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TOTAL SYNTHESIS OF RACEMIC LIGULARONE AND ISOLIGULARONE

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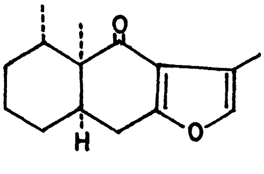
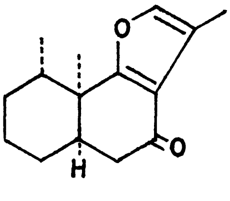
Racemic ligularone and isoligularone were synthesized from 8α,8aα-dimethyl-1,3-dioxo-1,2,3,4,4aα,5,6,7,8,8a-decahydronaphthalene, which was stereoselectively derived from 8aα-methyl-1,6-dioxo-1,2,3,4,4aα,5,6,8a-octahydronaphthalene, using the KF-catalyzed reaction with 1-nitro-1-phenylthiopropene.

Despite much effort has been devoted over the past decade to the synthesis of sesquiterpenoids related to the eremophilane family,[1] only a few papers have been published on the total synthesis of furanoeremophilanes via Diels-Alder addition routes.[2]

We recently reported that the 3-methyl-4-oxo-4,5,6,7-tetrahydrobenzofuran system was readily accessible from the reaction of 1-nitro-1-phenylthiopropene (**3**) and cyclic 1,3-diones, and that usefulness of the reaction was shown by an efficient synthesis of a furanomonoterpene, evodone.[3] In order to illustrate the potential of this new 3-methylfuran annulation on more complex systems, it was projected to synthesize ligularone[4,5] (**1**), a representative furanoeremophilanoid, and its thermal isomerization product, isoligularone[6] (**2**).



1



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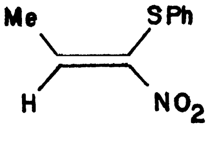
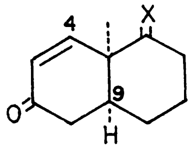


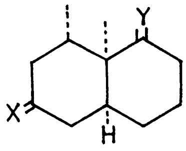
3

The bicyclic dione (11), the key intermediate in this synthesis, was stereoselectively synthesized starting from the known enedione[7] (4). Selective monoacetalization (ethyleneglycol, p-toluenesulfonic acid, benzene) of 4 gave the oily ethylene acetal (5) in 95% yield. In the nmr spectrum of 5, the C(4)-proton (δ, 6.76) was observed as a double doublet (J, 10 and 2 Hz). The smaller coupling constant due to a long-range coupling between the C(4)- and C(9)-protons provides convincing evidence of nonsteroid conformation (14) of 5.[8]



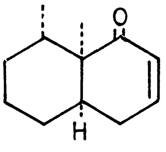
4; X = O

5; X = $\langle^{O}_{O}\rbrack$



6; X = O, Y = $\langle^{O}_{O}\rbrack$

7; X = H_2, Y = O



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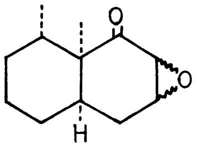

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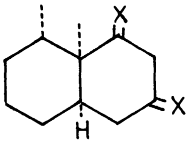
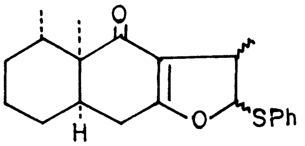


10; X = H, OH

11; X = O



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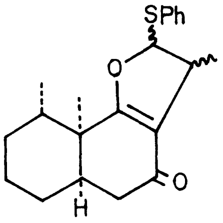

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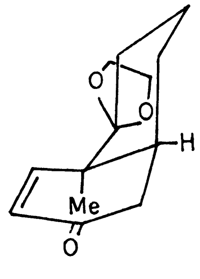

14

Conjugate addition of lithium dimethylcuprate to 5 in ether occurred selectively from the convex face of 5 yielding the dimethyldecalone[9] (6), m.p. 67°C, in 87% yield, and this ensured the cis-disposed vicinal dimethyl grouping which is the distinct structural unit of eremophilanoids. These results demonstrate that steric factor dominates the stereochemical outcome in the conjugate addition over stereoelectronic factor.[10]

Huang-Minlon reduction of 6 followed by treatment with aqueous acetic acid gave the decalone (**7**) in 80% yield, which was converted into the enone (**8**) on bromination (phenyltrimethylammonium tribromide, THF) followed by dehydrobromination (Li_2CO_3, DMA) in 88% yield. Oxidation of **8** with alkaline hydrogen peroxide afforded a mixture of epoxides (**9**) (84% yield), which was then treated, without purification, with lithium in liquid ammonia giving the diol (**10**) as a diastereomeric mixture in 93% yield. Jones oxidation of **10** gave the required dione (**11**), m.p. 130-131°C, in 72% yield.

Reaction of **11**, **3** (1.3 mole equiv.), and KF (0.2 mole equiv.) in DME at 50-60°C for 6 h, followed by consecutive treatment with KF (0.2 mole equiv.) in benzene at 80°C for 7 h,[11] produced a 1:2 mixture of the dihydrofurans (**12** and **13**) (62% yield) which consist of diastereomers respectively. The isomeric mixtures **12** and **13** were cleanly separated on silica gel chromatography. Oxidation of **12** with $NaIO_4$ in aqueous methanol to the corresponding sulfoxides and subsequent elimination of benzenesulfenic acid in refluxing benzene containing pyridine and active alumina afforded (±)-ligularone[12] in 47% yield, m.p. 70.5-71°C (lit.[2a] 68-70°C). By the same sequence of reactions, **13** was transformed into (±)-isoligularone, m.p. 111-114°C, in 54% yield.

We thank Professors T. Takahashi and T. Tsuyuki for providing authentic samples of natural ligularone and isoligularone.

References and Notes

1) E. Piers and M. B. Geraghty, Can. J. Chem., 51, 2166 (1973).

2) a) K. Yamakawa and T. Satoh, Chem. Pharm. Bull., 25, 2535 (1977); b) F. Bohlmann, H.-J. Förster, and C.-H, Fischer, Justus Liebigs Ann. Chem., 1976, 1487; c) T. Tatee and T. Takahashi, Bull. Chem. Soc. Jpn., 48, 281 (1975); d) I. Nagakura, S. Maeda, M. Ueno, M. Funamizu, and Y. Kitahara, Chem. Lett., 1975, 1143.

3) M. Miyashita, T. Kumazawa, and A. Yoshikoshi, J. Chem. Soc. Chem. Comm., 1978, 362.

4) H. Ishii, T. Tozyo, and H. Minato, Tetrahedron, 21, 2603 (1965).

5) Two total syntheses of (±)-ligularone were recently reported (Ref. 2a and 2b).

6) M. Tada and T. Takahashi, Tetrahedron Lett., 1973, 3999.

7) S. Danishefsky and T. Kitahara, J. Org. Chem., 40, 538 (1975).

8) For analogous examples, see T. Nozoe, Y. S. Cheng, and T. Toda, Tetrahedron Lett., 1966, 3663; M. Miyashita, H. Uda, and A. Yoshikoshi, Chem. Commun., 1969, 1396.

9) Rigorous confirmation of the stereostructure assigned to 6 was obtained by comparison with the corresponding cis decalone possessing a trans-disposed vicinal dimethyl group. Details will be published in due course.

10) J. A. Marshall and N. H. Andersen, J. Org. Chem., 31, 667 (1966); J. A. Marshall and C. M. Cohen, ibid., 36, 877 (1971).

11) The two-step procedure described here gave the annulation product in better yield than does one-step treatment in benzene. The initial reaction in DME gave the normal Michael adduct along with minor amount of 12 and 13.

12) Identified on spectral comparison with the natural compound.

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