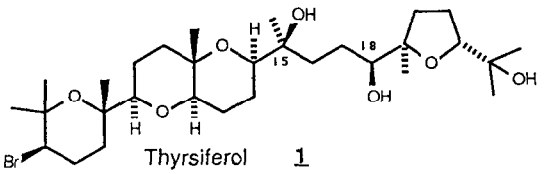
Tetrahedron Letters,Vol.28,No.42,pp 4993-4996,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

SYNTHETIC STUDIES ON THYRSIFEROL

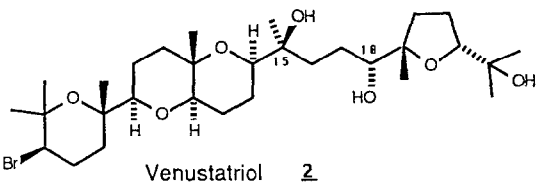
Chris A. Broka*, Linda Hu, Wen Jee Lee, and Tong Shen
University of Illinois at Urbana-Champaign
Department of Chemistry, Roger Adams Laboratory
1209 W. California Street, Urbana, Illinois 61801-3731

Summary: A *mercuricyclization-oxidative demercuration* strategy for construction of the central ring system of thyrsiferol and venustatriol is described.

Thyrsiferol (1)[1], venustatriol (2)[2], and their congeners dehydrothyrsiferol[3] and thyrsiferol 23-acetate[4] are squalene-derived tetracyclic ethers elaborated by red algae belonging to the genus Laurencia.



Thyrsiferol 1

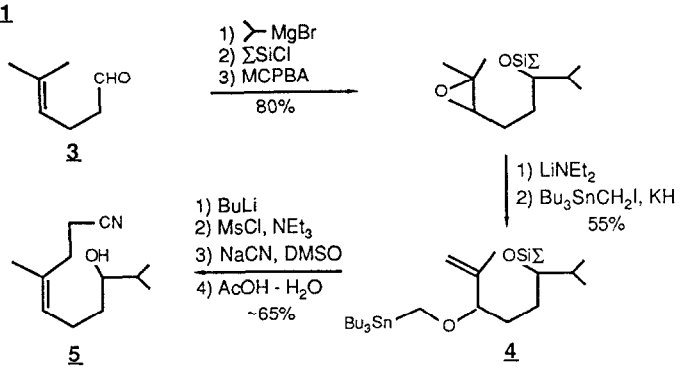


Venustatriol 2

Studies[4] have demonstrated that both thyrsiferol and its 23-acetate are highly cytotoxic. Against P388 lymphocytic leukemia cell lines their ED_{50} values were determined to be 10 ng/ml and 0.3 ng/ml respectively. The recent work[2] which resulted in the isolation of venustatriol and led to the establishment of the correct absolute and relative stereochemistry of thyrsiferol also demonstrated that these compounds possess significant antiviral activity. In addition to their interesting biological activity, these compounds present intriguing synthetic challenges. Many of these involve the central trans-fused pyranopyran ring system which, X-ray structures show, adopts a chair-twist boat conformation so as to avoid a 1,3-diaxial interaction between its angular methyl group and the neighboring side chain. In this report we outline a short, stereoselective approach to this ring system.[5]

The early steps in this approach are shown below (Scheme 1).

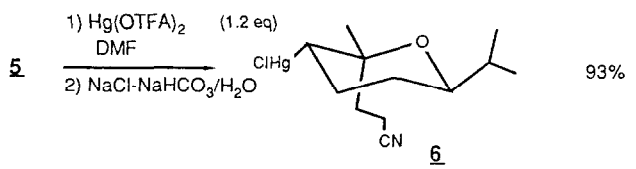
Scheme 1



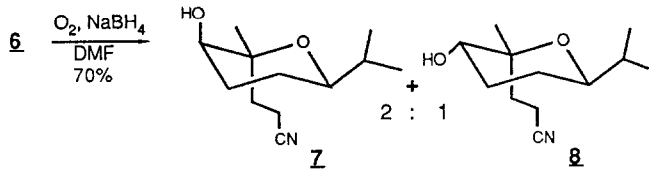
The aldehyde 3[6] was converted to 4 by a straightforward series of reactions which proceeded in 45% overall yield. Treatment of 4 with BuLi (THF, -78° → 0°) gave the rearranged (Z) homoallylic alcohol in accord with the results of Still.[7] NMR failed to reveal any of the (E) isomer and the stereochemistry of the product was inferred on the basis of literature precedent as well as from the ^{13}C chemical shift of the allylic methyl (23.4 ppm) which would have experienced shielding from a compression effect had the product possessed the (E) stereochemistry. Mesylation and treatment with NaCN in DMSO at 70° gave the nitrile which was deprotected under acidic conditions.

We intended to assemble the first tetrahydropyran ring of our target by mercuric ion promoted cyclization of 5. Trisubstituted olefinic alcohols such as 5 are known to undergo mercuricyclization to give tetrahydropyrans in preferences to tetrahydrofurans.[8] In mercury promoted cyclizations where the choice is between formation of tetrahydrofurans and tetrahydropyrans, it is generally the more substituted carbon atom of the double bond (i.e. the one best able to support partial positive charge) which accepts the nucleophile. This is in contrast to the situation which obtains in other electrophilic etherification reactions where exo cyclization is often favored.[9,10]

Treatment of 5 with mercuric trifluoroacetate in DMF (20°, 24 h) followed by quenching of the reaction mixture with buffered aqueous sodium chloride[11] afforded mercurial 6, in excellent yield, as a single stereoisomer. The cyclization evidently proceeds through a chair-like transition state with relative asymmetric induction being provided by the equatorially disposed i-propyl group.



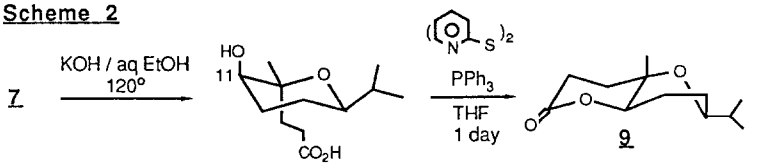
Mercurial 6 was next submitted to Whitesides' oxidative demercuration[12] procedure to obtain the desired 7 along with a smaller amount of 8. These alcohols are easily separated by chromatography.



The stereoselectivity shown by this reaction is perhaps not surprising. The predominant formation of axially substituted products from cyclohexyl radicals has been documented[13] and the tetrahydropyranyl radical generated from 6 apparently behaves in a similar fashion. The unwanted 8 can be converted to 7 by oxidation to the ketone (PCC, CH_2Cl_2, NaOAc) followed by K-selectride reduction although the stereoselectivity of the latter reaction is poor (~1.2:1 in favor of 7). The structure of 7 was verified by a single-crystal X-ray analysis of its benzoate (m.p. 116-117°).

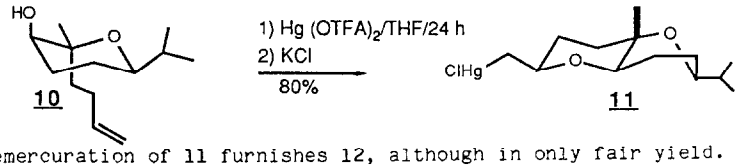
We have developed several methods for constructing the chair-boat pyranopyran ring system from 7. One of these proceeds as follows (Scheme 2).

Scheme 2

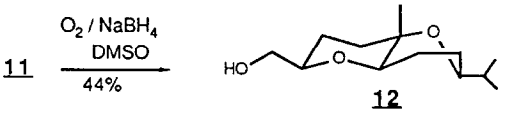


Hydrolysis of the nitrile gave the acid in excellent yield. We attempted to generate the Corey-Nicolaou thiolester[14] by the usual method thinking that it would have to be isolated and lactonized at high temperature in a separate step. In fact, its cyclization proceeded at 20° giving 9 in ~75% yield. Apparently chair-twist boat inter-conversion is a relatively facile process in these tetrahydropyranyl systems.[15] The C-11 proton (thyrsiferol numbering system) of 7 and its derived hydroxyacid appears as a narrow triplet (J = 6 Hz) as would be expected if it is equatorially oriented. The corresponding proton in 9 is a broad doublet of doublets (J = 6, 12 Hz), consistent with the tetrahydropyran ring's having adopted a twist boat conformation.

We have also prepared olefin 10 from 7 (i-TBDMS-OTf, $EtN(i\text{-}Pr)_2$; ii-DIBAL/CH_2Cl_2/-78°; iii-$Ph_3P{=}CH_2$/DMSO/20°; iv-TBAF/THF) (67% overall) and have found that it undergoes a facile mercuricyclization giving 11.



Oxidative demercuration of 11 furnishes 12, although in only fair yield.



We are presently attempting to improve the yield of this last step and to elaborate 12 into a tricyclic system including the leftmost bromotetrahydropyran ring of 1 and 2. Results of our continuing investigations in this area will be reported in due course.

Acknowledgement: We thank the research board of the University of Illinois, Research Corporation, and the donors of the Petroleum Research Fund administered by the American Chemical Society for their support of this work.

References and Notes

1. J. W. Blount, M. P. Hartshorn, T. J. McLennan, M. H. G. Munro, W. T. Robinson and S. C. Yorke, Tetrahedron Lett., 69 (1978).
2. S. Sakemi, T. Higa, C. W. Jefford, G. Bernardinelli, Tetrahedron Lett., 4287 (1986).
3. A. G. Gonzalez, J. M. Arteaga, J. J. Fernandez, J. D. Martin, M. Norte, J. Z. Ruano, Tetrahedron, 40, 2751 (1984).
4. T. Suzuki, M. Suzuki, A. Furusaki, T. Matsumoto, A. Kato, Y. Imanaka, E. Kurosawa, Tetrahedron Lett., 26, 1329 (1985).
5. New compounds, with the exception of several intermediates on route to 6, have been fully characterized by IR, ^{1}H and ^{13}C NMR, and high-resolution mass spectrometry.
6. R. Marbet, G. Saucy, Helv. Chim. Acta. 50, 2095 (1967).
7. a) W. C. Still, A. Mitra, J. Am. Chem. Soc., 100, 1927 (1978). b) W. C. Still, J. H. McDonald III, D. B. Collum, A. Mitra, Tetrahedron Lett., 593 (1979).
8. a) M. L. Milhailovic, D. Marinkovic, N. Orbovic, S. Gojkovic, S. Konstantinovic, Bull. Chim. Soc. Beograd, 45, 497 (1980) and references cited therein.
9. J. E. Baldwin, J. Chem. Soc. Chem. Commun., 734 (1976).
10. P. A. Bartlett in "Asymmetric Synthesis"; Academic Press; Vol. 3, pp. 411-454 (1984).
11. A mildly basic workup is essential in the case of mercurial 6.
12. C. L. Hill, G. M. Whitesides, J. Am. Chem. Soc., 96, 870 (1974) (see also J.-R. Pougny, M. A. M. Nassr, P. Sinay, J. Chem. Soc. Chem. Commun., 375 (1981) and V. Spéziale, A. Lattes, J. Heterocyclic Chem., 16, 465 (1979)).
13. L. Kaplan in "Free Radicals", O. K. Kochi, Ed.; Interscience: New York, 1973; Vol. 2, p. 361.
14. E. J. Corey, K. C. Nicolaou, J. Am. Chem. Soc., 96, 5614 (1974).
15. E. L. Eliel, N. L. Allinger, S. J. Angyal, G. A. Morrison in "Conformational Analysis;" Interscience: New York, 1965; p. 244.

(Received in USA 26 June 1987)