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Highly diastereoselective Markovnikov hydration of 3,4-dialkoxy-1-alkenes and 4,5-dialkoxy-2-alkenes via a hydroboration–oxidation process

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Abstract

Hydroboration–oxidation of 3,4-dialkoxy- and 3,4,5-trialkoxy-1-alkenes and 4,5-dialkoxy-2-alkenes occurs to give high proportions of the secondary alcohols (Markovnikov hydration) with excellent diastereoselectivity (*anti* to the allylic alkoxide).

Keywords: Markovnikov hydration; diastereoselective hydroboration–oxidation; allylic stereocontrol.

A year ago we reported a very efficient de novo total synthesis of 2-deoxy L-ribose **1** from 1,4-pentadien-3-ol **2** which utilized a Sharpless kinetic resolution to give the epoxy alcohol **3** as the first step (Scheme 1).[1] A three-step conversion of **3** into the 3,4,5-tris(benzyloxy)pent-1-ene **4** set the stage for an *anti*-Markovnikov hydration of **4** via hydroboration–oxidation to give the primary alcohol **5** as the major product in 73% isolated yield. This alcohol was then taken on to **1** in good yield by oxidation of the alcohol and hydrogenolysis of the benzyl ethers. However, we were surprised to find that a large amount (20%) of the hydroboration–oxidation product mixture was the secondary alcohol **6** resulting from the Markovnikov hydration of the alkene **4**. This product was largely (≥5:1) one diastereomer although its stereochemistry was undetermined.[2] We report herein the structure of this compound and the generality of this highly diastereoselective Markovnikov hydration process.

The hydroboration–oxidation of simple 1-alkenes is well known to proceed with very high regioselectivity favoring the *anti*-Markovnikov product even when using the simple and relatively unhindered borane–THF reagent (for example, 1-hexene gives a 94:6 ratio of 1-hexanol to 2-hexanol).[3] The directing effects of allylic or homoallylic substituents have not been well established.[4] Therefore we decided to study first whether the allylic or the homoallylic alkoxy function was the major influence in causing the surprisingly large amount of Markovnikov hydration. Hydroboration–oxidation of 3-benzyloxy-1-pentene **7** afforded nearly exclusively the primary alcohol **8**, the product of *anti*-Markovnikov hydration,

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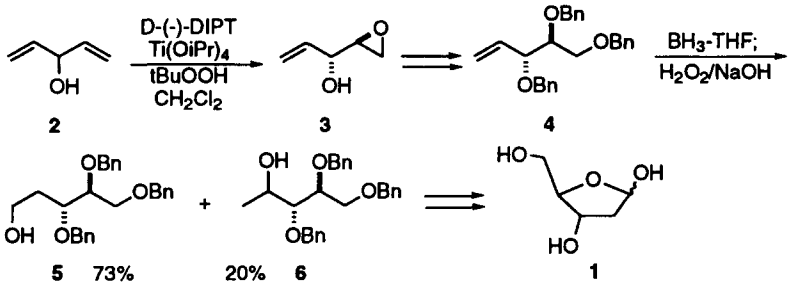
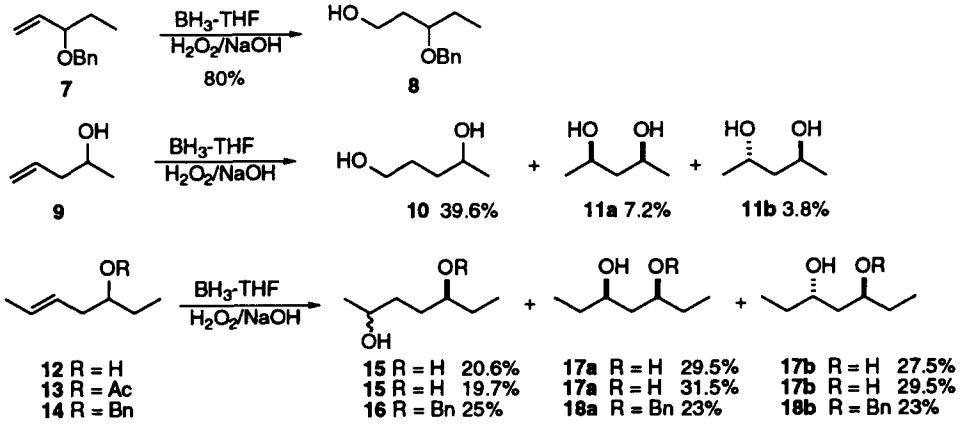


Scheme 1.

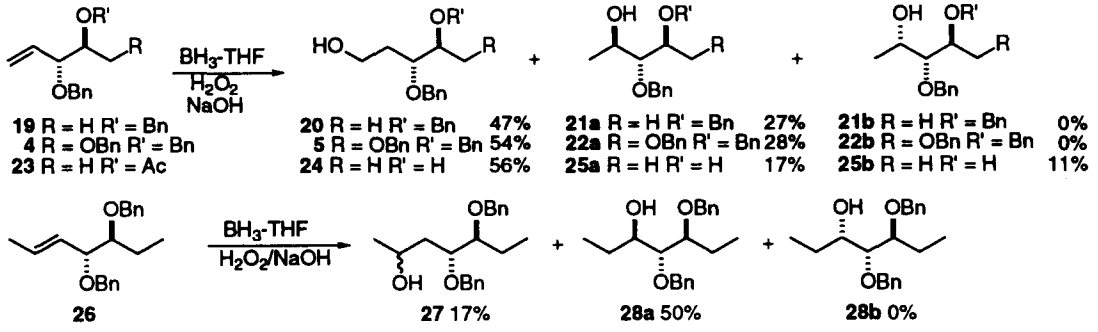
in 80% yield (Scheme 2). Similar reaction of the homoallylic alcohol **9** gave a mixture of the two regioisomeric compounds, the primary alcohol **10** and the two diastereomeric secondary alcohols **11ab**, in yields of 39.6% and 11%, respectively. Therefore the homoallylic function plays the major role in affording proximal oxidation (namely Markovnikov hydration). The ratio of the *syn* and *anti* products was shown to be about 2:1 in favor of the *syn* product **11a**, although the water solubility of these products makes an exact determination somewhat questionable. When the alkene is disubstituted so that there is no Markovnikov vs *anti*-Markovnikov preference, the ratio of the proximal oxidation rises. For example, the three 5-alkoxy-2-heptene substrates, **12**, **13**, and **14**, all give smaller amounts of the distal oxidation products, **15** and **16**, than the proximal products **18** and **19** (cleavage of the acetate occurs during the oxidation step). The diastereomer ratio of the products **15** and **16** was not determined although crude proton NMR showed it to be nearly 1:1. The structures of the diols **11ab** and **17ab** were determined either by comparison of their proton NMR spectra to the known spectra or by spectroscopic analysis of the derived acetonides.[5] In all cases, the ratio of the diastereomers resulting from proximal oxidation (**17ab** and **18ab**) were very nearly 1:1. Thus the homoallylic oxygen functionality is the major influence on the regioselectivity but has essentially no effect alone on the stereoselectivity of the oxidation process.



Scheme 2.

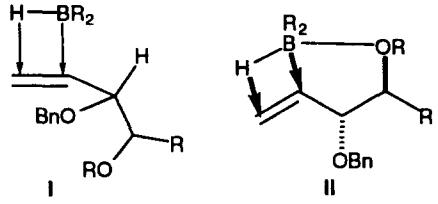
Hydroboration–oxidation of the 3,4-bis and the 3,4,5-tris(benzyloxy)-1-pentenes, **19** and **4**, under our standard conditions afforded a mixture of only two products, the primary alcohols **20** and **5**, in yields of 47% and 54%, respectively, and the *syn* secondary alcohols **21a** and **22a** in 27% and 28% yield, respectively (Scheme 3). No more than a trace of the *anti* alcohols **21b** and **22b** were observed. Thus although the regioselectivity is poor for the secondary alcohols, the diastereoselectivity is extremely high. When the homoallylic benzyl ether of **19** was changed to an acetate, e.g., compound **23**, we now observed a mixture of diastereomeric secondary alcohols, **25ab**, again favoring the *syn*

isomer (17% vs 11%). Thus the benzyl ether is more diastereoselective than the acetate. Again using the corresponding 1,2-disubstituted alkene **26** in which there is no Markovnikov/*anti*-Markovnikov competition, hydroboration–oxidation afforded the *syn* secondary alcohol **28a** from proximal oxidation as the major isomer in 50% yield with only 17% of the distal oxidation product **27** being isolated. Again no more than traces of the *anti* alcohol **28b** were observed. The structures of the alcohols **21a** and **28a** were determined by spectroscopic analysis of the derived benzyl ethers[6] while the structure of the alcohol **22a** was assigned by comparison of the proton NMR of the derived tetra benzyl ether with that of an authentic sample.[7] Thus the combination of both an allylic and a homoallylic oxygen function affords excellent diastereoselectivity for the proximal oxidation product.

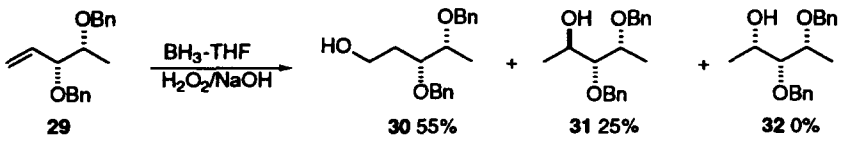


Scheme 3.

In principle, either the allylic or homoallylic oxygen function could be responsible for the observed diastereocontrol. It was most likely that the allylic stereocenter was the dominant stereocontrol element since one would expect the most reactive conformation of the alkene to be that in which the allylic oxygen function was nearly in plane (eclipsed) with the alkene to minimize the inductive electron-withdrawing effect of that function which, if overlapping with the π-bond, would make the alkene less electron-rich and thus less reactive as a nucleophile as shown in **I**.[8] The approach of the borane would then be expected to occur *trans* to the large alkyl group and give mainly the product in which the new alcohol center is *anti* to the existing allylic oxygen functionality. There was also the possibility that the homoallylic oxygen functionality served to complex the borane (displacing the THF) and therefore deliver the reagent intramolecularly to the face *syn* to the homoallylic oxygen function, as in **II**. In order to determine which of these two possibilities were correct, we carried out the hydroboration–oxidation of the *syn* isomer of **19**, namely **29** (Scheme 4). This reaction afforded the *anti*-Markovnikov product **30** in 55% yield along with, in 25% yield, only the diastereomeric alcohol **31** in which the hydroxyl group has been added to the face of the molecule opposite to the allylic oxygen functionality. Thus the most likely transition state picture is that proposed in **I**.



We have carried out other hydroboration–oxidation reactions which are in general agreement with the results listed here, namely the presence of a homoallylic oxygen functionality causes a higher proportion of Markovnikov hydration than expected while an allylic oxygen functionality is the key stereocontrol element. Further work on the use of this process is underway in our laboratories.



Scheme 4.

Acknowledgements

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References

1. Jung, M. E.; Nichols, C. J. *Tetrahedron Lett.* **1998**, *39*, 4615.
2. Nichols, C. J. PhD Thesis, UCLA, 1998. Since our research goal in this project was the total synthesis of **1**, we did not spend the time to determine the structure of this undesired minor product.
3. For good reviews, see: (a) Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Synthesis via Boranes*; Wiley: New York, 1975. (b) Brown, H. C. *Boranes in Organic Synthesis*; Cornell University Press: Ithaca, NY, 1972. (c) Smith, K.; Pelter, A. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed. Hydroboration of C=C and C≡C. Pergamon: Oxford, 1991; Vol. 8, Chapter 3.10, p. 703.
4. (a) Brown, H. C.; Chen, J. C. *J. Org. Chem.* **1981**, *46*, 3978. (b) Brown, H. C.; Unni, M. K. *J. Am. Chem. Soc.* **1968**, *90*, 2902. (c) Brown, H. C.; Gallivan Jr., R. M. *J. Am. Chem. Soc.* **1968**, *90*, 2906. (d) Brown, H. C.; Sharp, R. L. *J. Am. Chem. Soc.* **1968**, *90*, 2915. These authors report significant elimination of the allylic oxygen substituent, a process that we do not observe here. (e) Also see the discussion in Ref. 3c, in which allyl and homoallyl ethers or acetates afford about 10–20% oxidation to give the secondary alcohol. An exception is intramolecular hydroboration in which a homoallylic borane (formed from a diene with a substituted borane) directs the hydroboration of the adjacent alkene.[3]
5. The acetonides derived from the C_s symmetric **11a** and the C_2 symmetric **11b** are easily distinguished by simple proton and carbon NMR.
6. The tribenzyl ethers derived from **21a** and **25a** each have a plane of symmetry and thus their proton and carbon NMR spectra are greatly simplified compared to those expected of the benzyl ethers derived from **21b** and **25b**.
7. Dihydroxylation of the dibenzyl ether **19** with OsO_4 and NMO afforded mainly the diol in which the hydroxyls were added to the face opposite the allylic benzyl ether. Bis-benzylation afforded the enantiomer of the tetra benzyl ether formed from **22a**. See: Babine, R. E. *Tetrahedron Lett.* **1986**, *27*, 5791.
8. (a) For a discussion of this 'inside-alkoxy' effect, see: Houk, K. N.; Moses, S. R.; Wu, Y.-D.; Rondan, N. G.; Jäger, V.; Schohe, R.; Fronczek, R. R. *J. Am. Chem. Soc.* **1984**, *106*, 3880. (b) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.* **1983**, *23*, 3943. (c) Stork, G.; Kahn, M. *Tetrahedron Lett.* **1983**, *23*, 3951.