expected for the ammonium group.[22,24,25] When comparing the k_{cat}/K_m (= 0.361 M^{-1} s^{-1}) of $DodNH_3^+BzlNAH$ with k_2 (= 1.26 × 10^{-2} M^{-1} s^{-1}) of DodBzlNAH, the rate increment of 29-fold was attained through the recognition of the ammonium group.

Conclusion

As a crown ether flavin mimic, crFl, has brought forth several novel phenomena: (i) a change in the absorption and fluorescence spectra by added metal cations, (ii) efficient intramolecular fluorescence quenching by chromophores having the ammonium group, (iii) a change in the reactivity by added metal cations, and (iv) Michaelis-Menten type saturation kinetics in the reaction with $DodNH_3^+BzlNAH$. These phenomena imitate well several biological concepts important in enzyme chemistry: for example, allosteric effectors, competitive inhibition, recognition of metal cations, intracomplex reactions, etc. The close imitation can be achieved because crFl has within a molecule flavin as a catalytic site and crown ether as a recognition site, which are the minimum constituents required for the enzyme model system. One may say, therefore, that in a sense crFl is a well-constructed miniature of flavoenzymes. Since a crown ether family has a wide variety of association abilities, including the asymmetric recognition, we believe that modification of the crown moiety would lead to the further development of novel flavin chemistry.

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Registry No. 1, 86996-27-2; **2**, 86996-28-3; **3**, 86996-29-4; **4**, 86996-30-7; **5**, 86996-31-8; **6**, 86996-32-9; CrFl, 86996-33-0; CrFl (Na^+ complex), 88729-62-8; CrFl (K^+ complex), 88729-63-9; CrFl (Rb^+ complex), 88729-64-0; CrFl (Cs^+ complex), 88729-65-1; BzlNAHCOOK, 86996-34-1; $DodNH_2BzlNAH$, 88704-70-5; LFl, 18636-32-3; BzlNAH, 952-92-1; DodBzlNAH, 83239-12-7; DodNHBzlNAH·HCl, 88704-77-2; H_2NCH_2COOEt, 459-73-4; NaCl, 7647-14-5; KCl, 7447-40-7; RbCl, 7791-11-9; CsCl, 7647-17-8; NH_4Cl, 12125-02-9; $AgNO_3$, 7761-88-8; $Pb(OCOCH_3)_2$, 301-04-2; $HgCl_2$, 7487-94-7; Na^+, 17341-25-2; Rb^+, 22537-38-8; Cs^+, 18459-37-5; K^+, 24203-36-9; NH_4^+, 14798-03-9; 4'-aminobenzene-18-crown-6, 68941-06-0; alloxane, 50-71-5; nicotinyl chloride, 10400-19-8; glycine ethyl ester hydrochloride, 623-33-6; N^3-((ethoxycarbonyl)methyl)nicotinamide, 54466-74-9; N^3-((ethoxycarbonyl)methyl)-1-benzylnicotinamide bromide, 88704-66-9; N^3-((ethoxycarbonyl)methyl)-1-benzyl-1,4-dihydronicotinamide, 88704-67-0; N^3-dodecylnicotinamide, 81475-38-9; 2,4-dinitrochlorobenzene, 97-00-7; N^3-dodecyl-1-(2,4-dinitrophenyl)nicotinamide perchlorate, 88704-69-2; *p*-xylylenediamine, 539-48-0; N^3-dodecyl-1-(*p*-(ammoniomethyl)-benzyl)nicotinamide dichloride, 88704-71-6; 2-(aminomethyl)benzimidazole hydrochloride, 7757-21-3; 2-(2-aminoethyl)benzimidazole hydrochloride, 88704-72-7; 2-(3-aminopropyl)benzimidazole hydrochloride, 88704-73-8; 2-(3-aminopropyl)benzimidazole dihydrochloride, 88765-77-9; 2-(5-aminopentyl)benzimidazole hydrochloride, 88704-74-9; 2-(7-aminoheptyl)benzimidazole hydrochloride, 88704-75-0; 2-(10-aminodecyl)benzimidazole hydrochloride, 88704-76-1; L-phenylalanine methyl ester hydrochloride, 7524-50-7; L-tyrosine ethyl ester hydrochloride, 4089-07-0; histamine hydrochloride, 23758-34-1; tryptamine hydrochloride, 14733-29-0; 2-aminobenzimidazole hydrochloride, 26893-41-4.

Total Synthesis of 3-(5-Tetrazolyl)carbapenems

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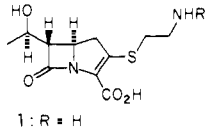
Contribution from the Merck Sharp & Dohme Research Laboratories, P.O. Box 2000, Rahway, New Jersey 07065. *Received September 22, 1983*

Abstract: The synthesis of the title compounds, β-lactam antibiotics, is described. A new tetrazole protecting group, (((*p*-nitrobenzyl)carbonyl)oxy)methyl, was successfully applied. Substitution of carboxyl by tetrazole on the carbapenem nucleus results in stability to a degradative renal enzyme.

Synthetic modifications of carbapenem natural products, represented by thienamycin (**1**), have yielded many potent new antibiotics.[1] In particular, formimidoylation of thienamycin has resulted in a derivative, MK0787 (**2**) selected for clinical studies.[2]



1: R = H
2: R = CH=NH

In considering other sites on the carbapenem nucleus for analogue studies, we were struck by the paucity of literature precedent for carboxylic acid substitution.[3] Herein we describe our work on 3-(5-tetrazolyl)carbapenems[4] which was directed toward renal dehydropeptidase, the major degradative enzyme for carbapenems in vivo.[5]

Our synthetic plan was initially designed to incorporate the efficient chemistry developed at Merck.[6] Utilizing a chiral intermediate **3**,[7] the tetrazolyl moiety was to be appended by the magnesium-mediated homologation procedure[6,8] used to prepare the corresponding keto esters. The success of subsequent transformations was then dependent upon the chemically equivalent behavior of the protected tetrazole and ester functional groups.

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(4) Conversion of the C-3 carboxyl of the penam antibiotic amoxycillin to a 5-tetrazolyl group resulted in enhanced activity against many bacterial strains and increased β-lactamase stability: English, A. R.; Retsema, J. A.; Lynch, J. E. *Antimicrob. Agents Chemother.* **1976**, *10*, 132. For other examples of tetrazole/carboxyl substitution see H. Singh et al. *Prog. Med. Chem.* **1980**, *17*, 151-183.

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(7) (a) Prepared from 1-(*tert*-dimethylsilyl)-3(*S*)-[1(*R*)-((*tert*-butyldimethylsilyl)oxyl)ethyl])-2-oxo-4(*R*)-azetidineacetic acid[7b] (1 equiv of *n*-Bu_4NF, THF, -78 °C). (b) Liu, T. M. H.; Melillo, D. G.; Ryan, K. M.; Shinkai, I.; Sletzinger, M. U.S. Patent 4 349 687, 1983.

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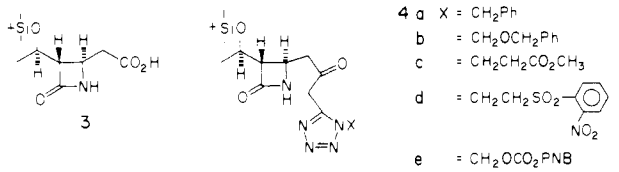
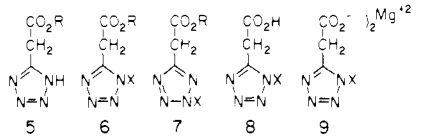
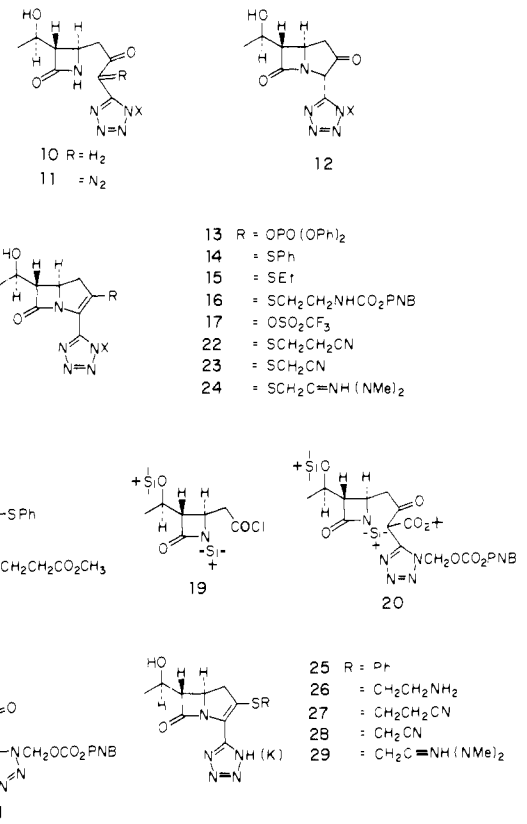
To begin the synthesis, regioselective benzylation (**6a**:**7a**/4:1) was effected by treatment of **5** (R = Et)[10] with bis(tributyltin) oxide followed by addition of benzyl bromide.[11] Saponification of **6a**,[12,13] and deprotonation of **8a** with dibutylmagnesium (0.5 equiv, THF/heptane, 0 °C) gave the magnesium salt **9a**. Re-





action of **9a** with the imidazolide of **3** (carbonyl diimidazole, THF) gave **4a** in 80% yield. With the tetrazole and the β-lactam moieties linked together, desilylation[14] (HF, H_2O, CH_3CN) of **4a**, followed by diazo transfer[15] to **10a** [Et_3N, p-($C_{12}H_{25}$)$C_6H_4SO_2N_3$, CH_2Cl_2] afforded **11a**. Rhodium-mediated carbenoid insertion[16] was effected by refluxing **11a** in dichloromethane with a catalytic amount of rhodium(II) acetate dimer to give a quantitative yield of **12a**. Proton NMR of **12a** showed a single C-3 isomer, presumed to be the more stable α-isomer, with the tetrazole ring lying on the less sterically crowded, convex side. Phosphorylation of **12a** [$ClPO(OPh)_2$, 2-Pr_2NEt, CH_3CN] gave **13a** which could be isolated but was most effectively reacted in situ with thiols (thiophenol, ethanethiol, *N*-*p*-nitrobenzyl)oxy)carbonyl)cysteamine[17]) to give carbapenems **14a**, **15a**, and **16a**, respectively, accompanied by products formed by competitive attack at the β-lactam ring. Exposure of **14a**, **15a**, and **16a** to a variety of hydrogenation conditions returned only starting material and β-lactam opened products.

A different tetrazole protecting group not reliant on nitrogen–carbon hydrogenolysis was required. Hydrogenolysis of the (benzyloxy)methyl group is based on oxygen–carbon cleavage followed by deformylation, releasing the free tetrazole.[18] Treatment of **5** (R = Et) with benzyl chloromethyl ether afforded a separable mixture of 1- and 2-isomers **6b** and **7b** (1.2:1) and the transformation **6b** to **12b** was conducted in a manner strictly analogous to that described for **12a**. Exposure of **12b** to trifluoromethanesulfonic anhydride and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in THF at −78 °C afforded enol triflate **17b**, which was superior to **13b** as a precursor to carbapenems **14b**, **15b**, and **16b**.[19] Hydrogenation, again failing to produce the free tetrazoles using many solvents, catalysts, and extreme hydrogen pressure, produced only traces of bioactive material.



Now convinced that removal of a tetrazole protecting group by hydrogenolysis was not feasible, we turned our attention to the 1-(2-(methoxycarbonyl)ethyl) protecting group.[9a] In a model reaction, retro Michael cleavage of **6c** with 1,5-diazabicyclo-[4.3.0]non-5-ene (DBN) gave **5** (R = Et) and the inert DBN–methyl acrylate addition adduct. The requisite magnesium salt **9c** was prepared by Michael addition of **5** (R = $CH_2C_6H_5$)[10] to methyl acrylate, producing a separable mixture (**6c**:**7c**/1:1.7) of regioisomers. After synthesis of **14c** in 5 steps from **9c**, addition of 1 equiv of DBN to a chloroform or tetrahydrofuran solution of **14c** caused rapid conversion to the Δ^1-isomer **18**.[20] Since weaker bases (Et_3N, (*N*,*N*-dimethylamino)pyridine, pyrrolidine) returned **14c** unchanged, deprotection required a stronger acidifying group than the methyl ester. In a model deprotection study, **6c** was converted to **5** (R = $CH_2C_6H_5$) in 3 h at 25 °C by DBN or DBU, while deprotection of **6d** (R = *t*-Bu) was immediate. However, after applying **6d** to the synthesis of **15d** as before, treatment of **15d** with 1 equiv of DBN at 0 °C resulted in decomposition.

A solution to the tetrazole deprotection problem was found in a new protecting group. In light of the observations detailed above, we reasoned that a (((*p*-nitrobenzyl)carbonyl)oxy)methyl group could be removed by a reduction/solvolysis sequence, liberating free tetrazole along with carbon dioxide, formaldehyde, and benzyl alcohols bearing reduced nitrogen moieties. The requisite alkylating agent, ((((*p*-nitrobenzyl)oxy)carbonyl)oxy)methyl chloride (mp 62 °C, made by acylation of *p*-nitrobenzyl alcohol by chloromethyl chloroformate,[21] see Experimental Section), alkylated *tert*-butyl ester tetrazole **5** (R = *t*-Bu)[10] (Et_3N, CH_3CN, 25 °C) to give **6e** and **7e** in a 1:1.3 ratio. Attempted deesterification of the *tert*-butyl group from **8e** failed, giving an intractable mixture. Since the requisite acid **8e** was inaccessible, the tetrazole and β-lactam fragments were connected by an enolate acylation

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(12) Based on literature precedent (Huff, H.; Henry, R. *J. Med. Chem.* **1970**, *13*, 777), the 1-isomer **6a** was assigned the structure shown due to its higher melting point, lower R_f value (TLC), and further upfield (^{1}H NMR) N-1benzylic protons and further downfield C-5 methylene protons relative to the 2-isomer **7a**. The 1-isomers (**6**) were used because of the greater inductive effect at C-5 necessary in subsequent reactions.
(13) Assigned structures are fully supported by IR, ^{1}H NMR (200 MHz), mass spectroscopy, and UV. Yields refer to isolated chromatograpically homogeneous materials. Spectroscopic data can be found in the supplementary material.
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(20) Double bond isomerization has been effected by DBU in dimethyl sulfoxide on *N*-(((*p*-nitrobenzyl)oxy)carbonyl)thienamycin *p*-nitrobenzyl ester to give the corresponding Δ^1-isomer. Deblocking of the protecting groups gave Δ^1-thienamycin, nearly devoid of antibacterial activity: Shih, D. H.; Ratcliffe, R. W. *J. Med. Chem.* **1981**, *24*, 639.
(21) chloromethyl chloroformate (bp 101 °C) was prepared by photolysis of methyl chloroformate while bubbling in chlorine gas. Ambient temperature was maintained with a water bath.

whereby **6e** (R = *t*-Bu) was treated with 2 equiv of lithium triethylcarboxide ($LiOCEt_3$) at −78 °C and quickly followed by the acid chloride **19**.[22] The resulting acylation product **20** was treated with trifluoroacetic acid to effect decarboalkoxylation and O-desilylation to give **21**. Further treatment with hydrofluoric acid gave **10e** in 45% overall yield from **19**. Elaboration of **10e** to carbapenems **14e**, **16e**, **22e**, and **23e** proceeded as described above in average overall yields of 30%. By an alternate procedure,[23] triflate **17e** was converted (NaSH, *i*-Pr_2NEt, DMF) to the enesulfide followed by alkylation [$ClCH_2CN$, $ClCH_2C{=}NH(NMe_2)$] to give **23** and **24**, respectively. Hydrogenation/solvolysis (40 psi H_2, PdC, THF, EtOH, pH 7 aqueous phosphate) of **14e**, **16e**, **22e**, and **24** proceeded rapidly to give the 3-(5-tetrazolyl)carbapenems **25-29** in good yield. For example, **28** was isolated (reverse phase prep TLC) in 82% yield from **23**.

While the antibacterial potencies of **25–29** compare quite favorably with most antibiotics in current clinical use, their minimum inhibitory concentrations against a variety of Gram-positive and Gram-negative bacteria are approximately ten times those of the corresponding 5-carboxylcarbapenems. Our initial hypothesis was confirmed by the finding that **25–29** were stable to renal dehydropeptidase.

Experimental Section

Preparation of ((((*p*-Nitrobenzl)oxy)carbonyl)oxy)methyl Chloride. *p*-Nitrobenzyl alcohol (30.6 g, 200 mmol) was dissolved in 160 mL of dry tetrahydrofuran and 16.2 mL (200 mmol) of pyridine and the solution was cooled to 0 °C. Chloromethyl chloroformate (17.0 mL, 200 mmol) in 25 mL of ether was added dropwise with stirring over 30 min. When the addition was complete, the bath was removed and the mixture was stirred 1 h at room temperature. The mixture was then diluted with ether (300 mL), the precipitated pyridine hydrochloride was filtered, and the filtrate was evaporated to yield 45 g of crude product. Purification was effected by chromatography on 1000 mL of silica gel with an ether–hexane gradient to yield 29.9 of pure *p*-nitrobenzylchloromethyl carbonate (61% yield): mp 62 °C; IR 1774, 1610, 1430 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.30 (2 H, d, *J* = 9), 7.60 (2 H, d, *J* = 9), 5.78 (2 H, s), 5.35 (2 H, s); mass spectrum, 245 (M^+), 196, 152, 136.

Preparation of *tert*-Butyl (1-(((((*p*-Nitrobenzyl)oxy)carbonyl)oxy)methyl)tetrazol-5-yl)acetate (6e) and *tert*-Butyl (2-(((((*p*-Nitrobenzyl)oxy)carbonyl)oxy)methyl)tetrazol-5-yl)acetate (7e). Triethylamine (8.8 mL, 0.063 mol) was added to *tert*-butyl 5-tetrazolylacetate (7.65 g, 0.042 mol) in 50 mL of acetonitrile at 50 °C. ((((*p*-Nitrobenzyl)oxy)carbonyl)oxy)methyl chloride (9.10 g, 0.037 mol) was added in one portion. After warming to room temperature and stirring under nitrogen for 16 h, the solution was heated to 60 °C for 1 h. After cooling to 0 °C 100 mL of diethyl ether was added and stirred for 10 min. Triethylammonium chloride crystals were filtered. Solvent removal in vacuo of the eluate gave an orange oil. Chromatography on silica gel (ethyl acetate:hexane, 1:3) gave, in order of elution, 7.35 g (51%) of **7e** and 5.42 g (37%) of **6e** as colorless oils. Trituration of **6e** with diethyl ether gave crystals: mp 72–76 °C; IR ($CHCl_3$) 1760, 1725, 1525 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.26 2 H, d, *J* = 9), 7.52 (2 H, d, *J* = 9), 6.37 (2 H, s), 5.30 (2 H, s), 4.17 (2 H, s), 1.45 (9 H, s); mass spectrum, 378 (M^+ − 15), 338, 337, 320, 293, 246. Anal. calcd: C, 48.86; N, 17.80; H, 4.86. Found: C, 49.13; N, 17.55; H, 4.85.

Preparation of (3*S*,4*R*)-1-(*tert*-Butyldimethylsilyl)-3-[(*R*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl]-4-[2-oxo-3-(*tert*-butoxycarbonyl)-3-(1-(((((*p*-nitrobenzyl)oxy)carbonyl)oxy)methyl)tetrazol-5-yl)propyl]azetidin-2-one (20). A heterogeneous mixture of (3*S*,4*R*)-1-*tert*-butyldimethylsilyl-3-[(*R*)-2-((*tert*-butyldimethylsilyl)oxy)ethyl]-2-oxo-azetidin-4-acetic acid (2.07 g, 5.17 mmol), sodium carbonate (0.60 g, 5.69 mmol), 10 mL of tetrahydrofuran, and 2 mL of acetonitrile was heated at 50 °C for 1 h. After cooling to room temperature, the solvent was removed under vacuum. The resulting solid was suspended in 50 mL of dichloromethane and 0.01 mL of dimethylformamide and cooled to −15 °C. oxalyl chloride (0.54 mL, 6.20 mmol) was added dropwise by syringe, causing vigorous gas evolution. The orange solution was maintained at −15 °C and used within several hours. In a separate flask, **6e** (1.83 g, 4.65 mmol) was dissolved in 20 mL of tetrahydrofuran and cooled to −78 °C. A hexane solution of lithium triethylcarboxide (8.7 mL, 1.07 molar, 9.31 mmol) was added by syringe, effecting a brownish-orange solution. After 10 min at −78 °C, the −15 °C solution of (3*S*,4*R*)-1-(*tert*-butyldimethylsilyl)-3-[(*R*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl]acetidin-2-one-4-acetyl chloride was transferred rapidly by cannula, followed by rinsing with 10 mL of dichloromethane. After 45 min at −78 °C, 10 mL of pH 7, 0.1 M potassium phosphate buffer was added to the brownish-orange solution, causing it to lighten. The mixture was diluted with 500 mL of diethyl ether and washed with 100 mL of aqueous solutions of 5% KH_2PO_4, saturated sodium bicarbonate, and saturated sodium chloride. The organic layer was dried over magnesium sulfate, filtered, and concentrated under vacuum to a yellow oil. Silica gel chromatography (ethyl acetate:hexane, 1:3) gave 2.366 g (66%) of **20** as a white solid: mp 113–118 °C; IR ($CHCl_3$) 1760, 1740, 1525 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.29 (2 H, d, *J* = 8), 7.56 (2 H, d, *J* = 8), 6.20 (2 H, AB quartet, *J* = 8), 5.31 (2 H, 5), 4.18 (1 H, m), 3.98 (1 H, m), 3.05 (1 H, dd, J = 2.5, 4.5), 2.86 (1 H, dd, *J* = 4.5, 14.5), 2.62 (1 H, dd, *J* = 9, 14.5), 1.41 (9 H, s), 1.18 (3 H d, *J* = 7), 0.88 (18 H, 5), 0.16 (3 H, s), 0.10 (3 H, s), 0.07 (3 H, s), 0.05 (3 H, s); mass spectrum, 732 (M^+ − 44), 654, 619, 571, 460.

Preparation of (3*S*,4*R*)-1-(*tert*-Butyldimethylsilyl)-3-[(*R*)-1-hydroxyethyl]-4-[2-oxo-3-(5-(1-((((*p*-nitrobenzyl)oxy)carbonyl)oxy)-methyl)tetrazolyl)propyl]azetidin-2-one (21). Trifluoroacetic acid (15 mL) was added to **20** (1.40 g, 1.8 mmol) in 20 mL of dichloromethane at 0 °C. The solution was allowed to warm to room temperature and stirred under nitrogen for 6 h. After 20 mL of toluene was added, the volatiles were removed under a stream of nitrogen. Total solvent removal under vacuum left an oil which was triturated with ether to give **21** as a white solid: ^1H NMR ($CDCl_3$) δ 8.18 (2 H, d, *J* = 8), 7.48 (2 H, d, *J* = 8), 6.18 (2 H, s), 5.20 (2 H, s), 4.30 (2 H, s), 4.0 (2 H, m), 3.9 (3 H, m), 1.20 (3 H, d, *J* = 7), 0.92 (9 H, s), 0.18 (3 H, s), 0.14 (3 H, s).

Preparation of (3*R*,4*R*)-3-[(*R*)-1-Hydroxyethyl]-4-[2-oxo-3-(1-(((((*p*-nitrobenzyl)oxy)carbonyl)oxy)methyl)tetrazo-5-yl)propyl]azetidin-2-one (10e). A 24.5 M solution of hydrofluoric acid (0.5 mL, 12 mmol) was added to **21** (0.89 g, 1.6 mmol) in 12 mL of acetonitrile at −10 °C. The pale yellow solution was stored at −10 °C for 18 h and then diluted with 300 mL ethyl acetate. After washing with 0.1 M, pH 7 phosphate buffer and saturated sodium chloride solutions, the organic phase was dried over magnesium sulfate and filtered. Removal of solvent under vacuum gave **10e** (0.72 g, 1.6 mmol) as a yellow oil which solidified on standing: ^1H NMR (acetone-d_6) δ 8.29 (2 H, d, *J* = 9), 7.73 (2 H, d, *J* = 9), 7.17 (1 H, br s), 6.44 (2 H, s), 5.43 (2 H, s), 4.60 (2 H, s), 4.04 (1 H, m), 3.86 (1 H, m), 3.30 (1 H, dd, *J* = 5, 18), 3.15 (1 H, dd, *J* = 9, 18), 2.83 (1 H, dd, *J* = 2, 7), 1.23 (3 H, d, *J* = 7).

Preparation of (3*S*,4*R*)-3-[(*R*)-1-Hydroxyethyl]-4-[2-oxo-3-diazo-(1-(((((*p*-nitrobenzyl)oxy)carbonyl)oxy)methyl)tetrazol-5-yl)propyl]azetidin-2-one (11e). A hexane solution of *p*-dodecylbenzenesulfonylazide (0.89 M, 2.5 mL, 2.2 mmol) was added rapidly to **10e** (0.72 g, 1.6 mmol) in 80 mL of dichloromethane at −15 °C. Triethylamine (0.40 mL, 1.7 mmol) was added dropwise to the stirred solution. After 1 h, the solvent was removed under vacuum. Chromatography of the dark oil on silica gel gave 0.302 g (0.64 mmol) of **11e** (35% yield from **20**) as a yellow foam: IR ($CHCl_3$) 3420, 2120, 1760 (br), 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.26 (2 H, d, *J* = 9), 7.54 (2 H, d, *J* = 9), 6.51 (2 H, AB quartet, *J* = 10), 6.25 (1 H, br s), 5.29 (2 H, s), 4.20 (1 H, m), 4.10 (1 H, m), 3.16 (1 H, dd, *J* = 5.5, 17), 3.02 (1 H, dd, *J* = 8, 17), 2.86 (1 H, dd, *J* = 2, 6.5), 1.34 (3 H, d, *J* = 6.5).

Preparation of (5*R*,6*S*)-3,7-Dioxo-6-[(*R*)-1-hydroxyethyl]-2-(1-(((((*p*-nitrobenzyl)oxy)carbonyl)oxy)methyl)tetrazol-5-yl)-1-azabicyclo[3.2.0]heptane (12e). A mixture of **11e** (0.290 g, 0.61 mmol), rhodium acetate dimer (2 mg), and 35 mL of dichloromethane was heated at reflux for 1 h. after cooling to room temperature, the pink solution was filtered through a pad of magnesium sulfate, eluting with tetrahydrofuran. Solvent removal under vacuum gave 0.243 g (0.54 mmol) of **12e** (89%) as an off-white solid: ^1H NMR ($CDCl_3$) δ 8.25 (2 H, d, *J* = 9), 7.56 (2 H, d, *J* = 9), 6.47 (2 H, AB quartet, *J* = 11), 5.85 (1 H, s), 5.30 (2 H, s), 4.38 (1 H, m), 4.30 (1 H, M), 3.32 (1 H, dd, *J* = 2, 6.5), 3.06 (1 H, dd, *J* = 7, 19), 2.69 (1 H, dd, *J* = 7.5, 19), 1.38 (3 H, d, *J* = 6.5).

Preparation of (5*R*,6*S*)-2-((Cyanomethyl)thio)-6-[(*R*)-1-hydroxyethyl]-2-(1-((((*p*-nitrobenzyl)oxy)carbonyl)methyl)tetrazol-5-yl)-1-azabicyclo[3.2.0]hept-2-en-7-one (23e). 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.045 mL, 0.30 mmol) was added to a solution of **12e** (0.111 g, 0.249 mmol) and 5 mL of dry tetrahydrofuran at −78 °C. After stirring 20 min, trifluoromethanesulfonic anhydride (0.050 mL, 0.30 mmol) was added. After 40 min, the solvent was removed under vacuum at −20 °C. Dissolution of the residue in 1.5 mL of dry dimethylformamide and cooling to −20 °C was followed by the addition of sodium hydrogen sulfide (0.017 g, 0.30 mmol) as a solid and diisopropylethylamine (0.052 mL, 0.30 mmol). After 2 h at −20 °C, chloroacetonitrile (0.057 mL, 0.90 mmol) and diisopropylethylamine (0.052 mL, 0.30 mmol) were added. The solution was allowed to warm to room temperature and stirred for 3 h. After dilution with 100 mL of ethyl acetate, the solution was washed with 50-mL solutions of 5% potassium dihydrogen phosphate, saturated

(22) See ref 7a; ClCOCOCl, pyridine, CH_2Cl_2.

(23) Yamamoto, K.; Yoshioka, T.; Kato, Y.; Ishiki, K.; Nishino, M.; Nakamura, F.; Shimauchi, Y.; Ishikura, T. *Tetrahedron Lett.* **1982**, 897.

sodium bicarbonate, and saturated sodium chloride. The organic phase was dried over magnesium sulfate, filtered, and concentrated to give a brown oil, which was chromatographed on silica gel to give 0.041 g (33%) of **23e** as a white solid: ^{1}H NMR ($CDCl_3$) δ 8.25 (2 H, d, J = 9), 7.56 (2 H, d, J = 9), 6.64 (2 H, AB quartet, J = 11), 5.29 (2 H, 2), 4.47 (1 H, qd, J = 3, 8), 4.31 (1 H, m), 3.68 (2 H, AB quartet, J = 18), 3.49 (1 H, dd, J = 10, 18), 3.43 (1 H, dd, J = 3, 5), 3.37 (1 H, dd, J = 8, 18), 1.35 (3 H, 3, J = 6); UV λ_{max} (dioxane) 313, 264 nm.

Preparation of Potassium (5*R*,6*S*)-2-((Cyanomethyl)thio)-6-[(*R*)-1-hydroxyethyl]-3-(5-tetrazolyl)carbapenem (28). A mixture of **23e** (0.055 g, 0.11 mmol), 0.06 g of 10% palladium on carbon, 2 mL of 0.1 M dipotassium hydrogen phosphate/potassium dihydrogen phosphate, pH 7 buffer, 4 mL of water, 8 mL of terahydrofuran, and 2 mL of ethanol was hydrogenated at 45 psi hydrogen for 1 h. The mixture was filtered through Celite, eluting with water. The filtrate was washed with 50 mL of diethyl ether and concentrated under vacuum to a volume of 3 mL. Reverse-phase preparative TLC chromatography (5% ethanol in H_2O) allowed isolation of a band R_f = 0.8. The silica was eluted with 40 mL of acetonitrile:water/4:1. Concentration and lyophilization gave 0.030 g (82%) of **28** as a white powder: IR (KBr) 3400, 2950, 2250, 1770, 1620 cm^{-1}; ^{1}H NMR (D_2O) δ 4.48 (1 H, m, J = 2.5, 8, 9.5), 4.35 (1 H, quintet, J = 6.5), 3.92 (2 H, AB quartet, J = 17), 3.61 (1 H, dd, J = 2.5, 6.5), 3.48 (1 H, AB quartet, J = 9.5, 17), 3.37 (1 H, AB quartet, J = 8, 17), 1.37 (3 H, d, J = 6.5); UV λ_{max} 294 nm.

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Registry No. 3, 88669-70-9; **4a**, 88669-71-0; **5** (R = Et), 13616-37-0; **5** (R = CH_2Ph), 76812-76-5; **6a** (R = Et), 88669-72-1; **6b** (R = Et), 88669-73-2; **6c** (R = Et), 88669-74-3; **6d** (R = *t*-Bu), 88669-75-4; **6e** (R = *t*-Bu), 88669-76-5; **7a** (R = Et), 88669-77-6; **7b** (R = Et), 88669-78-7; **7c** (R = CH_2Ph), 88669-79-8; **7e** (R = *t*-Bu), 88669-80-1; **8a**, 64953-18-0; **8e**, 88669-81-2; **9a**, 88669-82-3; **9c**, 88669-83-4; **10a**, 88669-84-5; **10e**, 88669-85-6; **11a**, 88669-86-7; **11e**, 88669-87-8; **12a**, 88669-88-9; **12b**, 88669-89-0; **12e**, 88669-90-3; **13a**, 88669-91-4; **14a**, 88669-92-5; **14b**, 88669-93-6; **14c**, 88669-94-7; **14e**, 88669-95-8; **15a**, 88669-96-9; **15b**, 88669-97-0; **15d**, 88669-98-1; **16a**, 88669-99-2; **16b**, 88670-00-2; **16e**, 88685-62-5; **17b**, 88670-01-3; **17e**, 88670-02-4; **18**, 88670-03-5; **19**, 88728-84-1; **19** (acid), 88670-04-6; **20**, 88670-05-7; **21**, 88685-63-6; **22e**, 88670-06-8; **23e**, 88670-07-9; **24e**, 88670-08-0; **25**, 88670-09-1; **26**, 88670-10-4; **27**, 88670-11-5; **28**, 88670-12-6; **29**, 88670-13-7; $ClCH_2C{=}NH(NMe_2)$, 88670-14-8; *p*-nitrobenzyl chloromethyl carbonate, 50780-46-6; *tert*-butyl 5-tetrazolylacetate, 88670-15-9; *p*-nitrobenzyl alcohol, 619-73-8; chloromethyl chloroformate, 22128-62-7; methyl acrylate, 96-33-3.

Supplementary Material Available: Spectral data (4 pages). Ordering information is given on any current masthead page.

Total Synthesis of Tri-*O*-methylolivin

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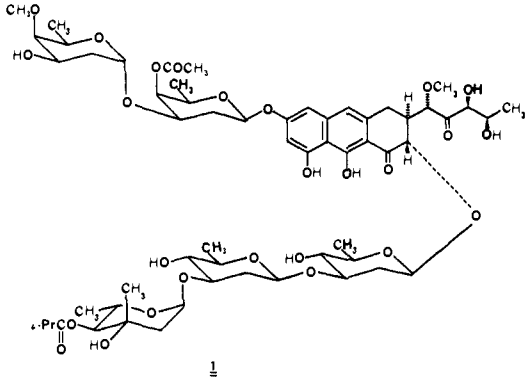
Abstract: Olivin (**2**) is the aglycon of the antitumor antibiotic olivomycin A (**1**). A total synthesis of **3**, the trimethyl ether of olivin, has been successfully achieved by a convergent route. The key β-methoxyenone synthon **15** was prepared from 3,5-dimethoxyphenylacetic acid (**4**) and ketal ester **5**. Condensation of **15** and methyl orsellinate dimethyl ether gave tricyclic ketone **17** which was subsequently elaborated into **3**.

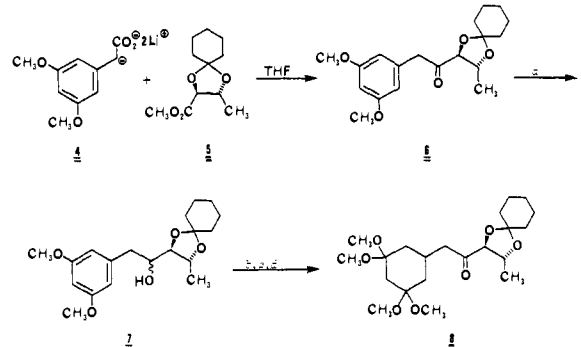
Olivomycin A (**1**) is a clinically effective cancer chemotherapy agent produced by *Streptomyces olivoreticuli*. This compound is a member of the aureolic acid group of antitumor antibiotics which are characterized by a complex tricyclic aglycon attached to various di- and trisaccharides.[1a] Acidic hydrolysis of **1** affords



1

the aglycon olivin having the structure and absolute stereochemistry shown in formula **2**.[1b] Relatively little synthetic work has been reported in this area to date. Franck,[2] Thiem,[3] and Roush[4] have described preliminary approaches to olivin using carbohydrate synthons. Recently we delineated a general annulation strategy for convergent synthesis of the aureolic acid aglycons and we have

Scheme I[a]



[a] Key: (a) $NaBH_3$, EtOH, room temperature, 2 h. (b) Li/NH_3, EtOH, 1 h. (c) Puridinium *p*-toluenesulfonate, MeOH room temperature, 14 h. (d) Pyridine/CrO_3, CH_2Cl_2, 0 °C–room temperature, 40 min.

(1) (a) For reviews see: Remers, W. A. "The Chemistry of Antitumor Antibiotics"; John Wiley: New York, 1979; pp 133–175. Skarbek, J. O.; Brady, L. R. *Lloydia* **1975**, *38*, 369. (b) Bakhaeva, G. P.; Berlin, Y. A.; Chuprunova, O. A.; Kolosov, M. N.; Peck, G. Y.; Piotrovich, L. A.; Shemyakin, M. M.; Vasina, I. V. *J. Chem. Soc., Chem. Commun.* **1967**, 10 and references cited therein.

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(3) Thiem, J.; Wessel, H. P. *Liebigs Ann. Chem.* **1981**, 2216.
(4) Roush, W. R.; Harris, D. J.; Lesur, B. M. *Tetrahdron Lett.* **1983**, *24*, 2227.

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