wt % aqueous fluoroboric acid (80 mg) were treated with hydrogen at 1000 psi and 80 °C for 8 h. The resulting mixture was filtered, concentrated in vacuo, dissolved in ethyl formate (5 mL) and triethylamine (1 mL), and heated to reflux for 50 min. The mixture was concentrated in vacuo and the residue was dissolved in tetrahydrofuran (5 mL) and then treated with a 1.0 M solution of lithium aluminum hydride in diethyl ether (4 mL) at 30–40 °C for 12 h. Aqueous sodium hydroxide (0.2 mL) was added and the resulting precipitate was removed by filtration. The filtrate was evaporated to give an oil (0.9 g), which, without further purification, was treated with 4-benzo[*b*]furanacetyl chloride [from 4-benzo[*b*]furanacetic acid (430 mg) according to the general method below] to give **14**, **15**, **13**, and **8**. (±)-(1β,2β,4α)-*N*-Methyl-*N*-[4-methoxy-2-(1-pyrrolidinyl)cyclohexyl]-4-benzo[*b*]-furanacetamide (**14**): 54 mg; 0.15 mmol; 7% from **12**; IR (neat) 1636 cm^{-1}; MS *m/e* (CI) 371 (5); NMR δ ($CDCl_3$) 7.61 (1 H, d, *J* = 2.3), 7.40 (1 H, d, *J* = 8), 7.22 (1 H, t, *J* = 8), 7.09 (1 H, d, *J* = 8), 6.90 (1 H, m), 4.40 (1 H, m, C_1-H), 3.95 (2 H, s), 3.34 (1 H, m, C_4-H), 3.31 (3 H, s), 3.00 (3 H, s), 2.40 (3 H, m), 2.20–1.85 (3 H, m), 1.7–1.1 (9 H, m). (±)-(1β,2β,4β)-*N*-Methyl-*N*-[4-methoxy-2-(1-pyrrolidinyl)cyclohexyl]-4-benzo[*b*]furanacetamide (**15**): 112 mg; 0.30 mmol; 14% from **12**; IR (neat) 1536 cm^{-1}; MS *m/e* (EI) 355 (3), 339 (5); NMR δ ($CDCl_3$) 7.60 (1 H, d, *J* = 2.2), 7.40 (1 H, d, *J* = 8), 7.22 (1 H, t, *J* = 8), 7.10 (1 H, d, *J* = 8), 6.89 (1 H, m), 4.70 (1 H, m, C_1-H), 3.98 (2 H, s), 3.36 (3 H, s), 3.26 (3 H, s), 3.26 (1 H, m, C_4-H), 2.5–2.2 (5 H, m), 2.1–1.8 (2 H, m), 1.7–1.4 (8 H, m). **13**: 38 mg; 1.0 mmol; 5% from **12**. **8**: 32 mg; 0.86 mmol; 4% from **12**.

(−)-(5α,7α,8β)-*N*-Methyl-7-(1-pyrrolidinyl)-1-oxaspiro[4.5]decan-8-amine [(−)-20]. (±)-(5α,7α,8β)-*N*-Methyl-7-(1-pyrrolidinyl)-1-oxaspiro[4.5]decan-8-amine (racemic **20**,[11] 4.6 g, 19 mmol) and L-(−)-di-*p*-toluoyltartaric acid (Aldrich Chemical Co., 7.8 g, 19 mmol) were dissolved in propan-2-ol (28 mL). The solution was cooled and left to stand at room temperature for 18 h and then filtered to give the mono L-(−)-di-*p*-toluoyltartaric acid salt of diamine **20** as white crystals (3.8 g, 6 mmol, 63%): $[\alpha]^{20}_D$ = −41.8° (*c* = 1, EtOH); mp = 151–152 °C. Anal. C, H, N. The parent diamine **20** was obtained by placing the above salt in 1 M aqueous sodium hydroxide solution (100 mL) and extracting with dichloromethane (4 × 25 mL). The combined dichloromethane extracts were dried over magnesium sulphate and concentrated in vacuo.

General Method for Formation of Amides 17, 18, 21–23, 25, and 26. A solution of the aromatic acetyl chloride (1.0 mmol) [prepared by the action of thionyl chloride on either 4-benzo[*b*]furanacetic acid[2] or 4-benzo[*b*]thiopheneacetic acid[2]] in dichloromethane (5 mL) was added dropwise to a stirred solution of diamine **16**,[11] **20**, or **24**[11] (1.0 mmol) in dichloromethane at 0 °C. After stirring for 10 min, diethyl ether was added until no further precipitation occurred. The product was collected by filtration, washed with diethyl ether, and dried in vacuo to yield the amine hydrochloride. Products were purified by recrystallization (recrystallization solvents in Table I) or by medium-pressure chromatography on silica gel using dichloromethane–methanol as eluant.

The enantiomeric purity of the separated enantiomers of amine **20** and of amides **21–23** was assayed by ^1H NMR spectroscopy using the chiral solvating agent method of Pirkle and Hoover[12] as described in part 1[2] of this series.

(+)-(5α,7α,8β)-*N*-Methyl-*N*-[7-(1-pyrrolidinyl)-1-oxaspiro[4,5]dec-8-yl]benzo[*b*]furan-4-acetamide monohydrochloride (**22**) has $[\alpha]^{20}_D$ = +28° (*c* = 0.9, CH_2Cl_2). (−)-(5β,7β,8α)-*N*-Methyl-*N*-[7-(1-pyrrolidinyl)-1-oxaspiro[4,5]dec-8-yl]benzo[*b*]furan-4-acetamide monohydrochloride (**21**) has $[\alpha]^{20}_D$ = −28° (*c* = 0.9, CH_2Cl_2). (−)-(5β,7β,8α)-*N*-Methyl-*N*-[7-(1-pyrrolidinyl)-1-oxaspiro[4,5]dec-8-yl]benzo[*b*]thiophene-4-acetamide monohydrochloride (**23**) has $[\alpha]^{20}_D$ = −23° (*c* = 0.56, CH_2Cl_2).

Biological Assays. μ and κ opioid receptor binding assays and analgesia assay were performed as previously described.[2] δ opioid receptor binding assay was performed by the method of Paterson.[13]

Acknowledgment. Elemental analyses were determined by CHN Analysis Limited, Leicester, UK. The NMR data were determined by Dr. D. Neuhaus (MRC Unit, Cambridge, UK). We thank Dr. I. Pattison for skilled experimental assistance.

Supplementary Material Available: 2D-absorption-mode double-quantum filtered COSY NMR Spectra of compound **13** and a discussion thereof (4 pages). Ordering information is given on any masthead page.

(12) Pirkle, W. H.; Hoover, D. J. *Top. Stereochem.* **1982**, *13*, 263.
(13) Cotton, R.; Kosterlitz, H. W.; Paterson, S. J.; Rance, M. J.; Traynor, J. R. *Br. J. Pharmac.* **1985**, *84*, 927.

Cephalosporins to Carbapenems: 1-Oxygenated Carbapenems and Carbapenams

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The photo "Wolff" rearrangement of readily available 2-diazoceph-3-em oxides (**1**) directly affords carbapen-2-ems, allowing a facile entry into a ring system previously accessible only by total synthesis, lengthly semisynthesis or fermentation. The chirality of the cephalosporin is accurately translated into the corresponding carbapenem. The resulting 1-oxocarbapenems (**2**) were selectively transformed through reduction into 1-oxygenated carbapenems and carbapenams (**3** and **4**, respectively). On microbiological screening, a carbapenem (**3c**) was found to possess a broad spectrum of activity. An interesting antibacterial profile was discovered for a carbapenam (**26**).

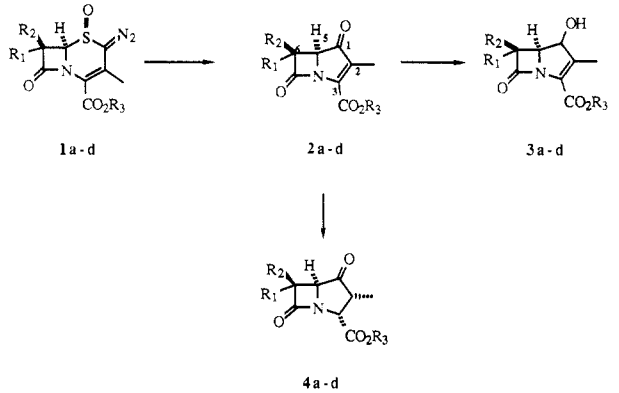
A prior communication[1] from our laboratory described chemistry leading to the synthesis of 1-substituted carbapenems. Since that time the 1-substituted carbapenem structural type has become a very productive area of research.[2] Our synthesis (Scheme I) transforms cephalosporins **1** directly into the corresponding 1-oxocarbapenems **2** with retention of chirality, thus leading to the synthesis of agents having the natural configuration at the crucial C-5; carbapenems **2** in turn can be reduced selectively to either 1-hydroxycarbapenems **3**, or to carbapenams **4** possessing the natural configuration at C-3.

We would now like to detail our studies utilizing this chemistry to synthesize substances with antibacterial activity. To this end, previously described carbapenem **3a** and carbapenam **4b** must be modified at C-6 to maximize antibacterial effectiveness. Accordingly, thienamycin-like **3c** and penicillin V-like **4d** were chosen as target structures,

(1) Rosati, R. L.; Kapili, L. V.; Morrissey, P. *J. Am. Chem. Soc.* **1982**, *104*, 4262.
(2) Shih, D. H.; Baker, F.; Cama, L.; Christensen, B. G. *Heterocycles* **1984**, *21*, 29 and references cited therein.

0022-2623/90/1833-0291$02.50/0

Scheme I

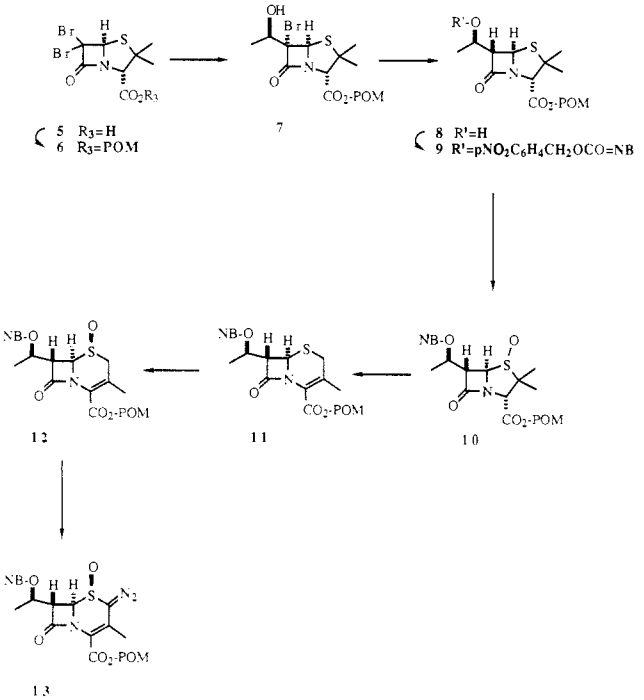


1a-d 2a-d 3a-d

4a-d

a $R_1=R_2=H$ $R_3=CH_2O_2CC(CH_3)_3$ =POM
b $R_1=R_2=H$ $R_3=CH(C_6H_5)_2$
c R_1= (R) $CH_3(OH)CH$ R2=H R_3=POM
d $R_1=H$ $R_2=C_5H_5CH_2OCONH$ R_3=POM

Scheme II



5 R_3=H
6 R_3=POM

7

8 R'=H
9 R'=p$NO_2C_6H_4CH_2OCO$=NB

10 11 12

13

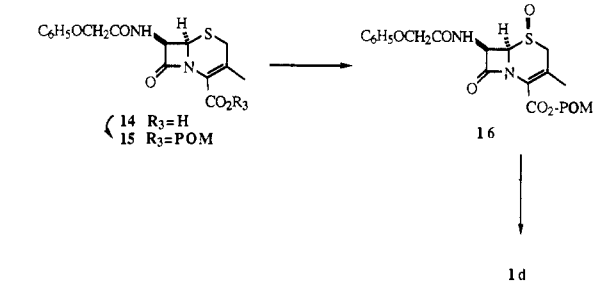
each possessing C-6 functionality appropriate to a carbapenem and a carbapenam nucleus, respectively. Since the free acids corresponding to **3c** and **4d** were expected to be extremely labile on the basis of our previous experience in the **3**/**4** series, we chose to prepare and screen for antibacterial activity the corresponding (pivaloyloxy)methyl ester prodrugs (POM).

Chemistry

The preparation of target carbapenem **3c** and carbapenam **4d** utilizing the chemistry of Scheme I necessitates the synthesis of the corresponding diazo cephalosporanates, which are subsequently subjected to photorearrangement conditions. Studies to extend the scope of the photorearrangement to diazo sulfones and to the 3-thio cephalosporanate case were also carried out and are detailed below.

Preparation of Diazo Cephalosporanate Sulfoxides. In order to prepare carbapenem **3c**, diazo cephalosporin precursor **1c** is required. To minimize possible side reactions arising from the presence of a free hydroxyl functionality, the photolysis should be performed on a

Scheme III

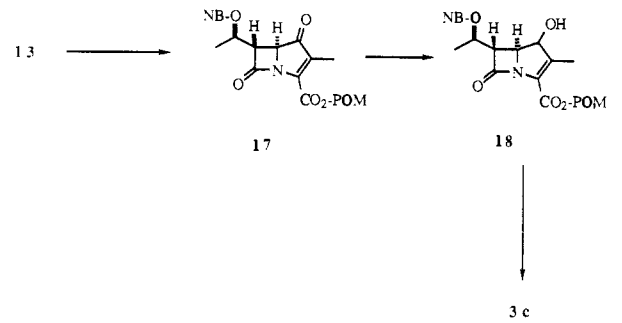


14 R_3=H
15 R_3=POM

16

1d

Scheme IV



13

17

18

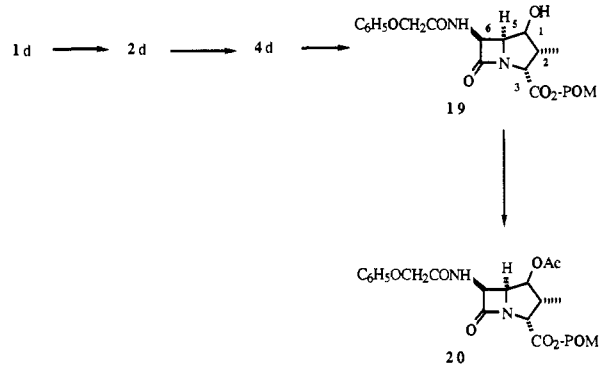
3c

protected form of **1c**. Accordingly, our immediate goal then became [(*p*-nitrobenzyl)oxy]carbonyl diazo sulfoxide **13** (Scheme II). The key intermediate in the synthesis of **13** is cephalosporin **11**, which we chose to prepare through rearrangement of an α-(*R*)-hydroxyethyl penicillin precursor. With use of the halogen-metal exchange chemistry of Kellogg,[3] 6,6-dibromopenicillanic acid (**5**) was transformed into the protected penicillin sulfoxide template **10**, which contains at C-5, C-6, and C-8 the "correct" stereochemistry for the ultimate carbapenem. On treatment with hot pyridinium phosphate,[4] penicillin sulfoxide **10** rearranged to cephalosporin **11**. After oxidation of **11** with hydrogen peroxide/formic acid,[5] two sulfoxides are obtained. It is necessary to separate isomers to obtain the pure β-sulfoxide **12** (major isomer) since the corresponding α-sulfoxide is resistant to diazo transfer; subsequent treatment of **12** with picryl azide[6]/diisopropylethylamine afforded diazo sulfoxide **13** (51%). Initial oxidation experiments on **11** employing the more sterically demanding *m*-chloroperbenzoic acid resulted in a mixture containing a higher proportion of the undesired α-sulfoxide. The reluctance of the α-sulfoxide corresponding to **12** (Scheme II) to undergo diazo transfer may be a consequence of the preference of cyclic sulfoxide carbanions to undergo electrophilic attack from the direction anti to the SO bond;[7] in the case of the α-cephalosporanate oxide, anti attack would require reagent approach from the more crowded β-face.[8]

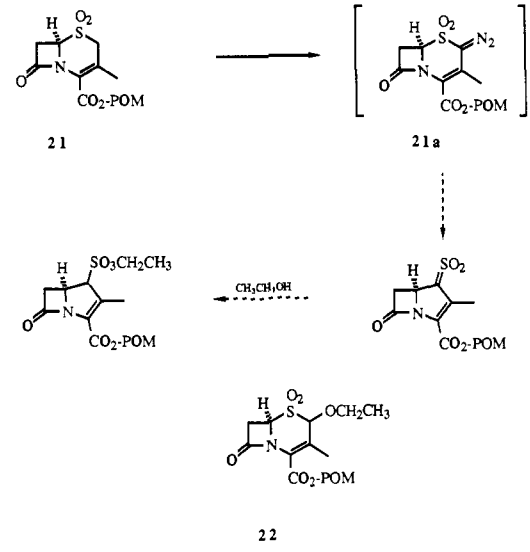
In order to prepare carbapenam **4d** (Scheme I) the diazo sulfoxide precursor **1d** is required. In a straightforward manner (Scheme III), phenoxyacetamido desacetoxy

(3) (a) Aimetti, J. A.; Kellogg, M. S. *Tetrahedron Lett.* **1979**, 3805. Also; DiNinno, F.; Beattie, T. R.; Christensen, B. G. *J. Org. Chem.* **1977**, *42*, 2960. (b) **5**: Clayton, J. P. *J. Chem. Soc.* C **1969**, 2123.
(4) Ellerton, N. V.; Paradise, W. F.; Sandford, P. E. U.S. Patent 3,725,399, April 3, 1973.
(5) Mangia, A. *Synthesis* **1978**, 361.
(6) Ebbinghaus, C. F.; Morrissey, P.; Rosati, R. L. *J. Org. Chem.* **1979**, *94*, 4697.
(7) Bory, S.; Marquet, A. *Tetrahedron Lett.* **1973**, 4155.
(8) Bremner, D. H.; Campbell, M. M. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2298.

Scheme V



Scheme VI



cephalosporin 14[9] was converted into the desired diazo sulfoxide **1d**. Sulfoxide separation is not an issue here since only the β-sulfoxide[10] **16** is formed in the oxidation of **15**.

Photorearrangement of 2-Diazo Cephalosporanates and Subsequent Chemistry. Photorearrangement of [(*p*-nitrobenzyl)oxy]carbonyl diazo cephalosporanate **13** (Scheme IV) proceeded uneventfully at −78 °C in methylene chloride (Pyrex vessel, sunlamp) to afford 1-oxocarbapenem **17**. A pyrex vessel allows passage of light in the wavelength range where diazocephalosporin oxides exhibit an intense UV absorption band (316–318 nm[8]); furthermore, Pyrex eliminates the more energetic UV light thus minimizing any secondary photochemistry of enone **17**. Because of its lability at room temperature, **17** was immediately reduced at −78 °C with tetrabutylammonium borohydride to afford one diasteromeric carbapenem alcohol **18** of undetermined configuration at C-1 but presumed to be β (58% from **13**); it is critical for a successful reduction to quench with acetic acid before pH 7.0 buffer workup to avoid strongly basic conditions that could destroy **18**. The presumed stereochemical course of the reduction would be consistent with borohydride attack from the less hindered α-face, which is analogous to the experience with 2-oxo-Δ^3-carbacephems[11]. Deblocking of **18** using Pd/C-catalyzed hydrogenolysis afforded target carbapenem **3c**, which was subsequently screened for microbiological activity. Spectral data on **3c** was totally consistent with the structure; proton NMR decoupling experiments confirmed that the protons assigned at C-1, C-5, C-6, and C-8 are attached on contiguous carbons. A β-lactam IR band is present at 1770 cm^{-1} and a confirmatory peak is observed in the mass spectrum at *m/e* 323 (high-resolution confirmed, $M^+ - H_2O$). The importance of the 6-(hydroxyethyl) side chain[12] to the stability of such structures is emphasized by our previous observation[1] that the corresponding C-6 unsubstituted carbapenem is unstable at room temperature.

Photorearrangement of diazocephalosporanate **1d** possessing the penicillin V side chain (Scheme V) gave enone **2d**, which was immediately reduced with zinc[13]/acetic acid/tetrahydrofuran at 0 °C to afford carbapenam **4d** as a single diastereomer (50% from **1d**); highly reactive Rieke zinc was necessary for a successful reduction due to rapid reaction at 0 °C, where **2d** is stable. Relative stereochemistry at C-2 and C-3 was assigned by analogy with **4b** (Scheme I), a structure solved by X-ray diffraction analysis.[1] The observed stereochemical result which involves formal cis addition of hydrogen to the enedione-like funtionality from the more hindered β-direction is noteworthy; zinc/acetic acid reduction of enediones[14] also proceeds with formal cis addition, but the hydrogens (in contrast to our case) prefer to approach from the least hindered direction. Two additional carbapenam analogues were synthesized; tetrabutylammonium borohydride reduction of **4d** gave hydroxycarbapenam **19** (one diastereomer, configuration at C-1 unknown) and subsequent treatment of **19** with acetic anhydride in the presence of 4-(dimethylamino)-pyridine afforded its corresponding acetate **20**. In contrast to the case of carbapenem **17**, the presumed stereochemical result of the borohydride reduction of carbapenam **4d** is less predictable with functionality on both the α- and β-faces. Proton NMR decoupling experiments on **19** allow for assignment and connectivity of the carbapenam ring protons at C-3, C-2, C-1, C-5, and C-6, but the small coupling constant variations in 5-membered rings are inadequate to allow a convincing assignment of configuration at C-1. Carbapenams **4d**, **19**, and **20** were subsequently examined for microbiological activity.

Mechanism and Scope of the Photorearrangement. The photorearrangement of diazo cephalosporanate sulfoxides is analogous to a Wolff rearrangement. The reaction apparently proceeds[1] with retention of configuration at the migratory center to afford an intermediate sulfine,[15] which in a facile second step extrudes sulfur to give the isolated enone. Our evidence for retention was based on an analysis of the coupling constant between the hydrogens at C-5 and C-6 in a 6-(acylamido)-1-oxocarbapenem, coupled with the reasonable assumption that the stereochemical marker at C-6 would not change configuration during the course of photolysis. A similar analysis performed on **3c** and **4d** confirms retention. For **3c**, $J_{5,6}$ equals 2 Hz, and for **4d**, $J_{5,6}$ equals 6 Hz, translating to a trans and cis relationship, respectively.[16]

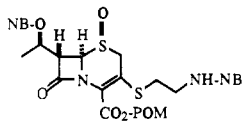
(9) van Heyningen, E. M.; Ahern, L. K. *J. Med. Chem.* **1968**, *11*, 933.
(10) Cooper, R. D. G.; DeMarco, P. V.; Cheng, J. C.; Jones, N. D. *J. Am. Chem. Soc.* **1969**, *91*, 1408.
(11) Martel, A.; Doyle, T. W.; Luh, B. *Can. J. Chem.* **1979**, *57*, 614.
(12) Cama, L. D.; Christensen, B. G. *J. Am. Chem. Soc.* **1978**, *100*, 8006.
(13) Rieke, R. D.; Uhm, S. J. *Synthesis* **1975**, 452.
(14) Pradhan, S. K.; Subrahmanyam, G.; Ringold, H. J. *J. Org. Chem.* **1967**, *32*, 3004 and references cited therein.
(15) Attempts to trap the sulfine by performing the photolysis in the presence of 2-mercaptobenzothiazole or 1,3-diphenylisobenzofuran failed to afford adducts.
(16) Demarco, P. V.; Nagarajan, R. *Cephalosporins and Penicillins: Chemistry and Biology*, Flynn, E. H., Ed.; Academic Press: New York, 1972; p 311.

Table I. In Vitro Susceptibility[a,b]

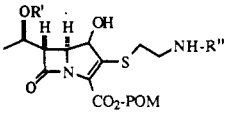
organism	MIC, μg/mL							
	3c	4d	19	20	26	T[c]	V	C
Streptococcus pyogenes 203	0.78					≤0.025	<0.025	0.05
S. aureus 005	3.12	100	25	>200	25	≤0.025	≤0.025	1.56
S. aureus 400	1.56	>200	50	>200	>200	<0.025	50	3.12
H. influenzae 012	6.25					0.78	6.25	3.12
E. coli 266	6.25	>200	>200	>200	6.25	0.1	100	3.12
E. coli 129	6.25	>200	>200	>200	>200	0.39	>200	50
K. pneumoniae 009	6.25					0.2	>200	1.56
K. pneumoniae 079		>200	>200	>200	12.5		>200	
M. morganii 001	50	>200	>200	>200	≤0.39	6.25	>200	>200
Serr. marc. 095		>200	>200	>200	25		>200	
Citrobacter diversus 031		>200	>200	>200	12.5		>200	
Enterococcus cloacae 009	12.5	>200	>200	>200	12.5	0.39	>200	>200
Pseudomonas aeruginosa 104	100	>200	>200	>200	200	3.12	>200	>200

[a] MIC (minimum inhibitory concentration) was determined by 2-fold serial dilution in brain–heart infusion broth as described previously.[26] [b] Prodrugs tested in presence of hog liver esterase (1:1.5). [c] T = thienamycin V = penicillin V, C = cefaclor.

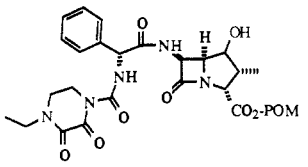
Chart I



23



24 R'=R"=NB
25 R'=R"=H



26

If diazo sulfones were to photorearrange analogously, carbapenemsulfonates (Scheme VI) might be produced. To test this possibility, cephalosporanate sulfone **21** was synthesized and by using the diazo-transfer reaction (picryl azide/diisopropylethylamine/potassium *tert*-butoxide) converted to diazo sulfone **21a**; **21a** is much more reactive than the corresponding sulfoxide[1,6] and cannot be isolated without decomposition. Ambient conditions are sufficient to decompose **21a** in the presence of ethanol; unfortunately, the only isolated product of this reaction arises from an insertion pathway (**22**). The Wolff rearrangement is thought to proceed through the intermediacy of a singlet carbene.[17] Diazo sulfoxides may favor the Wolff pathway since presumably the sulfoxide moiety can better stabilize a singlet carbene (resonance delocalization of the sulfur lone pair into the empty *p* orbital of the adjacent electron deficient sp^2-hybridized carbon atom).

Attempted Synthesis of 1-Hydroxythienamycin. With a carbapenem synthesis in hand, an obvious synthetic goal is 1-hydroxythienamycin POM ester **25** (Chart I). The precursor sulfoxide **23**[18] was subjected to diazo transfer and photorearrangement, followed by borohydride reduction to give carbapenem alcohol **24**.[19] However all attempts to remove the blocking groups through hydrogenolysis failed to afford **25**[20] but instead resulted in the formation of non-β-lactam-containing decomposition products, perhaps due to the mutual incompatibility of a highly activated β-lactam and a strongly nucleophilic amine. Strategies to replace the 1-hydroxyl of **24** by hydrogen using a variety of activation methods followed by reduction were thwarted by the propensity of **24** to decompose with β-lactam cleavage on attempted activation (for example: carbon tetrabromide/triphenylphosphine, carbon disulfide/methyl iodide). Concurrent studies employing organometallic and Wittig reagents were carried out to install a carbon–carbon bond at C-1 of the enone precursor to **24**; in all cases lack of success was due to β-lactam destruction.[21]

Microbiology of 1-Oxygenated Carbapenems and Carbapenams. Table I contains antibiotic screening data on carbapenem **3c** and carbapenams **4d**, **19**, and **20** along with data for thienamycin (T), penicillin V (V), and cefaclor (C). The broth dilution assays were performed in the presence of hog liver esterase in order to transform in situ the POM prodrug moiety to the corresponding acid, thus allowing the expression of antibacterial activity. Hydroxycarbapenem **3c** is a broad-spectrum antibiotic active against *Klebsiella pneumoniae* and demonstrating equal potency against both sensitive and β-lactamase producing *Staphylococcus aureus* and *Escherichia coli*[22];

(17) Meier, H.; Zeller, K. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 32.

(18) Cephalosporanate **23** was prepared from penicillin **10** (Scheme II) by employing the chemistry of Kukolja et al. and Scartazzini et al.: (a) Kukolja, S.; Lammert, S. R.; Gleissner, M. R. *J. Am. Chem. Soc.* **1976**, *98*, 5040. (b) Scartazzini, R.; Bickel, H. *Helv. Chem. Acta* **1974**, *57*, 1919. (c) Scartazzini, R.; Schneider, P.; Bickel, H. *Helv. Chem. Acta* **1975**, *58*, 2437. **23**: ^{1}H NMR ($CDCl_3$) δ 1.2 (s, 9 H), 1.5 (t, 3 H, *J* = 7 Hz), 2.8 (t, 2 H, *J* = 6 Hz), 4.5 (br s, 1 H), 5.1 (s, 2 H), 5.2 (s, 2 H), 7.3 (d, 2 H, *J* = 9 Hz), 7.4 (d, 2 H, *J* = 9 Hz), 8.1 (d, 2 H, *J* = 9 Hz), 8.2 (d, 2 H, *J* = 9 Hz).

(19) Proton NMR decoupling data on **24** allowed assignment and connectivity of protons at C-1, C-5, C-6, and C-8; ^{1}H NMR ($CDCl_3$) δ 1.2 (s, 9 H), 1.5 (d, 3 H, *J* = 7 Hz), 3.45 (dd, 1 H, *J* = 3, 7 Hz), 4.0 (dd, 1 H, *J* = 3, 6 Hz), 5.1 (m, 1 H), 5.45 (d, 1 H, *J* = 6 Hz), 5.9 (AB q, 2 H), 5.2–5.3 (m, 4 H); IR (CH_2Cl_2) 1780 cm^{-1}; UV (CH_2Cl_2) λ_{max} 326 nm; MS *m/e* 367.1133 (M^+ – $NO_2C_6H_4CH_2OCONH_2$ – $NO_2C_6H_4CH_2OCO_2H$) ($C_{17}H_{21}NO_6S$).

(20) After this work was completed, 1-hydroxythienamycins were reported to be synthesized and found to be less active than thienamycin. Andrus, A.; Baker, F.; Bouffard, F. A.; Cama, L. D.; Christensen, B. G.; Guthikonda, R. N.; Heck, J. V.; Johnston, D. B. R.; Leanza, W. J.; Ratcliffe, R. W.; Salzmann, T. N.; Schmitt, S. M.; Shih, D. H.; Shah, N. V.; Wildonger, K. J.; Wilkening, R. R. *Recent Advances in the Chemistry of β-Lactam Antibiotics*; Brown, A. G.; Roberts, S. M., Eds.; Royal Society of Chemistry: London, 1985; Special Publication No. 52, p 86.

(21) Similar synthetic studies in the carbapenam series (**19**,**4d**) likewise failed for the same reason.

however its spectrum and potency while similar to that of a cephalosporin (cefaclor) do not compare favorably to thienamycin in potency. As a control when the broth dilution assay was conducted in the absence of hog liver esterase, **3c** was inactive.

The 6-(phenoxyacetamido)carbapenams (**4d**, **19**, and **20**), on the other hand, were found to be poor antibiotics, much less active than penicillin V; of the three structural types, the carbapenam alcohol **19** was the most active, exhibiting a weak Gram-positive spectrum. Realizing that the 6-phenoxyacetamido (penicillin V) side chain was perhaps suboptimal for the carbapenam nucleus, we accordingly employed the chemistry of Schemes III/V to prepare the piperacillin-like carbapenam alcohol **26** (Chart I). Upon antibacterial testing, **26**[23] (Table I) was found to possess an interesting Gram-negative spectrum, with high potency against *Morganella morganii*. Apparently, as in the penicillin situation, the spectrum of carbapenams can be varied by modification at the 6-position.

Conclusions

Our photorearrangement directly relates the cephalosporin and carbapenem classes of β-lactam antibiotics. While at this time our chemistry is limited to the synthesis of the 1-oxygenated structural types, the utility of the rearrangement to afford substances with antibacterial activity has been demonstrated.

Experimental Section

Melting points (uncorrected) were determined with a Thomas-Hoover capillary apparatus. NMR spectra were recorded with a Varian T-60 spectrometer using tetramethylsilane (Me_4Si) as an internal standard and also on a Varian XL-100 spectrometer. Chemical shifts are reported in parts per million relative to Me_4Si as an internal standard. Mass spectra (MS) were recorded with an AEI MS-30 spectrometer equipped with a DS-50 data system. Infrared spectra (IR) were recorded on a Perkin-Elmer 237B spectrophotometer, and ultraviolet spectra (UV) were obtained on a Beckman DB spectrophotometer. TLC was performed by using precoated 0.25 mm thick silica gel 60 plates (Merck) and column chromatography with silica gel (Merck, 70–230 mesh). Sensitive compounds were in general chromatographed on either Mallinckrodt "Silicar CC-7" or on formamide deactivated silica gel (prepared by evaporation to dryness of an acetone slurry containing 30 g of silica gel and 15 mL of formamide).

(Pivaloyloxy)methyl 6,6-Dibromopenicillanate (6). 6,6-Dibromopenicillanic acid (**5**)[3b] (10 g, 29 mmol) in 200 mL of dimethylformamide containing triethylamine (4.17 mL, 30 mmol) and potassium bicarbonate (3.0 g, 30 mmol) was treated with chloromethyl pivalate (4.3 mL, 29.9 mmol). After stirring for 5 h at room temperature, reaction monitoring by TLC (18:1 acetone/water) indicated appreciable starting material. Further portions of chloromethyl pivalate (4.3 mL, 29.9 mmol) and potassium bicarbonate (3.0 g, 30 mmol) were added, and the reaction was allowed to proceed for an additional 16 h at room temperature. The reaction mixture was evaporated to dryness in vacuo and the residue was chromatographed on silica gel using 30:1 methylene chloride/ethyl acetate as eluant (monitored by TLC). There resulted (pivaloyloxy)methyl 6,6-dibromopenicillanate (**6**) as a foam (1.73 g, 12.6%): R_f 0.77 (18:1 acetone/water); IR (CH_2Cl_2) 1790, 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.1 (s, 9 H), 1.45 (s, 3 H), 1.65 (s, 3 H), 4.55 (s, 1 H), 5.8 (m, 2 H).

(Pivaloyloxy)methyl 6α-Bromo-6β-[1(*R*)-hydroxyethyl]-penicillanate (7). Under a nitrogen atmosphere and in a flame-dried three-neck flask, (pivaloyloxy)methyl 6,6-dibromopenicillanate (**6**, 1.0 g, 2.11 mmol) was dissolved in 25 mL of dry, freshly distilled tetrahydrofuran and the resulting solution was cooled to −78 °C. A 2.7 M ether solution of *tert*-butylmagnesium chloride (1.03 mL, 2.78 mmol) was added via a syringe and the reaction mixture was stirred for 1 h at −78 °C. Acetaldehyde (0.29 mL, 5.19 mmol) was then added, and the reaction was allowed to proceed for an additional hour at −78 °C. The reaction mixture was quenched by the addition of acetic acid (0.22 mL, 3.86 mmol), allowed to warm to room temperature, and evaporated to dryness in vacuo. The residue was distributed between equal volumes of chloroform and water, and the aqueous phase was extracted with 2 fresh portions of chloroform. The chloroform phase and washes were combined, back-washed with water, washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated to dryness to yield (pivaloyloxy)methyl 6α-bromo-6β-[1-(*R*)-hydroxyethyl]penicillanate (**7**, 1.01 g, quantitative, oil): IR (CH_2Cl_2) 1775, 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.4 (s, 9 H), 4.6 (s, 1 H), 5.9 (m, 2 H).

(Pivaloyloxy)methyl 6α-[1(*R*)-Hydroxyethyl]penicillanate (8). Hydrogenolysis catalyst (1.01 g of 10% palladium on carbon) was slurried in 10 mL of water and prehydrogenated for 0.25 h (50 psi, room temperature). (Pivaloyloxy)methyl 6α-bromo-6β-[1(*R*)-hydroxyethyl]penicillanate (**7**, 1.01 g, assume 2.11 mmol) in 10 mL of tetrahydrofuran was added and hydrogenolysis was allowed to proceed for 1.5 h. After filtration to remove the catalyst, the tetrahydrofuran was evaporated in vacuo from the combined filtrate and washes. The product was extracted from the aqueous residue into 4 portions of ethyl acetate, and the ethyl acetate extracts were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated to yield (pivaloyloxy)-methyl 6α-[1(*R*)-hydroxyethyl]penicillanate (249 mg). The catalyst cake was slurried in approximately 100 mL of tetrahydrofuran, the catalyst was removed by filtration, and the filtrate was evaporated in vacuo to yield an additional 278 mg of **8**. The combined yield of **8** was 527 mg (70%, foam): R_f 0.48 (4:1 chloroform/ethyl acetate); IR (CH_2Cl_2) 1770, 1760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.2 (s, 9 H), 3.3 (dd, 2 H, J = 3, 7 Hz), 4.4 (s, 1 H), 5.8 (m, 2 H).

(Pivaloyloxy)methyl 6α-[1(*R*)-[[[(*p*-Nitrobenzyl)oxy]-carbonyl]oxy]ethyl]penicillanate (9). (Pivaloyloxy)methyl 6α-[1(*R*)-hydroxyethyl]penicillanate (**8**, 3.2 g, 9.54 mmol) was dissolved in 100 mL of methylene chloride and cooled to 0 °C. Diisopropylethylamine (2.19 mL, 12.7 mmol), 4-(dimethylamino)pyridine (1.28 g, 10.5 mmol) and *p*-nitrobenzyl chloroformate (2.72 g, 12.6 mmol) were added. The reaction mixture, after stirring for 16 h at room temperature, was washed with water, dried over anhydrous sodium sulfate, filtered, and evaporated to crude product, which was chromatographed on silica gel using 15:1 chloroform/ethyl acetate as eluant to yield purified (pivaloyloxy)methyl 6α-[1(*R*)-[[[(*p*-nitrobenzyl)oxy]carbonyl]oxy]-ethyl]penicillanate (**9**, 5 g, 97%, oil): R_f 0.7 (ether); ^1H NMR ($CDCl_3$) δ 1.0 (s, 9 H), 1.5 (s, 3 H), 1.6 (s, 3 H), 4.4 (s, 1 H), 7.4 (d, 2 H, J = 8 Hz), 8.2 (d, 2 H, J = 8 Hz).

(Pivaloyloxy)methyl 6α-[1(*R*)-[[[(*p*-Nitrobenzyl)oxy]-carbonyl]oxy]ethyl]-1-oxopenicillanate (10). (Pivaloyloxy)-methyl 6α-[1(*R*)-[[[(*p*-nitrobenzyl)oxy]carbonyl]oxy]ethyl]-penicillanate (**9**, 5 g, 9.28 mmol) was allowed to react with *m*-chloroperbenzoic acid (2.2 g, 80% pure, 10.2 mmol) in 200 mL of methylene chloride at 0 °C for 16 h. The reaction mixture was extracted with saturated aqueous sodium bicarbonate and water,

(22) (a) Acetylation of the C-1 or C-8 hydroxyl results in abolition of antibacterial activity. Thienamycin C-8 acetate has been reported to be less active than thienamycin: Leanza, W. J., Wildonger, K. J.; Hannah, J.; Shih, D. H.; Ratcliffe, R. W.; Barash, L.; Walton, E.; Firestone, R. A.; Patel, G. F.; Kahan, F. M.; Kahan, J. S.; Christensen, B. G. *Recent Advances in the Chemistry of β-Lactam Antibiotics*; Gregory, G. I., Ed.; Royal Society of Chemistry: London, 1980; Special Publication No. 38, p 240. (b) The free acid corresponding to **3c** (synthesized by hydrogenolysis of the analogously prepared benzyl ester precursor) was discovered to be less active, presumably due to instability.

(23) Spectral data of **26**: IR (CH_2Cl_2) 1775, 1750, 1715, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) 1.1 (d, 3 H, J = 7 Hz), 1.2 (s, 9 H), 2.8 (m, 1 H), 3.6–3.8 (m, 4 H), 3.9–4.1 (m, 4 H), 4.2 (d, 1 H, J = 7 Hz), 5.2 (t, 1 H, J = 5 Hz), 5.5 (d, 1 H, J = 6 Hz), 5.9 (AB q, 2 H), 7.2–7.7 (m, 5 H).

(24) There was a very low mass balance in the chromatography which may be due to the use of silica gel absorbent rather than less active "Silicar CC-7" or formamide-deactivated silica gel.

(25) Kemp, J. E. G.; Closier, M. D.; Stefaniak, M. H. *Tetrahedron Lett.* **1979**, 3785.

(26) Retsema, J. A.; English, A. R.; Girard, A. E. *Antimicrob. Agents Chemother.* **1980**, *17*, 615.

dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was chromatographed using 4:1 chloroform/ethyl acetate to yield (pivaloyloxy)methyl 6α-[1(*R*)-[[[(*p*-nitrobenzyl)oxy]carbonyl]oxy]ethyl]-1-oxopenicillanate (**10**, 2.55 g, 50%, foam): R_f 0.6 (4:1 chloroform/ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 1.2 (s, 9 H), 1.5 (d, 3 H, J = 7 Hz), 1.65 (s, 3 H), 3.8 (dd, 1 H, J = 3, 7 Hz), 4.5 (s, 1 H), 5.0 (d, 1 H, J = 3 Hz), 5.8 (AB q, 2 H).

(Pivaloyloxy)methyl 7α-[1(*R*)-[[[(*p*-Nitrobenzyl)oxy]carbonyl]oxy]ethyl]-3-methylceph-3-em-4-carboxylate (**11**). A solution of (pivaloyloxy)methyl 6α-[1(*R*)-[[[(*p*-nitrobenzyl)oxy]carbonyl]oxy]ethyl]-1-oxopenicillanate (**10**, 2.5 g, 4.6 mmol) in 400 mL of dioxane (Soxhlet apparatus with thimble containing 4-Å molecular sieves and activity grade I alumina) was allowed to reflux for 20 h in the presence of 1 mL of 80% phosphoric acid[4] and 30 mL of pyridine. The dioxane solution was evaporated to dryness and the residue was dissolved in methylene chloride. After washes with saturated sodium bicarbonate and brine, followed by drying over anhydrous sodium sulfate, the methylene chloride solution was evaporated to dryness and the residue was chromatographed on a silica gel column employing 30:1 chloroform/ethyl acetate as eluant. The yield of (pivaloyloxy)methyl 7α-[1(*R*)-[[[(*p*-nitrobenzyl)oxy]carbonyl]oxy]ethyl]-3-methylceph-3-em-4-carboxylate (**11**) was 570 mg (23%, foam): R_f 0.5 (ether), ^{1}H NMR ($CDCl_3$) δ 1.2 (s, 9 H), 1.4 (d, 3 H, J = 7 Hz), 2.0 (s, 3 H), 4.6 (d, 1 H, J = 2 Hz), 5.8 (AB q, 2 H).

(Pivaloyloxy)methyl 7α-[1(*R*)-[[[(*p*-Nitrobenzyl)oxy]carbonyl]oxy]ethyl]-3-methyl-1β-oxoceph-3-em-4-carboxylate (**12**). (Pivaloyloxy)methyl 7α-[1(*R*)-[[[(*p*-nitrobenzyl)oxy]carbonyl]oxy]ethyl]-ceph-3-em-4-carboxylate (**11**, 570 mg, 1.06 mmol) was dissolved in 75 mL of methylene chloride. Formic acid (0.30 mL, 7.95 mmol) and 30% hydrogen peroxide (0.22 mL, 2.15 mmol) were added and the mixture was stirred for 2 days at room temperature. The reaction mixture was extracted with water, dried over anhydrous sodium sulfate, filtered, and evaporated in vacuo. The residue was chromatographed on silica gel, using 1:3 chloroform/ethyl acetate as eluant with TLC monitoring. The yield of (pivaloyloxy)methyl 7α-[1(*R*)-[[[(*p*-nitrobenzyl)oxy]carbonyl]oxy]ethyl]-3-methyl-1β-oxoceph-3-em-4-carboxylate (**12**) was 224 mg (38%, amorphous solid): R_f 0.1 (4:1 chloroform/ethyl acetate); IR (CH_2Cl_2) 1775, 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.2 (s, 9 H), 1.4 (d, 3 H, J = 7 Hz), 2.0 (br s, 3 H), 4.4 (br s, 1 H), 5.2 (s, 2 H), 5.8 (AB q, 2 H). The corresponding α-sulfoxide was also isolated (99 mg, R_f 0.3).

(Pivaloyloxy)methyl 7α-[1(*R*)-[[[(*p*-Nitrobenzyl)oxy]carbonyl]oxy]ethyl]-2-diazo-3-methyl-1β-oxoceph-3-em-4-carboxylate (**13**). (Pivaloyloxy)methyl 7α-[1(*R*)-[[[(*p*-nitrobenzyl)oxy]carbonyl]ethyl]-3-methyl-1β-oxoceph-3-em-4-carboxylate (**12**, 224.4 mg, 0.406 mmol) was allowed to react in 75 mL of methylene chloride with picryl azide (339.5 mg, 1.34 mmol) in the presence of diisopropylethylamine (0.137 mL, 0.797 mmol) for 24 h at −10 to 0 °C. Additional reagents (50% more azide and amine) were added the next day. After a total reaction time of 2.3 days at 0 °C, the reaction mixture was evaporated to dryness and the crude product was chromatographed on "Silicar CC-7" using 10:1 chloroform/ethyl acetate as eluant to yield purified (pivaloyloxy)methyl 7α-[1(*R*)-[[[(*p*-nitrobenzyl)oxy]carbonyl]oxy]ethyl]-2-diazo-3-methyl-1β-oxoceph-3-em-4-carboxylate (**13**, amorphous solid, 120 mg, 51%): R_f 0.75 (4:1 chloroform/ethyl acetate); IR (CH_2Cl_2) 2080, 1775, 1725 cm^{-1}.

(Pivaloyloxy)methyl 6α-[1(*R*)-[[[(*p*-Nitrobenzyl)oxy]carbonyl]oxy]ethyl]-2-methyl-1-oxocarbapen-2-em-3-carboxylate (**17**). A solution of (pivaloyloxy)methyl 7α-[1(*R*)-[[[(*p*-nitrobenzyl)oxy]carbonyl]oxy]ethyl]-2-diazo-3-methyl-1β-oxoceph-3-em-4-carboxylate (**13**, 120 mg, 0.21 mmol) in 120 mL of methylene chloride was irradiated in a Pyrex vessel for 0.75 h with a sun lamp (rapid stream of nitrogen) at a −55 °C pot temperature. IR was employed to follow the loss of the 2080-cm^{-1} diazo band. When reaction was complete, IR confirmed the presence of (pivaloyloxy)methyl 6α-[1(*R*)-[[[(*p*-nitrobenzyl)oxy]carbonyl]oxy]ethyl]-2-methyl-1-oxocarbapen-2-em-3-carboxylate (**17**, 1810 cm^{-1}). The reaction solution was immediately evaporated to dryness and **17** employed in the next step (quantitative yield assumed).

(Pivaloyloxy)methyl 6α-[1(*R*)-[[[(*p*-Nitrobenzyl)oxy]carbonyl]oxy]ethyl]-1-hydroxy-2-methylcarbapen-2-em-3-carboxylate (**18**). Freshly prepared (pivaloyloxy)methyl 6α-[1(*R*)-[[[(*p*-nitrobenzyl)oxy]carbonyl]oxy]ethyl]-2-methyl-1-oxocarbapen-2-em-3-carboxylate [**17**, synthesized from 120 mg (0.21 mmol) of **13**] in 20 mL of methylene chloride was cooled to −78 °C and treated with 67 mg (0.26 mmol) of tetrabutylammonium borohydride. After 1 h, 4 μL (0.07 mmol) of acetic acid was added and the solution was washed with pH 7.0 buffer, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was chromatographed on "Silicar CC-7" using 10% chloroform/ethyl acetate as eluant to yield 62.6 mg (58% from **13**, foam) of (pivaloyloxy)methyl 6α-[1-[[[(*p*-nitrobenzyl)oxy]carbonyl]oxy]-ethyl]-1-hydroxy-2-methylcarbapen-2-em-3-carboxylate (**18**): R_f 0.25 (4:1 chloroform/ethyl acetate); IR (CH_2Cl_2) 1775, 1750 cm^{-1}.

(Pivaloyloxy)methyl 6α-[1(*R*)-Hydroxyethyl]-1-hydroxy-2-methylcarbapen-2-em-3-carboxylate (**3c**). (Pivaloyloxy)-methyl 6α-[1(*R*)-[[[(*p*-nitrobenzyl)oxy]carbonyl]oxy]ethyl]-1-hydroxy-2-methylcarbapen-2-em-3-carboxylate (**18**, 62.6 mg, 0.12 mmol) was hydrogenolyzed in 2 mL of ethyl acetate over 30 mg of 5% Pd/C for 0.75 h. After evaporation to dryness, the residue was chromatographed on "Silicar CC-7" with ethyl acetate as eluant to afford purified (pivaloyloxy)methyl 6α-[1(*R*)-hydroxyethyl]-1-hydroxy-2-methylcarbapen-2-em-3-carboxylate (**3c**, 21.1 mg, 51.3%, foam): R_f 0.5 (ethyl acetate); IR (CH_2Cl_2) 1770, 1730 (sh), 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.3 (s, 9 H), 1.4 (d, 3 H, J = 6 Hz), 2.2 (br s, 3 H), 3.1 (m, 1 H), 3.9 (dd, 1 H, J = 2, 5 Hz), 4.2 (m, 1 H), 5.0 (br d, 1 H, J = 5 Hz), 5.9 (AB q, 2 H); UV (CH_2Cl_2) λ_{max} 275 nm; MS m/e 323.1362 ($M^+ - H_2O$)($C_{16}H_{21}NO_6$).

(Pivaloyloxy)methyl 3-Methyl-7-(2-phenoxyacetamido)-ceph-3-em-4-carboxylate (**15**). 3-Methyl-7-(2-phenoxyacetamido)ceph-3-em-4-carboxylic acid (**14**,[9] 69.6 g, 0.2 mol) was dissolved in 300 mL of dimethylformamide and treated in sequence with triethylamine (20.2 g, 0.2 mol), potassium bicarbonate (40 g, 0.4 mol), and chloromethyl pivalate (33 g, 0.22 mol). After 24 h, the reaction mixture was poured into 3 L of ether. The ether mixture was washed with water, 1 N aqueous hydrochloric acid, and brine, dried over anhydrous sodium sulfate, filtered, and evaporated to dryness to afford (pivaloyloxy)methyl-3-methyl-7-(2-phenoxyacetamido)ceph-3-em-4-carboxylate (**15**, 75.5 g, 82%, oil): IR (CH_2Cl_2) 1776, 1750, 1685 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.2 (s, 9 H), 2.0 (s, 3 H), 3.4 (AB q, 2 H), 5.1 (d, 1 H, J = 5 Hz), 6.0 (m, 2 H).

(Pivaloyloxy)methyl 3-Methyl-1β-oxo-7-(2-phenoxyacetamido)ceph-3-em-4-carboxylate (**16**). (Pivaloyloxy)methyl 3-methyl-7-(2-phenoxyacetamido)ceph-3-em-4-carboxylate (**15**, 73.9 g, 0.16 mol) in 2 L of methylene chloride, maintained at 0–5 °C, was oxidized with *m*-chloroperbenzoic acid (34.5 g, 80% pure, 0.16 mol), which was added in 2 portions over ca. 1 h. After 2 h, the reaction mixture was washed with saturated aqueous sodium bicarbonate and brine, dried over anhydrous sodium sulfate, and evaporated to dryness to yield crystalline (pivaloyloxy)methyl 3-methyl-1β-oxo-7-(2-phenoxyacetamido)ceph-3-em-4-carboxylate (**16**, 41 g, 54%): mp 138–140 °C (from methylene chloride); ^{1}H NMR ($CDCl_3$) δ 1.1 (s, 9 H), 2.0 (s, 3 H), 3.8 (s, 2 H), 4.4 (s, 2 H), 4.9 (d, 1 H, J = 5 Hz), 5.7–6.1 (m, 3 H), 6.7–7.4 (m, 5 H), 8.0 (d, 1 H, J = 10 Hz).

(Pivaloyloxy)methyl 2-Diazo-3-methyl-1β-oxo-7-(2-phenoxyacetamido)ceph-3-em-4-carboxylate (**1d**). (Pivaloyloxy)-methyl 3-methyl-7-(2-phenoxyacetamido)ceph-3-em-4-carboxylate (**16**, 4.78 g, 10 mmol) in 400 mL of methylene chloride was treated sequentially at 0 °C with diisopropylethylamine (1.9 g, 15 mmol), potassium *tert*-butoxide (1.7 g, 15 mmol) and picryl azide (5.08 g, 20 mmol). After 0.5 h, the reaction mixture was treated with 2.22 mL (30 mmol) of trifluoroacetic acid (to neutralize the bases), filtered, and evaporated to a black gum. The crude product was chromatographed on silica gel (4:1 methylene chloride/ethyl acetate as eluant) to yield (pivaloyloxy)methyl 2-diazo-3-methyl-1β-oxo-7-(2-phenoxyacetamido)ceph-3-em-4-carboxylate (**1d**, 2.4 g, 48%, foam): R_f 0.33 (4:1 chloroform/ethyl acetate); IR (CH_2Cl_2) 2080, 1800, 1725, 1720, 1690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.2 (s, 9 H), 2.3 (s, 3 H), 4.5 (s, 2 H), 4.8 (d, 1 H, J = 5 Hz), 5.8 (AB q, 2 H), 6.2 (dd, 1 H, J = 5, 10 Hz), 6.7–7.3 (m, 5 H), 7.9 (d, 1 H, J = 10 Hz).

(Pivaloyloxy)methyl 2-Methyl-1-oxo-6-(2-phenoxyacetamido)carbapen-2-em-3-carboxylate (**2d**). (Pivaloyloxy)methyl 2-diazo-3-methyl-1β-oxo-7-(2-phenoxyacetamido)ceph-3-em-4-carboxylate (**1d**, 200 mg, 0.4 mmol) in 50 mL of methylene chloride

at a pot temperature of −55 °C was photolyzed for 0.5 h (Pyrex vessel, sun lamp, stream of nitrogen). IR confirmed the presence of (pivaloyloxy)methyl 2-methyl-1-oxo-6-(2-phenoxyacetamido)carbapen-2-em-3-carboxylate (**2d**, 1805 cm^{-1}). The reaction was presumed to proceed quantitatively. Before evaporation to dryness, 0.5 g of W-2 Raney nickel (sulfur scavenger) was added; after 0.5 h at −55 °C, the reaction mixture was filtered and the filtrate was evaporated to dryness (used immediately); IR (CH_2Cl_2) 1805, 1740, 1715, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.1 (s, 9 H), 2.0 (s, 3 H), 4.1 (d, 1 H, J = 8 Hz), 4.8 (t, 1 H, J = 8 Hz), 5.8 (AB q, 2 H), 6.8–7.2 (m, 5 H), 7.4 (d, 1 H, J = 8 Hz).

(Pivaloyloxy)methyl 2-Methyl-1-oxo-6-(2-phenoxyacetamido)carbapenam-3-carboxylate (4d). Freshly prepared (pivaloyloxy)methyl 2-methyl-1-oxo-6-(2-phenoxyacetamido)-carbapen-2-em-3-carboxylate [**2d**, prepared from 200 mg (0.4 mmol) of (pivaloyloxy)methyl 2-diazo-3-methyl-1β-oxo-7-(2-phenoxyacetamido)ceph-3-em-4-carboxylate (**1d**)] was taken up into 1 mL of tetrahydrofuran, and the solution was added to a stirred slurry of 2 g (31 mmol) of Rieke zinc powder[13] in 6 mL of acetic acid/tetrahydrofuran (7:3) maintained at 0–5 °C. After stirring for 1 h at this temperature, the reaction mixture was diluted with toluene, filtered, and evaporated to dryness in vacuo to yield (pivaloyloxy)methyl 2-methyl-1-oxo-6-(2-phenoxyacetamido)carbapenam-3-carboxylate (**4d**, 89 mg, 50% from **1d**, foam). This material is of sufficient purity for subsequent chemistry. For spectral and biological-screening purposes, a purer sample can be obtained by chromatography on formamide-deactivated silica gel using chloroform/ethyl acetate 6:1 as eluant: R_f 0.34 (6:1 chloroform/ethyl acetate); IR (CH_2Cl_2) 1790, 1750, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.2 (s, 9 H), 4.1 (d, 1 H, J = 6 Hz), 4.4 (s, 2 H), 5.0 (t, 1 H, J = 6 Hz), 5.2 (d, 1 H, J = 9 Hz), 5.8 (m, 2 H), 6.8–7.4 (m, 5 H); MS m/e 312.1325 ($M^+ - C_6H_5OCH{=}CO$)($C_{14}H_{20}N_2O_6$).

(Pivaloyloxy)methyl 1-Hydroxy-2-methyl-6-(2-phenoxyacetamido)carbapenam-3-carboxylate (19). (Pivaloyloxy)-methyl 2-methyl-1-oxo-6-(2-phenoxyacetamido)carbapenam-3-carboxylate (**4d**, 102 mg, 0.23 mmol) in 3 mL of methylene chloride at −78 °C was allowed to react with tetrabutylammonium borohydride (15 mg, 0.06 mmol). After 1 h, acetic acid (13 μL, 0.23 mmol) was added and the solution was extracted with water and brine, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was chromatographed on silica gel (4:1 methylene chloride/ethyl acetate) to afford (pivaloyloxy)methyl 1-hydroxy-2-methyl-6-(2-phenoxyacetamido)carbapenam-3-carboxylate (**19**, 13 mg, 13%,[24] foam): R_f 0.26 (4:1 chloroform/ethyl acetate); IR (CH_2Cl_2) 1775, 1750, 1675 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.1 (d, 3 H, J = 7 Hz), 1.2 (s, 9 H), 2.8 (m, 1 H), 3.8 (t, 1 H, J = 5 Hz), 4.2 (t, 1 H, J = 5 Hz), 4.6 (d, 1 H, J = 7 Hz), 4.65 (s, 2 H), 5.1 (t, 1 H, J = 5 Hz), 5.8 (AB q, 2 H), 6.8–7.2 (m, 5 H).

(Pivaloyloxy)methyl 1-Acetoxy-2-methyl-6-(2-phenoxyacetamido)carbapenam-3-carboxylate (20). (Pivaloyloxy)-methyl 1-hydroxy-2-methyl-6-(2-phenoxyacetamido)carbapenam-3-carboxylate [**19**, prepared as previously described from **4d** (135 mg, 0.3 mmol) and used without purification] in 15 mL of methylene chloride was cooled to −10 °C and treated in sequence with pyridine (24 mg, 0.3 mmol), acetic anhydride (31 mg, 0.3 mmol), and 4-(dimethylamino)pyridine (4 mg, 0.03 mmol). After 1 h at −10 °C, TLC (4:1 chloroform/ethyl acetate) indicated complete acetylation. The reaction mixture was diluted with toluene and evaporated to dryness in vacuo. Chromatography on silica gel (20:1 methylene chloride/ethyl acetate) gave (pivaloyloxy)methyl 1-acetoxy-2-methyl-6-(2-phenoxyacetamido)carbapenam-3-carboxylate (**20**, 10 mg, 7%,[24] foam): R_f 0.36 (4:1 chloroform/ethyl acetate); IR (CH_2Cl_2) 1780, 1750, 1685 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.2 (s, 9 H), 2.0 (s, 3 H), 5.8 (AB q, 2 H), 6.7–7.4 (m, 5 H).

(Pivaloyloxy)methyl 3-Methylceph-3-em-4-carboxylate Sulfone (21). According to the procedure for the preparation of **6**, 3-methylceph-3-em-4-carboxylic acid[25] (12.9 g, 65 mmol) was converted into the corresponding POM ester (15.8 g, 79%, oil): IR (CH_2Cl_2) 1770, 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.2 (s, 9 H), 2.1 (s, 3 H), 4.7 (dd, 1 H, J = 2, 5 Hz), 5.8 (m, 2 H). (Pivaloyloxy)methyl 3-methylceph-3-em-4-carboxylate (15.7 g, 50 mmol) in 1 L of methylene chloride was cooled to 0 °C and treated with 21.56 g (100 mmol, 80% pure) of *m*-chloroperbenzoic acid. After stirring at 0 °C for 1 h and at 25 °C for 24 h, the reaction mixture was washed with water and brine, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was chromatographed on silica gel using ethyl acetate as eluant to yield 16.0 g (97%) of **21** (amorphous solid): R_f 0.4 (4:1 chloroform/ethyl acetate); ^1H NMR (DMSO-d_6) δ 1.2 (s, 9 H), 2.0 (s, 3 H), 5.2 (dd, 1 H, J = 2, 5 Hz), 5.8 (AB q, 2 H).

(Pivaloyloxy)methyl 2-Ethoxy-3-methylceph-3-em-4-carboxylate Sulfone (22). A solution of 1.04 g (3 mmol) of (pivaloyloxy)methyl 3-methylceph-3-em-4-carboxylate sulfone (**21**) in 90 mL of methylene chloride at 0 °C was treated sequentially with 426 mg (3.3 mmol) of diisopropylethylamine, 370 mg (3.3 mmol) of potassium *tert*-butoxide, and 1.5 g (6 mmol) of picryl azide. At 0.5 h, TLC indicated that the reaction had proceeded to completion, and IR spectroscopy confirmed the presence of the diazo functionality of **21a** (2080 cm^{-1}). After trifluoroacetic acid (0.49 mL, 6.6 mmol) was added to neutralize the basic reagents, the reaction mixture was filtered into ethanol and evaporated to dryness. The residue was redissolved into 1:1 ethanol/methylene chloride (50 mL) and allowed to stir at 25 °C for 1 h, at which time IR established the disappearance of the diazo intermediate. In order to facilitate the subsequent chromatography, 426 mg (3.3 mmol) of diisopropylethyl amine was added to destory the remaining picryl azide (1 h). The reaction mixture was evporated to dryness and chromatographed on silica gel (deactivated with formamide) using 1:1 chloroform/hexane as eluant to yield 96 mg (8%) of crystalline **22**: mp 143–144 °C (from chloroform/hexane); IR (CH_2Cl_2), 1795, 1755 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.2 (s, 9 H), 1.3 (t, 3 H, J = 7 Hz), 2.0 (s, 3 H), 4.2 (s, 1 H), 4.8 (t, 1 H, J = 4 Hz), 5.8 (AB q, 2 H); MS m/e 325 ($M^+ - SO_2$). Anal. Calcd for $C_{16}H_{23}NO_8S$: C, 49.35; H, 5.95; N, 3.60. Found: C, 48.98; H, 5.68; N, 3.60.

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