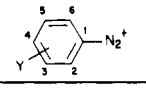
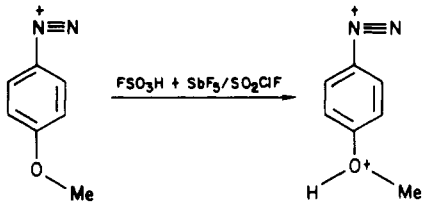
Table I. Carbon-13 Chemical Shifts[a] of Benzenediazonium Salts in Superacid Solvents[b] and SO_2[c]



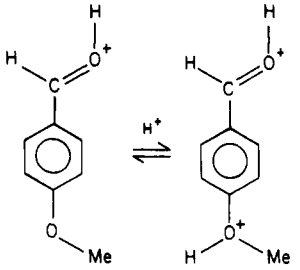
Y	solvent system	C-1	C-2	C-3	C-4	C-5	C-6	CH_3
H	SO_2	112.2	131.9	131.5	141.9	131.5	131.9	
	FSO_3H–SbF_5 (1:4)/SO_2ClF	111.6	131.8	131.3	142.4	131.3	131.8	
4-OMe	SO_2	100.1	135.2	117.6	169.8	117.6	135.2	56.8
4-OMe	FSO_3H–SbF_5 (1:4)/SO_2ClF	114.9	136.4	120.9	157.9	120.9	136.4	75.3
4-OMe	FSO_3H–SbF_5 (1:1)/SO_2ClF	112.8	135.8	119.6	158.4	119.6	135.8	70.6
2-OMe	SO_2	98.3	162.8	114.1	144.6	122.7	131.1	57.8
2-OMe	FSO_3H–SbF_5 (1:4)/SO_2ClF	98.1	162.8	114.1	144.6	122.7	131.1	58.2

[a] In ppm from external capillary Me_4Si. [b] At −75 °C. [c] At −30 °C.

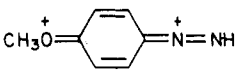
at low temperature (−75 °C) in SO_2ClF, $\delta_{^{13}C(OMe)}$ 75.3 ($\Delta\delta$ = 18.5). Whereas the C_1, $C_{2,6}$, and $C_{3,5}$ are expectedly deshielded as compared to the spectrum of 1 in SO_2, the C_4 absorption shows a small shielding effect (see Table I). In FSO_3H–SbF_5 (1:1)/SO_2ClF superacid system at −75 °C, the methoxy absorption is less deshielded at $\delta_{^{13}C(OMe)}$ 70.6 ($\Delta\delta$ = 13.8) and indicates somewhat faster exchange with the solvent acid due to a decrease in acidity.[6] No demethylation or demethoxylation was observed.



The ^1H NMR spectrum of 1 in FSO_3H–SbF_5 (1:4)/SO_2ClF shows a deshielded methoxy $\delta_{^1H}$ 4.42 and two aromatic singlet absorptions at $\delta_{^1H}$ 7.25 and 7.93 for the $H_{3,5}$ and $H_{2,6}$ with an integral ratio of 3:2:2, respectively. The acidic $HOMe^+$ signal could not be observed as a separate distinct signal in the ^1H NMR spectrum even at −75 °C as it is still exchanging on the NMR time scale with the solvent acid. Similar observations were made in HF–SbF_5/SO_2ClF solvent. This is analogous to the behavior of diprotonated *p*-methoxybenzaldehyde in HF–SbF_5 or FSO_3H–SbF_5, studied by Sommer et al.,[7] which resulted in a general deshielding of the ^1H NMR signals and a decrease in rotational barrier for phenyl–carbonyl bond on diprotonation. Similarly, deshielding of the methoxy carbon and shielding of the C_4 ring carbon was observed in the ^{13}C NMR spectrum upon diprotonation.



Protonation of the β-^{15}N labeled 1 ($\delta_{^{15}N}$ 321 from NH_3) in FSO_3H–SbF_5 (1:4)/SO_2ClF resulted in an upfield shift of the $^{15}N_\beta$ signal ($\delta_{^{15}N}$ 313.2; $\Delta\delta_{^{15}N}$ 7.8). This indicates that the para substituent is strongly electron withdrawing[8] and is in accord with the formation of a dication. In a coupled spectrum the β-^{15}N remained a singlet, ruling out possible N-protonation of the tautomeric form, i.e.,



Attempts to O-methylate 1 with $MeF/SbF_5/SO_2$ or with $MeI/AgSbF_6/SO_2$ at low temperature were unsuccessful.

Unlike the 4-methoxybenzenediazonium ion, 2-methoxybenzenediazonium ion is not O-protonated under similar conditions due to the proximity of the developing positive charge with the N_2^+.

Experimental Section

3,5-Dimethylbenzene- and β-^{15}N labeled *p*-methoxybenzenediazonium ion tetrafluoroborate were prepared by diazotization of their anilines with $NaNO_2$ and $Na^{15}NO_2$, respectively, and were precipitated from CH_3NO_2/ether. All other diazonium ion salts were commercially available (Ozark-Mahoning or Aldrich) and were purified by precipitation from CH_3NO_2/ether and repeated washing with dry ether and drying under vacuum.

^1H, ^{13}C and ^{15}N NMR spectra were recorded on Varian FT-80 and XL-200 spectrometers.

Preparation of the Ions. To the diazonium ion salt (50–70 mg) stirred in SO_2ClF and cooled to −75 °C was added the superacid (ca. 1 mL) diluted in SO_2ClF (1 mL) with Vortex mixing until homogeneous.

Acknowledgment. Support of our work by the National Science Foundation is gratefully acknowledged.

Registry No. 1, 459-64-3; 1-β-^{15}N, 96845-60-2; *p*-$MeOC_6H_4N_2^+ \cdot H^+$, 96845-61-3; *p*-$MeOC_6H_4N{\equiv}{}^{15}N^3 \cdot H^+$, 96845-62-4; *o*-$MeOC_6H_4N_2^+$, 17356-93-3; PhN_2^+, 2684-02-8.

(6) (a) Gold, V.; Laali, K.; Morris, K. P.; Zdunek, L. Z. *J. Chem. Soc., Chem. Commun.* **1981**, 769. (b) Gold, V.; Laali, K.; Morris, K. P.; Zdunek, L. Z. *J. Chem. Soc., Perkin* Trans. 2, in press.

(7) Sommer, J.; Canivet, P.; Schwartz, S.; Rimmelin, P. *Nouv. J. Chim.* **1981**, *5*, 45.

(8) Casewit, C.; Roberts, J. D.; Bartsch, R. A. *J. Org. Chem.* **1982**, *47*, 2875. See also: Levy, G. C.; Lichter R. L. in "Nitrogen-15 Nuclear Magnetic Resonance Spectroscopy"; Wiley-Interscience: New York, 1976; p 97.

Facile Synthesis of Chiral Glycine from D-Ribose

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The development of the general synthetic method of hexoses and pentoses with chirally deuterated hydroxymethyl groups[1] prompted us to utilize these monosaccharides as the synthetic starting materials of other biologically important, chirally deuterated compounds. We selected chiral glycine as our first synthetic target. As the

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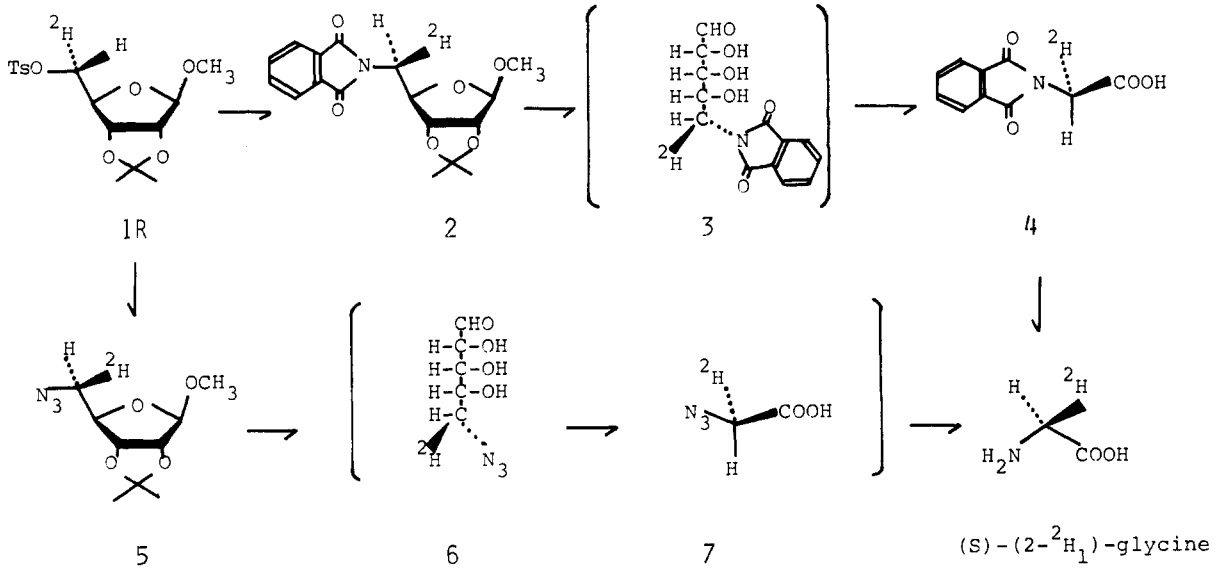
0022-3263/85/1950-3007$01.50/0

Scheme I



stereospecific conversion of chiral glycine to chiral acetic acid[2] and chiral glycolic acid[3] has been reported, the synthesis of chiral glycine also means the synthesis of these bioligically important chiral compounds.

Several syntheses of chiral glycine have been reported and some of them involve one or two steps of enzyme-mediated reactions,[2,4-7] and others are entirely chemical syntheses.[8,9] In this paper, we describe two different chemical syntheses of chiral glycine from D-ribose.

The starting material of our synthesis is methyl (5*R*)-[5-$^2H_1$]-2,3-*O*-isopropylidene-5-*O*-(*p*-tolylsulfonyl)-β-D-ribofuranoside (**1*R***) which has been prepared from D-ribose by five steps.[1c,e]

Reaction of **1*R*** with 1.5 equiv of potassium phthalimide in hexamethylphosphoric triamide (HMPT) at 120 °C for 2 h gave methyl (5*S*)-[5-$^2H_1$]-5-deoxy-2,3-*O*-isopropylidene-5-phthalimido-β-D-ribofuranoside (**2**)[10] in 90% yield. The stereochemistry at C-5 was assigned to be *S*, because this type of reaction should proceed in an S_N2 manner.

Acid hydrolysis of both the *O*-isopropylidene group and the glycosidic linkage of **2** with a 1:1 mixture of acetic acid and 5 N sulfuric acid at 50 °C for 1 h gave free sugar **3** quantitatively (by TLC), which was oxidized without isolation[11] with potassium permanganate at room temperature to give (*S*)-*N*-phthaloyl [2-$^2H_1$]glycine (**4**) in 85%. The chiral purity of **4** was estimated to be more than 93% on the basis of its mass spectrum (M^+ = 206, 100%, M^+ = 205, 7.5%) and ORD curve.

Since the deprotection of **4** to chiral glycine was already established[8,9] and some loss of deuterium during the process was also reported,[9] this route was not further studied and we turned our attention to the development of a different synthetic route to chiral glycine from **1*R***.

Our new synthetic strategy is to use an azide group as a potential amino group without reducing it to amino group at the early stage of the synthesis, because we know that the azide group is stable against not only acidic conditions[12] but also oxidation to give an α-azide carboxylic acid with retention of configuration[13] and further this synthetic route can avoid both the protection and deprotection of amino function which have been inevitable in other chemical syntheses of chiral glycine.[8,9]

Reaction of **1*R*** with sodium azide in *N*,*N*-dimethylformamide (DMF) at 100 °C for 1.5 h gave methyl (5*S*)-[5-$^2H_1$]azido-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranoside (**5**) in 95% yield. The stereochemistry at C-5 of **5** was assigned to be *S* on the basis of the same reason described above.

Treatment of **5** with a mixture of acetic acid and 5 N sulfuric acid at room temperature for 2 h gave 5-azido-5-deoxypentose (**6**)[11] quantitatively (by TLC), which was oxidized with potassium permanganate at room temperature for 5 h to give (*S*)-[2-$^2H_1$]azido acetic acid (**7**).

Compound **7** was reduced (without isolation[11]) catalytically over 10% Pd–C in acetic acid to give (*S*)-[2-$^2H_1$]-glycine in a 60% yield from **5**.

The chiral purity of our (*S*)-(2-$^2H_1$)glycine is estimated to be 92% on the basis of its ORD curve ($[\alpha]^{25}_{220(max)}$ −80.0°, $[\alpha]^{25}_{227}$ −68.0°, $[\alpha]^{25}_{238}$ −36.1°) and mass spectrum [*m*/*e* 76 (M^+, 100), *m*/*e* 75 (M^+ − 1, 8, 6)].

The enantiomeric (*R*)-[2-$^2H_1$]glycine could be synthesized similarly from methyl (5*S*)-[5-$^2H_1$]-2,3-*O*-isopropylidene-5-*O*-(*p*-tolylsulfonyl)-β-ribofuranoside (**1*S***).[1c,d]

Since our synthesis is straightforward starting from a chirally pure compound with established absolute configuration, this work is an unequivocal confirmation of the absolute configuration of chiral glycine.[3]

Experimental Section

All melting points were uncorrected. NMR spectra were recorded at 100 MHz, with Me_4Si in $CDCl_3$ as the internal standard.

(2) Kajiwara, M.; Lee, S. F.; Scott, I. *J. Chem. Soc., Chem. Commun.* **1978**, 967.
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(5) Battersby, A. R.; Staunton, J.; Summers, M. C. *J. Chem. Soc., Chem. Commun.* **1974**, 954.
(6) Fuganti, C.; Mazza, M. *J. Chem. Soc. Perkin Trans. 1* **1973**, 954.
(7) Leister, E.; Spenser, I. D. *J. Chem. Soc., Chem. Commun.* **1975**, 378.
(8) Armarego, W. L. F.; Milloy, B. A.; Pendergast, W. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2229.
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(10) Nondeuterated **2**. Leonard, N. J.; Carraway, K. L. *J. Heterocycl. Chem.* **1966**, *3*, 485.
(11) In order to minimize the undesirable epimerization and the losses of deuterium and materials, the isolations of **3**, **6**, and **7** were not carried out.
(12) Ohrui, H.; Kuzuhara, H.; Emoto, S. *Agric. Biol. Chem.* **1970**, *34*, 375.
(13) Ohrui, H.; Kuzuhara, H.; Emoto, S. *Tetrahedron Lett.* **1971**, 4267.

Mass spectra were measured at 25 eV. Thin layer chromatography (TLC) was performed on Merk Kieselgel 60 GF_{254}.

Methyl (5*S*)-[5-$^2H_1$]-5-Deoxy-2,3-*O*-isopropylidene-5-phthalimido-β-D-ribofuranoside (2). A mixture of **1*R*** (1.1 g) and potassium phthalimide (427 mg) in HMPT (40 mL) was stirred for 1 h at 120 °C. Water (40 mL) was added to the cooled mixture, and it was then extracted three times with 40 mL of ether. The extracts were washed with water and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure to give crude crystalline product, which was recrystallized from methanol to give pure crystalline **2** (926 mg, 90%): mp 128 °C; $[\alpha]^{25}_D$ −45.2° (*c* 2.5 in $CHCl_3$); NMR (in $CDCl_3$) δ 1.27 and 1.44 (isopropylidene methyls), 3.38 (3 H, s, OCH_3), 3.8–4.9 (4 H, m, H_2, H_3, H_4, H_5), 7.8–8.0 (4 H, m, aromatic). Anal. Calcd for $C_{17}H_{18}DNO_6$: C, 61.07; H + D, 6.03; N, 4.19. Found: C, 61.00; H + D, 6.08; N, 4.15.

(*S*)-*N*-Phthaloyl[2-$^2H_1$]glycine (4). To a solution of **2** (668 mg) in acetic acid (50 mL) was added 5 N H_2SO_4 (50 mL), and the mixture was kept for 1 h at 50 °C and then cooled to room temperature. TLC indicated the complete hydrolysis of **2** to the free sugar **3** [$CHCl_3$–CH_3OH (3:1), R_f 0.58]. $KMnO_4$ (1.5 g) was added to the solution (5 min), and the solution was stirred at room temperature for 3 h. The excess reagent was decomposed by addition of aqueous 10% sodium thiosulfate. The mixture was extracted three times with 50 mL of CH_2Cl_2, and the combined CH_2Cl_2 extracts were dried over $MgSO_4$. Evaporation of the solvent gave crude crystalline **4**, which was recrystallized from 10% ethanol to give 350 mg (85%) of **4**: mp 192 °C; ORD $[\alpha]^{25}_{405}$ +2.90°, $[\alpha]^{25}_{435}$ +2.34°, $[\alpha]^{25}_{546}$ +1.430° and $[\alpha]^{25}_{77}$ +1.22° (*c* 10.5 in CH_3OH); (lit.[9] $[\alpha]^{25}_{405}$ +2.70°; $[\alpha]^{25}_{436}$ +2.18°, $[\alpha]^{25}_{546}$ +1.22°, $[\alpha]^{25}_{578}$ +0.94°); I ^{r}, 1780 and 1740 (CO and COOH) and 3000 cm^{-1} (OH); MS, *m/e* (relative intensity) M^+ = 206 (100), M^+−1 = 205 (7.5). Anal. Calcd for $C_{10}H_6DNO_4$: C, 58.25; H + D, 3.90; N, 7.00. Found: C, 58.54; H + D, 4.00; N, 6.90.

Methyl (5*S*)-[5-$^2H_1$]-5-Azido-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranoside (5). A mixture of **1*R*** (810 mg) and sodium azide (222 mg) in DMF (50 mL) was stirred for 1.5 h at 100 °C. Water (50 mL) was added to the cooled mixture, and it was then extracted three times with 50 mL of ether. The extracts were washed with water and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave syrup **5** (496 mg, 95%): $[\alpha]^{25}_D$ −39.0° (*c* 1 in $CHCl_3$); NMR ($CDCl_3$) δ 1.26 and 1.46 (isopropylidene methyls), 3.38 (3 H, s, OCH_3), 3.40 (1 H, d, $J_{4,5}$ = 7.8 Hz, H-5), 5.00 (1 H, s, H-1). Anal. Calcd for $C_9H_{14}DN_3O_4$: C, 46.95; H + D, 7.00; N, 18.25. Found: C, 47.00; H + D, 6.95; N, 18.22.

(*S*)-[2-$^2H_1$]Glycine. To a solution of **5** (220 mg) in acetic acid (25 mL) was added 5 N H_2SO_4 (25 mL). The mixture was kept for 2 h at room temperature. TLC indicated the presence of only 5-azido-5-deoxyribose **6** [$CHCl_3$–CH_3OH (3:2), R_f 0.26]. $KMnO_4$ (500 mg) was added to the solution (5 min), and the solution was stirred at room temperature for 5 h. The excess reagent was decomposed by addition of aqueous 10% sodium thiosulfate. The mixture was extracted three times with 25 mL of CH_2Cl_2, and combined CH_2Cl_2 extracts were dried over $MgSO_4$. After evaporation of CH_2Cl_2, the acetic acid solution was vigorously shaken with 10% palladium on charcoal (200 mg) under a hydrogen atmosphere for 1 h. The catalyst was filtered off and washed with acetic acid (10 mL). The combined filtrate was evaporated under reduced pressure to give a crude crystalline product, which was recrystallized from aqueous methanol to give 47 mg (60%) of pure (*S*)-[2-$^2Hh_1$]glycine: mp 233–234 °C (dec; ORD $[\alpha^{25}_{210}$ −7.90°, $[\alpha]^{25}_{220(max)}$ −80.0°, $[\alpha]^{25}_{227}$ −68.0°, $[\alpha]^{25}_{238}$ −40.0°, $[\alpha]^{25}_{250}$ −25.0°, $[\alpha]^{25}_{275}$ −14.0° (*c* 2.0 in H_2O); MS, *m/e* (relative intensity) M^+ = 76 (100), M^+ −1 = 75 (8.6). Anal. Calcd for $C_2H_4DNO_2$: C, 31.58;% H + D, 7.95; N, 18.41. Found: C, 31.90; H + D, 8.20; N, 8.31.

Acknowledgment. We are very grateful to Yamasashoyu Co. LTD. for a gift of D-ribose and to Mrs. Chieko Suzuki for measurement of NMR spectra. This work was supported in part by a grant from the Ministry of Education, Science and Culture, Japan.

Registry No. **1R**, 97254-21-2; **2**, 97254-22-3; **3**, 97254-23-4; **4**, 62061-63-6; **5**, 97254-24-5; **6**, 97254-25-6; **7**, 97254-26-7; (*S*)-[2-$^2H_1$]glycine, 62061-52-3; potassium phthalimide, 1074-82-4; glycine, 56-40-6; D-ribose, 50-69-1.

Formation of Cyclic Ethers in the Double Baeyer–Villiger Oxidation of Ketals Derived from Cyclic Ketones[1]

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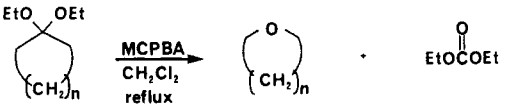
We recently reported that the formal equivalent of a double Baeyer–Villiger oxidation may be accomplished by oxidation of dialkyl ketals with *m*-chloroperoxybenzoic acid (MCPBA) in CH_2Cl_2 solution at room temperature.[2] This exothermic process, which normally converts the ketal to an orthocarbonate or its hydrolysis products, provides an efficient method for the removal of a carbonyl function from a ketone.[2] Exploration of the scope of the reaction has revealed that oxidation of diethyl ketals derived from certain five- and six-membered cyclic ketones may lead to the formation of cyclic ethers via oxidative loss of the latent carbonyl moiety *when conducted at reflux temperatures in CH_2Cl_2 solution.*



As shown in Table I, the yield of cyclic ether is strongly dependent on the structure of the ketal employed in the reaction. Thus, although tetrahydropyrans are produced in 20–63% yield in the double Baeyer–Villiger oxidation of ketals derived from cyclohexanones (Table I, entries 1–3) and THF is formed in 44% yield upon oxidation of the diethyl ketal of cyclopentanone (Table I, entry 4), ether formation is negligible in the oxidation of ketals prepared from 2-alkylcyclopentanones or cycloheptanone (Table I, entries 5–6).

The formation of cyclic ethers is most likely a consequence of the facile loss of diethyl carbonate from the orthocarbonate produced in the oxidation[2] (Scheme I). Indeed, an intermolecular variant of this novel transformation has long been known in the acid-catalyzed conversion of tetraethyl orthocarbonate to diethyl ether and diethyl carbonate.[3]

The modest yields of tetrahydrofurans and tetrahydropyrans produced upon oxidation of the appropriate ketals at reflux temperatures compares favorably with the overall yields of a recently reported, four-step transformation of cyclic ketones to cyclic ethers.[4] The relative ease with which ethers may be isolated from the bulk of the carbonates, benzoates, and diols produced in the double Baeyer–Villiger reaction[2] suggests that this facile oxidative replacement of a carbonyl group with an oxygen atom may be of some synthetic utility.

Experimental Section

Proton magnetic resonance spectra were recorded on Varian EM-360 or Bruker WH-90 instruments and shifts are referenced with respect to internal Me_4Si. Carbon-13 magnetic resonance spectra were obtained at 22.6 MHz on a Bruker WH-90 spectrometer using $CDCl_3$ solutions; shifts are referenced with respect

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