SYNTHESIS OF OPTICALLY ACTIVE 6α-METHOXY PENEM

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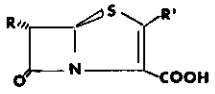
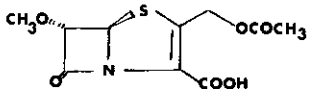
Abstract — Synthesis of 6α-methoxy-2-acetoxymethyl-2-penem-3-carboxylic acid starting from penicillin V is described.

Among non classical β-lactams, penems[1] have been receiving strong attention by our group.[2-4] Since 6-unsubstituted compounds (I, R = H) showed powerful antibacterial activity[5,6] but were ineffective against β-lactamases producing bacteria, we hoped to overcome this problem by introducing a methoxy group in the 6α position (II), resembling the cephamycin and the more recent sulfazecin[7] families. Here we wish to report the synthesis of compound II.

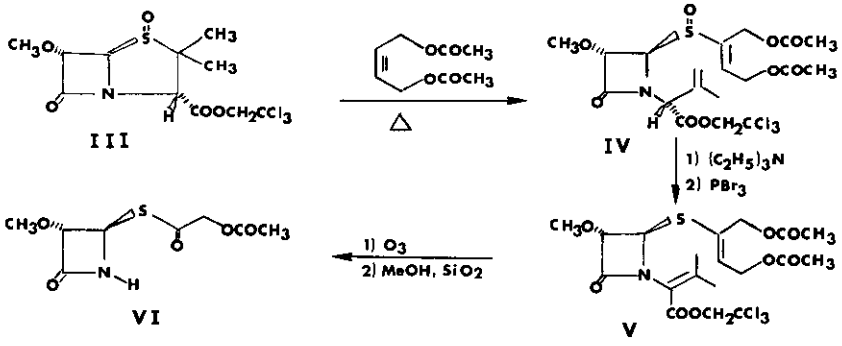


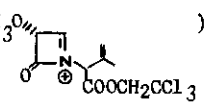
I



II

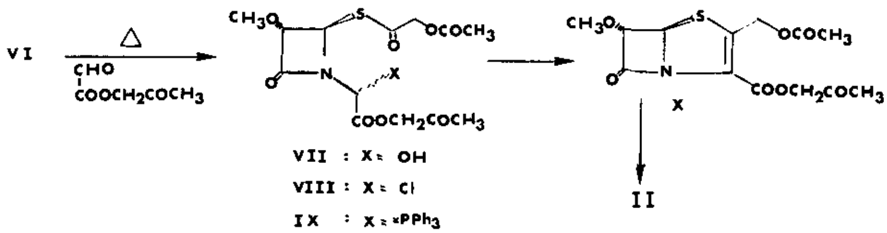
Following our previous work,[2,8] trichloroethyl-6α-methoxypenicillanate S-oxide (III)[9] was chosen as starting material. Whilst our work was in progress, a synthesis of 6α-methoxy-2-methylpenem-3-carboxylic acid by a different trapping reaction on (III) was communicated.[10]



Compound (III) was refluxed in toluene with excess butyndiol diacetate affording (IV) in 65% yield ; PMR ($CDCl_3$): 2.01 (bs, 3H, $=\!\!\diagdown\underline{CH_3}$); 2.08, 2.10 (two s, 6H, $OCO\underline{CH_3}$, $OCO\underline{CH_3}$); 3.45 (s, 3H, $O\underline{CH_3}$); 4.85 (s, 2H, $COO\underline{CH_2}$); 4.75-5.00 (m, 6H, H-4, CHCOO, $\underline{CH_2}OAc$, $\underline{CH_2}OAc$); 5.15 (bs, 2H, $=\underline{CH_2}$); 5.27 (d, J = 1.5 Hz, 1H, H-3); 6.57 (bt, J = 6.0 Hz, 1H, H); Field Desorption Mass Spectrum (FD-MS)[11] : m/z 547 ($M^{+\cdot}$); 328 ().

Isomerization of the isopropenyl double bond [$(C_2H_5)_3N$, r.t., 100%] and reduction of the sulphoxide (PBr_3, -20°C, 90%) gave (V) [PMR ($CDCl_3$): 2.10, 2.14, 2.40 (three s, 12H, CH_3, CH_3, $OCOCH_3$, $OCOCH_3$); 3.49 (s, 3H, OCH_3); 4.82 (s, 2H, CH_2CCl_3); 4.88 (bs, 2H, $=CH_2$); 4.91 (d, J = 6 Hz, 2H, CH_2); 4.95 (d, J = 2 Hz, 1H, H-3); 5.23 (d, J = 2 Hz, 1H, H-4); 6.60 (bt, J = 6 Hz, 1H, =H)], which was ozonized on both double bonds (CH_2Cl_2, -78°C, 80%) and finally hydrolyzed in its oxamide moiety to (VI) (MeOH, r.t., SiO_2); PMR ($CDCl_3$): 2.21 (s, 3H, $OCOCH_3$); 3.55 (s, 3H, OCH_3); 4.62 (dd, J = 1.5, 1.5 Hz, 1H, H-3); 4.78 (s, 2H, CH_2O); 5.23 (d, J = 1.5 Hz, 1H, H-4) FD-MS: m/z 233 ($M^{+\cdot}$); 190 ($M-CH_3CO^{\cdot}$).

From now on the suitable N-appendage was rebuilt following the well known Woodward-Scartazzini procedure.[12]



Condensation of (VI) with acetonyl glyoxylate[1d] in refluxing benzene afforded (VII) which was chlorinated to (VIII) ($SOCl_2$, py, THF, 0°C), and then transformed into (IX) (PPh_3, py, THF, 40°C) *in 52% overall yield (VI ⟶ IX).*

Compound (IX) was cyclised to penem (X) in toluene (N_2, 100°C, 2 hours) in good yield; ^{13}C-NMR (20 MHz, acetone-d_6): 20.2 ($OCOCH_3$); 25.9 ($COCH_3$); 58.00 (C-8); 59.7 (CH_2OCO); 68.7 (C-5); 69.4 (CH_2COCH_3); 93.8 (C-6); 120.0 (C-3); 151.6 (C-2); 158.8 ($COOCH_2$); 170.1 ($OCOCH_3$); 172.2 (C-7); 201.3 ($COCH_3$). PMR ($CDCl_3$): 2.11, 2.22 (two s, 6H, $OCOCH_3$, $COCH_3$); 3.57 (s, 3H, OCH_3); 4.78 (s, 2H, CH_2CO); 4.96 (d, J = 1.5 Hz, 1H, H-5); 5.04, 5.48 (dd, J = 12.7 Hz, 2H, CH_2OCO); 5.59 (d, J = 1.5 Hz, 1H, H-6).

Careful hydrolysis (NaOH 0.1 N, THF, 0°C) finally afforded (II) in poor yield; PMR ($CDCl_3$): 2.16 (s, 3H, $OCOCH_3$); 3.61 (s, 3H, OCH_3); 5.03 (d, J = 1.4 Hz, 1H, H-5); 5.32 (dd, 2H, CH_2OCO); 5.62 (d, J = 1.4 Hz, 1H, H-6).

Unfortunately, compound (II) did not show the expected biological activity on both sensitive and resistent strains. We presume that this negative result is due to the inherent instability of the compound, rather than to the molecule intrinsic inactivity. In fact (II) showed a half-life of a few hours (38°C, pH 7.4), considerably different from the much more stable parent compound [(I, R = H, R' = CH_2OCOCH_3)]. Same results were obtained by CIBA-GEIGY Group.[10]

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