Preliminary experiments have shown that this method is applicable to a wide variety of molecules in photoexcited triplet states and should be of general value in photochemistry. For example it is possible to use photosensitization to produce the triplet state of a molecule whose line broadening is of interest as has been shown for the naphthalene–benzophenone system, where little broadening is observed on direct irradiation of naphthalene in the absence of benzophenone. The application of this method to determine hyperfine interactions and thus structural information as well as relative triplet energies for biologically important molecules such as chlorophyll will be reported shortly.

References and Notes

(1) Supported by NSF Grant GP-37481 and equipment Grants NSF GP-33116 and The University of Chicago Cancer Center Grant CA-14599.
(2) For a review see R. W. Kreilick, *Adv. Magn. Reson.*, **6**, 141 (1973).
(3) M. Cocivera, *Chem. Phys. Lett.*, **2**, 529 (1968).
(4) Bromobenzene as solvent is reported to retard the dimerization of anthracene: see E. J. Bowen, *Adv. Photochem.*, **1**, 36 (1963).
(5) R. H. Clarke and C. A. Hutchison, Jr., *J. Chem. Phys.*, **54**, 2962 (1971); a_β was not determined; the value used here is for the anthracene cation; see A. Carrington and A. D. McLachlin, "Introduction to Magnetic Resonance", Harper and Row, New York, N.Y., 1967, p 90.
(6) Cocivera[3] came to the same conclusion by comparing the measured diamagnetic lifetime with that extrapolated from the intersystem crossing yield, and estimated light flux and triplet excitation lifetime.
(7) The concentration of anthracene in these experiments was high enough over the range studied so that the number of light quanta absorbed did not change significantly.
(8) This equation is strictly valid only for one nuclear spin.[2] However, for systems where the nuclear spin–spin coupling constants are small compared to chemical shift differences, it provides a good approximation to the line widths obtained from a solution of the equation of motion of the total density matrix for the coupled system.
(9) Best fit curves were obtained by a direct search method using "Subroutine Stepit" written by J. P. Chandler and available from the Quantum Chemistry Program Exchange.
(10) Another computer fitting was attempted in which the a_i's were also treated as variables. It is interesting to note that the program converged to values which deviate by less than 15% from the known a_i's,[5] and the remaining three parameters determined by the more restricted search procedure. Of course, the determination of both hyperfine coupling constants and τ_p is only possible if T_{1e} is comparable to or smaller than τ_p.
(11) The value of k corresponds to a diffusion rate constant of $2k$ since the maximum probability for degenerate exchange is 0.5.
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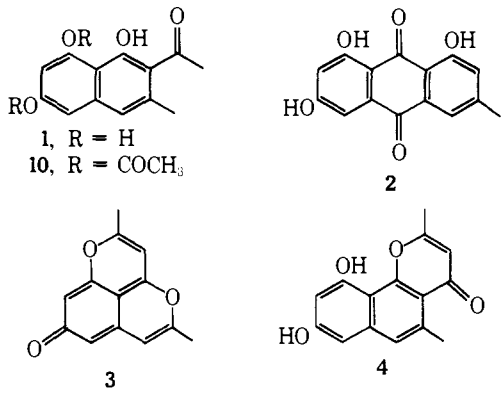
Received January 25, 1975

Biogenetic-Type Syntheses of Polycyclic Polyketide Metabolites Using Partially Protected β-Hexa- and β-Heptaketones: 6-Hydroxymusizin, Barakol, Emodin, and Eleutherinol

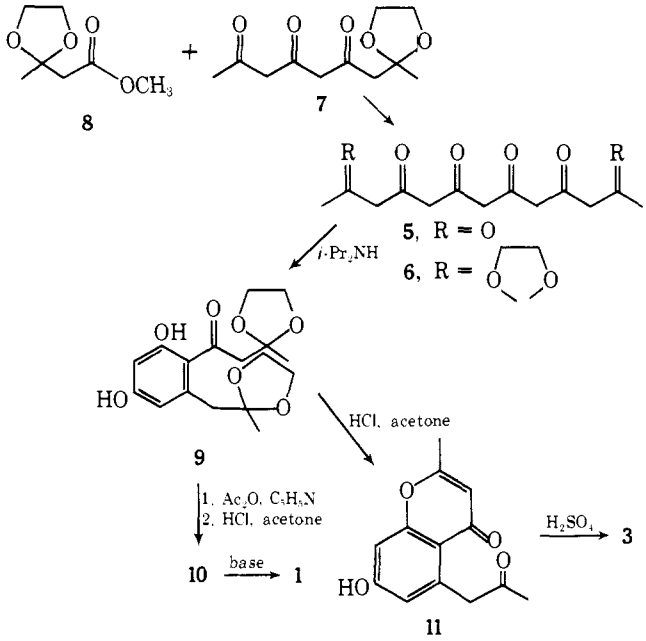
Sir:

Biogenetically modeled syntheses of polyketide-type aromatic natural products have recently attracted attention.[1] Numerous syntheses of monocyclic compounds have been reported which involve free or partially protected β-tetracarbonyl compounds as precursors, but the corresponding use of higher polycarbonyl compounds or their derivatives has not, as yet, led to any naphthalenoid or anthracenoid natural products.[2] We now report biogenetic-type syntheses of 6-hydroxymusizin (**1**) and emodin (**2**), as well as the related heterocyclic metabolites barakol (**3**) and eleutherinol (**4**). The present approach involves polyketones having the two terminal carbonyl groups protected as ketals; these facilitate synthesis of the polycarbonyl compounds and direct their subsequent cyclizations.

Bis(ethylene ketal) **6**[3] of hexaketone **5** was employed for the synthesis of **1** and **3** and was prepared by acylation



Scheme I

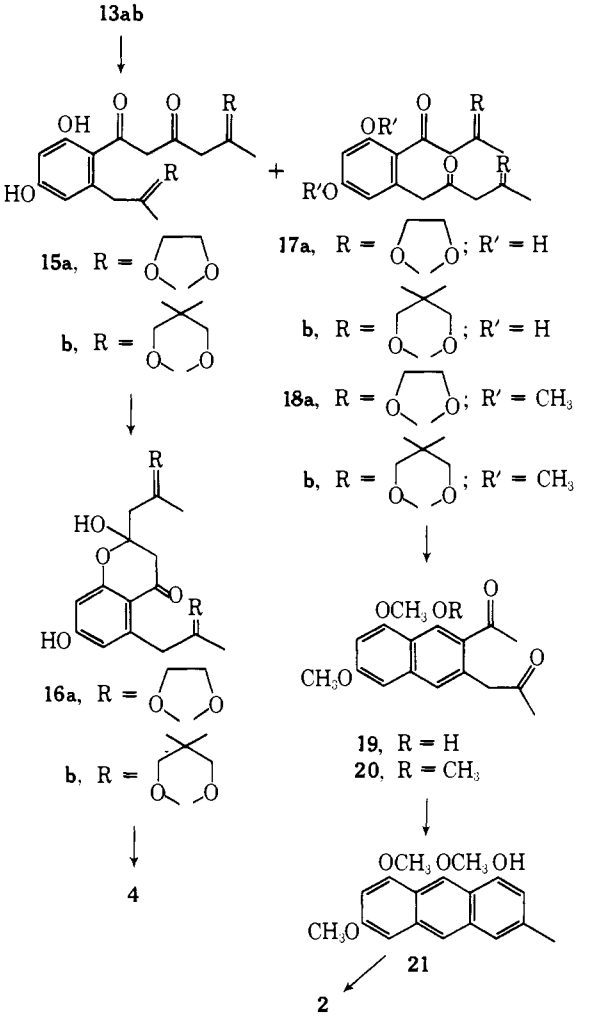


(30–45%) of the trilithium salt (0.03 mol, prepared with *i*-Pr_2NLi) of protected tetraketone **7**[3,4] with ester **8** (0.015 mol) in THF at −78° (Scheme I). The only cyclization pathway readily available to **6** is formation of resorcinol **9;** an 80% yield of **9**[3] was obtained when **6** was treated with *i*-Pr_2NH (C_6H_6, reflux, 0.5 hr). After acetylation (Ac_2O, C_6H_5N, 25°, 40 hr) of **9,** the ketal groups were removed, and the second ring was closed to give naphthol **10**[3] (55%) by treatment with 1:40 hydrochloric acid–acetone (25°, 10 hr). Saponification of **10** under N_2 (4 *M* KOH, 25°, 25 min) gave 70% of 6-hydroxymusizin (**1**), identical with an authentic sample.[5]

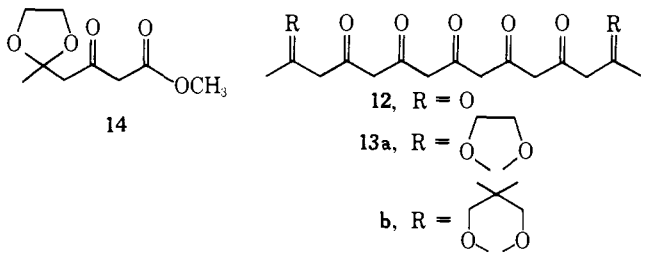
If **9** was not acylated prior to removal of the ketal groups, chromone **11** was formed instead (87%). Chromone **11,** on treatment with concentrated H_2SO_4 (1 hr, 25°), cyclized further to give barakol (**3,** 80%), which was identical with an authentic sample.[6,7] Both **3** and **11** are constituents of *Cassia siamea*.[8]

The initial approach to **2** involved bis(ethylene ketal) **13a** of heptaketone **12** (Scheme II). Acylation of the trilithium salt (0.03 mol, formed with *i*-Pr_2NLi) of **7** with the sodium salt (0.015 mol, formed with NaH) of ester **14**[3,9] gave **13a** (THF, 18 hr, 25°, 17%),[10] which, although relatively stable at ambient temperature, could not be purified fully by chromatography on silica gel. Cyclization of **13a** could give either resorcinol **15a** or **17a,** but under all conditions examined **15a** was the major product, only traces of **17a** being formed. For example, treatment with Et_3N in toluene (3 min, reflux) gave 57% of **15a** (which cyclized spontaneously

Scheme II



to hemiketal **16a**[3]) and 3% of **17a** (isolated as dimethyl ether **18a** (CH_2N_2, Et_2O-MeOH)). The quantity of **18a** which could be prepared was inadequate to justify completion of the emodin synthesis using this intermediate. However, isomeric **16a** is a potential precursor of eleutherinol (**4**). Treatment of **16a** with a 0.5:6:14 mixture of hydrochloric acid, water, and acetone (8 hr, 25°) followed by *i*-Pr_2NH (benzene, 5 min, 25°) closed the naphthalene ring; subsequent treatment with CF_3CO_2H (0.5 hr, 25°) closed the pyrone ring to give **4**[11] (19% from **16a**).



For the synthesis of emodin, the relative proportion of attack at the 6 vs. the 4 position of heptaketone **12** was increased by using the more bulky ketals of 2,2-dimethyl-1,3-propanediol. Diprotected heptaketone **13b**, prepared analogously (11%) to **13a**, cyclized (*i*-Pr_2NH, toluene, reflux, 3 min) to give 54 and 10% yields of resorcinols **15b** and **17b**, with the former cyclizing spontaneously to **16b** and the latter being isolated as dimethyl ether **18b**[3] (CH_2N_2, Et_2O-MeOH). Further cyclization of **18b** under more basic conditions (NaOMe, MeOH, 50°, 2 hr), followed by acid-catalyzed deketalization (0.4:6:14 hydrochloric acid, H_2O, and acetone, 25°, 16 hr) gave dimethoxynaphthol **19**, which, when it failed to undergo further aldol cyclization, was methylated (Me_2SO_4, K_2CO_3, acetone, reflux, 2 hr) to give trimethyl ether **20**.[3] The latter cyclized readily in the presence of NaOMe (MeOH, 60°, 0.5 hr) to anthracene **21**, which by treatment with HI in acetic acid (3 hr, reflux) and then with CrO_3 in aqueous acetic acid (5 min, 50°) gave emodin (**2**) (20% yield based on **18b**).[11,12]

In the present study, the terminal carbonyl groups were protected because model studies[13] had indicated that in polyketones **5** and **12** these groups would be too susceptible to intramolecular attack. The approach is highly effective for the synthesis of 6-hydroxymusizin, barakol, and eleutherinol but only marginally useful for emodin because the wrong initial cyclization predominates. We are currently investigating an alternate approach to direct the cyclizations, namely, the use of ketals to prevent participation of the adjacent methylene groups in aldol reactions. Hopefully through use of a combination of these protective devices, pretetramid and other complex polyketide metabolites can be synthesized.

Acknowledgment. We thank Drs. U. Weiss and B. W. Bycroft for helpful discussions and Dr. R. L. Foltz of the Battelle Mass Spectroscopy Laboratory for determining the chemical ionization spectrum. This research was supported by the U.S. Public Health Service (Research Grant GM-12848).

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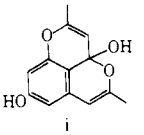
(2) See A. I. Scott, H. Guilford, J. J. Ryan, and D. Skingle, *Tetrahedron*, **27**, 3025 (1971); A. I. Scott, D. G. Pike, J. J. Ryan, and H. Guilford, *ibid.*, **27**, 3051 (1971); P. J. Wittek and T. M. Harris, *J. Am. Chem. Soc.*, **95**, 6865 (1973).
(3) This compound gave satisfactory elemental analyses and spectra consistent with the assigned structure.
(4) Prepared in high yield by condensation of dilithioacetylacetone with ester **8**.
(5) We wish to thank Dr. U. Weiss and K. S. Brown for this sample; see K. S. Brown, D. W. Cameron, and U. Weiss, *Tetrahedron Lett.*, 471 (1969).
(6) We thank Dr. B. W. Bycroft for providing a sample of **3**; see B. W. Bycroft, A. Hassaniali-Walji, A. W. Johnson, and T. J. King, *J. Chem. Soc. C*, 1686 (1970).
(7) Barakol crystallizes as a hydrate, which was assigned by the original workers[6] as *i* rather than as a solvate of **3**. Electron impact and chemical ionization mass spectra of barakol which had been carefully freed of chromone **11** support a molecular weight of 214 for **3**, not 232 for *i*; the uv spectrum (λ_{MAX} 384 nm in EtOH and 408 nm in $CHCl_3$) and the lemon yellow color of crystalline material further argue against the original assignment.



i

(8) S. Arora, H. Deymann, R. D. Tiwari, and E. Winterfeldt, *Tetrahedron*, **27**, 981 (1971).
(9) Prepared by acylation (THF, reflux, 10 hr, 36%) of the monoketal of acetylacetone with dimethyl carbonate in the presence of sodium methoxide. Bram has prepared the ethyl ester by another route; G. Bram, *Tetrahedron Lett.*, 4069 (1967).
(10) For similar procedures, see T. P. Murray and T. M. Harris, *J. Am. Chem. Soc.*, **94**, 8253 (1972).
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(12) Identified by comparison with authentic material.
(13) Unpublished results, P. J. Wittek and T. M. Harris.

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Received December 10, 1974