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SYNTHETIC STUDY OF CARBAPENEM ANTIBIOTICS I. (±)-2-CYCLOPROPYL-6-(1'-HYDROXYETHYL)-1-CARBAPEN-2-EM-3-CARBOXYLIC ACID

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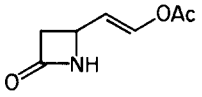
A synthetic scheme extensively utilizing silylation-desilylation reactions to achieve the total synthesis of 2,6-substituted carbapenem antibiotics from readily available azetidinones is reported. An epimeric pair of new 2,6-substituted carbapenems, (±)-2-cyclopropyl-6-(1'-hydroxyethyl)-1-carbapen-2-em-3-carboxylic acids were synthesized.

Descysteaminylthienamcyin,[1] the first analog of thienamycin in which the cysteamine side chain was replaced, was shown to retain most of the antibacterial activity of the parent including activity against Pseudomonas sp. However, this change destabilized the carbapenem ring system both chemically and metabolically. A synthetic scheme which allows one to prepare a variety of 2,6-substituted carbapenems[2] is essential in the study of structure-activity relationships of side chain replacement analogs of thienamycin. We now wish to report a general synthesis of 2,6-substituted carbapenems via extensive utilization of selective silylation and desilylation reactions. The functionalization of the carbapenem ring system is achieved from readily available azetidinone building blocks such as **1** to **3** prepared from reaction of chlorosulfonylisocyanate with olefins.[3]



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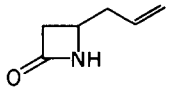

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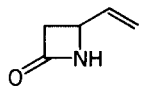

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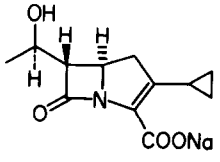
This synthetic scheme is demonstrated by the preparation of racemic epimers of 2-cyclopropyl-6-(1'-hydroxyethyl)carbapenems **4** and **5** from 4-(2'-acetoxyvinyl)azetidinone **1.**



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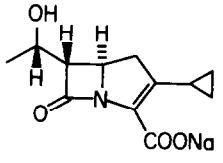

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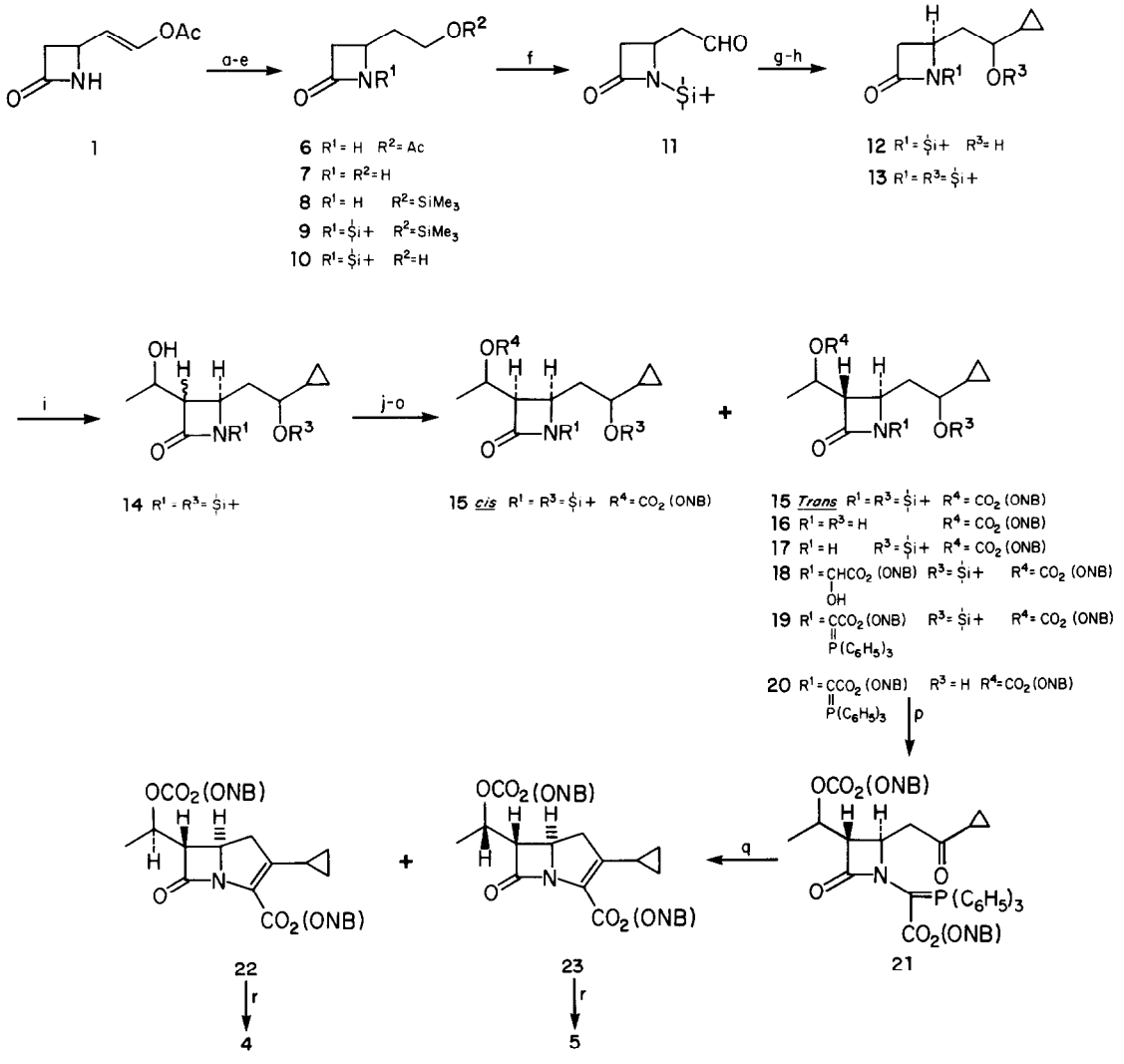
Catalytic hydrogenation of 4-(2'-acetoxyvinyl)azetidinone **1** provided a quantitative yield of 4-(2'-acetoxyethyl)azetidinone **6**, which upon deacetylation gave hydroxy azetidinone **7** as a crystalline solid. Treatment of **7** with trimethylchlorosilane/hexamethyldisilazane in THF gave O-trimethylsilyl azetidinone **8.**[4] The crude product **8** was isolated as oil by filtering off ammonium chloride and subsequent removal of THF in vacuo. Without further purification, intermediate **8** was dissolved in DMF and was treated with t-butyldimethylchlorosilane/triethylamine at room temperature to give N-(t-butyldimethylsilyl)-O-tri-methyl-silyl azetidinone **9.** Selective desilylation of **9** by exposure to 30% aqueous acetic acid in methanol at room temperature gave the desired N-(t-butyldimethylsilyl)-4-(2'-hydroxyethyl)azetidinone **10** which was isolated as an oil.



(a) H_2, 10% Pd/C, EtOAc, 3 hr., 100 %; (b) NaOMe/MeOH, 0°C, 1 hr. 90%; (c) $Me_3SiCl/(Me_3Si)_2NH/THF$; (d) $ClSi+/Et_3N/DMF$; (e) 30% AcOH/H_2O in MeOH, 0.5 hr., 52% from 12; (f) $CrO_3 \cdot Py_2/CH_2Cl_2$, 0°C 0.5hr. 44%; (g) ▷-MgBr/THF-ether, 85% (h) $ClSi+/Et_3N/DMF$, 6 hrs. 90%; (i) LDA/CH_3CHO/THF, -78, 70 %; (j) $ClCO_2(ONB)/Me_2N$-(4-pyridyl) / CH_2Cl_2, 1.5 hrs. 60% HPLC separation, (k) 2.5 N HCl/MeOH, 90%; (l) $ClSi+$/imidazole/DMF; (m) $OHCCO_2(ONB)$/benzene, $-H_2O$, 8 hrs. 95%; (n) $SO_2Cl/Py/THF$ then $P(C_6H_5)_3$/DMF, 5 hrs. 50%; (o) Conc. HCl/THF, 10 min. 100%; (p) Jones reagent, 15 min., 100%; (q) Refluxing xylene, TLC separation of epimers, 50% EtOAc/cyclohexane, 50%; (r) H_2, 10% Pd/C, THF-EtOH-sodium phosphate buffer, pH 7.0, 1.5 hrs. purified by a XAD-2 column eluting with D.I. water.

Oxidation of **10** with chromium trioxide dipyridine complex[5] gave the expected aldehyde **11**[6] which was immediately treated with one equivalent of cyclopropylmagnesium bromide in THF/ether solution at room temperature to give carbinol **12** as an epimeric mixture. Before further functionalization of azetidinone **12** at C-3, the free hydroxy group was protected with t-butyldimethylsilyl to give N,O-bis-silyl protected azetidinone **13**. The azetidinone enolate generated in situ from **13** with lithium diisopropylamide in THF was allowed to react with acetaldehyde at -78°C to give an isomeric mixture of aldol products **14**, which was then treated with o-nitrobenzyloxycarbonyl chloride and 4-(N,N-dimethylamino)pyridine to yield the carbonate protected azetidinone **15**. The geometric isomers of **15** were separated by HPLC to give trans-**15** (80%) and cis-**15** (20%).

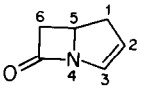
Since the trans-hydroxyethyl side chain of known thienamycin analogs is the more active isomer, further synthesis was carried out with trans-**15** only. To obtain the requisite N-unprotected species **17** for condensation with glyoxylate, trans-**15** was first completely desilylated by treatment with 2.5 N hydrochloric acid to give **16** which was then selectively silylated with t-butyldimethylchlorosilane/imidazole in DMF to produce the O-silyl azetidinone **17**.[7] Condensation of **17** with o-nitrobenzyl glyoxylate in refluxing benzene by azeotropic removal of water gave carbinol **18** in quantitative yield. The carbinol was then sequentially treated with thionyl chloride/pyridine in THF and triphenylphosphine in DMF to give the expected ylide **19**. Desilylation of **19** with one equivalent concentrated hydrochloric acid in THF provided free hydroxy ylide **20** which was oxidized with manganese dioxide or Jones reagent to give cyclopropyl keto ylide **21**.

Ring closure of **21** was achieved by heating in refluxing xylene for two hours. The epimeric mixture of trans-hydroxyethyl carbapenem was separated by TLC to give carbapenem esters **22** (trans-8R) and **23** (trans-8S) in 5:1 ratio in favor of **22**. Deblocking of **22** and **23** by catalytic hydrogenolysis in THF/ethanol/sodium phosphate buffer at 40 psi of hydrogen gave the expected sodium salts of racemic 2-cyclopropyl-6-(1'-hydroxyethyl)-1-carbapen-2-em-3-carboxylate **4** and **5**, respectively. The structural assignments of epimers **22** and **23** were based on proton NMR coupling constants ($J_{H_6-H_8}$) by comparison to the known epimeric pair of thienamycin and 8-epi-thienamycin.[8] The stereochemistry of the 8R epimer **22** was further confirmed by comparison to an authentic sample prepared from a chiral synthetic scheme which will be described in a subsequent paper. Both carbapenems, **4** and **5** showed significant antibacterial activity against both gram-positive and gram-negative microorganisms. Like thienamycin and epi-thienamycin, the 8R epimer **4** was more potent than the 8S epimer **5**. The chemical stabilities of **4** and **5** were poorer than that of thienamycin.[9]

Acknowledgments. We thank Dr. C. Shunk and Mr. A. Matzuk for the preparation of 4-(2'-acetoxylvinyl)-azetidinone, Ms. J. Kahan for antibacterial assays, Dr. B. Arison and Mr. H. Flynn for 300 MHz NMR spectra, Mr. J. Smith for mass spectra, Dr. L. Cama for helpful discussions during this work, and Ms. Jean Garoniak for her help in preparing this manuscript.

References and Notes

1. D. H. Shih, J. Hannah and B. G. Christensen, J. Amer. Chem. Soc., 1978, **100**, 8004.
2. The term "carbapenem" adopted throughout this paper is referring to the "carbapen-2-em" ring system. The conventional numbering of the ring system in beta-lactam chemistry is adopted:



3. (a) D. B. R. Johnston, S. M. Schmitt, F. A. Bouffard and B. G. Christensen, J. Amer. Chem. Soc., 1978, **100**, 313; (b) A. J. G. Baxter, K. H. Dickinson, P. M. Roberts, T. C. Smale and R. Southgate, Chem. Commun., 1979, 236; (c) T. Durst and M. J. O'Sullivan, J. Org. Chem., 1970, **35**, 2043.
4. There was a small amount of N-$SiMe_3$ product.
5. R. W. Ratcliffe and R. Rodehorst, J. Org. Chem., 1970 **35**, 4000.
6. For preparation of **11**, also see R. W. Ratcliffe, T. Salzmann and B. G. Christensen, Tet. Lett., 1980, 31.
7. The selective desilylation can also be accomplished by n-$Bu_4N^+F^-$.
8. (a) S. M. Schmitt, D. B. R. Johnston and B. G. Christensen, J. Org. Chem., 1980 **45**, 1142; (b) P. J. Cassidy, E. O. Stapley, R. T. Goegelman, T. W. Miller, B. H. Arison, G. Albers-Schonberg, S. B. Zimmerman and J. Birnbaum, Abstracts, 17th Interscience Conference on Antimicrobial Agents and Chemotherapy, New York, 1977, No. 81; (c) E. O. Stapley, P. Cassidy, S. A. Currie, D. Daoust, R. Goegelman, S. Hernandez, M. Jackson, J. M. Mata, A. K. Miller, R. L. Monaghan, J. B. Tunac, S. B. Zimmerman and D. Hendlin, ibid., No. 80.
9. Compounds **4** and **5** survived well on XAD-2 column chromatography but considerable decomposition occurred during lyophilization and therefore NMR spectra were not obtained. However, these compounds showed very characteristic hydroxyamine extinguishable UV absorption at 278 nm before lyophilization.
10. Spectra Data: **23**: NMR (300 MHz, in $CDCl_3$), 0.75 (m,2H, cyclopropyl H_{2a}), 1.00 (m, 2H, cyclopropyl H_{2b}), 1.50 (d, 3H, J = 6.0 Hz, CH_3CHOH), 2.56 (d, 2H, J_{1-5} = 9.2 Hz, H_1), 2.84 (m, 1H, cyclopropyl H_{1b}), 3.46 (q, 1H, J_{6-5} = 3.0 Hz, J_{6-8} = 5.2 Hz, H_6), 4.06 (sextet, 1H, J_{5-6} = 3.0 Hz, J_{5-1} = 9.2 Hz, H_5), 5.21 (m, 1H, H_8), 5.55 (d, 1H, J = 15 Hz, CO_2CH_2-), 5.94 (d, 1H, J = 15 Hz, CO_2CH_2-), 5.60 (d, 2H, J = 3.0 Hz, OCO_2CH_2-), 7.48 (m), 7.60 (m), 8.03 (d), and 8.16 (m) (aromatic protons); IR ($CHCl_3$), 1779 (β-lactam), 1754 (ester) and 1727 cm^{-1} (urethane); MS: m/e 551 (M^+), 415 (M^+-136), 371 (M^+-180), 355 (M^+-196). **22**: NMR (300 MHz, $CDCl_3$), 0.74 (m, 2H, cyclopropyl H_{2a}), 1.00 (m, 2H, cyclopropyl H_{2b}), 1.50 (d, 3H, J = 6.0 Hz, CH_3CHOH), 2.56 (d, 2H, J_{1-5} = 9.8 Hz, H_1), 2.83 (m, 1H, cyclopropyl H_{1b}), 3.29 (q, 1H, J_{6-5} = 3.0 Hz, J_{6-8} = 8.0 Hz, H_6), 4.11 (sextet, 1H, J_{5-6} = 3.0 Hz, J_{5-1} = 9.8 Hz, H_5), 5.19 (m, 1H, H_8), 5.54 (d,1H, J = 16 Hz, CO_2CH_2-), 5.92 (d, 1H, J = 16 Hz, CO_2CH_2-), 5.59 (d, 2H, J = 3.0 Hz, OCO_2CH_2), 7.49 (m), 7.68 (m), 7.98 (d), and 8.15 (d) (aromatic protons); IR ($CHCl_3$, 1779 (β-lactam), 1754 (ester), and 1726 (urethane); MS: m/e 551 (M^+), 415 (M^+-136), 327 (M^+-224), 371 (M^+-180), 355 (M^+-196). **21**: IR ($CHCl_3$); 1736 (β-lactam and carbonate), 1695 (cyclopropyl ketone), and 1613 cm^{-1} (ylide ester); MS: m/e 829 (M^+). **20**: 60 MHz NMR ($CDCl_3$): 0.20-0.50 (m, cyclopropyl protons), 1.50 (d, 3H, CH_3CHOH), 7.20-8.40 (m, aromatic protons). **19**: 60 MHz NMR ($CDCl_3$): δ 0.04 (s, 3H, Si-CH_3), 0.06 (s, 3H, Si-CH_3), 0.20-0.60 (m, cyclopropyl protons), 0.92 [s, 9H, $SiC(CH_3)_3$] 1.45 (d, 3H, CH_3CHOH), 7.40-8.40 (m, aromatic protons). **18**: 60 MHz NMR ($CDCl_3$): δ 0.05 (s, 6H, Si-CH_3), 0.20-0.60 (m, cyclopropyl protons), 0.90 [s, 9H, $SiC(CH_3)_3$], 1.50 (d, 3H, CH_3CHOH), 1.95 (m), 3.20 (m),4.15 (m), 5.60 (d), 7.30-8.20 (m, aromatic protons). **17**: 60 MHz NMR ($CDCl_3$): δ 0.04 (s, 3H, Si-CH_3), 0.06 (s, 3H, Si-CH_3), 0.90 [s, 9H, $SiC(CH_3)_3$], 1.43 (d, 3H, CH_3CHOH), 2.00 (m), 3.20 (m), 3.90 (m), 5.20 (m), 5.60 (s), 6.38 (s, 1H, NH), 7.40-8.40 (m, aromatic protons). **16**: 60 MHz NMR ($CDCl_3$): δ 0.32 and 0.55 (m, cyclopropyl protons), 1.28 (d, 3H, CH_3CHOH), 1.92 (m), 2.50 (m), 3.00 (m), 3.70 (m), 5.10 (m), 5.58 (s), 6.60 (s, NH), 7.30-8.20 (m, aromatic protons). **15**-trans: 300 MHz NMR ($CDCl_3$): δ 0.05 (s, 6H, Si-CH_3), 0.24 (s, 3H, Si-CH_3), 0.29 (s, 3H, Si-CH_3), 0.88 [s, 9H, $SiC(CH_3)_3$], 0.98 [s, 9H, $SiC(CH_3)_3$], 1.30 (d, 3H, CH_3CHOH), 1.75 (m), 2.15 (m), 2.98-3.80 (m), 5.12 (m), 5.62 (m), 7.55 (m), 7.69 (m), and 8.20 (d); MS: m/e 591 (M^+-15), 549 (M^+-57). **13**: 60 MHz NMR ($CDCl_3$): δ 0.02 (s, 6H, Si-CH_3), 0.21 (s, 3H, Si-CH_3), 0.27 (s, 3H, Si-CH_3), 0.88 [s, 9H, $SiC(CH_3)_3$], 0.97 [s, 9H, $SiC(CH_3)_3$], 0.40-0.50 (m, cyclopropyl protons), 1.70-4.00 (m); MS: m/e 383 (M^+), 368 (M^+-15), 3.26 (M^+-57). **12**: 60 MHz NMR ($CDCl_3$): δ 0.20 (s, 6H, Si-CH_3), 0.90 [s, 9H, $SiC(CH_3)_3$], 0.3-0.50 (cyclopropyl protons), 1.60-1.90 (m), 2.60-3.10 (m), 3.40-3.80 (m). **11**: 60 MHz NMR ($CDCl_3$): δ 0.17 (s, 6H, Si-CH_3), 0.92 [s, 9H, $SiC(CH_3)_3$], 2.54 (q, 1H, J = 3.0 and 15 Hz, $H_{3\beta}$), 2.76 (m, 2H, CH_2CHO),3.34 (q, 1H, J = 5.0 and 15 Hz, $H_{3\alpha}$), 3.81 (m, 1H), 9.78 (m, 1H, CHO); MS: m/e 228 (M^++1), 170 (M^+-57). **10**: 60 MHz NMR ($CDCl_3$): δ 0.28 (s, 6H, Si-CH_3), 1.00 [s, 9H, $SiC(CH_3)_3$], 1.90 (m, H, CH_2CH_2OH), 2.62 (q, 1H, J = 2.8 and 15 Hz, $H_{3\beta}$), 3.15 (q, 1H, J = 5.6 and 15 Hz, $H_{3\alpha}$), 3.61 (m, 3H, H_4 and CH_2CH_2OH).

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