

Total Synthesis of Khellin via a Chromium Carbene Complex

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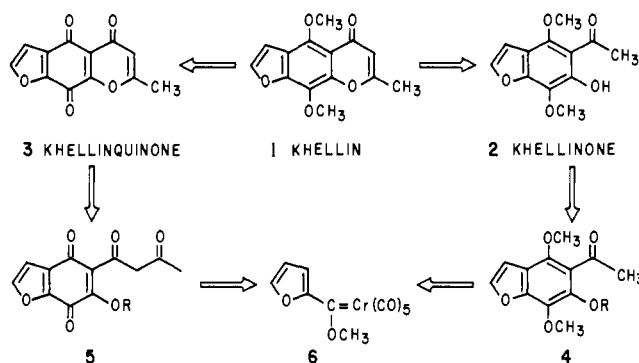
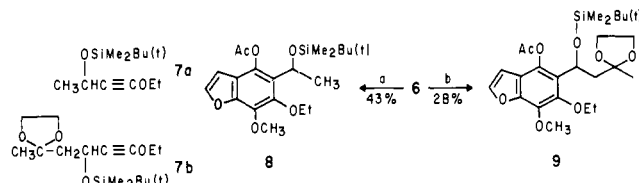
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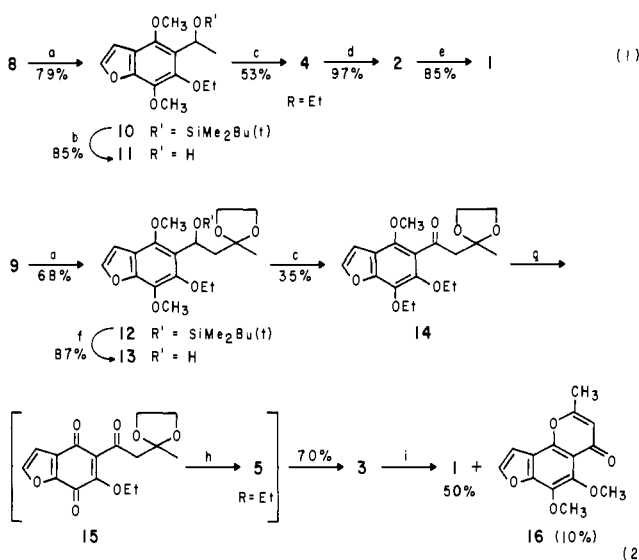
Khellin (**1**)¹ is one member of a group of furochromones, isolated from *Ammivivsnaga* L., a perennial herbaceous plant that grows wild in many Mediterranean countries.² Khellin, along with other analogues, such as ammiol and visnagan, was found to possess desirable lipid-altering activity,³ viz., decreasing the atherogenic VLDL + LDL-cholesterol fraction and elevating the antiatherogenic HDL-cholesterol fraction in animal models as well as in man.⁴ In this paper, we wish to report two new approaches to furochromone synthesis. These provide both a formal total synthesis of khellin (**1**) and a general methodology for the synthesis of furochromone analogues useful for structure-activity evaluation in the antiatherosclerosis area.

Our strategy (Scheme I) involves cycloaddition reaction of a furan chromium carbene complex **6**⁵ with a substituted alkoxyalkyne for the direct construction of the benzofurans **4** and **5**, which bear the functional groups necessary for the γ -pyrone ring formation. Since khellinone (**2**) and khellinquinone (**3**) have previously been converted to **1**,^{1,2} our strategy further relies on (i) selective cleavage of protecting group (R = Et) from the intermediate **4** and (ii) acid-catalyzed pyrone ring formation from the β -diketone **5**. Our studies have shown that direct preparation of the benzofuran bearing the carbonyl group from cycloaddition reaction of **6** with alkynes—such as acetyl acetylene and ethyl propiolate—proceeded in poor yield.⁶ For this reason, longer but higher yielding routes were developed. These involve the reaction

Scheme I

Scheme II^a

^a (a) **7a**, Ac₂O, NEt₃, THF, 65 °C, 10 h; (b) **7b**, Ac₂O, NEt₃, THF, 65 °C, 72 h.

Scheme III^a

^a (a) NaH, MeI, HMPA, THF, 0 → 23 °C; (b) *n*-Bu₄NF·3H₂O, DMF, 23 °C; (c) PDC, CH₂Cl₂, 23 °C; (d) BF₃·Et₂O, CH₂Cl₂, 0 → 23 °C; (e) (i) NaH, EtOAc, reflux, (ii) aqueous HCl, MeOH, 23 °C; (f) *n*-Bu₄NF·3H₂O, DMF, 55 °C; (g) CAN, CH₃CN, H₂O, 0 °C; (h) aqueous 1 N HCl, MeOH, 23 °C; (i) NaHSO₃, catalytic HCl, 100 °C; (ii) MeI, K₂CO₃, acetone, reflux.

of **6** with **7a**⁷ and **7b**⁷ (Scheme II). We have reported the first use of **7a** in the carbene reaction, which revealed that the carbene carbon attached the ethoxy-bearing carbon of **7a** with 100% desired regioselectivity.^{8,9} Best results were obtained when the

(1) For khellin synthesis: (a) Murti, V. V. S.; Seahandri, T. R. *J. Sci. Ind. Res., Sect. B* **1949**, *8*, 112. (b) Murti, V. V. S.; Seahandri, T. R. *Proc.—Indian Acad. Sci., Sect. B* **1949**, *30*, 107. (c) Clarke, J. R.; Robertson, W. J. *J. Chem. Soc.* **1949**, 302. (d) Baxter, R. A.; Ramage, G. R.; Timson, J. A. *Ibid.* **1949**, 30. (e) Gardner, T. S.; Wenis, E.; Lee, J. *J. Org. Chem.* **1950**, *15*, 841. (f) Geissman, T. A.; Walsall, T. G. *J. Am. Chem. Soc.* **1951**, *73*, 1280. (g) Dann, O.; Illing, G. *Liebigs Ann. Chem.* **1957**, *605*, 146. (h) Aneja, R.; Mukerjee, S. K.; Seahandri, T. R. *J. Sci. Ind. Res., Sect. B* **1958**, *17*, 382. (i) Dann, O.; Zeller, H. *Chem. Ber.* **1960**, *93*, 2829. (j) Aneja, R.; Mukerjee, S. K.; Seahandri, T. R. *Ibid.* **1960**, *93*, 297. (k) Gammill, R. B.; Hyde, B. R., *J. Org. Chem.* **1983**, *48*, 3863. (l) Gammill, R. B. *Tetrahedron Lett.* **1985**, *26*, 1385.

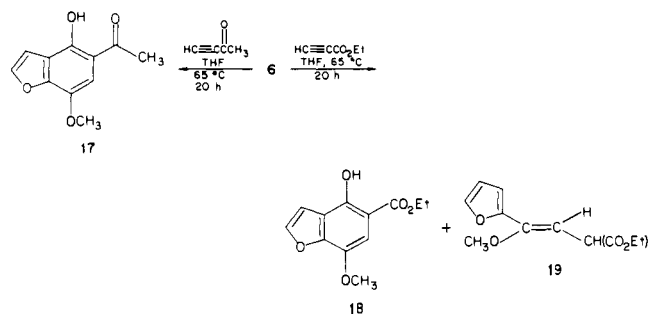
(2) Späth, E.; Gruber, W. *Chem. Ber.* **1938**, *71*, 106.

(3) (a) Levy, R. I. *Arteriosclerosis (Dallas)* **1981**, *1*, 312. (b) Zlversmit, O. B. *Circulation* **1979**, *60*, 473. Fredrickson, D. S.; Levy, R. J. "The Metabolic Basis of Inherited Disease", 3rd ed.; Stanburg, J. B., Wyngaarden, J. B., Fredrickson, D. S., Eds.; McGraw-Hill: New York, 1972; p 545. (c) Camejo, G. "Low Density Lipoproteins"; Day, C. E., Levy, R. S., Eds.; Plenum Press: New York, 1976; p 351. (d) Tall, A. R.; Small, D. M. *N. Engl. J. Med.* **1978**, *299*, 1232. (e) Miller, N. E. *Lipids* **1978**, *13*, 914. (f) Gordon, R.; Costelli, W. P.; Hjortland, M. C.; Kannel, W. B.; Dawber, T. R. *Am. J. Med.* **1977**, *62*, 707. (g) Miller, G. J.; Miller, N. E. *Lancet* **1975**, *2*, 16.

(4) Gammill, R. B.; Day, C. E.; Schurr, P. E. *J. Med. Chem.* **1983**, *26*, 1672.

(5) The furan chromium complex **6** was prepared as before: Dötz, K. H.; Dietz, R. *Chem. Ber.* **1978**, *48*, 38.

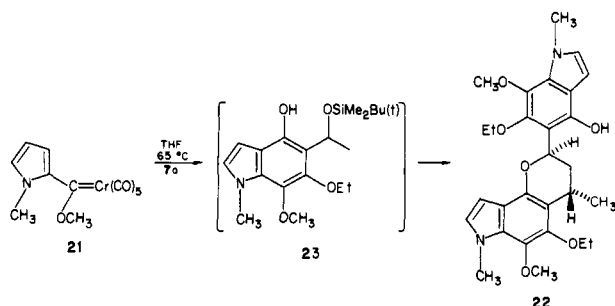
(6) For example, the reaction of **6** with acetylacetylene in THF at 65 °C gave only 13% yield of the ketone **17** after 20 h. Ethyl propiolate reacted with **6** in THF at 65 °C, producing the ester **18** (21%) and the vinyl ether **19** (20%) after 20 h.



reactions of **6** and **7a** and **7b** were carried out in the presence of acetic anhydride (Ac₂O) and triethylamine (NEt₃).¹⁰ A solution of **6**, **7a** (1.5 mol equiv), Ac₂O (2 mol equiv), and NEt₃ (2 mol equiv) in tetrahydrofuran (THF, 30 mmol/mL) was heated under argon at 65 °C (bath temperature) for 10 h, providing the acetylated benzofuran **8** as the only isolated product in a 43% yield (based on **6**).¹¹ Similarly, heating of **6**, **7b** (1.5 mol equiv), Ac₂O (1.1 mol equiv), and NEt₃ (1.1 mol equiv) in THF at 65 °C for 72 h under argon produced **9** (28%).¹²

The route to khellin utilizing **8** requires conversion of the acetate to a methyl ether, selective cleavage of the ethyl ether, and pyrone ring formation (Scheme III, eq 1). The first of these objectives was carried out without isolation of the intermediate phenol which, being labile, readily lost the silyloxy group, producing an alkene.⁸ Thus, treatment of **8** with sodium hydride (3 mol equiv) and methyl iodide (excess) in HMPA/THF [0 °C then 23 °C] directly produced the methyl ether **10**.¹³ The alcohol **11** was freed from its silyl ether [*n*-Bu₄NF·3H₂O (3 mol equiv), DMF, 23 °C, 85%] and oxidized to the ketone **4** (R = Et) (PDC, CH₂Cl₂, 53%, 13% recovery of **11**). Selective cleavage of the ethyl ether was effected with BF₃·Et₂O (10 mol equiv, dry CH₂Cl₂, 0 °C then 23 °C)¹⁴ to provide **2**.^{15,1b-d,f} No demethylated product was detected. Khellin (**1**)¹⁶ was generated from **2** through a Claisen-type condensation and subsequent acid-catalyzed pyrone ring formation.^{1c,2}

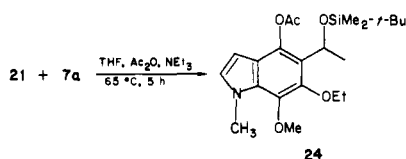
(8) The reaction of a pyrrole chromium complex **21** with **7a** (THF, 65 °C, 4 h) provided the Diels-Alder dimer **22** (68%) of the expected monomer **23**.



However, under identical conditions, **6** was totally inert to react with **7a**, resulting in the recovery of **6**. Yamashita, A.; Scahill, T. A.; Chidester, C. G. *Tetrahedron Lett.* **1985**, *26*, 1159.

(9) This result was consistent with earlier observations of a dominating steric effect. (a) Dötz, K. H.; Fügen-Köster, B. *Chem. Ber.* **1980**, *113*, 1449. (b) Wulff, W. D.; Tang, P. C.; McCullum, J. S. *J. Am. Chem. Soc.* **1982**, *103*, 7677.

(10) The method was developed with the pyrrole-carbene complex **21** with alkynes. The reaction of **21** with **7a** in the presence of acetic anhydride and triethylamine gave the acetylated product **24** (64%). No Diels-Alder dimer



was observed. Yamashita, A.; Scahill, T. A.; Toy, A. *Tetrahedron Lett.* **1985**, *26*, 2969.

(11) All yields refer to isolated yields of analytically pure material.

(12) The regiochemistry of two functional groups in **8** and **9** was determined on the basis of the earlier observation; see ref 8. Both reactions of **6** with **7a** and **7b** without triethylamine took considerably longer, and the yields of **8** and **9** were lower. The mechanism and roles of Ac₂O and NEt₃ in these reactions are presently unestablished.

(13) The reaction presumably proceeded by initial formation of the ketene from the acetate by sodium hydride, followed by methylation of the sodium phenoxide. For example, phenyl acetate was converted to anisole under the same conditions [sodium hydride (2.2 mol equiv), MeI (excess), HMPA, THF, 23 °C].

(14) Methyl ether at the 6-position of the 5-acetyl-4,6,7-trimethoxybenzofuran derivative was selectively cleaved by treatment with AlCl₃; Horton, W. J.; Paul, E. G. *J. Org. Chem.* **1959**, *24*, 2000. The mechanism of selective cleavage of ethyl ether in the presence of methyl ethers in the same aromatic ring is presently unestablished.

(15) Mp 97-99 °C; the physical behavior of the product was the same as that of the authentic sample obtained from alkaline degradation of khellin.

(16) Mp 148-150 °C (undepressed on admixture with a natural specimen, mp 151-152.5 °C).

Khellin was also generated from **9** (Scheme III, eq 2). As above, direct conversion of the acetate to the methyl ether was effected by sodium hydride and methyl iodide in THF, providing **12** (68%). Cleavage of the silyl ether (*n*-Bu₄NF, DMF, 55 °C) produced an alcohol **13** (89%), which on oxidation (PDC, CH₂Cl₂) gave the ketone **14** (35%) and the recovered **13** (30%). Oxidation of the *p*-dimethoxy benzene ring of **14** with ceric ammonium nitrate (3 mol equiv) in acetonitrile/water (3:1 mixture) at 0 °C,¹⁷ followed by aqueous acid treatment (1 N HCl, MeOH) led to **3**¹⁸ (70% overall from **14**). The reaction presumably proceeded by CAN oxidation of **14** to a quinone **15**. Under aqueous acid, ketal was cleaved to the β-diketone **5** (R = Et), which with acid cyclized to **3**. Reduction of **3** (NaHSO₃, catalytic HCl, 100 °C),¹¹ followed by dimethylation (MeI, K₂CO₃, acetone, reflux), produced **1** (50%) and isokhellin (**16**, 10%).¹⁹

In summary, we have described two very facile syntheses of khellin in yields of 13% and 5% requiring only six and seven steps, respectively. These results exploit a cycloaddition reaction of a furan chromium carbene complex producing the key intermediates: substituted benzofurans.²⁰

Supplementary Material Available: Characterization data (¹H NMR, IR, mass and combustion analysis) on all new compounds (4 pages). Ordering information is given on any current masthead page.

(17) Rapoport, H.; Falling, S. N. *J. Org. Chem.* **1980**, *45*, 1260.

(18) Mp 204-208 °C; the physical behavior of the product was the same as that of the authentic sample obtained from oxidation of khellin.

(19) Conversion of Khellinquinone to isokhellin: (a) see ref 1e. (b) Fukushima, S.; Ueno, A.; Akahori, Y. *Chem. Pharm. Bull.* **1964**, *12* (3), 307.

(20) All new compounds isolated during this work have been characterized by satisfactory combustion and spectral (high-resolution mass, IR, NMR) analysis, and these data are recorded as supplementary material.

Photolysis of Dibenzyl Ketones in the Presence of Pentasil Zeolites. Examples of Size/Shape Selectivity and Molecular Diffusional Traffic Control

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The pentasil family of zeolites has received wide attention because of its versatility as catalysts,¹ particularly in size- and shape-selective reactions.² The dynamics of molecular diffusion through the differing channel systems of the ZSM-5 have evoked the concept of molecular diffusional traffic control³ to explain catalytic selectivity in the preparation of *p*-xylene. The latter has been explained in terms of a shape/size effect by which *o*-xylene

(1) For a recent review, see: Minachev, K. M.; Kondralev, D. A. *Russ. Chem. Rev. (Engl. Transl.)* **1983**, *52*, 1113. The pentasil family of zeolites is composed of five-membered rings of (Al,Si)O₂ tetrahedra arranged with different crystal symmetries to form zeolites with channels of dimensions of 5-6 Å. The internal surface of LZ-105 is typical of zeolites and the ZSM family, i.e., intersecting channels. For a discussion, see: Derouane, E. G. "Catalysis by Zeolites"; Imelik, B., et al. Eds.; Elsevier: Amsterdam, 1980; p 5.

(2) For recent reviews, see: Csicsery, S. M. *Zeolites* **1984**, *4*, 202. Kokotailo, G. T.; Meler, W. M. *Spec. Publ.—Chem. Soc.* **1979**, *No. 33*, 133.

(3) Derouane, E. G. In "Intercalation Chemistry"; Whittingham, M. S., Jacobson, A. J., Eds.; Academic Press: New York, 1982, p 101. The term "molecular traffic control" was coined to describe selective diffusion within different (linear and zig-zag) channel systems of pentasil zeolites. In the spirit of this concept we extend the term to embrace selective diffusion on the external or internal surface of a pentasil zeolite.