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CHIROSPECIFIC SYNTHESIS OF (+)-PS-5 FROM L-GLUTAMIC ACID

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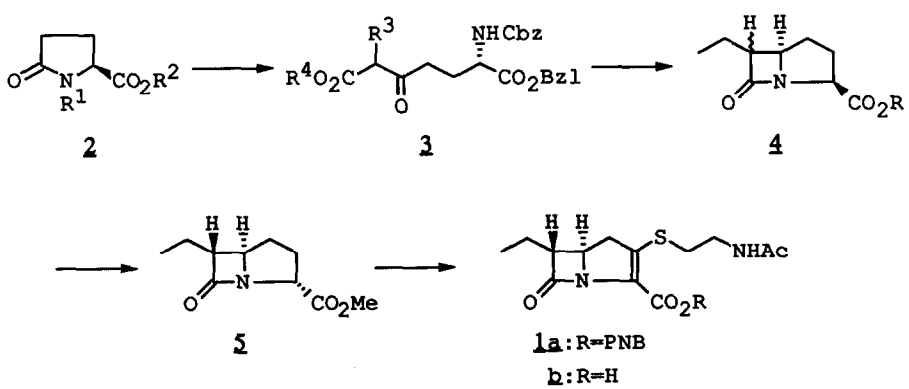
Abstract: (+)-PS-5 p-nitrobenzyl (PNB) ester (1a) has been synthesized from N-Cbz-L-pyroglutamate (2a). The key reactions were the reductive pyrrolidine ring formation from the 5-oxoamino acid derivative (3) and stereo-differential protonation at C-6 of the dienolate derived from the carbapenam (4).

In connection with our recent study on nitrogen-containing natural products,[1] we planned the synthesis of carbapenem antibiotics from L-glutamic acid which is one of the most abundant chiral resources. The key reactions we adopted were a direct chain elongation of N-Cbz-L-pyroglutamates (2a),[2] the reductive pyrrolidine ring formation from 5-oxoamino acid derivatives (3) and the diastereophase differential protonation at C-6 of the dienolate derived from the carbapenam (4). Here we wish to report an efficient synthesis of (5R, 6R)-carbapenam (5) from which (+)-PS-5[3,4] PNB ester (1a) has been synthesized.

As shown in the preceding paper[2], the lithium enolate of esters can be efficiently added to the N-carbamoylpyroglutamates (2) giving 5-oxoamino acid derivatives (3). Preservation of the S-configuration at C-2 was proven by the reaction with L-menthyl pyroglutamate (2b). Following the above addition reaction, the 5-oxoamino acid derivative (3) was treated with hydrogen catalyzed with 5% or 10% Pd-C at medium pressure, 4.5 kg/cm^2.

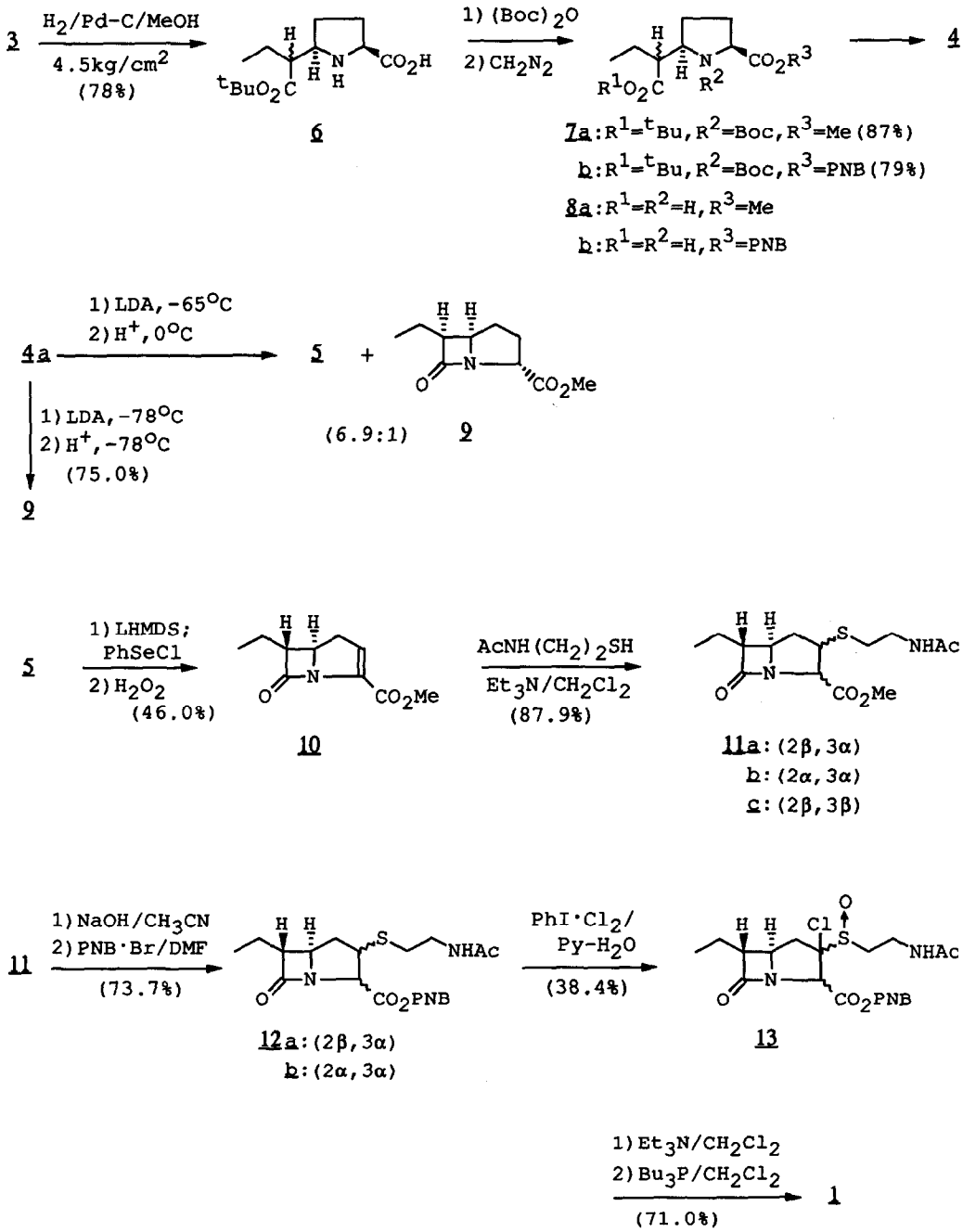
Scheme 1.



2 3 4 5

1a: R=PNB
b: R=H

Scheme 2.


3
H2/Pd-C/MeOH
4.5kg/cm2
(78%)
6
1) (Boc)2O
2) CH2N2
7a: R1=tBu, R2=Boc, R3=Me (87%)
b: R1=tBu, R2=Boc, R3=PNB (79%)
8a: R1=R2=H, R3=Me
b: R1=R2=H, R3=PNB
4
4a
1) LDA, -65°C
2) H+, 0°C
5
(6.9:1)
9
1) LDA, -78°C
2) H+, -78°C
(75.0%)
9
5
1) LHMDS; PhSeCl
2) H2O2
(46.0%)
10
AcNH(CH2)2SH
Et3N/CH2Cl2
(87.9%)
11a: (2β, 3α)
b: (2α, 3α)
c: (2β, 3β)
11
1) NaOH/CH3CN
2) PNB·Br/DMF
(73.7%)
12a: (2β, 3α)
b: (2α, 3α)
PhI·Cl2/
Py-H2O
(38.4%)
13
1) Et3N/CH2Cl2
2) Bu3P/CH2Cl2
(71.0%)
1

Hydrogenolysis followed by hydrogenation of the intermediate pyrroline[5] afforded 2,5-cis 5-substituted proline (6), mp 156-158 °C, in 78% yield after silica gel chromatography (CH_3CN-MeOH, 7:3). The pyrrolidine (6) thus obtained was transformed to β-amino acid (8) as illustrated in scheme 2.

Table 1. Synthesis of Carbapenams 4 from Pyrrolidines 7.

7	Deprotection methods	Time(h)	Yield(%)[c] of 4 from 7
a	HCl[a]	44	59.9
a	TMSOTf[b]	2	69.8
b	TMSOTf[b]	2	75.6

a. 4N HCl/DOX., 0 °C - room temp.
b. Procedure is described in the text.
c. Lactamization of 8: DCC (1.3 eq.), Et_3N (4.5 eq.), CH_2Cl_2, 0 °C - room temp., 17-20h.

The deprotection of t-butyl substituent of the ester (7) with hydrogen chloride[6] took much longer than that with trimethylsilyl triflate (TMSOTf)[7] as shown in Table 1. In the latter process, the pyrrolidine (7b, 1.12 g, 3.02 mmol) in CH_2Cl_2 (30 ml) was treated with TMSOTf (1.75 ml, 9.05 mmol) and 2,6-lutidine (1.23 ml, 11.2 mmol) for 2 h at room temperature. Successive addition of 4N HCl in dioxane (7 ml) at 0 °C and evaporation gave HCl salt of β-amino acid (8) which was converted to the carbapenam (4a, 415 mg).[6] No signal due to (3S,5S)-isomer, the diastereomer of carbapenam 5 or 9, could be detected in ^1H NMR (500 MHz) spectrum of 4a.[8] The ratio of 5,6-cis and 5,6-trans diastereomers was ca 2:1 which was determined by ^1H NMR.

Stereocontrol at C-6 of the carbapenam (4) was possible when the lithium dienolate of the carbapenam (4a) was protonated either at 0 °C or at -78 °C. This process was not applicable to the PNB ester (4b[9]). (3R,5R,6R)-Carbapenam (5) or (3R,5R,6S)-derivative (9) was obtained with the above protonation, respectively. For the thermodynamic protonation, the carbapenam (4a, 4.17 g, 21.2 mmol) in THF (50 ml) was treated with LDA in THF (150 ml) prepared from diisopropyl amine (6.8 ml, 48.5 mmol) and 15% n-butyllithium in n-hexane (30 ml, 46.7 mmol) at -65 °C. The reaction mixture was stirred at -65 °C for 1 h, quenched with AcOH-MeOH (1:1, 15 ml) at 0 °C. Carbapenams 5 and 9 were separated on silica gel (n-hexane-EtOAc, 9:1 elution) to give methyl (3R,5R, 6R)-carbapenam (5[10], 2.76 g, 66.2%), $[\alpha]_D^{27}$ +188.82° (c 0.68, $CHCl_3$). 5,6-Cis carbapenam (9[11], 399 mg, 9.6%) was eluted prior to the 5,6-trans derivative (5). The stereochemistry of those carbapenams (5 and 9) were detemined with J values between H-5 and H-6, J=2.1 Hz for 5 and J=5.6 Hz for 9, and with relatively lower H-3 chemical shifts, δ 4.41 for 5 and 4.35 for 9, compared to that of the 3,5-cis carbapenam (4a), δ 3.88 (dd, J=1.5, 8 Hz).

Phenylselenylation[6] at C-3 of the carbapenam (5) following by deseleninylation gave the carbapenem (10), $[\alpha]_D^{32}$ +159.48° (c 1.644, $CHCl_3$). Michael addition of 2-acetamidoethanethiol to the carbapenem (10) afforded the sulfide (11, a:b:c=5:2:1) as a diastereoisomeric mixture.[6,12] The sulfide (11) was hydrolyzed and the resulting sodium salt was treated with p-nitrobenzyl

bromide in DMF to give the PNB ester (12).[6] ^{1}H NMR (500 MHz) of the ester showed signals due to H-3 at δ 4.79 (d, J=6.9 Hz, 12a) and 4.33 (d, J=5.0 Hz, 12b) in the ratio 9:1.

The PNB ester (12) was oxidized to the α-chlorosulfoxide (13) according to the reported procedures.[6,12] Dehydrochlorination of the sulfoxide (13) and successive reduction[6] with tributylphosphine afforded (+)-PS-5 PNB ester (1a), mp 170-172 °C, lit.[4a] mp 172-174 °C, $[\alpha]_D^{25}$ +67.6° (c 1.03, $CHCl_3$), lit.[3] $[\alpha]_D^{22}$ +70.7° (c 1.0, $CHCl_3$), whose spectroscopic data were identical with others reported.[3] The PNB ester (1a) has previously been converted to (+)-PS-5 (1b).[4a]

References and Notes

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8. Carbapenam 4b derived from unpurified pyrrolidine 6 was found to be a mixture of (3S,5R)- and (3S,5S)-isomers in a ratio of 49:1 on the basis of ^{1}H NMR.
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10. ν ($CHCl_3$) 1760, 1745 cm^{-1}; δ_H ($CDCl_3$, 500 MHz) 1.04 (3H, t, J=7.5 Hz), 2.79 (1H, ddd, J=2.1, 6.4, 8.1 Hz), 3.62 (1H, ddd, J=2.1, 5.6, 7.3 Hz), 3.73 (3H, s), 4.41 (1H, dd, J=5.6, 6.8 Hz); m/z 197.1057 (M^+).
11. ν ($CHCl_3$) 1760, 1740 cm^{-1}; δ_H ($CDCl_3$, 500 MHz) 0.99 (3H, t, J=7.3 Hz), 3.34 (1H, ddd, J=5.6, 7.3, 9.8 Hz), 3.74 (3H, s), 3.95 (1H, ddd, J=5.6, 6.4, 7.9 Hz), 4.35 (1H, dd, J=7.3, 7.3 Hz); m/z 197.1070 (M^+).
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