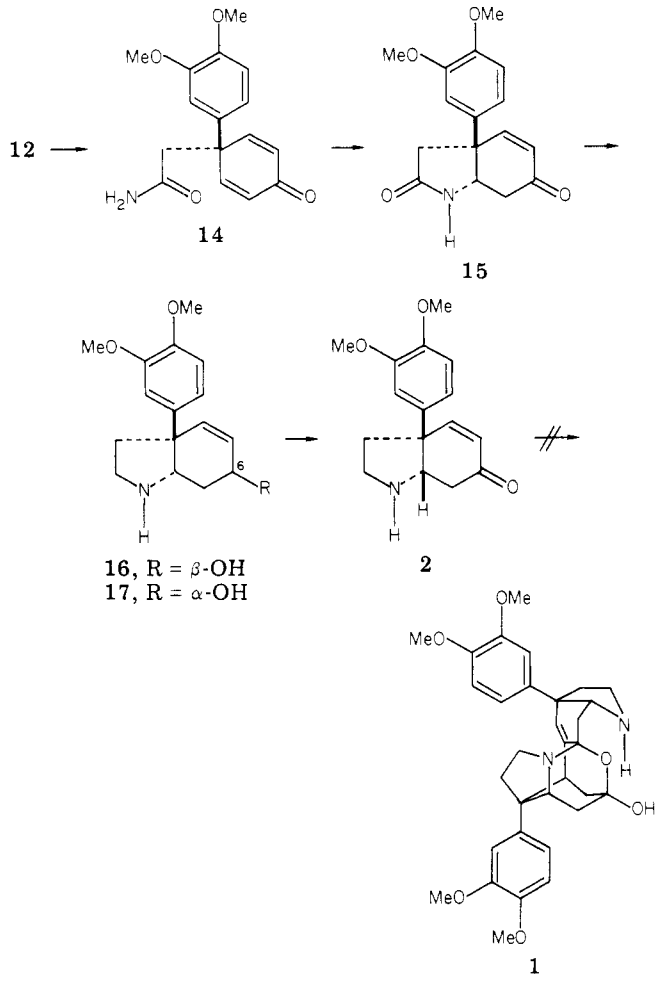
Scheme II



conversion to the acid chloride **9**. Transformation of **9** to the keto amide **10** was accomplished with 2.2 equiv of methylamine in methanol at 25 °C. Contrastingly, when **9** was reacted in the presences of excess methylamine in methanol at room temperature, 2-oxomesembrine (**11**) was obtained directly. Although the conversion of **10** to jourbertinamine required only the requisite reduction of the amide and enone functions, preferably in the latter case with appropriate stereochemical control,[6] the accomplishment of these seemingly trivial transformations was achieved only after considerable experimentation. Ultimately the conversion of **10** to (±)-joubertinamine (**6**) was achieved in 65% yield by a carefully controlled reduction with excess $LiAlH_4$ in THF at 0–10 °C for 2 h and 25 °C for 70 h. Increasing the temperature of this reaction led only to products that arise from reductive cleavage of the ethanamide side chain. The overall yield of (±)-joubertinamine from **3** by this route is 17%.

While the foregoing synthesis of (±)-mesembrine and (±)-joubertinamine provided the basis for a synthetic plan for (±)-*N*-demethylmesembrenone, two additional aspects required examination. Namely, a method for introduction of unsaturation represented by the 4,5-double bond and an effective procedure for the formation of the secondary γ-lactam were required. In the latter situation, the previous failure to effect the direct transposition of the keto lactone (**4**) to the corresponding secondary lactam with ammonia led us to examine a stepwise procedure for this transformation. In the event, conversion of **4** to the intermediate **9** and subsequent reaction of the latter with ammonia provided the amide **12**. Intramolecular Michael addition of the amide anion derived from **12** and LDA in DMF at 25 °C gave quantitative cyclization to the model cis octahydroindolone **13**. Following this success, introduction of the required unsaturation into the carbocyclic ring system was effected by oxidation of the enone amide **12** to the symmetrical dienone **14** with DDQ (Scheme II). Cyclization of the dienone with LDA–DMF afforded the γ-lactam **15**, which was reduced with $LiAlH_4$ to give a 80:20 mixture of the two epimeric *N*-demethylmesembrenols **16** and **17**. In view of the postulated origin of channaine,[2] it appeared desirable to generate *N*-demethylmesembrenone under neutral conditions. Attempts to effect this conversion by oxidation of **16** and **17** with activated MnO_2 in a range of solvents was unsuccessful. Fortunately, oxidation of mixture of the two allylic alcohols proceeded smoothly with pyridinium chlorochromate in CH_2Cl_2 to give (±)-*N*-demethylmesembrenone (**2**) in 95% yield.

Having successfully completed these syntheses, we now wished to test the biosynthetic hypothesis discussed above. If channaine is indeed an artifact, it should by produced in an acid- or base-catalyzed self-condensation of *N*-demethylmesembrenone. However, all attempts to effect this conversion were unsuccessful. In particular, (±)-*N*-demethylmesembrenone was recovered unchanged from 3 N HCl following basification, also from exposure to 2 N NaOH, and on elution from basic alumina. Since the foregoing conditions were generally representative, or in some cases more drastic than those used in the isolation of channaine from *S. strictum*, we reluctantly conclude that (±)-channaine should be considered as a natural product until further evidence is obtained to indicate otherwise.

Acknowledgment. We are indebted to the National Institute of Environmental Health Sciences for a training grant in support of R.R. (Grant 5-T32-ES-07031).

Registry No. (±)-**2**, 81255-05-2; (±)-**3**, 87014-17-3; (±)-**4**, 87014-19-5; (±)-**5**, 6023-73-0; (±)-**6**, 71357-60-3; (±)-**7**, 87014-18-4; (±)-**8a**, 87014-20-8; (±)-**8b**, 87014-22-0; (±)-**9**, 87014-23-1; (±)-**10**, 87014-24-2; (±)-**11** (R = Me), 21104-34-7; (±)-**12**, 87014-25-3; (±)-**13**, 87014-26-4; (±)-**14**, 87014-27-5; (±)-**15**, 87039-28-9; (±)-**16**, 87068-15-3; (±)-**17**, 87068-16-4; methylamine, 74-89-5.

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Total Synthesis of the Lipid-Altering and Antiatherosclerotic Furochromone Khellin. The Furoic Acid Route to Highly Functionalized Benzofurans

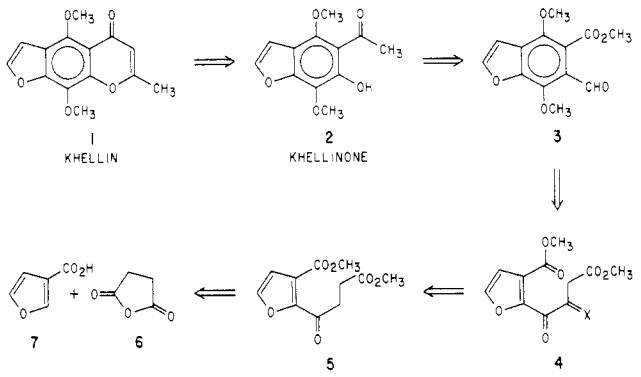
Summary: 3-Furoic acid is converted to enaminone diester **8**, which undergoes Dieckmann cyclization to yield the highly functionalized benzofuran **9**. Methylation, Baeyer–Villager oxidation (CHO → OH) and conversion of the resulting hydroxy ester **10** to khellinone constitutes a formal synthesis of khellin.

Sir: Khellin (**1**) is one of several furochromones that can be isolated from *Ammi visnaga L.*, a perennial herbaceous plant that grows wild in many Eastern Mediterranean countries.[1] As early as 2270 B.C. the Egyptians were using

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

0022-3263/83/1948-3863$01.50/0

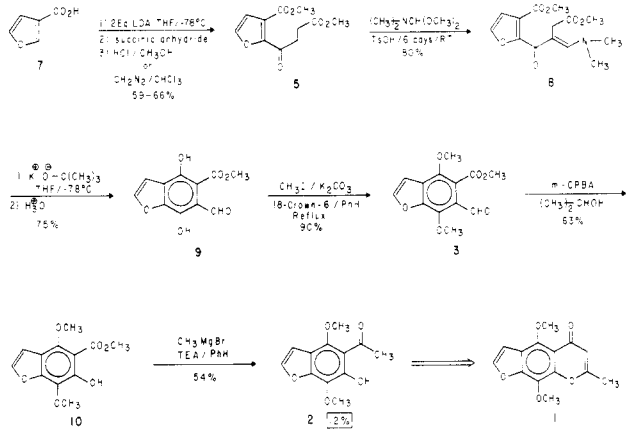
Scheme I



"Mem" (hieroglyphic name) to treat a variety of painful spasmodic conditions such as biliary and renal colic.[2,3] Recently, khellin, along with several analogues, was found to possess desirable lipid-altering activity,[4] i.e., lowering the atherogenic VLDL + LDL–cholesterol fraction and elevating the antiatherogenic (i.e., protective against atherosclerosis) HDL–cholesterol fraction, in animal models[5,6] as well as in man.[7] These results have renewed our interest in the preparation of furochromone analogues. In this communication we describe a new approach to furochromone synthesis that in addition to yielding the natural product provides methodology for the preparation of targets previously not considered.

While a number of total syntheses of khellin have appeared,[8] all lacked the flexibility and practicality that we felt were necessary for the synthesis of specific "key" analogues required for structure–activity evaluation in the atherosclerosis area. The problems associated with the construction of highly oxygenated furochromones such as khellin are two-fold. First, the construction of a fully substituted aromatic B ring is required. In earlier syntheses this was accomplished through the sequential addition of carbon and oxygen appendages to a pyrogallol or phloroglucinol intermediate. While this was a workable strategy, low yields were almost always encountered when the final carbon or oxygen atom was added to the pentasubstituted system.

Scheme II. Furoic Acid Route to Khellin



A second problem encountered is the need to differentiate the four oxygen atoms on the B ring during the course of the synthesis. In the past this problem necessitated the use of numerous protecting groups, thus requiring many additional steps.

In this communication we report a formal synthesis of khellin that (1) exploits a new synthetic approach to furochromones that does not require the excessive use of protecting groups, (2) has considerable flexibility with regard to analogue synthesis, and (3) represents a general method for the quick assemblage of highly functionalized benzofurans.

Our synthetic plan is outlined in Scheme I. Since khellinone (**2**) had previously been converted to khellin through a Claisen-like condensation/acid-catalyzed cyclodehydration sequence,[1] benzofuran **2** became our target. In order to incorporate flexibility in our synthesis and to eliminate the need for protecting groups, we established the aldehyde–ester **3** as our subtarget. Benzofuran **3** represented a fully differentiated (oxygen substitution, CHO → OH), completely substituted (B ring), and potentially versatile analogue system. We envisioned **3** as arising from the acyclic precursor **4** through a Dieckmann cyclization. Keto diester **4**, containing the enaminone system (to be used as a directing group for cyclization and aldehyde equivalent) would then be available through a condensation between the dianion of 3-furoic acid and succinic anhydride followed by introduction of the aminomethane group.

The keto diester **5** was readily available from 3-furoic acid and succinic anhydride (Scheme II). Rapid addition of succinic anhydride (1.1 equiv/THF) to the dianion of 3-furoic acid (2 equiv of LDA/THF/−78 °C),[9] followed by esterification (HCl/CH_3OH or $CH_2N_2/CHCl_3$) of the crude diacid yielded, after chromatography (silica gel; 5% EtOAc/$CHCl_3$), keto diester **5** (59–66%) as a colorless oil.[10]

Regiospecific introduction of the (dimethylamino)methylene unit[11] adjacent to the ketone was accomplished by treatment of a neat mixture of **5** and *N*,*N*-dimethyformamide dimethyl acetal (DMF–DMA) (1:1.1) with TsOH at room temperature for 6 days.[12] This yielded

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(3) For the pharmacological development of khellin see: Osher, H. L.; Katz, K. H. *Boston Med. Q.* **1950**, *1*, 11. Anrep, G. V.; Barsoum, G. S.; Kenawy, M. R.; Misrahy, G. *Br. Heart J.* **1946**, *8*, 171–177. Anrep, G. V.; Kenawy, M. R.; Barsoum, G. S.; Fahmy, I. R. *Gaz., Faculty Med. Univ. Cairo* **1947**, *14*, 1.

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(6) Day, C. E.; Stafford, W. W.; Schurr, P. E., unpublished results, The Upjohn Company.

(7) Harvengt, F.; Desagn, J. P., unpublished results, Laboratoire de Pharmacotherapie, Uiversite Catholique de Louvain, Bruxelles, Belgium.

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(10) Silica gel TLC, R_f 0.39 (5% EtOAc/$CHCl_3$); IR ν_{max} ($CHCl_3$) 3050, 1735, 1695, 1590, 1480, 1440, 1400, 1360, 1305, 1280, 1160 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.5 (d, 1 H, J = 2 Hz), 6.83 (d, 1 H, J = 2 Hz), 3.90 (s, 3 H, OCH_3), 3.71 (s, 3 H, OCH_3), 3.30 (t, 2 H, J = 8 Hz), 2.75 (t, 2 H, J = 8 Hz); ^{13}C NMR (20 MHz, $CDCl_3$) 187.75, 172.94, 162.94, 150.96, 144.58, 122.36, 113.63, 52.41, 51.76, 35.02, 27.56 ppm. Anal. Calcd ($C_{11}H_{12}O_6$) C, H.

(11) For additional examples, see: Abdulla, R. F.; Brinkmeyer, R. S. *Tetrahedron* **1979**, *35*, 1675.

the desired acyclic precursor 8[13] (80%) as a yellow oil after Florisil chromatography (20% EtOAc/CH_2Cl_2).[14] Dieckmann cyclization of **8** (2 equiv of potassium *tert*-butoxide/THF/−78 °C) followed by acid treatment (2 N HCl/THF/4 h) yielded the fully substituted and oxygen-differentiated benzofuran **9** (75%) as a yellow solid (mp 159.7–160.5 °C). Methylation (CH_3I/K_2CO_3/18-crown-6/PhH/Δ) of **9** yielded the highly versatile benzofuran intermediate **3** (90%).[15] Baeyer–Villiger oxidation (2.1 equiv, *m*-CPBA/2-propanol/16 h/room temperature) of **3** followed by a basic workup (10% aqueous Na_2CO_3/ether/30 min/room temperature) yielded the known hydroxy ester **10** (63%).[16] Conversion of **10** to khellinone was then achieved through the addition of methylmagnesium bromide (6 equiv) to **10** in the presence of triethylamine (17 equiv) in benzene (8–10 °C/6.5 h)[17]. The yield in this final step was 54%. The overall yield of khellinone from **7** was 12%.

This synthesis represents several important advances with respect to furochromone synthesis and particularly analogue synthesis. This new approach (furan → benzofuran → furochromone) to furochromone construction dealt very effectively with the assemblage of the fully substituted B ring and with the oxygen differentiation problems encountered in earlier syntheses of khellin. Furthermore, because of the extremely short route and method of benzofuran construction (furan → benzofuran), this synthesis represents a practical and flexible route that can accommodate changes in either early or late stages of the synthesis.

Acknowledgment. We are indebted to Dr. Mike Lipton for providing large quantities of keto diester **5**. The technical assistance of P. Gold is acknowledged.

Registry No. **1**, 82-02-0; **2**, 484-51-5; **3**, 87145-68-4; **5**, 87145-69-5; **6**, 108-30-5; **7**, 488-93-7; **8**, 87145-70-8; **9**, 87145-71-9; **10**, 87145-72-0; DMF–DMA, 4637-24-5.

Supplementary Material Available: Experimental procedures and spectral and analytical data for compounds **2**, **3**, **5**, **8**, **9**, and **10** (5 pages). Ordering information is given on any current masthead page.

(12) The amide acetal reactions carried out at room temperature for 3 days or less returned substantial amounts (20–30%) of the starting keto diester. Those reactions carried out at higher temperatures were more complex and rarely yielded starting material. We have also found that treatment of a mixture of **5** and *N,N*-dimethylformamide dimethyl acetal in refluxing THF with potassium *tert*-butoxide (25 mol %) likewise yields **8**. However, on scaleup (50–100-g scale), the acid-catalyzed reaction is superior. On a 10–20-mmol scale the base-catalyzed reaction works well (70–76%).

(13) Silica gel TLC, R_f 0.4 (5% CH_3OH/EtOAc); UV_{max} (EtOH) 260 nm (ε 9600), 309 (ε 13 650); IR ν_{max} ($CHCl_3$) 3000, 2950, 1725, 1640, 1560, 1430, 1405, 1390, 1320, 1160 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.45 (d, 1 H, J = 2 Hz), 6.95 (s, 1 H, vinyl proton), 6.73 (d, 1 H, J = 2 Hz), 3.82 (s, 3 H, OCH_3), 3.68 (s, 5 H, OCH_3, CH_2), 3.07 (s, 6 H, $N(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ 183.61, 173.21, 163.17, 156.87, 155.38, 142.26, 117.08, 111.01, 104.84, 52.00, 51.78, 43.53, 29.94 ppm. Anal. Calcd ($C_{14}H_{17}NO_6$) C, H, N.

(14) Compound **8** slowly hydrolyzes on silica gel. On basic or neutral Woelm alumina, it is virtually destroyed.

(15) Silica gel TLC, R_f 0.44 (5%; EtOAc/$CHCl_3$); mp 89.9–90.8 °C; UV_{max} (EtOH) 209 nm (ε 15 550), 232 (ε 21 500), 282 (ε 12 350), 334 (ε 6250); IR ν_{max} ($CHCl_3$) 1730, 1680, 1600, 1470, 1440, 1390, 1340, 1305, 1290, 1060, 980, 930 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.4 (s, 1 H, aldehyde), 7.83 (d, 1 H, J = 2 Hz), 6.97 (d, 1 H, J = 2 Hz), 4.38 (s, 3 H, OCH_3), 3.98 (s, 6 H, OCH_3). Anal. Calcd ($C_{13}H_{12}O_6$) C, H.

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(17) Kikkawa, I.; Yorifuji. *Synthesis* **1981**, 877.

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A New Strategy for the Synthesis of Spiroketals

Summary: The syntheses of various 1-(ω-hydroxyalkyl)-dihydropyran derivatives and their spirocyclizations are described.

Sir: The cyclocondensation of activated conjugated dienes with aldehydes, under the influence of Lewis acids, has broad possibilities for the synthesis of various oxygen heterocycles[1] and acyclic arrays which can be derived by disconnection of such rings.[2] Recently, in probing the range of feasibility of this reaction, it was found that cycloaddition can be realized with dienes bearing a carbon substituent at the 1-position and a silyloxy function at carbon 3 of the diene.[3] Thus, 1,3-dioxygen substitution[1] is not a sine qua non for the success of this reaction. It was of some interest to investigate the possibility that hetero-Diels–Alder processes might provide a new route to spiroketals.[4] The antiparasitic capabilities of the milbemycins[5] and the avermectins,[6] as well as the antibiotic properties of the polyether ionophores,[7] underscore the importance of gaining ready and versatile access to the spiroketal moieties of such systems. A new approach to this problem is described herein.

(Triethylsilyl)oxy dienes **3a**,[8a] and **3b**[8a] used in this study, were obtained (ca. 90%) from the reaction of the enones **2** with triethylsilyl triflate in the presence of triethylamine in ether.[9] The enones are easily prepared from the ω-(silyloxy) aldehydes **1**[10] by a Wadsworth–Emmons process (eq 1).[11]

Cyclocondensation of diene **3a** with benzaldehyde or propionaldehyde could be carried out at room temperature by using several Lewis acids. With benzaldehyde, either zinc chloride (ca. 1 equiv) in tetrahydrofuran or catalytic

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(2) Danishefsky, S.; Larson, E. R.; Askin, D. *J. Am. Chem. Soc.* **1982**, *104*, 6457.

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(7) (a) For a review, see: Wierenga, W. "The Total Synthesis of Natural Products", ApSimon, J., Ed.; Wiley-Interscience: New York, 1981; Vol. 4, pp 263–351. (b) For syntheses of monensin: Fukuyama, T.; Akasaka, K.; Karenewsky, D. J.; Wang, C.-L. J.; Schmid, G.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 262. Collum, D. B.; McDonald, J. H., III; Still, W. C. *Ibid.* **1980**, *102*, 2121.

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(10) Aldehydes **1a** and **1b** were prepared from 1,5-pentanediol and 1,4-pentanediol, respectively, by silylation (1.1 equiv of *t*-$BuMe_2SiCl$, 1.2 equiv of NEt_3, catalytic DMAP in CH_2Cl_2) followed by oxidation (1.5 equiv of PCC in CH_2Cl_2). Full details may be found in the supplementary material.

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