

Total Synthesis of (\pm)-Clavulanic Acid

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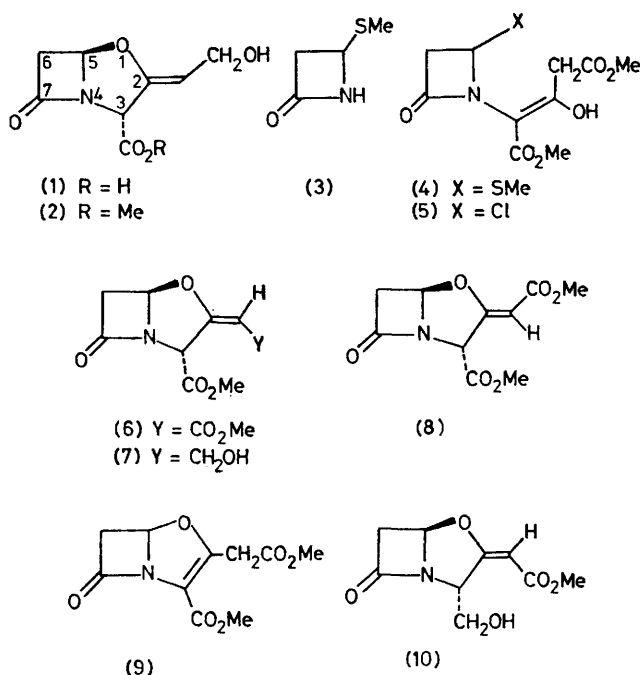
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Summary A formal total synthesis of racemic clavulanic acid has been achieved commencing with (\pm)-4-methylthioazetidin-2-one (**3**).

CLAVULANIC acid is a naturally occurring β -lactamase inhibitor with the novel fused β -lactam structure (**1**).¹ We report here total syntheses of (\pm)-methyl clavulanate (**2**) and (\pm)-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 esters² are each convertible into clavulanic acid, our methods constitute the first total synthesis of (\pm)-(**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.



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

[‡] 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 (8) are from tetramethylsilane for solutions in deuteriochloroform. DBN = 1,5-diazabicyclo[4.3.0]non-5-ene.

[¶] (10), λ_{max} 234 nm, can be obtained from (6) using LiAlH₄.

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. Eglinton, *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.

(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, exchangeable with DBN-D₂O) 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, exchangeable with DBN-D₂O, 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.[¶]

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