# Total Synthesis of (±)-Clavulanic Acid

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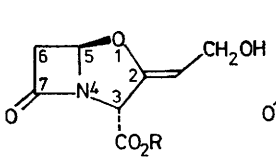
*Summary* A formal total synthesis of racemic clavulanic acid has been achieved commencing with (±)-4-methylthioazetidin-2-one (**3**).

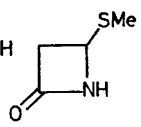
CLAVULANIC acid is a naturally occurring β-lactamase inhibitor with the novel fused β-lactam structure (**1**).[1] We report here total syntheses of (±)-methyl clavulanate (**2**) and (±)-methyl isoclavulanate (**7**) from the racemic intermediate, methyl *E*-3-methoxycarbonylmethylene-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane-2-carboxylate (**6**). Since the corresponding optically active esters[2] are each convertible into clavulanic acid, our methods constitute the first total synthesis of (±)-(**1**).

Using 2 equiv. of sodium hydride in dimethylformamide, (**3**)[3] was alkylated with dimethyl 2-bromo-3-oxoglutarate to provide in 29% yield the β-ketodiester (**4**) which from spectroscopic data† is largely enolised as indicated. Treatment of the latter with a slight excess of chlorine in carbon tetrachloride gave the chloro derivative (**5**), which was stirred with anhydrous potassium carbonate in dry dimethylformamide. Following aqueous work up, chromatography led to a single, racemic bicyclic diester (**6**) m.p. 109–110 °C, in 34% yield from (**4**). Irradiation of a benzene solution of (**6**) with a low-pressure mercury source provided quantitatively a 3:2 mixture of (**6**) and the corresponding *Z*-isomer (**8**), which proved too unstable for chromato-

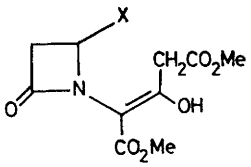
† Satisfactory analytical and spectroscopic data were obtained for all new compounds herein reported.



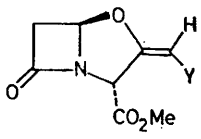
(1) R = H
(2) R = Me



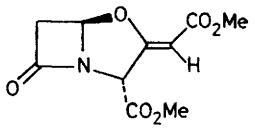
(3)



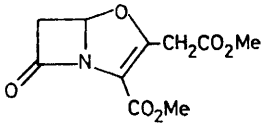
(4) X = SMe
(5) X = Cl



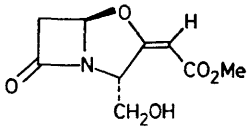
(6) Y = $CO_2Me$
(7) Y = $CH_2OH$



(8)



(9)



(10)

graphic isolation. Reduction of the mixture with di-isobutylaluminium hydride in toluene at −70 °C furnished in low yield a separable mixture of the racemic esters (**2**)‡ and (**7**). Alternatively reduction of (**6**) alone with the same reagent gave a low yield of racemic (**7**).‡

When the cyclisation of (**5**) was carried out with 1 equiv. of triethylamine in dry ether, the crude product obtained following filtration and evaporation was shown by $^1H$ n.m.r. spectroscopy and t.l.c. to contain approximately equal amounts of (**8**) and the bicycloheptene (**9**) along with some (5—20%) (**6**).[4]

Our evidence for assigning structures (**6**)[5] and (**8**) to the two diesters follows from their $^1H$ n.m.r. spectra and their conversion into the known compounds (**2**) and (**7**). In (**6**) resonances are observed *inter alia* at δ 5·60 (d, *J* 1 Hz), 5·71 (d, *J* 1 Hz, exchangable with DBN–$D_2O$) and 5·74 (dd, *J* 3 and 0·5 Hz) which are assigned to the vinyl, C-3, and C-5 protons respectively.§ In the mixture of (**6**) and (**8**) additional signals appear at δ 5·15 and 5·20 (each d, *J* 1 Hz, exchangable with DBN–$D_2O$, vinyl and C-3-H), and 5·91 (dd, C-5-H). The lower chemical shift for the vinyl proton in (**6**) reflects a *cis* relationship to the oxygen atom.[6] The cyclisation of (**5**) under basic conditions was expected to give rise to bicycloheptanes, *e.g.* (**6**), in which the relative stereochemistry at C-3 and C-5 is the same as in clavulanic acid.[7] Finally the lack of any significant u.v. absorption (>210 nm) in the reduction product from (**6**) allowed the isomeric structure (**10**) to be ruled out.¶

(*Received, 1st August* 1977; *Com.* 796.)

‡ Spectral properties were identical with those for the compounds previously obtained from natural (**1**).

§ Numbering follows that used in penicillins, shown in (**1**). Chemical shifts (δ) are from tetramethylsilane for solutions in deuteriochloroform. DBN = 1,5-diazabicyclo[4.3.0]non-5-ene.

¶ (**10**), $\lambda_{max}$ 234 nm, can be obtained from (**6**) using $LiAlH_4$.

[1] T. T. Howarth, A. G. Brown, and T. J. King, *J.C.S. Chem. Comm.*, 1976, 266.
[2] (+)-(**2**) (ref. 1) is hydrolysable to clavulanic acid by keeping a dilute aqueous tetrahydrofuran solution at pH 9 followed by acidification, J. B. Harbridge unpublished results from these laboratories. Irradiation of a benzene solution of (+)-(**7**) with a low-pressure Hg source provided a separable mixture (1 : 1) of (+)-(**7**) and (+)-(**2**), M. L. Gilpin, unpublished results. For interconversion of the corresponding benzyl esters of (**1**) and (**7**) see A. G. Brown, T. T. Howarth, I. Stirling, and T. J. King, *Tetrahedron Letters*, 1976, 4203.
[3] K. Clauss, D. Grimm, and G. Prossel, *Annalen*, 1974, 539.
[4] The synthesis of compounds related to (**9**) will be reported elsewhere. See also A. J. Eglington, *J.C.S. Chem. Comm.*, in the press.
[5] The structure of (**6**) has since been confirmed by *X*-ray crystallographic analysis, T. J. King, unpublished results.
[6] See cited references in L. M. Jackman and S. Sternhell, 'Applications of N.M.R. Spectroscopy in Organic Chemistry,' Pergamon, Oxford, 1969, p. 187.
[7] Recently a synthetic 3-*epi* analogue was shown to epimerise at C-3 under basic conditions, P. H. Bentley, unpublished results. See also A. G. Brown, D. F. Corbett, and T. T. Howarth, *J.C.S. Chem. Comm.*, 1977, 359.