 (s,3H), ir (CCl_4) 1700, 1600, uv (MeOH) λmax = 292 (3.4), 223 (4.0).

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16. Spectroscopically identical (nmr, ir, ms, uv) to a sample of natural material graciously provided by Prof. I. Kubo, University of California, Berkeley.

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