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TOTAL SYNTHESIS OF β-LACTAM ANTIBIOTICS IX
(±)-1-OXABISNORPENICILLIN G

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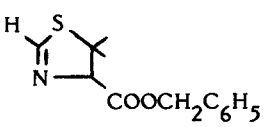
In 1974 we reported on the total synthesis of (±)-1-oxacephalothin[1] in which the sulfur atom of a cephalosporin antibiotic was replaced by an oxygen atom. Since this replacement resulted in enhancement of antibiotic activity, we were encouraged to effect the same transformation with a penicillin. A recent report[2] on the synthesis of 1-oxapenicillin and its bisnor derivative[3] prompts us to report our synthesis of 1-oxabisnorpenicillin G (**13**), which involves a considerably different chemical approach, and the use of a novel intramolecular cyclization to synthesize the oxazolidine ring.[4] This scheme represents the first total synthesis of a penicillin analog utilizing a C-3 to N closure.

Treatment of benzyl 2-thiazoline-5,5-dimethyl-4-carboxylate (**1**)[5] with NaH (2 eq) in THF (0°, N_2 atmos., 1 hr) followed by MeI (1.1 eq, 0°, 3 hrs) gave benzyl 1-methyl-1-thioimidato-3-methyl-1-butenoate, **2**: IR[6] 1724 (ester), 1574 (C=N); NMR[6] 1.82 (s, H-C=N), 2.55 (s, C_6H_5), 4.79 (s, CH_2-C_6H_5), 7.63 (s, CH_3-S), 8.06 (s, propenyl methyl), 95% yield. Addition of a CH_2Cl_2 solution of azidoacetyl chloride (1.1 eq) to a solution of **2** and Et_3N (1.1 eq) at 0° over 3 hrs gave trans 1-(1-benzyloxycarbonyl-2-methyl-1-propenyl)-3-azido-4-methythio-2-azetidinone **3**[7]: IR 2120 (N_3), 1780 (β-lactam), 1724 (ester), 1640 (C=C); NMR 2.65 (C_6H_5), 4.76 (ABq, CH_2-C_6H_5), 5.16 (d, J = 2, C-3 H), 5.6 (d, J = 2, C-4 H), 7.73 (s, S-CH_3), 8.02 (s, propenyl methyl), in 65% yield. Azetidinone **3** was quantitatively converted to a mixture of cis and trans chloro-azetidinones **4** by treatment with 1.5 eq of Cl_2 in CCl_4 at RT for 1 min, IR 2120 (N_3), 1800 (β-lactam), 1730 (ester), 1640 (C=C); NMR 4.02 (d, J = 4, cis C-4 H), 4.34 (d, J = 2, trans C-4 H), 5.32 (cis and trans C-3 H).

The chloroazetidinone mixture **4** was treated with benzyl N-t-butyloxycarbonyl-serine[8] (2 eq) and $AgOSO_2CF_3$ (1.2 eq) in a minimum amount of CH_2Cl_2 (RT, 20 min) to give, after silica gel chromatography (12% EtOAc/C_6H_6), a mixture of cis and trans 1-(1-benzyloxycarbonyl-2-methylprop-1-enyl)-3-azido-4-(2-t-butyloxycarbonylamino-2-benzyloxycarbonyl)-ethoxy-2-azetidinone **5**: IR 2120 (N_3), 1780 (β-lactam), 1740-1724 (ester and carbamate), 1640 (C=C); 65% yield based on **4** consumed (33% conversion).

Oxidation of **5** ($KMnO_4$, 2 eq, aqueous acetone, pH 7 phosphate buffer, 20 min, RT) resulted in removal of the nitrogen substituent to give a mixture of epimeric cis-azetidinones **6**: IR 3330 (NH), 2120 (N_3), 1780 (β-lactam), 1750 (carbamate); NMR 4.43 (d, NH of carbamate), 4.93 and 5.0 (C-4 H, 2 epimers, J = 2.5), 5.46 (NH-CH-COO, 2 triplets), 5.7 and 5.76 (3-H, 2 epimers), 6.03 (t, OCH_2-CH), 8.56 (t-butyl), 22%: and epimeric trans azetidinones **7**: IR 3365 (NH), 2130 (N_3), 1780 (β-lactam), 1750 (ester), 1710 (carbamate); NMR 4.5 (d, NH of carbamate), 5.3 and 5.36 (C-4 H, J = 1.5, 2 epimers), 5.53 (NH-CH-COO-, 2 triplets), 5.73 and 5.87 (C-3 H, J = 1.5, 2 epimers), 6.16 (O-CH_2-CH), 8.6 (s, t-butyl) 37%. Stereochemistry at the β-lactam was assigned on the basis of NMR splitting constants for C-3 and C-4 hydrogens (J = 1.5 Hz for trans and J = 2.5 Hz for cis).



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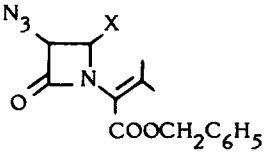
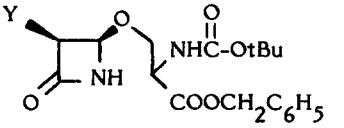
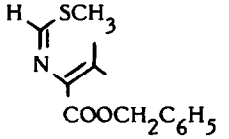


3, X = trans SCH_3
4, X = cis-trans Cl
5, X = cis-trans



6, Y = N_3
7, trans **6**
8, Y = NH_2
9, Y = $C_6H_5CH_2CNH$ (=O)



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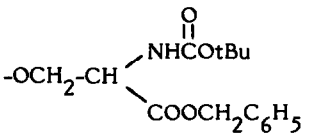
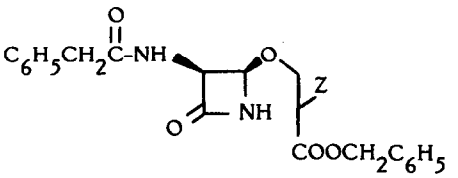
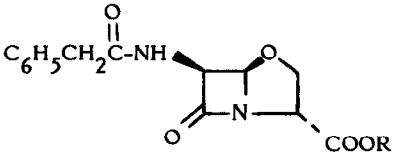


6 dissolved in CH_2Cl_2, cooled to 0°, and treated with 2 eq of Et_3N and H_2S gas (bubbled for 5 min at 0° and 1/2 hr without ice-bath, when IR showed absence of azide) gave the mixture of cis-3-amino derivatives **8** (epimeric mixture at serine tertiary C). **8** was acylated with phenylacetyl chloride, 1.1 eq (CH_2Cl_2, 0°, pyridine 1.6 eq) to give the crude phenyl acetamido derivatives **9**. A crystalline isomer of **9** was obtained from hot ethyl acetate in 42% yield (from **6**): IR 3390 (NH), 1780 (β-lactam), 1750 (ester), 1720 (carbamate), 1680 (amide); NMR ($CDCl_3$, D_2O) 2.65 and 2.72 (C_6H_5); 4.70 (d, J = 4, C-3 H), 4.8 (s, C_6H_5-CH_2-CO), 5.12 (d, J = 4, C-4 H), 5.56 (m, NH-CH-COO), 6.25 (m, O-CH_2-CH), 6.46 (s, C_6H_5-CH_2-CO), 8.55 (s, Me_3C). Purification of the mother liquors by preparative TLC gave 40% of an oily isomer, IR 3424 (NH), 1785 (β-lactam), 1718 (carbamate), 1680 (amide); NMR ($CDCl_3$, D_2O): 2.73 and 2.79 (C_6H_5), 4.73 (d, J = 4, C3 H), 4.85 (s, $C_6H_5CH_2O$), 5.12 (d, J = 4, C-4 H), 5.6 (m, NH-CH-COO), 6.26 (m, O-CH_2-CH), 8.58 (s, Me_3C). The crystalline or oily **9** when treated with trifluoroacetic acid at 0°, 4 min, evaporated under reduced pressure and extracted into CH_2Cl_2 from excess 5% $NaHCO_3$ solution gave cis-3-phenylacetamido-4-(2-diazo-2-benzyloxycarbonylethoxy)-2-azetidinone (**10**). IR 3225 (NH), 1780 (β-lactam), 1740 (ester), 1665 (amide), 1525 (amide II). **10** from crystalline or oily **9** without purification was diazotized (CH_2Cl_2, H_2O, 0°, $NaNO_2$ equal wt. p-TSA, 0.2 eq, 40 min) to give cis-3-phenylacetamido-4-(2-diazo-2-benzyloxycarbonylethoxy)-2-azetidinone **11**, 50%, after preparative TLC on silica gel, 50% EtOAc/C_6H_6, IR 3225 (NH), 2110 (diazo), 1780 (β-lactam), 1670 and 1660 (ester and amide); NMR 2.72 and 2.80 (C_6H_5). 2.93 (β-lactam NH), 3.56 (d, J = 8, amide NH), 4.7 (d of d, J = 9, J = 4, C-3 H), 4.83 (s, C_6H_5-CH_2-O), 4.92 (d, J = 4, C-4 H), 5.7 (s, O-CH_2-C), 6.45 (s, $C_6H_5CH_2$-CO).

Cyclization to the 1-oxapenam nucleus was achieved by a novel intramolecular insertion of the carbenoid species derived from the diazo compound **11** into the N-H bond of the β-lactam. Though intermolecular insertion of the carbenoid derived from diazoesters are known,[9,10] to our knowledge this is the first intramolecular version of this reaction. Treatment of **11** with catalytic amounts of rhodium acetate (1% by wt)[11] in C_6H_6 at RT for 3 hrs gave, after preparative TLC on silica gel 50% EtOAc/C_6H_6, the less polar benzyl 6β-phenylacetamido-1-oxabisnorpenicillinate (**12a**) 10%. IR 3335 (NH), 1810 (β-lactam), 1750 (ester), 1675 (amide); NMR ($CDCl_3$) (HA 100): 2.69 and 2.74 (s, C_6H_5), 4.14 (d, J = 9, NH), 4.45 (d of d, J = 9, J = 3, C-6 H), 4.74 (d, J = 3, C-5 H), 4.84 (s, O-$CH_2C_6H_5$), 5.44 (d of d, J = 6.3, J = 7.6, C-3 H), 5.68 and 5.94 (d of d each, J_{gem} = 8.2, C-2 H), 6.4 (s, $C_6H_5\underline{CH_2}$-C=O); m/e 380; and its C-3 epimer **12b**, 4.5%. IR 3335 (NH), 1810 (β-lactam), 1750 (ester), 1675 (amide); NMR ($CDCl_3$, HA 100): 2.72 and 2.81 (C_6H_5), 4.08 (d, J = 9, NH), 4.58 (d of d, J = 9, J = 3, C-6 H), 4.98 (s, $C_6H_5\underline{CH_2}O$), 4.91 (d, J = 3, C-5 H), 5.91 (d of d, J = 6.5, J = 4.5, C-3 H), 5.71 and 5.99 (d of d each, J_{gem} = 11.5), 6.51 (s, $C_6H_5\underline{CH_2}CO$). Stereochemistry at C-3 for **12a** and **12b** is assigned from the NMR shift of the C-3 proton, which in the desired epimer **12a** appears at lower field 5.44 versus 5.91 for **12b**. This is in agreement with the general observation that in penicillins[12] as well as 1-oxapenicillins[13] the C-3 epimer with the lower field C-3 H has the desired (natural) stereochemistry.





10, Z = $\overset{H}{\underset{\sim}{}}NH_2$

11, Z = N_2

12a, R = $CH_2C_6H_5$

12b, C-3 epimer of **12a**

13, R = Na

Hydrogenolysis of **12a** (H_2, 40 lbs, dioxane, water, 1 eq $NaHCO_3$, 10% Pd/C) gave sodium 6β-phenylacetamido 1-oxabisnorpenicillinate, IR: 3335 (NH), 1805 (β-lactam), 1665 (amide), 1610 (COO^-). The compound showed activite (agar plate assay) against B. subtilis and P. vulgaris which was much lower than that of Penicillin G or bisnorpenicillin G.[12] Compound **13** showed limited stability in aqueous solution at 37°.

References

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2. R. G. Alexander and R. Southgate, J. Chem. Soc. Chem. Comm., 405 (1977).
3. Reference 2 mentions the synthesis of benzyl 6β-phenoxyacetamido 1-oxadethiapenam-3-carboxylate but does not describe the stereochemistry at 3 or its conversion to the free acid.
4. Reported initially, L. D. Cama, R. A. Firestone and B. G. Christensen, 10th ACS Middle Atlantic Regional Meeting, Philadelphia, Pennsylvania, 1976.

5. I was made following the procedure (for the corresponding methyl ester) of M. R. Bell, J. A. Carlson and R. Oesterlin, J. Amer. Chem. Soc., **92**, 2177 (1970) with minor modifications, TFA reflux 5 min, followed by removal of TFA by distillation under reduced pressure, and treatment of the residue with NH_3 as described therein.
6. IR spectra were run as thin film and are reported in cm^{-1}; NMR spectra, unless otherwise specified, were run in $CDCl_3$ on a Varian T-60 instrument and are reported to τ.
7. We thank Dr. R. Ratcliffe of Merck Sharp & Dohme Research Laboratoreis for providing us with the conditions of converting $1 \rightarrow 2 \rightarrow 3$ and for helpful discussions in the course of this work.
8. Benzyl N-t-butyloxycarbonylserine, m.p. 75-77°, was prepared as follows: Treatment of serine with t-butyloxycarbonyl azide (dioxane, water, pH 9, 50°, 3 hrs) to give the N-t-butyloxycarbonyl serine, the sodium salt of which was treated with benzyl bromide in DMF, 18 hrs, RT, to give the product.
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