incorporate unnatural sialic acids into oligosaccharides.

Acknowledgment. This work was supported by the NIH (GM44154) and Cytel Co., San Diego, CA.

Supplementary Material Available: A listing of complete experimental details and analytical and spectral data for all new compounds (**3–8, 11–14**) (9 pages). Ordering information is given on any current masthead page.

Stereocontrolled Hydride Reductions of β-Hydroxy Oximino Ethers

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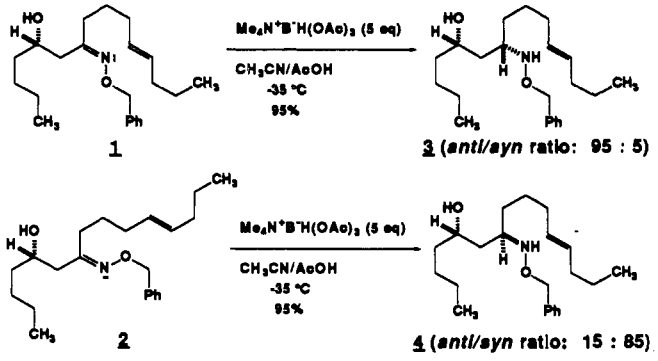
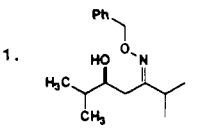
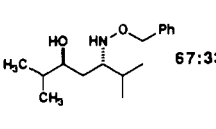
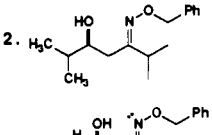
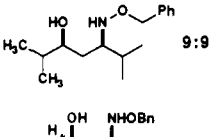
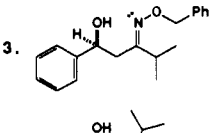
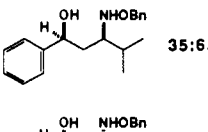
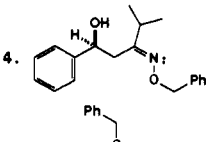
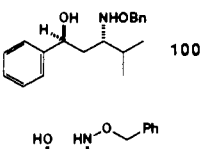
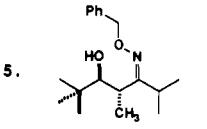
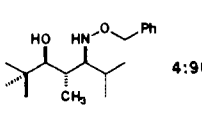
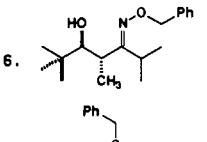
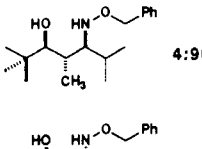
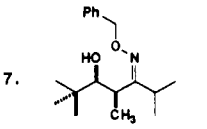
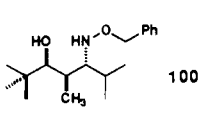
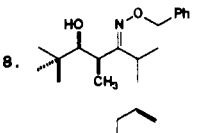
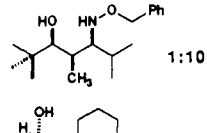
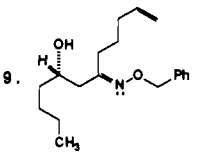
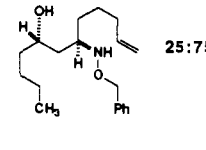
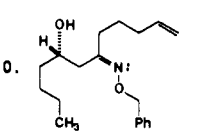
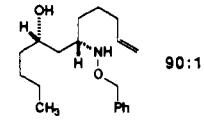
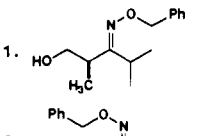
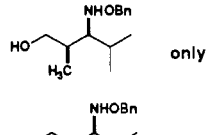
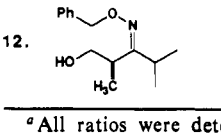
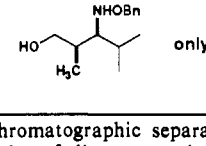
Received June 15, 1992

In recent years, the development of "internally-directed" reagents through participation of a proximate hydroxyl function has afforded fundamental advances for directed epoxidations, hydrogenations, hydride reductions, and conjugate additions. Naraska[1] and Evans[2] have reported complementary reagent-based strategies for preparation of 1,3-*syn*- and 1,3-*anti*-diols via reductions of acyclic β-hydroxy ketones. Additional developments have been reported which continue to expand the scope of stereoselective reductions to provide 1,3-diols and related derivatives.[3] In connection with our interest in alkaloid synthesis, we have examined opportunities for preparation of 1,3-amino alcohols wherein the diastereofacial selectivity of hydride delivery to an imino (C=N) bond is affected by a neighboring hydroxyl group.[4] Herein, we illustrate our findings for 1,3-asymmetric induction in reductions of β-hydroxy oximino ethers. Our initial observations resulted from individual reductions of pure (*Z*)- and (*E*)-oximino benzyl ethers **1** and **2** with tetramethylammonium triacetoxyborohydride (TABH) in anhydrous acetic acid–acetonitrile (1:1



by volume) at −35 °C. (*Z*)-Oxime **1** afforded smooth conversion to the 1,3-anti product **3**, while the corresponding (*E*)-oxime **2** gave mostly the 1,3-syn arrangement **4**.[5] Diastereoselectivity was achieved based upon geometry of the starting oximino ethers.

Table I. Diastereofacial Hydride Reduction of β-Hydroxy Oximino Ethers

Entry	Oxime	Rxn. Conditions	Major Product[a]	Ratio[b] (anti:syn)	Yield
1.		TABH (5 eq) -35 °C; 6 hr then 22 °C; 1 hr		67:33	100%
2.		TABH (5 eq) -35 °C; 6 hr then 22 °C; 1 hr		9:91	94%
3.		TABH (5 eq) -35 °C; 6 hr		35:65	95%
4.		TABH (5 eq) -35 °C; 6 hr		100:1	92%
5.		TABH (8 eq) -15 °C; 12 hr then 22 °C; 2 hr		4:96	94%
6.		TABH (8 eq) -15 °C; 12 hr then 22 °C; 2 hr		4:96	93%
7.		TABH (10 eq) -35 °C; 4 hr then 22 °C; 4 hr		100:1	75%
8.		TABH (8 eq) -35 °C; 4 hr then 22 °C; 4 hr		1:100	27%[c]
9.		TABH (5 eq) -35 °C; 6 hr		25:75	85%
10.		TABH (5 eq) -35 °C; 6 hr		90:10	90%
11.		TABH (5 eq) -35 °C; 4 hr		only	92%
12.		TABH (5 eq) -35 °C; 4 hr		only	93%

[a] All ratios were determined by chromatographic separation and product isolations. In some cases ratios of diastereomeric products were also confirmed by ^{1}H NMR of crude mixtures. [b] Anti/syn products were identified by ^{1}H NMR and conversion to their cyclic carbamates (carbonyldiimidazole, benzene, heat) for proton decoupling studies. [c] Largely starting oxime (70%) was recovered.

This behavior is typical for a variety of substrates as summarized in Table I. Yields generally range from 80–95%. In cases of lower yields, considerable amounts of starting oxime ethers were recovered. Such examples (entry 8) exhibited significant steric interactions and very slow reaction times. In all cases of incomplete reactions, reisolated oximes showed no evidence of *E*/*Z* isomerization under the reaction conditions. The significance of

(1) Narasaka, K.; Pai, F.-C. *Tetrahedron* **1984**, *40*, 2233.
(2) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560 and references therein. Evans, D. A.; Hoveyda, A. H. *J. Org. Chem.* **1990**, *55*, 5190.
(3) Mohr, P. *Tetrahedron Lett.* **1991**, *32*, 2219. Boger, D. L.; Curran, T. T. *J. Org. Chem.* **1992**, *57*, 2235. Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447.
(4) Narasaka, K.; Ukaji, Y.; Yamazaki, S. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 525.
(5) The individual *anti*- and *syn*-oxime isomers were separated by silica gel flash chromatography. Determination of oxime geometry was based on ^{13}C and ^{1}H NMR data. The assignments of chemical shifts of α-carbons located syn to the benzyloxy substituent are observed upfield relative to the corresponding anti isomers due to steric compression. Proton signals for α-methylene units of *syn*-oximino benzyl ethers appear at slightly lower field compared to the anti isomers. Karabatsos, G. J.; Hsi, N. *Tetrahedron* **1967**, *23*, 1079. See, also: ref 4.

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(*E*/*Z*)-oxime geometry for diastereofacial selectivity contrasts with previous results of lithium aluminum hydride reductions.[4] Derivatives resulting from acetylation or ether protection of the proximate hydroxyl gave oximino benzyl ethers which were not reduced by TABH. Parent oximes (C=N—OH) and oximino benzyl ethers lacking a proximate (α or β) hydroxy function were also recovered unchanged.

Three independent investigations corroborate the stereochemical assignments of our products. Firstly, the aminoolefin cyclizations (I_2, CH_2Cl_2, $NaHCO_3$, 22 °C) of **3** and **4** followed by dehydrohalogenations with subsequent reactions leading to reductive cleavage of the N–O bond afforded materials which were spectroscopically (^1H and ^{13}C) compared to substances available via the nitrone cycloaddition route from substituted 2,3,4,5-tetrahydropyridine 1-oxides and terminal alkenes.[6] Secondly, our 1,3-amino alcohols were converted to their corresponding six-membered *N*-benzyloxy carbamates (1,1′-carbonyldiimidazole, benzene, reflux) for extensive proton decoupling studies.[7] Finally, unambiguous stereochemical assignments were directly available from the X-ray diffraction study of the *anti*-1,3-*N*-benzyloxyamino alcohol from entry 3 of Table I.[8]

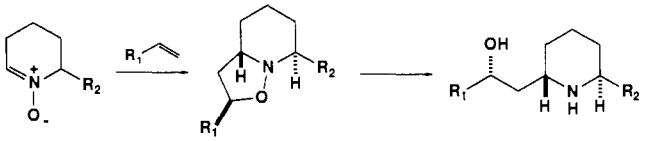
An additional chiral center at C-2 has a profound effect on the course of our TABH reductions. The anti arrangement of vicinal hydroxyl and methyl substitutents of entries 5 and 6 overcame the influence of oxime geometry, delivering predominantly the 1,3-syn product. On the other hand, entries 7 and 8 (vicinal syn OH/CH_3) exhibited enhancement of the usual mode of stereocontrol. The (*E*)- and (*Z*)-oxime isomers of the primary alcohol (entries 11 and 12) were cleanly reduced to a single amino alcohol.

In summary, our reductions of acyclic β-hydroxyoximino ethers demonstrate the importance of the proximate hydroxyl as well as the geometry (*E*/*Z*) of the starting oxime for stereocontrolled production of 1,3-*syn*- and 1,3-*anti*-amino alcohols in high yields. Further efforts and rationalizations of these results are in progress.

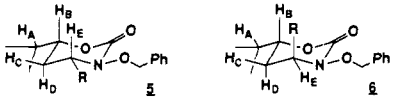
Acknowledgment. We gratefully acknowledge financial assistance provided by the National Institutes of Health (GM-41560) and the National Science Foundation (CHE86-18955).

Supplementary Material Available: Data of (*E*)- and (*Z*)-oximes and the pure 1,3-*syn*- and 1,3-*anti*-amino alcohol products are provided with a general experimental procedure for these TABH reductions (12 pages). Ordering information is given on any current masthead page.

(6) Cycloadditions of terminal alkenes with 2,3,4,5-tetrahydropyridine-*N*-oxide take place exclusively in the exo mode. Tufariello, J. J. 1,3-Dipolar Cycloaddition Chemistry; Padwa, A., Ed.; Wiley: 1984; Vol. 2, p 83. Carruthers, W.; Coggins, P.; Weston, J. B. *J. Chem. Soc., Perkin Trans 1* **1990**, 2323.



(7) The 1,3-syn isomers **5** demonstrated the expected trans diaxial proton coupling (J_{DE} = 11 Hz), whereas **6** provided coupling constants in keeping with the usual data for vicinal axial–equatorial (J_{DE} = 7–8 Hz) and equatorial–equatorial (J_{CE} = 2–4 Hz) arrangements. Modeling indicates a small dihedral angle for the vicinal axial HD–equatorial HE hydrogens of **6** resulting from planarization of the six-membered carbamate. This accounts for the relatively large coupling constant J_{DE} compared to J_{CE}. A similar relationship exists in **5** for protons HC and HE.



(8) Structure determination of a colorless crystalline sample $C_{19}H_{25}NO_2$ (mp 58–60 °C, CH_2Cl_2) of the minor diastereoisomer produced as illustrated in entry 3 of Table I was established by X-ray diffraction at −172 °C. All atoms, including hydrogens, were refined by full-matrix least-squares to final residuals of $R(F)$ = 0.0347 and $R_w(F)$ = 0.0422. Crystallographic data are available from Indiana University Chemistry Library. Request Molecular Structure Center Report 90257.

2,2-Dialkoxy-Δ^3-1,3,4-oxadiazolines: Convenient Thermal Sources of Dialkoxycarbenes

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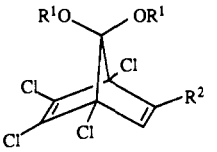
Department of Chemistry, McMaster University Hamilton, Ontario, L8S 4M1 Canada

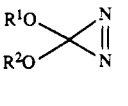
Received July 8, 1992

Dialkoxy- and diaminocarbenes are species with low chemical reactivity[1] and a large singlet/triplet energy gap.[2] Both properties are attributed to resonance stabilization of the singlet (Scheme I), which imparts nucleophilic properties to dimethoxycarbene (DMC).[2,3]

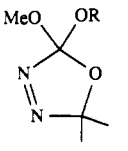
There are only two well-established precursors of dialkoxycarbenes.[4] The one based on thermolysis of **1**[5,6] has at least two limitations. First, only DMC has been generated effectively by that route, and it is unsuitable, in any case, for unsymmetric carbenes, $R^1O\ddot{C}OR^2$. Second, there are major coproducts of high molecular mass that must be separated from products of reaction



1



2



3 a: R=Me; b: R=Et; c: R=$CH_2CH_2C{\equiv}CH$

of DMC with a substrate in a synthetic application of DMC. The other method, involving the decomposition of dialkoxydiazirines (**2**), has been restricted, to date, to dimethoxycarbene[3g,7] and methoxyphenoxycarbene.[8] Although compounds **2** have an advantage, because the carbenes can be generated photochemically for low-temperature and matrix isolation studies, they are poor sources for studies of the chemistry of dialkoxycarbenes because compounds **2** are obtained as relatively unstable materials, highly diluted with hydrocarbon solvent.

Dialkoxycarbenes are particularly interesting as potential synthons of carbonyl compounds. Conventional carbene cycloadditions to alkenes and alkynes lead, at least in principle, to cyclopropanone[3a,h,8] and cyclopropenone ketals while insertion reactions would afford masked, acyclic carbonyl compounds (Scheme II).

We now report that 2-alkoxy-2-methoxy-Δ^3-1,3,4-oxadiazolines (**3**) are readily accessible, shelf-stable liquids that serve as convenient sources of dialkoxycarbenes, by thermolysis at 100 °C in solution.

Compounds **3** were prepared by oxidative cyclization[9] of the (methoxycarbonyl)hydrazone of acetone (**4**) with lead tetraacetate in alcohol ROH (for **3a**, **3b**) or in CH_2Cl_2 containing ROH (for **3c**), in yields ranging from 40 to 80% (reaction 1). Their

$$\underset{\mathbf{4}}{Me_2C{=}NNHCO_2Me} \xrightarrow[ROH]{Pb(OAc)_4} \mathbf{3} \qquad (1)$$

structures were established by ^1H and ^{13}C NMR spectroscopy ($CDCl_3$, δ: C2, 136.7–137.9; C5, 118.7–119.4) and by mass spectrometry.[10]

Thermolysis of **3a** in benzene (sealed NMR tube) at 100 °C followed the first-order rate law with $k = 1.2 \times 10^{-5}$ s^{-1}. Both **3a** and **3b** afforded acetone (>80%) and the appropriate tetraalkoxyethene(s) (70–88%) as major products. Dimerization of ethoxymethoxycarbene occurred with little or no discrimination;

† McMaster University undergraduate, 1992 (K.K.), 1989 (T.T.).

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