Tetrahedron Letters,Vol.25,No.6,pp 595-598,1984
Printed in Great Britain

0040-4039/84 $3.00 + .00

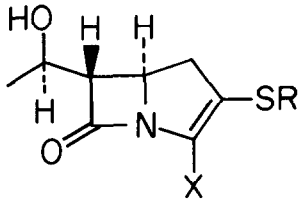
SYNTHESIS OF 3-METHYLPHOSPHONYL THIENAMYCIN AND RELATED 3-PHOSPHONYL CARBAPENEMS

Alex Andrus,* B. G. Christensen and James V. Heck

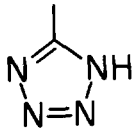
Merck Sharp & Dohme Research Laboratories, Rahway, New Jersey 07065

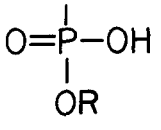
Summary: The synthesis and some biological properties of the title compounds, beta-lactam antibiotic analogs, are described.

The discovery of the carbapenem family of highly potent antibacterial agents, exemplified by thienamycin,[1] has prompted research in a number of laboratories directed toward the synthesis of analogs with optimized pharmacological properties.[2] We have recently described the synthesis of some 3-(5-tetrazolyl), carboxyl-replaced analogs of carbapenems **2**,[3] which are stable to renal dehydropeptidase (DHP-I), an enzyme responsible for the metabolic inactivation of carbapenems in vivo.[4] Herein we describe the synthesis and biological activity of a series of 3-phosphonate carbapenem, carboxyl-replaced analogs **3**.[5]

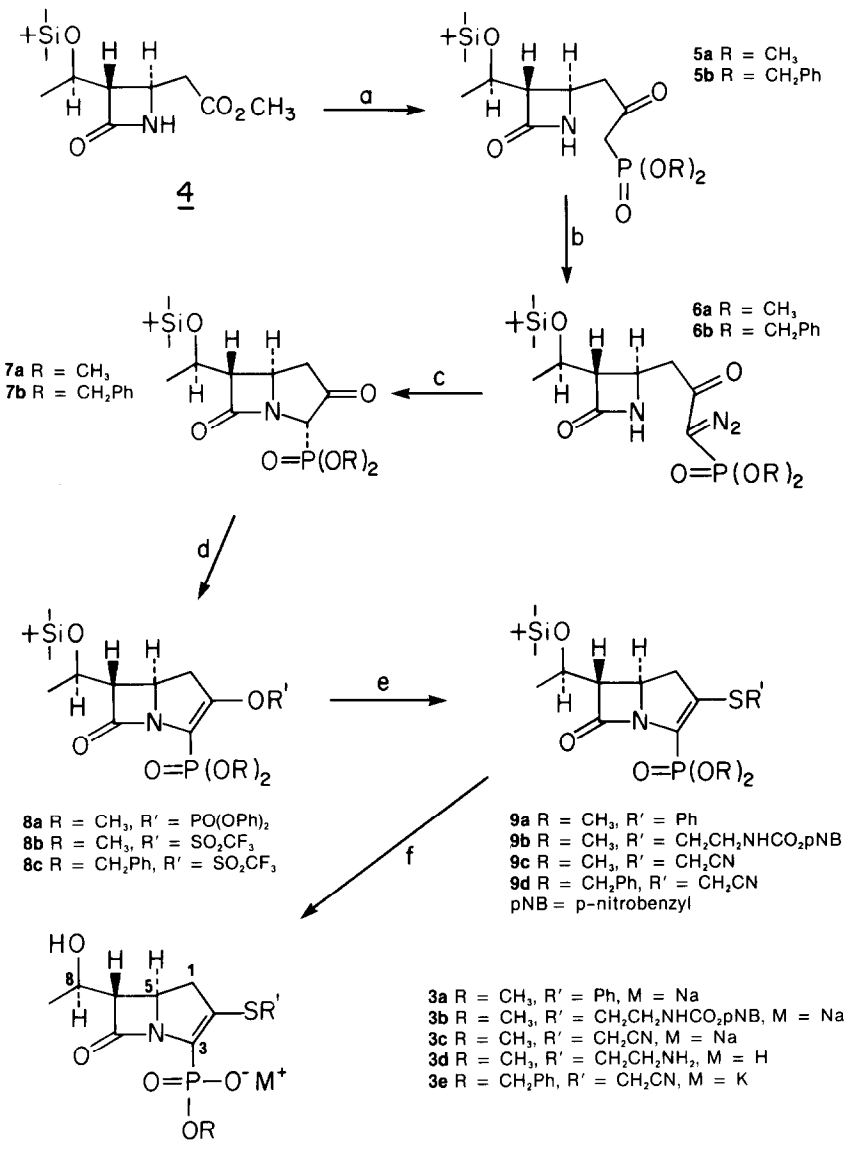


1 X = CO_2H, $R = CH_2CH_2NH_2$

2 X = 

3 X = 

The methyl phosphonyl group (**3**, R = CH_3) was chosen due to its proven utility as a carboxyl mimic.[6] A chiral azetidinone intermediate **4**[7] possessing all three asymmetric centers in the correct configuration, was exposed to three equivalents of lithium methyldimethylphosphonate[8] affording the keto-phosphonate **5a**.[9] The azetidinone ring is protected from nucleophilic attack by deprotonation of the nitrogen by the excess reagent. This first reaction is the only carbon-carbon bond formation required in the sequence.



a) **4** ⟶ **5a**: nBuLi, $CH_3PO(OCH_3)_2$, THF, -78°, then **4**; 70%
4 ⟶ **5b**: nBuLi, $CH_3PO(OCH_2Ph)_2$, THF, -78°, then **4**; 53%

b) **5a, 5b** ⟶ **6a,6b**: $p(C_{12}H_{25})C_6H_4SO_2N_3$,DBU,$CH_2Cl_2$; **6a** 66%, **6b** 71%

c) **6a, 6b** ⟶ **7a, 7b**: $Rh_2(OAc)_4$,CH_2Cl_2; **7a** 74%, **7b** 74%

d) **7a** ⟶ **8a**: $ClPO(OPh)_2$,DBU,CH_3CN, -15°
7a,7b ⟶ **8b,8c**: $PhN(SO_2Ct_3)_2$, DBU,THF, -15°; or $(CF_3SO_2)_2O$, DBU,THF, -78°

e) **8b** ⟶ **9a**: HSPh,Et_3N; 24% from **7a**
8b ⟶ **9b**: $HSCH_2CH_2NHCO_2pNB$, Et_3N; 19% from **7a**
8b,8c ⟶ **9c,9d**: NaHS,iPr_2NEt,DMF, 0°, then $ClCH_2CN$, iPr_2NEt; **9c** 26% from **7a**, **9d** 26% from **8c**

f) **9a-c** ⟶ **3a-c**: nBu_4NF,AcOH,THF, then NaI, acetone; **3a** 40%, **3b** 33%, **3c** 9%
3b,9d ⟶ **3d,3e**: H_2, 10% Pd/C, EtOH,THF, 0.1m potassium phosphate pH7 buffer; **3d** 90%, **3e** 55%

The synthetic route from **5a** closely follows the Merck carbapenem process.[10] Diazo-transfer proceeded rapidly with p-dodecylbenzenesulfonylazide[11] and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as base. Refluxing **6a** with a catalytic amount of rhodium acetate dimer[12] in dichloromethane gave pure **7a** after simple filtration. Only one diastereomer at position 3 was formed and, by analogy with the tetrazole[3] and carboxylate ester analogs,[6] the phosphonyl group was assumed to be in the α position. Activation of position 2 for the introduction of the thioether side chain was accomplished by conversion of **7a** to the enol-phosphate **8a**. However, no reaction was observed upon exposure of **8a** to benzenethiol and triethylamine in acetonitrile. As we had previously observed in the tetrazolyl series,[3] the enol-triflate[13] proved a more reactive electrophile toward thiols. Treatment of **8a** with DBU and freshly distilled trifluoromethanesulfonic anhydride, followed by exposure with benzenethiol or N-p-nitrobenzyloxy-carbonylcysteamine gave **9a** and **9b**, respectively. Addition of sodium hydrogen sulfide to the triflate solution followed by alkylation of the intermediate thioenolate with chloroacetonitrile, provided **9c**. For this purpose, a superior triflating reagent was N-phenyltrifluoromethanesulfonimide [$PhN(SO_2CF_3)_2$], a stable, crystalline solid.[14] This reagent effected triflation at a rate comparable to trifluoromethanesulfonic anhydride, and unlike the anhydride, does not cause polymerization of the tetrahydrofuran solvent. After desilylation, **9a-c** were mono-demethylated with several equivalents of sodium iodide in acetone at reflux. Products **3a-c** were isolated by reverse-phase preparative thin-layer chromatography of the evaporated reaction mixture. Hydrogenation of **3b** gave 3-methylphosphonyl thienamycin **3d**. A benzyl phosphonyl derivative **3e** was synthesized by the same procedures used for **3c**, starting from lithium methyldibenzylphosphonate and **4**. Hydrogenolysis of **9d** gave **3e**, with no detectable amount of the diacid phosphonate **3** ($R' = CH_2CN$, $R = H$).

The 3-phosphonyl carbapenems **3a**, **3c-e** were stable to DHP-I by an in vitro enzyme assay. However, their antibacterial activity was considerably diminished relative to the 3-carboxyl and 3-(5-tetrazolyl) carbapenems.

Acknowledgment. We thank Jean Kahan for antimicrobial assays and Helmut Kropp for DHP-I susceptibility measurements.

References and Notes

1) R. W. Ratcliffe and G. Albers-Schonberg in Chemistry and Biology of Beta-Lactam Antibiotics, R. B. Morin and M. Gorman, eds., Academic Press, Vol 2, 227 (1982).

2) G. Albers-Schönberg, B. H. Arison, O. D. Hensens, J. Hirshfield, K. Hoogsteen, E. A. Kaczka, R. E. Rhodes, J. S. Kahan, F. M. Kahan, R. W. Ratcliffe, E. Walton, L. J. Ruswinkle, R. B. Morin and B. G. Christensen, J. Amer. Chem. Soc., **100**, 6491 (1978).

3) A. Andrus, J. Heck, B. G. Christensen and B. Partridge, in press.

4) H. Kropp, J. G. Sundelof, R. Hajdu and F. M. Kahan, Antimicrob. Ag. Chemother., **22**, 62 (1982); N. Shibamoto, M. Sakamoto, H. Iguchi, H. Tone, Y. Fukugawa and T. Ishikura, J. Antibiotics, **35**, 721 (1982).

5) After we had prepared **3a**, a report appeared[5a] on the synthesis and antibacterial inactivity of several non-sulfur containing beta-lactam phosphonic acid derivatives. Some chemistry claimed therein not to be successful is shown to be useful here.

5a) C.-P. Mak, C. Mayerl and H. Fliri, Tetrahedron Letters, **24**, 347 (1983).

6) W. H. Koster, R. Zahler, H. W. Chang, C. M. Cimarusti, G. A. Jacobs and M. Ferri, J. Amer. Chem. Soc., **105**, 3743 (1983); Pfizer Inc., Belgium Patent, BE 846755 (1977); B. G. Christensen and R. W. Ratcliffe, Ann. Reports in Med. Chem., **11**, 272 (1976); G. M. Hakimelahi and G. Just, Helv. Chim. Acta, **65**, 1359 (1982).

7) T. M. H. Liu, D. G. Melillo, K. M. Ryan, I. Shinkai and M. Sletzinger, U. S. Patent 4,349,687, Merck & Co. (1982).

8) E. J. Corey and G. T. Kwiatkowski, J. Amer. Chem. Soc., **88**, 5654 (1966).

9) All compounds are chiral with the configuration as depicted. Assigned structures are fully supported by IR, 1H NMR (200 MHz), mass spectoscopy and C, H, N analysis. Yields refer to isolated, chromatographically pure compounds. Selected physical data: **5a**: mp 136°, IR ($CHCl_3$) 3410, 1755, 1715 cm^{-1}, ^1H NMR ($CDCl_3$) δ 6.06 (1 H, br s), 4.18 (1 H, m), 3.98 (1 H, m), 3.77 (6 H, d, J_{HP} = 10), 3.12 (2 H, d, J_{HP} = 22), 2.8 (3 H, m), 1.20 (3 H, d, J = 6), 0.87 (9 H, s), 0.07 (6 H, s); MS: 393 (M^+), 336, 293, 292. Anal Calcd: C, 48.84; H, 8.20; N, 3.56. Found: C, 48.81; H, 8.23; N, 3.48. $[\alpha]_D^{25}$ = +18.4° (c = 1, CH_3OH). **6a**: IR ($CHCl_3$) 3410, 2120, 1755, 1645 cm^{-1}, ^1H NMR ($CDCl_3$) δ 6.10 (1 H, br s), 4.21 (1H, dq, J = 5, 6), 4.02 (1 H, ddd, J = 2.5, 3.5, 9.5), 3.88 (6 H, d, J = 13), 3.08 (1 H, dd, J = 3.5, 17.5), 2.85 (1 H, dd, J = 2.5, 5), 2.74 (1 H, dd, J = 9.5, 17.5), 1.24 (3 H, d, J = 6), 0.88 (9 H, s), 0.08 (6 H, s). **7a**: mp 124-25°, IR ($CHCl_3$) 1760 cm^{-1}, ^1H NMR ($CDCl_3$) δ 4.47 (1 H, d, J_{HP} = 18.5), 4.32 (1 H, dq, J = 5, 6), 4.19 (1 H, ddd, J = 2, 7, 7.5), 3.88 (3 H, d, J = 11), 3.85 (3 H, d, J = 11), 3.14 (1 H, dd, J = 2, 5), 2.93 (1 H, dd, J = 7.5, 19), 2.39 (1 H, dd, J = 7, 19), 1.28 (1 H, d, J = 6), 0.90 (9 H, s), 0.08 (6 H, s); $[\alpha]_D^{25}$ = +54.8° (c = 1, $CHCl_3$). **7b**: IR ($CHCl_3$) 1770, 1260 cm^{-1}, ^1H NMR ($CDCl_3$) δ 7.40 (10 H, br s), 5.10 (4 H, m), 4.48 (1 H, d, J_{HP} = 18.5), 4.16 (1 H, m), 4.07 (1 H, dt, J = 2, 7), 3.11 (1 H, dd, J = 2, 5.5), 2.81 (1 H, dd, J = 7, 19.5), 2.37 (1 H, dd, J = 7, 19.5), 1.25 (3 H, d, J = 6), 0.86 (9 H, s), 0.07 (3 H, s). **9b**: IR ($CHCl_3$) 1783, 1720 cm^{-1}, ^1H NMR ($CDCl_3$) δ 8.26 (2 H, d, J = 8), 7.56 (2 H, d, J = 8), 6.80 (1 H, br, N-H), 5.22 (2 H, s), 4.26 (2 H, m), 3.91 (3 H, d, J = 11), 3.89 (3 H, d, J = 11), 3.56 (2 H, m), 2.76, -3.36 (5 H, m), 1.24 (3 H, d, J = 6), 0.88 (9 H, s), 0.07 (3 H, s), 0.06 (3 H, s); UV (dioxane) λ_{max} 280 nm. **3d**: ^1H NMR (D_2O) δ 4.2 (2 H, m), 3.58 (3 H, d, J = 11), 3.41 (1 H, dd, J = 2, 6), 2.9-3.15 (m, 6 H), 1.25 (3 H, d, J = 6); UV λ_{max} (H_2O) 282 nm. **3a**: ^1H NMR (D_2O) δ 7.6 (2 H, m), 7.5 (3 H, m), 4.22 (1 H, dq, J = 5.5, 6), 4.16 (1 H, dt, J = 2.5, 9), 3.68 (3 H, d, J_{HP} = 12), 3.15 (1 H, dd, J = 2.5, 5.5), 2.76 (2 H, m), 1.23 (3 H, d, J = 6), UV λ_{max} (H_2O) 290 nm. **3c**: ^1H NMR (D_2O) δ 4.3 (2 H, m), 3.87 (2 H, AB, quartet, J = 17.5), 3.60 (3 H, d, J_{HP} = 11), 3.49 (1 H, dd, J = 2.5, 5.5), 3.35 (1 H, ddd, J = 1.5, 10, 17.5), 3.19 (1 H, ddd, J = 4, 9, 17.5), 1.32 (3 H, d, J = 6.5); UV λ_{max} (H_2O) 284 nm. **3e**: ^1H NMR (D_2O) δ 7.40 (5 H, br s), 4.95 (2 H, d, J_{HP} = 9), 4.10 (2 H, m), 3.80 (1 H, d, J = 17), 3.69 (1 H, d, J = 17), 3.33 (1 H, dd, J = 2.5, 6); UV λ_{max} (H_2O) 285 nm.

10) T. N. Salzmann, R. W. Ratcliffe, B. G. Christensen and F. A. Bouffard, J. Amer. Chem. Soc., **102**, 6163 (1980).

11) G. G. Hazen, L. M. Weinstock, R. Connell and F. W. Bollinger, Syn. Comm., **11**, 947 (1981).

12) R. W. Ratcliffe, T. N. Salzmann and B. G. Christensen, Tetrahedron Letters, **21**, 31 (1980).

13) M. Sletzinger, T. Liu, R. A. Reamer and I. Shinkai, Tetrahedron Letters, **21**, 4221 (1980).

14) J. McMurry and W. J. Scott, Tetrahedron Letters, **24**, 979 (1983).

(Received in USA 7 November 1983)