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STEREOCONTROLLED, STRAIGHTFORWARD SYNTHESIS OF 3-SUBSTITUTED METHYL 7α-METHOXY-1-OXACEPHEMS[1]

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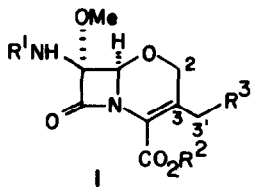
Summary: Stereocontrolled and industrially feasible synthesis of a new antibiotic 1a and related derivatives, which is characterized by using all the carbon atoms of the penicillin skeleton, is described.

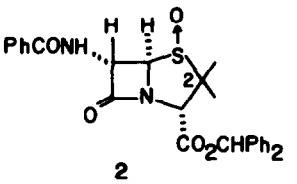
In our previous synthesis[2a] of an optically active 7α-methoxy-1-oxacephem derivative 1a, carbon 2 and the attached two methyls of penicillins are removed eventually and a new three-carbon unit is introduced for building up carbons 2, 3, and 3' of 1a. In development of this clinically important antibiotic[2b] having unique and superior antibacterial activity, we have been urged to improve this synthesis which is not suitable for industrial production, though essentially stereocontrolled and practical on laboratory scales. We now report an industrially feasible synthesis of 1a and related derivatives which is characterized by utilizing all the carbon atoms of the penicillin skeleton for constructing the 1-oxacephem skeleton with controlling the stereochemistry. The synthetic route consists of allylic functionalization of azetidinone-epioxazoline 3 to allylic alcohol 4, its intramolecular stereospecific cyclization to 7α-benzoylamino-3-methylene-1-oxacepham 17, and its transformation to the desired compounds 1.

After all attempts were made unsuccessfully to obtain 4 directly by allylic oxidation of 3 prepared easily from 6-epipenicillin sulfoxide 2 (PPh_3, toluene/$(CH_2Cl)_2$, reflux; 80%),[3] we turned our attention to allylic halogenation. Reaction of 3 with N-bromosuccinimide (catalytic azobisisobutyronitrile, CCl_4, reflux) which has been well employed for allylic bromination in the β-lactam chemistry[4] gave allylic bromide 5[5] in only 14% yield accompanied by an isomeric mixture of conjugated compounds 6 (38%) and dibromide 7 (15%).[6] This first difficulty was solved by the finding that chlorine[7] (AcOEt, 20-30 °C) smoothly reacted with 3 to give azetidinone chloride 8 as a major product, which on subsequent base treatment (aqueous $NaHCO_3$, 20-30 °C) was transformed to the desired allylic chloride 9[3] in 75% yield[6] from 3. The by-products isolated[6] in this process were isomeric mixtures (each in ∿5% yield) of conjugated compounds 10, dichlorides 11, and β-lactones 12. This smooth allylic chlorination can be explained by assuming the ene-type reaction as illustrated in A which is supported by formation of the chloromethyl-deuterated product 9 from substrate 3 deuterated at olefinic methylene (C_4)[8] and by a large negative entropy of activation ($\Delta S^{\ddagger}$ = -52 eu) observed in a preliminary kinetic study.

The chloride 9 thus obtained was found to be poorly reactive and attempts to convert it directly into alcohol 4 failed. The first successful conversion of 9 into 4[9] was made in 58% overall yield[6] by a modification of Evans' three-step process[10] (PhSNa, PhSH, Me_2CO-MeOH, 35 °C;



1



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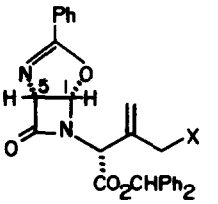
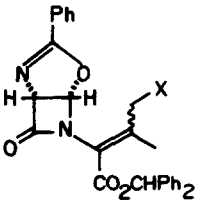


3, 4, 5, 9, 13, 14, 15, 16



6, 10

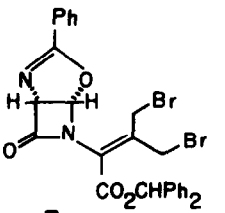
a. R^1 = HO-C$_6$H$_4$-CH(CO$_2$Na)CO- ; R^2 = Na; R^3 = STet

b. R^1 = PhCO; R^2 = $CHPh_2$; R^3 = Cl

c. R^1 = PhCO; R^2 = $CHPh_2$; R^3 = STet

d. R^1 = H; R^2 = $CHPh_2$; R^3 = STet

STet:



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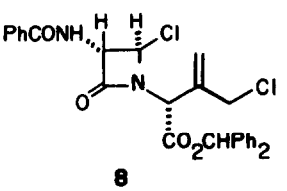

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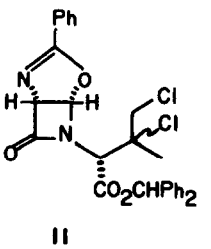

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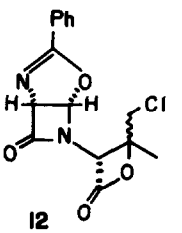
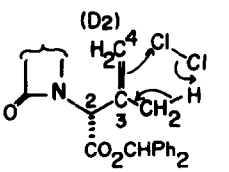
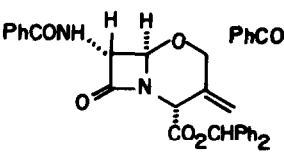


12



A



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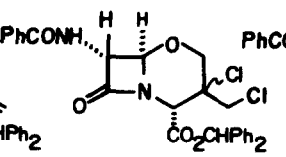

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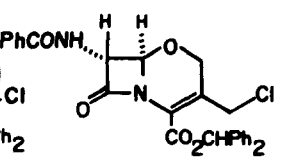

19

m-chloroperbenzoic acid, CH_2Cl_2, -10 °C; PPh_3, MeOH-C_6H_6, reflux) via 13 and 14. In search for more efficient processes, 9 was transformed (NaI, Me_2CO, 25 °C, ∿100%) to reactive iodide 15,[11] which without purification was converted into 4 by hydrolysis ($AgClO_4$, $CaCO_3$, aqueous Me_2CO, 25 °C) or by nitrate formation ($AgNO_3$, Me_2CO, 25 °C) to 16[12] followed by reduction (Zn, AcOH, CH_2Cl_2, 0 °C, ∿100%) in 74 or 85% yield,[6] respectively. Our attention was then focused to replace the silver salts by inexpensive reagents. We found that the hydrolysis of 15 to 4 (90%[6]) was effected with Cu_2O in Me_2SO-H_2O at 50-60 °C and the nitrate formation to 16 (88%) was successful with excess $NaNO_3$ and methyl p-toluenesulfonate (Me_2SO, 55 °C, 50 mm). In these new processes, Me_2SO is essential for effecting the conversions, probably forming a more reactive alkoxysulfonium intermediate.[13] The Cu_2O in the former process acts as the HI scavenger and as the iodide-activating agent. In the latter process, the methyl p-toluenesulfonate reacts with NaI, giving MeI which is removed by evacuation to shift the iodide-nitrate

equilibrium.

Intramolecular etherification of 4 (catalytic $BF_3 \cdot Et_2O$, AcOEt, 25 °C) proceeded smoothly and in a completely stereospecific manner to give exomethylene 17[14] (90%). Chlorination (Cl_2, hν, CH_2Cl_2, -20 °C) to dichloride 18 and subsequent elimination (1,5-diazabicyclo[4.3.0]non-5-ene, -20°C) gave 3-chloromethyl-1-oxa-3-cephem 19[15] (86%). Methoxylation[16] (t-BuOCl, LiOMe, CH_2Cl_2-MeOH, -30 °C; AcOH, -30 °C; aqueous $Na_2S_2O_3$, 10 °C) to 1b[17] followed by substitution (sodium 1-methyl-1H-tetrazole-5-thiolate, catalytic n-Bu_4NBr, CH_2Cl_2-H_2O, 25 °C) gave 7α-methoxy-1-oxacephem 1c[18] (90%).[6] The side-chain cleavage (PCl_5, pyridine, CH_2Cl_2, 25 °C; MeOH, 0 °C; Et_2NH, -15 °C) proceeded with little epimerization at C-7[2a] to give the 1-oxacephem nucleus 1d[2,19] (90%).

Acylation of 1d followed by deprotection and salt formation as reported from our laboratories[2] afford the new antibiotic 1a. Apparently, modifications at positions 3 and 7 starting from compounds 17, 19, 1b, and 1d give a variety of 7α-methoxy-1-oxacephem antibiotics 1, which will be the subjects of future publications.

It should be noted that highly crystalline compounds 16, 19, and 1d can be isolated by crystallization of crude reaction products to make chromatographic separation unnecessary in the preparation of 1a and that the present synthetic route can be started from other penicillin derivatives having a variety of the side chains and the ester protecting groups, the selection being the subject of the process research. In conclusion, this synthetic route provides a stereocontrolled, straightforward, and industrially feasible synthesis of the new antibiotic 1a starting from penicillins.[20]

Acknowledgment. We thank Drs. S. Kamata, I. Kikkawa, and T. Konoike and Messers M. Murakami, H. Itani, Y. Nishino, K. Nakano, T. Yorifuji, I. Yamada, S. Shinomoto, and S. Ando for doing related studies whose results are not disclosed herein.

References and Notes

(1) Synthetic Studies on β-Lactam Antibiotics. 17. Part 16: H. Onoue, M. Narisada, S. Uyeo, H. Matsumura, K. Okada, T. Yano, and W. Nagata, Tetrahedron Lett. 1979, 3867.

(2) (a) S. Uyeo, I. Kikkawa, Y. Hamashima, Y. Nishitani, H. Ona, K. Okada, T. Kubota, K. Ishikura, Y. Ide, K. Nakano, and W. Nagata, J. Am. Chem. Soc. 101, 4403 (1979). (b) M. Narisada, T. Yoshida, H. Onoue, M. Ohtani, T. Okada, T. Tsuji, I. Kikkawa, N. Haga, H. Satoh, H. Itani, and W. Nagata, J. Med. Chem. 22, 757 (1979). Compound 1a (code number: 6059-S) is now under clinical study.

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(4) (a) S. Wolfe, J. B. Ducep, K. C. Tin, and S. L. Lee, Can. J. Chem. 52, 3996 (1974). (b) J. A. Webber, G. W. Huffman, R. E. Koehler, C. F. Murphy, C. W. Ryan, E. M. Van Heyningen, and R. T. Vasileff, J. Med. Chem. 14, 113 (1971). (c) S. Nakatsuka, H. Tanino, and Y. Kishi, J. Am. Chem. Soc. 97, 5008 (1975).

(5) 5: foams; IR ($CHCl_3$) 1788, 1757, 1636 cm^{-1}; NMR ($CDCl_3$) δ 4.03 (s, 2, CH_2Br), 5.15 (s, 1, $>CHCO_2CHPh_2$), 5.27 and 5.58 (each s, 1, $=CH_2$), 5.33 and 6.00 (each d, 1, $J_{1,5}$ = 3.5 Hz, C_1 H and C_5 H), 6.90 (s, 1, $CHPh_2$), 7.1-8.0 (m, 15, ArH).

(6) The product(s) were separated or purified by chromatography (silica gel, C_6H_6-AcOEt), when necessary, followed by crystallization. The purification, though practically unnecessary in most cases, was made to know the yield(s).

(7) The chlorination was effected also with SO_2Cl_2 or $PhICl_2$, the yield of 9 being slightly inferior.

(8) Diphenylmethyl 2β-methyl-deuterated 6β-benzoylaminopenicillanate sulfoxide prepared by Cooper's method [R. D. Cooper, J. Am. Chem. Soc. 92, 5010 (1970)] was converted, after epimerization, into deuterated 3.

(9) Pure 4: mp 103-105 °C; $[\alpha]^{25}D$ -26.6° (c 1.047, $CHCl_3$); IR ($CHCl_3$) 3620, 3470, 1779, 1749, 1633 cm^{-1}; NMR ($CDCl_3$) δ 2.75 (br s, 1, OH), 4.15 (s, 2, CH_2OH), 5.03 (s, 1, $>CHCO_2CHPh_2$), 5.18 and 5.43 (each s, 1, $=CH_2$), 5.28 and 6.03 (each d, 1, $J_{1,5}$ = 3.5 Hz, C_1 H and C_5 H), 6.89 (s, 1, $CHPh_2$), 7.1-8.0 (m, 15, ArH).

(10) D. A. Evans, G. C. Andrews, Acc. Chem. Res. 7, 147 (1974) and references cited therein.

(11) Pure 15: mp 95-96 °C; $[\alpha]^{25}D$ -36.5° (c 0.989, $CHCl_3$); IR ($CHCl_3$) 1782, 1750, 1633 cm^{-1}; NMR ($CDCl_3$) δ 3.97 (s, 2, CH_2I), 5.15 (s, 1, $>CHCO_2CHPh_2$), 5.15 and 5.59 (each s, 1, $=CH_2$), 5.32 and 5.96 (each d, 1, $J_{1,5}$ = 3 Hz, C_1 H and C_5 H), 6.88 (s, 1, $CHPh_2$), 7.1-8.1 (m, 15, ArH).

(12) Pure 16: mp 138-140 °C; IR ($CHCl_3$) 1786, 1751, 1640 cm^{-1}; NMR ($CDCl_3$) δ 5.03 (s, 3, CH_2ONO_2 and $>CHCO_2CHPh_2$), 5.32 and 6.00 (each d, 1, $J_{1,5}$ = 3.5 Hz, C_1 H and C_5 H), 5.43 and 5.58 (each br s, 1, $=CH_2$), 6.90 (s, 1, $CHPh_2$), 7.2-8.0 (m, 15, ArH).

(13) C. F. Murphy, and J. A. Webber, In "Cephalosporins and Penicillins, Chemistry and Biology", E. D. Flynn, Ed.; Academic: New York, 1972; p 170.

(14) Pure 17: mp 167-169.5 °C; $[\alpha]^{25}D$ -47.2° (c 0.974, $CHCl_3$); IR ($CHCl_3$) 3452, 1774, 1746, 1678 cm^{-1}; NMR ($CDCl_3$) δ 4.19 (s, 2, C_2 methylene), 4.99 (d, 1, J = 8 Hz, C_7 H), 5.17 (s, 1, C_4 H), 5.28 (s, 2, 3'-methylene), 5.33 (s, 1, C_6 H), 6.85 (s, 1, $CHPh_2$) 7.1-8.0 (m, 16, NH and ArH). The NMR pattern at δ 5.17-5.33 varies with the sample concentration.

(15) Pure 19: mp 132-134 °C; IR ($CHCl_3$) 3375, 1790, 1728, 1670 cm^{-1}; NMR ($CDCl_3$) δ 4.35 and 4.48 (each s, 2, CH_2Cl and C_2 methylene), 4.98 (s, 1, C_6 H), 5.02 (d, 1, J = 6 Hz, C_7 H), 6.90 (s, 1, $CHPh_2$), 7.1-8.0 (m, 16, NH and ArH).

(16) G. A. Koppel, and R. E. Koehler, Tetrahedron Lett. 1973, 1943.

(17) 1b: foams; IR ($CHCl_3$) 3430, 1787, 1728, 1682 cm^{-1}; NMR ($CDCl_3$) δ 3.63 (s, 3, OCH_3), 4.50 and 4.55 (each s, 2, CH_2Cl and C_2 methylene), 5.25 (s, 1, C_6 H), 7.00 (s, 1, $CHPh_2$), 7.1-8.0 (m, 16, NH and ArH).

(18) Pure 1c: mp 101-103 °C (from C_6H_6-Et_2O; it has about 0.8 molar equiv of crystallization benzene); $[\alpha]^{25}D$ -80.3° (c 1.032, $CHCl_3$); IR ($CHCl_3$) 3440, 1788, 1721, 1690 cm^{-1}; NMR ($CDCl_3$) δ 3.62 (s, 3, OCH_3), 3.77 (s, 3, $N-CH_3$), 4.26 and 4.63 (each s, 2, CH_2STet and C_2 methylene), 5.18 (s, 1, C_6 H), 6.93 (s, 1, $CHPh_2$), 7.03 (s, 1, NH), 7.1-8.0 (m, 20, ArH including 0.8 C_6H_6).

(19) Pure 1d: mp 167-168 °C; $[\alpha]^{23}D$ -202.8° (c 0.988, $CHCl_3$). For spectral data see ref 2b.

(20) The structure assignments of new compounds whose physical data are not given are supported by their IR and NMR data. Correct combustion analyses were obtained for all the crystalline compounds whose melting points (uncorrected) were given.

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