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A SHORT SYNTHESIS OF (±) 7-OXO-3-OXA-1-AZABICYCLO[3.2.0] HEPTANE-2-CARBOXYLIC ACID.

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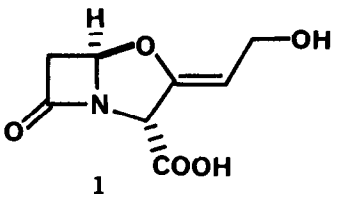
A short 4-step synthesis of the title compound **3** , an inhibitor of ß-lactamases, is presented. The essential step utilizes the palladium(0)-catalyzed deprotection of an allyl ester.

A major problem in the treatment of bacterial infections with ß-lactam antibiotics is the rapid breakdown of sensitive compounds by the ß-lactamase enzymes of "resistant" bacteria. This situation initiated an intensive search for natural or synthetic inhibitors of ß-lactamases, resulting in the discovery of, for example, clavulanic acid **1**[1] and sulbactam **2**[2].



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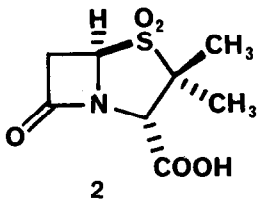

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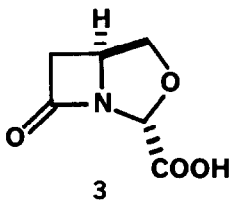


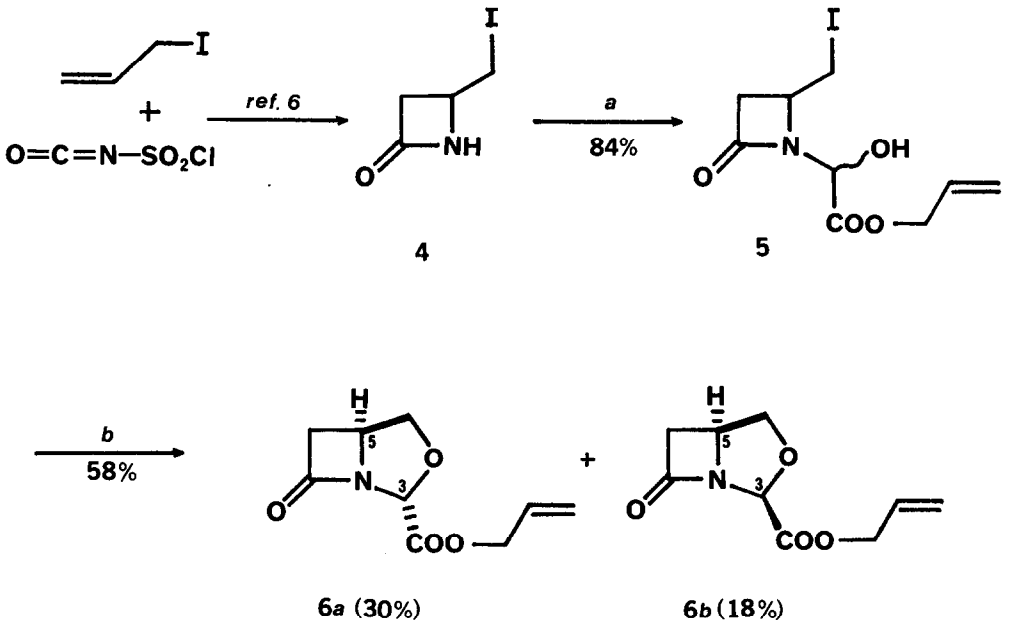
3

A new, structurally related compound, 7-oxo-3-oxa-1-azabicyclo[3.2.0]heptane-2-carboxylic acid **3** could also be of interest in this respect.

Stoodley et al.[3] have reported the synthesis of esters thereof via a lengthy route, the key step being the closure of the 3-4 bond. Just et al.[4] adopted another strategy for the construction of the isooxapenam ring, closing the 2-3 bond as key step. By its very nature, this route only provides access to the chemotherapeutically less interesting 2,2-disubstituted derivatives. All attempts to cleave the ester function on the highly strained isooxapenam ring system have so far resulted in destruction of the ß-lactam ring[5].

We report the successful solution of this problem by use of palladium(0)-catalyzed deprotection of the corresponding allyl ester **6a**. In addition we present a short 4-step synthesis of sodium-7-oxo-3-oxa-1-azabicyclo[3.2.0] heptane-2-carboxylate (±) **3a** analogous to the later steps of Stoodley's approach[3].

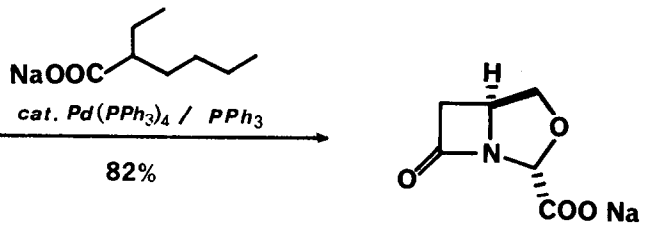
Thus 4-iodomethylazetidin-2-one **4**, prepared according to Tanaka et al.[6], reacted with allyl glyoxylate[7] in the presence of 4Å molecular sieve (0.15 m in toluene: DMF 4:1, 20 h, r.t.) to give the alcohol **5**[8] (84% after chromatography) as a mixture of diastereomers. Intramolecular O-alkylation of **5** (0.2 m in THF, HMPA-2 equiv., n-BuLi-1 equiv., -78° ⟶ 0°C) yielded, in contrast to Stoodley's cyclization method[3], a mixture of the allyl esters **6** (58%) which could be separated by SiO_2 chromatography to afford the diastereomers **6a** (30%) and **6b** (18%)[9,10].



reagents: a: $(HO)_2CHCO_2CH_2CH=CH_2$ 2 equiv., mol. sieves 4Å, DMF, 20 h r.t.
b: n-BuLi, THF, HMPA-2 equiv., -78°C ⟶ 0°C.

The unambigious assignment of structure to the two isomers was possible by NMR spectroscopy. The chemical shifts of the H-3 protons (penicillin numbering system) in **6a** (δ = 5.65 ppm) and **6b** (δ = 4.86 ppm) differ by $\Delta\delta$ = 0.79 ppm. They therefore correspond very well to the general rule that in penicillins

and clavulanic acids and esters the H-3 proton anti to H-5 is deshielded by about 0.5 ppm relative to the H-3 syn to H-5[11]. Furthermore, the major isomer **6a** has the thermodynamically favored stereochemistry[12] which in turn is the configuration bearing biological activity in the corresponding free acids. Finally, of the palladium(0)-catalyzed deprotection methods examined, McCombie's procedure[13] gave the best results, affording the hygroscopic sodium salt **3a** [9,14,15] in 82% yield.



3a

3a is an inhibitor of various clinically relevant ß-lactamases and is itself almost devoid of antibacterial activity.

References and Notes

1 T.T. Howarth, A.G. Brown, and T.J. King, J.Chem.Soc., Chem.Commun., (1976) 266.

2 R.A. Volkmann, R.D. Carroll, R.B. Drolet, M.L. Elliott, and B.S. Moore, J.Org.Chem., 47 3344 (1982) and references cited therein.

3 J. Brennan, G. Richardson, and R.J. Stoodley, J.Chem.Soc., Chem.Commun. (1980) 49.

4 G.H. Hakimelahi, and G. Just, Can.J.Chem., 59 941 (1981).

5 The hydrogenolytic cleavage of a p-nitrobenzylester was successful in only one case, in a 2-phenyl-2-carboxylate 4.

6 T. Tanaka, and T. Miyadera, Heterocycles, 19 1497 (1982).

7 E. Ivan, J. Gostelli and R.B. Woodward (CIBA-GEIGY AG) German Patent 2 655 298 (7. Dec. 1976) pg 138.

8 Lesspolar isomer **5** : R_F= 0.30 (ethyl acetate:toluene 35:65) - IR ($CHCl_3$) 3526 (OH), 1767 (C=O, ß-lactam), 1746 cm^{-1} (C=O, ester) - ^{1}H-NMR (250 MHz, $CDCl_3$) δ = 2.78 (dd, J=15 Hz, 2 Hz, 1H, H-3), 3.19 (dd, J=15 Hz, 5.5 Hz, 1H, H-3'), 3.32 (dd, J=10 Hz, 10 Hz, 1H, CH_2I), 3.60 (dd, J=10 Hz, 5 Hz, 1H, CH_2I), 3.9-4.0 (m, 1H, 4-H), 4.10 (bs, 1H, OH), 4.77 (m, 2H, CH_2-CH=CH_2), 5.3-5.45 (m, 2H, CH=CH_2), 5.52 (s, 1H, CH(OH)CO_2R), 5.85-6.05 (m, 1H, CH=CH_2).
More polar isomer **5** : R_F= 0.26 (ethyl acetate:toluene 35:65) - similar data. mixture: Anal.calcd. for $C_9H_{12}NIO_4$: C 33.3 H 3.7 N 4.3, found: C 33.1 H 3.7 N 4.4.

9 All compounds are racemic. For the sake of clarity the descriptors for one antipode are omitted.

10 Less polar isomer **6a**: R_F= 0.46 (ethyl acetate:toluene 1:2) - IR ($CHCl_3$) 1790 (C=O, ß-lactam), 1755 cm^{-1} (C=O, ester) - ^{1}H-NMR (250 MHz, $CDCl_3$) δ = 2.90 (dd, J=17 Hz, 2.5 Hz, 1H, H-6ß), 3.50 (dd,

J=17 Hz, 6 Hz, 1H, H-6α), 3.95 (dd, J=10 Hz, 5 Hz, 1H, H-1), 4.23 (m, 1H, H-5), 4.45 (dd, J=10 Hz, 8 Hz, 1H, H-1'), 4.46 (m, 2H, $\underline{CH_2}$-CH=CH_2), 5.26-5.4 (m, 2H, CH=$\underline{CH_2}$), 5.65 (s, 1H, H-3), 5.85-6.02 (m, 1H, CH_2-$\underline{CH}$=CH_2) - MS (70 eV): m/e=198 (M^++H); calcd.: 197.2 - Anal.calcd. for $C_9H_{11}NO_4$: C 54.82 H 5.62 N 7.10 found: C 54.5 H 5.5 N 7.1.
More polar isomer **6b** : R_F= 0.36 (ethyl acetate:toluene 1:2) - mp: 36°C - IR ($CHCl_3$) 1787 (C=O, ß-lactam), 1755 cm^{-1} (C=O, ester) - ^{1}H-NMR (250 MHz, $CDCl_3$) δ = 2.86 (dd, J=17 Hz, 1.5 Hz, 1H, H-6ß), 3.32 (dd, J=17 Hz, 5 Hz, 1H, H-6α), 3.9-4.0 (m, 2H, H-1), 4.3 (m, 1H, H-5), 4.75 (m, 2H, $\underline{CH_2}$-CH=CH_2), 4.86 (s, 1H, 3-H), 5.25-5.45 (m, 2H, -CH=$\underline{CH_2}$), 5.9-6.1 (m, 1H, CH_2-$\underline{CH}$=CH_2). - Anal.calcd. for $C_9H_{11}NO_4$: C 54.82 H 5.62 N 7.10, found: C 55.1 H 5.9 N 6.7.

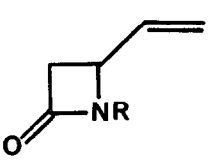
11 P.G. Sammes, Topics in Antibiotic Chemistry Vol. 4, The Chemistry and Antimicrobial Activity of New Synthetic ß-Lactam Antibiotics, Ellis Horwood Ltd. 1980 pg 53 ff.

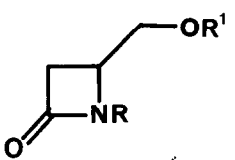
12 See footnote ¶ in ref. 3.

13 P.D. Jeffrey and S.W. McCombie, J.Org.Chem., 47 587 (1982).

14 **3a** : IR (KBr) 1766 cm^{-1} (C=O) - ^{1}H-NMR (250 MHz, DMSO) δ = 2.77 (dd, J=16 Hz, 2.5 Hz, 1H, H-6ß), 3.34 (dd, J=16 Hz, 5 Hz, H-6α), 3.74 (dd, J=8 Hz, 3 Hz, 1H, H-1), 3.98 (m, 1H, H-5), 4.32 (dd, J=8 Hz, 8 Hz, 1H, H-1'), 5.01 (s, 1H, H-3).

15 In a parallel series of experiments (±)**3a** was also obtained via a longer route starting from 4-vinyl-azetidin-2-one **7** . In the course of this work the (1,2-dimethylpropyl)dimethylsilyl group turned out to be a valuable N-protecting group easily cleaved at room temperature by THF containing 5% TFA. Thus N-protection (Cl-SiR_3 1.02 equiv., NEt_3 1.1 equiv., DMF, 0°C→r.t.) to yield **8** followed by reductive ozonization (a. O_3 CH_2Cl_2:MeOH 1:1, Me_2S, -78°C ⟶ -25°C; b. $NaBH_4$ 5 equiv. -25°C ⟶ 0°C) gave the alcohol **9** , which was successively converted into the mesylate **10** and deprotected (0.4 m in THF, 5% TFA, 1 h r.t.) affording the azetidinone **11** (overall 25% from **7**); Anal.calcd.: C 33.5 H 5.1 N 7.8, found: C 33.7 H 5.1 N 7.6). Condensation of **11** with allylglyoxylate (as described above for the preparation of **5**) gave the alcohol **12** (82%) which was cyclized to the allyl ester **6** (50%) as a mixture of diasteromers 2:1.





7: R = H

8: R = 

9: R =  , R^1 = H

10: R =  , R^1 = SO_2CH_3

11: R = H , R^1 = SO_2CH_3

12: R = $CH(OH)CO_2CH_2CHCH_2$, R^1=SO_2CH_3

Note added in proof: R.J. Stoodley et al., J.Chem.Soc., Perkin Trans. 1, 649 (1983), have also succeeded in synthesizing (±) 3a.

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