enabling us to calculate τ_c and (e^2qQ/h) from a linear approximation[12] as 3.14×10^{-9} s/rad and 0.87 MHz, respectively. A Stokes-Einstein-Debye calculation gave a $\tau_{rotational}$ of 1.2×10^{-8} s/rad for α-CHT.[13] Therefore, the boron environment at the active center is much more mobile than the gross tumbling rate of the enzyme.

The quadrupolar coupling constant estimated for the active center-bound ^{11}B is 0.87 MHz characteristic of a tetrahedral boronate,[15] as is the bound chemical shift of -12.9 ppm (compared to 13.4 for the unbound PBA at this pH).[16] Both quantities confirm a transition statelike structure in solution.

This study demonstrates the potential of ^{11}B NMR to study the active center of enzymes in solution.

(11) Forsen, S.; Lindeman, B. *Methods of Biochemical Analysis*; Glick, D., Ed.; 1981; Vol. 27, pp 323-326.

(12) Bull, T. E.; Norne, J. E.; Reimarsson, P.; Lindeman, B. *J. Am. Chem. Soc.* **1978**, *100*, 4643-4647. The linear approximation equations employed are as follows:

$$R_1 = \frac{1}{T_1} = \frac{2\pi^2}{5}(e^2qQ/h)^2\left[\frac{0.2\tau_c}{1+\omega_1^2\tau_c^2} + \frac{0.8\tau_c}{1+4\omega_1^2\tau_c^2}\right]$$

$$R_2 = \frac{1}{T_2} = \frac{2\pi^2}{5}(e^2qQ/h)^2\left[0.3\tau_c + \frac{0.5\tau_c}{1+\omega_1^2\tau_c^2} + \frac{0.2\tau_c}{1+4\omega_1^2\tau_c^2}\right]$$

(13) Reference 6, p 39, an effective radius of 22.5 Å was used in calculation. Under our experimental conditions of large excess of PBA over α-CHT (<0.4 mM), ionic strength (0.15), and temperature, the fraction of dimerized enzyme is estimated to be small,[14a,b] and the effect on the calculated result negligible.

(14) (a) Rao, M. S. N.; Kegeles, G. *J. Am. Chem. Soc.* **1958**, *80*, 5724-5729. (b) Nichol, L. W.; Jackson, W. J. H.; Winzor, D. J. *Biochemistry* **1972**, *11*, 585-591.

(15) Cuthbert, J. D.; Macfarlane, W. T.; Patch, H. E. *J. Chem. Phys.* **1965**, *43*, 173-177.

(16) (a) Excluding halogen containing compounds. (b) Kidd, G. R. In *NMR of Newly Accessible Nuclei*; Laszlo, P., Ed.; Academic Press: New York, 1983; Vol. 2, pp 49-77. (c) Chemical shifts were measured relative to external trimethylborate with upfield shift taken as negative. These chemical shifts can be related to Et_2OBF_3 as standard according to $\delta[Et_2OBF_3] = \delta[(MeO)_3B] + 18.3$. See: *Annual Review NMR Spectroscopy*; Mooney, E. F., Ed.; Academic Press: New York, 1969; Vol. 2, p 221.

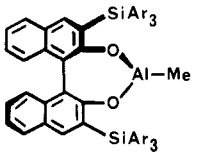
Asymmetric Hetero-Diels-Alder Reaction Catalyzed by Chiral Organoaluminum Reagent

Keiji Maruoka, Takayuki Itoh, Tadashi Shirasaka, and Hisashi Yamamoto*

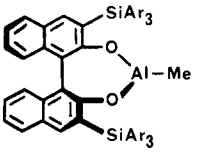
Department of Applied Chemistry
Nagoya University, Chikusa, Nagoya 464, Japan

Received March 2, 1987

The importance of chiral Lewis acid catalysts in organic synthesis has been tremendously demonstrated in recent years.[1] However, the asymmetric hetero-Diels-Alder reaction (Danishefsky reaction), which is quite useful in natural product syntheses,[2] has never been developed to a useful level due to the lack of the well-designed asymmetric catalysts.[3] Here we wish to report a first solution to this problem by using the newly devised chiral organoaluminum catalyst of type (*R*)-**1** and (*S*)-**1**.[4]



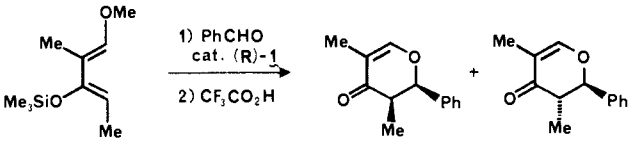
(R)-1



(S)-1

The optically pure (*R*)-(+)-3,3′-bis(triarylsilyl)binaphthol[5] ((*R*)-**2**) requisite for preparation of (*R*)-**1** can be synthesized in two steps from (*R*)-(+)-3,3′-dibromobinaphthol.[6] Reaction of (*R*)-**2** in toluene with Me_3Al produced the chiral organoaluminum reagent (*R*)-**1** as a pink to wine-red solution. Its molecular weight, found cryoscopically in benzene, corresponds closely with the value calculated for monomeric species of **1** (Ar = Ph).

Treatment of a mixture of benzaldehyde and siloxydiene **3** in toluene under the influence of catalytic (*R*)-**1** (Ar = Ph: 10 mol%) at -20 °C for 2 h furnished, after exposure of the resulting hetero-Diels-Alder adducts to trifluoroacetic acid in CH_2Cl_2, *cis*-dihydropyrone **4** (77%) and its trans isomer **5** (7%).[7] The



3 4 5

major cis adduct **4** was shown to be 95% ee.[8] Further, use of sterically more hindered aluminum reagent (*R*)-**1** (Ar = 3,5-xylyl) has proved to exhibit the excellent cis and enantioselectivity (93% yield; cis/trans = 30:1; 97% ee in **4**).

Some examples are listed in Table I. The present catalytic method is applicable to various siloxydienes[9] and aldehydes with high enantioselectivity. The new chiral organoaluminum reagent **1** disclosed herein exhibited the following characteristic features. (1) The optical yield appeared to be independent of the amount (5-100 mol%) of **1** but increased gradually by lowering the reaction temperature (entries 1-3, 7, and 8). (2) Choice of the bulky triarylsilyl moiety in **1** is crucial for obtaining the high enantioface differentiation of prochiral aldehydes, and switching the triarylsilyl

(1) (a) Morrison, J. D. *Asymmetric Synthesis*; Academic Press: New York, 1984; Vol. 3B. (b) Bosnich, B. *Asymmetric Catalysis*; Martinus Nijhoff Publishers: Dordrecht, 1986.

(2) (a) Danishefsky, S. *Aldrich. Acta* **1986**, *19*, 59. (b) Danishefsky, S.; DeNinno, M. P. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 15.

(3) Previous attempt on asymmetric hetero-Diels-Alder reactions with a chiral catalyst: (a) Bednarski, N.; Maring, C.; Danishefsky, S. *Tetrahedron Lett.* **1983**, *24*, 3451. (b) Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1986**, *108*, 7060. (c) Quimpere, M.; Jankowski, K. *J. Chem. Soc., Chem. Commun.* **1987**, 676. For similar reactions using chiral aldehydes and their applications to natural product syntheses, see: Danishefsky, S. J.; Larson, E.; Askin, D.; Kato, N. *J. Am. Chem. Soc.* **1985**, *107*, 1246. Danishefsky, S. J.; Pearson, W. H.; Harvey, D. F.; Maring. C. J.; Springer, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 1256. For a recent review on the hetero-Diels-Alder reactions, see: Schmidt, R. R. *Acc. Chem. Res.* **1986**, *19*, 250.

(4) For synthetic application of binaphthol or substituted binaphthol-modified chiral Lewis acids, see: (a) Kelly, T. R.; Whiting, A.; Chandrakumar, N. S. *J. Am. Chem. Soc.* **1986**, *108*, 3510. (b) Reetz, M. T.; Kyung, S.-H.; Bolm, C.; Zierke, T. *Chem. Ind.* **1986**, 824. (c) Chapuis, C.; Jurczak, J. *Helv. Chim. Acta* **1987**, *70*, 436.

(5) (*R*)-**2** (Ar = Ph): $[\alpha]_D$ +125° (*c* 1.10, THF); (*S*)-**2** (Ar = Ph): $[\alpha]_D$ -125° (*c* 1.04, THF); (*R*)-**2** (Ar = 3,5-xylyl): $[\alpha]_D$ +135° (*c* 1.02, THF).

(6) (*R*)-(+)-3,3′-Dibromobinaphthol was converted with Ar_3SiCl/imidazole in DMF to bis-silyl ether (>95% yield), which on treatment with *t*-BuLi underwent a remarkably smooth 1,3-rearrangement to furnish optically pure (*R*)-**2** in 80-95% yield. The details of this process and its application to other phenol derivatives will be reported in due course. For preparation of the starting dibromobinaphthol, see: Lingenfelter, D. S.; Helgeson, R. C.; Cram, D. J. *J. Org. Chem.* **1981**, *46*, 393.

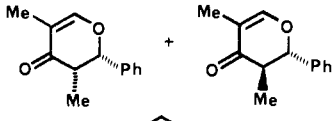
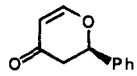
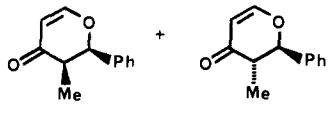
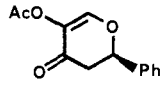
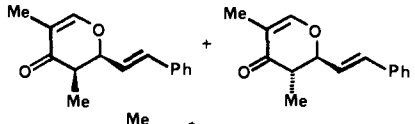
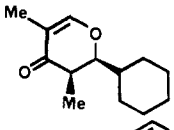
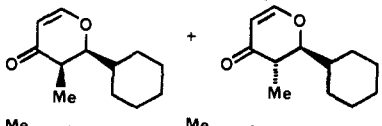
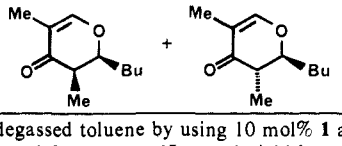
(7) A typical experimental procedure is exemplified by the reaction of benzaldehyde with the diene **3** (entry 2). To a degassed solution of (*R*)-(+)-3,3′-bis(triphenylsilyl)binaphthol (*R*)-**2** (Ar = Ph) (88 mg, 0.11 mmol) in dry toluene (5 mL) was added a 0.5 M hexane solution of Me_3Al (0.2 mL, 0.1 mmol), and the resulting wine-red solution was stirred at room temperature for 1 h. After having been cooled to -20 °C, benzaldehyde (0.102 mL, 1 mmol) and the diene **3** (220 mg, 1.1 mmol) were added. The mixture was stirred at -20 °C for 2 h, poured into 10% HCl, and extracted with ether. The combined extracts were concentrated in vacuo to give the crude adducts which were redissolved in CH_2Cl_2 (30 mL) and treated with trifluoroacetic acid (0.092 mL, 1.2 mmol) at 0 °C for 1 h. The reaction mixture was then poured into saturated $NaHCO_3$, extracted with CH_2Cl_2, and dried over Na_2SO_4. Evaporation of solvent and column chromatography of the residue on silica gel, eluting with 1:3 ether/hexane, gave a mixture of *cis*-dihydropyrone **4** (156 mg, 77%; $[\alpha]_D$ +7.1° (*c* 1.0, $CHCl_3$)) and the trans isomer **5** (14 mg, 7%; $[\alpha]_D$ -27.3° (*c* 0.75, $CHCl_3$)).

(8) The optical purity of the trans adduct **5** was 52% ee.

(9) The isomeric ratios of the dienes in Table I are as follows: **6** (*E*/*Z* = 84:16); **7** (*E*/*Z* = 1:1).

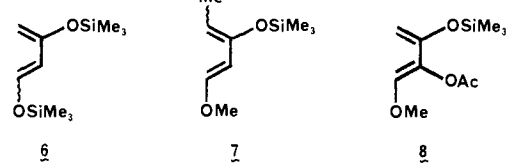
0002-7863/88/1510-0310$01.50/0

Table I. Asymmetric Hetero-Diels–Alder Reaction[a]

entry	aldehyde	diene[b]	catalyst (*R*)-**1** (Ar)	product	% yield[c,d]	$[\alpha]_D$[e] (deg)	% ee (config)
1	PhCHO	**3**	Ph[f]	**4** + **5**	89 (7)	6.1[h]	92[j] (2*R*,3*R*)[m]
2			Ph		77 (7)	7.1[h]	95[j] (2*R*,3*R*)[m]
3			Ph[g]		75 (7)	6.5[h]	95[j] (2*R*,3*R*)[m]
4			3,5-xylyl[f]		90 (3)	6.8[h]	97[j] (2*R*,3*R*)[m]
5			(*S*)-**1** (Ar = Ph)		86 (9)	−6.7[h]	95[j] (2*S*,3*S*)[m]
6		**6**	Ph		71	−74.1	67[k] (*R*)[n]
7			3,5-xylyl		81	−89.1	81[k] (*R*)[n]
8			3,5-xylyl[g]		88	−92.3	85[j,k] (*R*)[n]
9		**7**	Ph		91 (5)	*i*	95[k] (2*R*,3*R*)[m]
10		**8**	3,5-xylyl		83	−76.1	86[l] (*R*)[o]
11	(*E*)-PhCH=CHCHO	**3**	Ph		89 (10)	−158[h]	90[j] (2*S*,3*R*)[p]
12			3,5-xylyl[f]		93 (2)	−165[h]	96[j] (2*S*,3*R*)[p]
13	*c*-C_6H_{11}CHO	**3**	Ph		65	−163	91[j] (2*S*,3*R*)[p]
14		**7**	Ph		76 (9)	−159[h]	93[k] (2*S*,3*R*)[p]
15	$CH_3(CH_2)_3CHO$	**3**	Ph		62 (18)	−144[h]	86[j] (2*S*,3*R*)[m]

[a] Unless otherwise noted, the reaction was carried out in degassed toluene by using 10 mol% **1** and 1.1–2.2 equiv of the diene per aldehyde at −20 °C for several hours. [b] For structures of the dienes **3**, **6**, **7**, and **8** see text. [c] Isolated yield by column chromatography. [d] In case of the cis/trans mixture, the yield of the major cis isomer was designated, and the parentheses referred to that of the trans isomer. [e] In $CHCl_3$ (*c* 1.0). [f] The reaction was carried out at 0 °C. [g] At −78 °C. [h] The optical rotation value of the major cis adduct. [i] $[\alpha]_D \sim 0°$ (*c* 1.0, $CHCl_3$). [j] Determined by HPLC analysis of the (*S*)-(−)-MTPA ester of the alcohol, which was derived from the adduct by 1,4-reduction with L-Selectride followed by reduction of the resulting saturated ketone with $NaBH_4$. [k] The optical yield was substantiated by GC analysis after converting to the saturated ketone with L-Selectride and then to the acetal of (2*R*,4*R*)-(−)-pentanediol with catalytic Py·TsOH. [l] Determined by HPLC analysis after conversion to the saturated alcohol with PtO_2/H_2 and then to the (*S*)-(−)-MTPA ester. [m] The absolute configuration of the major cis adduct was ascertained via optical measurement after converting to β-hydroxy acid by the oxidative cleavage (O_3/MeOH; H_2O_2/KOH): Evans, D. A.; McGee, L. R. *J. Am. Chem. Soc.* **1981**, *103*, 2876. [n] Reference 3b. [o] Correlated to the product in entry 6. [p] Assigned by comparison with the optical rotation of authentic cis samples. See ref 3a.

substituent of the *tert*-butyldimethylsilyl or trimethylsilyl group led to the eminent loss of enantio as well as cis selectivity:[10] reaction to benzaldehyde with the diene **3** in the presence of catalytic (*R*)-**1** (Ar = Ph), its *tert*-butyldimethylsilyl analogue, or its trimethylsilyl analogue under similar conditions produced **4** and **5** in yields of 84% (ratio, 92:8; 95% ee in **4**), 91% (69:31, 84% ee), and 72% (53:47; 64% ee), respectively. (3) The catalyst (*R*)-**1** (Ar = Ph) was generally employable for the hetero-Diels–Alder reaction, and, in the case of the diene (**6**), use of



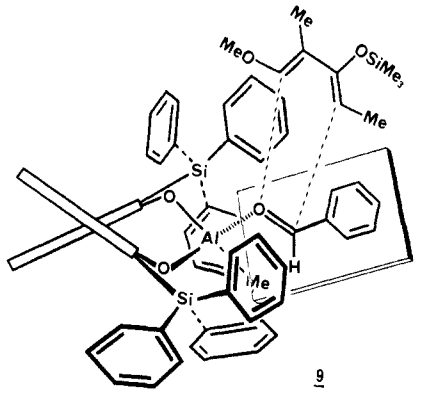
6 **7** **8**

sterically more hindered (*R*)-**1** (Ar = 3,5-xylyl) enhanced the enantioselectivity (entries 6–8).[11] (4) Nonpolar solvents such as toluene produced higher enantiofacial selectivity than polar solvents such as CH_2Cl_2, and ethereal solvents (ether and THF) significantly retarded the rate of the reaction. For example, treatment of the diene **3** and benzaldehyde with catalytic (*R*)-**1** (Ar = Ph: 10 mol%) in CH_2Cl_2 under similar conditions as described above produced the cis adduct **4** (72% yield: 82% ee) accompanied by the trans adduct **5** (16% yield). (5) Since (*S*)-**1** is equally accessible in optically pure form, the present method allows the synthesis of both antipodal products by choosing the handedness of the chiral auxiliary **2** (entry 1 vs 5).

The success of the present asymmetric hetero-Diels–Alder reaction is particularly owed to development of a new method of preparing optically active disilylbinaphthol **2**.[6] The chiral oxygenophilic organoaluminum catalyst **1** bearing such sterically hindered chiral auxiliary may form a stable 1:1 complex with benzaldehyde, allowing the enantioselective activation of carbonyl moiety as illustrated in **9**. Then the diene **3** would approach to benzaldehyde with an endo alignment of the aldehyde phenyl

(10) These optically pure bis-silylated binaphthols were prepared in a similar manner as described in **2**.

(11) Attempted reaction of benzaldehyde with Danishefsky's diene (1-methoxy-3-(trimethylsiloxy)-1,3-butadiene) in the presence of catalytic (*R*)-**1** (Ar = Ph) at −20 °C for 2 h gave dihydropyrone in 56% ee.



9

residue and 3 in order to minimize the steric repulsion between the incoming diene and the front triarylsilyl moiety, thereby yielding the cis adduct **4** predominantly in accord with the experimental findings. The observed higher cis as well as enantioselectivity by the use of the sterically more hindered triarylsilyl moiety in **1** would be accommodated in this explanation. It should be noted that the hetero-Diels–Alder adduct, once it formed, split off readily from the aluminum center in view of the steric release between the adduct and the aluminum reagent, resulting in regeneration of the catalyst **1** for further use in the catalytic cycle of the reaction. In marked contrast, the chiral organoaluminum reagent derived from Me_3Al and (*R*)-(+)-3,3′-dialkylbinaphthol (alkyl = H, Me, and Ph) was employable only as a stoichiometric reagent and gave fewer satisfactory results in reactivity and enantioselectivity in the hetero-Diels–Alder reaction.

Acknowledgment. We thank Dr. T. Ibuka (Kyoto University) for a generous supply of 1,3-bis(trimethylsiloxy)-1,3-butadiene. Financial support of this work was provided by the Kurata Foundation.

A Potent New Class of Active-Site-Directed Glycosidase Inactivators

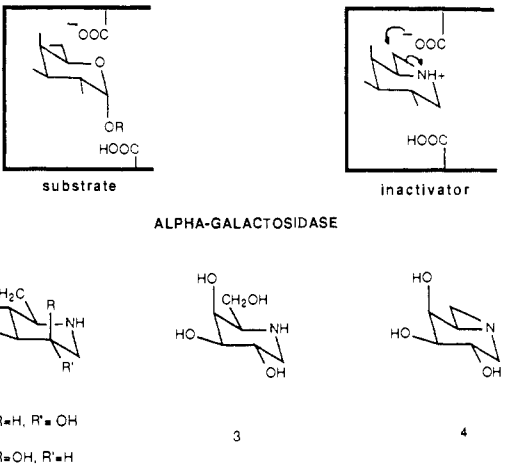
Michael K. Tong and Bruce Ganem*

Department of Chemistry, Baker Laboratory
Cornell University, Ithaca, New York 14853

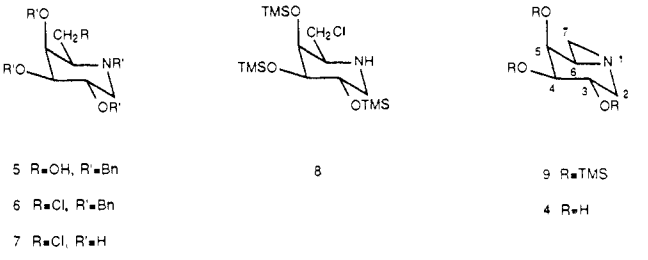
Received August 21, 1987

In the past several years, sugar- and anomer-specific inhibitors of glycosylhydrolases have helped unravel the catalytic mechanisms of these important enzymes.[1,2] The latest generation of such compounds manifests promising therapeutic applications as antiviral agents[3] and in the regulation of carbohydrate metabolic disorders.[1b] We wish to report a new class of potent active-site-directed glycosidase inactivators[4] capable of alkylating the key catalytic carboxylate group invoked in most currently accepted mono- or bilateral mechanisms of enzyme-assisted glycoside hydrolysis (Scheme I).[5]

Scheme I



Scheme II



In the lysozyme model (Scheme I),[6] competitive inhibition of gluco-, manno-, and galactosidases by azasugars like **1**,[7] **2**,[8] and **3**,[9] respectively, arises from H bonding and electrostatic interactions with a nearby carboxylate (Scheme I).[1b] We speculated that protonated aziridine[10] analogues like **4** might preferentially interfere with *α-glycoside* hydrolysis by S_N2 esterification of the enzyme's *β*-face carboxylate anion. There were several reasons for choosing galactosidases to test this hypothesis: (a) compared to **1** or **2**, azasugar **3** was 100-fold more active[9c] against its target, *α*-galactosidase, (b) reactive aziridine electrophiles were expected to be more stable at the near-neutral pH optima of most galactosidases, and (c) despite its metabolic significance, relatively little has been learned about the active site of *α*-galactosidase.[11]

The synthesis of aziridinyltriol **4**[12] from the known[9c] piperidine **5** is outlined in Scheme II. Mesylation and displacement of **5** afforded chloride **6** (76%) which could be hydrogenolyzed to triol **7** (100%). When direct cyclization of **7** to **4** proved impossible, the triol was exhaustively silylated [$(TMS)_2NH$, TMSCl, pyr, then H_2O] to afford **8** (88%). Exposure of **8** to *n*-butyllithium (1 equiv, THF, −78 °C) produced aziridine **9** (36–40%).[13]

(1) (a) Lalegerie, P.; Legler, G.; Yon, J. M. *Biochimie* **1982**, *64*, 977–1000. (b) Truscheit, E.; Frommer, W.; Junge, B.; Muller, L.; Schmidt, D. D.; Wingender, W. *Angew Chem., Int. Ed. Engl.* **1981**, *20*, 744–761.

(2) (a) Secemski, I. I.; Lienhard, G. E. *J. Am. Chem. Soc.* **1971**, *93*, 3549–3550. (b) Hehre, E. J.; Genghof, G. S.; Sternlicht, H.; Brewer, C. F. *Biochemistry* **1979**, *16*, 1780–1786. (c) Lehmann, J.; Schlesselmann, P. *Carbohydr. Res.* **1983**, *113*, 93–99.

(3) Dagani, R. *Chem. Eng. News* **1987**, (Jun 29), 25–27.

(4) For other types of active-site-directed irreversible glycosidase inhibitors, see: (a) Legler, G.; Herrchen, M. *FEBS Lett.* **1981**, *135*, 139–144. (b) marshall, P. J.; Sinnott, M. L.; Smith, P. J.; Widdows, D. *J. Chem. Soc., Perkin Trans. 1* **1981**, 366–376.

(5) Fersht, A. *Enzyme Structure and Mechanism*, 2nd ed.; Freeman: New York, 1985.

(6) Imoto, T.; Johnson, L. M.; North, A. C. T.; Phillips, D. C.; Rupley, J. A. *The Enzymes*; Academic Press: New York, 1972; Vol. 7.

(7) Schwarz, R. T.; Datema, R. *Trends Biochem. Sci.* **1984**, *9*, 32–34.

(8) Fellows, L. E.; Bell, E. A.; Lynn, D. G.; Pilkiewicz, F.; Miura, I.; Nakanishi, K. *J. Chem. Soc., Chem. Commun.* **1979**, 977–978.

(9) (a) Paulsen, H.; Hayauchi, Y.; Sinnewell, V. *Chem. Ber.* **1980**, *113*, 2601–2608. (b) Legler, G.; Pohl, S. *Carbohydr. Res.* **1986**, *155*, 119–129. (c) Bernotas, R. C.; Pezzone, M. A.; Ganem, B. *Carbohydr. Res.* **1987**, *167*, 305–311.

(10) The pK_A of an aziridine like **4** is expected to be ca. 8.0–9.5: *Small Ring Heterocycles*; Hassner, A., Ed.; Wiley: New York, 1983; Part 1, pp 9–10.

(11) For a leading reference, see: Tsuji, T.; Martin, B. M.; Kaslow, D. C.; Migeon, B. R.; Choudary, P. V.; Stubblefield, B. K.; Mayor, J. A.; Murray, G. J.; Barranger, J. A.; Ginns, E. I. *Eur. J. Biochem.* **1987**, *165*, 275–280.

(12) (3*S*,4*R*,5*S*,6*R*)-1-Aza-3,4,5-trihydroxybicyclo[4.1.0]heptane.

(13) For **9**: ^1H NMR (300 MHz, acetone-d_6) *δ* 4.42 (dd, H-5, *J* = 3.6, 5.5 Hz), 3.82 (ddd, H-3, *J* = 3.4, 4.3, 5.9 Hz), 3.71 (dd, H-4, *J* = 3.6, 5.9 Hz), 3.08 (dd, H-2*β*, *J* = 3.4, 13.4 Hz), 2.87 (dd, H-2*α*, *J* = 4.3, 13.4 Hz), 2.06 (ddd, H-6, *J* = 2.7, 5.5, 5.5 Hz), 1.85 (d, H-7*β*, *J* = 2.7 Hz), 1.65 (d, H-7*α*, *J* = 5.5 Hz); CMR (100 MHz, C_6D_6) 78.11, 76.89, 66.19, 61.28, 55.18, 43.59; CIMS (methane) *m/e* 362 (M + 1, 13%), 73 (100%).

0002-7863/88/1510-0312$01.50/0