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REDUCTION OF CYCLIC ENONE WITH BULKY TRIALKYLBOROHYDRIDES

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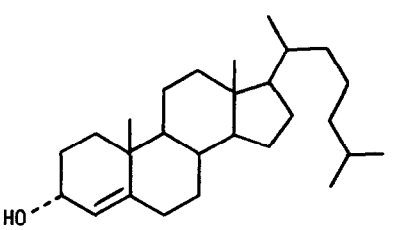
The development of stereoselective reducing agents has been a very active field of research, particularly the preparation of reagents that will yield the less thermodynamically stable axial alcohols from unhindered cyclic ketones. Currently, the most promising reagents for the preparation of axial alcohols are the bulky trialkylborohydrides.[1] Recently, cyclic enones have been shown to undergo conjugate reduction with K-Selectride, however, when a β-substituent is present on the enone functionality only 1,2 reduction was observed but the isomer ratios of the allylic alcohols formed were not determined.[2]

During the course of synthetic studies, there was need for 3α-cholest-4-enol (1). Reduction of 4-cholesten-3-one (2) with L-Selectride at -78° did not yield the desired product, but instead gave the β-allylic alcohol as the predominant product. When the reduction was repeated at 25°, slightly more of the α-alcohol was obtained. The predominant formation of the β-pseudoequatorial alcohol was shown not to be a characteristic of the steroid nucleus in that reduction of 3-cholestanone with L-Selectride or K-Selectride at -78° gave the α-axial alcohol as the major product (α:β:80:20).



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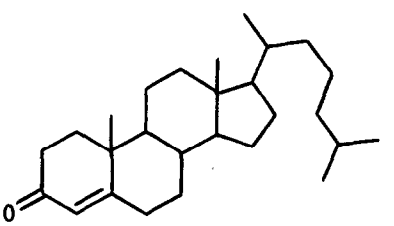

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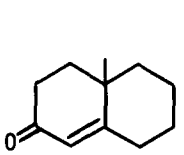
The reduction of some typical α,β-unsaturated cyclic ketones 3-7 has been studied using LAH and L-Selectride and the results are shown in the Table.



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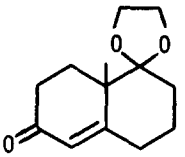

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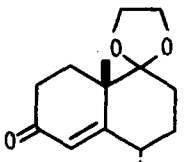

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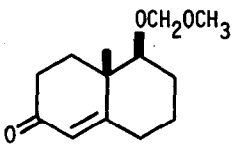

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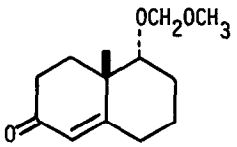

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Table: Hydride Reduction Product Ratio (α:β)[3]

Reducing Agent	Compound 2	3	4	5	6	7
LAH	20:80	17:83	29:71	37:63	24:76	28:72
L-Selectride (-78°)	15:85	17:83	91:9	95:5	27:73	72:28
L-Selectride (25°)	29:71	---	---	---	---	---
K-Selectride (-78°)	40:60	---	---	---	---	---
K-Selectride (25°)	40:60	---	86:14	---	---	---
Lithium trisiamyl borohydride - LTSBH (25°)	50:50	---	---	---	---	---

Reduction of compounds 2-5 with LAH gave the expected β-allylic alcohols as the predominant products. When compounds 2 and 3 were reduced with L-Selectride the β-allylic alcohols were again the major isomers. Reduction of 2 with K-Selectride or LTSBH gave a higher proportion of the α-allylic alcohol but mixtures always resulted. Reduction of the ketals 4 and 5 with L-Selectride gave markedly different results as the α-allylic alcohols were obtained as the major products. To determine whether the C-9α or β-oxygen of the ketals were responsible for the surprising reversal in the stereoselectivity in the reduction of 4 and 5, the ethers 6 and 7 were prepared.[4] Reduction with LAH gave a mixture of allylic alcohols in which the β-allylic alcohols were the major isomers for both 6 and 7.

When the reduction was repeated with L-Selectride, compound 6 again gave the β-allylic alcohol as the major isomer, however, compound 7 gave the α-allylic alcohol as the major isomer. These results indicate that the C-9α oxygen was markedly affecting the stereoselectivity of the Selectride reductions of the ketals 4 and 5.[5,6]

Reduction of rigid cyclic α,β-unsaturated ketones, in the absence of other polar substituents, with the bulky trialkylborohydrides yield a mixture of the pseudoaxial and pseudoequatorial allylic alcohols with the more thermodynamically stable pseudoequatorial alcohol generally predominating. Appropriately positioned ethers can dramatically alter the stereochemical course of the reduction of cyclic α,β-unsaturated ketones with the Selectrides.

ACKNOWLEDGEMENT

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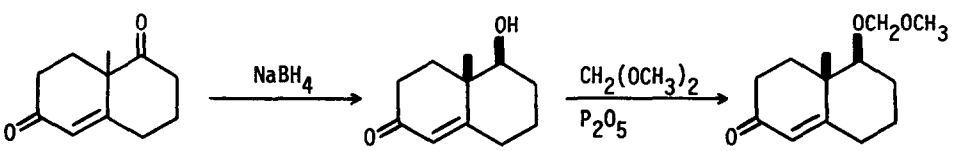
REFERENCES

1. S. Krishnamurthy and H. C. Brown, J. Am. Chem. Soc., 98, 3383 (1976) and references cited therein.

2. J. M. Fortunato and B. Ganem, J. Org. Chem., 41, 2194 (1976).

3. Product ratios were determined by integration of the vinyl proton of the 180MHz or 60MHz PMR spectra of the products. The vinyl proton of the β-allylic alcohols occur as a broadened singlet at slightly higher field than the vinyl proton (doublet, J=4.5 Hz) of the α-allylic alcohols.

4. Ethers 6 and 7 were prepared via the following schemes:



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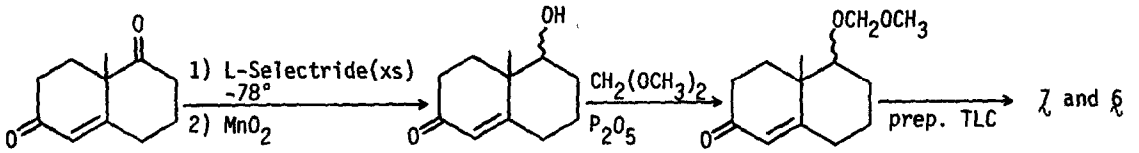

5. Complexation of L-Selectride with the C-9α oxygen could effectively hinder the underside (α-face) of the molecule, necessitating approach of another molecule of reducing agent from the top (β-face). The C-9α substituent is too far removed from the carbonyl carbon to assist in delivering the reducing agent via intramolecular assistance from the α-face.

6. a) For a recent example of intramolecular assistance by an ether oxygen during a Selectride reduction see: D. C. Wigfield and S. Feiner, Can. J. Chem., 56, 789 (1977).
b) For recent evidence of ether complexed $MBHR_3$ see: H. C. Brown, A. Khuri and S. Krishnamurthy, J. Am. Chem. Soc., 99, 6237 (1977) and H. C. Brown, A. Khuri and S. C. Kim, Inorg. Chem., 16, 2229 (1977).

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