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Synthesis of (2S,3S,5S)-3-Hydroxy-5-methyl-2-pyrrolidinecarboxylic Acid, a Component of Actinomycin Z_1

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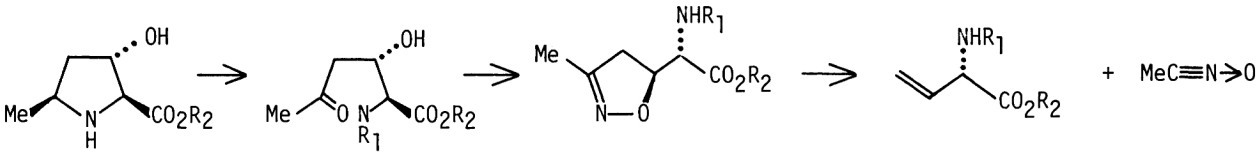
(2S,3S,5S)-3-Hydroxy-5-methyl-2-pyrrolidinecarboxylic acid and the enantiomer, the relative configurations of which are the same as that of the natural compound found in actinomycin Z_1 were synthesized and the optical properties were determened.

3-Hydroxy-5-methyl-2-pyrrolidinecarboxylic acid (3-hydroxy-5-methylproline) is an unusual imino acid identified as a component of a peptide antibiotic actinomycin Z_1.[1] The four diastereomers of the imino acid were synthesized by Mauger et al. and their relative stereochemistries were determined by NMR data and epimerization studies.[2] It has been demonstrated that 3-hydroxy-5-methylproline obtained from the hydrolyzate of actinomycin Z_1 was identical with one of the synthetic isomers which has 2,3-trans and 2,5-cis relative stereochemistry, however, the absolute configuration (2S,3S,5S or 2R,3R,5R) remains unknown.

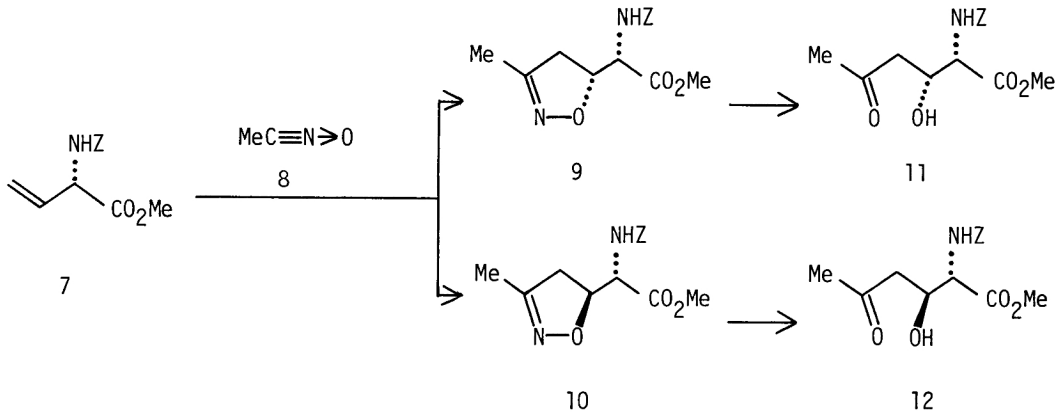
As a part of our efforts toward the synthesis of biologically active β-hydroxy-α-amino acid derivatives,[3] we planned to synthesize (2S,3S,5S)-3-hydroxy-5-methylproline (1) in order to reveal the optical properties based on the retrograde pathway A → B → C → D + E.



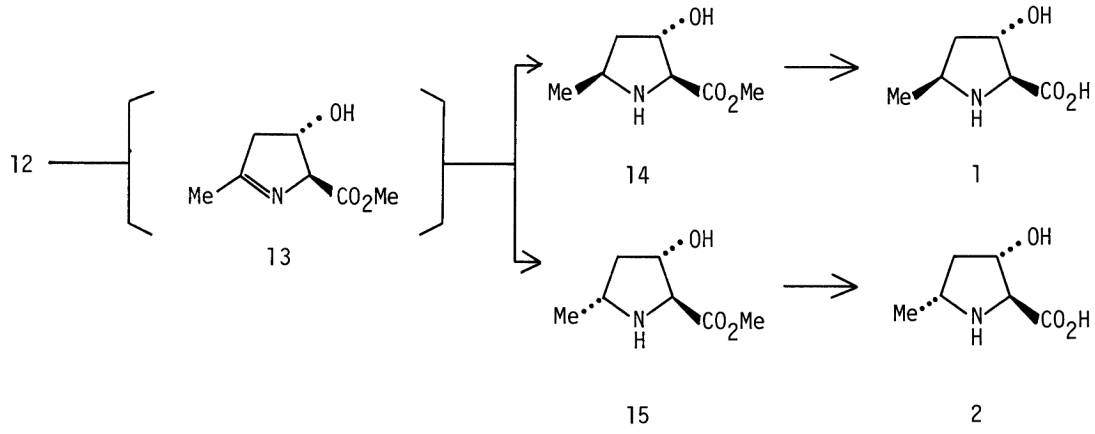
A B C D E

The main features are (i) [3+2] dipolar cycloaddition[4] of D and E, (ii) reductive cleavage of an isoxazole ring to a β-hydroxyketone[5a] (C → B), and (iii) reductive cyclization (B → A). The present communication describes an efficient synthesis of (2S,3S,5S)-3-hydroxy-5-methylproline (1) and the stereoisomers (2-6) along these lines.[6]

Reaction of L-vinylglycine 7[7] (Z: benzyloxycarbonyl) and nitrile oxide 8 generated in situ (nitroethane, p-chlorophenylisocyanate,[8] Et_3N, benzene, 25 °C, 19 h, then reflux, 6.8 h) afforded a 2.3:1 mixture of threo- and erythro-isoxazolines,[9] 9, $[\alpha]_D$ -0.69° (c 0.57, $CHCl_3$) and 10, $[\alpha]_D$ +71° (c 0.51, $CHCl_3$), respectively in 53% yield. These diastereomers were separated by column

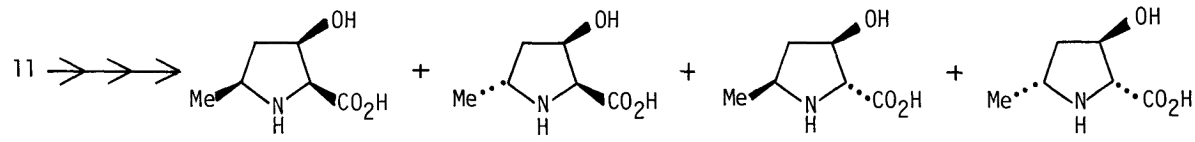


chromatography on silica gel (hexane/ethyl acetate, 2:1) and, the stereochemistry of the isolated compounds was determined by converting them to the corresponding proline derivatives shown below. Hydrogenolytic cleavage of isoxazoline 10 according to the Curran's method[5b] (Raney-Ni, $B(OH)_3$, $MeOH/H_2O$, H_2) afforded a β-hydroxyketone 12, $[\alpha]_D$ -6.5° (c 0.71, MeOH) in 88% yield. After removal of the amino protecting group of 12 (H_2/10% Pd-C, EtOH), the resulting cyclic imine 13 was reduced ($NaBH_3CN$, EtOH, pH 5)[10] to a diastereomeric mixture of 3-hydroxy-5-methylproline esters (14 and 15). The mixture was hydrolyzed (0.15 mol $Ba(OH)_2$, 20 °C, 4 h) without separation and the hydrolyzate was subjected to a Dowex 50W x 4 column chromatography eluting with ammonia-formate buffer (pH 2.70) to afford (2S,3S,5S)-3-hydroxy-5-methylproline 1, mp 247-249 °C (dec.), $[\alpha]_D$ -17° (c 0.50, H_2O) and (2S,3S,5R)-isomer 2, mp 252-255 °C (dec.), $[\alpha]_D$ -10° (c 0.48, H_2O) in 44% and 26% yields (from 12), respectively. The ^{1}H-NMR data of 1 and 2 were in accord with those reported about racemic 1 and 2, respectively.[2]



The threo-isoxazoline 9 was independently converted by the same series of reactions to 3-hydroxy-5-methylprolines via β-hydroxyketone 11,[11] $[\alpha]_D$ +2.8° (c 0.71, MeOH) (9 → 11, 83% yield). A mixture of (2S,3R,4S)- and (2S,3R,4R)-isomers (3/4, 2:1) was obtained in 23% yield (from 11) together with (2R,3R,4S) isomer 5 and (2R,3R,4R)-isomer 6 (7% and 5% yields, respectively).[12] These results

suggest that epimerization attributable to a tautomerism of the cyclic imine intermediate occurred at the C-2 position. The (2R,3R,5R)-isomer 6 and (2R,3R,5S)-isomer 5 exhibited the same spectral properties as those of 1 and 2, respectively except the opposite optical rotations, 6, $[\alpha]_D$ +18° (c 0.32, H_2O), 5, $[\alpha]_D$ +10° (c 0.20, H_2O).



3 4 5 6

In conclusion, we demonstrated an efficient synthesis of optically active 3-hydroxy-5-methylprolines (1-6) and clarified their optical properties, which will serve to elucidate the absolute configuration of the natural compound from actinomycin Z_1.[13]

The present methodology seems to be very useful for preparations of β-hydroxy-α-amino and imino acids especially considering the wide variation of molecules containing nitryl oxide groups.

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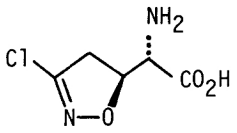
References

1) E. Katz, K. T. Mason, and A. B. Mauger, Biochem. Biophys. Res. Commun., 63, 502 (1975).
2) A. B. Mauger, O. A. Stuart, E. Katz, and K. T. Mason, J. Org. Chem., 42, 1000 (1977).
3) T. Tashiro, S. Fushiya, and S. Nozoe, Chem. Pharm. Bull., submitted.
4) Review: A. P. Kozikowski, "Comprehensive Heterocyclic Chemistry," ed by A. R. Katritzky, Pergamon Press, Oxford (1984).
5) a) A. P. Kozikowski, Acc. Chem. Res., 17, 410 (1984); b) D. P. Curran and C. J. Fenk, Tetrahedron Lett., 27, 4865 (1986).
6) All new compounds reported in this work gave satisfactory spectral (^{1}H-NMR, IR, MS) and analytical data.
7) A. Afzali-Ardahani and H. Rapoport, J. Org. Chem., 45, 4817 (1980).
8) A. P. Kozikowski and P. D. Stein, J. Am. Chem. Soc., 104, 4023 (1982).
9) The ratio of the diastereomers was determined by ^{1}H-NMR analysis of the purified mixtures. The coupling constants between $C_{(\alpha)}$-H and $C_{(\beta)}$-H in the ^{1}H-NMR spectra of threo-isomer 9 and erythro-isomer 10 are 2.0 and 4.0 Hz respectively. These values do not correspond to those of AT-125 (erythro, 3.0 Hz) (16) and the $C_{(3)}$-epimer (threo, 7.0 Hz) (17). J. E. Baldwin, L. I. Kruse, and J. K. Cha, J. Am. Chem. Soc., 103, 942 (1981); Low stereoselectivity was observed in nitrile oxide cycloadditions to chiral terminal

alkenes. See, A. P. Kozikowski and A. K. Ghosh, J. Am. chem. Soc., 104, 5788 (1982) and P. A. Wade, S. M. Singh, and K. Pillay, Tetrahedron, 40, 601(1984).



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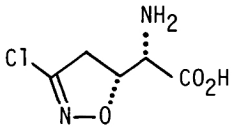

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10) R. F. Borch, M. D. Bernstein, and H. D. Durst, J. Am. Chem. Soc., 93, 2897 (1971).

11) In this case, Kozikowski's procedure using $AlCl_3$ in the place of $B(OH)_3$ was used. See Ref. 5a.

12) The mixture of 3 and 4 could not be separated under the chromatographic condition (Dowex 50w x 4, pH 2.70 buffer) however, the structures and the ratio were confirmed by comparison of ^{1}H-NMR spectrum of the mixture with those of racemic 3 and 4.

13) The natural 3-hydroxy-5-methylproline from actinomycin Z_1 was not obtained in sufficient quantity for optical rotation. Private communication from Dr. A. B. Mauger.

14) ^{1}H-NMR data: 9 (100 MHz, $CDCl_3$) δ 1.80 (3H, br s), 2.69-3.06 (2H, m), 3.68 (3H, s), 4.39 (1H, dd, J=2.0, 10.0 Hz, $H_{(\alpha)}$), 4.79-5.59 (2H, m, $H_{(\beta)}$ and NH), 5.03 (2H, s), 7.24 (5H, s). 10 (100 MHz, $CDCl_3$) δ 1.94 (3H, br s), 3.07 (2H, br d, J=8.0 Hz), 3.69 (3H, s), 4.40 (1H, dd, J=4.0, 8.2 Hz, $H_{(\alpha)}$), 4.78 (1H, dt, J=4.0, 8.0 Hz, $H_{(\beta)}$), 5.09 (2H, s), 5.63 (1H, br d, J=8.2 Hz), 7.30 (5H, s). 11 (100 MHz, $CDCl_3$) δ 2.13 (3H, s), 2.68 (2H, br d, J=6.2 Hz), 3.35 (1H, br d, J=3.2 Hz, OH), 3.73 (3H, s), 4.34 (1H, br d, J=9.2 Hz, $H_{(\alpha)}$), 4.47-4.83 (1H, m, $H_{(\beta)}$), 5.11 (2H, s), 5.65 (1H, br d, J=9.2 Hz, NH), 7.32 (5H, s). 12 (100 MHz, $CDCl_3$) δ 2.14 (3H, s), 2.74 (2H, br d, J=5.6 Hz), 3.55 (1H, br d, J=4.2 Hz, OH), 3.71 (3H, s), 4.08-4.45 (2H, m, $H_{(\alpha)}$, $H_{(\beta)}$), 5.06 (2H, s), 5.70 (1H, br d, J=8.0 Hz, NH), 7.27 (5H, s). 1 (500 MHz, D_2O) δ 1.51 (3H, d, J=6.7 Hz, Me), 1.76 (1H, ddd, J=4.3, 11.5, 14.1 Hz, $H_{(4a)}$), 2.20 (1H, ddd, J=1.0, 6.0, 14.1 Hz, $H_{(4b)}$), 4.07 (1H, br s, $H_{(2)}$), 4.07 (1H, ddd, J=6.0, 6.7, 11.5 Hz, $H_{(5)}$), 4.68 (1H, br dd, J=1.0, 4.3 Hz, $H_{(3)}$). 2 (500 MHz, D_2O) δ 1.48 (3H, d, J=6.8 Hz, Me), 1.74 (1H, dddd, J=1.0, 4.6, 7.4, 14.0 Hz, $H_{(4b)}$), 2.44 (1H, ddd, J=5.9, 8.0, 14.0 Hz, $H_{(4a)}$), 3.93 (1H, ddd, J=6.8, 7.4, 8.0 Hz, $H_{(5)}$), 4.03 (1H, dd, J=1.0, 3.1 Hz, $H_{(2)}$), 4.62 (1H, ddd, J=3.1, 4.6, 5.9 Hz, $H_{(3)}$).

15) ^{13}C-NMR data: 1 (25 MHz, D_2O) δ 17.4 (q), 39.7 (t), 56.0 (d), 69.9 (d), 74.6 (d), 172.0 (s). 2 (25 MHz, D_2O) δ 17.9 (q), 38.9 (t), 55.0 (d), 68.1 (d), 73.8 (d), 171.9 (s).

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