Tetrahedron Letters,Vol.27,No.49,pp 5939-5942,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

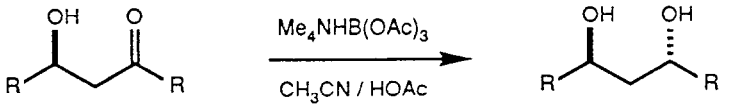
THE DIRECTED REDUCTION OF β-HYDROXY KETONES EMPLOYING $Me_4NHB(OAc)_3$

David A. Evans* and Kevin T. Chapman

Department of Chemistry
Harvard University
Cambridge, Massachusetts 02138

Abstract: The diastereoselective reduction of a range of acyclic β-hydroxy ketones with triacetoxyborohydride is described. In all cases, the anti 1,3-diol diastereomer is the principal product (eq 1).

Chemical reactions which may be actively directed by substrate functionality have proven to be valuable in stereoselective synthesis.[1-3] We have recently focused our attention on the development of such reactions wherein stereochemical information from hydroxyl-bearing stereogenic centers might be propagated during the course of olefin hydrogenation.[1] In the present Letter we wish to report some of our related studies on the hydroxyl-directed hydride reduction of acyclic β-hydroxy ketones using the reducing agent $Me_4NBH(OAc)_3$ (eq 1).



(1)

Diastereoselection 20-50 : 1

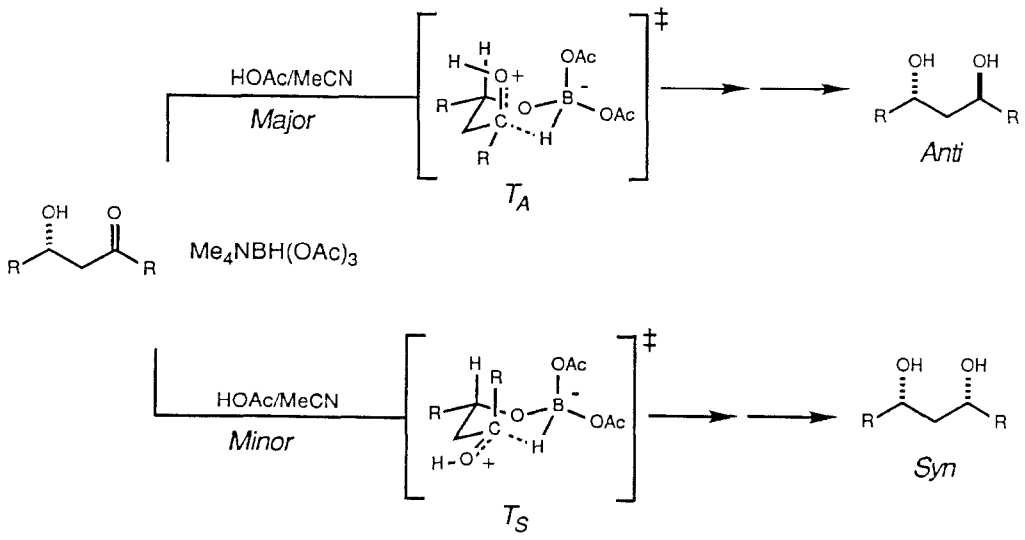
It has been well documented that both $NaBH(OAc)_3$ and $Bu_4NBH(OAc)_3$, even at elevated temperatures or prolonged reaction times, fail to reduce completely simple ketones such as acetophenone or 2-heptanone.[4] In contrast, several cyclic β-hydroxy ketones have been reduced under mild conditions with in situ generated $NaBH(OAc)_3$.[5] The stereochemical information gained from these cases is consistent with a hydroxyl-mediated reduction, a mechanistic postulate first suggested by Gribble.[4b] In pursuing studies in this area, we were interested in both the synthetic and mechanistic aspects of these reactions. As a first objective, we sought to produce a stable, fully characterized triacyloxyborohydride which might also be utilized in metal counterion studies.[6] The reagent of choice which has been developed is $Me_4NBH(OAc)_3$, a colorless, hygroscopic solid, mp 96.5 -98° C, which is stable at room temperature for several months.[7] Since previously reported acyloxyborohydrides have been characterized only by their infrared spectra and hydrolysis products,[9] we chose to verify that we indeed were dealing with a homogeneous hydride. The reagent, freely soluble in CH_2Cl_2, $CHCl_3$ and numerous other common solvents, has spectral properties and combustion analysis fully consistent with the indicated structure. An abbreviated description of the synthesis of this reagent follows:

Tetramethylammonium Triacetoxyborohydride. A 500-mL Schlenk flask equipped with a Schlenk filter was charged with 10.8 g (121 mmol) of tetramethylammonium borohydride[8] and 300 mL of freshly distilled benzene. The mixture was cooled to 10° C, and 24.3 mL (425 mmol) of anhydrous acetic acid was added dropwise over 15 min. The mixture was warmed to ambient temperature, stirred for 3 h, and filtered. The white semisolid was washed with five 100-mL portions of freshly distilled ether, and dried overnight in vacuo to give a free-flowing white powder: mp 96.5-98.0° C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.4 (br, 1H, BH), 3.34 (s, 12 H, $(CH_3)_4N$), 2.02 (s, 9H, CH_3CO_2B); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.60, 55.63, 23.24; ^{11}B NMR (96.3 MHz, CD_3CN, BF_3 etherate as external reference) δ +0.71 ppm (d, 1B, BH, J_{BH} = 136 Hz).

Anal. Calcd. for $C_{10}H_{22}NO_6B$: C, 45.65; H, 8.43; Found C, 45.64; H, 8.39.

The range of acyclic hydroxy ketones included in this study is illustrated in the Table. A solvent system of 1:1 acetic acid-acetonitrile was chosen for the following reasons. First, this reaction medium does not freeze at the lower reaction temperatures employed (-40° C); and second, Bronsted acids such as HOAc were determined to be important in facilitating the actual reduction (vide infra). As illustrated in the Table, these reductions exhibit both good levels of reaction diastereoselection and an impressive degree of generality. It is of particular interest that both the anti and syn aldol adducts (Entries 2,3) also exhibit high levels of anti reduction. One must presume that asymmetric induction from the distal hydroxyl-bearing stereocenter overrides the proximal α-methyl stereocenters in either configuration. Finally, it is noteworthy that the diketo ester illustrated in Entry 10 also undergoes reduction. In comparison, related β-keto esters are not reduced. We postulate that this reduction proceeds through an enolborohydride intermediate where the double bond is not conjugated to the carbonyl center undergoing reduction.

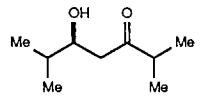
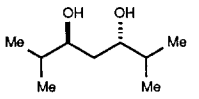
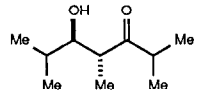
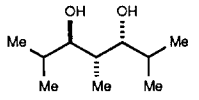
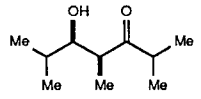
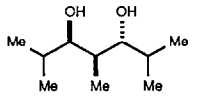
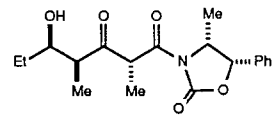
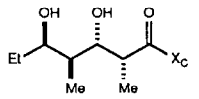
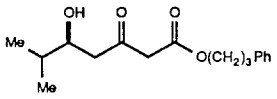
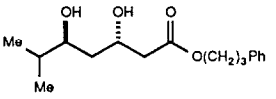
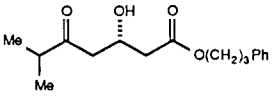
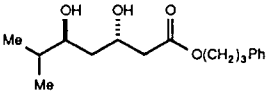
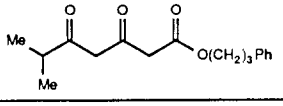
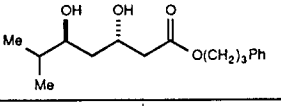
The stereochemical course of these reductions may be rationalized via the transition states illustrated below. Ligand exchange between substrate hydroxyl and the labile borohydride ligands affords an intermediate substrate-bound alkoxydiacetoxy borohydride which is not only capable of intramolecular hydride delivery but is actually a stronger hydride donor than the parent borohydride.[11]



The diastereoselectivity is then easily rationalized via the chair-like transition states T_A and T_S. It is presumed that the 1,3-diaxial interactions present in transition state T_S destabilize it relative to the analogous nonbonding interactions in transition state T_A. Similar arguments have recently been extended to explain the high anti selectivity observed in the reduction of β-hydrosilyloxy ketones.[12]

Several additional pieces of evidence are relevant to the mechanism of this reaction. First we have observed that $Me_4NBH(OAc)_3$ requires the presence of either acids such as HOAc or metal ions such as Na^+ or Li^+ to reduce hydroxy ketones. The same requirements must also be met to effect ligand exchange between 2-propanol and $Me_4NBH(OAc)_3$. We have followed the reductions of β-hydroxy ketones by ^{11}B NMR spectroscopy and have not observed the buildup of metastable borohydride intermediates. Based upon this information we have tentatively concluded that ligand exchange rather than hydride transfer is rate determining. Finally, the presumed intramolecularity of these reductions can be demonstrated by the fact that β-hydroxy ketone reduction can be carried out in acetone-acetic acid! The selective reductions described herein nicely complement the recently reported syn-selective reductions.[13]

Table. Diasteroselective Hydroxy Ketone Reductions with $Me_4NBH(OAc)_3$.[10]

Entry	Reactant	Product	Time (Temp)	Ratio[a] Anti:Syn	Yield, %[b]
1			5 h (–20°C)	96 : 4	86
2			18 h (–20°C)	98 : 2	92
3			18 h (–20°C)	98 : 2	84
4			30 min (+25°C)[c,d]	>98 : 2	99
5			18 h (–40°C)	95 : 5	92
6			3h (+25°C)	92 : 8	89
7			30 min (+25°C)[d]	87 : 13	78
8			18 h (–40°C)	95 : 5	90
9			18 h (+25°C)	89 :11	83
10			6h (+25°C)	92 : 8	69

[a] Diastereomer ratios were determined by HPLC. [b] Values refer to isolated yields of major isomer of >99% purity. [c] Neat acetic acid used as solvent. [d] $NaHB(OAc)_3$ used as reducing agent.

Representative reduction procedure: To a solution of 5 mmol of tetramethylammonium triacetoxyborohydride in 4.0 mL of anhydrous acetonitrile and 4.0 mL of anhydrous acetic acid at -40° C is added a solution of 1 mmol of hydroxyketone in 1.0 mL of anhydrous acetonitrile. After the reaction has stirred for the indicated time at the indicated temperature (Table), it is quenched by the addition of 15 mL of 0.5 **N** aqueous sodium potassium tartrate with vigorous stirring for 30 min. The mixture is then diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The aqueous layer is back extracted several times with dichloromethane, and the combined organic layers are again washed with saturated aqueous sodium bicarbonate. The aqueous layer is back extracted several times with dichloromethane, and the combined organic layers are dried with anhydrous sodium sulfate, filtered, and concentrated. The desired products may be purified by flash chromatography on silica gel.

Acknowledgements: This research has been supported by the National Science Foundation and the National Institutes of Health. The NIH-BRS Shared Instrumentation Grant Program 1-S10-RR01748-01A1 is also acknowledged for providing NMR facilities.

References and Notes

1. For earlier work on directed hydrogenation reactions see:
(a) Evans, D.A.; Morrissey, M.M. Tetrahedron Lett. **1984**, 25, 4637.
(b) Evans, D.A.; Morrissey, M.M. J. Am. Chem. Soc. **1984**, 106, 3866.
(c) Evans, D.A.; Morrissey, M.M.; Dow, R.L. Tetrahedron Lett. **1985**, 26(49), 6005.
2. Stork, G.; Kahne, D.E. J. Am. Chem. Soc. **1983**, 105, 1072.
3. Crabtree, R.H.; Davis, M.W. J. Org. Chem. **1986**, 51, 2655.
4. (a) For an excellent review of borohydride reductions in acidic media see: Gribble, G.W.; Nutaitis, C.F. Organic Preparation and Procedures Int. **1985**, 17, 317-84.
(b) Gribble, G.W.; Nutaitis, C.F. Tetrahedron Lett. **1983**, 24, 4287.
5. (a) Saksena, A.K.; Mangiaracina, P. Tetrahedron Lett. **1983**, 24, 273.
(b) Turnbull, M.D.; Hatter, G.; Ledgerwood, D.E. Tetrahedron Lett. **1984**, 25, 5449.
6. In the above studies (Ref. 4b, 5), the borohydride species were never fully characterized.
7. After a six-month period the reagent does not completely dissolve in solvents other than acetic acid. This does not, however, lead to a drop in reduction yield or stereoselectivity.
8. Banus, M.D.; Bragdon, R.W.; Gibb, Jr., T.R.P. J. Am. Chem. Soc. **1952**, 74, 2346.
9. (a) Wartik, T.; Pearson, R.K. J. Inorg. Nucl. Chem. **1958**, 7, 404-11.
(b) Marchini, G.; Liso, A.; Reho, F.; Liberatore, F.; Moracci, F.M. J. Org. Chem. **1975**, 40, 3453.
(c) Oklobdzija, M.; Fajdiga, T.; Kovak, T.; Zonno, F.; Sega, A.; Sunjic, V. Acta Pharm. Jugosl. **1980**, 30, 121; Chem. Abs. **1981**, 94, 121481g.
10. Satisfactory spectral data and elemental analyses were obtained for all compounds reported.
11. For comparisons of reactivity of acyloxyalkoxy borohydrides see:
(a) Hirao, A.; Itsuno, S.; Owa, M.; Nagami, S.; Mochizuki, H.; Zoorov, H.H. A.; Niakahama, S.; Yamazaki, N. J. Chem. Soc. Perkin I **1981**, 900.
(b) Nasipuri, D.; Sakar, A.; Konar, S.K.; Ghosh, A. Indian J. Chem. **1982**, 21B, 212-5.
12. Anwar, S.; Davis, A.P., J. Chem. Soc. Chem. Commun. **1986**, 831-832.
13. Kathawala, F.G., Prager, B.; Prasad, K.; Repic, O.; Shapiro, M.J.; Stabler, R.S.; Widler, L. Helv. Chim. Acta **1986**, 69, 803-805 and references reported therein.

(Received in USA 3 September 1986)