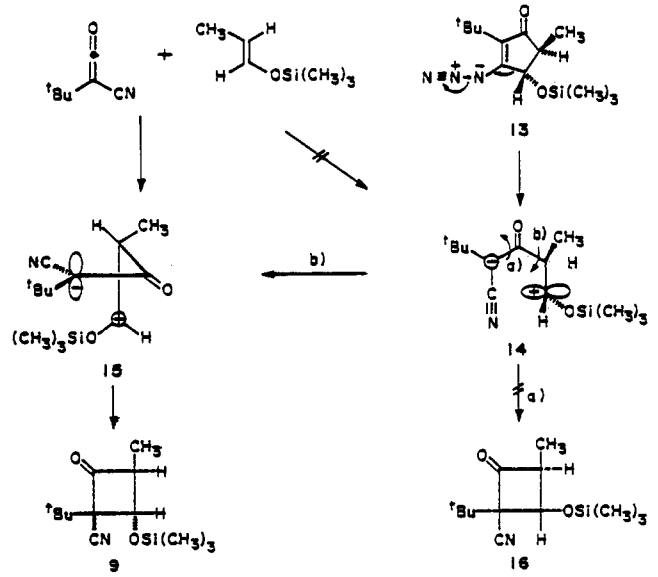
Scheme II



be anticipated. However, it was observed that thermolysis of **13** (80 °C, benzene) gave **9** (91%), the same product obtained in the TBCK cycloaddition itself. As a result, if **14** does result from the thermolysis of **13**, it most likely releases steric interactions and undergoes conformational change to **15** (rotation mode b).[9,10] This then gives **9** upon ring closure. In a comparison experiment the cis isomer of **13** was subjected to thermolysis (80 °C, 30 min) in refluxing benzene. This resulted in **7**, **8**, and **9** (1:1.4:0.12), the same products as are observed when the cycloaddition of TBCK and *cis*-1-(trimethylsiloxy)propene was carried out in refluxing benzene.[11,12]

Taken together, these data provide strong evidence that the TBCK/siloxy enol ether cycloadditions described here are dipolar in character and specifically involve zwitterionic intermediate of structural type **2**. Furthermore, they provide a very important generalization. That is, caution should most certainly be exercized when utilizing one or more of the three experimental criteria noted above as necessarily providing solid evidence for a concerted cycloaddition.

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Registry No. **4**, 6651-34-9; **5**, 96504-33-5; **6**, 96504-34-6; **7**, 96504-35-7; **8**, 96612-31-6; **9**, 96612-32-7; **10**, 96504-36-8; **11**, 96612-33-8; *cis*-**13**, 96504-37-9; *trans*-**13**, 96504-38-0; TBCK, 29342-22-1; *cis*-1-(trimethylsiloxy)propene, 50300-18-0; *trans*-1-(trimethylsiloxy)propene, 39162-68-0; *cis*-(*tert*-butyldimethylsiloxy)propene, 96504-39-1; *trans*-(*tert*-butyldimethylsiloxy)propene, 96504-40-4.

(9) The nonconcerted nature of certain ketene/alkene cycloadditions was further revealed by a secondary kinetic isotope study recently presented by Holder, R. W.; Graf, N. A.; Duesler E.; Moss, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 2929.

(10) A crossover control showed that the azidocyclopentenone **13** was not simply cleaving to TBCK and the enol ether and that these were then undergoing cycloaddition. For example, thermolysis (80 °C) of the 5,5-dimethyl analogue of **13** in the presence of 1 equiv of *cis*-1-(trimethylsiloxy)propane gave a 3:2 mixture of respectively **7** and **5**. Yet when TBCK was generated in the presence of a 1:1 mixture of *cis*-1-(trimethylsiloxy)propene and 1-(trimethylsiloxy)-3-methylpropene, only **7** was observed.

(11) Here, the ketone (TBCK) was generated from the thermolysis (80 °C) of 2,5-diazido-3,6-di-*tert*-butyl-1,4-benzoquinone in the presence of the silyl enol ether.

(12) Becker, D.; Brodsky, N. C. *J. Chem. Soc., Chem. Commun.* **1978**, 237.

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A Stereocontrolled Synthesis of 1,3,5-Tri-*O*-benzoyl-α-D-ribofuranose

Summary: The synthesis of a valuable carbohydrate intermediate, 1,3,5-tri-*O*-benzoyl-α-D-ribofuranose (**4**), has been achieved in a convenient, one-step process from commercially available 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**7**).

Sir: A great deal of interest has developed in the preparation of 2-deoxyfuranosyl nucleosides as a result of their reported antiviral and antitumor activity.[1] Of paramount importance to the synthesis of this series of nucleosides is a preparation of the carbohydrate portion in a manner which allows selective manipulation of the C_2 hydroxyl.[2]

Fletcher and co-workers[3a] during a study of the solvolysis of **3a,b** to **5** (see Scheme I) also obtained another product in 40% yield which was identified as the ortho acid **4'**. The structure of this material was correctly assigned in later work by the same authors[3b,c] as **4**. The four-step method of Fletcher is frequently quoted in the literature as the means of preparing the valuable intermediate **4** in about 40% yield. The mechanism proposed by Fletcher and Ness[3c] (see Scheme II) involves the formation of a 1,2-benzoxonium ion, **6**, which undergoes solvolysis with water.

We have prepared **4** by this method but found the yield varied from 0% to 40% for reasons that were not clear. A study of the solvolysis of **3a,b** to identify the problems associated with this reaction was carried out in acetone-d_6 and D_2O using 360-MHz ^1H NMR to follow the course of the reaction. While the β-bromo sugar **3b** reacted rapidly upon addition of D_2O, the α-bromo sugar **3a** reacted slowly. In the NMR spectrum the anomeric protons are for **3b**, a singlet at 6.7 ppm, **3a**, a doublet at 6.98 ppm, and **4**, a doublet at 6.45 ppm. In another experiment, **3a,b** was prepared in CD_2Cl_2, and then D_2O was added to this reaction mixture with vigorous stirring. NMR monitoring showed that **3b** was consumed in less than 2 h but **3a** was unreacted even after 5 days.

According to the mechanism proposed by Fletcher, it appeared to us that only the β-bromo anomer can form the desired product. Although Hanessian and Pernet[4] were able to prepare the anomerically pure chloro analogue of **3b**, bromination under various conditions gave at best 1:1 mixtures of anomers.

The brominations of either **7** or **2** previously reported were performed in the presence of acetic acid or with a

(1) (a) Watanabe, K. A.; Su, T.-L.; Reichman, U.; Greenberg, N.; Lopez, C.; Fox, J. J. *J. Med. Chem.* **1984**, *27*, 9. (b) Watanabe, K. A.; Su, T.-L.; Klein, R. S.; Chu, C. K.; Matsuda, A.; Lopez, C.; Fox, J. J. *J. Med. Chem.* **1983**, *26*, 152. (c) Wright, J. A.; Taylor, N. F.; Fox, J. J. *J. Org. Chem.* **1969**, *34*, 2632. (d) Su, T.-L.; Klein, R. S.; Fox, J. J. *J. Org. Chem.* **1982**, *47*, 1506.

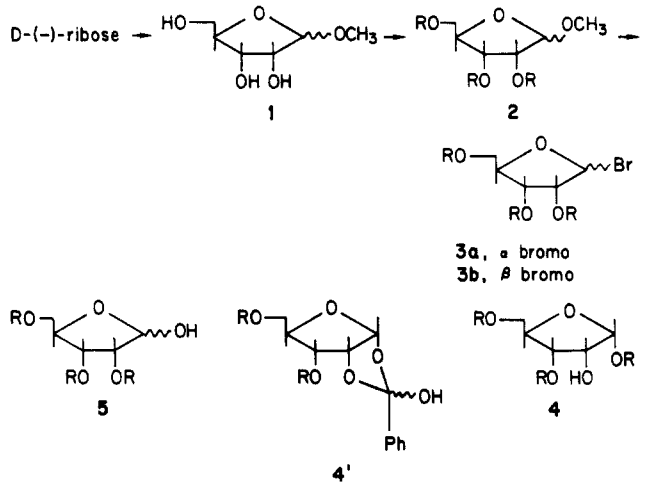
(2) Chavis, C.; Dumont, F.; Wightman, R. H.; Ziegler, J. C.; Imbach, J. L. *J. Org. Chem.* **1982**, *47*, 202.

(3) (a) Ness, R. K.; Diehl, H. W.; Fletcher, H. G. *J. Am. Chem. Soc.* **1954**, *76*, 763. (b) Ness, R. K.; Fletcher, H. G. *J. Am. Chem. Soc.* **1954**, *76*, 1663. (c) Ness, R. K.; Fletcher, H. G. *J. Am. Chem. Soc.* **1956**, *78*, 4710.

(4) Hanessian, S.; Pernet, A. G. *Can. J. Chem.* **1974**, *52*, 1280.

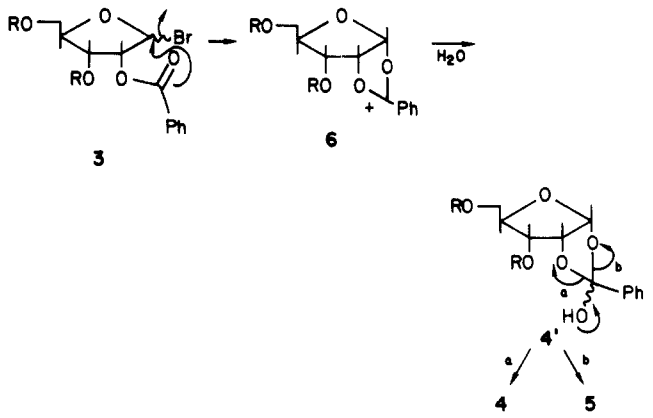
0022-3263/85/1950-2597$01.50/0

Scheme I[a]



[a] R = COPh.

Scheme II

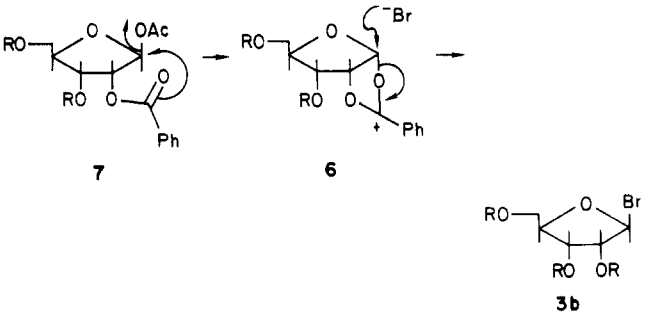


large excess HBr. When we carried out the reaction with 1.1 equiv of HBr in CH_2Cl_2 at 0 °C, the pure β-anomer **3b** was obtained. Using a 0.5 molar solution of HBr in CH_2Cl_2, only the β-bromo anomer was observed to form with 2, 4, or 10 equiv of HBr. However, as reported, a mixture of bromo anomers was obtained when HBr was bubbled directly into a CH_2Cl_2 solution of 8 at 0 °C.

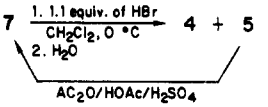
Thus the bromination of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**7**) with 1.1 equiv of HBr in CH_2Cl_2 at 0 °C resulted in a smooth conversion to the β-anomer **3b** as shown in Scheme III. After 1 h, when the bromination was complete, water was added and the two phases were vigorously stirred. Both the bromination and solvolysis were monitored for completion by observing the respective anomeric protons in the NMR spectrum. The crystalline product **4** was obtained in 63% yield by addition of heptane to the dried CH_2Cl_2 solution.[5] The filtrate resulting from the removal of **4** was shown by NMR to contain the mixture of anomers **5**. After removal of the solvent, **5** was recycled to **7** by treatment with acetic anhydride, acetic acid, and sulfuric acid[6] in 78% yield.

The process described in Scheme IV gives an 81% yield of 1,3,5-tri-*O*-benzoyl-α-D-ribofuranose (**4**) with a single recycle of **5**. The material prepared in this manner has been used to prepare 2-substituted sugars and the corresponding nucleosides which will be the subject of a companion paper.[7]

Scheme III



Scheme IV



Registry No. **3b**, 16205-60-0; **4**, 22224-41-5; **5** (α-anomer), 79439-67-1; **5** (β-anomer), 67525-66-0; **8**, 6974-32-9.

(5) This reaction was successfully carried out on a 1.8-mol scale in 50–60% yield by D. G. Mikolasek and L. A. Reif of Chemical Process Development, Bristol-Myers Pharmaceutical Research and Development, Evansville, IN.

(6) Recondo, E. F.; Rinderknecht, H. *Helv. Chim. Acta* **1959**, *42* (121), 117.

(7) Tann, C. H.; Brodfuehrer, P. R.; Brundidge, S. P.; Sapino, C.; Howell, H. G. *J. Org. Chem.*, in press.

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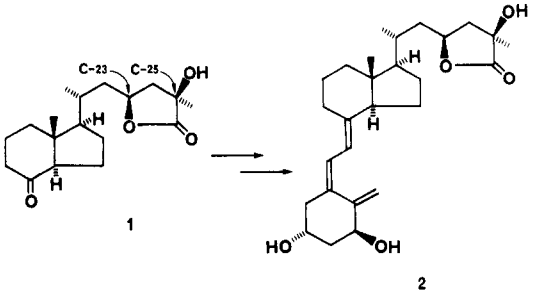
A Highly Stereoselective Route to Calcitriol Lactone[1]

Summary: Keto lactone **1**, the key intermediate for producing the title substance **2**, has been synthesized from the known diol **3** by a highly stereoselective scheme involving chiral acetal methodology (**7** + **8** → **9**) for producing the C-23 center (23*S*:23*R* = 98.5:1.5) and Bartlett iodocyclization methodology (**12** → **13**) followed by hydrolytic inversion (**14** → **15**) for generating the C-25 chiral center (25*R*:25*S* = 93:7).

Sir: The lactone **1**, having six chiral centers, is the key intermediate for the impressive Hoffmann-La Roche–U.C. Riverside synthesis[2] of calcitriol lactone (**2**), a major metabolite of vitamin D_3. This synthesis of **1** suffered only



(1) This paper represents paper 11 in the series "Asymmetric Synthesis via Acetal Templates". For paper 10, see: Johnson, W. S.; Edington, C.; Elliott, J. D.; Silverman, I. R. *J. Am. Chem. Soc.* **1984**, *106*, 7588–7591.

(2) Wovkulich, P. M.; Baggiolini, E. G.; Hennessy, B. M.; Uskokovic, M. R.; Mayer, E.; Norman, A. W. *J. Org. Chem.* **1983**, *48*, 4433–4436.

0022-3263/85/1950-2598$01.50/0