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A Novel Case of Cationic Rearrangement Involving a Phenonium Ion

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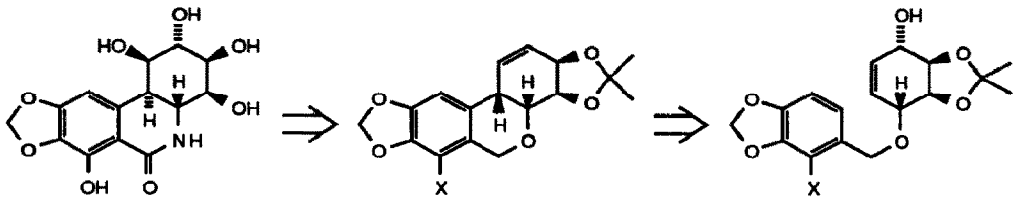
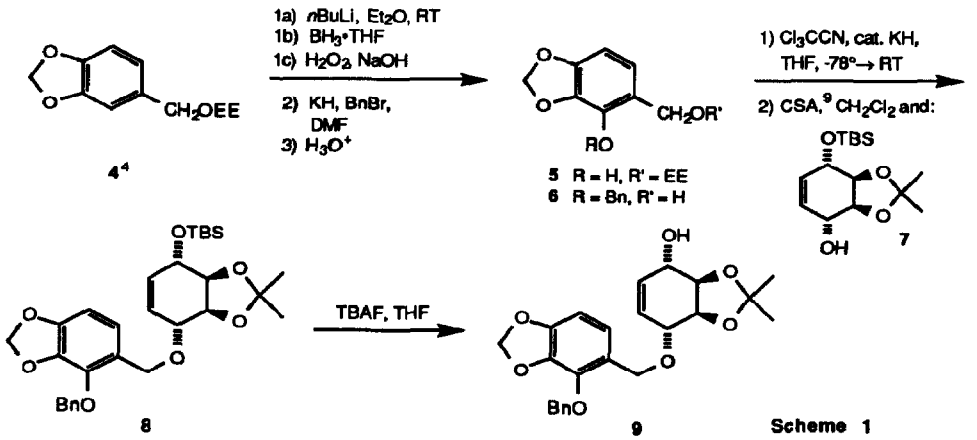
Abstract: A cationic rearrangement was observed in the intramolecular electrophilic substitution of a trioxygenated benzyl ether. The crystal structure of the product is presented.

In the course of synthetic studies on the anticancer agent pancratistatin (**1**),[1] we have examined the possibility of forming the central C-C bond of the target skeleton by intramolecular electrophilic aromatic substitution (**3** → **2**).[2] Our primary concern was the degree of stereoselectivity which might be induced in this cyclization.[3] In this Letter we describe how, under selected conditions, one substrate was converted not to **2** or the *trans*-fused isomer of **2** but instead to a constitutional isomer. The crystal structure of the product is presented and a mechanism for the implicit rearrangement is proposed.



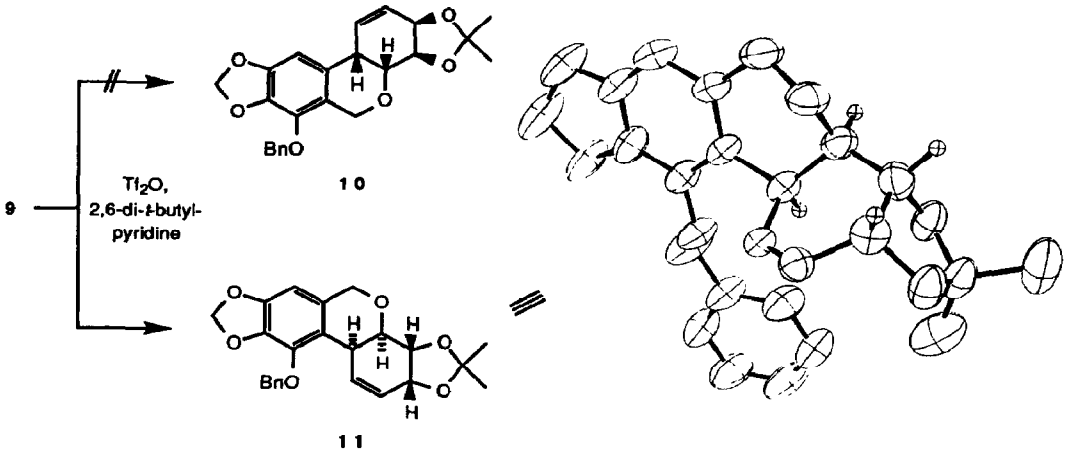
1 Pancratistatin **2** **3**

The substrate for cyclization was prepared as follows. 1-Ethoxyethyl-protected piperonyl alcohol (**4**) was metalated[4] by the action of *n*-BuLi in diethyl ether (0°C → RT). The aryl lithium species was quenched with borane[5] to provide the borohydride, which was in turn cleaved with basic peroxide. From this sequence we obtained an 85% yield of phenol **5**.[6a] The phenol was converted to its benzyl ether (80%)[6a] and the EE group removed by acid hydrolysis (92%) to yield **6**.[6a] Alcohol **6** was coupled to conduritol **7**[6a,7] using trichloroacetimidate methodology (two steps, 23-26% overall).[9] Further optimization of this coupling was envisioned, but postponed pending a satisfactory outcome of the subsequent cyclization step. Ether **8**[6a] was desilylated by TBAF in THF to give alcohol **9**[6a] in 93% yield.

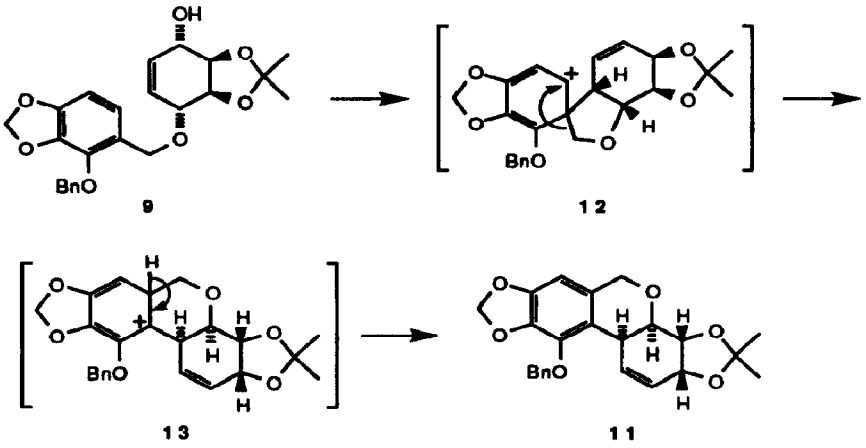


Scheme 1

We attempted to induce cyclization by triflating the free hydroxyl group of **9**. Specifically, exposure of **9** to trifluoromethanesulfonic anhydride and 2,6-di-*tert*-butylpyridine (CH_2Cl_2, 0° → RT) generated a major product (*50%*), the ^1H NMR and MS data of which were consistent with the expected pentacycle **10**. The stereochemistry of the new ring junction was not clear from NMR experiments, so a single crystal X-ray diffraction analysis was undertaken. The result is shown in the Figure below.[10]



A mechanism which explains the formation of pentacycle **11**[6] is shown in Scheme 2. Attack by the electrophilic cyclitol component at the aromatic position ipso to the tethering element appears to be favored over ortho attack. Presumably this is because the positive charge of the resulting phenonium ion (**12**) is stabilized by resonance effects involving two oxygens instead of one.[11] Migration of the alkoxymethyl substituent in **12** followed by loss of the ortho proton would provide **11**.[12]



Scheme 2

The pitfall represented by the transformation of **9** to **11** should be noteworthy to those engaged in or considering a synthesis of pancratistatin or related phenanthridone alkaloids.[1e-j,2] Furthermore the corresponding general reaction, spirocyclization of an *ipso*-activated arylmethyl ether followed by alkoxymethyl migration, may offer significant synthetic utility. It will be instructive to determine with simpler substrates: 1) the necessary degree of ipso vs. ortho activation, 2) the consistency with which an alkoxymethyl group migrates in preference to a series of alternative substituents, and 3) the range of ring sizes which can be prepared.

ACKNOWLEDGMENT

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2. Others have recently described convergent syntheses of (+)-lycoricidine, a less potent but more studied congener of pancratistatin. Each of these syntheses have united aromatic and cyclitol components by an intramolecular Heck coupling. See: (a) Chida, N.; Ohtsuka, M.; Ogawa, S. *Tetrahedron Lett.* **1991**, *32*, 4525-4528; *J. Org. Chem.* **1993**, *58*, 4441-4447. (b) Hudlicky, T.; Olivo, H. F. *J. Am. Chem. Soc.* **1992**, *114*, 9694-9696. (c) Su, L.; Johnson, C. R. Thirty-third National Organic Chemistry Symposium, Bozeman, Montana, June, 1993, abstract #A-119. See also: (d) McIntosh, M. C.; Weinreb, S. M. *J. Org. Chem.* **1993**, *58*, 4823-4832.
3. Structure **2** possesses the same skeleton and stereochemistry as a late-stage intermediate in the Danishefsky-Lee synthesis of pancratistatin (ref. 1e). We therefore expect the conversion of **3** to **2** to facilitate the development of a concise formal synthesis of pancratistatin. This advantage is not obtained when the central C-C bond is formed by a Heck reaction (ref. 2).
4. Napolitano, E.; Giannone, E.; Fiaschi, R.; Marsili, A. *J. Org. Chem.* **1983**, *48*, 3653-3657.
5. Thorpe, F. G.; Pickles, G. M.; Podesta, J. C. *J. Organomet. Chem.* **1977**, *128*, 305-312.
6. (a) This structure is consistent with ^{1}H NMR, IR, and MS data. (b) This compound gave a satisfactory elemental analysis.
7. This alcohol was prepared in two steps (99%) from optically active conduritol A acetonide acetate.[8]
8. (a) Johnson, C. R.; Plé, P. A.; Adams, J. P. *J. Chem. Soc., Chem. Commun.* **1991**, 1006-1007. (b) Dumortier, L.; Liu, P.; Dobbelaere, S.; Van der Eycken, J.; Vandewalle, M. *Synlett* **1992**, 243-245.
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10. X-ray quality crystals of **11** formed upon concentration of a 1:4 ethyl acetate/hexane solution. A crystal of dimensions 0.71 x 0.54 x 0.51 mm was selected for analysis. The intensity data were collected on a Syntex diffractometer using the omega scan mode. Compound **11** crystallizes in the monoclinic P21 space group with cell dimensions a = 7.2210(20)Å, b = 16.122(4)Å, c = 8.8700(20)Å, beta = 94.600(20) and cell volume V = 1029.29Å^3. The formula weight of **11** is 408.45; the calculated density is 1.318 g/cm^3. For 1761 significant reflections, R_f = 0.051, R_w = 0.056, and GoF = 1.787.
11. For a discussion of spirocyclizations involving phenonium ions, see: (a) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*; 3rd ed., Harper and Row, Inc.: New York. 1987; pp. 434-448. For electronically similar cyclizations directed by oxygen substituents, see: (b) Lombardo, L.; Mander, L. N.; Turner, J. V. *J. Am. Chem. Soc.* **1980**, *102*, 6626-6628. (c) Nicolaou, K. C.; Zipkin, R. E. *Angew. Chem., Intl. Ed. Engl.* **1981**, *20*, 785-786.
12. Preferential migration may be due to an ability of the alkoxymethyl oxygen atom to stabilize positive charge by a conjugative effect. A similar influence operates in the solvolysis of alkoxymethyl halides. See: Streitweiser, A. Jr. *Solvolytic Displacement Reactions;* McGraw-Hill: New York. 1962; pp. 102-103. Another analogy can be found in the rearrangement of 3,3-disubstituted indolenines to 2,3-disubstituted indoles. The migrations involved here can be directed by oxygen or nitrogen. See: Jackson, A. H.; Smith, A. E. *Tetrahedron* **1968**, *24*, 403-413; Jackson, A. H.; Smith, P. *Tetrahedron* **1968**, *24*, 2227-2239; Biswas, K. M.; Jackson, A. H. *Tetrahedron* **1969**, *25*, 227-241.

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