An Efficient Synthetic Route to (±)-Altholactone *via* Cis-2,5-disubstituted Dihydrofuran

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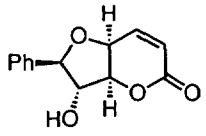
In principle, there are two possible approaches to the synthesis of tetrahydrofuran-based molecules. While one is the construction of properly functionalized acyclic derivatives followed by cyclization,[1] the other is the formation of tetrahydrofuran followed by requisite functionalization. Since more stereocontrolled functionalization can be achieved in a ring system, probably the latter approach is sometimes advantageous depending on the target structures. In this regard we developed the stereoselective routes to 2,5-disubstituted tetrahydrofurans.[2] In this paper we wish to describe the successful application of the second approach to the synthesis of (±)-altholactone **1**[3] using cis-2,5-disubstituted tetrahydrofuran, of which (+)-enantiomer displays cytotoxicity *in vitro* (BS, 9KB) and inhibitory activity *in vivo* against P388 leukemia.[4]



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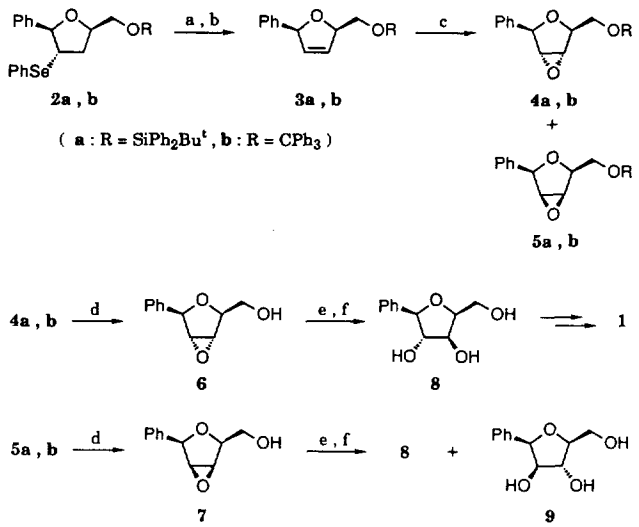
Phenylselenyl ethers **2a** and **2b**[2a] reacted with MCPBA in the presence of potassium carbonate and 3-*t*-butyl-4-hydroxy-5-methylphenyl sulfide (BHMPS), and then the resulting selenoxides were heated at 55℃ to furnish 2,5-dihydrofurans **3a** and **3b** in 74% and 77% overall yield, respectively (Scheme 1).[5] Epoxidation of **3a** with MCPBA in the presence of sodium bicarbonate and BHMPS[6] produced epoxides **4a** and **5a** in 48% yield along with 17% of recovered **3a** after 3 days at room temperature, and in 58% yield at 50℃. On the other hand, 2,5-dihydrofuran **3b** under the same reaction conditions afforded epoxides **4b** and **5b** in 73% yield at room temperature, and in 77% yield at 50℃.[5,7] After chromatographic separation, **4a** and **5a** were treated with tetra-*n*-butylammonium fluoride to provide alcohols **6** and **7** in 96% and 94% yield, respectively. On the other hand, **4b** and **5b** were deprotected with *p*-toluenesulfonic acid in methanolic THF to give **6** and **7** in 91% and 88% yield, respectively.

The next sequence by our original plan was to oxidize **6** to the corresponding aldehyde followed by *cis*-olefination using t-butyl (phosphoranylidene)acetate[8] and acid-catalyzed cyclization. However, much efforts to convert **6** into the desired aldehyde failed, and instead 5-phenyl-2-furaldehyde was obtained as the major product. Accordingly, hydrolysis of the epoxy groups of **6** and **7** was attempted. Epoxides



Reagents: **a**. MCPBA (10 eq.)/K_2CO_3/BHMPS (0.2 eq.)/THF-H_2O (3 : 1)/0℃. **b**. 55℃. **c**. MCPBA (2.5 eq.)/$NaHCO_3$/BHMPS (0.2 eq.)/$ClCH_2CH_2Cl$/RT, 3d or 50℃, 8 h. **d**. **4a**→**6** and **5a**→**7** : *n*-Bu_4NF/aq. THF/RT. **4b**→**6** and **5b**→**7** : *p*-TsOH (1.5 eq.)/THF-MeOH (3 : 1)/RT. **e**. $ZnCl_2$ (0.1 eq.)/HCOOH/RT. **f**. K_2CO_3/MeOH/RT.

Scheme 1.

6 was solvolyzed in formic acid in the presence of zinc chloride[9] and the resulting formates in methanol in the presence of potassium carbonate to furnish only the desired triol **8** in 95% overall yield. The same sequential treatment of **7** produced the desired **8** in 73% overall yield along with 11% of the isomeric triol **9**.[10] Since **8** was already transformed into (+)-altholactone **1**,[3b] our synthetic route to triol **8** corresponds to a formal synthesis of (±)-altholactone.

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References and Notes

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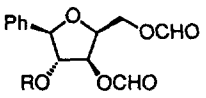
2. (a) S. H. Kang, T. S. Hwang, W. J. Kim, and J. K. Lim, *Tetrahedron Lett.*, **32**, 4015 (1991); **31**, 5917 (1990); (b) *idem*, *Bull. Korean Chem. Soc.*, **11**, 455 (1990).
3. (a) S. H. Kang and W. J. Kim, *Tetrahedron Lett.*, **30**, 5915 (1989); (b) Y. Ueno, K. Tadano, S. Ogawa, J. L. McLaughlin, and A. Alkofahi, *Bull. Chem. Soc. Jpn.*, **62**, 2328 (1989); (c) J. G. Gillhouley and T. K. M. Shing, *J. Chem. Soc., Chem. Commun*, 976 (1988); (d) J.-P. Gesson, J.-G. Jacquesy, and M. Mondon, *Tetrahedron Lett.*, **28**, 3945, 3949 (1987).
4. (a) A. E. El-Zayat, N. R. Ferrigini, T. G. McCloud, A. T. McKenzie, S. R. Byrn, J. M. Cassady, C. J. Chang, and J. L. McLaughlin, *Tetrahedron Lett.*, **26**, 955 (1985); (b) J. W. Loder and R. H. Nearn, *Heterocycles*, **7**, 113 (1977).
5. Carefully controlled reaction conditions were necessary to minimize the formation of 2-alkoxymethyl-5-phenyl-furan.
6. Y. Kishi, M. Aratani, H. Tanino, T. Fukuyama, T. Goto,

S. Inoue, S. Sugiura, and H. Kakoi, *Chem. Commun.*, 64 (1972).
7. Other peroxides including dimethyldioxirane did not produce the desired epoxides cleanly.
8. J. M. Tronchet and B. Gentile, *Hel. Chim. Acta.*, **62**, 2091 (1979).
9. In the absence of zinc chloride the reaction was very slow and did not proceed cleanly. The resulting products were a mixture of **8**, **8a** and **8b** (5 : 30 : 65).



8a: R = H
8b: CHO

10. All new compounds and triol **8** showed satisfactory spectral data.