

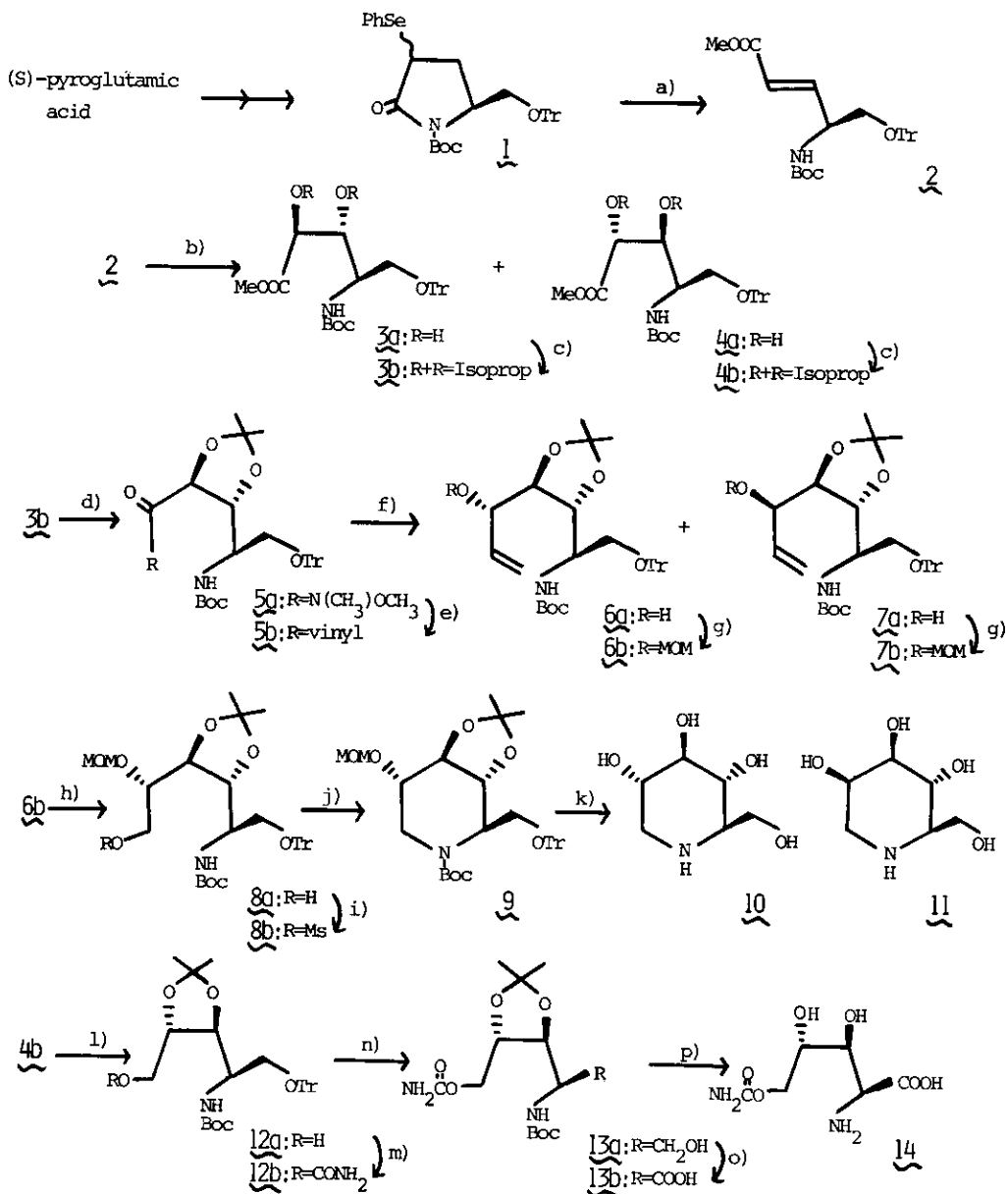
SYNTHESIS OF (+)-1-DEOXYNOJIRIMYCIN FROM (S)-PYROGLUTAMIC ACID

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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 reactions² 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-butoxy-carbonyl)-3-(phenylseleno)-5-(trityloxymethyl)-2-pyrrolidinone (1)^{1d} with aqueous LiOH in THF, followed by esterification with diazomethane and subsequent oxidation (30% H₂O₂, AcOEt) afforded the trans- α,β -unsaturated ester (2)⁵ in 65% yield. Cis hydroxylation of 2 using a catalytic amount of OsO₄ 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 corresponding acetonide 3b and 4b. The major isomer 3b (mp 124°C, [α]_D +5.8° (c=1, CHCl₃)) 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, $0^\circ\text{C} \rightarrow$ r.t. b) cat. OsO_4 -NMO/aq. acetone, -40°C , 13 h. c) $(\text{CH}_3\text{O})_2\text{C}(\text{CH}_3)_2$, *p*-TsoH, acetone, r.t. d) i, aq. NaOH/THF-MeOH, r.t.; ii, $\text{NH}(\text{Me})\text{OME} \cdot \text{HCl}$ -diethyl phosphorocyanidate-TEA/ CH_2Cl_2 , r.t. 10 h. e) vinylmagnesium bromide/THF, -40°C , 1.5 h. f) NaBH_4 - $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ /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) $\text{KOC}(\text{CH}_3)_3$ /THF, 0°C , 1 h. k) 10% aq. HCl/MeOH(1:2), 70°C , 1 h. 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 / $\text{CH}_3\text{CN}-\text{H}_2\text{O}-\text{CCl}_4$, r.t., 1 h. p) CF_3COOH /MeOH(10:1), r.t., 1 h, then Dowex 50W-X8.

113°C, $[\alpha]_D -9.5^\circ$ ($c=0.8$, CHCl_3) in 40% yield from 3b. Reduction of the enone 5b with $\text{NaBH}_4/\text{CeCl}_3$ in MeOH ⁷ gave the allylic alcohols (6a and 7a, yield 86%), which were separated by column chromatography on silica gel ($\text{AcOEt}:\text{hexane}=1:5$) 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 2.9:1⁸ based on the ^1H nmr spectrum. Oxidation of the olefin 6b ($[\alpha]_D^{20} +21^\circ$ ($c=0.8$, 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, $[\alpha]_D^{20} +35^\circ$ ($c=1$, H_2O); lit.^{3b} mp 203°C, free base mp 193-194°C; $[\alpha]_D^{20} +46^\circ$ ($c=0.6$, H_2O), lit.^{3a} mp 196°C; $[\alpha]_D^{21} +47^\circ$ (H_2O)). By a parallel series of reactions, the compound 7b ($[\alpha]_D^{20} -20.8^\circ$ ($c=0.6$, CHCl_3)) was transformed to the hydrochloride of (-)-1-deoxymannojirimycin (11, mp 170-171°C; $[\alpha]_D^{20} -11.5^\circ$ ($c=0.6$, H_2O), lit. mp 172.5-173.5°C^{4b}; $[\alpha]_D^{20} -10.9^\circ$ ($c=0.3$, 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 ($[\alpha]_D^{20} -29.8^\circ$ ($c=1$, 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); $[\alpha]_D^{20} +3.3^\circ$ ($c=1.6$, H_2O); ^{13}C nmr (D_2O , internal standard:dioxane $\delta=67.4$) 58.73, 66.33, 68.77, 71.64, 159.89, 173.39, lit.^{10a} mp 226-232°C (dec); $[\alpha]_D^{22} +1.3^\circ$ ($c=1.04$, 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 ($\text{CF}_3\text{COOH}/\text{MeOH}=10:1$) 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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