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STEREOCONTROLLED TOTAL SYNTHESIS OF THE PENICILLANATE ESTER (2S,5R)-BENZYL 3,3-DIMETHYL-7-OXO-4-THIA-1-AZABICYCLO[3.2.0]HEPTANE-2-CARBOXYLATE

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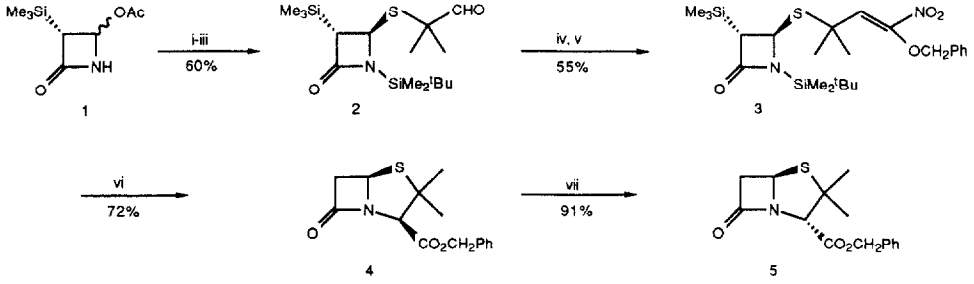
Abstract: (3R)-4-Acetoxy-3-trimethylsilyl-2-azetidinone, was converted into optically pure benzyl penicillanate in seven steps (22%) using (benzyloxy)nitromethane as a reagent for ring annulation.

β-Lactams are outstanding antibiotics, and novel, concise chemistry for their elaboration is constantly being sought. The utility of nitro alkenes in carbapenam construction was demonstrated by Shibuya,[1] and a 1,1-bis(alkylthio)nitro alkene intermediate was used in Hanessian's penam synthesis.[2] We recently reported[3] the use of (phenylthio)nitromethane for the preparation of bicyclic β-lactam phenylthio esters from monocyclic precursors. Unfortunately, subsequent selective hydrolysis of the phenylthio ester substituent, to release the corresponding β-lactam carboxylic acid, proved difficult in several cases. Additionally, we were unable to prepare the penam skeleton using (phenylthio)nitromethane since the required 1-nitro-1-phenylthio-3-propenyl sulfide intermediates were too unstable. Herein, we report that (benzyloxy)nitromethane[4] is a most useful reagent for the synthesis of benzyl penicillanate.

The optically pure acetate 1, which was prepared from L-aspartic acid using the Weis procedure,[6] was converted into sulfide 2 by sequential reaction with 2-methyl-3-butene-2-thiol,[7] t-butyldimethylsilyl chloride and ozone (Scheme). Competitive sulfoxide formation was not a problem during the ozonolysis step providing that the course of reaction was carefully monitored. Aldehyde 2 reacted smoothly with (benzyloxy)nitromethane followed by acetyl chloride to give the nitro alkene 3. Attempted dehydration of the β-nitro alcohol intermediate using methanesulfonyl chloride gave 3 in only poor yield. We were particularly pleased that 3 was a stable crystalline compound (m.p. 106-107°C) since we failed to isolate the phenylthio analog due to its instability. This underscores two advantages of (benzyloxy)nitromethane relative to (phenylthio)nitromethane. Firstly, it is less acidic (5 pKa units[4]) and undergoes Henry reaction at greatly accelerated rates. Secondly, 1-benzyloxy-1-nitro alkenes are much less electrophilic and are, therefore, much easier to prepare and isolate. Reaction of 3 with tetrabutylammonium fluoride followed by ozone resulted in double desilylation and cyclization to produce only the endo benzyl ester 4.[8] Subsequent epimerization using DBU gave benzyl penicillanate 5.[9] It is again noteworthy that sulfoxide formation was not a complication during the ozonolysis step providing that the progress of the reaction was carefully followed. It is clear from these results, that (benzyloxy)nitromethane is a most useful reagent in β-lactam chemistry.

Scheme



Reagents:

(i) $Me_2C(SH)CH{=}CH_2$, NaOMe, MeOH, (ii) $^tBuMe_2SiCl$, $(^{iso}Pr)_2NEt$, DMAP, CH_2Cl_2; (iii) O_3, CH_2Cl_2, -78°C; Me_2S, (iv), $PhCH_2OCH_2NO_2$, KO^tBu, ^tBuOH, THF; (v) AcCl, Et_3N, 10°C; (vi) Bu_4NF, THF, -78°C; CH_2Cl_2, O_3; (vii) DBU, $CDCl_3$, 25°C.

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5. For examples see P.G. Sammes, "Topics in Antibiotic Chemistry," Ellis Horwood Ltd., Chichester, **1980**, vol. 4.

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7. This particularly vile thiol was prepared from 3-methyl-2-buten-1-ol, via the S-methyl xanthate, [3,3] sigmatropic rearrangement and hydrolysis using 3-amino-1-propanol. See also T. Taguchi, Y. Kiyoshima, O. Komori and M. Mori, Tetrahedron Lett. **1969**, 3631. K. Harano and T. Taguchi, Chem. Pharm. Bull. **1972**, 20, 2348.

8. All new compounds were authenticated by spectral data and microanalyses or high resolution mass ion measurements.

9. The isomerization of 4 to produce 5 was essentially quantitative and the yield of 91% represents the isolated material after chromatography. None of the endo isomer 4 remained after isomerization. The product benzyl penicillanate 5 exhibited the following characteristics: $[\alpha]_D$ +334° (c=1.0, $CHCl_3$); IR (neat) ν_{max} 2978, 1775, 1745, 1605, 1582, 1500, 1452, 1295, 1200, 1175, 1155, 1125, 1090, 1000, 950, 745 and 695 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) δ 7.38-7.36 (m, 5H), 5.28 (dd, 1H, J=4.4, 2.0Hz), 5.22 (d, 1H, J=10.8Hz), 5.165 (d, 1H, J=10.8Hz), 4.49 (s, 1H), 3.54 (dd, 1H, J=16.0, 4.4Hz), 3.06 (dd, 1H, J=16.0, 2.0Hz), 1.63 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (400MHz, $CDCl_3$) δ 172.27, 167.85, 134.82, 128.62, 128.58, 70.17, 67.28, 65.67, 60.59, 46.48, 31.74, 26.62; Mass spectrum (FAB) m/e 292 (M^++H, 27), 291 ($M^{+\circ}$, 8), 263(9), 251(15), 250(100), 220(6), 219(38), 217(3), 200(3), 165(3); High resolution mass spectrum (FAB) Calc for: $C_{15}H_{18}NO_3S$ (M^++H), 292.1007. Found: (M^++H), 292.1001. Additionally, these data were in agreement with literature values for 5; see V.J. Brennan and F.H.S. Hussain, Synthesis **1985**, 749.

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