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FACILE SYNTHESIS OF CHIRAL GLYCINE USING D-GLUCOSE AS A CHIRAL TEMPLATE

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Abstract: A facile synthetic method of chiral glycine and a new access to chiral acetic acid based on a concept of chirality transfer from glucose are described.

Recently, we demonstrated usefulness of a technique consisting of the stereospecific chiral labeling of a prochiral methylene group by deuterium and ^{2}H-NMR spectroscopy for the stereochemical studies on the biosynthesis of aminocyclitol antibiotics,[1] during which (6R)- and (6S)-[6-^{2}H]-D-glucose were prepared by a totally chemical method on the basis of the chirality of D-glucose itself.[2]

As an extension of this methodology, necessity of chiral glycine for the studies of antibiotic biosynthesis prompted us to exploit a facile method to prepare chiral methylene functionalities by the deuterium labeling.

Previous chemical and/or biochemical methods for chiral methylene and methyl groups were reviewed[3,4] and a few preparative method of chiral glycine were also reported.[5,6]

Our basic concept was conversion of acetylene molecule into chiral glycine, the chirality of which would be transferred from a suitable chiral ketone *via* addition of acetylene to the ketone, followed by manipulation of the ethynyl group and oxidative cleavage to a desired precursor of chiral glycine. Prerequisites were: 1) no enzymic process is employed; 2) carbohydrate is utilized as a chiral template; 3) fewer operations of diastereomer separation are needed; and 4) the chiral template is desirably regenerated, and finally chosen for the chiral template was 1,2:5,6-di-O-isopropylidene-α-D-*ribo*-3-hexulofuranose **1**, because of its readily availability[7,8] and stereochemical requirements. The synthetic route employed was rather straightforward and is shown in the Scheme.

Addition of acetylene to **1** was affected *via* either ethynyllithium or ethynylmagnesium bromide to give exclusively, after recrystallization, a 3-C-ethynyl-D-allose derivative **2**,[9] mp 105°; IR: 3250 and 2130 cm^{-1} (C≡C-H); ^{1}H-NMR: δ 2.65 (H-2'), in 88% yield. Separation of diastereomers was unnecessary. Reduction of **2** with LiAl^{2}H$_4$ (MSD Canada Ltd., 99 Atom%) in THF at room temp gave regio- and stereospecifically (Z)-olefin **3**,[9] mp 72°; ^{1}H-NMR: δ 5.80 (br.d, J=11.5 Hz, H-2') and δ 5.32 (d, J=11.5 Hz, H-1'); MS: m/z 271 (M^+-CH$_3$, d_0) vs. m/z 272 (d_1) = 3.6:100, in 81% yield. This regiochemistry was different from the previously reported

similar reduction of simple alkyl ethynyl carbinols.[10]

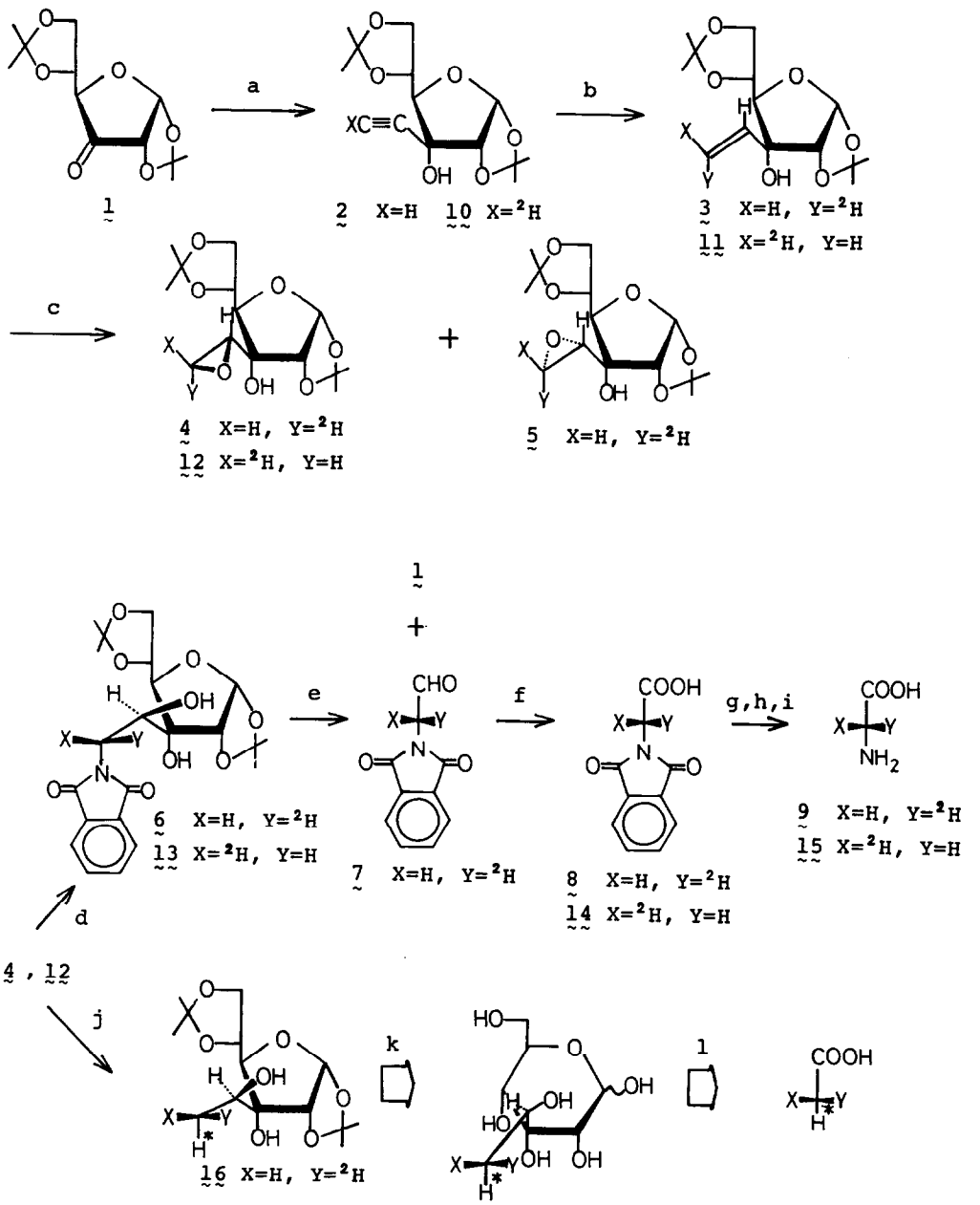
Epoxidation of the deuteroolefin 3 was expected to take place by attack of an electrophile from the less hindered side due to the bulky substituent on the C-4 position of the furanose ring, and in fact, m-chloroperbenzoic acid oxidation underwent stereoselectively to provide in 87% yield a diastereoisomeric mixture of epoxides 4,[9] mp 92-3°; ^{1}H-NMR: δ 3.05 (d, J=4 Hz, H-1') and δ 2.83 (d, J=4 Hz, H-2'), and 5,[9] mp 97°, ^{1}H-NMR: δ 3.05 (d, J=4 Hz, H-1') and δ 2.78 (d, J=4 Hz, H-2'), in a ratio of ca. 5 : 1, which were separated by medium pressure column chromatography[11] and were further purified by recrystallization. The stereochemistry at C-1' and C-2' of the major epoxide 4 was tentatively assigned at this stage to be (R) on the basis of the abovementioned steric effects.

Nitrogen functionality was introduced stereospecifically to the C-2' position with inversion of configuration by treatment of 4 with potassium phthalimide to give 6,[9] 39% yield, mp 150°; IR: 1780 and 1725 cm^{-1} (C=O); ^{1}H-NMR: δ 4.38 (br.d, J=9 Hz, H-1') and δ 3.87 (br.d, J=9 Hz, H-2').

Attempted oxidative cleavage of the glycol system of 6 with $NaIO_4$ was unsuccessful, probably because of the anti-conformation of the glycol, however, $Pb(OAc)_4$ in acetic acid-methanol effectively cleaved to give phthaloyl [2-^{2}H]-glycinal 7, and the starting chiral template 1 was regenerated. The regenerated 1 could be recovered chromatographically, however, no efforts to isolate 1 were made in this case, since 1 is readily obtainable. The mixture of 7 and 1 was oxidized under the reported conditions ($KMnO_4$-H_2SO_4)[5] to give chiral phthaloyl [2-^{2}H]-glycine 8,[9] mp 194°; IR: 1780, 1740 and 1725 cm^{-1}; MS: m/z 205 (M^+, d_0) : m/z 206 (d_1) = 12.3 : 100, in 71% yield (from 6). Now, the stereochemistry of 8 was determined to be (S) by the optical rotation, $[\alpha]_{578}^{25}$ +1.09°, $[\alpha]_{546}^{25}$ +1.22°, $[\alpha]_{436}^{25}$ +2.18° and $[\alpha]_{405}^{25}$ +2.70° (c 10.5, MeOH), and the aforementioned stereochemical considerations were fully confirmed. Deprotection of 8 was again undertaken by the reported procedures[5] to give (S)-[2-^{2}H]-glycine 9,[9] mp 235-241° (dec.); ORD: $[\alpha]_{350}^{25}$ -45.5° and $[\alpha]_{338}^{25}$ -27.8° (c 2.0, H_2O); MS: m/z 75 (M^+, d_0) : m/z 76 (d_1) = 19.3 : 100, in 79% yield. Partial loss of deuterium was observed under these deprotection conditions.

To obtain the enantiomeric (R)-[2-^{2}H]-glycine, the ethynyl carbinol 2 was first deuterated by treatment with either ethylmagnesium bromide or n-butyllithium followed by hydrolysis with ^2H_2O to give in 97% yield a deuteroacetylene 10,[9] IR: 2580 and 1975 cm^{-1} (C≡C-^{2}H). Reduction of 10 with $LiAlH_4$ in THF at room temperature afforded (E)-olefin 11,[9] mp 73°; ^{1}H-NMR: δ 5.80 (br.d, J=18 Hz, H-1') and δ 5.50 (d, J=18 Hz, H-2'). Following the same manipulations of 10 as described above, i.e. epoxidation to obtain a major epoxide 12,[9] mp 92-3°; ^{1}H-NMR: δ 3.05 (2H s, H-1' and H-2'), displacement of the epoxide with potassium phthalimide to give 13,[9] mp 146-7°; ^{1}H-NMR: δ 4.40 (br.t, J=4 Hz, H-1') and δ 4.30 (br.d, J=4 Hz, H-2'), oxidative cleavage and further oxidation provided

Scheme



Reagent: a, HC≡CLi or HC≡CMgBr; b, $LiAl^2H_4$ or $LiAlH_4$; c, MCPBA; d, Potassium Phthalimide; e, $Pb(OAc)_4$ in AcOH-MeOH; f, $KMnO_4$-H_2SO_4; g, CH_2N_2; h, H_2N-NH_2·AcOH; i, HCl; j, $LiAlH_4$*; k, H^+; l, CrO_3-H_2SO_4

phthaloyl (R)-[2-^{2}H]-glycine 14,[9] mp 189°; $[\alpha]_{578}^{25}$ -1.01°, $[\alpha]_{546}^{25}$ -1.16°, $[\alpha]_{436}^{25}$ -2.11° and $[\alpha]_{405}^{25}$ -2.67° (c 10.0, MeOH), which is being deprotected as described above to (R)-[2-^{2}H]-glycine 15.

Versatility of the present methodology can be illustrated as a novel access to chiral acetic acid in quantity. Thus, the epoxide 4 was proved to be reduced quantitatively with $LiAlH_4$ to the monodeuteromethyl carbinol 16,[9] mp 118-9°; ^{1}H-NMR: δ 1.28 (2H m, H-2') and δ 4.25 (1H br.t, H-1'). Since the hydride attack is believed to proceed with inversion of configuration at C-2', reduction of the epoxide 4 or 12 with tritiated $LiAlH_4$ would apparently yield a methyl carbinol having a chiral methyl group of (R)- or (S)-configuration, respectively. Therefore, subsequent deprotection under acidic conditions, followed by Kuhn-Roth oxidation is to give (R)- and (S)-[H,^{2}H,^{3}H]-acetic acid, respectively.

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