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Acid-Catalyzed Rearrangement of Pyran Derivatives. An Approach to the Stereoselective Synthesis of 1,3-Diol Derivatives

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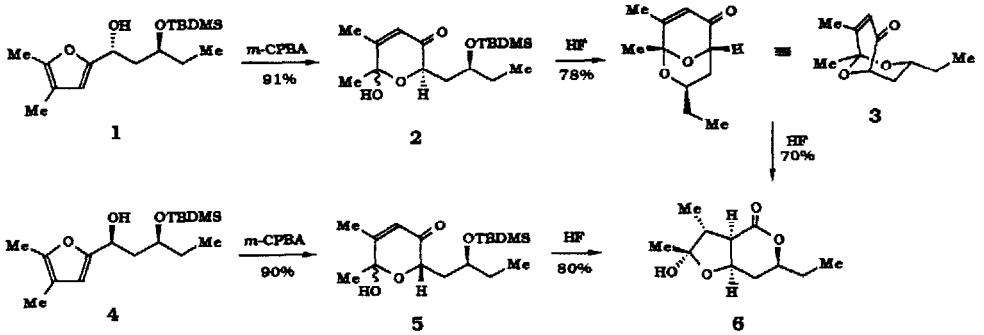
Abstract Peracid oxidation and HF-catalyzed treatment of furfuryl alcohol derivatives affords lactone products arising from a highly stereoselective rearrangement process. The lactones serve as precursors of highly functionalized *anti*-1,3-diol derivatives.

During the studies directed toward the total synthesis of tirandamycin A[1] and the pheromone of the male swift moth *Hepialus hecta L.*[2] it was demonstrated that the 2,6-dioxabicyclo[3.3.1]nonane ring system of the natural products (**3**) could be synthesized by peracid oxidation of *anti*-furfuryl alcohol derivative **1** and subsequent acid-catalyzed ketalization of the resulting pyranone **2** (Scheme 1).[3] To our surprise, oxidation and acid treatment of the diastereomeric *syn*-alcohol **4** afforded bicyclic lactone **6**, rather than the anticipated diastereomeric ketal. Lactone **6** resulted from a novel acid-catalyzed rearrangement of pyranone intermediate **5**. In this Communication, preliminary studies relating to this rearrangement process for pyranone derivatives are reported which demonstrate that both furfuryl alcohol **1** and its diastereomer **4** undergo oxidation-rearrangement in a completely stereoselective manner to yield a single product, lactone **6**. Also, the rearrangement is general for furfuryl alcohol analogues and appears to possess potential as an approach to the stereoselective synthesis of acyclic derivatives (*vide infra*).

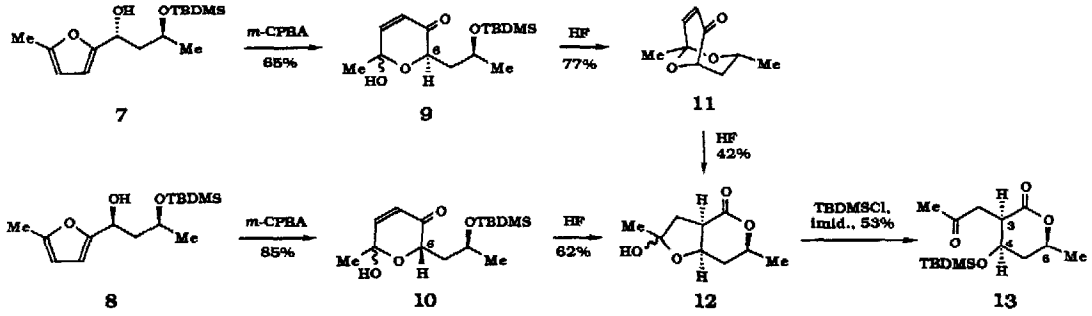
Scheme 1



The generality of the rearrangement process was evaluated initially using the least complex stereochemical system, racemic furfuryl alcohols **7** and **8** (Scheme 2).[4,5] Oxidation of *anti*-alcohol derivative **7**[6] with *m*-CPBA gave pyranone **9**[6] as a mixture of anomers, which underwent intramolcular ketalization in 5% HF-acetonitrile at room temperature to furnish a mixture of bicyclic ketal **11**[6] (77%) and bicyclic lactone **12**[6] (trace). Under identical conditions, *syn*-furfuryl alcohol **8** gave **exclusively** lactone **12** *via* diastereomeric pyranone **10**[5,6] (Scheme 2).

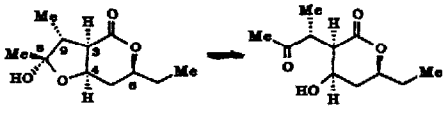
Prolonged exposure of ketal **11** *to 5% HF-acetonitrile resulted in complete rearrangement of the ketal* **11** *to lactone* **12**! Therefore, *irrespective of whether pyranone* **9** *or* **10** *served as the progenitor of lactone* **12**, *a single lactone was obtained from the rearrangement*! Accordingly, the stereocenter at C-6 of the pyranone had undergone epimerization during the rearrangement, and the excellent stereoselectively observed in the rearrangement was controlled **solely** by the distal stereogenic center on the sidechain. Plausible mechanisms for the rearrangement and epimerization at C-6 are discussed below (*vide infra*). The stereochemistry of lactone **12** was established by single crystal X-ray analysis of lactone **13**[6,7] which was synthesized under conditions which do not epimerize the stereogenic center adjacent to the lactone carbonyl.[7]

Scheme 2



Having established that both diastereomers of the furfuryl alcohol system had afforded lactone **12** with complete stereoselectivity, the rearrangement of alcohols **1** and **4** was reinvestigated. Oxidation of alcohols **1** and **4** provided the diastereomeric pyranones **2** and **5**,[5,6] respectively, which underwent HF-catalyzed rearrangement. Lactone **6** was the sole stereoisomer obtained, irrespective of whether pyranone **2** or **5** or bicyclic ketal **3** was the substrate for the rearrangement reaction. The stereochemical relationships in lactone **6** were also confirmed by single crystal X-ray analysis[7] (Scheme 1).

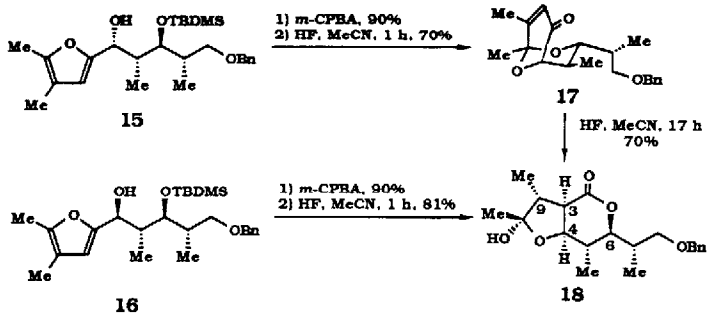
As in the less complex system, lactone **6** possesses the C-3,C-4-*syn*, C-4,C-6-*syn* stereochemical relationship analogous with lactone **12** which indicates that epimerization of C-6 in the pyranone (C-4 in the lactone) has occurred during the rearrangement. The additional stereocenters at C-8 and C-9 of lactone **6** presumably are controlled by post-rearrangement equilibration *via* keto alcohol **14**. Molecular mechanics calculations demonstrate that the relative stereochemistry observed at C-8 and C-9 in lactone **6** constitutes the thermodynamically most stable configuration.[8]



The generality of the rearrangement sequence was also investigated in the stereochemically complex system of furfuryl alcohols **15** and **16**[5,6] (Scheme 3). Oxidation of alcohol **15** and brief treatment with 5% HF-

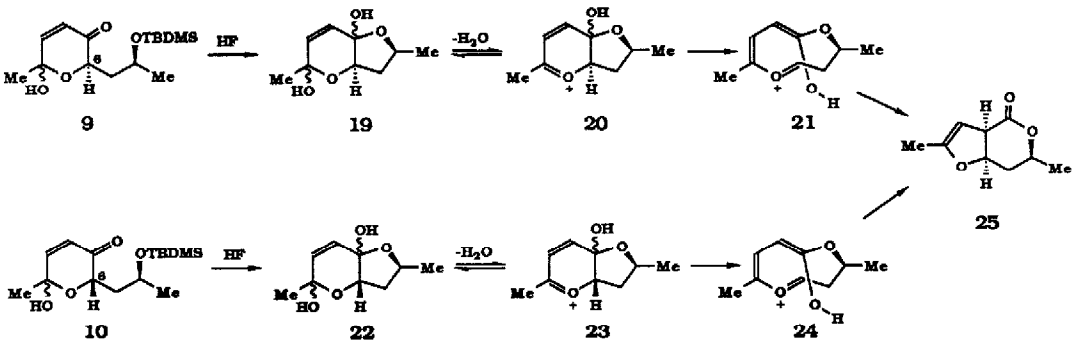
acetonitrile afforded bicyclic ketal **17**[5,6] whose stereochemistry was confirmed by transformation into tirandamycin A.[1] Prolonged exposure of ketal **17** to the acidic conditions, however, resulted in the conversion of ketal **17** to lactone **18**.[5,6] Alternatively, lactone **18** was demonstrated to be the exclusive product obtained from oxidation and rearrangement of diastereomeric furfuryl alcohol **16** (Scheme 3). The relative stereochemistry at C-3, C-4, C-6, and C-9 of lactone **18** is analogous to the systems discussed above. The excellent stereoselectivity observed in this system demonstrates that the two additional stereogenic centers present in alcohols **15** and **16** have no apparent influence upon the stereochemical outcome of the rearrangement.

Scheme 3

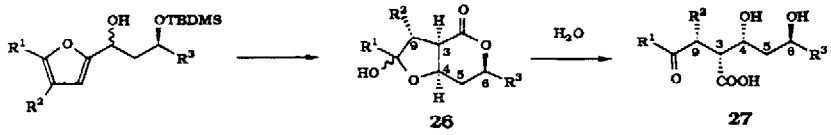


We speculate that the mechanism of the rearrangement occurs as depicted in Scheme 4.[10] Desilylation of pyranone **9** affords hemiketal **19** which dehydrates and undergoes electrocyclic ring-opening[9] to give oxonium ion **21**. Diastereomeric pyranone **10** follows an analogous pathway to generate **24**. Presumably, at this stage the epimerization of the C-6 center in the pyranone occurs.[10] Intramolecular capture of the oxonium ion by enol (**21** or **24**) yields enol ether and establishes the stereochemistry at the two new stereogenic centers. Overman has observed an analogous process in iminium[11] and oxonium[12] ion systems.

Scheme 4



The sequence of reactions comprises a unique approach to the stereoselective synthesis of *anti*-1,3-diol derivatives in which a single existing stereogenic center in the furfuryl alcohol defines the relative stereochemistry at three remote stereogenic centers in lactone **26**. Since lactone **26** is functionally equivalent to diol-acid **27**, we anticipate that this sequence of transformations will serve as the basis of an efficient method for the stereoselective synthesis of *anti*-1,3-diol derivatives in which five contiguous stereogenic centers can be established. Relative stereochemistry at centers C-3, C-4, and C-9 in lactone **26** (or **27**) are controlled by the configuration of the center at C-6 (*vide supra*), while a pre-existing stereocenter at C-5 will



26 27

have no influence on the stereochemistry of the other centers as evidenced by the results shown in Scheme 3. Additional experiments to evaluate the generality of this oxidation-rearrangement sequence are in progress and shall be reported in due course.

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References and Notes

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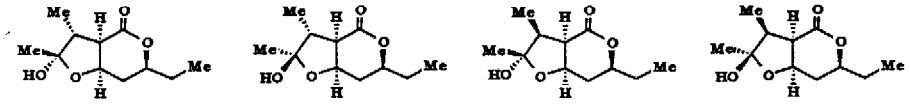
(3) See also Achmatowicz, O., Jr.;Bukowski, P.; Szechner, B.; Zwierzchowska, Z.; Zamojski, A. *Tetrahedron* **1971**, *27*, 1973. Weeks, P. D.; Brennan, T. M.; Brannegan, D. P.; Kuhla, D. E.; Elliot, M. L.; Watson, J. A.; Wlodecki, B.; Breitenbach, R. *J. Org. Chem.* **1980**, *45*, 1109. Hendrickson, J. B.; Farina, J. S. *ibid.* **1980**, *45*, 3359. Piancatelli, G.; Scettri, A.; D'Auria, M. *Tetrahedron* **1980**, *36*, 661. Ziegler, F. E.; Wester, R. T. *Tetrahedron Lett.* **1984**, *25*, 617. Martin, S. F.; Gluchowski, C.; Campbell, C. L.; Chapman, R. C. *Tetrahedron*, **1988**, *44*, 3171.
(4) Preparation of alcohols **7** and **8** was accomplished by condensation (77%) of 2-lithio-5-methylfuran and 3-(*tert*-butyldimethylsiloxy)butanal according to the standard protocol.[1,2]
(5) Pyranones **2/5** and **9/10** exhibited markedly different chromatographic and spectral (IR, ^1H and ^{13}C NMR) characteristics.
(6) All compounds afforded IR, ^1H and ^{13}C NMR, mass spectra, and elemental analysis consistent with the proposed structures.
(7) Single crystal X-ray data for compounds **6**, **13**, and **18** will be reported elsewhere.
(8) Molecular mechanics calculations on diastereomers **6/i-iii** were performed using MacroModel®, v. 2.0, MM2 parameter set. Analogous results were obtained using PC Model® on a Mac II microcomputer, Serena Software, MMX parameter set.



6 3.9 kcal/mole | **i** 6.9 kcal/mole | **ii** 5.8 kcal/mole | **iii** 6.9 kcal/mole

(9) For examples of the analogous electrocyclic process in the aza series see Katritzky A. R.; Rees, C. W. "Comprehensive Heterocyclic Chemistry"; vol. 2A; Pergamon Press; Oxford; 1984; pp. 416-7, and references cited therein.
(10) Alternative mechanisms for the rearrangement and epimerization of the stereocenter at C-6 can be envisioned; however, these alternatives are not consistent with the observation that the epimerization does not involve loss of a proton to the reaction medium; unpublished results, David M. Simpson.
(11) (a) Jacobsen, E. J.; Levin, J.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 4329. (b) Doedens, R. J.; Meier, G. P.; Overman, L. E. *J. Org. Chem.* **1988**, *53*, 685.
(12) (a) Hopkins, M. H.; Overman, L. E. *J. Am. Chem. Soc.* **1987**, *109*, 4748. (b) Herrington, P.M.; Hopkins, M. H.; Mishra, P.; Brown, M. J.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 3711.

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