(8 mL) at room temperature and the mixture brought to reflux for 6 h. The flask was then cooled to 0 °C and its contents were carefully treated with aqueous KOH (2 M, 0.9 mL, 1.8 mmol). After 5 min, more THF (15 mL) was added and the mixture again brought to reflux for 0.5 h, then cooled, and allowed to stand overnight. The supernatant was decanted, more THF (15 mL) added to the residue, and decanting repeated. The combined THF layers were concentrated and the residue was flash chromatographed ($CH_2Cl_2/CH_3OH/NH_4OH$, 2:2:1) to afford *trans*-alkene **3** (0.025 g, 62%) as an oil, along with recovered **1** (0.010 g). For **3**: ^1H NMR (D_2O) 5.79, 5.67 (dt, 2 H, J = 15.5, 6 Hz), 3.21 (t, 4 H), 2.67 (t, 2 H), 2.61 (t, 2 H), 1.64 (m, 2 H); IR (film) 3300, 2930, 2860, 1600, 1140, cm^{-1}; HRMS (20 eV) calcd for $C_7H_{17}N_3$ 143.2334, found 143.2238.

N^1,N^4-Bis(3-azidopropyl)-1,4-diamino-2-butyne (8). A solution of 1,4-diamino-2-butyne (0.326 g, 3.88 mmol) in CH_3OH (10 mL) was added to 3-azidopropionaldehyde (1.52 g, 15.35 mmol) in CH_3OH (15 mL) at room temperature. Sodium cyanoborohydride (1.75 g) was added in portions and the pH adjusted to 6 with methanolic HCl. After stirring 16 h, the product was isolated as above for **7** and purified by flash chromatography to afford **8** (0.24 g, 46%) as an oil: ^1H NMR ($CDCl_3$) 3.43 (s, 4 H), 3.39 (t, 4 H), 2.77 (t, 4 H), 1.77 (m, 4 H); IR (film) 3300, 2940, 2820, 2100 (N_3) 1450, 1260, 1030 cm^{-1}; CIMS, m/e (relative intensity) 251 (M + 1, 100), 168 (16).

N^1,N^4-Bis(3-aminopropyl)-1,4-diamino-2-butyne (4). A mixture of diazide **8** (0.035 g, 0.14 mmol) and triphenylphosphine (0.075 g, 0.28 mmol) in THF (4 mL) containing water (0.0075 g, 0.28 mmol) was stirred at room temperature for 16 h. The bulk of solvent was removed in vacuo and the residue was flash chromatographed ($CH_2Cl_2/CH_3OH/NH_4OH$, 2:2:1) to afford 0.025 g (90%) of **4** as an oil: ^1H NMR (D_2O) 3.40 (3, 4 H), 2.73 (t, 4 H), 2.70 (t, 4 H), 1.67 (m, 4 H); IR (film) 3300, 2940, 2860, 1320 cm^{-1}; HRMS (20 eV) calcd for $C_{10}H_{22}N_4$ 198.3136, found 198.3001.

N^1,N^4-Bis(3-aminopropyl)-1,4-diamino-*cis*-2-butene (5). A mixture of **8** (0.066 g, 0.262 mmol) and Lindar's catalyst (0.02 g) in CH_3OH (15 mL) was stirred under 1 atm of hydrogen for 8 h. The catalyst was removed by filtration and washed with CH_3OH. The combined filtrates were concentrated and chromatographed ($CH_2Cl_2/CH_3OH/NH_4OH$, (2:2:1) to afford 0.030 g (57%) of **5** as an oil: ^1H NMR (D_2O, 200 MHz) 5.65 (m, 2 H), 3.31 (s, 2 H), 3.28 (d, 2 H) 2.73 (t, 4 H), 2.65 (t, 4 H), 1.68 (m, 4 H); IR (film) 3310, 2950, 2860, 1455, 1310, 11 cm^{-1}; CIMS, m/e (relative intensity) 201 (M + 1, 100), 127 (63).

Acknowledgment. We are grateful to the National Institutes of Health (AM 26754) for generous support of this program. The Cornell Nuclear Magnetic Resonance Facility is supported by grants from NSF (CHE 7904825, PCM 8018643) and NIH (RR02002).

Registry No. 1, 110319-63-6; 2, 110319-64-7; 3, 110319-65-8; 4, 110319-67-0; 5, 110319-68-1; 6, 53878-96-9; 7, 110319-62-5; 8, 110319-66-9; $N_3(CH_2)_2CHO$, 58503-60-9.

Polycyclic Heterocycles from Glutaraldehyde in One Reaction

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We have found that glutaraldehyde adducts (see Scheme I) readily react under anhydrous acidic conditions with the three possible positional isomers of piperidinecarboxamide, **5** (pipecotamide), **6** (nipecotamide), and **7** (isonipecotamide), to give the novel heterocycles **1–3**, respectively. The ready formation of these polycyclic, multifunctional molecules in a single reaction entails generation of three new bonds and a new stereogenic center.

Scheme I

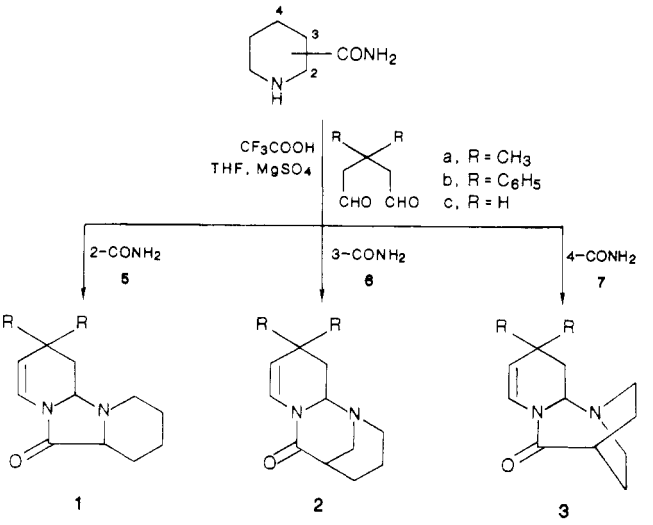
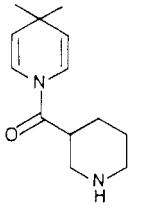


Table I. Product Characterization

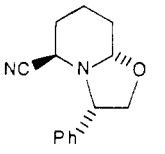
compound	yield, %[a]	isomer ratio[b]	mp,[c] °C
1a	14 (88)	91:9	113–115
1b	16 (70)	95:5[d]	159.5–162
2a	48 (79)	83:17	93–94.5 97.5–99 (trans)
2b	31 (81)	86:14	252–254[e]
2c	7 (65)	75:25[f]	50.5–53
3a	4 (22)		93–95.5

[a] Yields are not maximized and represent analytically pure samples. Crude mass return is given in parentheses, and gas chromatography showed the isomeric products to account for 90–95% of the mixture. [b] Determined by gas chromatography from crude reaction mixtures and isomers verified by GC/MS. [c] For major isomer (cis) unless indicated. [d] This ratio determined from isolated masses after chromatography. [e] 2-Naphthalenesulfonic acid salt of 93:7 isomer mixture. [f] The minor isomer was never isolated.

A related reaction of glutaraldehyde with chiral aminoethanol derivatives and KCN at pH 3–4 has been reported to give a versatile chiral intermediate, **8**, which was further elaborated to several enantiomerically pure alkaloids.[1]



4



8

Using the reaction conditions outlined in Scheme I, we expected to obtain dihydropyridine **4** from 3,3-dimethylglutaraldehyde and nipecotamide, as precedented by Fraenkel's previous reports.[2] Instead, a product was obtained with an ^1H NMR spectrum inconsistent with such a symmetrical structure. Closer examination showed that a mixture of diastereomeric products had been formed in a ratio of 79:21 (see Table I). These were chromatographically separated and analyzed by 360-MHz ^1H NMR to determine that the structure of the isolated product was **2a**.[3] The relative stereochemistry of the bridgehead

(1) Royer, J.; Husson, H.-P. *J. Org. Chem.* **1985**, *50*, 670. Husson, H.-P. *J. Nat. Prod.* **1985**, *48*, 894.

(2) Foos, J.; Killian, W.; Rizvi, S.; Unger, M.; Fraenkel, G. *Tetrahedron Lett.* **1978**, 1407.

(3) Detailed analyses of the ^1H NMR spectra of these compounds will be submitted for publication in a separate article.

0022-3263/87/1952-5046$01.50/0

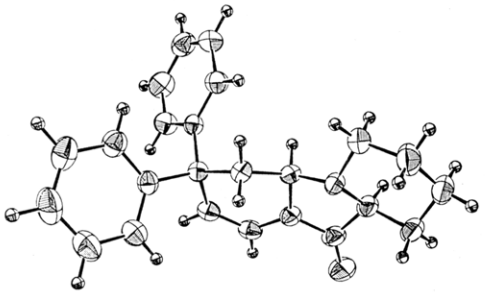
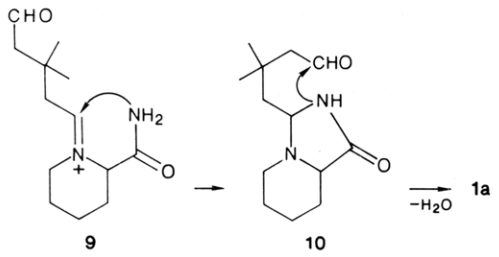


Figure 1. ORTEP drawing of **1b**.[6]

Scheme II

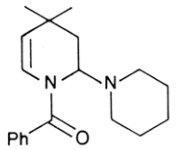


protons of each diastereomer of **2a** was also examined by NMR to ascertain that the major isomer had the protons in a cis configuration.[3] These features were verified by X-ray crystal analyses of the major (cis) isomers of both **1b** and **2a**. The ORTEP representation of the former is reproduced in Figure 1.

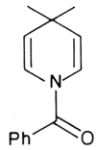
A limited number of examples of this reaction were carried out and are listed in Table I. In all the conversions to **1** and **2**, a mixture of stereoisomers was obtained, and the ratio of isomers is also indicated. Structure **3** has only one stereogenic center so that cis and trans isomers are not possible. By X-ray analysis, we have established in one example each that the major isomers of both ring systems **1** and **2** have cis stereochemistry. Subsequently, we assumed that the substituents on the glutaraldehyde starting material would not have significant influence on the stereochemical outcome and that the major isomers were always cis.

The mechanism of these reactions to form **1–3** is undetermined. We feel that the most logical sequence of events is represented in Scheme II for formation of **1a**. It would involve initial attack of 3,3-dimethylglutaraldehyde by the more nucleophilic amine nitrogen of **5** to form an enamine. Subsequent protonation would result in formation of iminium intermediate **9**; cyclization to **10** would establish the stereochemistry of the ultimate product **1a** after cyclodehydration. However, we have carefully monitored the progress of the reactions by TLC and have not detected an intermediate such as **10**. Such ring systems have been isolated previously but were reported to be unstable to aqueous acid conditions.[4] Whether they would be stable and observable under the present reaction conditions is undetermined. In that regard, we attempted to generate a similar intermediate by reacting nipecotamide (**6**) with isovaleraldehyde, a compound lacking a second aldehyde function, under the conditions of Scheme I. We were unable to detect or isolate a product. We interpreted that to mean that an intermediate such as **10** was unstable under these conditions, without the option of a subsequent condensation to stable product such as **1**.

In another model experiment, reaction of 3,3-dimethylglutaraldehyde, piperidine, and benzamide under the conditions of Scheme I gave none of the expected **11**



11



12

but lead to **12** as the sole product. This finding failed to support the mechanism proposed, but it can be explained on the basis of instability or reactivity of the proposed product preventing its isolation. The tetrahydropiperidine **11**, unlike the bicyclic counterparts **1–3**, has a freely rotating piperidine ring, which could align properly for trans elimination to the observed product **12**.

Another possible mechanism to the observed bicyclic systems **1–3** might have been initial formation of a dihydropyridine derivative such as **4**, which could result from double condensation of the primary amide with glutaraldehyde. This reaction is well precedented[2] and was in fact the expected product when this work began. One could envision acid-catalyzed cyclization of **4** leading to **2a**. In order to rule out that mechanism, dihydropyridine derivative **4** was synthesized by an alternate route.[5] When subjected to the reaction conditions of Scheme I, it was apparently inert, and formation of **2a** was not detected.

The reason for the preponderant formation of the cis isomers is not known to us. We have shown that both the mixture **2a** (79:21 ratio of isomers) and pure samples of the minor or major isomers were stable to the reaction conditions, and no isomerization occurred. In separate experiments of this type, 1 equiv of water was added either to a pure sample of the major isomer of **2a** or to the isolated isomer ratio (75:25) heated at 70 °C with 1 equiv of TFA in THF. After 15 h, there was no evidence of isomerization by GLC analyses. Thus the mixtures **1–3** do not revert to starting materials, and the ratio of diastereomers is not the result of equilibration of the final products under thermodynamic control.

We are actively exploring the limits and usefulness of this novel ring forming reaction to make other heterocyclic ring systems.

Experimental Section

^{1}H NMR spectra were recorded on a Bruker AM 360WB or Varian EM 390 spectrometer. Selected spectra are reported in the experimentals to reflect each of the different ring systems **1–3**.[3] Infrared spectra were obtained on a Perkin-Elmer spectrometer in $CHCl_3$. Melting points were obtained on a Thomas-Hoover apparatus, are uncorrected, and are reported in Table I. Elemental analyses were determined by Atlantic Micro-Analysis of Atlanta, GA.

Anhydrous Glutaraldehyde. A commercial (Aldrich) 25% wt solution of glutaraldehyde was saturated with sodium chloride and extracted with THF. The organic phase was dried with $MgSO_4$ and concentrated in vacuo to yield glutaraldehyde as a colorless oil in ca. 40% yield. This was used without further purification.

3,3-Diphenylglutaraldehyde. To a rapidly stirred solution of diethyl 3,3-diphenylglutarate[7] (14.24 g, 0.04 mol) in dry toluene (320 mL) at −78 °C under argon was added a freshly titrated toluene solution of 1.86 M diisobutylaluminum hydride (61.12 mL, 0.11 mol) over 4 min. After 40 min, 40 mL of MeOH was added to the −78 °C mixture. After an additional 5 min, 80 mL of water was added over 5 min. The reaction was then allowed

(4) Davis, A.; Levy, A. *J. Chem. Soc.* **1951**, 3479.

(5) Treatment of **2a** with 1 equiv of 1-chloroethyl chloroformate (Olofson, R.; Abbot, D. *J. Org. Chem.* **1984**, *49*, 2795), followed by refluxing in methanol, gave nearly a quantitative yield of **4**.

(6) X-ray analysis was done by Molecular Structure Corp., College Station, TX 77840.

(7) Ivanov, H.; Anghelova, I. *C. R. Acad. Bul. Sci.* **1965**, *18*, 529.

to warm to ambient temperature and stirred for an additional 1 h. The precipitated salts were removed by filtration and washed with 300 mL of hot toluene and then 300 mL of hot CH_2Cl_2. The organic phase of the filtrate was separated, dried with $MgSO_4$, and concentrated in vacuo to yield 11.58 g (theoretical, 10.72 g) of clear oil, which was 77% pure by GLC (SE-30). This was used without further purification.

3,4,5,10,11,11a-Hexahydro-1,5-methano-10,10-dimethyl-1*H*-pyrido[1,2-*a*][1,3]diazocin-6(2*H*)-one (2a). To a refluxing solution of THF (185 mL) containing 4.5 g (35 mmol) of nipecotamide (**6**), 3.0 mL (39 mmol) of trifluoroacetic acid, and 9.0 g (75 mmol) of anhydrous $MgSO_4$ under nitrogen was added 4.5 g (35 mmol) of 3,3-dimethylglutaraldehyde[8] in 75 mL of THF over a period of 20 min. After 3 h, the reaction mixture was cooled, filtered, and concentrated to 11.24 g of brown oil. This material was dissolved in CH_2Cl_2, washed with 15% NaOH and then brine, dried with $MgSO_4$, and concentrated to yield 6.10 g (79%) of brown oil, which was 96% pure product by gas chromatographic analysis (SE-30). As indicated in Table I, the ratio of isomers was 83:17. The diastereomers were separated, and the product was further purified by column chromatography on silica gel with an elution system of 5:1 methyl ethyl ketone/$CHCl_3$. A sample of the major isomer was recrystallized from acetonitrile to obtain a crystal appropriate for X-ray analysis. The free base was converted to the 2-naphthalenesulfonate with 1 equiv of the acid in a mixture of ether and ethanol to give analytically pure product in 48% yield, mp 223-225 °C. Major isomer, cis: free base ^1H NMR ($CDCl_3$, TMS) δ 1.1 (s, 6 H, 2 CH_3), 1.4 (br d, 1 H), 1.5-1.7 (m, 1 H), 1.7-1.9 (m, 3 H), 2.1 (br d, 1 H), 2.5 (br s, 1 H), 2.9 (dt, 1 H), 3.2 (d, 1 H), 3.3 (br d, 2 H), 4.6 (dd, 1 H, NCHN), 4.9 (d, 1 H, NC*H*=CH), 7.1 (d, 1 H, NCH=C*H*); IR 1637 (C=O) cm^{-1}. Minor isomer, trans: free base ^1H NMR ($CDCl_3$, TMS) δ 1.0 (s, 3 H, CH_3), 1.1 (s, 3 H, CH_3), 1.4 (br d, 1 H), 1.5-1.9 (m, 4 H), 2.1 (br d, 1 H), 2.4 (br s, 1 H), 2.9-3.1 (m, 3 H), 3.15 (br d, 1 H), 4.2 (dd, 1 H, NCHN), 4.9 (dd, 1 H, NCH=C*H*), 7.05 (d, 1 H, NC*H*=CH); IR 1638 (C=O) cm^{-1}. Anal. Calcd for $C_{13}H_{20}N_2O/C_{10}H_8O_3S$: C, 64.46; H, 6.59; N, 6.54. Found: C, 64.52; H, 6.67; N, 6.51.

3,4,5,10,11,11a-Hexahydro-1,5-methano-10,10-diphenyl-1*H*-pyrido[1,2-*a*][1,3]diazocin-6(2*H*)-one (2b). This material was synthesized from 3,3-dimethylglutaraldehyde and **6** by the procedure given for **2a**. Reflux time was 4 h. The crude product was converted directly into a 2-naphthalenesulfonic acid salt for analysis. Anal. Calcd for $C_{23}H_{24}N_2O/C_{10}H_8O_3S$: C, 71.72; H, 5.84; N, 5.07. Found: C, 71.82; H, 6.09; N, 4.97.

3,4,5,10,11,11a-Hexahydro-1,5-methano-1*H*-pyrido[1,2-*a*][1,3]diazocin-6(2*H*)-one (2c). This material was synthesized from anhydrous glutaraldehyde and **6** by the procedure described for **2a**. Reflux time was 1 h. The crude oil obtained after workup was flash chromatographed on silica gel with 10% acetone/CH_2Cl_2 as the elutant to yield a crystalline isomer mixture (see Table I). Trituration three times with cyclohexane gave pure cis isomer. Anal. Calcd for $C_{11}H_{16}N_2O$: C, 68.72; H, 8.39; N, 14.57. Found: C, 68.74; H, 8.43; N, 14.53.

2,3,4,5a,6,7-Hexahydro-7,7-dimethyl-1*H*-dipyrido[1,2-*a*:1′,2′-*c*]imidazol-11-one (1a). This material was obtained from 3,3-dimethylglutaraldehyde and **5** by the same procedure described for **2a**. Reflux time was 22 h. The crude product was a brown solid, which was recrystallized twice from hexane with decolorizing charcoal to yield white needles for analysis. Anal. Calcd for $C_{13}H_{20}N_2O$: C, 70.87; H, 9.15; N, 12.72. Found: C, 70.91; H, 9.23; N, 12.71.

2,3,4,5a,6,7-Hexahydro-7,7-diphenyl-1*H*-dipyrido[1,2-*a*:1′,2′-*c*]imidazol-11-one (1b). This material was obtained from 3,3-diphenylglutaraldehyde and **5** by the same procedure described for **2a**. Reflux time was 48 h. The crude product was flash chromatographed on silica gel with 20% ethyl acetate/hexane as the elutant. The crystals obtained were washed with ethanol and ether prior to analysis. Major isomer, cis: ^1H NMR ($CDCl_3$ TMS) 1.15-1.35 (1 H, m), 1.35-1.7 (3 H, m), 1.9 (1 H, d), 2.05 (1 H, d), 2.15 (1 H, t), 2.25 (1 H, t), 2.6 (1 H, d), 2.75 (1 H, dt), 3.0 (1 H, br d), 3.75 (1 H, d, NCHN), 5.4 (1 H, dd, NC*H*=CH), 6.95 (1 H, d, NCH=C*H*), 7.1-7.4 (10 H, m, aromatics). Anal. Calcd for $C_{23}H_{24}N_{20}$: C, 80.20; H, 7.02; N, 8.13. Found: C, 80.21; H, 7.09; N, 8.13. A small sample was dissolved in ethanol/ethyl acetate, and crystals were allowed to slowly separate for X-ray analysis (see Figure 1). IR spectra of the two isomers were examined for the prescence of Bohlman bands. Indeed, the major isomer had the characteristic series of peaks indicative of a cis relationship of the bridgehead protons. These were absent in the minor isomer. Major isomer: IR 3010, 2948, 2860, 2799, 2708 (CH), 1714 (C=O) cm^{-1}. Minor isomer: IR 3012, 2946, 2864 (CH), 1706 (C=O) cm^{-1}.

2,3,10,10a-Tetrahydro-9,9-dimethyl-1*H*,9*H*-1,4-ethanopyrido[1,2-*a*]diazapin-5(4*H*)-one (3a). This material was synthesized from 3,3-dimethylglutaraldehyde and **7** by the same procedure described for **2a** except that dimethylformamide was used for the reaction solvent in order to dissolve starting material **7**. The reaction mixture was heated at 90 °C for 5.5 h. The crude product was converted to the 2-naphthalenesulfonic acid salt, which was recrystallized from ethanol to yield white needles for analysis: mp 231-233 °C; free base ^1H NMR ($CDCl_3$ TMS) 1.1 (6 H, s, 2 CH_3), 1.5-2.5 (6 H, m), 2.6-3.4 (5 H, m), 4.35 (1 H, dd, NCHN), 4.8 (1 H, br d, NC*H*=CH), 6.9 (1 H, d, NCH=C*H*). Anal. Calcd for $C_{13}H_{20}N_{20}/C_{10}H_8O_3S$: C, 64.46; H, 6.59; N, 6.54. Found: C, 64.35; H, 6.64; N, 6.60.

Acknowledgment. We thank Martin Mutter for all high-field NMR spectra including a number of detailed decoupling studies[3] and Dr. Steven V. Ley for spirited discussions about the structures of the initially isolated products.

Registry No. *cis*-**1a**, 110392-30-8; *trans*-**1a**, 110454-62-1; *cis*-**1b**, 110392-31-9; *trans*-**1b**, 110454-63-2; *cis*-**2a**, 110392-27-3; *trans*-**2a**, 110454-61-0; *cis*-**2b**, 110392-28-4; *cis*-**2b** (2-naphthalenesulfonic acid salt), 110454-66-5; *trans*-**2b**, 110454-64-3; *trans*-**2b** (2-naphthalenesulfinc acid salt), 110507-65-8; *cis*-**2c**, 110392-29-5; *trans*-**2c**, 110454-65-4; **3a**, 110392-32-0; **3a** (2-naphthalenesulfonic acid salt), 110392-33-1; **5**, 19889-77-1; **6**, 4138-26-5; **7**, 39546-32-2; glutaraldehyde, 111-30-8; 3,3-diphenylglutaraldehyde, 64516-58-1; diethyl 3,3-diphenylglutarate, 3531-26-8; 3,3-dimethylglutaraldehyde, 67402-86-2.

Supplementary Material Available: Details of the X-ray analysis of **1b** are included (3 pages). Ordering information is given on any current masthead page.

(8) Foos, J.; Steel, F.; Rizvi, S.; Fraenkel, G. *J. Org. Chem.* **1979**, *44*, 2522.

tert-Butyl Hydroperoxide–Pyridinium Dichromate: A Convenient Reagent System for Allylic and Benzylic Oxidations

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A number of methods are currently available for allylic and benzylic oxidations using chromium(VI) complexes.[1] Some of these traditional methods of oxidation suffer from drawbacks such as the use of a very large excess of reagent, large volumes of solvent, and long reaction times. There is a continual search for milder, inexpensive, and more convenient methods for effecting these transformations. More recently, the use of *tert*-butyl hydroperoxide–chro-

(1) Wiberg, K. B. In *Oxidation in Organic Chemistry*; Wiberg, K. B., Ed.; Academic: New York, 1965; p 69; Cainelli, G.; Cardillo, G. In *Chromium Oxidations in Organic Chemistry*; Springer-Verlag: New York, 1984; p 23.

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