

Useful Syntheses of (3S)-2,3,4,5-Tetrahydropyridazine-3-carboxylic Acid and Its Dehydrotetrapeptide Derivatives

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The stereoselective synthesis of (3S)-2,3,4,5-tetrahydropyridazine-3-carboxylic acid (Pya), which is a cyclic α -amino acid at center of antrimycins (1), was successful. Moreover, the synthesis of the C-terminal dehydrotetrapeptide of 1 containing Pya residue at N-terminus is described.

Antrimycins (1)¹⁾ and cirratiomycins (1),²⁾ produced by Streptomyces (St.) xanthocidicus MGL25-CF1 and St. cirratus 248-Sg2, respectively, are the same substances. These are the first linear dehydroheptapeptides containing both three kinds of α -amino acid residues and either an α -dehydrovaline (Δ Val) or (Z)- α -dehydroisoleucine (Δ Ile) residue, as illustrated in Fig. 1. We reported already the convenient syntheses of the eight kinds of C-terminal dehydrotripeptides of 1 by the one-pot reaction of N-carboxy- Δ Val or - Δ Ile anhydride (Δ NCA) with both N- and C-component α -amino acids.³⁾ Here, we wish to report the useful synthetic method for structurally unique (3S)-2,3,4,5-tetrahydropyridazine-3-carboxylic acids (Pya) and the C-terminal dehydrotetrapeptide of 1 containing Pya residue at N-terminus.

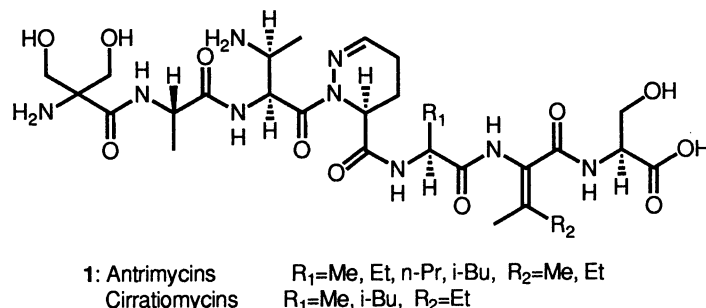
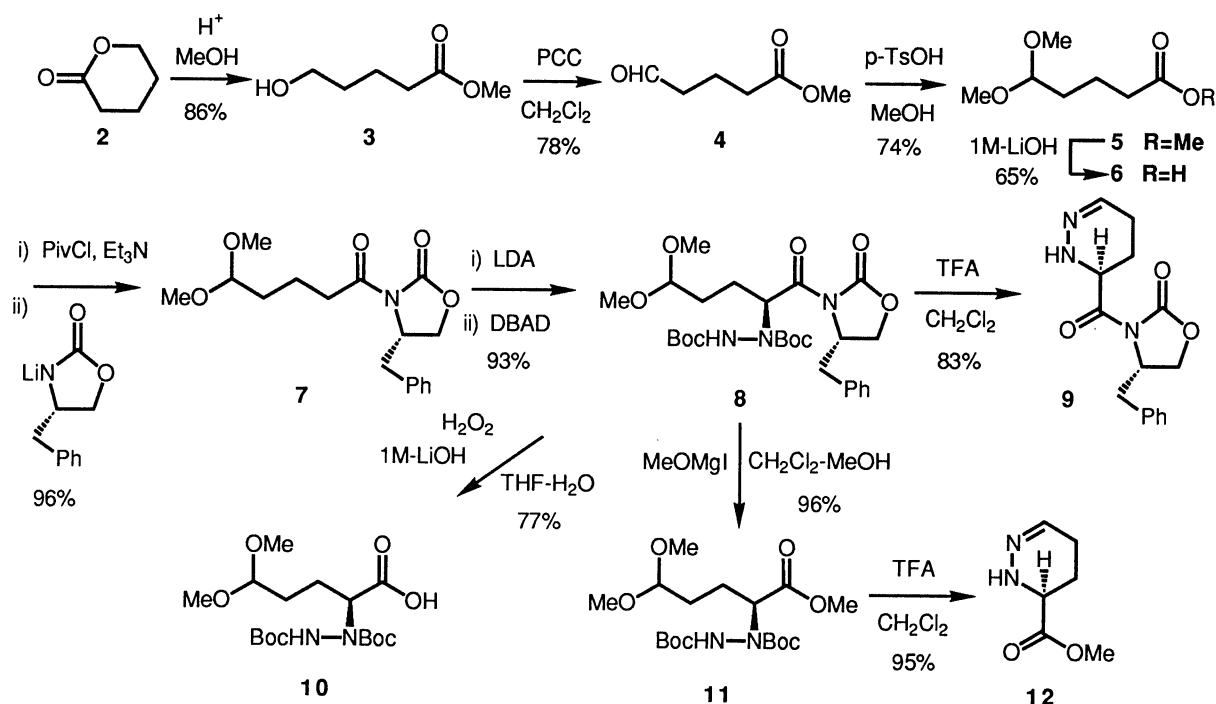


Fig. 1.

As illustrated in Scheme 1, the starting methyl 4-formylbutanoate [4; ¹H NMR (CDCl₃): δ 9.78 (t, 1H, J=1.1 Hz, -CHO)] was derived from lactone (2) via 5-hydroxypentanoate (3) by the oxidation with C₅H₅NH⁺·ClCrO₃⁻ (PCC) in CH₂Cl₂. Treatment of 4 with MeOH in the presence of p-toluenesulfonic acid (p-TsOH) gave the corresponding acetal ester [5; δ 3.61 and 3.26 (3s, 9H, -OMe x 3)], which was hydrolyzed with 1 M-LiOH in MeOH. The obtained acetal acid [6; δ 9.23 (bs, 1H, -COOH)] was treated with pivaloyl chloride



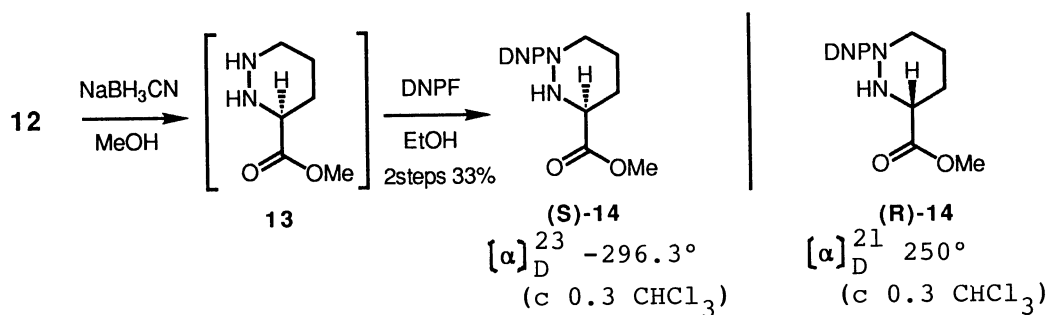
Scheme 1.

(PivCl) in the presence of Et_3N in THF at -78°C by the mixed anhydride method, followed by the coupling with N-lithium (4S)-4-benzyl-1,3-oxazolidin-2-one.⁴⁾ Subsequently, the expected N-acyloxazolidinone [7; δ 4.65 (m, 1H, $-\overset{1}{\text{N}}\text{CH}-$). $[\alpha]_{\text{D}}^{26}$ 83.57° (c 1.11 MeOH)] was reacted successively with N-lithium diisopropylamide (LDA) and di-*t*-butyl azocarboxylate (DBAD) in THF at -78°C to give the corresponding hydrazino adduct [8; δ 6.27 (bs, 1H, $-\text{NH}-$) and 3.97 (m, 1H, H-2). $[\alpha]_{\text{D}}^{26}$ 52.09° (c 2.09 MeOH)]. Simultaneous acetolysis of acetal and deprotection of two Boc groups in 8 with CF_3COOH in CH_2Cl_2 were performed, followed by the cyclization, giving the desired (4S)-3-(2,3,4,5-tetrahydropyridazine)carbonyl-oxazolidinone (9).⁵⁾

Furthermore, to remove the oxazolidinone ring, hydrolysis of 8 with 1 M-LiOH in the presence of 30% H_2O_2 in THF- H_2O (3 : 1) was carried out to give the hydrazino carboxylic acid [10; δ 7.71 (bs, 1H, $-\text{COOH}$) and 6.89 (bs, 1H, $-\text{NH}-$). $[\alpha]_{\text{D}}^{26}$ -18.04° (c 1.40 MeOH)]. On the other hand, methanalysis of 8 with MeOMgI in THF-MeOH at 0°C gave the corresponding hydrazino methyl ester [11; δ 3.72 (s, 3H, $-\text{COOMe}$). $[\alpha]_{\text{D}}^{26}$ -25.65° (c 1.11 MeOH)], which was further cyclized similarly as in the case of 9 to give methyl (3S)-2,3,4,5-tetrahydropyridazine-3-carboxylate (12).⁶⁾

The configurational structure of 9 and 12 were readily determined by the comparison of the 2,4-dinitrophenyl derivative of the hydrogenated 12 (13) with the authentic methyl (3R)-1-(2,4-dinitrophenyl)pyridazate.⁷⁾

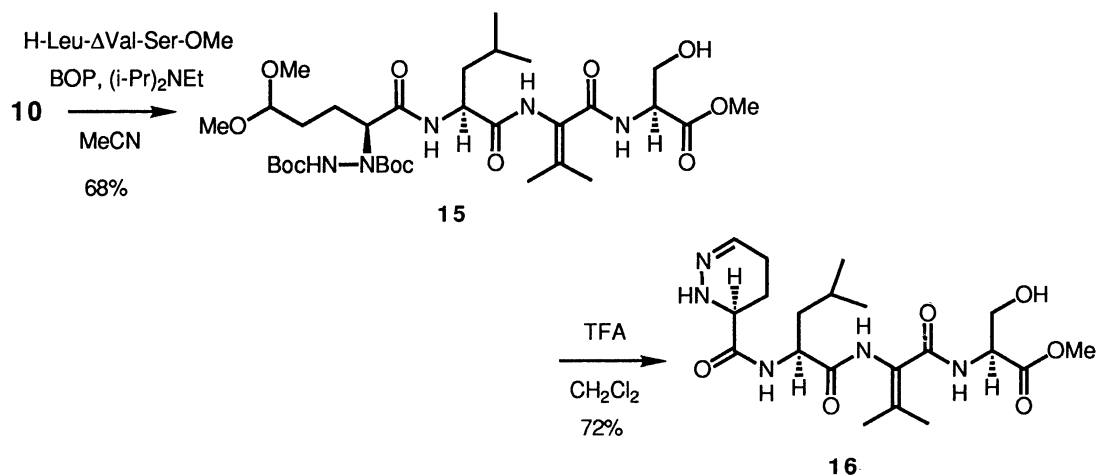
That is, as illustrated in Scheme 2, hydrogenation of 12 with NaBH_3CN in



Scheme 2.

MeOH and immediate substitution of the crude product (**13**) intact with 2,4-dinitrophenyl fluoride (DNP) in EtOH afforded the expected DNP-pyridazate (**14**; 33% from **12**). Since the specific rotation of **14** showed the reverse sign and value to the (R)-isomer of **14**,⁸⁾ the configuration of the Pya derivatives, thus obtained, could be confirmed to be (S)-isomer, which is identical with the Pya residue of **1**.

Finally, in order to apply and examine the pyridazine ring formation in peptide segment, the coupling of **10** with appropriate Δ^2 -dehydrotripeptide^{3,9)} was carried out in the following way. According to Scheme 3, Boc-L-Leu- Δ Val-L-Ser-OMe, prepared by the one-pot synthesis of Δ Val·NCA successive with C-component Boc-Leu-OH and N-component H-Ser-OMe, was deprotected with CF₃COOH and then subjected to the coupling with **10** in the presence of BOP¹⁰⁾ and diisopropylethylamine [(i-Pr)₂NEt] in MeCN to give the corresponding Δ^3 -dehydrotetrapeptide (**15**).^{9,11)} Quite similarly as in the case of **9** and **12**, the cyclization of N-terminal-pentanoyl moiety of **15** with CF₃COOH gave the expected Δ^3 -dehydrotetrapeptide, H-Pya-Leu- Δ Val-Ser-OMe (**16**)¹²⁾ as an important segment of eight kinds of antrimycins.



Scheme 3.

References

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- 2) T. Shiroza, N. Ebisawa, K. Furihata, T. Endo, H. Seto, and N. Ōtake, *Agric. Biol. Chem.*, **46**, 865 (1982).
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- 5) **9**; colorless prisms from EtOAc-hexane, mp 116-117 °C. $[\alpha]_D^{26}$ 167.5° (c 1.09 MeOH). IR (KBr): 1785, 1778 (C=O), 1698 (C=N) cm^{-1} . ^1H NMR (C_6D_6): δ 7.31-6.82 (m, 5H, Ph), 6.23 (bs, 2H, H-6, NH), 4.50 (bt, 1H, H-3), 4.16 (dddd, 1H, H-4'), 3.55 (dd, 1H, $J_{5a',4'}=9.0$ Hz, H-5a'), 3.32 (dd, 1H, $J_{5b',4'}=9.0$ Hz, H-5b'), 2.77 (dd, 1H, PhCH_2), 2.45 (dd, 1H, PhCH_2), 2.28-1.69 (m, 4H, $-\text{CH}_2-$ x 2).
- 6) **12**; yellow syrup. $[\alpha]_D^{26}$ 139.04° (c 0.83 MeOH). IR (KBr): 3388 (NH), 1740 (C=O) cm^{-1} . ^1H NMR (CDCl_3): δ 6.73 (bs, 1H, H-6), 5.20 (bs, 1H, NH), 3.86-3.66 (m, 4H, H-3, OMe), 2.34-1.76 (m, 4H, $-\text{CH}_2-$ x 2).
- 7) K. Bevan, J. S. Davies, C. H. Hassall, R. B. Morton, and D. A. S. Phillips, *J. Chem. Soc., C*, **1971**, 514.
- 8) **14**; yellow needles from EtOAc-hexane, mp 95-96 °C. $[\alpha]_D^{23}$ -296.3° (c 0.3 CHCl_3). IR (KBr): 3250 (NH), 1750 (C=O), 1608 (NO_2) cm^{-1} . ^1H NMR (CDCl_3): δ 8.38 (d, 1H, $J=2.6$ Hz, Ph), 8.18 (dd, 1H, $J=2.6$ Hz, $J=9.2$ Hz, Ph), 7.00 (d, 1H, $J=9.2$ Hz, Ph), 3.89-3.55 (m, 6H, NH, OMe), H-3, H-6a), 3.17 (m, 1H, H-6b), 2.23-1.59 (m, $-\text{CH}_2-$ x 2).
- 9) In this paper, the symbol Δ^2 and Δ^3 indicate the position of double bond of ΔVal residue from the N-terminus in sequence.
- 10) Benzotriazol-1-yl-oxy-tris(dimethylamino)phosphonium hexafluorophosphate.
- 11) **15**; colorless amorphous solid. $[\alpha]_D^{26}$ -30.4° (c 0.62 MeOH). IR (KBr): 3406 (NH), 1713, 1671 (C=O) cm^{-1} . ^1H NMR (CDCl_3): δ 9.50 (bs, 1H, NH), 7.98 (bs, 1H, NH), 7.17 (bs, 2H, NH x 2), 4.63-3.96 (m, 7H, $(\text{MeO})_2\text{CH}-$, Leu- α -H, Ser- α -, Ser- CH_2- , OH, $-\text{N}-\text{CH}-$), 3.75 (s, 3H, OMe), 3.33, 3.32 (s x 2, 3H x 2, $(\text{MeO})_2\text{CH}$), 2.19 (s, 3H, $\Delta\text{Val-Me}$), 1.90-1.65 (m, 10H, Leu- β - CH_2- , Leu- γ - CH_3 , $-\text{CH}_2-$ x 2), 1.51 (s, 9H, Boc), 1.42 (s, 9H, Boc), 0.94 (m, 6H, Leu-Me x 2).
- 12) **16**; colorless amorphous solid. $[\alpha]_D^{26}$ -30.96° (c 0.68 MeOH). IR (KBr): 3364 (NH, OH), 1746 (C=O), 1659 (C=O) cm^{-1} . ^1H NMR (CDCl_3): δ 8.56 (bs, 1H, NH), 7.36 (bd, 1H, $J=5.5$ Hz, NH), 7.29 (bd, 1H, $J=7.0$ Hz, NH), 6.78 (bs, 1H, $-\text{N}=\text{CH}$), 6.35 (bs, 1H, NH), 4.62-3.76 (m, 9H, α -H x 3, Ser- CH_2 -OH, OMe), 2.11-1.26 (m, 13H, $\Delta\text{Val-Me}$ x 2, Leu- CH_2 -CH-, $-\text{CH}_2-$ x 2), 0.94 (m, 6H, Leu-Me x 2).

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