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SYNTHESES OF (±)-WARBURGANAL AND (±)-ISOTADEONAL

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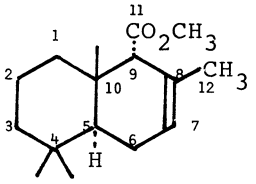
Methyl (±)-9-epidrimenate was oxidized with selenium dioxide at C-12 to give an aldehyde ester. The aldehyde group was protected by formation of an acetal, and then the methoxycarbonyl group was transformed into a formyl group. Hydrolysis of the acetal group gave (±)-isotadeonal. Stereoselective oxidation of the enolate generated from (±)-isotadeonal monoacetal gave (±)-warburganal monoacetal, which was hydrolyzed to (±)-warburganal.

Warburganal(8)[1] is a drimane-type sesquiterpene found in the East African trees Warburgia ugandensis and W. stuhmanii, and exhibits very strong antifeedant activity against the African army worms Spodoptera littoralis and S. exempta. In addition, it shows very potent antitumor, antifungal, antiyeast, and plant-growth regulatory activities.

We now wish to report the first synthesis of (±)-warburganal(8) from methyl (±)-9-epidrimenate(1), which was easily obtained by acid-catalyzed cyclization of methyl farnesoate[2]. Although selenium dioxide oxidation of methyl drimenate gave only a complex mixture, the epimer(1) was oxidized resioselectively at C-12 with selenium dioxide in dioxane to give an aldehyde ester(2) in 61% yield. 2; $bp_{0.03}$ 110-118°C(bath temp.); IR (CCl_4) 2710, 1732, 1689, and 1656 cm^{-1}; NMR (CCl_4) δ 0.93 (s, 3H), 0.96(s, 3H), 0.99(s, 3H), 3.05(s, 1H), 3.71(s, 3H), 7.02(m, 1H), and 9.48 (s, 1H). The aldehyde ester(2) was treated with ethanediol and a catalytic amount of p-toluenesulfonic acid to give an acetal ester(3) in 85% yield. 3; mp 64.5-66.0 °C; IR (CCl_4) 1735 cm^{-1}; NMR (CCl_4) δ 0.94(s, 9H), 2.66(s, 1H), 3.64(s, 3H), 3.8-4.0(m, 4H), 5.09(s, 1H), and 6.06(m, 1H); Found: C, 70.42; H, 9.32%; Calcd for $C_{18}H_{28}O_4$: C, 70.10; H, 9.15%. The acetal ester(3) was reduced with lithium aluminium hydride in ether at room temperature to give an alcohol acetal(4) almost quantitatively. 4; IR (CCl_4) 3430 cm^{-1}; NMR (CCl_4) δ 0.88(s, 6H), 0.92(s, 3H), 3.69 (bd, J=3Hz, 2H), 3.9-4.1(m, 4H), 5.12(s, 1H), and 6.06(bt, J=3Hz, 1H). The oxidation of 4 with the modified Collins reagent (chromium trioxide-pyridine complex in dichloromethane) at room temperature gave an aldehyde acetal(5) in 78% yield. 5; mp 67.0-68.5°C; IR (CCl_4) 2700 and 1723 cm^{-1}; NMR (CCl_4) δ 0.95(s, 9H), 2.52(d, J=5Hz, 1H), 3.7-4.1(m, 4H), 5.10(s, 1H), 6.19(m, 1H), and 9.54(d, J=5Hz, 1H); Found: C, 73.40; H, 9.47%; Calcd for $C_{17}H_{26}O_3$: C, 73.34; H, 9.41%. The acetal(5) was hydrolyzed with p-toluenesulfonic acid in aqueous tetrahydrofuran to give (±)-isotadeonal (6) in 96% yield. 6; mp 60.0-61.5°C; IR (CCl_4) 2710, 1729, 1687, and 1653 cm^{-1};

NMR (CCl_4) δ 0.98(s, 9H), 3.28(m, 1H), 7.05(m, 1H), 9.43(s, 1H), and 9.94(d, J=2Hz, 1H). These spectral data were identical with those of natural isotadeonal[3] isolated from Polugonum Hydropiper L.



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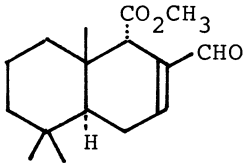

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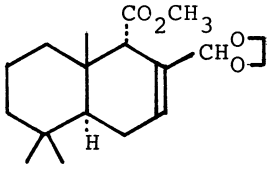

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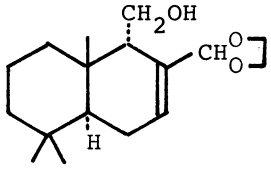

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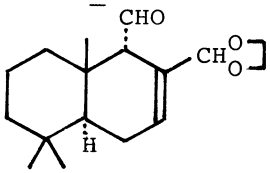

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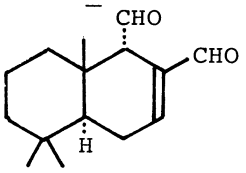

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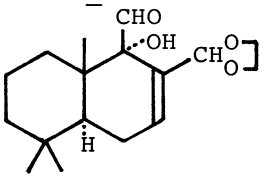

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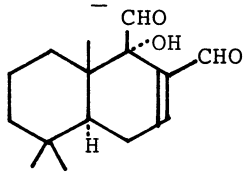

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A solution of the lithium enolate prepared from (±)-isotadeonal 12-monoacetal (5) by treatment with one equivalent of lithium hexamethyldisilazamide—hexamethyl phosphoric triamide complex[4] at -78°C in tetrahydrofuran was added to a suspension of oxodiperoxymolybdenum(pyridine)(hexamethyl phosphoric triamide)[5] in tetrahydrofuran at -78°C. After the usual work-up procedure two products(7) and (4) were isolated from the reaction mixture by chromatography on silica gel in 24% and 10% yields, respectively. Since the enolate anion was attacked by the voluminous oxidizing agent from the less hindered side, 7 was afforded stereoselectively. The abnormal product(4) would probably be formed by the Cannizzaro-type reaction, but the corresponding carboxylic acid derivative was not isolated. 7; IR (CCl_4) 3430 and 1714 cm^{-1}; NMR (CCl_4) δ 0.94(s, 6H), 0.98(s, 3H), 3.62(s, 1H, -OH), 3.8-4.0(m, 4H), 5.10(s, 1H), 6.29(m, 1H), and 9.82(s, 1H). The acetal(7) was hydrolyzed in aqueous acetone with p-toluenesulfonic acid to give (±)-warburganal(8) quantitatively. 8; mp 103.0-104.5°C; UV (CH_3OH) 223 nm (ε=12100); IR ($CHCl_3$) 3430, 2720, 1718, 1679, and 1648 cm^{-1}; NMR (CCl_4) δ 0.96(s, 3H), 1.00(s, 3H), 1.08(s, 3H), 3.78(s, 1H, -OH), 7.20(m, 1H), 9.49(s, 1H), and 9.75(s, 1H); Found: C, 72.11; H, 9.03%; Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86%. These spectral data of synthetic (±)-warburganal were identical with those of the natural one[6].

References

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