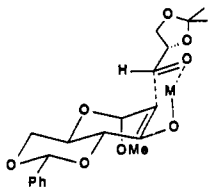
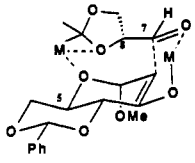
DIBAL (vide infra) gave a crystalline diol whose structure was assigned as **13** by X-ray analysis.[15]

It is of interest to examine the stereoselectivity of the reaction with respect to the two stereocenters that are being created in the aldol condensations in Scheme II. Addition from the β-face of enolate **2** to give axial adduct(s) is in keeping with the various *nucleophilic* additions to trigonal centers at C2.[17]

With respect to the other newly created center, C7, the Zimmerman–Traxler model[18] **15** correctly predicts[19-21]

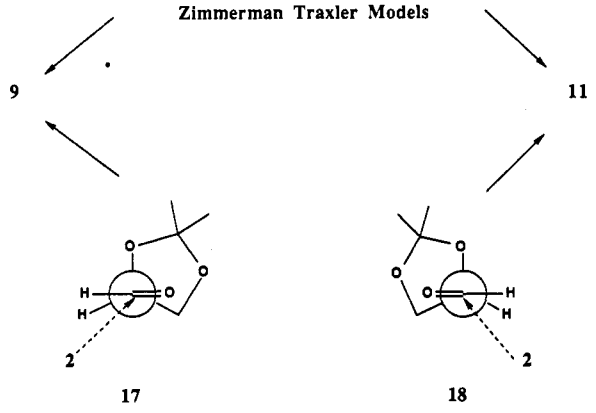


15



16

Zimmerman Traxler Models



17 **18**

Felkin-Anh Models

formation of the anti product **9** in agreement with aldol condensations involving enolates of cyclohexanones.[22] *In light of these considerations, the syn course of addition observed in 11 is an unexpected result.*[23] Thus, the corresponding transition state **16** seems highly unfavorable, since the bulky dioxolane residue is axially oriented on the six-membered chelate ring. It is tempting to note that a secondary chelation can be envisioned between O5 and O8, as indicated in **16**. Whether or not this would be enough to account for the unexpected stereochemical course remains to be seen.

As an alternative to the above, it should be noted that the Felkin–Anh models,[24,25] **17** and **18**, account for the formation of both **9** and **11**, in keeping with the preference normally observed for these aldehydes.[26]

An advantage of the homochiral primary aldol products **9** → **12** *is that, in all cases, the greater portion of the pyranosidic residue, particularly the valuable anomeric center, remains intact and available for further chemical manipulations.* The C3 carbonyl is a particularly valuable asset, as our work involving the spiro-Claisen rearrangement has shown.[27] With regard to its reduction, the equatorial or axial C3-OH, **13** and **14**, respectively, can be obtained as the overwhelming product, depending on the hydride reagent used. With lithium aluminum hydride, the result can be rationalized by postulating that the reagent chelates to the C7-OH so that the hydride ion is delivered exclusively from the β-face.

The formation of **9** → **12** indicates that the *pyranosidic core* can be a remarkably stereoselective nucleophile, complementing its traditional role as an electrophile. The basis for anti and syn selectivity (**9** vs. **11**) is intriguing and will be clarified by experiments that are currently underway.

Supplementary Material Available: Structures and tables listing details of the X-ray analyses of **8** and **12** (23 pages). Ordering information is given on any current masthead page.

(17) Several examples of these are given in ref 2a and 2b.
(18) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920.
(19) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1.
(20) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, 1984; Vol. 3, p 111.
(21) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.
(22) See ref 18 and 19 at pages 25 and 150, respectively.
(23) It is interesting to note that Masamune's concept of "matched and mismatched" pairs[21] is not being observed here. However, it should be noted that the concept was not tested with *E* enolates, such as **2**. Furthermore, the "secondary" chelation postulated in **16** would obviously be a perturbing factor.
(24) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. Anh, N. T. *Top. Curr.* Chem. **1980**, *88*, 145.
(25) McGarvey, G. J.; Kimura, M.; Oh, T.; Williams, J. M. *J. Carbohydr. Chem.* **1984**, *3*, 125.
(26) Jurczak, J.; Pikul, S.; Bauer, T. *Tetrahedron* **1986**, *42*, 447.
(27) Tulshian, D. B.; Tsang, R.; Fraser-Reid, B. *J. Org. Chem.* **1984**, *49*, 2347. Fraser-Reid, B.; Tulshian, D. B.; Tsang, R.; Lowe, D.; Box, V. G. S. *Tetrahedron Lett.* **1984**, *25*, 4579.

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A Short, Efficient Synthesis of Khellinone

Summary: Thermal ring expansion of a furyl-substituted cyclobutenone has been applied to the synthesis of khellinone, a precursor to the antiatherosclerotic furochromone khellin.

Sir: The naturally occurring furochromones isolated from the fruits and seeds of *Amni visnaga L.* have long been known to possess desirable physiological activity.[1] Khellin (**4**) was found to be the most potent of the active constituents, and exhaustive investigations of its clinical and pharmacological properties have been carried out. Particular interest in khellin and its furochromone analogues was renewed by recent findings of their desirable lipid-altering activity, thus making them potential antiatherosclerotic agents.[2,3] As a result, khellin has become a popular synthetic target, and remains as such as the objective of the work described here.[4]

In this paper we wish to report a six-step synthesis of khellinone (**12**) in 52% overall yield starting with diethyl squarate. This constitutes a very efficient synthesis of khellin since it has previously been shown to be directly available from khellinone in 85% yield.[4c] A key strategy

(1) The active ingredients of the khellah plant were used by the ancient Egyptians as an antispasmodic agent.
(2) For a summary of early studies on furochromones, see: Mustafa, A. *Furopyrans and Furopyrones*; Wiley-Interscience: New York, 1967; pp 102–159.
(3) Gammill, R. B.; Day, C. E.; Schurr, P. E. *J. Med. Chem.* **1983**, *26*, 1672 and references therein.
(4) For recent khellin syntheses, see: (a) Gammill, R. B.; Hyde, B. R. *J. Org. Chem.* **1983**, *48*, 3863. (b) Gammill, R. B. *Tetrahedron Lett.* **1985**, *26*, 1385. (c) Yamashita, A. *J. Am. Chem. Soc.* **1985**, *107*, 5823.

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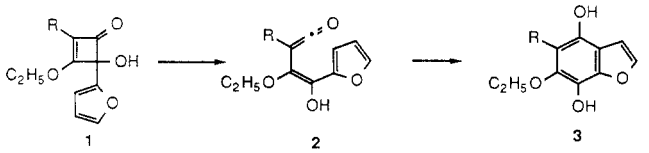
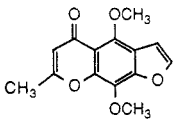
Scheme I



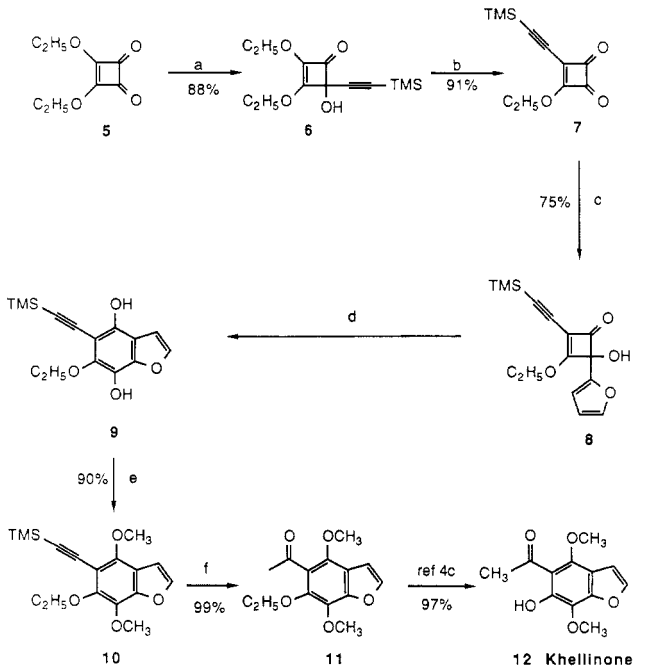


4 Khellin

in the synthesis reported here takes advantage of the facile ring expansion of 4-aryl-substituted cyclobutenones to annulated hydroquinones via conjugated ketene intermediates, a reaction we have found to generally proceed in very high yield and to have a wide synthetic scope.[5,6] Specifically, construction of the fully substituted aromatic B ring of khellinone was envisaged to arise via this ring expansion reaction as outlined in Scheme I starting with **1** (R = acyl or equivalent group). That is, thermolysis of an appropriately functionalized 3-ethoxy-4-furyl-4-hydroxycyclobutenone **1** would give the desired benzofuran **3** via electrocyclic ring closure of the conjugated ketene intermediate **2**. The ethoxy derivative was chosen since it has previously been shown to be deethylated to the corresponding phenol upon treatment with boron trifluoride–etherate.[4c] This choice also allowed utilization of commercially available diethyl squarate as the starting material.[7] Initial efforts were directed toward finding the most suitable synthetic equivalent for the acetyl group. For example, although the appropriate dithianylcyclobutanone adduct could be prepared, its thermolysis resulted in a complex mixture of products. Attempts at introducing a more functionalized acyl anion equivalent indicated that addition of 1-lithioalkynes to diethyl squarate proceeded in high yield. With this lead, (trimethylsilyl)acetylene proved to be an ideal reagent since it was introduced easily and could be readily converted to the methyl ketone under mild hydrolytic conditions.

The specific synthetic sequence is outlined in Scheme II. Diethyl squarate (**5**) was converted to the cyclobutenone **6** in 88% yield upon treatment with 1-lithio-2-(trimethylsilyl)ethyne at −78 °C in THF. An ethereal solution of **6** was treated at 0 °C with pyridine and trifluoroacetic anhydride. Aqueous workup generated the unsymmetrical dione **7** as a deep yellow oil in 91% yield after flash chromatography (CH_2Cl_2). The regioselective addition of 2-lithiofuran (1.1 equiv, *n*-butyllithium/THF/−15–0 °C) to the more electron-deficient carbonyl of **7** was accomplished at −100 °C in dilute THF/diethyl ether (1:1). Alcohol **8** was obtained in 75% chromatographed yield (10% ethyl acetate/hexane) as a beige solid (off-white crystals from CH_2Cl_2/hexane, mp 103.5–104.5 °C). Thermolysis of **8** in refluxing toluene (1 h) gave the corresponding hydroquinone **9** This reaction solution was cooled to ambient temperature and treated with CH_3I, K_2CO_3, 18-crown-6 to yield **10** as a pale yellow liquid, isolated in 90% after flash chromatography. Mercury-catalyzed hydrolysis (saturated $HgSO_4$ in 1% H_2SO_4/aqueous THF) converted the (trimethylsilyl)alkynyl moiety to the desired methyl ketone **11**, which was isolated in nearly quantitative yield after chromatography (CH_2Cl_2). This completed a formal synthesis of khellinone (**12**) since selective cleavage of the ethyl ether has been effected in 97% yield by treatment with excess boron trifluoride–etherate in CH_2Cl_2.[4c,8]

Scheme II[a]



[a] Reagents: (a) $Me_3SiC{\equiv}CLi$, THF; (b) TFAA, pyridine, ether; (c) 2-lithiofuran, THF/ether; (d) toluene reflux, 1 h; (e) MeI, K_2CO_3, 18-crown-6; (f) $HgSO_4$, H_2SO_4, THF.

This efficient synthesis of khellinone from commercially available starting materials was accomplished in 52% overall yield.[9] The highly convergent nature of this methodology should facilitate synthesis of analogues, especially through substitution or replacement of the furan ring. Utilization of this thermolytic ring expansion toward other naturally occurring target molecules is presently under way.

Acknowledgment. We thank the National Institutes of Health (CA-11890 and GM-36312) for financial support of this work.

(5) (a) Perri, S. T.; Foland, L. D.; Decker, O. H. W.; Moore, H. W. *J. Org. Chem.* **1986**, *51*, 3067. (b) Moore, H. W.; Decker, O. H. W. *Chem. Rev.* **1986**, *86*, 821.

(6) (a) The ring expansion has been successfully used in a formal synthesis of nanaomycin A and deoxyfrenolicin; see: Decker, O. H. W.; Moore, H. W. *J. Org. Chem.* **1987**, *52*, 1174. (b) For comparison, see ref 4c for a very interesting synthesis of khellin via a chromium carbene complex and: Semmelhack, M. F.; Keller, L.; Sato, T.; Spiess, E. J. *J. Org. Chem.* **1985**, *50*, 5566 for a related synthesis of nanaomycin A and deoxyfrenolicin.

(7) Available from Aldrich Chemical Company. Also, it is readily prepared by treatment of a solution of squaric acid in ethanol with gaseous HCl.

(8) A sample of khellinone was prepared according to the method described by Y. Yamashita (ref 4c) and shown to be identical with an authentic sample. We are grateful to Dr. Yamashita for providing us with a sample of khellinone.

(9) The highest previously reported yield to khellinone is 12% (ref 4a).

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