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A CHIRAL SYNTHESIS OF D-HOMOSERINE AND ITS APPLICATION TO THE SYNTHESIS OF NOCARDICIN A

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Recently the chemistry of the β-lactam antibiotics has received considerable impetus by the isolation[1,2,3] of several new β-lactam structural types, each possessing interesting but different microbiological properties.

In this and a concurrent communication,[4] we report the total synthesis of one of these, nocardicin A (1), an antibiotic isolated from a species of Nocardia.[3,5]

Our synthetic goal was to develop a synthesis in which we could utilize readily available, optically active starting materials and which would proceed in good yield and avoid tedious and wasteful chromatographic separations.[6]

Our synthetic objectives were concentrated initially on the glyoxylic acid 2 and the nucleus 3 (3-ANA). The side chain 2 is an O-phenyl substituted D-homoserine. Considering the availability of the D-amino acids from which the D-homoserine derivative could be obtained, we concluded that the most obvious choice was D-methionine (4), especially in light of the previous work of other investigators[8] who had obtained homoserine lactone from degradation of methionine containing peptides, albeit in low yields. We now wish to report a high yield synthesis of D-homoserine lactone (7) and its conversion into the side chain of nocardicin A.

^{t}Boc methionine (5) was treated with trimethylsilyl chloride (1 eq in acetonitrile at 25°C for 1/2 h) followed by methyl iodide (excess, 25°C, 14 h) to give the quarternary salt 6. Treatment of 6 with KOBu^{t} (THF, reflux 12 h) afforded a 70% yield of D-homoserine lactone derivative 7 (mp 125-7°C). $[\alpha]_{methanol}$ = +29°; NMR (T60) ($CDCl_3$) δ 1.5 (9H, singlet t-BOC CH_3), 2.2-3.0

(2H, multiplet, C_3-H), 4.0-4.6 (3H, multiplet), and 5.3 (1H, doublet, J=4, N-H).

Hydrolysis of the lactone 7 (1 eq KOH, aqueous dioxane 1:1, 25°C, 8 h) gave, after lyophilization, the potassium salt 8 as a white foam which was directly treated with benzhydryl bromide in the presence of 18-crown 6 (DMAC, 25°C, 48 h) to afford the ester 9 in 65-70% yield, mp 102-3°C; $[\alpha]_D$ (MeOH) +44°; ν max ($CHCl_3$) 1735, 1690 cm^{-1}; NMR ($CDCl_3$) δ 1.47 (9H, s), 3.67 (2H, m), 4.67 (1H, m), 5.43 (1H, d, J=8 Hz, collapses to singlet with $D_2O/NaHCO_3$), 6.95 (1H, s), and 7.20 (10H, s).

The glyoxylic ester was synthesized from p-hydroxymandelic acid (10). p-Hydroxymandelic acid (10) was esterified (1 eq $KOBu^t$, p-nitrobenzylbromide, DMF, 25°C, 6 h) and the resultant α-hydroxy ester 11 was oxidized to the glyoxylic ester 12 (Jones reagent) in 84% yield, mp 135-8°C.

Coupling of the glyoxylic ester 12 to the homoserine derivative 9 was achieved using $Ø_3P$/dimethylazodicarboxylate[9,10] to give the ether 13 in 68% yield, mp 92-4°C; $[\alpha]_D$ (EtOAc) +8.9°; ν max ($CHCl_3$) 1740, 1710, 1600 cm^{-1}; NMR ($CDCl_3$) δ 1.40 (9H, s), 2.35 (2H, m), 4.05 (2H, m), 4.63 (1H, m), 5.30 (1H, d, J=8 Hz), 5.47 (2H, s).

Finally, hydrolysis of the p-nitrobenzyl ester 13 using sodium hydroxide in aqueous dioxane (1 eq NaOH, 25°C, 1/2 h) gave the suitably protected side chain 2b in 90% yield, mp 65°C; $[\alpha]_D$ (MeOH) +10.9°; ν max ($CHCl_3$) 1740, 1710, 1600 cm^{-1}; NMR ($CDCl_3$) δ 1.38 (9H, s), 2.35 (2H, m), 4.06 (2H, m), 4.66 (1H, m), 5.35 (1H, d, J=8 Hz), 6.71 (1H, d, J=8 Hz, washes out with $D_2O/NaHCO_3$), 6.93 (1H, s), and 7.29 (10H, s). The synthesis of nocardicin A (1) from 3-ANA 3 and the side chain 2b is described in the concurrent communication[4] where the incorporation of the syn-oxime function is also reported.

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6. A previous synthesis has been reported[7] using dl-homoserine lactone which was then elaborated into the p-substituted o-phenyl homoserine structure required using the Williamson ether synthesis technique. Use of D-homoserine necessitated the application of a method of ether synthesis not having the proclivity of racemization of the contained chirality.

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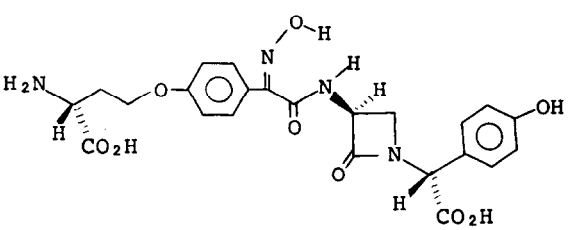
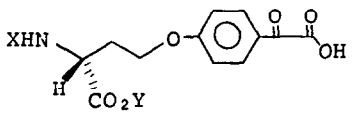
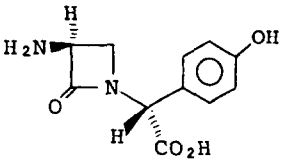


Nocardicin A
(1)



2a: X = Y = H
2b: X = ^{t}Boc, Y = -CHØ$_2$



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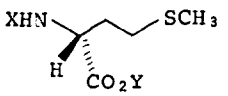
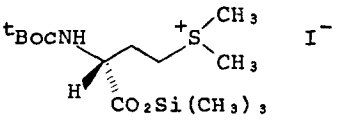


4: X = Y = H
5: X = ^{t}Boc, Y = H



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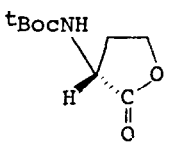

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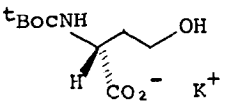

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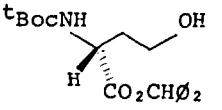

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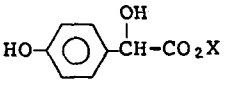
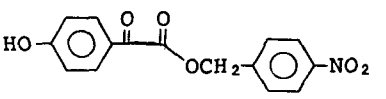


10: X = H
11: X = -H$_2$C-C$_6$H$_4$-NO$_2$



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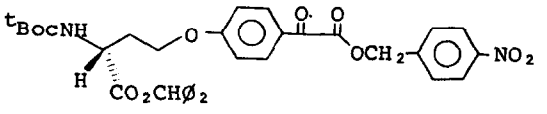

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