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The Synthesis of The 1-Carbapenem Antibiotic (±)-PS-5 and Its 6-Epi Analogue

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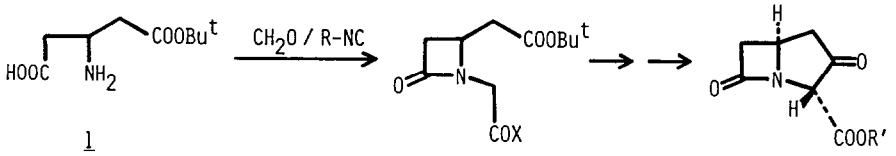
Summary: Total synthesis of the title compounds is described which includes, as the key step, regioselective Dieckmann reaction for constructing the 2-oxocarbapenam ring system.

PS-5 (18) is a highly potent, broad-spectrum β-lactam antibiotic having a 1-carbapenem ring system and a 6α ethyl side chain[1]. The unique structural features of this antibiotic have recieved considerable attention[2]. We now report a simple synthesis of PS-5 and its 6-epi analogue 19 using our previously developed method which includes, as outlined below, four component condensation followed by regioselective Dieckmann reaction as the key steps[3].

In the previous synthesis, conversion of the exocyclic carboxamide group



1

2, X = NH-R

3, X = OR'

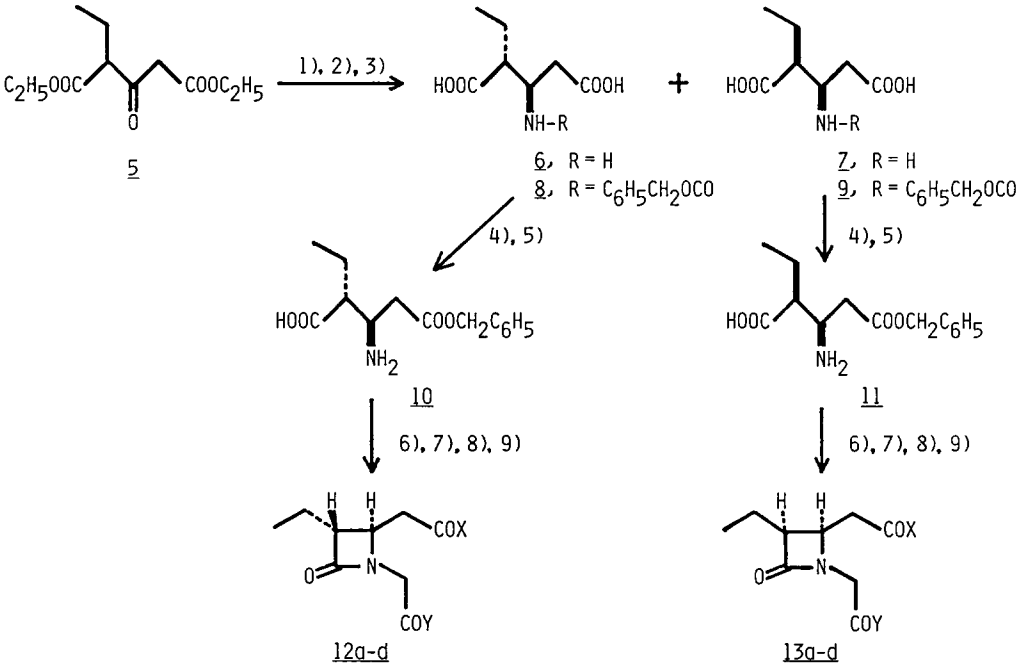
4

generated through the four component condensation[4] into the methyl ester was accomplished via the imino chloride. However, an attempt to prepare the other ester (e.g., benzyl ester) in this way was unsuccessful. We have therefore explored alternate method which involved use of p-nitrobenzylisocyanide as an isonitrile and transformation via N-nitrosation of the resulting four component condensation products to the p-nitrobenzyl ester[5]. Similar approach has been also reported which used diphenylmethylisocyanide as an isonitrile[6]. Here, successful application of p-nitrobenzylisocyanide to the carbapenem synthesis is demonstrated as follows.

When an equimolar mixture of 3-aminoglutaric acid mono-t-butyl ester (1), formaldehyde and p-nitrobenzylisocyanide in methanol was stirred at room temperature for 10 hours under high dilution (0.025 M), the azetidinone 2 (R=p-nitrobenzyl (PNB))[7] was obtained in 88% yield. The compound 2 (R=PNB) was then converted with nitrogen peroxide to the N-nitroso derivative, which, on heating in refluxing carbon tetrachloride, provided cleanly the p-nitrobenzyl ester 3 (R'=PNB) in 85% yield. Subsequent transformation to the 2-oxocarbapenam 4

(R'=PNB) could be achieved via modified Dieckmann reaction by the procedure reported previously. Thus, the simplified method was applied to the synthesis of PS-5 and 6-epi PS-5.

Reductive amination[8] of diethyl 2-ethyl-3-oxoglutarate (5)[9] and successive hydrolysis gave an inseparable mixture of the diastereomeric amino acids, 6 and 7[10], in a ratio of ca. 1:1. Fortunately, their N-benzyloxycarbonyl derivatives, 8 and 9, could be separated simply by crystallization; 9 was obtained as fine crystals while 8 as oil. The stereochemistry of these isomers was best determined by convertion into the azetidinones. The oily isomer 8 was converted

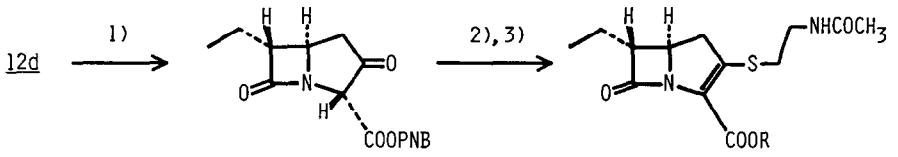


PNB = p-nitrobenzyl

a: X = $OCH_2C_6H_5$, Y = NH-PNB; b: X = OH, Y = NH-PNB; c: X = SC_6H_5, Y = NH-PNB; d: X = SC_6H_5, Y = OPNB.

1) $NaBH_3CN/AcONH_4/EtOH$; 2) 6N HCl/∇; 3) $C_6H_5CH_2OCOCl/MgO/H_2O$; 4) H_2/Pd-C; 5) $C_6H_5CH_2OH/TsOH$; 6) PNB-NC/CH_2O/MeOH/r.t./10 hrs; 7) $AlCl_3$/anisole/r.t./3 hrs; 8) 1. $N_2O_4/AcONa/CHCl_3/0°C/1$ hr, 2. reflux in CCl_4; 9) C_6H_5SH/DCC.

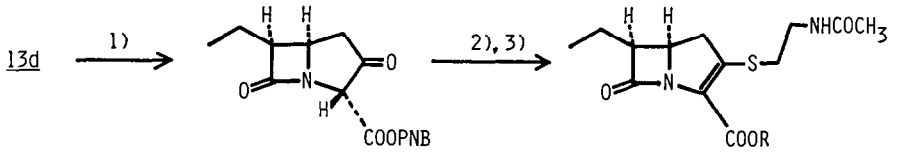
into crystalline mono-benzyl ester 10, in a free form from the isomer 11, by hydrogenolysis of the N-benzyloxycarbonyl group followed by selective esterification of the less hindered carboxyl group. Four component condensation of 10, formaldehyde and p-nitrobenzylisocyanide gave the trans-azetidinone 12a in 73% yield. Similarly, the crystalline isomer 9 was transformed to the cis-azetidinone 13a in 60% overall yield. In this case, four component condensation proceeded in 66% yield, indicating that this condensation was also useful to construct sterically crowded azetidinone. The stereochemistry of 12a and 13a was confirmed by the coupling constants (12a: $J_{3,4}$=2.2 Hz; 13a: $J_{3,4}$=5.6 Hz) observed in their 100 MHz ^{1}H-NMR spectra. The azetidinones 12a and 13a were



14

16, R = PNB

18, R = H: PS-5



15

17, R = PNB

19, R = H: 6-epi PS-5

1) 1. $(TMS)_2NLi$/THF/-78°C/3 min, 2. AcOH; 2) $(PhO)_2P(O)Cl$/i-Pr_2NEt/CH_3CN/ 0°C, 2. $HSCH_2CH_2NHCOCH_3$/i-Pr_2NEt/CH_3CN; 3) H_2/Pd-C

then converted into 12d and 13d in 53 and 58% overall yields, respectively, by a three step sequence consisting of: (i) cleavage of the benzyl ester; (ii) condensation with thiophenol; (iii) transformation of the p-nitrobenzylamide to the p-nitrobenzyl ester.

Modified Dieckmann reaction of the compounds 12d and 13d proceeded smoothly and regioselectively to give the 2-oxocarbapenams 14 and 15 in 83 and 80% yields, respectively. The physical data of the 2-oxocarbapenam 14 corresponded well with those reported by Kametani et.al.[2b], while the cis-orientation of the ethyl substituent in 15 was confirmed by means of the ^{1}H-NMR spectra ($J_{5,6}$=5.7 Hz). Further transformation of the 2-oxocarbapenams 14 and 15 to PS-5 (18) and 6-epi PS-5 (19) was accomplished by the well-established procedure involving conversion into the 2-(2-acetaminoethylthio)-carbapenems 16 and 17 with the Merk's method[11] followed by reductive removal of the p-nitrobenzyl groups.

References and Notes

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6. H.P. Isenring and W. Hofheinz, Synthesis, 385 (1981).
7. Selected data. 2 (R=PNB): ν (CH_2Cl_2) 1758, 1730 and 1685 cm^{-1}; δ ($CDCl_3$) 1.43 (9H, s, ^tBu), 2.61 (3H, midpoint of 3 dd, H_3 and $H_{4'}$), 3.17 (1H, dd, J=5.4, 15 Hz, H_3), 3.97 (2H, s, $H_{1'}$), 4.10 (1H, m, H_4), 4.51 (2H, d, J=6 Hz, NCH_2Ar), 7.44 (2H, d, J=8.4 Hz, Ar) and 8.13 (2H, d, J=8.4 Hz, Ar). 3 (R'=PNB): ν (liq. film) 1760 and 1740 cm^{-1}; δ ($CDCl_3$) 5.26 (2H, s, OCH_2Ar). 9: mp 160°C (decomp.). 10: mp 147-148°C. 11: mp 160-162°C. 12a: ν (CH_2Cl_2) 1755, 1730 and 1690 cm^{-1}; δ ($CDCl_3$) 0.97 (3H, t, J=7.3 Hz, CH_3), 1.69 (2H, m, CH_2CH_3), 2.67 (1H, dd, J=5.8, 16 Hz, $H_{4'}$), 2.84 (1H, dd, J=6.6, 16 Hz, $H_{4'}$), 2.80 (1H, ddd partially buried, $J_{3,4}$=2.2 Hz, H_3), 3.77 (1H, ddd, J=2.2, 5.8, 6.6 Hz, H_4), 3.90 (2H, s, $H_{1'}$), 4.47 (2H, d, J=6.1 Hz, NCH_2Ar), 5.09 (2H, s, OCH_2Ar), 6.82 (1H, m, NH), 7.35 (5H, s, Ar), 7.41 (2H, d, J=9 Hz, Ar) and 8.15 (2H, d, J=9 Hz). 13a: ν (CH_2Cl_2) 1755 1738 and 1690 cm^{-1}; δ ($CDCl_3$) 1.02 (3H, t, J=7.3 Hz), 1.60 (2H, m), 2.64 (1H, dd, J=5.8, 19 Hz, $H_{4'}$), 2.77 (1H, dd, J=7.5, 19 Hz, $H_{4'}$), 3.22 (1H, ddd, J=5.6, 7.3, 8.5 Hz, H_3), 3.92 (2H, broad s), 4.20 (1H, ddd, J=5.6, 5.8, 7.5 Hz, H_4), 4.48 (2H, d, J=6.1 Hz), 5.11 (2H, s), 6.46 (1H, m), 7.35 (5H, s), 7.40 (2H, d, J=8.8 Hz) and 8.13 (2H, d, J=8.8 Hz). 12d: ν (CH_2Cl_2) 1750 and 1700 cm^{-1}. 13d: ν (CH_2Cl_2) 1750 and 1700 cm^{-1}. 14: ν (CH_2Cl_2) 1770 and 1750 cm^{-1}; δ ($CDCl_3$) 1.10 (3H, t, 7.4 Hz, CH_3), 1.95 (2H, m, CH_2CH_3), 2.44 (1H, dd, J=7.7, 18.8 Hz, H_1), 2.92 (1H, dd, J=6.8, 18.8 Hz, H_1), 3.13 (1H, ddd, J=2.0, 6.8, 8.2 Hz, H_6), 3.89 (1H, ddd, J=2.0, 6.8, 7.7 Hz, H_5), 4.75 (1H, s, H_3), 5.25 (1H, d, J=13.3 Hz, OCH_2Ar), 5.34 (1H, d, J=13.3 Hz, OCH_2Ar), 7.53 (2H, d, J=8.8 Hz, Ar) and 8.24 (2H, d, J=8.8 Hz, Ar). 15: ν (CH_2Cl_2) 1770 and 1750 cm^{-1}; δ ($CDCl_3$) 1.03 (3H, t, J=7.3 Hz, CH_3), 1.70 (2H, m, CH_2CH_3), 2.44 (1H, dd, J=8.4, 18.8 Hz, H_1), 2.76 (1H, dd, J=7.1, 18.8 Hz, H_1), 3.72 (1H, ddd, J=5.7, 7.9, 9.1 Hz, H_6), 4.27 (1H, ddd, J=5.7, 7.1, 8.4 Hz, H_5), 4.69 (1H, s, H_3), 5.30 (2H, broad s, OCH_2Ar), 7.54 (2H, d, J=9.0 Hz, Ar) and 8.24 (2H, d, J=9.0 Hz, Ar). 16: ν (CH_2Cl_2) 1775, 1700 and 1675 cm^{-1}. 17: mp 148-151°C (lit[2a]., mp 143-144°C); λ_{max}(EtOH) 317 and 270 nm; ν (CH_2Cl_2) 1775, 1705 and 1675 cm^{-1}.
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