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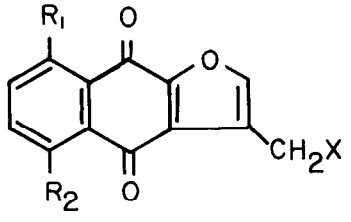
SYNTHESIS OF MATURONE

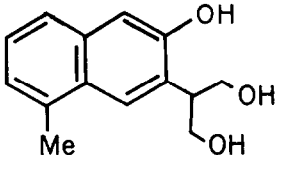
E. Ghera*, R. Maurya and Y. Ben-David
Department of Organic Chemistry,
The Weizmann Institute of Science, Rehovot, Israel

Summary: The first synthesis of maturone by a new annulation route is reported.

Maturone (**1**) is a sequiterpenoid isolated from *Cacalia decomposita*, a Mexican plant, the root extracts of which have been used for the treatment of diabetes and other diseases[1,2]. The initially assigned structure **2** was modified on biogenetic grounds by Thompson to **1**, but an attempt to synthesize maturone failed, although maturinone (**3**) could be obtained via the classical peroxide alkylation of quinones[3] or otherwise[4].

In connection with our program for the utilization of bifunctional aromatic annulating reagents[5], we wish to report herewith the first synthesis of maturone by a regioselective annulating approach which is also potentially useful for the synthesis of other natural naphthoquinones with an oxygen heterocycle fused to the quinone moiety[6].





1 $R_1 = H; R_2 = Me; X = OH$

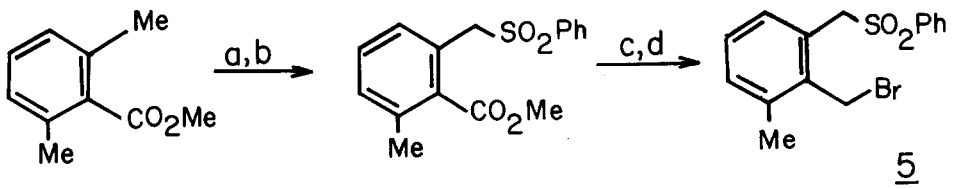
2 $R_1 = Me; R_2 = H; X = OH$

3 $R = H; R_2 = Me; X = H$

4

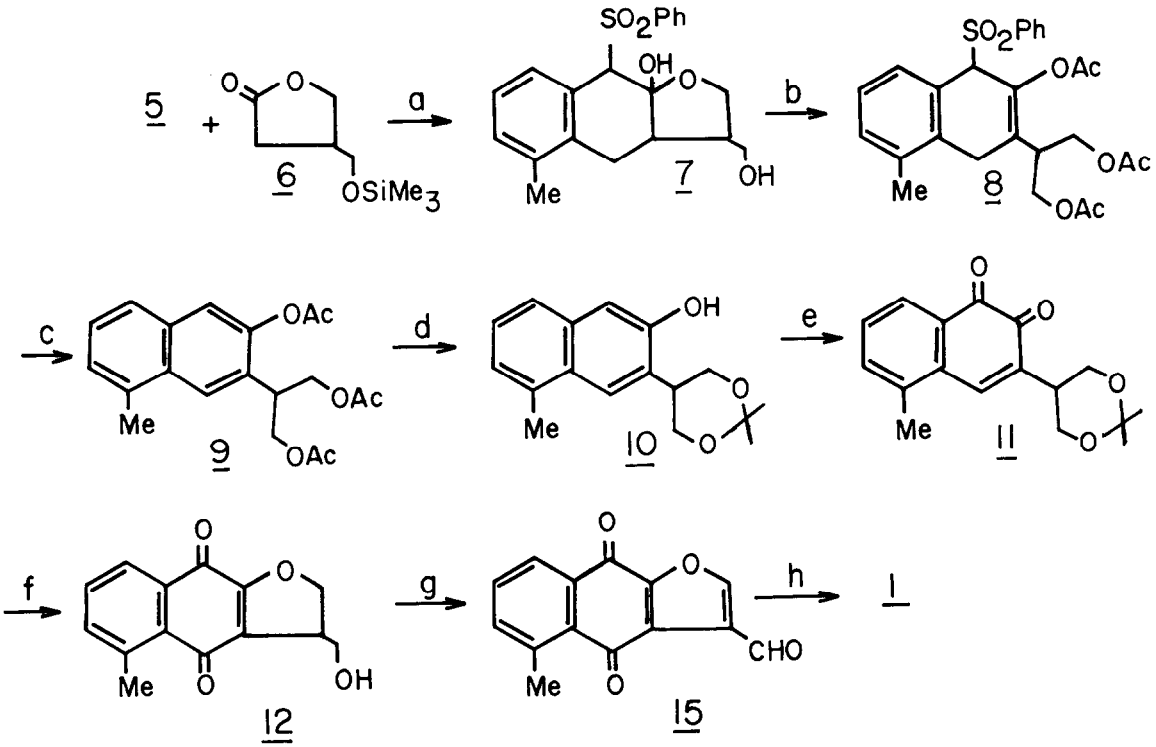
Our retrosynthetic approach visualized the triol **4** as a suitable precursor for the projected synthesis of **1** by providing the aromatic hydroxyl group for further oxidation to a quinone, as well as two hydroxyl groups in the side chain for the formation of the substituted furan ring. Our initial attempts to obtain **4** by reacting the bromosulfone **5** with appropriately substituted malonate derivatives, via a recently developed annulation route[7], were abortive and reflected the difficulties which we encountered for obtaining the required bis-hydroxylated isopropyl side chain adjacent to the aromatic ring in **4**. These difficulties were overcome by reacting the enolate of lactone **6**[8] with the bifunctional annulating reagent **5**, mp 141-143°C (prepared as shown in Scheme I), to give **7** (73%, stereoisomeric mixture) by a one-pot, two-step sequence[9] (Scheme II).

Scheme I



(a)NBS/CCl_4, hν, reflux 30 min; (b) $PhSO_2Na$, DMF, rt, 1h, (68%, 2 steps); (c) $LiAlH_4$, THF, 0°C, 75%; (d) NBS, CH_2Cl_2, Me_2S, -20°C, then 0°C, 3h, 87%.

Scheme II

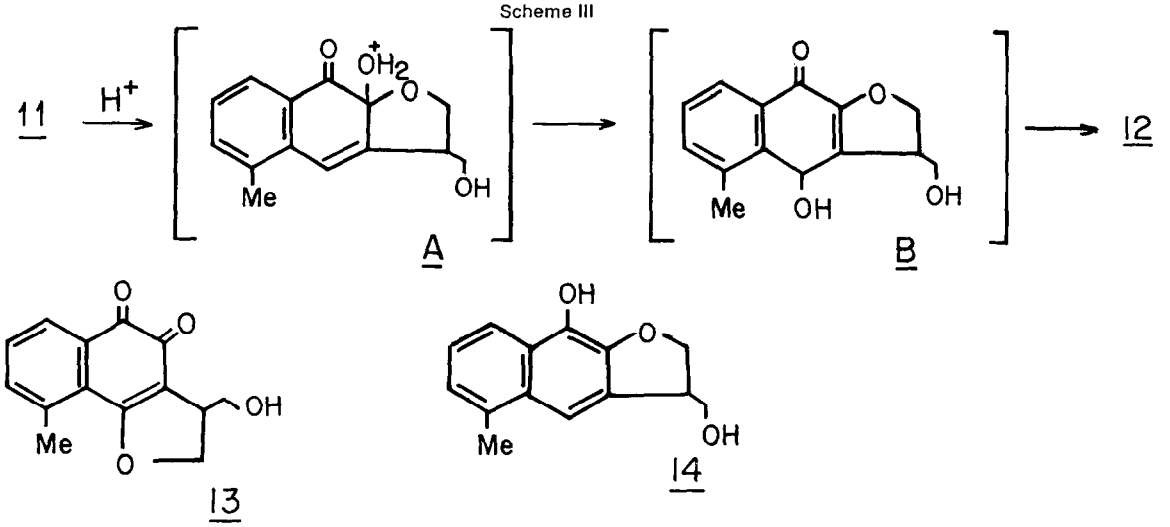


(a) LDA, THF, -78°C, then 10% HCl, ice[9], 73%. (b) AC_2O, pyridine, rt, 16h, (c) CrO_3-3,5-dimethylpyrazole, CH_2Cl_2, -20°C, 4h, then aq $NaHCO_3$, 69%. (d) $LiAlH_4$, THF, 0°C (91%), then $(CH_3)_2C(OCH_3)_2$, DMF, p-TsOH, 85%. (e) CuCl-O_2, CH_3CN, rt, 86%. (f) AgO, 0.5 M HNO_3, acetone, 65%. (g) $(COCl)_2$, DMSO, CH_2Cl_2, 30 min at -60°C, then Et_3N, 10 min at -60°C, then 30 min at rt, 77%. (h) $LiAlH_4$, THF, -78°C, 70%.

While the application of standard reductive desulfonylation procedures on **7** (Na-Hg, Al-Hg) was ineffective, we found that the elimination of the sulfone group concomitant with ring aromatization could be effected by prior acetylation to the triacetate **8**, and then conversion to **9** by treatment with the CrO_3-3,5-dimethylpyrazole complex[10,11]. The latter, utilized mostly for allylic oxidations,[10] was found to be the reagent of choice for the transformation 8 → 9 , which could not be induced by either deprotonation with base or by heating with LiI in 2,6-lutidine, a method found previously useful for similar

eliminations[7]. The acetonide **10**, obtained from triol of **4**, enabled effective oxidation to the o-quinone **11**[12], mp 197°C, by use of CuCl-O_2 complex[13]. Exposure of **11** to oxidative acidic conditions (AgO, HNO_3)[14] afforded regioselectively **12**[15,16], (68%) mp. 146°C, along with a small amount (8%) of the angular regioisomer **13**, mp 185-186°C[17]. In the absence of AgO, under various aqueous acidic conditions (such as p-TsOH in H_2O-THF), a 1:1 mixture of **12** and **14** (mp 157°)[18] was formed, (~60%) even when the reaction was carried out under complete exclusion of oxygen. We assume, therefore, that in the absence of an oxidating agent, the acid-induced cyclization is followed by an internal reduction-oxidation process involving an intermediate (e.g. **B**, Scheme III) to give equal amounts of **12** and **14**. Dehydrogenation to a furan ring was best achieved by Swern oxidation[19] which afforded **15**, mp 214-215°C[20], probably via the shift into the ring of the double bond of the enolic form of the aldehyde and then further oxidation. Reduction of **15** with $LiAlH_4$ afforded maturone, mp 169-170°C[21], which had identical physical and spectral data with the natural compound[22].

Scheme III



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References and Notes

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5. For the preceding report in this series, see E. Ghera and Y. Ben-David, *Tetrahedron Letters*, 1985, 6253.
6. See R.H. Thomson in "Naturally Occurring Quinones", Academic Press, London, 1971.
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8. K. Mori and K. Yamane, *Tetrahedron*, 1982, **38**, 2919.
9. To a stirred solution of lithium isopropylamide (4 mmol) in THF (8 ml) at -78°C under argon, the lactone **6** (1 mmol) was added dropwise in 4 ml THF. After 20 min stirring, the bromosulfone **5** (1.3 mmol) in 4 ml THF was added during 0.5h via a motor-driven syringe. After additional stirring during 15 min at -78°C, the reaction mixture was quenched (10% HCl, ice, 5 min) and the products, isolated by standard column purification, were characterized in the n.m.r. spectrum by the singlet δ 4.58 ($CHSO_2Ph$, major stereoisomer) and δ 4.50 and 4.73 (minor stereoisomers).

10. See W.G. Salmond, M.A. Barta and F.L. Havens *J. Org. Chem*, 2057 (1978) for the preparation of the complex. It is essential to use freshly dried chromium trioxide.

11. **9**: ^{1}H NMR ($CDCl_3$) δ 2.03 (s, 6H), 2.41 (s, 3H), 2.67 (s, 3H), 3.70 (m, 1H), 4.41 (d, J = 6 Hz, 4H), 7.26-7.39 (m, 2H), 7.56 (s, 1H), 7.63 (d, J = 8 Hz, 1H), 7.91 (s, 1H).

12. **11**: ^{1}H NMR ($CDCl_3$) δ 1.49 (s, 3H), 1.52 (s, 3H), 2.51 (s, 3H), 3.0 (1H, m), 4.07 (m, 4H), 7.26-7.42 (m, 2H), 7.90 (dd, J = 2 and 4 Hz, 1H), 8.22 (s, 1H). UV λ_{max} (EtOH) 237 (log ε 4.13), 256 (log ε 4.21), 351 (log ε 3.41), 422 (log ε 3.32). IR (KBr) 1665, 1693 cm^{-1}.

13. P. Capdevielle and H. Maumy, *Tetrahedron Letters*, 1983, 5611.

14. C.D. Snider and H. Rapoport, *J. Am. Chem. Soc.*, 1972, **94**, 227.

15. **12**: ^{1}H NMR δ 2.75 (s, 3H), 3.82 (brs, 4H), 4.42-4.98 (m, 2H), (m, 1H), 7.50 (s, 1H), 7.56 (d, J = 1 Hz, 1H), 8.03 (dd, J = 4 and 1 Hz, 1H). UV (EtOH): λ_{max} 253 (log ε 4.16), 289 (log ε 4.01), 355 (log ε 3.43). IR (KBr) 1637, 1669 cm^{-1}.

16. All compounds gave satisfactory analytical and mass spectral data.

17. **13**: ^{1}H NMR ($CDCl_3$) δ 2.61 (s,3H), 3.79 (brs, 3H), 4.10 (m, 1H), 4.55-4.96 (m, 2H), 7.40-7.46 (m, 2H), 7.93 (t, J = 5Hz, 1H), UV λ_{max} (ETOH) 265 (log ε 4.05), 338 (log ε 3.50), 436 (log ε 3.40). IR (KBr) 1553, 1600, 1630, 1683 cm^{-1}.

18. In view of the insolubility of **14** in $CDCl_3$, the ^{1}H NMR spectrum of its diacetate was recorded: δ 2.03 (s, 3H), 2.45 (s, 3H), 2.65 (s, 3H), 3.96-4.00 (brs, 1H), 4.20-4.81 (m, 4H), 7.18 (d, J = 7Hz, 1H), 7.34 (t, J = 7Hz, 1H), 7.61 (d, J = 8Hz, 1H), 7.74 (s, 1H).

19. A.J. Mancuso, S.L. Huang and D. Swern, *J. Org. Chem.*, 1978, **43**, 2480.

20. Lit[2] 215-217°C. ^{1}H NMR ($CDCl_3$) δ 2.84 (s, 3H), 7.59-7.67 (m, 2H), 8.14-8.25 (m, 1H), 8.32 (s, 1H), 10.54 (s, 1H). IR (KBr) 1582, 1670 cm^{-1}.

21. Lit[2] 169-170°C. ^{1}H NMR δ 2.81 (s, 3H), 3.81 (brs, 1H), 4.76 (s, 2H), 7.52-7.65 (m, 2H), 7.68 (s, 1H), 8.15 (d, J = 7 Hz, 1H), IR (KBr) 1665, 1687 cm^{-1}.

22. We thank Professor R.H. Thomson, University of Aberdeen, for a generous sample of maturone.

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