Notes

Enantioselective Synthesis of Optically Active Carbocyclic Sugars

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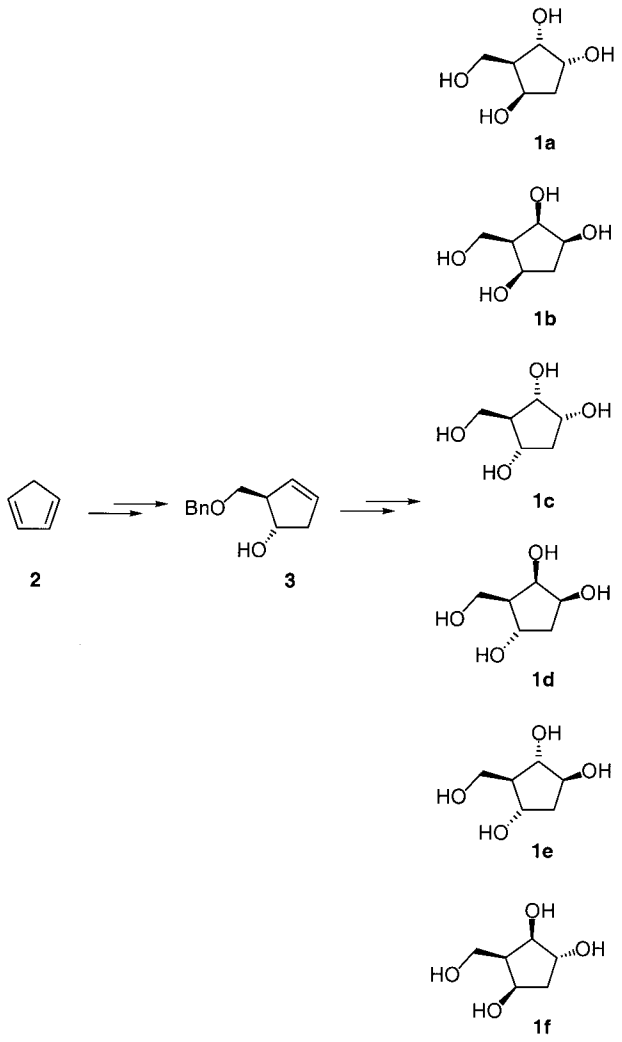
Introduction

Optically active carbocyclic sugars, having various types of biological activity, are important analogues of sugars.[1] These properties can be due to the carbocyclic sugar itself or the incorporation of the carbosugar fragment into other molecules. The presence of carbocyclic sugars in biologically active compounds includes the natural carbocyclic nucleosides such as aristeromycin[2] and neplanocin A,[3] which display antibiotic and antitumor activity. Synthetic carbocyclic nucleosides with important therapeutic properties have also been developed,[4] including carbovir[5] and structurally related compounds.[6]

The most widely used synthetic procedures for the preparation of optically active carbocyclic sugars are (i) modification of abundant optically pure compounds, usually carbohydrates, to the carbosugar structure[7] and (ii) synthesis by modification of achiral or racemic starting materials.[8]

Scheme 1



This paper presents a simple enantioselective approach for the preparation of the optically active carbocyclic sugars **1a**−**f** using cyclopentadiene as the carbon fragment (Scheme 1). All of the stereogenic centers in **1a**−**f** are directed by the two stereogenic centers in **3** introduced by an asymmetric hydroboration reaction of a substituted cyclopentadiene, prepared from cyclopentadiene **2**. It is possible to prepare both enantiomers of the hydroborating reagent used for the preparation of **3**, and thus the other enantiomer of **3** is also easily accessible. Alcohol **3** has been prepared before and is known as a

(1) For a review see, e.g., Crimmins, M. T. *Tetrahedron* **1998**, *54*, 9229.

(2) Kusaka, T.; Yamamoto, H.; Shibata, M.; Muroi, M.; Kishi, T.; Mizuno; K. *J. Antibiot.* **1968**, *21*, 255.

(3) Yaginuma, S.; Muto, N.; Tsujino, M.; Sudate, Y.; Hayashi, M.; Otani, M. *J. Antibiot.* **1981**, *34*, 359.

(4) See, e.g., (a) Jacobs, G. A.; Tino, J. A.; Zahler, R. *Tetrahedron Lett.* **1989**, *30*, 6955. (b) Slusarchyk, W. A.; Young, M. G.; Bisacchi, G. S.; Hockstein, D. R.; Zahler, R. *Tetrahedron Lett.* **1989**, *30*, 6453. (c) Diaz, M.; Ortuno, R. M. *Tetrahedron: Asymmetry* **1997**, *20*, 3421. (d) Ezzitouni, A.; Barchi, J. J., Jr.; Marquez, V. E. *J. Chem. Soc., Chem. Commun.* **1995**, 1345. (e) Biggadike, K.; Borthwick, A. D.; Exall, A. M.; Kirk, B. E.; Roberts, S. M.; Youlds, P. *J. Chem. Soc., Chem. Commun.* **1987**, 1083. (f) Biggadike, K.; Borthwick, A. D.; Exall, A. M.; Kirk, B. E.; Roberts, S. M.; Youlds, P.; Slawin, A. M. Z.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1987**, 255. (g) Morizawa, Y.; Nakayama, T.; Matsumura, Y.; Uchida, K.; Yasuda, A. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2714. (h) Ahmed, S. *Tetrahedron Lett.* **1991**, *32*, 6997. (i) Antle, V. D.; Caperelli, C. A. *Nucleosides Nucleotides* **1999**, *18*, 1911. (j) Comin, M. J.; Pujol, C. A.; Damonte, E. B.; Rodriguez, J. B. *Nucleosides Nucleotides* **1999**, *18*, 2219.

(5) See, e.g., (a) Vince, R.; Hua, M. *J. Med. Chem.* **1990**, *33*, 17. (b) Trost, B. M.; Madsen, R.; Guile, S. D.; Brown, B. *J. Am. Chem. Soc.* **2000**, *122*, 5947. (c) Jones, M. F.; Myers, P. L.; Robertson, C. A.; Storer, R.; Williamson, C. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2479.

(6) See, e.g., (a) Katagiri, N.; Nomura, M.; Sato, H.; Kaneko, C.; Yusa, K.; Tsutuo, T. *J. Med. Chem.* **1992**, *35*, 1882. (b) Hildbrand, S.; Leumann, C.; Scheffold, R. *Helv. Chim. Acta* **1996**, *79*, 702. (c) Daluge, S. M. U.S. Patent 5,034,394, 1991

(7) (a) Horneman, A. M.; Lundt, I.; Søtofte, I. *Synlett* **1995**, 918. (b) Horneman, A. M.; Lundt, I. *Tetrahedron* **1997**, *53*, 6879. (c) Callam, C. S.; Lowary, T. L. *Org. Lett.* **2000**, *2*, 167. (d) Horneman, A. M.; Lundt, I. *J. Org. Chem.* **1998**, *63*, 1919. (e) Johansen, S. K.; Lundt, I. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3615.

(8) (a) Marschner, C.; Baumgartner, Griengl, H. *J. Org. Chem.* **1995**, *60*, 5224. (b) Yakura, T.; Ueki, A.; Kitamura, T.; Tanaka, K.; Nameki, M.; Ikeda, M. *Tetrahedron* **1999**, *55*, 7461. (c) Landis, Y.; Rapado, P. *Eur. J. Org. Chem.* **2000**, 401. (d) Bodenteich, M.; Marquez, V. E. *Tetrahedron* **1992**, *48*, 5961. (e) Desire, J.; Prandi, J. *Tetrahedron Lett.* **1997**, *38*, 6189.

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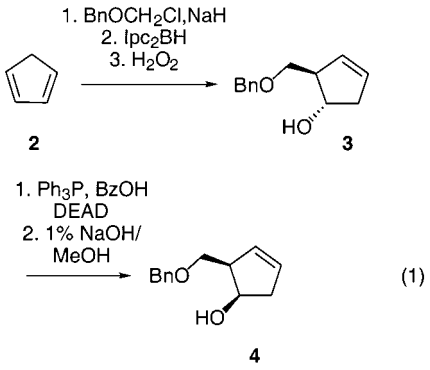
useful intermediate for synthesizing carbosugars and carbocyclic nucleosides.[4f,9]

Results and Discussion

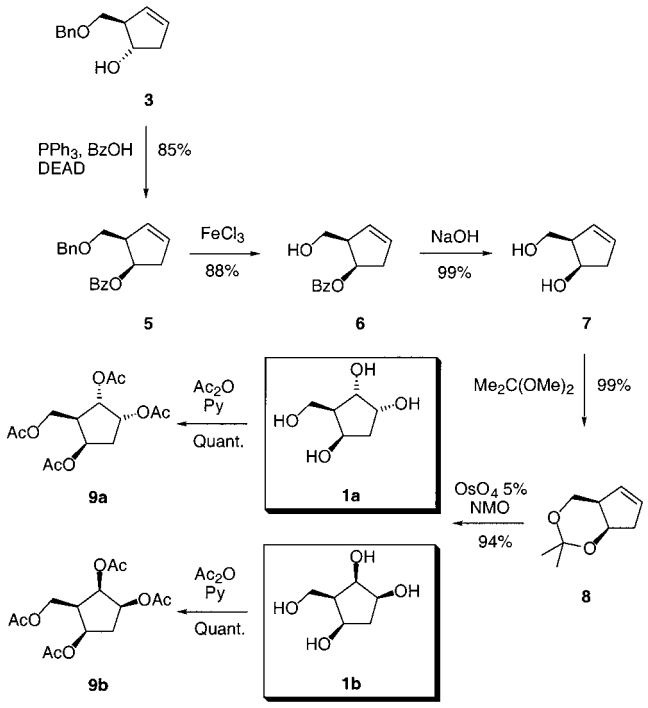
The two key compounds for the present enantioselective appoach of the carbocyclic sugars **1a**−**f** are the alcohols **3** and **4** (eq 1). According to the method developed by Biggadike et al.,[9a] **3** was prepared in multigram quantities by deprotonation of cyclopentadiene with NaH followed by quenching with benzyl chloromethyl ether and then reaction with diisopinocamphenylborane as the asymmetric hydroborating reagent.[9] Oxidative workup gave alcohol **3** having 94% ee, which was converted to alcohol **4** by inversion of the alcohol stereogenic center by the Mitsunobu method in good yield.[10]



(1)

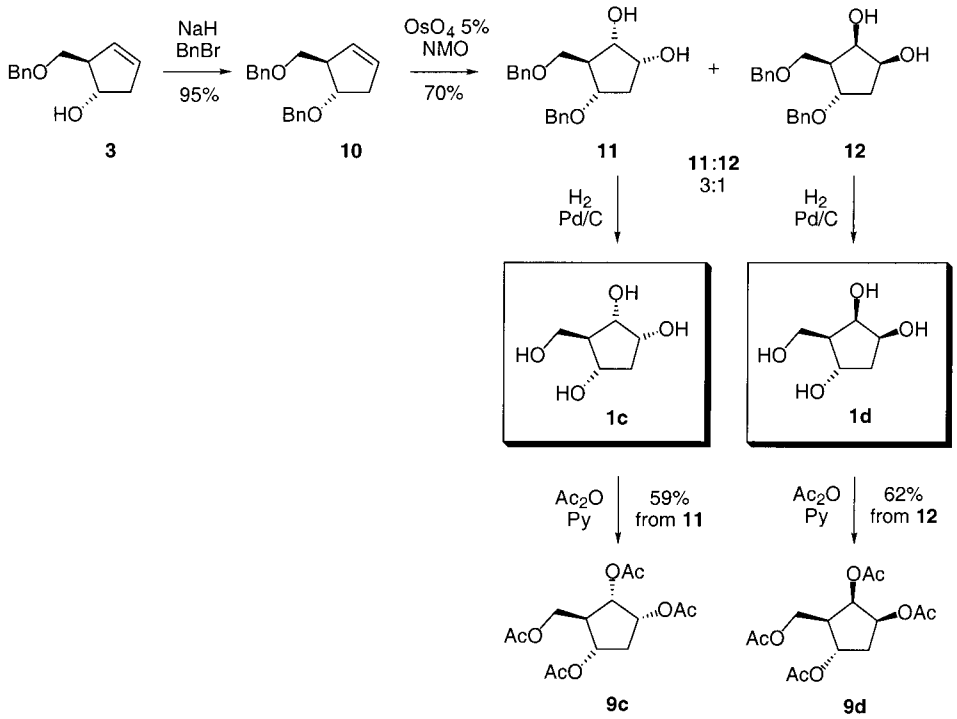
Scheme 2 shows the preparation of the carbosugars **1a** and **1b** from **3**. The first step is the Mitsunobu reaction affording the benzoyl-protected alcohol **5** in high yield. Deprotection of the benzyl group of **5** with $FeCl_3$ gave alcohol **6** in 88% yield. Subsequent removal of the benzoyl group by basic hydrolysis gave the *cis*-diol **7** in quantitative yield. Protection of the diol as the acetal **8** gave the required intermediate for the oxidation reactions. Dihydroxylation of **8** by OsO_4 (5 mol %)/NMO followed by acid hydrolysis of the acetal-protecting group gave a 2:1 mixture of the *anti*- and *syn*-tetraols **1a** and **1b** in a total yield of 94%. Acetylation of the mixture of **1a** and **1b**, quantitatively gave derivatives **9a** and **9b**, which could be separated by flash chromatography. Addition of pyridine to the osmylation reaction improved the *anti*:*syn* ratio slightly (2.5:1), maintaining the high total yield.

Scheme 2

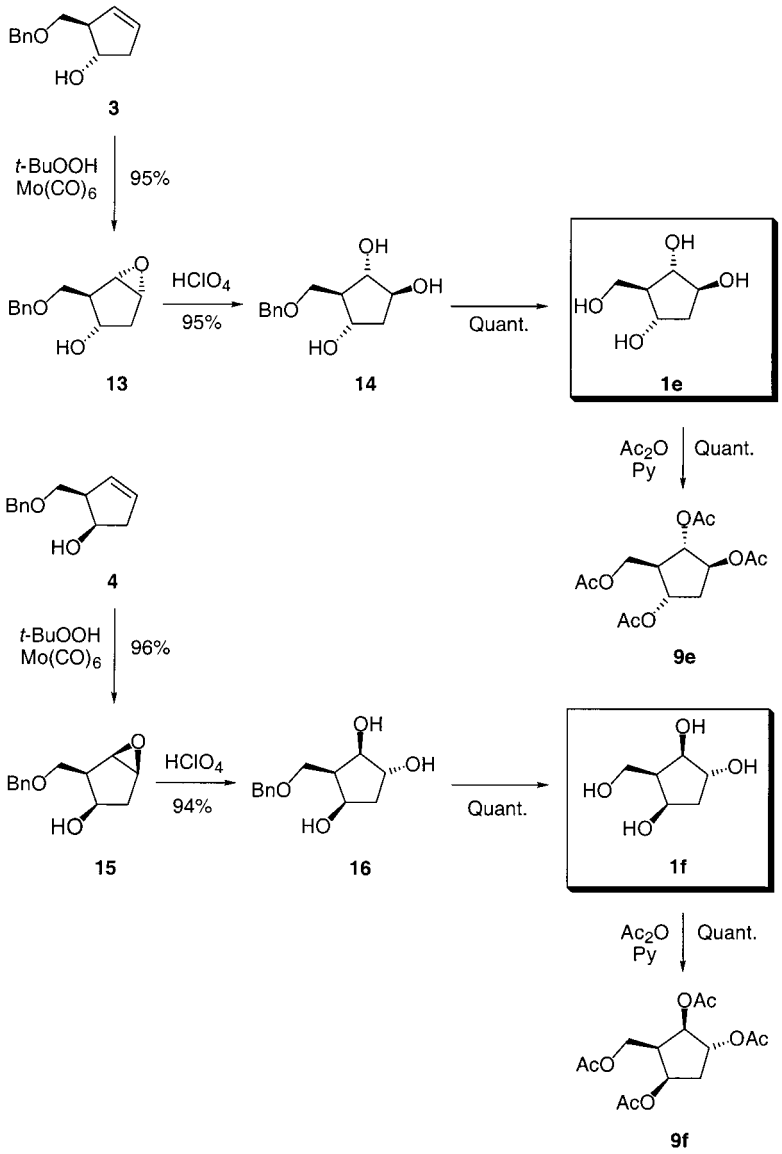


The selectivity in the dihydroxylation of the cyclopentene acetal **8** by OsO_4, giving a 2:1 mixture of the *anti*- and *syn*-tetraols **1a** and **1b**, has been investigated by theoretical calculations. The geometry of **8** was optimized using DFT calculations (BLYP-6-311G**)[11] and is shown

Scheme 3



Scheme 4



in Figure 1. It appears from the structure of **8** that the acetal has a concave face, which discriminates one side of the double bond to attack by one of the hydrogen atoms of the CH_2 group bound to the acetal, as indicated in Figure 1. The formation of **1a** as the major product in the osmylation reaction is thus due to a sheilding of the *syn*-face of the alkene by the CH_2 group of the acetal protecting group. As a result of the small steric bulk of this group, only moderate selectivity is observed. It

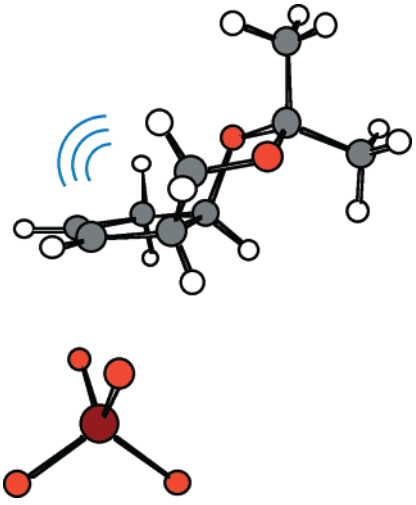


Figure 1. Optimized structure of **8** and suggested approach of OsO_4 *anti* to the CH_2 group of the acetal protecting group. Color code: gray, carbon; white, hydrogen; red, oxygen; brown, osmium.

(9) (a) Biggadike, K.; Borthwick, A. D.; Evans, D.; Exall, A. M.; Kirk, B. E.; Roberts, S. M.; Stephenson, L.; Youds P. *J. Chem. Soc., Perkin Trans. 1* **1988**, 549. (b) Partridge, J. J.; Chadha, N. K.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1973**, *95*, 532. (c) Bisacchi, G. S.; Chao, S. T.; Bachard, C.; Daris, J. P.; Innaimo, S.; Jacobs, G. A.; Kocy, O.; Lapointe, P.; Martel, A.; Merchant, Z.; Slusarchyk, W. A.; Sundeen, J. E.; Young, M. G.; Colonno, D.; Zahler, R. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 127. (d) Ezzitouni, A.; Russ, P.; Marquez, V. E. *J. Org. Chem.* **1997**, *62*, 4870.

(10) Mitsunobu, O. *Synthesis* **1981**, 1.

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should be noted that poor selectivity in osmylation of cyclopentene derivatives has been observed before.[12]

Scheme 3 shows the formation of the carbosugars **1c** and **1d** from the alcohol **3**; the first step being protection of the alcohol giving **10**[5c,9c,d] followed by osmylation leading to the alcohols **11** and **12** (3:1 ratio) in a total yield of 70%. The carbosugars **1c** and **1d** are formed by removal of the protection groups by hydrogenolysis. Acetylation of the mixture of **1c** and **1d**, gave derivatives **9c** and **9d** in high yield, which could be easily separated.

The formation of the carbosugars **1e** and **1f** is outlined in Scheme 4. Alcohol **3** underwent a $Mo(CO)_6$-catalyzed *syn*-directed epoxidation reaction using *t*-BuOOH as the oxidant, giving epoxide **13** in excellent yield.[9a] Opening of epoxide **13** to give **14** was completely regioselective as a result of the benzyl-protected alcohol moiety blocking one of the carbon centers of the epoxide.[13] Deprotection of the benzyl group by H_2-Pd/C proceeded quantitatively, followed by acetylation of the carbosugar **1e** to acetylated product **9e** for easy of purification and characterization.

We were interested to see if *cis*-diol **4** would also undergo the $Mo(CO)_6$-catalyzed *syn*-directed epoxidation reaction. The *cis* stereochemistry of **4** means that because of steric reasons the *syn*-epoxidation may not be favorable. However, it was also thought that the oxygen atom in the benzyl-protected alcohol group may in fact stabilize the cyclic molybdenum transition state. We were pleased to find that the directed epoxidation of **4** proceeded in excellent yield with only the *cis*-epoxide **15** formed. Opening of **15** was less selective than for the opening of epoxide **13** as a result of the *cis*-relative stereochemistry of the benzyl-protected alcohol and the epoxide. However, because of the steric bulk of the benzyl protecting group, when epoxide **15** was treated with $HClO_4$, compound **16** was prepared as a 5:1 mixture of the two diastereomers, which could be separated flash chromatography. Hydrogenolysis and acetylation of **16** gave the desired product **9f** in high yield.

In summary, we have shown that six different optically active carbosugars can be synthesized starting from a substituted cyclopentadiene using an enantioselective hydroboration reaction as the key step by which the first two stereogenic centers are introduced. These are used to direct the formation of the remaining stereogenic centers in the carbocyclic skeleton. The reactions proceed generally in very high yields and stereoselectivity. All experimental details are available as Supporting Information.

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Supporting Information Available: Complete experimental procedure, characterization, and ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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