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

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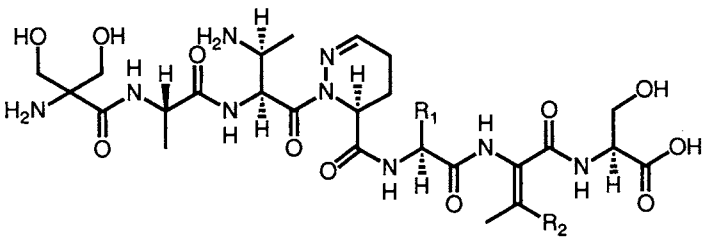
The stereoselective synthesis of (3S)-2,3,4,5-tetrahydropyridazine-3-carboxylic acid (Pya), which is a cyclic α-amino acid at center of antrimycins (**1**), was successful. Moreover, the synthesis of the C-terminal dehydrotetrapeptide of **1** containing Pya residue at N-terminus is described.

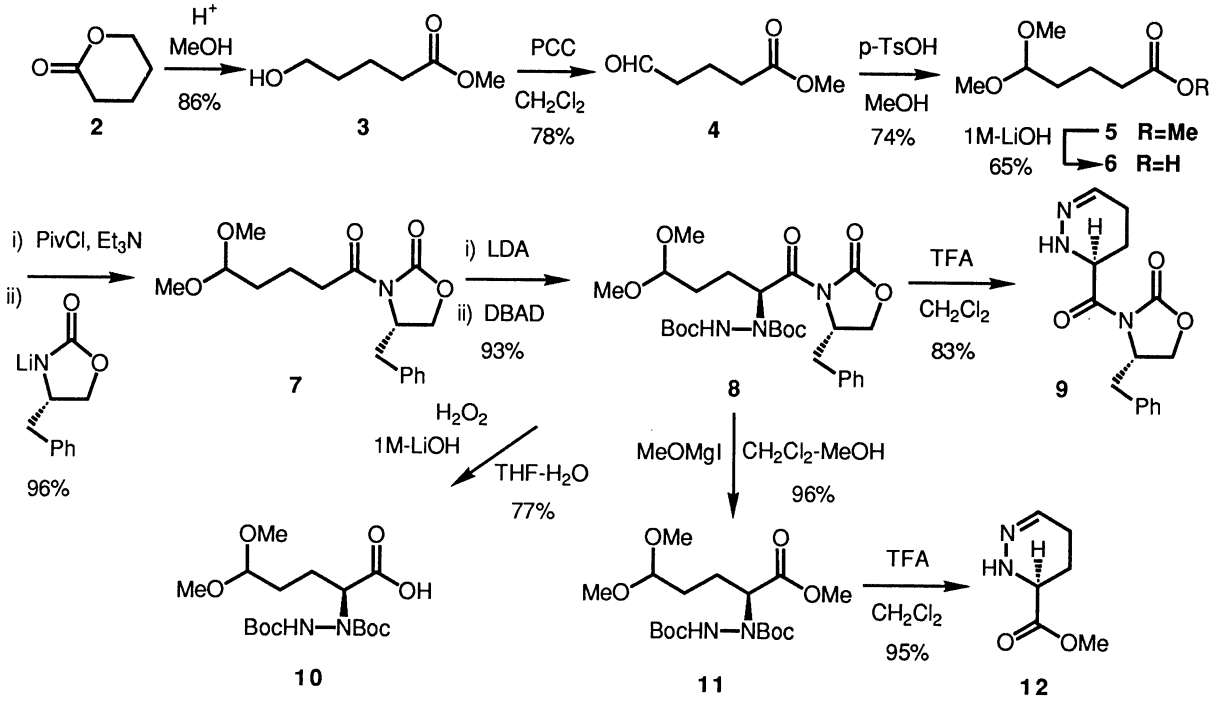
Antrimycins (**1**)[1] and cirratiomycins (**1**),[2] produced by Streptomyces (St.) xanthocidicus MG125-CF1 and St. cirratus 248-Sg2, respectively, are the same substances. These are the first linear dehydroheptapeptides containing both three kinds of α-amino acid residues and either an α-dehydrovaline (ΔVal) or (Z)-α-dehydroisoleucine (ΔIle) 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-ΔVal or -ΔIle anhydride (ΔNCA) 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.



1: Antrimycins R_1=Me, Et, n-Pr, i-Bu, R_2=Me, Et
Cirratiomycins R_1=Me, i-Bu, R_2=Et

Fig. 1.

As illustrated in Scheme 1, the starting methyl 4-formylbutanoate [**4**; ^{1}H NMR ($CDCl_3$): δ 9.78 (t, 1H, J=1.1 Hz, -CHO)] was derived from lactone (**2**) via 5-hydroxypentanoate (**3**) by the oxidation with $C_5H_5NH^+ \cdot ClCrO_3^-$ (PCC) in CH_2Cl_2. 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

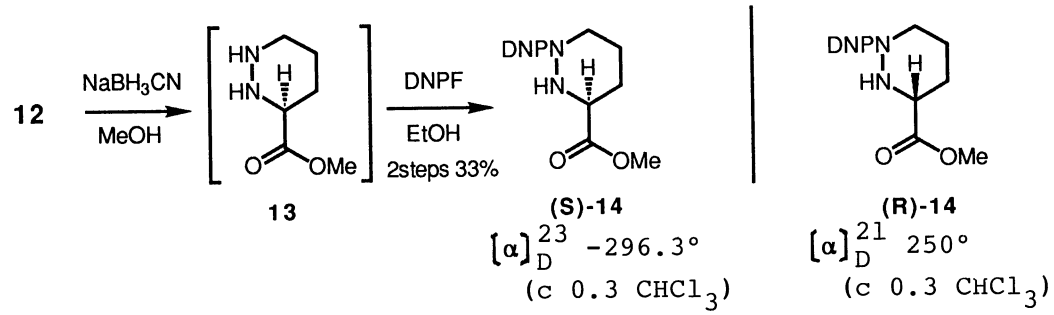


Scheme 1.

(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, $-\overset{|}{\underset{|}{N}}CH-$). $[\alpha]_D^{26}$ 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, -NH-) and 3.97 (m, 1H, H-2). $[\alpha]_D^{26}$ 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, -COOH) and 6.89 (bs, 1H, -NH-). $[\alpha]_D^{26}$ -18.04° (c 1.40 MeOH)]. On the other hand, methanolysis of **8** with MeOMgI in THF-MeOH at 0 °C gave the corresponding hydrazino methyl ester [**11**; δ 3.72 (s, 3H, -COOMe). $[\alpha]_D^{26}$ -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]

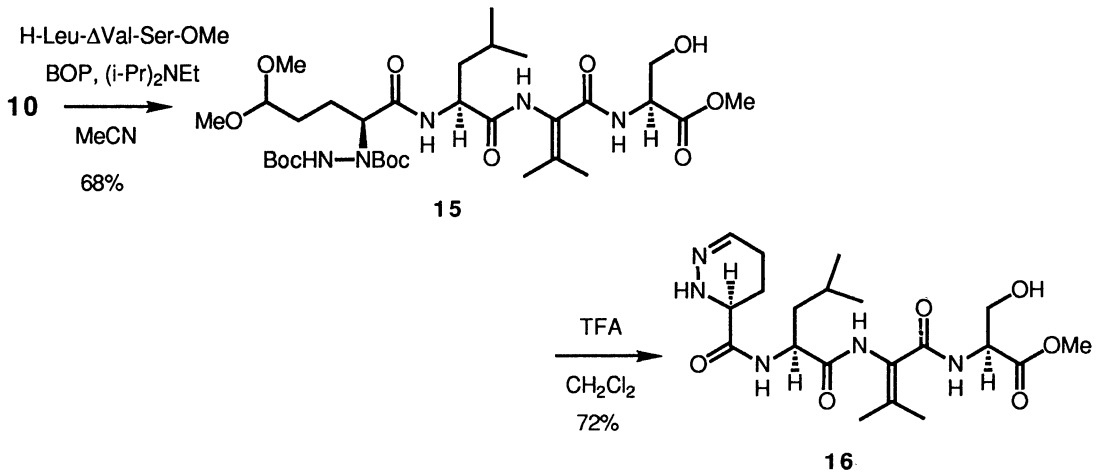
The configurational structure of **9** and **12** were readily determined by the comparison of the 2,4-dinitrophenyl derivative of the hydrogenated **12** (**13**) with the authentic methyl (3R)-1-(2,4-dinitrophenyl)pyridazate.[7] That is, as illustrated in Scheme 2, hydrogenation of **12** with $NaBH_3CN$ in



Scheme 2.

MeOH and immediate substitution of the crude product (**13**) intact with 2,4-dinitrophenyl fluoride (DNPF) 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-ΔVal-L-Ser-OMe, prepared by the one-pot synthesis of ΔVal·NCA successive with C-component Boc-Leu-OH and N-component H-Ser-OMe, was deprotected with CF_3COOH and then subjected to the coupling with **10** in the presence of BOP[10] and diisopropylethylamine [$(i\text{-}Pr)_2NEt$] 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 CF_3COOH gave the expected Δ^3-dehydrotetrapeptide, H-Pya-Leu-ΔVal-Ser-OMe (**16**)[12] as an important segment of eight kinds of antrimycins.



Scheme 3.

References

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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, $PhC\underline{H}_2$), 2.45 (dd, 1H, $PhC\underline{H}_2$), 2.28-1.69 (m, 4H, $-CH_2-$ 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, $-CH_2-$ 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, $-CH_2-$ 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, $(MeO)_2C\underline{H}-$, Leu-α-H, Ser-α-, Ser-CH_2-, OH, $-N-C\underline{H}-$), 3.75 (s, 3H, OMe), 3.33, 3.32 (s x 2, 3H x 2, $(\underline{Me}O)_2CH$), 2.19 (s, 3H, ΔVal-Me), 1.90-1.65 (m, 10H, Leu-β-$C\underline{H}_2-$, Leu-γ-$C\underline{H}_3$, $-CH_2-$ 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, -N=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, ΔVal-Me x 2, Leu-CH_2-CH-, $-CH_2-$ x 2), 0.94 (m, 6H, Leu-Me x 2).

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