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CHIRAL SYNTHESIS OF DUP 721, A NEW ANTIBACTERIAL AGENT[1]

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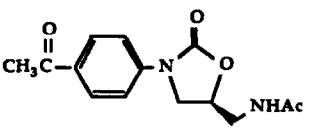
ABSTRACT: A chiral synthesis of DuP 721 [(S)-N-[3-(4-acetylphenyl)-2-oxo-5-oxazolidinylmethyl]acetamide] from 4-acetylphenyl isocyanate (1) and (R)-glycidyl butyrate (2) is described.

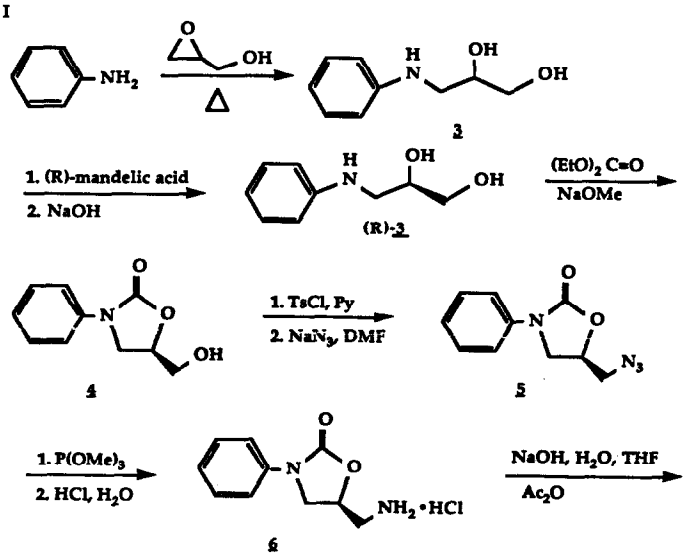
DuP 721 [(S)-N-[3-(4-acetylphenyl)-2-oxo-5-oxazolidinylmethyl]acetamide], developed by Du Pont Co., is a new synthetic antibacterial agent belonging to the oxazolidinone series.[2] It is structurally unrelated to any other class of antimicrobial agents currently available. Its antibacterial spectrum includes staphylococci, streptococci, and Bacteroides fragilis strains. The compound has equal activity against staphylococcal strains susceptible or resistant to β-lactam antibiotics, including methicillin-resistant strains.[3]

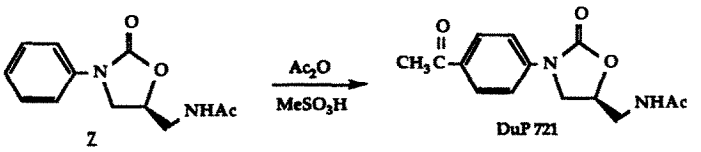


DuP 721

DuP 721 has been prepared according to the synthetic route outlined in Scheme I.[2] Alkylation of aniline with glycidol gave 3. Since only one enantiomer possessed antibacterial activity, compound 3 was resolved by (R)-mandelic acid to afford (R)-3 which was reacted with diethylcarbonate to yield the 5-hydroxymethyl compound 4. The hydroxy group in 4 was converted into the tosylate and the tosylate was displaced by sodium azide. The resulting azide 5 was reduced with trimethylphosphite followed by treatment with 10% aqueous hydrochloric acid to give the amine hydrochloride salt 6. Then the salt 6 was neutralized with 10% aqueous sodium hydroxide in THF and treated with acetic anhydride to afford 7. Finally, compound 7 was acylated to give DuP 721.

Scheme I





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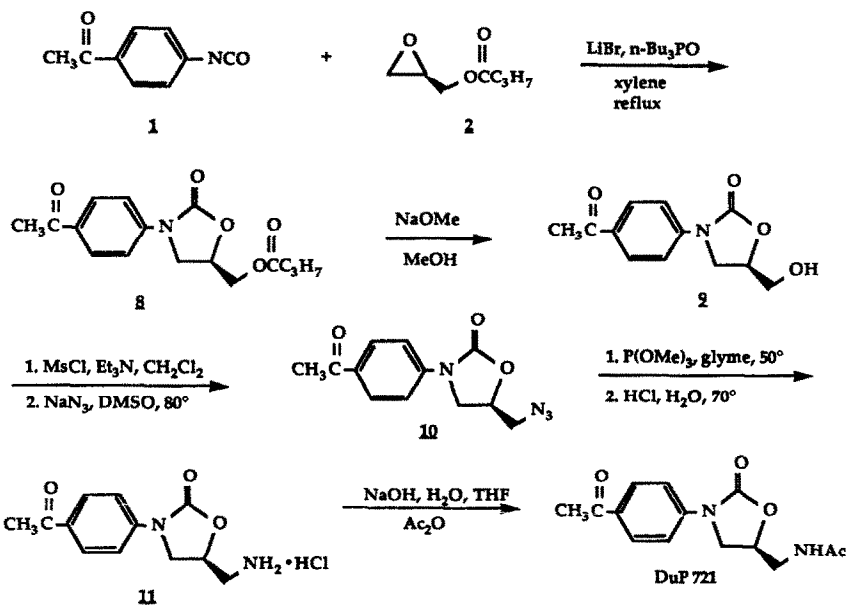
In view of a tedious resolution step involved in the above synthesis, we were seeking other efficient alternatives. Herein we describe a short, chiral synthesis of DuP 721 (Scheme II).

4-Acetylphenyl isocyanate (1) reacted smoothly with (R)-glycidyl butyrate (2)[4] in the presence of lithium bromide and tributylphosphine oxide[5] in refluxing xylene to give oxazolidinone ester 8 as a white crystalline solid after recrystallization from ethanol in 82% yield. Treatment of 8 with catalytic amount of sodium methoxide in methanol at room temperature afforded the alcohol 9 as a white solid after recrystallization from ethanol and water in 95% yield. The hydroxy group in 4 was converted into the mesylate by treating with mesyl chloride in the presence of triethylamine and then displaced with sodium azide in dimethylsulfoxide at 80°C. The resulting azide 10 was purified by flash column chromatography to provide pure 10 as a white solid in 87% yield from the alcohol 9. Finally, by following the steps for converting 5 into 7, the azide 10 was converted into DuP 721 as a white solid after recrystallization in 87% yield from 10.

Scheme II



1 2 8 9 10 11

In conclusion, we have developed a six-step chiral synthesis of DuP 721 in 60% overall yield. Many analogs were prepared according to the above synthetic sequence. Their structure-activity studies are going to be published elsewhere.[6]

Experimental

General:

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded in NaCl cell using Perkin-Elmer Model 21 and 137 spectrophotometers and are reported in reciprocal centimeters. ^{1}H NMR spectra were determined in the indicated solvent on Bruker SY-200 spectrometer and are reported in δ units (parts per million) downfield from tetramethylsilane as the internal reference. Ultraviolet spectra were taken in absolute ethanol using a Cary 21 spectrophotometer.

(R)-N-[3-(4-Acetylphenyl)-2-oxo-5-oxazolidinylmethyl]butyrate (8)

A mixture of anhydrous LiBr (1.45g, 0.016 mol) and tri-n-butylphosphine oxide (3.64g, 0.016 mol) in xylene (50 mL) was azeotropically dried for one hour, then the heat source was removed and a solution of 4-acetylphenyl isocyanate (44.7g, 0.277 mol) and (R)-glycidyl butyrate (40g, 0.277 mol) in xylene (50 mL) was added at a rate such that the mixture maintained gentle reflux. The resulting solution was refluxed for two hours, then the solvent was removed in vacuo and the crude product was recrystallized from ethanol to give 69.29g (82%) of 8, m.p. 89.5-90.5°C; IR (nujol): 1740, 1737, 1665, 1607 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 7.98 (d, 2H), 7.63 (d, 2H), 4.92 (m, 1H), 4.37 (dq, 2H), 4.18 (t, 1H), 3.88 (dd, 1H), 2.60 (s, 3H), 2.33 (t, 2H), 1.62 (hx, 2H), 0.90 (t, 3H); HRMS: m/z 305.1273 (M^+), calcd. for $C_{16}H_{19}NO_5$, 305.1263; Anal. Calcd: C, 62.94; H, 6.27. Found: C, 62.87; H, 5.94; $[\alpha]_D$ = -63° (c=1, CH_3CN).

(R)-N-[3-(4-Acetylphenyl)-5-hydroxymethyl-2-oxooxazolidinine] (9)

A solution of 8 (55g, 0.18 mol) and sodium methoxide (0.98g, 0.018 mol) in methanol (180 mL) was stirred at ambient temperature for two hours. The solution was then neutralized with 10% aqueous HCl, and the solvent removed in vacuo to afford the crude product, which was recrystallized from ethanol/water to give 40g (95%) of 9, m.p. 175-176°C; IR (nujol): 3362, 1741, 1719, 1664, 1602 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 8.00 (d, 2H), 7.71 (d, 2H), 4.73 (m, 1H), 4.15 (t, 1H), 3.90 (dd, 1H), 3.65 (dq, 2H), 2.56 (s, 3H); HRMS: m/z 235.0847 (M^+), calcd. for $C_{12}H_{13}NO_4$, 235.0844; Anal. Calcd: C, 61.27; H, 5.57. Found: C, 60.96; H, 5.66; $[\alpha]_D$ = -67.8° (c=1, acetone).

(R)-N-[3-(4-Acetylphenyl)-2-oxo-5-oxazolidinylmethyl]methanesulfonate

Treatment of 9 (32.7g, 0.139 mol) with methanesulfonyl chloride (20.93g, 0.18 mol) in the presence of triethylamine (25mL, 0.18 mol) in methylene chloride (325 mL) at room temperature for three hours. It was then washed with brine and the organic layer was dried (Na_2SO_4). Removal of the solvent gave the title compound, 43.5 g (100%), which was directly submitted to the next reaction.

(R)-N-[3-(4-Acetylphenyl)-2-oxo-5-oxazolidinylmethyl]azide (10)

A mixture of the above methanesulfonate (43.5g, 0.139 mol) and sodium azide (14.7g, 0.226 mol) in DMSO (225 mL) was heated at 80°C for two hours. It was diluted with water and extracted with methylene chloride. The separated organic layer was dried (Na_2SO_4). Removal of the solvent in vacuo yielded the crude product which was purified by flash column chromatography to afford 31.44g (87%) of 10, m.p. 79-80°C; IR (nujol): 2097, 1751,1666, 1605 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 7.98 (d, 2H), 7.65 (d, 2H), 4.83 (m, 1H), 4.15 (t, 1H), 3.93 (dd, 1H), 3.68 (dq, 2H), 2.60 (s, 3H);

HRMS: m/z 260.0913 (M^+), calcd for $C_{12}H_{12}N_4O_3$, 260.0909; Anal. Calcd: C, 55.30; H, 4.64. Found: C, 55.24; H, 4.62; $[\alpha]_D$ = -150° (c=1, CH_3CN).

(S)-N-[5-Aminomethyl-3-(4-acetylphenyl)-2-oxooxazolidine]hydrochloride (11)

Trimethylphosphite (12 mL, 0.1 mol) was added to a solution of 10 (24.5g, 0.094 mol) in glyme (50 mL) at 50°C dropwise. The mixture was stirred at 50°C for additional two hours after the addition. Then, aqueous HCl (18.75%, 24 mL) was added and it was heated at 70°C for two hours. The resulting solid was collected and washed with glyme. It was dried in vacuo to give 24.2g (95%) of 11, m.p. 256-257°C (dec).

(S)-N-[3-(4-Acetylphenyl)-2-oxo-5-oxazolidinylmethyl] acetamide (DuP 721)

A solution of 11 (24.6g, 0.09 mol) in THF-H_2O (100 mL-20 mL) was neutralized with 10% aqueous sodium hydroxide (30 mL) and then treated with acetic anhydride (15 mL, 0.16 mol) at room temperature for 30 minutes. The resulting solid was collected and recrystallized from CH_3CN to give 22.8 g (92%) of DuP 721, m.p. 190.5-191°C; IR (nujol): 1755, 1666, 1650, 1608, 1567 cm^{-1}; ^1H NMR (d_6-DMSO) δ: 8.24 (m, 1H), 7.99 (d, 2H), 7.68 (d, 2H), 4.76 (m, 1H), 4.18 (dd, 1H), 3.81 (dd, 1H), 3.44 (m, 2H), 2.55 (s, 3H), 1.83 (s, 3H); UV (EtOH): λmax (log ε) 283 (4.33) nm; Anal. Calcd. for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.78; H, 5.70; N, 10.22; $[\alpha]_D = -51°$ (c=1, DMF).

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1. Contribution No. 88-P16 from Medical Products Department.

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