acetoxy acetal **21**,[11] colorless oil, in 91% yield. Saponification of **21** with 10 equiv of methanolic potassium hydroxide (room temperature, 12 h) provided alcohol **22**,[11] which upon Collins oxidation gave the desired monoprotected dialdehyde **23**[11,20] (oil, ^{1}H NMR δ 9.70 (d, J = 5 Hz, CHO)) in 94% yield from **21**. Hydrolysis of the acetal with 2.5% aqueous hydrochloric acid in acetone (room temperature, 20 min) gave (±)-polygodial (**5**)[11,17] (mp 93–94 °C; IR ($CHCl_3$) 1720, 1680, 1640 cm^{-1}; ^{1}H NMR δ 7.12 (m, 7-H), 9.44 (s, 8-CHO), 9.51 (d, J = 4.5 Hz, 9-CHO)) in 83% yield.

Attention was now directed to the introduction of the axial-9-hydroxyl group. The enolate hydroxylation method of Vedejs[21] (LiN(i-Pr)$_2$, MoO_5·pyridine·HMPA) seemed to be well suited for this task, although, to the best of our knowledge, aldehyde-enolate hydroxylations utilizing this method have not been reported. Formation of the enolate of aldehyde **23** (1.2 equiv of LiN(i-Pr)$_2$, THF, −78 °C) and treatment with 1.5 equiv of MoO_5·pyridine·HMPA provided hydroxy aldehyde **24**:[11] IR (CCl_4) 3470, 1710 cm^{-1}; ^{1}H NMR δ 9.82 (d, J = 1.5 Hz, 9-CHO); 85% yield. Hydrolysis of the acetal with 2.5% aqueous hydrochloric acid in acetone (room temperature, 20 min) gave crystalline (±)-warburganal (**1**),[11,17] mp 98–99 °C, identical in TLC behavior and spectral (IR, ^{1}H NMR, CI-MS, and UV) properties with natural warburganal. The stereospecific total synthesis of warburganal was thus completed in 15.7% overall yield from diene **6** (see ref 22).

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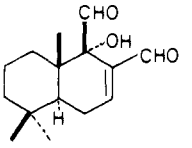
A Total Synthesis of (±)-Warburganal

Sir:

Warburganal (**1**), isolated from the bark of *Warburgia* (Canellaceae) (*W. stuhlmannii* and *W. ugandensis*) by Kubo, Nakanishi, and co-workers,[1] is a unique member of drimanic sesquiterpenes possessing both α-hydroxy aldehyde and enal units in the same ring and is reported to be an extremely effective antifeedant against the African army worms, *Spodoptera littoralis* and *S. exempta*. We report here the total synthesis of (±)-warburganal (**1**)[2] starting from readily available (±)-isodrimenin (**2**). The present work was under-



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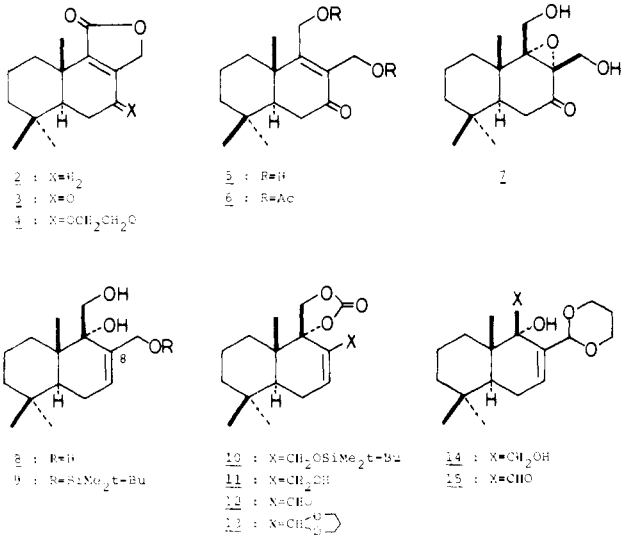
taken in the course of searching for biologically active compounds from drimanic sesquiterpenes and the related synthetic compounds.[3]

A large-scale preparation of (±)-isodrimenin (**2**) from β-ionone has recently been developed in this laboratory.[4a] Oxidation of **2** with CrO_3 in AcOH afforded the ketone **3**,[4c,5] which under the standard conditions (ethylene glycol, p-TsOH, benzene, reflux) was converted into the ketal **4**:[6] 94% yield; mp 89–90 °C; IR (CCl_4) 1760 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.84–4.17 (4 H, m), 4.68 (2 H, s). Reductive opening of the lactone ring of **4** with $LiAlH_4$ afforded, after the addition of 10% HCl, the keto dialcohol **5**: oil; IR (CCl_4) 3400, 1665 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.21–4.54 (4 H, m). Acetylation of **5** (Ac_2O, Py) gave the diacetate **6**: mp 87–88 °C; IR (CCl_4) 1745, 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.00 (3 H, s), 2.05 (3 H, s). The overall yield of **6** from **4** was 67%. Epoxidation of



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the α,β-unsaturated ketone **6** (30% H_2O_2, 10% NaOH, MeOH) gave exclusively a single product. As the β side of the double bond of **6** is highly hindered, the reagent should attack from the α side, producing thus the α-epoxide **7:** 82% yield; mp 117-118 °C; IR ($CHCl_3$) 3590, 3460, 1695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.54 (1 H, d, J = 12 Hz), 3.66 (1 H, d, J = 13 Hz), 4.24 (1 H, d, J = 13 Hz), 4.50 (1 H, d, J = 12 Hz). Formation of the allyl alcohol **8** (mp 137-138 °C; IR ($CHCl_3$) 3470 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.86 (1 H, br)) was effected by the reductive cleavage of **7** using 100% $NH_2NH_2 \cdot H_2O$[7] (90 °C for 5 min, then 120 °C for 15 min).

The crucial point of the present synthesis is in the strategy for the selective and effective protection of three different alcohols present in **8.** A selective protection of C-8 CH_2OH was first required. The crude **8** was, without purification, treated with t-$BuMe_2SiCl$[8] in DMF in the presence of imidazole to give the monosilyl ether **9** (oil; IR ($CHCl_3$) 3420 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.81 (1 H, br)) as a sole product in 55% overall yield from **7,** which shows that this bulky reagent could recognize a slight difference between two primary alcohols in **8.** The protection of vicinal alcohols in **9** should be achieved using a protective group stable to acid but sensitive to base because an acid-catalyzed selective deprotection of the above introduced silyl group is required in the next step. A carbonate protecting group[9] was presumed to be ideally suited for this purpose; thus **9** was converted into the corresponding carbonate **10** (100% yield; mp 59-60 °C; IR ($CHCl_3$) 1785 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.17 (2 H, s), 4.32 (1 H, d, J = 9 Hz), 4.75 (1 H, d, J = 9 Hz), 6.05 (1 H, br)) by refluxing in benzene with N,N'-carbonyldiimidazole. Here **10** was treated with camphorsulfonic acid[10] in methanol affording the allyl alcohol **11** (100% yield; mp 146-149 °C; IR ($CHCl_3$) 3600, 3400, 1785 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.19 (2 H, s), 4.36 (1 H, d, J = 9 Hz), 4.71 (1 H, d, J = 9 Hz), 6.15 (1 H, dd, J = 5, 2 Hz)), the carbonate group being retained as expected. Jones oxidation[11] of **11** gave the enal **12:** 100% yield; mp 133-135 °C; IR ($CHCl_3$) 1790, 1695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.34 (1 H, d, J = 9 Hz), 4.62 (1 H, d, J = 9 Hz), 7.21 (1 H, dd, J = 5, 2 Hz), 9.40 (1 H, s). The aldehyde **12** was converted into the acetal **13** (1,3-propanediol, p-TsOH, benzene, reflux): 97% yield; mp 167-168 °C; IR ($CHCl_3$) 1780 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.30 (1 H, d, J = 9 Hz), 5.04 (1 H, s), 5.12 (1 H, d, J = 9 Hz), 6.31 (1 H, dd, J = 5, 2 Hz). The carbonate group present in **13** was then cleaved by base treatment (10% NaOH-dioxane-H_2O (3:10:5), room temperature) to give the glycol acetal **14:** 98% yield; mp 99-100 °C; IR ($CHCl_3$) 3500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.14 (1 H, s), 6.23 (1H, br). This compound **14** was assumed to be quite sensitive to acids since it involves a labile allyl alcohol moiety; in addition its primary alcohol is located in a position which could assist in the acid-catalyzed cleavage of the cyclic acetal group; and in fact, **14** gives several spots on TLC when exposed to acid (p-TsOH, benzene).[12] Therefore, conversion of the glycol into the α-hydroxy aldehyde should be conducted under neutral or basic conditions. After several attempts,[13] this difficulty was overcome by use of the Moffatt oxidation.[14] The desired α-hydroxy aldehyde **15** (mp 114-116 °C; IR ($CHCl_3$) 3480, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.84 (1 H, s), 6.31 (1 H, br), 9.77 (1 H, d, J = 1 Hz)) was obtained in 73% yield by standard procedures (excess Me_2SO, Py (1.4 equiv), CF_3CO_2H (0.5 equiv), DCC (3 equiv), benzene, room temperature). Acid hydrolysis (p-TsOH, acetone, room temperature) of **15** gave (±)-warburganal (**1,** mp 111-112 °C) in quantitative yield. The spectral data (IR, NMR, mass spectra) were identical with those of the natural product.[15]

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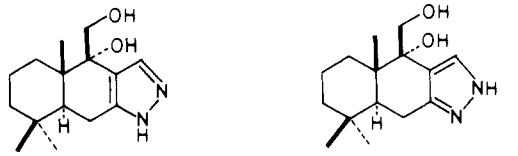

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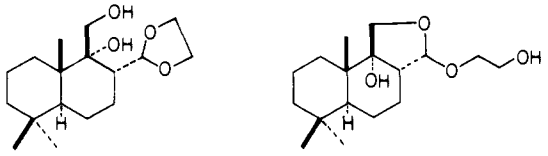

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(13) The corresponding ethylene acetal derivative gave less satisfactory result (33% yield). Moreover, the Corey's procedure for the oxidation of α-glycol used in gibberellin A_3 synthesis (Me_2SO, $(CCl_3CO)_2O$, followed by Et_3N treatment) (E. J. Corey, R. L. Danheiser, S. Chandrasekaran, P. Siret, G. E. Keck, and J.-L. Gras, *J. Am. Chem. Soc.*, **100,** 8031 (1978); see also, K. Omura, A. K. Sharma, and D. Swern, *J. Org. Chem.*, **41,** 957 (1976); S. L. Huang, K. Omura, and D. Swern, *ibid.*, 41, 3329 (1976)) gave **15** in only 7% yield, although the model compound iii afforded the corresponding aldehyde in much better yield (59%).
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Synthesis of Mokupalide

Sir:

Recently, Yunker and Scheuer reported the isolation of three unusual hexaprenes from a Pacific marine sponge.[1] These

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