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A VERSATILE TOTAL SYNTHESIS OF XENOGNOSIN

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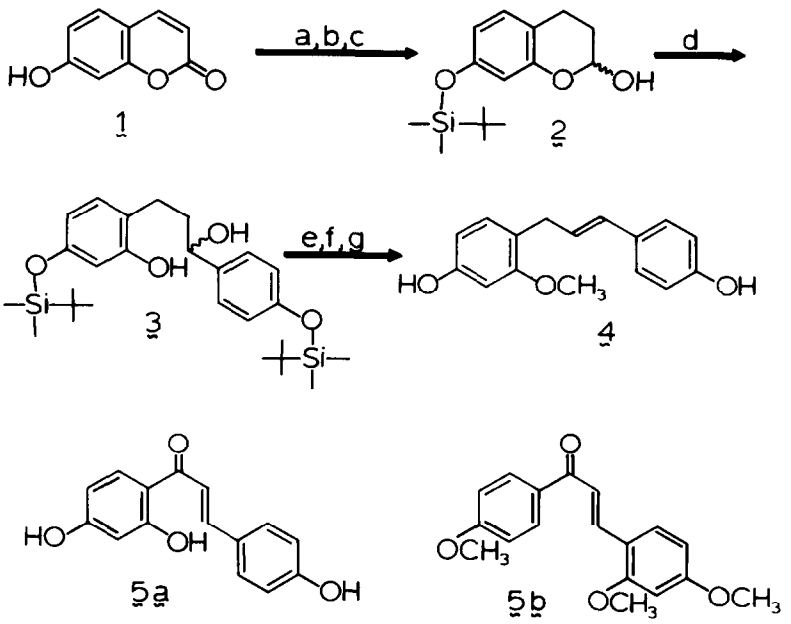
Abstract: Xenognosin, 4, the first identified host recognition substance for parasitic angiosperms has been synthesized by a route efficient for the preparation of several structural analogues.

Parasitic angiosperms are parasites which attack their hosts through the development of a specialized organ known as an haustorium.[1] Host recognition in the parasite Agalinis purpurea has been shown to be at the level of haustorial initiation[2] and we have been able to isolate and characterize xenognosin, 4, as the first host recognition substance for A. purpurea.[3] 2'-Hydroxyformononetin, 6, which co-occurs with xenognosin, has now been isolated as a second haustorial inducing principle for A. purpurea. Formononetin, 7, which also co-occurs with xenognosin, is surprisingly devoid of activity. The substituted meta-methoxy phenol functionality present in the active compounds 4 and 6, and the inactivity of 7, which lacks such functionality, have led us to develop a synthesis of xenognosin which will allow for great flexibility in the number and position of hydroxyl group functionalities.

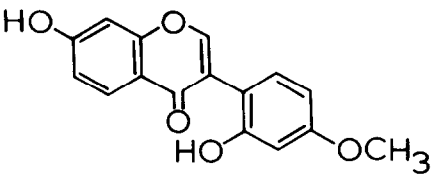
Umbelliferone, 1, a coumarin which occurs naturally in several plants, allows for the necessary synthetic differentiation of the two phenolic hydroxyl groups. Hydrogenation and protection of the free phenol of 1 as the tert-butyldimethylsilyl ether (TBDMS) followed by reduction with diisobutylaluminum hydride (DIBAL) gave the lactol, 2.[4] The completed carbon skeleton is accessible through the reaction of 2 with the Grignard reagent formed from the TBDMS protected p-bromophenol to give 3.[5] Methylation of the phenolic hydroxyl group with CH_2N_2 followed by dehydration of the secondary alcohol and removal of the silyl protecting groups allows for the total synthesis of xenognosin in 39% overall yield. ^{1}H-NMR, MS, and biological activity of the synthetic sample were identical with that of the isolated material.[6]



a. H_2, Pd/C (10%), ethanol, 40 PSI, 24 hr, 95%.
b. TBDMS-Cl, $(C_2H_5)_3N$, DMAP, CH_2Cl_2, 25°, 10 hr, quantitative.
c. 1 eq. DIBAL, toluene, -78°, 2 hr, 95%.
d. p-TBDMS-O-C_6H_4Br, Mg, THF, 25°, 1 hr, 85%.
e. $\overline{C}H_2N_2$, methanol, 4°, 8 hr, 95%.
f. CH_3SO_2Cl, $(C_2H_5)_3N$, THF, 25° 2 hr, 60%.
g. $(C_4H_9)_4NF$, THF, 25°, 0.5 hr, 90%.

The versatility of the synthesis allows for the ready preparation of the analogues 8 a-h.[7] Analogue 8a was prepared from 3 by protection of the phenolic hydroxyl group as the TBDMS ether followed by dehydration and removal of the protecting TBDMS groups. This methodology has greatly aided our ability to investigate the molecular basis for haustorial differentiation and several of the synthetic analogues are still under biological investigation.[8]

In addition, flavones, flavanones, isoflavones, and isoflavanones, which co-occur with coumarins, have been synthesized from an intermediate chalcone such as 5a.[9,10] It was hoped that this intermediate would be accessible from 3 by dehydration and oxidation providing access to the naturally occurring flavanoids such as 6. Unfortunately, all attempted oxidations of 3 gave exclusively the undesired regiochemistry, 5b.[11]



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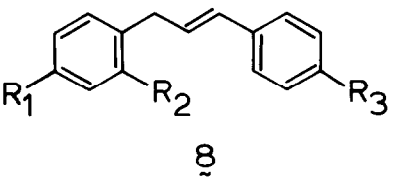

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a) $R_1 = R_2 = R_3 = OH$

b) $R_1 = R_2 = OH$, $R_3 = OCH_3$

c) $R_1 = OCH_3$, $R_2 = R_3 = OH$

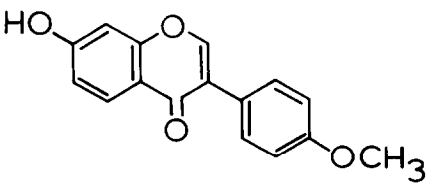
d) $R_1 = R_2 = R_3 = OCH_3$

e) $R_1 = OH$, $R_2 = R_3 = OCH_3$

f) $R_1 = OH$, $R_2 = OCH_3$, $R_3 = H$

g) $R_1 = H$, $R_2 = R_3 = OCH_3$

h) $R_1 = H$, $R_2 = OH$, $R_3 = OCH_3$



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References and Notes

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2. J. L. Riopel, L. J. Musselman, Am. J. Bot., 1979, 66, 570.

3. D. G. Lynn, J. C. Steffens, V. S. Kamat, D. W. Graden, J. Shabanowitz, J. L. Riopel, J. Am. Chem. Soc., 1981, 103, 1868.

4. ^{1}H-NMR, δ ($CDCl_3$) 0.20 (6H, s), 0.95 (9H, s), 1.75-2.0 (2H, m) 2.3-3.0 (2H, m), 5.5 (1H, dd, 3.0 & 6.0 Hz), 6.27 (1H, d, 2.5 Hz), 6.33 (1H, dd, 8.0 & 2.5 Hz), 6.83 (1H, d, 8.0 Hz).

5. ^{1}H-NMR, δ ($CDCl_3$) 0.20 (12H, s), 0.95 (18H, s), 1.7-2.1 (2H, m), 2.6-2.9 (2H, m), 4.5

(1H, dd, 4.0, 8.0 Hz) 6.32 (1H, dd, 8.0 & 2.5 Hz), 6.37 (1H, d, 2.5 Hz), 6.74 (2H, d, 8.0 Hz), 6.9 (1H, d, 8.0 Hz), 7.13 (2H, d, 8.0 Hz).

6. During the preparation of this manuscript we were informed by Professor F. S. El-Feraly of the University of Mississippi that he has completed a synthesis of xenognosin.

7. Sample 8f was obtained by dehydration of intermediate secondary alcohol by treating with p-toluene sulphonic acid in refluxing benzene. Samples 8g and 8h were prepared from the unsubstituted coumarin.

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11. For example, oxidation of 8d with SeO_2 in dioxane gave only 5b (50% after chromatography). Likewise, oxidation of 8g gave the same regiochemistry (70% after chromatography). The regiochemistry of the products was assigned by the deshielding of the aromatic protons ortho to the carbonyl function.

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