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TOTAL SYNTHESIS OF (±)-FURANOEREMOPHILANE-3,6-DIONE AND (±)-LIGULARONE BY A ROUTE INVOLVING ALKYLATION OF 2,4-DIMETHYL-3-FUROIC ACID

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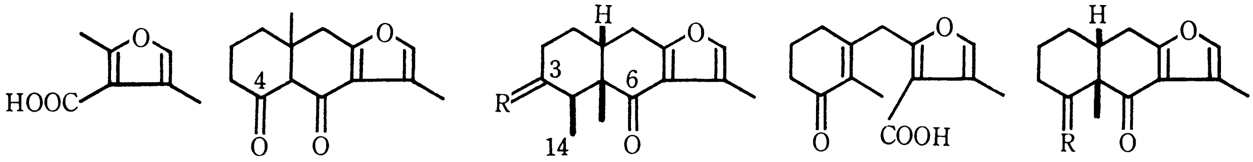
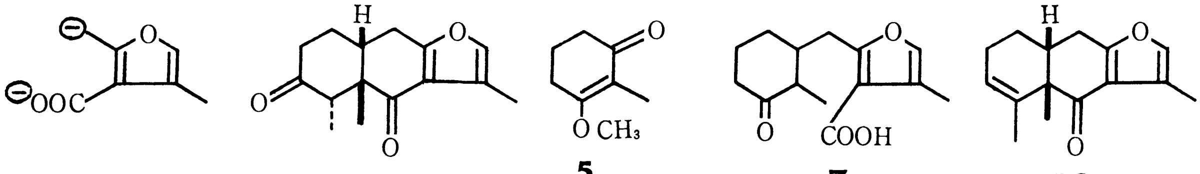
Treatment of a dianion generated from 2,4-dimethyl-3-furoic acid with 3-methoxy-2-methyl-2-cyclohexen-1-one gave 4-methyl-2-(3-oxo-2-methyl-1-cyclohexenylmethyl)-3-furoic acid. Catalytic hydrogenation of the alkylated product followed by dehydrative annelation yielded 14-norfuranoeremophilane-4,6-dione, which was converted in five steps into (±)-furanoeremophilane-3,6-dione. (±)-Ligularone has been derived from the 3,6-dione.

In a previous paper, we reported alkylation of a dianion (**A**) generated from 2,4-dimethyl-3-furoic acid (**1**) with 3-methoxy-2-cyclohexen-1-one and successive hydrogenation and ring closure to give 14-norfuranoeudesmane-4,6-dione (**2**), a useful intermediate for the synthesis of furanoeudesmanes and eudesmanolides.[1] The present communication deals with synthesis of furanoeremophilane derivatives, (±)-furanoeremophilane-3,6-dione (**3a**)[2] and (±)-ligularone (**4**),[2b,3] by the route involving alkylation of **1**.

The dianion (**A**) was formed from **1** by treatment with lithium diisopropylamide (in THF-hexane at -78 °C) as described previously.[1] When **A** was treated with one mole equivalent of 3-methoxy-2-methyl-2-cyclohexen-1-one (**5**) at 0 °C, a carboxylic acid (**6**; 74% yield) was obtained after acidification with hydrochloric acid. The alkylated product (**6**) was hydrogenated over palladium-charcoal in ethanol to yield its dihydro derivative (**7**; quantitative yield). Cyclization of **7** was effected by treatment with *p*-toluenesulfonic acid in diphenyl ether under reflux to afford (±)-14-norfuranoeremophilane-4,6-dione(**8**; 44% yield).[4] Methylation of **8** with 1.2 mole equivalent of methyllithium in ether at -78 °C proceeded regio-selectively to give a 4-methyl 4-hydroxy derivative (**9**; 99% yield).[5] The hydroxy ketone (**9**) was dehydrated with phosphoryl chloride in pyridine under reflux to yield a mixture of olefins, which was separated by preparative thin-layer chromatography, giving an *endo*-olefin (**10**; 69% yield) and an *exo*-olefin (**11**; 12% yield). The 3-ene (**10**) was subjected to hydroboration with diborane in tetrahydro-furan at 0 °C and then alkaline hydrogen peroxide oxidation. The product, without further purification, was oxidized with pyridinium chlorochromate[6] in dichloro-methane to afford (±)-furanoeremophilane-3,6-dione (**3a**; 4% yield)[2] and (±)-4βH-furanoeremophilane-3,6-dione (**3b**; 78% yield).[2b] Treatment of **3b** in benzene con-taining a catalytic amount of *p*-toluenesulfonic acid under reflux gave **3a** (94%



1 2 3a R = O; 4 R = H_2 6 8 R = O; 9 R = CH_3, OH; 11 R = CH_2



A 3b 5 7 10

yield) as described in the literature.[2b] (±)-3,6-Dione 3a was obtained from 1 in an overall yield of 17%. (±)-Ligularone (4) has been derived formally from (±)-3,6-dione (3a), since 3a has already been converted into 4.[2b] Compounds 3a, 8, 10, and 11 are useful intermediates for the synthesis of furanoeremophilane derivatives with oxygenated functional groups on $C_{(3)}$, $C_{(6)}$, and $C_{(14)}$.

Characterizations of 3a, 3b, and 6-11 are as follows. 3a: mp 176-177 °C, $C_{15}H_{18}O_3$;[7] IR (Nujol) 1710, 1660 cm^{-1}; NMR[8] δ 0.92 (3H, d, J=7), 1.12 (3H, s), 2.18 (3H, d, J=2), 2.91 (1H, dd, J=18, J=6), 3.27 (1H, dd, J=18, J=10), 7.11 (1H, m, $W_{1/2}$=4). 3b: mp 119.5-120 °C, $C_{15}H_{18}O_3$;[7] IR (Nujol) 1705, 1665 cm^{-1}; NMR δ 1.37 (3H, d, J=7), 1.41 (3H, s), 2.12 (3H, d, J=2), 2.71 (1H, dd, J=18, J=6), 3.30 (1H, dd, J=18, J=5), 7.07 (1H, m, $W_{1/2}$=4). 6: mp 115-116 °C, $C_{14}H_{16}O_4$;[7] IR ($CHCl_3$) 1680, 1660 cm^{-1}; NMR δ 1.90 (3H, s), 2.20 (3H, d, J=2), 4.05 (2H, s), 7.13 (1H, m), 11.1 (1H, br. signal). 7: mp 123-127 °C, $C_{14}H_{18}O_4$;[7] IR ($CHCl_3$) 1710, 1680 cm^{-1}; NMR δ 1.16 (3H, d, J=6), 2.17 (3H, d, J=2), 7.10 (1H, m), 9.1 (1H, br. signal). 8: mp 105.5-106 °C, $C_{14}H_{16}O_3$;[7] IR (Nujol) 1715, 1665 cm^{-1}; NMR δ 1.37 (3H, s), 2.19 (3H, d, J=2), 7.18 (1H, m). 9: mp 115-116 °C, $C_{15}H_{20}O_3$;[7] IR (Nujol) 3450, 1648 cm^{-1}; NMR δ 1.21 (3H, s), 1.37 (3H, s), 2.18 (3H, d, J=2), 5.74 (1H, br. signal disappeared on addition of D_2O), 7.13 (1H, m). 10: mp 69-69.5 °C, $C_{15}H_{18}O_2$;[7] IR (Nujol) 1675 cm^{-1}; NMR δ 1.39 (3H, s), 1.73 (3H, d, J=2), 2.17 (3H, d, J=2), 5.49 (1H, m), 7.10 (1H, m). 11; an oil, $C_{15}H_{18}O_2$;[7] IR (neat) 1675, 902 cm^{-1}; NMR δ 1.39 (3H, s), 2.20 (3H, d, J=2), 5.00 (1H, s), 4.79 (1H, s), 7.13 (1H, m).

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3) H. Ishii, T. Tozyo, and H. Minato, Tetrahedron, 21, 2605 (1965). 4) A cis A/B ring juncture was shown for 8 by its conversion into 3a (vide infra). 5) The product showed one spot on TLC and NMR methyl signals corresponding to one configurational isomer. 6) E. J. Corey and J. W. Suggs, Tetrahedron Lett., 1975, 2647.
7) Determined by elemental analysis. 8) All NMR spectra were measured in $CDCl_3$ and J and $W_{1/2}$ values were expressed in Hz.

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