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Communications

Synthesis of the Trioxa-Tricyclic Subunit of Saponaceolides via 2-Furyl Ketone Oxidation-Rearrangement

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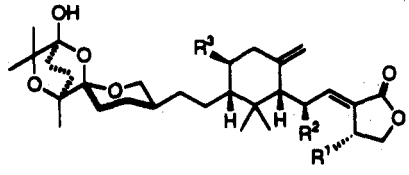
Summary: The inherent stereochemistry of the C_2 oxidized spiroketal 4 has been used to synthesize the tricyclic spiroketal subunit of the saponaceolides.

The saponaceolides (**1a-d**) are a series of fungal metabolites recently isolated from *Tricholoma saponaceum*, a mushroom species commonly found in the northern forests of Italy.[1] These triterpenoids display high in vitro



R^1	R^2	R^3		
OH	H	H	saponaceolide A	1a
H	H	H	saponaceolide B	1b
OH	OH	H	saponaceolide C	1c
OH	H	OH	saponaceolide D	1d

anticancer activity on human colon cell lines and contain a unique oxygenated tricyclic spiroketal subunit, thus presenting an interesting synthetic problem. Examination of the paper describing the structure elucidation of saponaceloide A revealed that the ORTEP-generated structure of the metabolite may be easily misinterpreted by viewing the authors' drawn structure. This has been resolved,[2] and the correct absolute stereochemistry of the metabolites is as shown here.

We have recently reviewed the different synthetic strategies toward spiroketal ring formation and the subsequent chemistry thereof.[3] With few exceptions,[4] the most common strategy used in complex spiroketal synthesis involves the construction of a fully functionalized acyclic precursor prior to spirocyclization. This strategy does not make use of the steric and stereoelectronic biases present in spiroketals and does not explore the possibility of using these biases to direct additional functionalization and manipulation. Research in our group has focused on the development of this untapped potential and begins with the synthesis of a 1,7-dioxaspiro[5.5]undecane-type spiroketal via the oxidation of an appropriately substituted 2-furyl ketone[3b] (Scheme I). Two possible structures for **3** are the syn and anti isomers, both with spiro centers having the preferred bis-axial C-O conformation. The thermodynamically favored isomer will probably be substituent-dependent and thus sets the stage for influencing further transformations. This approach has already been utilized to synthesize the spiroketal substructure of the aplysiatoxins,[5] and it was our desire to adapt this meth-

(1) (a) De Bernardi, M.; Garlashelli, L.; Gati, G.; Vidari, G.; Vita-Finzi, P. *Tetrahedron* **1988**, *44*, 235. (b) De Bernardi, M.; Garlashelli, L.; Toma, L.; Vidari, G.; Vita-Finzi, P. *Tetrahedron* **1991**, *47*, 7109. Geraci, C.; P. Iattelli, M.; Tringali, C. *Magn. Reson. Chem.* **1991**, *29*, 603.

(2) Personal communication with Prof. Giovanni Vidari. We thank Prof. Vidari for his assistance in this matter.

(3) (a) Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617. (b) Perron, F.; Albizati, K. F. *J. Org. Chem.* **1989**, *54*, 2044. (c) Vaillancourt, V.; Pratt, N. E.; Perron, F.; Albizati, K. F. The Total Synthesis of Spiroketal-Containing Natural Products. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley: New York, 1992; Vol. 8, pp 533-691.

(4) (a) Ireland, R. E.; Daub, J. P. *J. Org. Chem.* **1983**, *48*, 1303 and 1312. (b) Deshong, P.; Waltermire, R. E.; Ammon, H. L. *J. Am. Chem. Soc.* **1988**, *110*, 1901. (c) Ireland, R. E.; Wipf, P.; Miltz, W.; Vanasse, B. J. *J. Org. Chem.* **1990**, *55*, 1423.

(5) Stolze, D.; Perron-Sierra, F.; Albizati, K. F. *Tetrahedron Lett.* **1991**, *32*, 4081.

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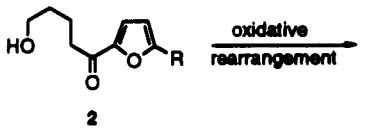
Scheme I



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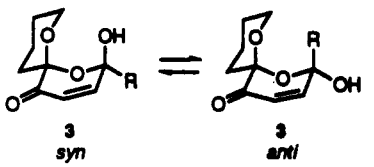
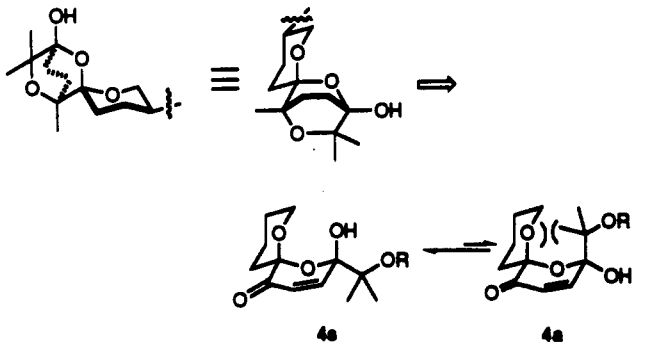
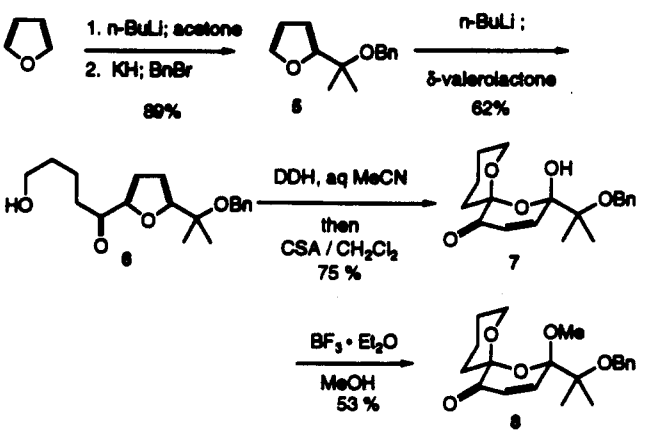


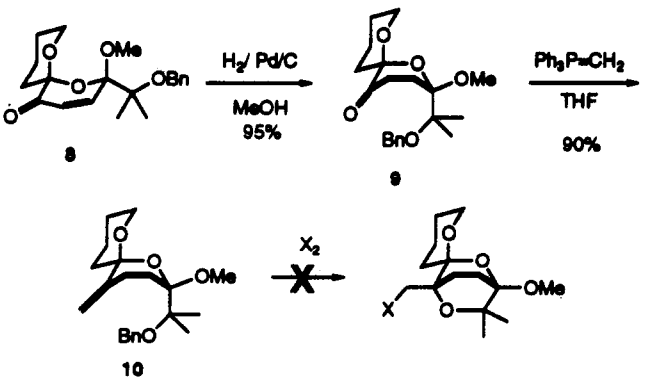
Scheme II



Scheme III



Scheme IV



odology to a model synthesis of the saponaceolide trioxatricyclic ring array.

We envisioned spiroketal **4s** with its syn stereochemistry as an appropriate precursor to the desired target (Scheme II). The required syn relationship is opposite that of previous spiroketals studied in our laboratory in which the major stereoisomer was found to have an anti relationship.[6] However, the desired syn relationship of **4s** seemed obtainable due to the unfavorable steric interactions that would be imposed by the *gem*-dimethyl groups in the anti configuration, **4a**. Thus, our first synthetic goal was to prepare the functionalized spiroketal **4** in which this important stereochemical relationship could be closely examined (Scheme III). Furan **5** was synthesized in good yield by deprotonation, addition to acetone, and protection as the benzyl ether.[7] Lithiation of **5** with n-BuLi and inverse addition to δ-valerolactone afforded furyl ketone **6** in 62% yield. Oxidation of **6** was effected by addition of 2 equiv of 1,3-dibromo-5,5-dimethyl hydantoin[8] (DDH) in aqueous acetonitrile. CSA-induced ring closure and equilibration in dry methylene chloride afforded hemispiroketal **7** in 75% yield as a 15:1 ratio of diastereomers.[9] NMR experiments were not useful in determining the relative stereochemistry of the major isomer. Therefore, we attempted to immobilize the labile C_2-hemiacetal and obtain a compound suitable for single-crystal X-ray

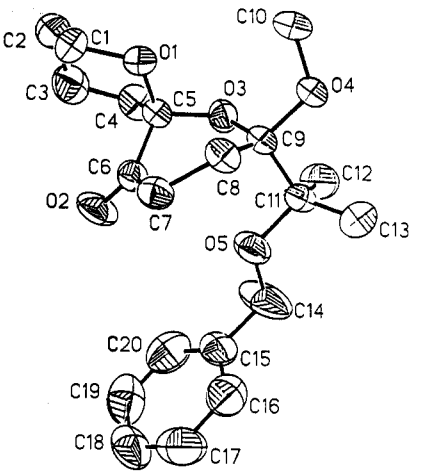
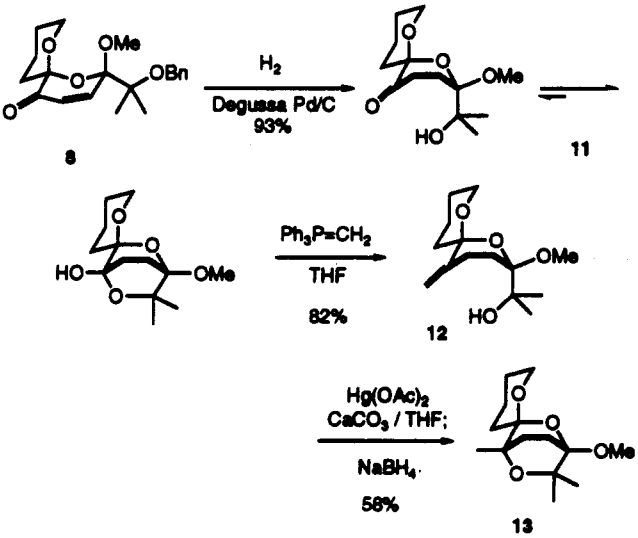


Figure 1

Scheme V



(6) Perron, F.; Ph.D. Dissertation, Wayne State University, 1990, Vol. 1.

(7) All new compounds have been fully characterized by ^1H NMR, ^{13}C NMR, IR, high-resolution mass spectrometry, and combustion analysis.

(8) Walters, T. R.; Zajac, W. W., Jr.; Woods, J. M. *J. Org. Chem.* **1991**, *56*, 316.

(9) This is a slight variation of previously employed oxidations which use NBS in 4:1 THF/H_2O and do not include the CSA closure and equilibration.

analysis. Treatment of 7 with BF_3·Et_2O in methanol at −15 °C gave 8 as a thick oil in 53% yield along with unidentifiable side products. Numerous attempts were made to improve this procedure but none were successful.

Hydrogenolysis (Scheme IV) of enone 8 gave rise to the crystalline ketone 9. X-ray crystallographic analysis revealed a boatlike geometry for the tetrahydropyranone ring of 9 and verified the anticipated syn relationship of the two ketal centers (Figure 1). At this juncture we set out to install the exocyclic methylene to set the stage for inducing electrophile-promoted cyclization with concomitant loss of the benzyl group.[10] Treatment of the hindered ketone 9 with triphenylphosphonium methylide following a procedure by Fitjer[11] afforded olefin 10 in 90% yield. However, 10 proved to be quite acid sensitive, and treatment with I_2, Br_2, or PhSeCl alone or in the presence of basic additives such as Et_3N or bicarbonate resulted in numerous unidentifiable products.

We next examined the removal of the benzyl group prior to cyclization so that milder cyclization methods could be employed. Hydrogenolysis of 8 with wet, Degussa-type Pd/C[12] in EtOAc efficiently removed the benzyl group but did not reduce the enone. Further experimentation showed that subsequent addition of Et_3N followed by MeOH as a cosolvent was needed to provide an efficient one-flask procedure for the formation of ketone 11 (Scheme V). Spectroscopic analysis of 11 showed the compound to exist predominantly in the closed hemiacetal form, clearly foreshadowing a favorable cyclization process. Treatment of 11 with 2.3 equiv of $Ph_3P{=}CH_2$ gave rise to 12 in 82% yield. This compound underwent smooth cyclization to form the targeted model tricycle 13 following a buffered alkoxymercuration–demercuration protocol[13] with $Hg(OAc)_2/CaCO_3$. The ^1H and ^{13}C NMR spectra of 13 closely match those reported in the degradation analysis of the natural sample.

Thus, we have completed a model synthesis of the saponaceolide trioxa-tricyclic subunit. Synthesis of the target molecule 13 was accomplished in eight steps from furan. Further studies on the total synthesis of these metabolites are currently underway.

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Supplementary Material Available: Experimental procedures and compound characterization data (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(10) Rychnovsky, S. D.; Bartlett, P. A. *J. Am. Chem. Soc.* **1981**, *103*, 3963.
(11) Fitjer, L.; Quabeck, U. *Synth. Commun.* **1985**, *15*, 855.
(12) This substance was obtained from the Aldrich Chemical Co.
(13) Reitz, A. B.; Nortey, S. O.; Maryanoff, B. E. *J. Org. Chem.* **1987**, *52*, 4191.