Registry No.—1, 525-76-8; **2a**, 62-53-3; **2b**, 106-49-0; **2c**, 99-98-9; **2d**, 106-50-3; **2e**, 104-94-9; **2f**, 150-13-0; **2g**, 98-16-8; **2h**, 591-27-5; **2i**, 95-53-4; **2j**, 578-54-1; **2k**, 90-04-0; **2l**, 88-05-1; **2m**, 579-66-8; **2n**, 118-92-3; **3n**, 58426-37-2; **4a**, 2385-23-1; **4b**, 22316-59-2; **4c**, 58426-38-3; **4d**, 27440-42-2; **4e**, 30507-16-5; **4f**, 4005-05-4; **4g**, 1788-98-3; **4h**, 40671-68-9; **4i**, 72-44-6; **4j**, 7432-25-9; **4k**, 4260-28-0; **4l**, 58426-39-4; **4m**, 58426-40-7; **4n**, 4005-06-5; **5a**, 34264-61-4; **5b**, 58426-41-8; **5c**, 58426-42-9; **5d**, 58426-43-0; **5e**, 58426-44-1; **5h**, 58426-45-2; **5l**, 58426-46-3; **6**, 89-52-1.

References and Notes

(1) Part 1: L. A. Errede, *J. Org. Chem.*, preceding paper in this issue.
(2) (a) G. Heller and G. Fiesselman, *Justus Liebigs Ann. Chem.*, **324**, 134 (1902); (b) R. Anschutz and O. Schmidt, *Ber.*, **35**, 3470 (1902); (c) M. T. Bogert and V. J. Chambers, *J. Am. Chem. Soc.*, **27**, 653 (1905); (d) M. T. Bogert and A. Bender, *ibid.*, **36**, 576 (1914).
(3) A. Katritsky, private communication.
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The Chemistry of Hindered Systems. 2. The Acyloin Reaction—an Approach to Regiospecifically Hydroxylated Tetramethylazacycloheptane Systems

Peter Y. Johnson* and Daniel J. Kerkman

Department of Chemistry, The Johns Hopkins University, Baltimore, Maryland 21218

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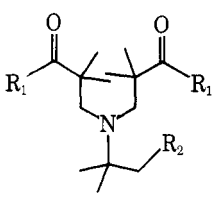
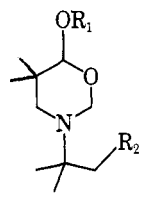
An unusually stable ϵ-lactone, **9**, has been synthesized in high yield by treating mixed animal **7** with 2 equiv of the Grignard reagent generated from ethyl 2-bromoisobutyrate in ether at 0–10 °C. A solvent dependence for this reaction was observed. Reaction of ester lactone **9** under modified acyloin conditions (5 equiv of chlorotrimethylsilane was used as an anion trapping agent) gave acyloin **18** in 68% yield. Infrared studies of the OH stretch region of **18** allowed assignment of several hydrogen bonds and helped to establish possible conformations of **18**. Reduction of **18** with $NaBH_4$ in ethanol at 25 °C was found to occur stereoselectively giving only cis triol **22**. Reduction of **18** with $LiAlH_4$ in refluxing THF gave a 9:1 ratio of cis **22** to trans **24**. The stereochemistry of the triols was established by ^1H NMR techniques employing both achiral and chiral shift reagents and by their ^{13}C NMR spectra. Oxidation of **22** was found to give dialdehyde **5** which was shown to exist in its ϵ-hemiacetal form **25**. In separate experiments, **25** was found to be unstable to prolonged exposure (8 days) to methanol at 25 °C or to heating at 100 °C for 3 h giving, in both cases, aldehyde **26** in high yield. Stereoelectronically controlled reverse Mannich reactions are postulated to explain the latter results. Several molecules, **8** (see ref 6) and **10**, isolated in these studies have been shown to display some anticancer activity.

Our continuing interest in the syntheses[1] and properties[2] of hindered *N-tert*-butyl-3,3′-iminodiesters such as **1** and its aldehyde analogue **2**, which has been shown to undergo a facile rearrangement in alcoholic solvents to give 6-alkoxytetrahydro-1,3-oxazines **3**,[1b,3] a new class of molecules which have been shown to display some anticancer properties,[4] has prompted us to undertake a study of the related hydroxylated systems **4**,[5] **5**, and **6** which we feel might be expected to show



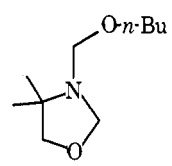
1, R_1 = OEt; R_2 = H
2, R_1 = R_2 = H
4, R_1 = OEt; R_2 = OH
5, R_1 = H; R_2 = OH



3a, R_1 = CH_3; R_2 = H
3b, R_1 = Et; R_2 = H
6, R_1 = CH_3; R_2 = OH

different solubility characteristics. Our efforts directed toward the syntheses of these molecules and studies of their properties will be discussed.

Synthesis of Diester 4 and Lactone 9. Since there are no regiospecific procedures for attaching an OH group to an unactivated alkyl group (e.g., the *tert*-butyl group on diester **1**), a modification of the approach used to synthesize **1**[2] which would allow incorporation of the desired OH group on **4** was devised. Mixed aminal **7** was prepared in 73% yield by treating 2-methyl-2-amino-1-propanol with 2 equiv of formaldehyde and 1 equiv of *n*-butyl alcohol. A minor product, bisoxazolidine **8**, was also isolated from this reaction in ca. 20% yield and was later synthesized by an independent route.[6]



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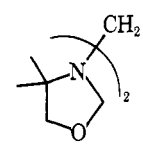
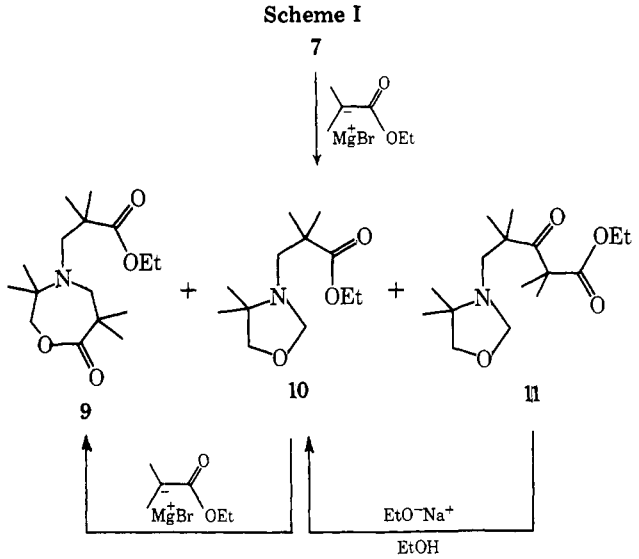


8

Treatment of aminal **7** (Scheme I) with 2 equiv of the Grignard reagent generated from ethyl 2-bromoisobutyrate under mild conditions in anhydrous ether gave, after normal acid–base work-up, a crude material which did not have the properties expected for the desired diester **4**, but which was identified after purification as ethyl *N*-2-(1-hydroxy-2-methylpropyl)-3,3′-imino-2,2,2′,2′-tetramethyldipropionate ϵ-lactone (**9**). An oil, which was identified as monoadduct **10**, was also isolated from this reaction along with small amounts of an isobutyrisobutyrate adduct **11**. The yields of **9** (35–62%) and **10** (10–35%) varied depending on the scale of the reaction and stirring efficiency since insoluble magnesium salts were formed during this reaction. When THF was used as the solvent in this reaction isobutyrisobutyrate adduct **11** and monoadduct **10** were isolated in 57 and 26% yields, respectively. No lactone was recovered in this case.

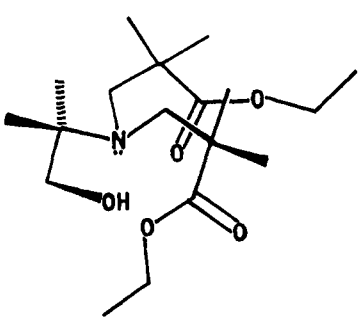
The overall recovery of lactone **9** from these reactions could be increased since: (1) diadduct **11** was found to undergo a reverse Claisen reaction to give **10** in high yield when treated with sodium ethoxide in refluxing ethanol; and (2) monoad-

Scheme I



duct **10** could be converted to lactone **9** in 50–60% yields when treated with 1 equiv of the ethyl isobutyrate Grignard reagent in ether at 0–10 °C. These reactions are shown in Scheme I. In the course of our studies it was noted that when the Grignard reaction was quenched at 0 °C with ice water and the aqueous phase extracted quickly with cold ether, the primary products, as determined by ^{1}H NMR analysis, were diester **4** rather than lactone **9**[5] and oxazolidine **10** and that diester **4** could be isolated in moderate yield and good purity by manipulation of the work-up and purification procedures related to the Grignard reaction (see Experimental Section). All attempts to purify **4** (e.g., GLC, TLC, or column chromatography using silicic acid) resulted in its conversion to **9**. Preliminary attempts to protect the OH group on **4** (e.g., via acylation) also resulted in its conversion to lactone **9**.

We feel that the ready lactonization of **4** occurs as a result of the close proximity of the hydroxymethyl OH group with at least one of the two ester groups of **4** and that this close proximity is due to restricted conformational preferences (see **12**) related to the hindered character of this molecule.[7] This



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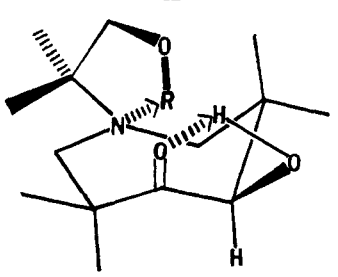
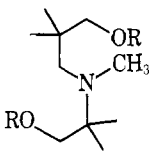


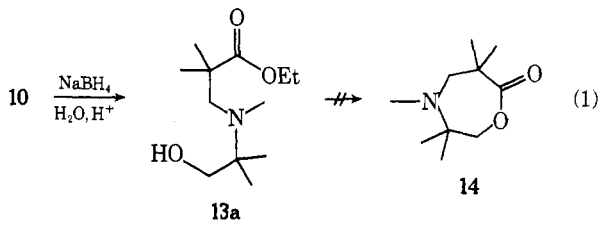
21, R = H
23, R = AlH_3

contention is supported in part by the observation that ester alcohol **13a**, which was synthesized by careful $NaBH_4$ reduc-



13b, R = H
13c, R = Ac

tion of **10** in aqueous acid (pH ~3) and which can readily exist in a linear conformation, could not be converted to ε-lactone **14** using conditions which readily converted **4** to **9** (eq 1).

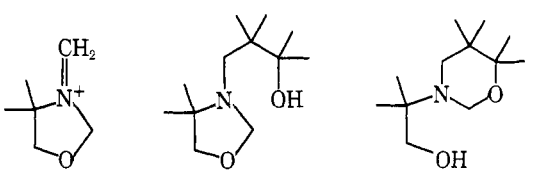


(1)

13a **14**

When **10** was treated with $NaBH_4$ in THF no reaction was observed; however, when a catalytic amount of zinc chloride was added to the reaction mixture, complete reduction of **10** occurred to give diol **13b** which was characterized as its diacetate **13c**.

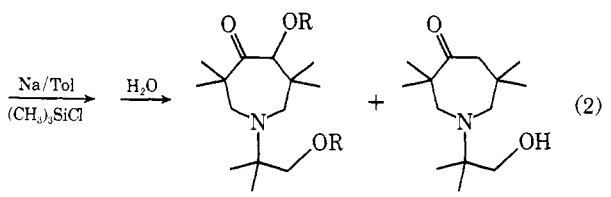
With regard to the formation of **10** and **4** (**9**), we feel our results indicate that initial reaction of the Grignard reagent with aminal **7** takes place at the exocyclic methylene carbon after Lewis acid catalyzed formation of immonium ion **15**. The



15 **16** **17**

fact that reaction of **10** with 4 equiv of methyllithium in THF at 35 °C gave only products resulting from attack at the ester carbonyl, namely a 4:1 mixture of oxazolidine **16** and tetrahydro-1,3-oxazine **17**, supports the intermediacy of a species such as **15** as opposed to direct nucleophilic attack on **7** by the Grignard reagent. It is interesting to note that treatment of this mixture of alcohols with zinc chloride in refluxing THF for 4 h resulted in the clean conversion of **16** to the thermodynamically more stable **17**.

Acyloin Reaction of Lactone 9. A Synthesis of 5. Treatment of ester lactone **9** under acyloin conditions[8] resulted in the formation of **18** in yields ranging from 35 to 62% depending on the reaction time and the scale of the reaction. The addition of 5 equiv of chlorotrimethylsilane[9] to this acyloin reaction seemed to consistently improve the isolated yield of **18** (e.g., 68% on a 0.01-mol scale). This modification, which would be expected to quench sodium ethoxide formed during the reaction, was tried when it was noticed that lactone **9** underwent complete decomposition when heated in the presence of sodium ethoxide in ethanol for extended periods. Conversion of **18** to diacetate **19** in nearly quantitative yield



(2)

18, R = H
19, R = Ac

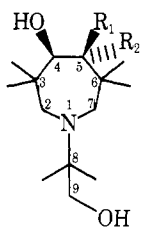
20

confirmed the existence of two OH groups in this molecule. A minor product, ketone **20**, was also isolated from these acyloin reactions in variable yields (eq 2).

Ketol **18** was characterized by its spectra, showning a molecular ion at *m/e* 257 in its mass spectrum and the expected six different methyl signals in both its ^1H and ^{13}C NMR spectra. The existence of a carbonyl band at 1700 cm^{-1} in its infrared spectrum indicated that transannular interactions resulting in hemiacetal formation are not important for **18**[10a] as has been the case for products isolated from the acyloin reaction of other ester lactone substrates[11] as well as other molecules in this series (i.e., **25**).

Careful studies of the OH (and C=O) stretch region of the infrared spectrum of **18**, obtained at various dilutions, and studies of models suggest that the primary hydroxy group and the carbonyl oxygen are in close proximity even though they are separated by six atoms, but do not indicate a transannular nine-membered ring hydrogen bond to the carbonyl.[10b] Specifically, absorptions at 3640 (free OH), 3515, and 3470 cm^{-1} indicate the presence of two associated OH groups having $\Delta\nu$'s of 125 and 170 cm^{-1}, respectively. Comparisons with model systems such as $HO(CH_2)_2N(CH_3)_2$, which shows a $\Delta\nu$ of 138 cm^{-1},[12a] and various α-ketols,[12] which show $\Delta\nu$'s ranging from 180 cm^{-1} (O=C-C-O dihedral angle $\approx$ 0°) to ca. 10 cm^{-1} (O=C-C-O dihedral angle $\geq$120°), suggest both a five-membered ring OH-NR_2 hydrogen bond and an α-ketol hydrogen bond with a O=C-C-O dihedral angle near 0° for **18**. An appropriate cycloheptanoid half-twist boat, half-chair conformation such as **21**, which we feel constitutes the preferred ground-state geometry for these hindered azacycloheptanone systems,[1b] would fit the infrared data while many other conformations can be ruled out because of their large O=C-C-O dihedral angle or CH_3-CH_3 interactions.

While reduction of **18** with $NaBH_4$ in ethanol was expected to parallel that of the *N-tert*-butyl analogue[1b] and give mainly cis triol **22**, it was hoped that reduction of **18** with $LiAlH_4$



22, R_1 = OH; R_2 = H
24, R_1 = H; R_2 = OH

might occur, at least to some extent, via delivery of hydride in a transannular manner from alumunate ester **23**[13] leading to a predominance of trans triol **24**. The reaction of **18** with $NaBH_4$ was found to be stereoselective giving only cis triol in contrast to its *N-tert*-butyl analogue, which gave an 8/2 mixture of cis and trans diols, respectively, under similar conditions.[1b] The reaction of acyloin **18** with $LiAlH_4$ in refluxing THF gave a 9/1 mixture of cis to trans triols. These results have led us to conclude that only steric factors related to the hydroxylated *tert*-butyl group are important in reductions of acyloin **18**.

The triols were separated by column chromatography using silicic acid with hexane–ether elution and were identified by ^1H and ^{13}C NMR techniques. Triol **22**, a meso compound, which was eluted after triol **24**, displayed a singlet at δ 1.02 ($CDCl_3$) integrating for 18 H in its ^1H NMR spectrum indicating that the protons on all six methyl groups of this molecule are isochronous. When the ^1H NMR spectrum was obtained in the presence of 0.2 or 0.4 equiv of the achiral shift reagent $Eu(fod)_3$, three signals of nearly equal intensity appeared indicating the presence of three pairs of enantiotopic

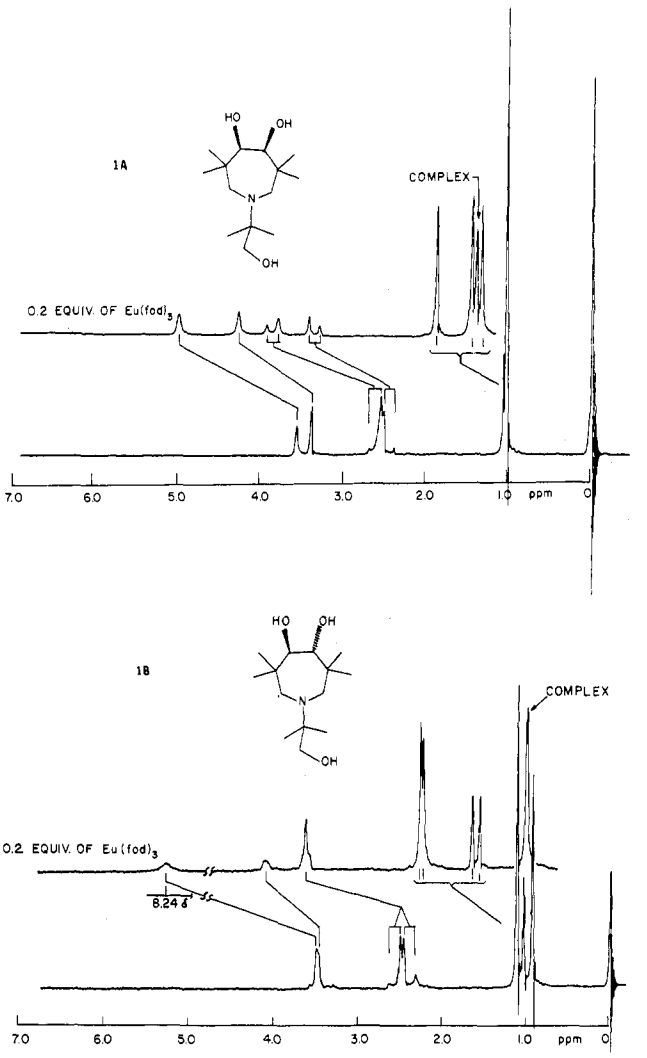


Figure 1. ^1H NMR spectra of triols **22** and **24**: A, **22** (ca. 5% in $CDCl_3$) with insert showing the ^1H NMR spectrum obtained in the presence of 0.2 equiv of $Eu(fod)_3$; B, **24** (ca. 5% in $CDCl_3$) with insert showing the ^1H NMR spectrum obtained in the presence of 0.2 equiv of $Eu(fod)_3$.

methyl groups. In the presence of chiral shift reagent [i.e., 0.4 equiv of $Eu(facam)_3$] the methyl groups became diastereotopic owing to the formation of a "pseudocontact" enantiomer[1b] and six signals of near equal intensity appeared.

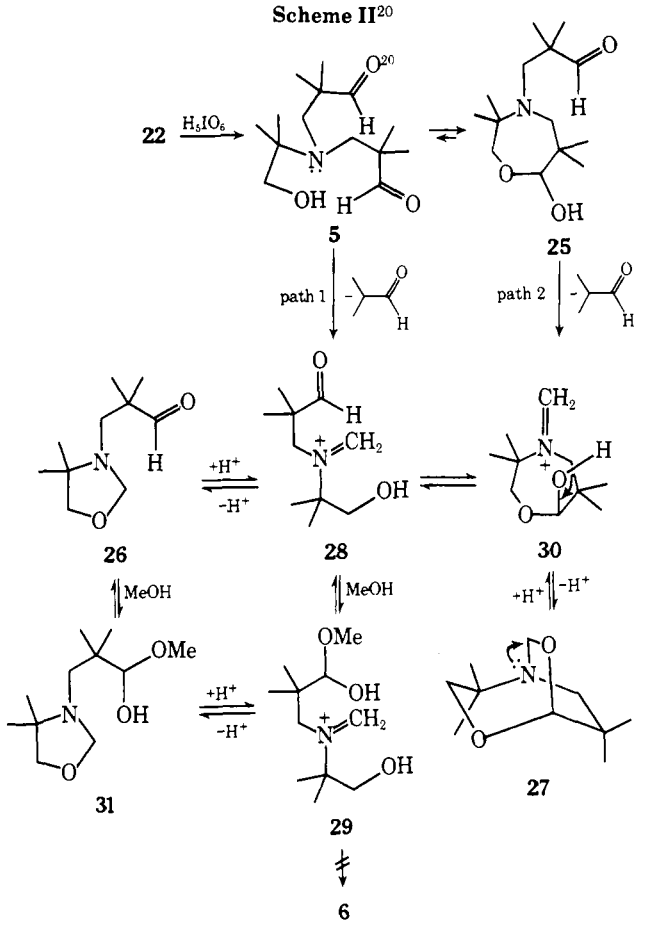
The ^1H NMR spectrum of triol **24** ($CDCl_3$) showed three signals in the methyl region of the spectrum occurring at δ 0.91 (6 H), 1.04 (3 H), and 1.12 (9 H). Because the signal at δ 1.12 appeared to have a shoulder at δ 1.13, the spectrum was obtained in the presence of $Eu(fod)_3$ which allowed resolution of the methyl region of the spectrum and showed two signals integrating for 6 H and two signals integrating for 3 H. This is the pattern one would expect for a trans 3,3,6,6-tetramethyl-1-azacycloheptane-4,5-diol moiety which possesses C_2 symmetry as a result of rapid inversion, rotation processes occurring at nitrogen and which is attached by a bond lying on the C_2 axis to a prochiral carbon[14] possessing two methyl groups. The two methyl groups at C-3 (see **24** for the numbering system) are diastereotopic as are the two at C-6, but since the pro-*R* methyl at C-3 and the pro-*R* methyl at C-6 are homotopic for each enantiomer at ambient temperatures as are the respective pro-*S* methyl groups, only two signals integrating for 6 H each are expected for the tetramethylazacycloheptane moiety. Because of the chirality associated with a group having C_2 symmetry, the two methyl groups on the exocyclic prochiral carbon, C-8, will be diastereotopic. This

accounts for the observed patterns.[15] The ^1H NMR spectra of **22** and **24**, including Eu(fod)$_3$ inserts, are shown in Figure 1.

The cis and trans assignments for **22** and **24** were further confirmed using ^{13}C NMR.[16] Triol **22** showed signals for the eight different carbons expected for this meso compound, while the trans isomer showed signals for nine different carbons reflecting the diastereotopic character of the methyl carbons attached to the exocyclic prochiral center at C-8 of **24**.

Oxidation of triol **22** (Scheme II) using 1 equiv of paraperiodic acid in either aqueous acid (pH ~3) or methanol at ambient temperatures led, after workup, to the same crude semisolid material which did not have the properties expected for dialdehyde **5** but which was identified after purification by careful sublimation (pot temperature ca. 50 °C) as ϵ-hemiacetal **25**[16] (mp 89–90 °C). Attempts to purify crude **25** by distillation led to the formation of a mixture of **25** and a new product which was identified as oxazolidine **26**. Subsequently it has been found that heating **25** in refluxing dioxane for 4 h leads to its quantitative conversion to **26**.

Scheme II[20]



Unlike *N-tert*-butyl dialdehyde **2** which decomposed to give tetrahydro-1,3-oxazine **3a** when stirred in methanol at 25 °C for 15 h, anomer **25**, which might be expected to be in equilibrium with its dialdehyde form **5** in polar solvents such as methanol, did not break down in this solvent to form either the desired 6-methoxytetrahydro-1,3-oxazine **6** or a hoped for [3.2.2]bicyclotetrahydro-1,3-oxazine **27**, which might have resulted from intramolecular capture of the hemiacetal OH group by the incipient immonium ion[17] (see Scheme II, path 2), but rather broke down over several days to give good yields of **26**. Because of the previously demonstrated preference for the formation of six-membered rings over five-membered rings in related systems (e.g., **16** → **17**), efforts were made to synthesize **6** by equilibrating the hemiacetal of **26** (i.e., **31**) generated in situ in the presence of methanol containing a catalytic amount of zinc chloride. While the zinc chloride caused the slow decomposition of **26**, no evidence for the formation of **6** was obtained upon examination of the ^1H NMR spectrum of the crude reaction mixture. The above reactions and possible intermediates involved in the formation of **26** are summarized in Scheme II. We feel that **5** and **25** are in an equilibrium which favors **25** under normal conditions and that formation of **26** results indirectly from intermediate ion **28**[20] (formed via path 1 or path 2). Experimental evidence indicates that immonium ions **28** and **30** may be formed via a reverse Mannich reaction[18] which involves the stereoelectronically controlled[19] loss of isobutyraldehyde from amines **5** and **25**, respectively.

While the lack of direct capture of the OH group on **30** to give the bicyclo system **27** could be explained by the overall lack of importance of path 2 (Scheme II) or by the strained nature of the product which might, if formed, revert back to **30** under the reaction conditions, our inability to isolate **6**, considering the viability of intermediate **29**, is harder to understand. Further work on the chemistry and properties of these hindered amines is in progress.

Experimental Section

Melting points were taken in capillary tubes on a Thomas-Hoover Unimelt and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 457 A spectrometer. The ^1H NMR spectra were taken either on a Varian A-60 spectrometer or on a Perkin-Elmer JEOL MH-100 spectrometer and are reported in parts per million downfield from tetramethylsilane. The ^{13}C NMR spectra were taken on a Varian CFT-20 spectrometer and are reported in parts per million downfield from tetramethylsilane. The abbreviations s, singlet; d, doublet; t, triplet; q, quartet refer to the multiplicity of the absorption in an off-resonance decoupled spectrum. Mass spectra were determined on a Perkin-Elmer Hitachi RMU-6D spectrometer. Ultraviolet spectra were taken on a Cary 14 recording spectrophotometer. Gas chromatography was carried out using programmed temperature control on a Hewlett-Packard 5750 B instrument equipped with 8- and 10-ft stainless steel columns packed with SE-30 on 80–100 mesh Chromosorb P. Mallinckrodt AR 100 mesh silicic acid was used for all column chromatography. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

***N*-*n*-Butoxymethyl-4,4-dimethyl-1,3-oxazolidine (7).** To a mixture of 74 g (1.0 mol) of 1-butanol, 60 g (2.0 mol) of paraformaldehyde, and 400 ml of benzene was added dropwise 89 g (1.0 mol) of 2-amino-2-methyl-1-propanol. The mixture was brought to reflux and water removed as an azeotrope using a Dean-Stark trap. After removal of the theoretical amount of water, the solvents were distilled off at 100 mm pressure and finally the crude oil remaining was distilled under high vacuum to give 136 g (73%) of pure **7** as a clear liquid: bp 59–60 °C (0.3 mm); ir (CCl_4) no C=O; ^1H NMR (CCl_4) δ 0.91 (t, 3), 1.17 (s, 6), 1.44 (m, 4), 3.35 (t, 2), 3.48 (s, 2), 4.19 (s, 2), 4.57 (s, 2); mass spectrum (70 eV) *m/e* (rel intensity) 187 (trace, M^+), 114 (37), 70 (39), 57 (70), 56 (36), 55 (23), 42 (100), and 41 (55).

Bisoxazolidine **8** was also isolated as a high-boiling oil in ca. 20% yield from this reaction (see below).

***N,N'*-Methylenebis(4,4-dimethyl-1,3-oxazolidine) (8).** To a refluxing mixture of 1.29 g (0.043 mol) of trioxane and 200 ml of benzene was added dropwise 2.54 g (0.029 mol) of 2-amino-2-methyl-1-propanol. After removal of water and workup as described for **7**, **8** was isolated by distillation in 35% yield: bp 80–83 °C (0.3 mm); ir (CCl_4) no C=O; ^1H NMR (CCl_4) δ 1.09 (s, 12), 3.39 (s, 2), 3.52 (s, 4), 4.41 (s, 4).

Reactions of 7. A. Diethyl *N*-2-(1-Hydroxy-2-methylpropyl)-3,3'-imino-2,2,2',2'-tetramethyldipropionate (4). Into a flame-dried three-neck Morton flask equipped with an overhead stirrer, addition funnel, and condenser was added 12.15 g (0.5 mol) of clean magnesium turnings and 50 ml of dry ether. To the stirring mixture, which was under N_2 and cooled to 10–20 °C, was added, over several hours, 82.0 g (0.4 mol) of ethyl 2-bromoisobutyrate in 200 ml of ether. After complete formation of the Grignard reagent (determined by GLC analysis), 37.4 g (0.2 mol) of aminal **7** in 300 ml of ether was added to

the flask over several hours (stirring becomes difficult as 7 is added) and the reaction mixture was stirred for an additional 1 h at 10–20 °C. After the mixture was cooled to 0 °C, ice water was added and the mixture extracted three times with cold ether. The ether was dried over K_2CO_3 and evaporated under vacuum to give a crude oil which was shown by ^1H NMR analysis to contain monoadduct **10** and diester **4**. The crude mixture was rapidly distilled to give **10** (ca. 20% yield, see below) and a high-boiling fraction which was shown to be a mixture of **4** and lactone **9**. The high-boiling mixture was dissolved in a small amount of hexane and allowed to cool at −10 °C for 24 h causing **9** to precipitate. Lactone **9** was removed from the hexane mixture by vacuum filtration and the hexane solvent removed from the mother liquor under high vacuum to give an oil which was not further purified but was characterized as diester **4**: yield ca. 50%; bp 123–127 °C (0.1 mm) with decomposition to **9**; ir ($CHCl_3$) 3500, 2960, 1720, 1260, 1145, and 1090 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (s, 6), 1.20 (s, 12), 1.27 (t, 6, J = 7 Hz), 2.82 (s, 4), 2.91 (br s, 1, absent in D_2O), 3.32 (s, 2), and 4.12 (q, 4, J = 7 Hz).

Anal. Calcd for $C_{18}H_{35}NO_5$: C, 62.58; H, 10.21. Found: C, 64.85; H, 10.45.

Reactions of 7. B. Ethyl *N*-2(1-Hydroxy-2-methylpropyl)-3,3′-imino-2,2,2′,2′-tetramethyldipropionate ε-Lactone (9). The Grignard reaction was run as described above to obtain a crude material which was subjected to an acid–base work-up. The crude amines were added to a flask containing ethanol in which a trace of sodium had been dissolved and were heated for 0.5 h. After removal of the ethanol in vacuo and an acid–base work-up the crude material was distilled to give 15.5 g (34%) of **10** (see below) and 31 g (52%) of lactone **9**.

For **9**: bp 133–138 °C (0.2 mm); mp (hexane) 76–77 °C; ir ($CHCl_3$) 2978, 1725, 1467, 1392, 1370, and 1140 cm^{-1}; ir (CCl_4) 1730 and 1715 cm^{-1}; ^1H NMR ($CDCl_3$, 25 °C[5]) δ 1.06 (s, 6), 1.19 (s, 6), 1.27 (s, 6), 1.28 (t, 3, J = 7 Hz), 2.57 (s, 2), 2.71 (s, 2), 3.99 (s, 2), and 4.13 (q, 2, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 14.01 (q), 19.99 (broad, q), 24.58 (q), 26.81 (q), 43.22 (s), 44.83 (s), 57.32 (s), 57.84 (t), 58.34 (t), 60.49 (t), 74.07 (t), 177.16 (s), 177.53 (s); mass spectrum (70 eV) m/e (rel intensity) 299 (6, M^+), 284 (1), 198 (6), 184 (100), 112 (43), 84 (83), 70 (60), and 55 (25) with metastable peaks at m/e 113.0 ($184^2/299$), 68.0 ($112^2/184$), and 63.2 ($84^2/112$).

Anal. Calcd for $C_{16}H_{29}NO_4$: C, 64.18; H, 9.76; N, 4.68. Found: C, 64.51; H, 9.72; N, 4.79.

Reactions of 7. C. Ethyl 2,2-Dimethyl-3-[*N*-(4,4-dimethyl-1,3-oxazolidine)]propionate (10) and Ethyl 2,2,4,4-Tetramethyl-5-[*N*-(4,4-dimethyl-1,3-oxazolidine)]-3-oxopentanoate (11). The Grignard reaction was run as described above but THF was used as the solvent for the reaction in place of ether. Acid–base work-up and purification by distillation gave 12.5 g (26%) of mono adduct **10** and 34 g (57%) of diadduct **11**.

For **10**: bp 80–81 °C (0.1 mm); ir (CCl_4) 2970, 2870, 1735, 1475, 1273, 1250, 1145, 1100, 1030, and 947 cm^{-1}; ^1H NMR (CCl_4) δ 1.01 (s, 6), 1.12 (s, 6), 1.22 (t, 3, J = 7 Hz), 2.58 (s, 2), 3.49 (s, 2), 4.08 (q, 2, J = 7 Hz), 4.29 (s, 2); mass spectrum (70 eV) m/e (rel intensity) 229 (1, M^+), 114 (100), and 42 (85).

Anal. Calcd for $C_{12}H_{23}NO_3$: C, 62.85; H, 10.11; N, 6.11. Found: C, 62.80; H, 10.07; N, 6.18.

For **11**: bp 114–118 °C (0.2 mm); ir (CCl_4) 2970, 2870, 1742, 1695, 1465, 1260, and 1145 cm^{-1}; ^1H NMR (CCl_4) δ 0.98 (s, 6), 1.12 (s, 6), 1.25 (t, 3, J = 7 Hz), 1.30 (s, 6), 2.52 (s, 2), 3.42 (s, 2), 4.12 (q, 2, J = 7 Hz), 4.21 (s, 2); mass spectrum (70 eV) m/e (rel intensity) 299 (trace, M^+), 114 (100), and 42 (75).

Anal. Calcd for $C_{16}H_{29}NO_4$: C, 64.18; H, 9.76. Found: C, 63.96; H, 9.76.

Conversion of 11 to 10. Diadduct **11**, 2 g (6.7 mmol), was refluxed under N_2 in 150 ml of ethanol in which 0.1 g of sodium had been previously dissolved. Solvent was removed steadily from the flask via a Dean-Stark trap until the volume of solvent was near 50 ml (ca. 20 h). The remaining solvent was removed in vacuo and the crude residue extracted with water–ether. The ether layer was dried with K_2CO_3 and evaporated to give an oil which was distilled to give 1.07 g (70%) of pure **10**.

Grignard Reaction of 10. These reactions were run in ether solvents using 1 equiv each of magnesium, ethyl 2-bromoisobutyrate, and monoadduct **10** as described above for the reactions of **7**. The products isolated, **4** or **9** (50–60%), depended on the workup employed (see above).

Reduction of 10. Ethyl 6-Hydroxy-2,2,4,5,5-pentamethyl-4-azahexanoate (13a). To a mixture of 0.98 g (4.3 mmol) of **10** in 25 ml of ethanol and enough 6 N HCl to obtain a pH of ca. 3 was added dropwise, over 1 h, 0.17 g (4.5 mmol) of $NaBH_4$ dissolved in water containing a trace of base as a stabilizer. The pH of the reaction mixture was maintained at ca. 3 with 6 N HCl as the reaction progressed. After being allowed to stir for 15 min the reaction was quenched with cold aqueous KOH and the ethanol removed in vacuo. Water–ether extraction of the crude residue followed by evaporation of the ether and distillation of the organic material gave 0.65 g (65%) of ester **13a**: bp 92–95 °C (0.2 mm); ir ($CHCl_3$) 3640, 3425, 2920, 1720, 1265, 1145, and 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (s, 6), 1.17 (s, 6), 1.23 (t, 3, J = 7 Hz), 2.14 (s, 3), 2.57 (s, 2), 3.2 (br s, 1, absent D_2O), 3.28 (s, 2), and 4.06 (q, 2, J = 7 Hz); mass spectrum (70 eV) m/e (rel intensity) 231 (none, M^+), 213 (1, $-H_2O$), 185 (2, −HOEt), 98 (100), and 44 (40). Reduction of **10** using $NaBH_4$ in THF containing zinc chloride or using $LiAlH_4$ in THF resulted in near quantitative formation of diol **13b** which was characterized as its diacetate **13c** synthesized by treating **13b** with acetic anhydride–pyridine.

For **13b**: bp 90–91 °C (0.2 mm); ir ($CHCl_3$) 3600, 3380, 2920, and 1060 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (s, 6), 1.02 (s, 6), 2.28 (s, 3), 2.42 (s, 2), 3.39 (s, 2), 3.42 (s, 2), and 4.6 (br s, 2, absent D_2O).

For **13c**: bp 97–98 °C (0.2 mm); ir ($CHCl_3$) 2950, 1735, 1725, 1235, and 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (s, 6), 1.03 (s, 6), 2.04 (s, 6), 2.25 (s, 3), 2.30 (s, 2), 3.80 (s, 2), and 3.90 (s, 2); mass spectrum (70 eV) m/e (rel intensity) 273 (trace, M^+), 98 (100), and 43 (27).

Reaction of 10 with Methyllithium. 2,3,3-Trimethyl-4-[*N*-(4,4-dimethyl-1,3-oxazolidine)]-2-butanol (16) and 2-Methyl-2-[*N*-(5,5,6,6-tetramethyltetrahydro-1,3-oxazine)]-1-propanol (17). To 0.38 g (1.65 mmol) of oxazolidine **10** dissolved in 25 ml of dry THF under N_2 at 35 °C was added 5.05 ml (6.55 mmol) of 1.3 M methyllithium in ether. The mixture was heated for 40 min, cooled to 25 °C, and extracted with water–ether. The ether layer was dried over K_2CO_3 and evaporated to give 0.32 g (90%) of a 4:1 mixture of **16** to **17** as judged by ^1H NMR.

Treatment of this mixture (0.30 g, 1.4 mmol) with a catalytic amount of zinc chloride in 25 ml of refluxing THF for 3 h under N_2 allowed the isolation, after acid–base work-up, of 0.27 g (90%) of oxazine **17**.

For **16**: ir ($CHCl_3$) 3645, 3280, no C=O, and 1090 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (s, 6), 1.16 (s, 6), 1.21 (s, 6), 2.59 (s, 2), 3.58 (s, 2), and 4.52 (s, 2); mass spectrum (70 eV) m/e (rel intensity) 215 (1, M^+).

For **17**: bp 76–77 °C (0.2 mm); ir ($CHCl_3$) 3645, 3280, no C=O, and 1085 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (s, 6), 1.05 (s, 6), 1.18 (s, 6), 2.45 (s, 2), 3.33 (s, 2), and 4.32 (s, 2); mass spectrum (70 eV) m/e (rel intensity) 215 (1, M^+).

Anal. Calcd for $C_{12}H_{25}NO_2$: C, 66.93; H, 11.70. Found: C, 66.75; H, 11.66.

Acyloin Reaction of Lactone 9. *N*-2-(1-Hydroxy-2-methylpropyl)-3,3,6,6-tetramethyl-1-azacycloheptan-4-on-5-ol (18). Into a dried three-neck 500-ml Morton flask equipped with an overhead stirrer, addition funnel, and condenser was added 200 ml of dried toluene and 1.3 g (0.057 mol) of sodium metal. The toluene was brought to reflux and the sodium converted to a fine sand in a N_2 atmosphere using high-speed stirring. Lactone **9** (3.53 g, 0.012 mol) in 50 ml of toluene and 10 ml (0.08 mol) of chlorotrimethylsilane were added simultaneously, but from separate addition funnels (one was placed on top of the condenser) over 0.5 h. After the reaction mixture was allowed to reflux for 4 h, it was cooled to 0 °C and quenched with 10% aqueous NH_4Cl. The pH of the mixture was adjusted to 14 using KOH and the aqueous layer extracted several times with ether which was evaporated in vacuo to give a crude material. The crude mixture was stirred in methanol containing 10% aqueous HCl for 3 h in order to hydrolyze any sililated oxygen groups. Acid–base work-up gave 2.06 g (68%) of ketol **18**: mp (sublimed) 67–69 °C; ir ($CHCl_3$) 3640, 3515, 3470, 2970, 2865, 1700, 1470, 1400, 1380, 1362, 1210, 1050, and 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.71 (s, 3), 0.99 (s, 3), 1.03 (s, 3), 1.06 (s, 3), 1.13 (s, 3), 1.28 (s, 3), 2.53 (br s, 1, absent D_2O), 2.61 (AB, 2, J = 14 Hz), 2.73 (AB, 2, J = 16 Hz), 3.41 (AB, 2, J = 11 Hz), 3.82 (d, 1, J = 6 Hz, absent in D_2O), and 4.23 (d, 1, J = 6 Hz, s in D_2O); ^{13}C NMR ($CDCl_3$) δ 19.52 (q), 20.38 (q), 23.18 (q), 24.21 (q), 25.75 (q), 25.87 (q), 40.00 (s), 47.04 (s), 58.87 (s), 59.60 (t), 64.06 (t), 68.80 (t), 79.40 (d), and 217.38 (s); mass spectrum (70 eV) m/e (rel intensity) 257 (2, M^+), 255 (3), 239 (4), 226 (100), 198 (25), 84 (20), 83 (20), 70 (33), 57 (50), and 43 (40); uv λ_{max} (EtOH) 290 nm (ϵ 53), 248 (shoulder, 200).

Anal. Calcd for $C_{14}H_{27}NO_3$: C, 65.33; H, 10.58. Found: C, 64.94; H, 10.49.

When this reaction was run on a larger scale the yield of **18** generally decreased. When run in the absence of chlorotrimethylsilane the yields of **18** varied from 35 to 62%. A minor product, which was observed in as high as 5% yields and which could be isolated pure by column chromatography using silicic acid with hexane–ether elution, was identified as *N*-2-(1-hydroxy-2-methylpropyl)-3,3,6,6-tetramethyl-1-azacycloheptan-4-one (**20**): mp (sublimation) 78–80 °C; ir ($CHCl_3$) 3500, 2965, 2870, 1696, and 1048 cm^{-1}; ir (CCl_4) 3640, 3515,

and 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (s, 6), 1.00 (s, 12), 2.32 (br s, 1, absent D_2O), 2.39 (s, 2), 2.47 (s, 2), 2.71 (s, 2), 3.34 (br s, 2, sharp in D_2O, CH_2OH); ^{13}C NMR ($CDCl_3$) δ 22.16 (q), 23.98 (q), 27.73 (q), 34.43 (s), 48.77 (s), 52.19 (t), 59.01 (s), 61.09 (t), 65.39 (t), 68.91 (t), 215.46 (s); mass spectrum (70 eV) *m/e* (rel intensity) 241 (3, M^+), 223 (15), 210 (30), 198 (18), 182 (100), 84 (45), 70 (40), 55 (50), 43 (70), and 41 (70).

***N*-2-(1-Acetoxy-2-methylpropyl)-3,3,6,6-tetramethyl-5-acetoxy-1-azacycloheptan-4-one (19).** Diacetate **19** was synthesized by refluxing 0.5 g of ketol **18** in a 1/1 mixture of acetic anhydride–acetic acid (6 ml total) for 3 h. Acid–base workup gave 0.60 g (90%) of **19**: mp (sublimed) 76–79 °C; ir ($CHCl_3$) 2965, 1740, 1725, 1245, and 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (s, 3), 0.97 (s, 3), 1.06 (s, 3), 1.12 (s, 6), 1.17 (s, 3), 2.06 (s, 3), 2.10 (s, 3), 2.68 (AB, 2, J = 13 Hz), 2.87 (AB, 2, J = 14 Hz), 3.98 (s, 2), and 5.11 (s, 1); mass spectrum (70 eV) *m/e* (rel intensity) 341 (trace, M^+), 268 (100), 222 (32), and 43 (80); uv λ_{max} (EtOH) 290 nm (ϵ 55), 244 (shoulder, 270).

Anal. Calcd for $C_{18}H_{31}NO_5$: C, 63.31; H, 9.15. Found: C, 63.59; H, 9.27.

Reduction of 18. *cis*-*N*-2-(1-Hydroxy-2-methylpropyl)-3,3,6,6-tetramethyl-1-azacycloheptane-4,5-diol (22) and Trans Triol 24. A mixture of 0.937 g (3.64 mmol) of ketol **18** and excess $NaBH_4$ was stirred at 25 °C in ethanol for 19 h. After removal of the ethanol in vacuo and acid–base workup, a crude solid was isolated. Analysis by GLC, TLC, and ^1H NMR indicated that only one diastereomer was obtained. Sublimation of the solid gave 0.836 g (85%) of pure cis **22**: mp 136–137 °C; ir ($CHCl_3$) 3595, 3440, 2940, 2875, and 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03 (s, 18), 2.56 (AB, 4, J = 14 Hz), 3.03 (br s, 3, absent in D_2O), 3.41 (s, 2), and 3.59 (s, 2); ^{13}C NMR ($CDCl_3$) δ 21.96 (q), 25.37 (q), 28.07 (q), 38.17 (s), 58.79 (s), 60.88 (t), 68.99 (t), and 81.12 (d); mass spectrum (70 eV) *m/e* (rel intensity) 259 (trace, M^+) and 228 (100).

Anal. Calcd for $C_{14}H_{29}NO_3$: C, 64.82; H, 11.27. Found: C, 65.08; H, 11.28.

When **18** was reduced by adding it to a refluxing mixture of $LiAlH_4$ in THF a ca. 9:1 mixture of cis **22** and trans **24** triols was obtained. These could be separated by careful column chromatography using silicic acid with hexane–ether–ethanol elution. Triol **24** was eluted first.

For **24**: mp (sublimed) 161–163 °C; ir ($CHCl_3$), 3635, 3515, 2950, 1035, and 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (s, 6), 1.04 (s, 3), 1.12 (s, 9), 2.48 (AB, 4, J = 13 Hz), 2.36 (br s, 3, absent in D_2O), 3.44 (br s, 2), and 3.48 (br s, 2); ^{13}C NMR ($CDCl_3$) δ 19.93 (q), 20.89 (q), 23.06 (q), 27.65 (q), 37.47 (s), 58.84 (s), 63.99 (t), 69.18 (t), and 74.48 (d); mass spectrum (70 eV) *m/e* (rel intensity) 259 (1, M^+), and 228 (100).

Anal. Calcd for $C_{14}H_{29}NO_3$: C, 64.82; H, 11.27. Found: C, 64.87; H, 11.18.

Oxidation of 22. *N*-2-(1-Hydroxy-2-methylpropyl)-3,3′-imino-2,2,2′,2′-tetramethyldipropanal ϵ-Hemiacetal (25). Triol **22** (3.80 g, 0.0147 mol) and paraperiodic acid (3.60 g, 0.015 mol) were stirred in methanol solvent for 24 h at 25 °C. The methanol was removed in vacuo and the residue was extracted with 10% aqueous K_2CO_3–ether. The ether layer was dried with K_2CO_3 and evaporated to give 1.8 g of a crude semisolid. Purification by sublimation (pot temperature ≤50 °C) gave 1.7 g (44%) of pure **25**: mp 89–90 °C; ir ($CHCl_3$) 3680, 3400, 2960, 2810, 2700, 1720, 1468, 1365, and 1085 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (s, 3), 0.94 (s, 3), 0.98 (s, 3), 1.06 (s, 6), 1.14 (s, 3), 2.16 (d, 2, J = 14 Hz), 2.60 (AB, 2, J = 14 Hz), 2.62 (d, 2, J = 14 Hz), 3.26 (d, 2, J = 14 Hz), 3.40 (br s, 1, absent D_2O), 3.82 (d, 2, J = 14 Hz), 4.57 (s, 1), and 9.62 (s, 1).

Anal. Calcd for $C_{14}H_{27}NO_3$: C, 65.33; H, 10.58. Found: C, 65.16; H, 10.55.

Heating **25** above its melting point (e.g., attempted purification by distillation) led to its conversion to **26**.

2,2-Dimethyl-3-[*N*-(4,4-dimethyl-1,3-oxazolidine)]propanal (26). A. Hemiacetal **25** (250 mg, 1 mmol) was stirred in methanol for 8 days at which time the methanol (and isobutyraldehyde) were removed in vacuo giving **26** as the only product detectable by GLC or ^1H NMR.

B. Hemiacetal **25** (500 mg, 2 mmol) was heated at reflux in dry dioxane for 4 h, then cooled, and the solvent removed in vacuo to give 320 mg (89%) yield of **26** as the only product.

For **26**: bp (pot) ca. 80 °C (0.5 mm); ir ($CHCl_3$) 2925, 2860, 2815, 2710, 1725, 1465, and 1090 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.07 (s, 6), 1.09 (s, 6), 2.64 (s, 2), 3.62 (s, 2), 4.38 (s, 2), 9.50 (s, 1); mass spectrum (70 eV) *m/e* (rel intensity) 185 (5, M^+), 184 (6), 170 (20), 155 (30), 114 (56), 100 (54), 70 (47), and 42 (100).

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Registry No.—**4**, 58384-41-1; **7**, 58384-42-2; **8**, 58384-43-3; **9**, 40910-26-7; **10**, 40910-25-6; **11**, 40910-27-8; **13a**, 58384-44-4; **13b**, 58384-45-5; **13c**, 58384-46-6; **16**, 58384-47-7; **17**, 58384-48-8; **18**, 58384-49-9; **19**, 58384-50-2; **20**, 58384-51-3; **22**, 58384-52-4; **24**, 58384-53-5; **25**, 58384-54-6; **26**, 58384-55-7; 1-butanol, 71-36-3; 2-amino-2-methyl-1-propanol, 124-68-5; ethyl 2-bromoisobutyrate, 600-00-0; methyllithium, 917-54-4.

Supplementary Material Available. The ^{13}C NMR spectra of triols **22** and **24** (Figure 2) and the ^1H NMR spectrum of ϵ-hemiacetal **25** (Figure 3) (2 pages). Ordering information is given on any current masthead page.

References and Notes

(1) (a) Presented in part at the 6th Northeast Regional Meeting of the American Chemical Society, Burlington, Vt., August 18, 1974; (b) P. Y. Johnson, I. Jacobs, and D. J. Kerkman, *J. Org. Chem.*, **40**, 2710 (1975); (c) P. Y. Johnson and I. Jacobs, *Synth. Commun.*, **4**, 51 (1974).

(2) P. Y. Johnson and I. Jacobs, *J. Chem. Soc., Chem. Commun.*, 925 (1972).

(3) (a) H. Möhrle and D. Schnädelbach, *Arch. Pharm. (Weinheim, Ger.)*, **308**, 352 (1975); (b) H. Möhrle and D. Schnädelbach, *ibid.*, **308**, 783 (1975).

(4) P. Y. Johnson and R. Silver, *J. Heterocycl. Chem.*, 1029 (1973).

(5) A preliminary report on some aspects of this work has appeared: P. Y. Johnson and M. Davis, *Tetrahedron Lett.*, 293 (1973).

(6) This molecule, which could be looked at as a potential 1,5-dialkylating agent in its diimmonium form, has been shown to display some activity against lymphocytic leukemia (P-388). Testing was performed by the National Cancer Institute.

(7) For dynamic ^1H NMR studies of related acyclic systems see ref 1b and references cited therein. Dynamic ^1H and ^{13}C NMR studies on lactone **9** have also been performed. A $\Delta G^{\ddagger}$ for nitrogen invession processes of 13.4 kcal/mol was found.

(8) For an early report on the acyloin reaction of an ester lactone containing molecule in the synthesis of colchicine see E. E. van Tamelen et al., *J. Am. Chem. Soc.*, **81**, 6341 (1959). For a discussion of this unusual type of acyloin reaction see J. J. Bloomfield, D. C. Owsley, and J. M. Nelke, *Org. React.*, **23**, 74 (1975).

(9) For a review of the reagent as an anion trapping agent see K. Rühlmann, *Synthesis*, 236 (1971).

(10) (a) The carbonyl band of *N-tert*-butyl-3,3,6,6-tetramethyl-1-azacycloheptan-4-on-5-ol[1b] also accurs at 1700 cm^{-1} when its infrared spectrum is taken under the same conditions. (b) Such a hydrogen bond would be expected to lower the carbonyl stretching frequency relative to the nonhydroxylated system given above.

(11) (a) E. E. van Tamelen et al., *Tetrahedron*, **14**, 8 (1961); (b) E. Fujita et al., *Tetrahedron Lett.*, 2573 (1969), and references cited therein.

(12) (a) P. v. R. Schleyer and L. Joris, *J. Am. Chem. Soc.*, **90**, 4599 (1968); (b) M. Oki et al., *Bull. Chem. Soc. Jpn.*, **41**, 176 (1968).

(13) M. Akhtar and S. Marsh, *J. Chem. Soc. C*, 937 (1966).

(14) For a review of chemical shift nonequivalence in prochiral groups see W. B. Jennings, *Chem. Rev.*, **75**, 307 (1975).

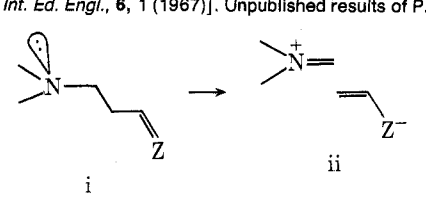
(15) While one would expect eight signals (four showing 6 H and four showing 3 H) attributable to the methyl protons in the ^1H NMR spectrum of **24** in the presence of a chiral shift reagent due to the formation of "pseudocontact" diastereomers,[1b] this experiment was not run owing to lack of sample.

(16) See paragraph at end of paper regarding supplementary material.

(17) For examples of intramolecular capture of an OH group by an incipient immonium ion: (a) to give polycyclic systems see Y. Ban et al., *Tetrahedron Lett.*, 727 (1975); (b) to give a [3.3.1] bicyclic system see A. I. Meyers and C. C. Shaw, *ibid.*, 717 (1974).

(18) Mannich and reverse Mannich reactions involving 2,2-disubstituted ketones (but not aldehydes) have been the subject of considerable controversy. A discussion of the problem has been treated by G. L. Buchanan, A. C. Curran, and R. T. Wall, *Tetrahedron*, **25**, 5503 (1969), and references cited therein.

(19) Studies in our laboratories of the facile reverse Mannich reaction of hindered amino dialdehydes (e.g., **2** → **3**) indicate that stereoelectronic control in these systems seems to involve both (a) stereopopulation control [R. T. Borchardt and L. A. Cohen, *J. Am. Chem. Soc.*, **94**, 9166 (1972), and references cited therein] and (b) synchronous heterolytic fragmentation shown generalized below (i.e., i → ii) [C. A. Grob and P. W. Schiess, *Angew. Chem., Int. Ed. Engl.*, **6**, 1 (1967)]. Unpublished results of P. Y. Johnson.



i ii

(20) While we feel that ions **28** and **29** are intermediates in these reactions, direct five-membered ring formations (i.e., **28** → **26** and **29** → **31**) are unlikely since such processes would involve highly unfavorable endocyclic ring closures.