TOTAL SYNTHESIS OF (±)-8S*-DESCYSTEAMINYLTHIENAMYCIN PROTECTED WITH o-NITROBENZYL GROUPS

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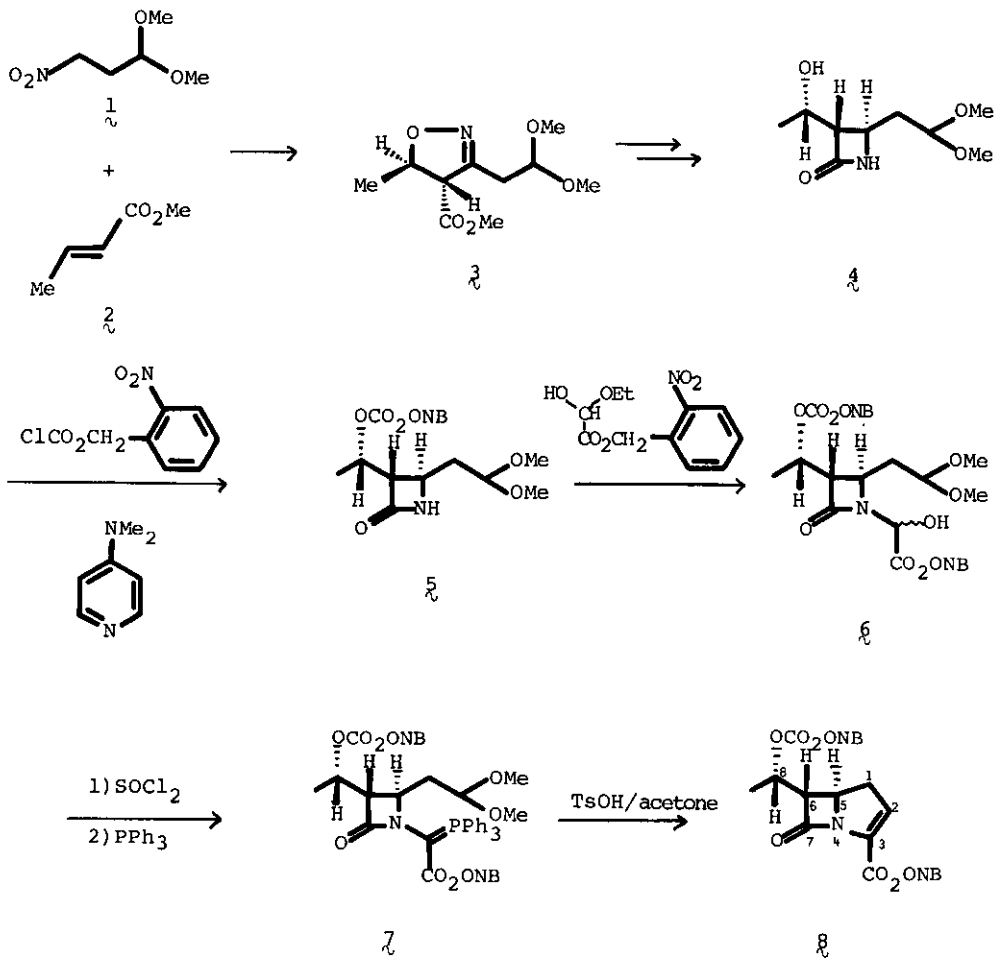
Abstract —— (±)-trans-4-(2',2'-Dimethoxyethyl)-3-(1'S*-hydroxyethyl)-2-azetidinone (4), prepared from an isoxazoline derivative (3), was converted to (±)-8S*-descysteaminylthienamycin protected with o-nitrobenzyl groups (8) using an intramolecular Wittig reaction.

Conversion of (±)-trans-4-(2',2'-dimethoxyethyl)-3-(1'S*-hydroxyethyl)-2-azetidinone (4), prepared as described in a preceding paper,[1] into (±)-8S*-descysteaminylthienamycin protected with o-nitrobenzyl groups was accomplished as follows. Reaction of the azetidinone (4) with o-nitrobenzyl chloroformate in the presence of N,N-dimethylaminopyridine in methylene chloride at -5 ∿ 0°C for 1 h gave trans-4-(2',2'-dimethoxyethyl)-3-(1'S*-o-nitrobenzyloxycarbonyloxyethyl)-2-azetidinone (5), ir $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450 (NH), 1760, 1750 (C=O); nmr ($CDCl_3$) δ : 1.46 (3H, d, J = 6.5 Hz, MeCH(OH)), 3.15 (1H, d of d, J = 6 and 2 Hz, C_3-H), 3.34 (6H, s, 2xOMe), 3.65 (1H, t of d, J = 7 and 2 Hz, C_4-H), m/e 383 (M^+ + 1), in 84 % yield. Condensation of 5 with o-nitrobenzyl glyoxalate ethylhemiacetal, using activated molecular sieves (3Å)[2] in dimethylformamide and toluene at room temperature for 24 h, yielded a epimeric mixture of the alcohol 6, ir $\nu_{max}^{CHCl_3}$ cm^{-1}: 1760 (C=O), nmr ($CDCl_3$) δ : 3.33 (6H, s, 2xOMe), in 69 % yield. On reaction with thionyl chloride and 2,6-lutidine in tetrahydrofuran at room temperature for 30 min, the alcohol 6 gave the unstable chloro compound, which without purification was converted to the phosphoran (7) in 74 % yield after purification by silica gel column chromatography, ir $\nu_{max}^{CHCl_3}$ cm^{-1}: 1750 (C=O); nmr ($CDCl_3$) δ : 1.40 (3H, d, J = 6.5 Hz, MeCH(OH)), 3.23 (6H, s, 2xOMe). Deacetalisation was carried out using p-toluenesulfonic acid in acetone at room temperature for 2 h, and on evaporation of the solvent and basification with saturated aqueous sodium hydrogen carbonate spontaneous intramolecular Wittig

Scheme



reaction occurred to give, in 39 % yield, o-nitrobenzyl 6-(1'S*-o-nitrobenzyloxycarbonyloxyethyl)-1-carba-2-penem-3-carboxylate (8), ir $\nu_{max}^{CHCl_3}$ cm^{-1}: 1778, 1740, 1720 (C=O); nmr ($CDCl_3$) δ : 1.55 (3H, d, J = 6.5 Hz, MeCH(OH)-), 3.46 (1H, d of d, J = 2 and 4.5 Hz, C_6-H), 4.30 (1H, d of t, J = 2 and 7 Hz, C_5-H), 6.60 (1H, t, J = 2 Hz, C_2-H), which would be an important synthetic precursor of (±)-8S*-descysteaminylthienamycin.[3]

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