SYNTHESIS OF (+)-1-DEOXYNOJIRIMYCIN FROM (S)-PYROGLUTAMIC ACID

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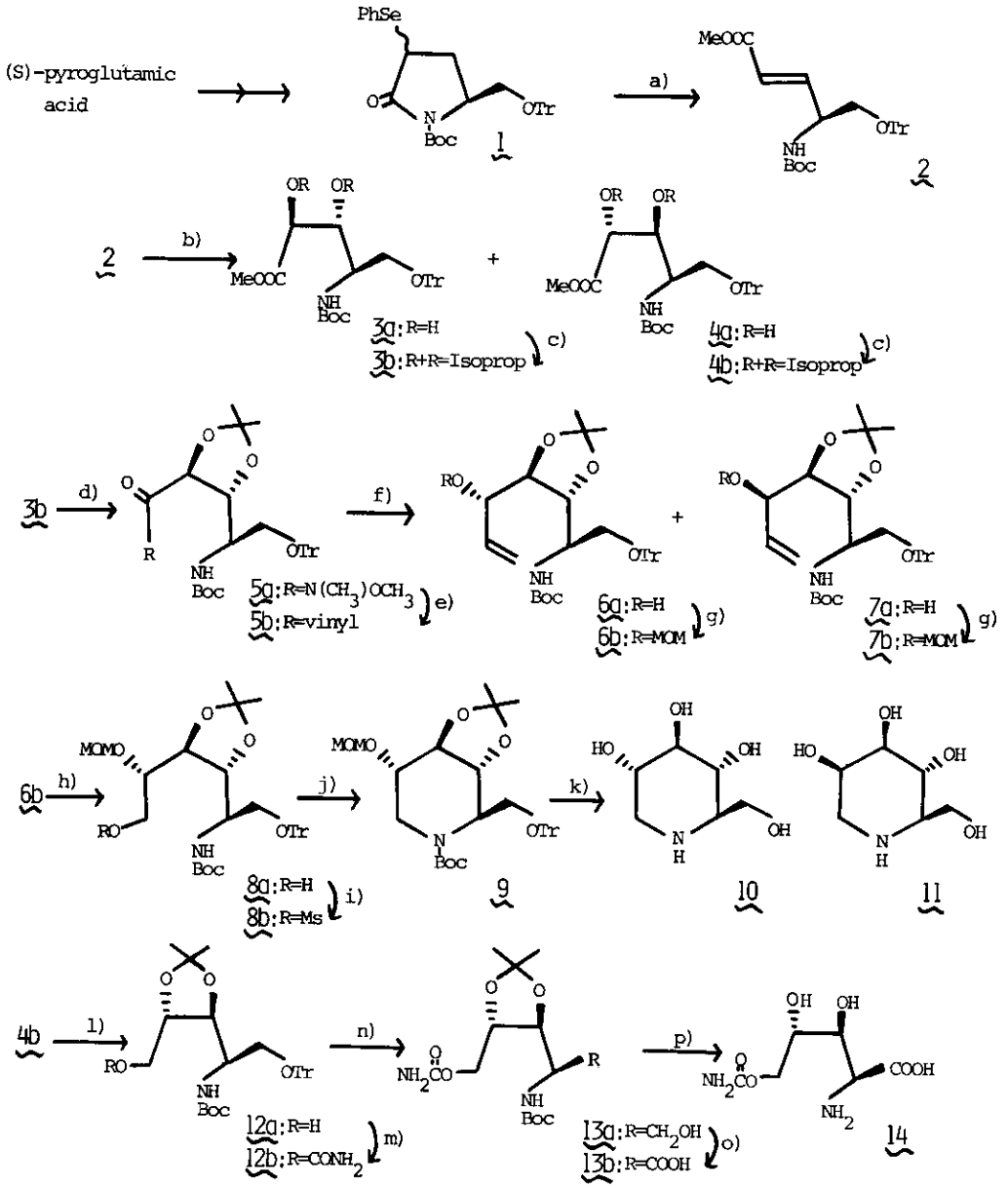
Abstract —— The synthesis of (+)-1-deoxynojirimycin (10) has been achieved from (S)-pyroglutamic acid by cis hydroxylation of the trans-α,β-unsaturated ester 2 and reduction of the enone 5b as the key reactions. 5-O-Carbamoylpolyoxamic acid (14) and (+)-1-deoxymannojirimycin (11) were also synthesized from 4b and 7b, obtained by the above reactions as the minor diastereomer, respectively.

We have recently reported the stereoselective synthesis of (-)-swainsonine and its stereoisomers,[1a,b] Geissman-Waiss lactone,[1c] and (2S,3S,4S)-4-amino-2,3-dihydroxyhexanedioic acid derivatives[1d] from (S)- or (R)-pyroglutamic acid. In continuation of our work on the utility of chiral pyroglutamic acid derivatives for asymmetric reactions[2] and for natural product synthesis, we now describe the new approach for the synthesis of polyhydroxylated piperidine alkaloids such as (+)-1-deoxynojirimycin (10)[3] and (-)-1-deoxymannojirimycin (11)[4] from (S)-pyroglutamic acid. Treatment of a diastereomeric mixture of (3S,5S)- and (3R,5S)-1-(tert-butoxycarbonyl)-3-(phenylseleno)-5-(trityloxymethyl)-2-pyrrolidinone (1)[1d] with aqueous LiOH in THF, followed by esterification with diazomethane and subsequent oxidation (30% H_2O_2, AcOEt) afforded the trans-α,β-unsaturated ester (2)[5] in 65% yield. Cis hydroxylation of 2 using a catalytic amount of OsO_4 with N-methylmorpholine N-oxide in aqueous acetone at -40°C provided the dihydroxy compounds 3a and 4a (78% yield) in a 3.1:1 ratio based on the analysis of ^1H nmr spectrum. The two diastereomers were well separated by column chromatography on silica gel (AcOEt: hexane=1:3.5) after the conversion of 3a and 4a into the coresponding acetonide 3b and 4b. The major isomer 3b (mp 124°C, $[\alpha]_D$ +5.8°(c=1, $CHCl_3$)) was then hydrolyzed and converted into the N,O-dimethylhydroxyamine amide 5a,[6] which was reacted with vinylmagnesium bromide (2.2 equiv.) in THF at -40°C to give the enone 5b (mp 112-



Reagents and Conditions

a) i, aq. LiOH/THF, r.t.; ii, CH_2N_2/ether, r.t.; iii, 30%H_2O_2/AcOEt, 0°C→r.t. b) cat. OsO_4-NMO/aq. acetone, -40°C, 13 h. c) $(CH_3O)_2C(CH_3)_2$, p-TsOH, acetone, r.t. d) i, aq. NaOH/THF-MeOH, r.t.; ii, NH(Me)OMe·HCl-diethyl phosphorocyanidate-TEA/CH_2Cl_2, r.t. 10 h. e) vinylmagnesium bromide/THF, -40°C, 1.5 h. f) $NaBH_4$—$CeCl_3 7H_2O$/MeOH, -20°C, 10 min. g) MOMCl-*N*,*N*-diethylaniline, CH_2Cl_2, r.t. h) cat. OsO_4-$NaIO_4$/aq. *tert*-BuOH, r.t., then $NaBH_4$/THF, r.t. i) MsCl-TEA/CH_2Cl_2, 0°C, 1 h. j) $KOC(CH_3)_3$/THF, 0°C, 1 h. k) 10% aq. HCl/MeOH(1:2), 70°C, 1h. l) $NaBH_4$/EtOH, r.t. m) i, 4-nitrophenyl chloroformate-TEA-pyridine/ether-THF, r.t., 12 h; ii, NH_3-MeOH, 0°C, 20 min. n) conc. HCl/MeOH(1:50), r.t., 30 min. o) cat. $RuCl_3$-$NaIO_4$/CH_3CN-H_2O-CCl_4, r.t., 1 h. p) CF_3COOH/MeOH(10:1), r.t., 1 h, then Dowex 50W-X8.

113°C, $[\alpha]_D$ -9.5°(c=0.8, $CHCl_3$)) in 40% yield from 3b. Reduction of the enone 5b with $NaBH_4/CeCl_3$ in MeOH[7] gave the allylic alcohols (6a and 7a, yield 86%), which were separated by column chromatography on silica gel (AcOEt:hexane=1:5) after the protection of hydroxy group in 6a and 7a as a methoxymethyl ether (6b and 7b, yield 82%). The ratio of 6b/7b was 2.9:1[8] based on the ^1H nmr spectrum. Oxidation of the olefin 6b ($[\alpha]_D^{20}$ +21°(c=0.8, $CHCl_3$)) with a catalytic amount of OsO_4 in the presence of $NaIO_4$ in aqueous tert-BuOH,[9] followed by reduction with $NaBH_4$ in THF gave the alcohol 8a, which led to the mesylate 8b in 68% yield from 6a. Under basic condition (tert-BuOK/THF), the fully protected piperidine 9 was obtained in 87% yield. Removal of the protecting groups in 9 by treatment with 10% aqueous HCl-MeOH at 70°C provided the hydrochloride of 10 in 86% yield (mp 204°C, $[\alpha]_D^{20}$ +35°(c=1, H_2O); lit.[3b] mp 203°C, free base mp 193-194°C; $[\alpha]_D^{20}$ +46°(c=0.6, H_2O), lit.[3a] mp 196°C; $[\alpha]_D^{21}$ +47°(H_2O)). By a parallel series of reactions, the compound 7b ($[\alpha]_D^{20}$ -20.8°(c=0.6, $CHCl_3$)) was transformed to the hydrochloride of (-)-1-deoxymannojirimycin (11, mp 170-171°C; $[\alpha]_D^{20}$ -11.5°(c=0.6, H_2O), lit. mp 172.5-173.5 C[4b]; $[\alpha]_D^{20}$ -10.9°(c=0.3, H_2O)[4c]) in 45% yield. ^1H and ^{13}C nmr spectra of 10 and the hydrochloride of 11 were identical with those reported.[3c,4a] The compound 2 ($[\alpha]_D^{20}$ -29.8°(c=1, $CHCl_3$)), minor isomer of cis hydroxylation of 2, was also transformed into the 5-O-carbamoylpolyoxamic acid[10] (14, mp 222-225°C (dec); $[\alpha]_D^{20}$ +3.3°(c=1.6, H_2O); ^{13}C nmr(D_2O,internal standard:dioxane δ=67.4) 58.73, 66.33, 68.77, 71.64, 159.89, 173.39, lit.[10a] mp 226-232°C (dec); $[\alpha]_D^{22}$ +1.3°(c=1.04, H_2O)), the major acyclic component of the polyoxin family of antifungal antibiotics,[10a] in the following procedures in 22% yield; (i) reduction of 2 with $NaBH_4$ in EtOH, (ii) 5-O-carbamoylation, (iii) selective cleavage of trityl group in 12b (concentrated HCl/MeOH=1:50, room temperature, 30 min), (iv) oxidation of 13a using $RuCl_3$ with $NaIO_4$,[11] (v) removal of Boc and isopropylidene group (CF_3COOH/MeOH=10:1) in 13b followed by treatment with Dowex 50W-X8 (H^+ form). Thus, we showed the facile synthesis of the hydroxylated piperidine alkaloids and related compounds from (S)-pyroglutamic acid derivative. The present method seems to be useful for preparations of polyhydroxylated α-amino acid derivatives such as destomic acid.[12]

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