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A STEREOSELECTIVE SYNTHESIS OF 2-AMINO-2-DEOXY-D-RIBOSE

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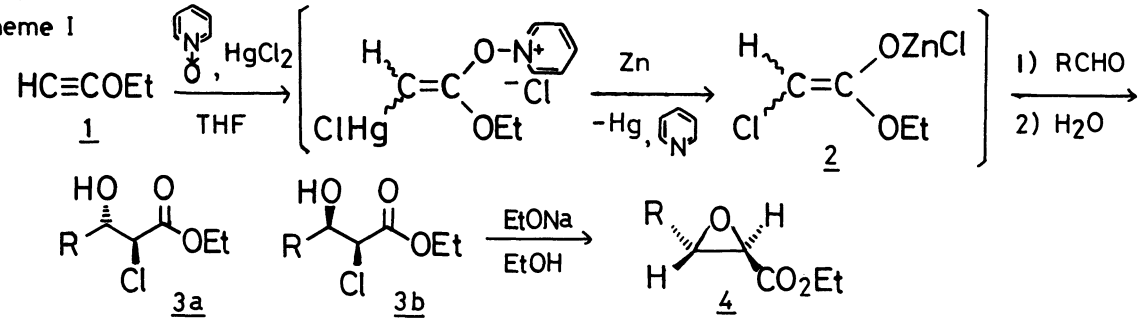
2-Benzyloxycarbonylamino-2-deoxy-D-ribose was conveniently synthesized via α-chloro-β-hydroxyester prepared from 2,3-O-isopropylidene-D-glyceraldehyde and ethoxyacetylene by the stereoselective aldol reaction.

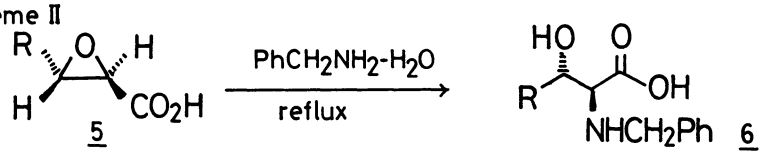
The carbohydrates constitute a highly significant class of natural products, and are frequently employed in organic synthesis as chiral synthons and templates for the stereospecific syntheses of compounds containing multiple asymmetric centers.[1] Many methods have been developed for the syntheses of a variety of sugars, however, exploration of a new and efficient process is still strongly desired in this area. Recently, we have reported[2] several examples of the syntheses of sugar derivatives using newly explored carbon-carbon bond-forming reactions. In this communication, we wish to report a new and convenient method for the synthesis of 2-amino-2-deoxy-D-ribose via α-chloro-β-hydroxyester (8), prepared from 2,3-O-isopropylidene-D-glyceraldehyde and ethoxyacetylene.

Previously, we reported[3] that an ester enolate anion (2), generated by treatment of ethoxyacetylene (1) with mercury(II) chloride, pyridine-1-oxide and zinc dust, reacted with aldehydes to give the corresponding α-chloro-β-hydroxyesters (3) in good yields and that 3 were further converted to trans-2,3-epoxyesters (4) accompanied by isomerization on treatment with sodium ethoxide (Scheme I). It is generally known[4] that trans-2,3-epoxyacids (5) react regioselectively and stereospecifically with benzylamine to give anti-α-benzylamino-β-hydroxyacids (6) (Scheme II).[5]

Scheme I

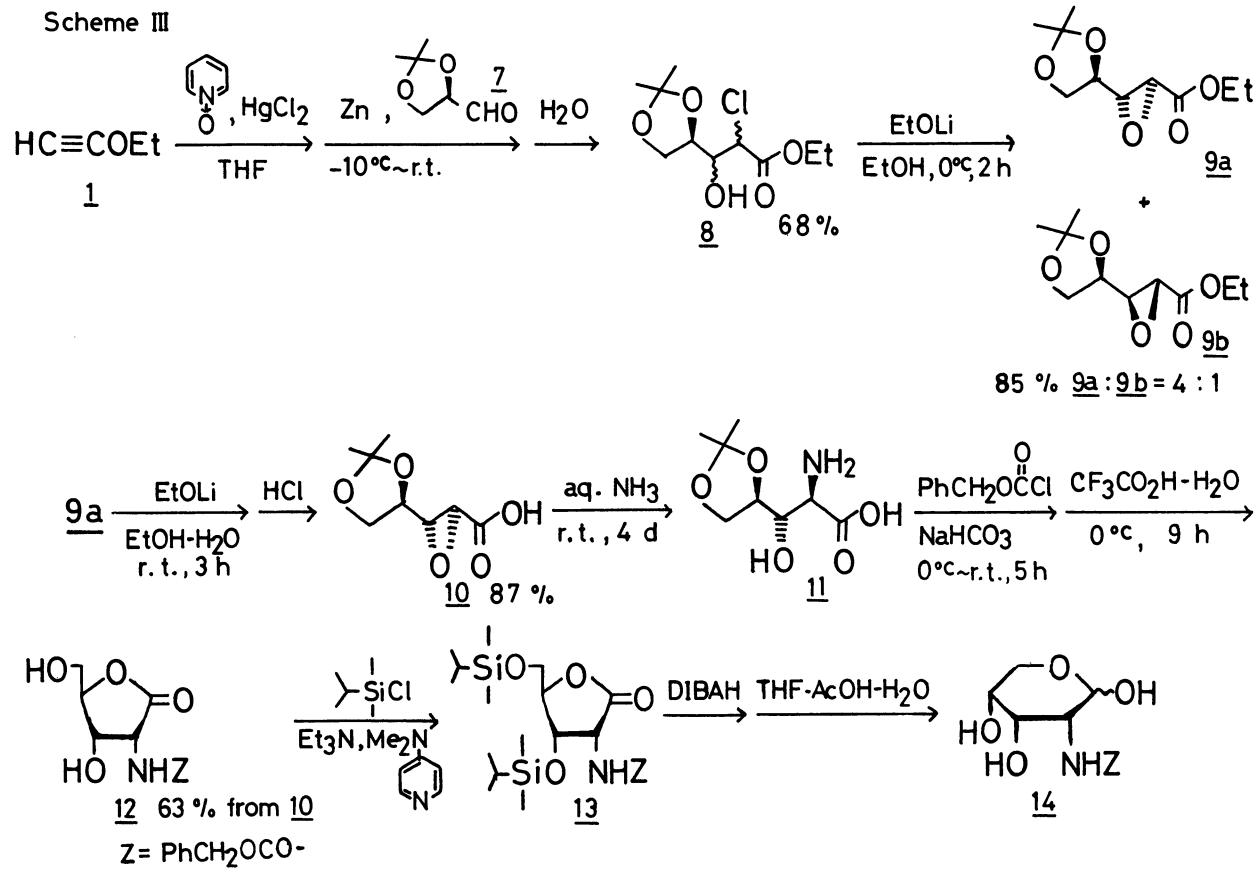


Scheme II



Based on these facts, we studied on the synthesis of 2-amino-2-deoxy-D-pentose according to Scheme III. In the first place, α-chloro-β-hydroxyester (8),[6] a mixture of diastereoisomers, was prepared in 68% yield from ethoxyacetylene (1) and 2,3-O-isopropylidene-D-glyceraldehyde (7) by the similar procedure as previously reported.[7] Then, 8 was treated with lithium ethoxide (1.1 equiv.) in ethanol at 0°C for 2 h to give 2,3-epoxyester (9, 85%). ^{13}C-NMR of 9 indicated that 9 consisted of two diastereoisomers. The mixture was separated into 9a[8] and 9b[9] by the flash column chromatography and the diastereomers ratio (9a : 9b) was determined to be 4 : 1.[10] ^{1}H-NMR showed that both 9a and 9b had trans configuration about the oxiran ring. Next, the major isomer (9a) was hydrolyzed with lithium ethoxide (1.2 equiv.) in aqueous ethanol (room temperature, 3h) to give trans-2,3-epoxyacid (10)[11] in 87% yield after acidification with 1N aq. HCl solution. Then epoxyacid (10) was treated with 28% aq. NH_3 solution at room temperature for 4d and the oxiran ring of 10 was regioselectively and stereospecifically opened at α-position to give anti-α-amino-β-hydroxyacid (11). The crude α-aminoacid (11) was benzyloxycarbonylated with benzyloxycarbonyl chloride (1.6 equiv.) in ether-toluene-1N aq. $NaHCO_3$ solution (0°C - room temperature, 5h). After evaporation of solvent in vacuo, the residue was treated with trifluoroacetic acid containing a small amount of H_2O (0°C, 9h) to give 2-(N-benzyloxycarbonylamino)-2-deoxy-1,4-pentanolactone (12, 63% from 10)[12]. N-Protected 2-aminolactone (12) was converted[13] to 2-(N-benzyloxycarbonylamino)-2-deoxypentose (14)[14] according to the procedure in the previous report.[2e]

Scheme III



The pentose (14) was identified as an expected isomer, that is, 2-amino-2-deoxyribose by comparison of TLC, optical rotation, melting point, and IR with those of an authentic sample [2e].

In the synthesis of 11, an original chiral center at C-4 position was derived from the chiral aldehyde (7) and two new asymmetric centers were efficiently created at C-2 and C-3 positions. Concerning the C-3, C-4-stereochemistry, anti-product was predominantly formed by the aldol reaction and this could be explained by assuming the Felkin's model [15] in the transition state. C-2, C-3-Stereoselection was achieved by base-catalyzed isomerization of 8 to the thermodynamically more stable anti-diastereoisomer in the step of oxiran formation (8 → 9), and regioselective and stereospecific ring-opening of 10 by ammonia (10 → 11).

It should be noted that the new aldol reaction developed by us is successfully applied to the synthesis of 2-amino-2-deoxyribose and that the present method provides a new and efficient route to 2-aminosugars.[16]

References

1) See for a review: S. Hanessian, Acc. Chem. Res., 12, 159 (1979).
2) a) M. Yamaguchi and T. Mukaiyama, Chem. Lett., 1981, 1005.
b) T. Harada and T. Mukaiyama, ibid., 1981, 1109.
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e) T. Mukaiyama, T. Miwa, and T. Nakatsuka, ibid., 1982, 145.
f) M. Murakami and T. Mukaiyama, ibid., 1982, 241.
3) T. Mukaiyama and M. Murakami, ibid., 1981, 1129.
4) Y. Liwschitz, Y. Rabinsohn, and D. Perera, J. Chem. Soc., 1962, 1116.
5) Syn and anti are based on Masamune's nomenclature: S. Masamune, Sk. A. Ali, S. L. Snitman, and D. S. Garvey, Angew. Chem., Int. Ed. Engl., 19, 557 (1980).
6) 8: ^{1}H-NMR (CCl_4) δ 1.28 (3H, t, J=7Hz), 1.28 (3H, s), 1.34 (3H, s), 3.5 - 4.6 (6H, m) 4.17(2H, q, J=7Hz): IR (neat) 3450, 1740 cm^{-1}.
7) Ethoxyacetylene, mercury (II) chloride, pyridine-1-oxide, and 2,3-O-isopropylidene-D-glyceraldehyde were mixed as previously reported. Zinc dust was added at -10°C over 10 min and then the reaction temperature was raised to room temperature. After stirring 15h at that temperature, the reaction mixture was poured into vigorously stirred phosphate buffer solution (pH7) at 0°C and worked up as usual.
8) 9a: ^{1}H-NMR ($CDCl_3$) δ 1.29 (3H, t, J=7Hz), 1.32 (3H, s), 1.41 (3H, s), 4.20 (2H, q, J=7Hz); ^{13}C-NMR($CDCl_3$) δ 14.1, 25.2, 26.4, 51.7, 57.8, 61.7, 66.7, 74.7, 110.2, 168.2: IR (neat) 1745, 900 cm^{-1}; $[\alpha]_D^{21}$ + 33° (C 1.2, CH_2Cl_2); Found: C, 55.26: H, 7.66%. Calcd for $C_{10}H_{16}O_5$; C, 55.55; H, 7.46%.

9) 9b: ^{1}H-NMR ($CDCl_3$) δ 1.28 (3 H, t, J=7Hz) 1.35 (3 H, s), 1.41 (3 H, s), 3.2 - 3.4 (1 H, m), 3.47 (1 H, d, J=2Hz), 3.7 -4.3 (3 H, m), 4.21 (2 H, q, J=7Hz); IR (neat) 1740, 905 cm^{-1}; $[\alpha]_D^{20}$ -7.0° (C 1.0, CH_2Cl_2)

10) 2,3-O-Dibenzyl-D-glyceraldehyde was found to be less selective than 7 in the present aldol reaction giving a diastereomers ratio of 2 : 1.

11) 10 : ^{1}H-NMR ($CDCl_3$) δ 1.37 (3 H, s), 1.46 (3 H, s) 3.2 - 3.4 (1 H, m), 3.42 (1 H, d, J=1.5Hz), 3.8 - 4.3 (3 H, m), 10.6 (1 H, s); IR (neat) 3450, 1740, 905 cm^{-1}.

12) 12 : ^{1}H-NMR ($CDCl_3$ - CD_3OD) 2.6 - 3.2 (2 H, m), 3.6 - 3.9 (2 H, m), 4.2 - 4.5 (2 H, m), 4.6 - 4.9 (1 H, m), 5.05 (2 H, s), 5.92 (1 H, d, J=8Hz); 7.24 (5 H, s), IR (neat) 3400, 1775, 1700 cm^{-1}.

13) At the stage of O-silyllactone (13), ^{13}C-NMR was measured and it was found that 13 thus obtained consisted of one isomer. 13 : ^{13}C-NMR ($CDCl_3$) -4.7, -4.1, 14.3, 14.4, 16.69, 16.74, 53.9, 62.1, 67.2, 70.8, 86.3, 128.08, 128.14, 128.5, 136.1, 156.1, 174.2.

14) 14 : ^{1}H-NMR (DMSO-d^6) δ 3.2 - 3.9 (6 H, m), 4.9 - 5.2 (3 H, m), 5.01 (2 H, s), 6.3 - 6.9 (1 H, m), 7.32 (5 H, s); IR (KBr) 3400, 1665 cm^{-1}: $[\alpha]_D^{21}$ -10.7° (C 1.0, MeOH, after 2 h, lit.[2e] -10.7°), mp 150 - 152°C (MeOH, lit.[2e] 146 - 148°C).

15) M. Chérest, H. Felkin, and N. Prudent, Tetrahedron Lett., 1968, 2199.

16) Recently, synthesis of 2-amino-2-deoxy- D-pentitols via a different route from 7 was reported by Kishi et al.: N. Minami, S. S. Ko, and Y. Kishi, J. Am. Chem. Soc., 104, 1109 (1982).

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