Tetrahedron Letters,Vol.23,No.11,pp 1193-1196,1982 0040-4039/82/111193-04$03.00/0
Printed in Great Britain

NEW METHODS AND REAGENTS IN ORGANIC SYNTHESIS. 24.[1] A NEW SYNTHESIS OF PRUMYCIN AS AN APPLICATION OF THE DIRECT C-ACYLATION USING DIPHENYL PHOSPHORAZIDATE (DPPA)

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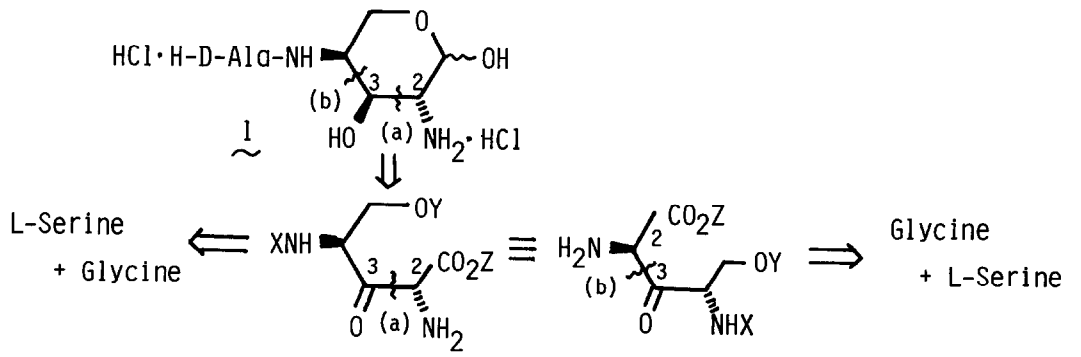
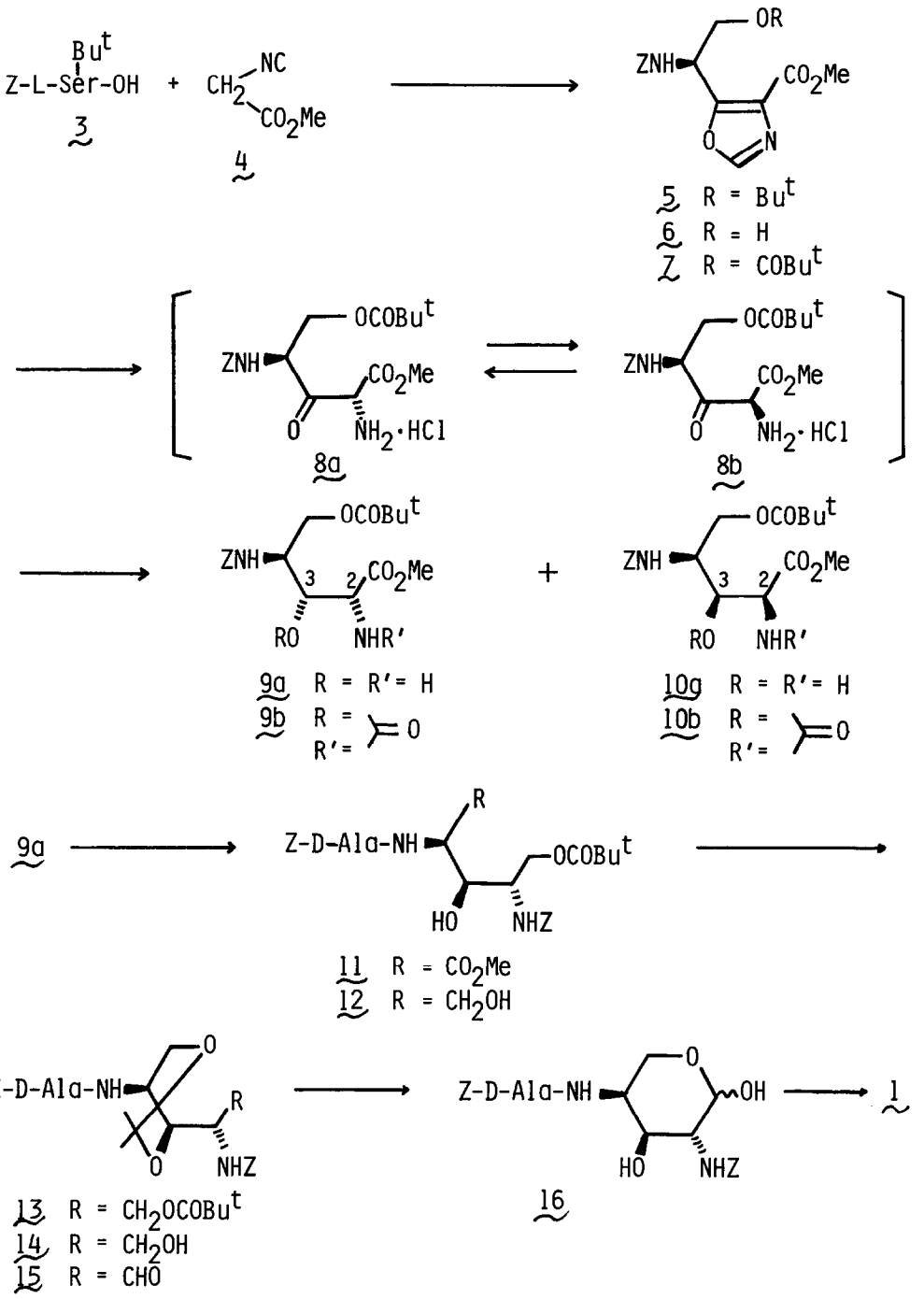
The 5-substituted 4-methoxycarbonyloxazole 5 derived from L-serine derivative 3 using diphenyl phosphorazidate (DPPA) has been converted to a 2,4-diaminosugar antibiotic, prumycin.

Recent publication[2] from our laboratories has disclosed that optically active 5-substituted 4-methoxycarbonyloxazoles can be efficiently prepared from optically active carboxylic acids and methyl isocyanoacetate by the direct C-acylation using diphenyl phosphorazidate (DPPA, $(C_6H_5O)_2P(O)N_3$)[3] in combination with potassium carbonate. These oxazoles can be considered as protected derivatives of sensitive C-acylamino acid esters and synthetic equivalents of β-hydroxyamino acids as well as 2-amino-1,3-diols. As an application of the oxazole synthesis using DPPA, we wish to describe a new facile synthesis of prumycin dihydrochloride 1.

Prumycin, 4-(D-alanylamino)-2-amino-2,4-dideoxy-L-arabinose,[4] is an antifungal antibiotic and has been recently[5] revealed to have an interesting antitumor activity. The synthesis of prumycin has been reported by three laboratories[6] using conventional procedures: conversion of sugars to sugars. Our synthesis has been initiated from α-amino acids since the 2,4-diaminosugar moiety of prumycin may be retrosynthesized into two α-amino acids, L-serine and glycine, via the C-acylamino acid 2 by either threo((a) route)- or erythro((b) route)-selective reduction (2a or 2b) at C-2 and C-3. We chose Z-L-Ser(Bu^t)-OH[7] 3 and methyl isocyanoacetate 4 as L-serine and glycine equivalents, respectively.



Direct C-acylation of methyl isocyanoacetate (4, 5 eq) with Z-L-Ser(Bu^t)-OH 3 using DPPA (1.1 eq) and potassium carbonate sesquihydrate (2 Mol.eq) in dimethylformamide (0°C, 2 hr; room



temp., 14 hr) afforded the key intermediate oxazole 5 in 62 % yield as a colorless oil ($[\alpha]_D^{23}$ +6.78° (c=1, MeOH)), containing the requisite function of the 2,4-diaminosugar. Treatment of 5 with trifluoroacetic acid (CH_2Cl_2, room temp., 2 hr) followed by acylation of the resulting alcohol 6 with pivaloyl chloride (4-N,N-dimethylaminopyridine, Et_3N, CH_2Cl_2, 0°C, 30 min) gave

the nicely crystalline oxazole 7 in 85 % yield. After one recrystallization from ethyl acetate -hexane (1:4), the optically pure oxazole 7 was obtained in 67 % yield from 5 as colorless needles (mp 105-107°, $[\alpha]_D^{23}$+9.87° (c=1, MeOH)). Ring cleavage of 7 with 7 % methanolic hydrogen chloride (40°, 2.5 hr) resulted in an equilibrium mixture of C-acylamino acid esters 8a and 8b, which were neutralized in ethanol with saturated aqueous sodium bicarbonate and reduced with sodium borohydride (1 Mol.eq) in ethanol at -10° for 1 hr to give a mixture of two erythro aminoalcohols 9a and 10a in a 3:2 ratio[8] in 62 % yield. Erythro configurations at C-2 and C-3 of 9a and 10a were proved by $J_{2,3}$-values of NMR spectra[9] of the oxazolidone derivatives 9b ($J_{2,3}$= 9.6 Hz, mp 115-117°, $[\alpha]_D^{23}$-1.78° (c=0.5, MeOH)) and 10b ($J_{2,3}$= 8 Hz, mp 160-162°, $[\alpha]_D^{23}$+6.15° (c=0.5, MeOH)), which were prepared from 9a and 10a ($ClCO_2CCl_3$, sat.aq.K_2CO_3, CH_2Cl_2, room temp., 2 hr), respectively.

The major isomer 9a with the lyxo configuration was coupled with Z-D-Ala-OH using diethyl phosphorocyanidate (DEPC, $(C_2H_5O)_2P(O)CN$)[10] and triethylamine to give the amidoalcohol 11 in 76.5 % yield as a colorless oil ($[\alpha]_D^{23}$+8.8° (c=0.5, MeOH)). Of two ester functions of 11, the methyl ester function was selectively reduced with lithium chloride-sodium borohydride (1:1, 1 Mol.eq) in ethanol-tetrahydrofuran (4:3)(room temp., 2.4 hr) to give the 1,3-diol 12 in 90.4 % yield as a colorless oil. Protection of the diol function of 12 was achieved with 2,2-dimethoxypropane and a catalytic amount of pyridinium p-toluenesulfonate in methylene chloride (reflux, 14 hr), giving the isopropylidene derivative 13 in 81.5 % yield as colorless needles (mp 150-152°, $[\alpha]_D^{23}$+20.5° (c=1, MeOH)). For the removal of the pivaloyl group, usual procedures (NaOH, NaOMe, $MeNH_2$ in MeOH) resulted in a complex mixture. However, treatment of 13 with lithium chloride-sodium borohydride (1:1, 10 Mol.eq) in ethanol-tetrahydrofuran (5:3) under argon (room temp., 14 hr) cleanly yielded the β-aminoalcohol 14 in virtually quantitative yield as a colorless oil ($[\alpha]_D^{23}$+26.5° (c=1, MeOH)). Parikh-Doering oxidation[11] of 14 with sulfur trioxide pyridine complex (3 eq)-triethylamine (3 eq)-dimethylsulfoxide (20°, 10 min) rapidly proceeded to give the α-amino aldehyde 15 with the arabino configuration in quantitative yield as a colorless oil(IR $\nu_{max}^{CHCl_3}$ 3 cm^{-1}: 1710 cm^{-1}, NMR ($CDCl_3$) δ 9.48 ppm, s). Acid hydrolysis of 15 with 46 % aqueous hydrogen fluoride-acetonitrile[12](1:6)(room temp., 10 min) afforded N,N'-dibenzyloxycarbonyl-L-prumycin 16 in 90.4 % yield as colorless needles. The structure of 16 (mp 186-188°, $[\alpha]_D^{21}$+52.6° (c=0.25, MeOH)) was identified by comparison (TLC, mp, IR and NMR spectra, elemental analysis, $[\alpha]_D^{21}$) with an authentic sample[4b](mp 184-185°, $[\alpha]_D^{21}$+53.3° (c=0.25, MeOH)) prepared from natural prumycin. The synthetic material 16 was catalytically reduced over 5 % palladium-carbon in 50 % aqueous tetrahydrofuran containing a small amount of acetic acid (room temp., 5 hr, H_2 bubbled). The reaction mixture was filtered, and a stoichiometric amount of hydrochloric acid was added to the filtrate. Evaporation at low temperature afforded prumycin dihydrochloride 1 in 95.6 % yield as a glassy solid ($[\alpha]_D^{23}$ +91.6° (c=0.55, MeOH)). Recrystallization of the amorphous solid 1 from methanol yielded the crystalline β-anomer of 1 as colorless needles of the dihydrochloride monohydrate (mp 195-199° (dec.), $[\alpha]_D^{23}$+119° (c=0.5, MeOH)). The IR and NMR spectra, TLC behavior, specific rotation and elemental analysis of the synthetic crystalline prumycin were identical with those of natural one.[4b]

The above reaction sequence comprises a facile synthsis of prumycin in 12 steps from Z-L-Ser(Bu^t)-OH with an overall yield of 7.5 % which is not inferior to those from sugar derivatives.[6]

Acknowledgement We are grateful to Prof. S. Ōmura of Kitasato University for the gift of natural prumycin. Partial support of this research by Grants awarded by the Foundation for the Promotion of Research on Medicinal Resources, the Naito Foundation, and the Ministry of Education, Science and Culture, Japan (No. 567366) is gratefully acknowledged.

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(Received in Japan 8 December 1981)