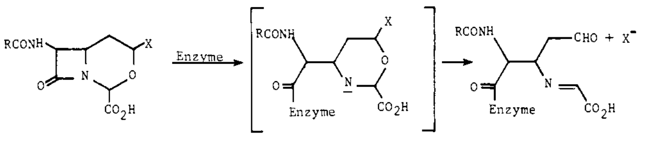
Communications to the Editor

Nuclear Analogues of β-Lactam Antibiotics.[1] 6. 3-Oxa-1-azabicyclo[4.2.0]octan-8-one-2-carboxylic Acids

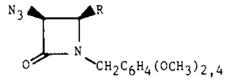
Sir:

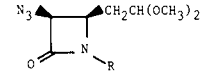
The biological action of the β-lactam antibiotics including both penicillins and cephalosporins is believed to result from inactivation of one or more transpeptidase enzymes critical for the synthesis of bacterial cell walls.[2] This inactivation presumably results from acylation of a nucleophilic group within the active site of the enzyme by the reactive β-lactam.[3] We have had a continuing interest in the total synthesis of novel β-lactam ring systems which, like penicillins and cephalosporins, may function as irreversible inhibitors of bacterial transpeptidases. In particular, we have been intrigued by those ring systems which, by undergoing further fragmentation upon cleavage of the β-lactam bond, facilitate β-lactam cleavage and generate secondary reactive centers capable of interacting within the enzyme. One such nuclear analogue of the cephalosporins is the 3-oxa-1-azabicyclo[4.2.0]octan-8-one-2-carboxylic acid **1**. We report here the total synthesis of **1** (X = OCH_3), the first example of a saturated 4:6 bicyclic β-lactam with potent antibacterial activity.

Azetidinone **2**, prepared by cycloaddition of an azidoketene precursor to *N*-2,4-dimethoxybenzyliminoacetic ester,[4] was selectively reduced ($NaBH_4$, aqueous THF, 70%) to the alcohol **3**. Oxidation of **3** to the aldehyde **4** (Me_2SO, TFAA, Et_3N, −78 °C) and condensation with nitromethane (Et_3N, Me_2SO, room temp, 94%) gave the nitro alcohol **5**. Dehydration and subsequent reduction (Ac_2O, pyr; $NaBH_4$, MeOH, 0 °C, 45%) afforded the saturated nitroethylazetidinone **6** which was quantitatively transformed ($NaOCH_3$; H_2SO_4–CH_3OH, 0 °C, 95%) to the acetal **7** by a modified Nef reac-



1





2, R = CO_2CH_3

3, R = CH_2OH

4, R = CHO

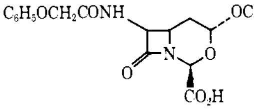
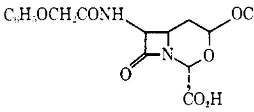
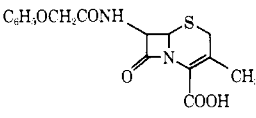
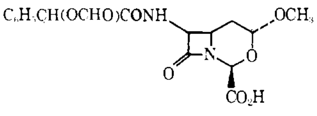
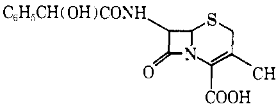
5, R = $CH(OH)CH_2NO_2$

6, R = $CH_2CH_2NO_2$

7, R = $CH_2C_6H_4(OCH_3)_2,4$

8, R = H

Table I. Minimum Inhibitory Concentrations[a]

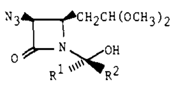
structure	*Staph. aureus* HH 127	*Strep. faecalis* HH 34358	*E. coli* SK&F 12140	*Kleb. pneumoniae* SK&F 1200	*Proteus morgani* 179	*Salmonella paratyphi* ATCC 12178	*Serratia marcescens* ATCC 13880	*Enterobacter cloacoe* HH 31254	in vivo: ED_{50},[b] *E. Coli* SK&F 12140 sc	in vivo: ED_{50},[b] *E. Coli* SK&F 12140 po
 12[c]	50	>200	100	50	200	50	>200	200		
 14	>400	>400	>400	>400	>400	>400	>400	>400		
 16	0.8	200	>400	>400	>400	>400	>400	>400		
 13[c]	100	>200	6.3	6.3	25	3.1	25	6.3	15.5	25
 17	16	25	3.1	1.6	200	1.6	200	3.1	6.2	100

---

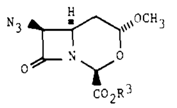
[a] Micrograms/milliliter. [b] Protective dose (milligrams/kilogram) against a lethal infection of *E. coli* bacterium in rats. [c] One isomer of **12** and **13** would be expected to have twice the activity of the racemic mixture.

0002-7863/79/1501-4730$01.00/0

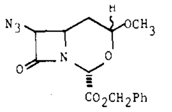
tion.[5] Oxidative cleavage of the dimethoxybenzyl protecting group ($K_2S_2O_8$, aqueous CH_3CN, pH 6, 80 °C, 83%) gave azetidinone **8** which condensed thermally with benzhydryl glyoxylate (toluene, 90 °C, 70%) to give a mixture of diastereomeric carbinolamides **9a** and **9b**, separable by chromatography on silica gel. Cyclization of **9a** (*p*-toluenesulfonic acid, 4-Å sieves, CH_2Cl_2, room temperature, 65%) gave a single cyclic acetal (**10a**): IR (Nujol) ν_{max} 2120 (azide), 1775 (β-lactam), 1750 (ester); NMR ($CDCl_3$) δ 7.3 (m, $(C_6H_5)_2$), 7.0 (s, $CHPh_2$) 5.1 (s, C-2 H), 5.05 (q, $J_{4,5a}$, $J_{4,5e}$ = 2.0, 2.5 Hz, C-4 H), 4.8 (d, $J_{6,7}$ = 4 Hz, C-7 H), 4.0 (m, C-6 H), 3.38 (s, OCH_3), 1.9 (m, C-5 H_2). Carbinolamide **9b** under similar conditions gave an inseparable mixture (3:1) of diastereomeric acetals **11**: NMR ($CDCl_3$) δ 2.95 and 3.25 (s, OCH_3), 5.82 and 5.58 (s, C-2 H).



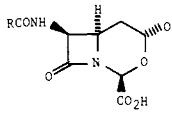
9a, R^1=H, R^2=CO_2CHPh_2
9b, R^1=CO_2CHPh_2, R^2=H



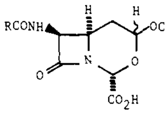
10a, R^3=$CHPh_2$
10b, R^3=CH_2Ph



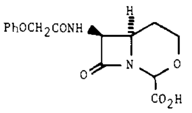
11



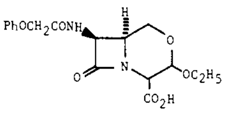
12, R = $PhOCH_2$-
13, R = PhCH(OCHO)-



14, R = $PhOCH_2$-
15, R = PhCH(OCHO)-



18



19

The stereochemistry of acetals **10a** and **11** was assigned as follows. Assuming a chair conformation for the oxazine ring, the methoxy group could be assigned an axial configuration on the basis of NMR coupling constants[6] ($J_{4,5a}$ = 2.0, $J_{4,5e}$ = 2.5 Hz). Since cyclization occurred under equilibrating conditions, the observation of a single isomer would infer that cyclization occurred from that diastereomer (**9a**) which would result in an equatorial carboxyl conformation.[7] Steric crowding in a 1,3-diaxial conformer should result in the formation of a significant proportion of the equatorial methoxyl isomer on cyclization of the opposite diastereomer **9b**, as observed.[8] On this basis, structures **10** and **11** were tentatively assigned as shown.

Hydrogenation of the cyclic acetal **10a** (H_2, PtO_2, EtOAc, 1 atm), acylation of the resulting amine with phenoxyacetyl chloride or *O*-formylmandelic acid (DCC, 0 °C), and hydrogenolysis of the benzhydryl ester (H_2, Pd/C, EtOH, 1 atm) afforded acids **12** and **13**, respectively. **13**: IR (Nujol) ν_{max} 1760 (β-lactam), 1740 (ester), 1695 (amide); mass spectrum (field desorption) *m/e* 378. Similarly, acids **14** and **15** were prepared from acetal **11**.[9]

The antibacterial activities of acids **12**, **13**, and **14** are compared with that of the analogous naturally derived cephalosporins **16** and **17** in Table I. The 2β-carboxy-4α-methoxy-3-oxa-1-dethiacephams **12** and **13** exhibited diminished Gram-positive activity but were somewhat superior to the analogous cephalosporins (**16** and **17**) against Gram-negative bacteria. Moreover, low doses of **13** protected rats against a lethal infection of *E. coli*. The oral (po) dose required for protection was significantly lower than that of the corresponding cephalosporin **17**. Surprisingly, the corresponding 2α-carboxylic acids **14** and **15** (not in Table I) were considerably less active.[10] The demethoxy analogue **18** (carboxyl stereochemistry uncertain) showed no antibacterial activity at concentrations as high as 500 μg/mL,[10,11] a concentration at which both **12** and **14** exhibited significant inhibition of bacterial growth.

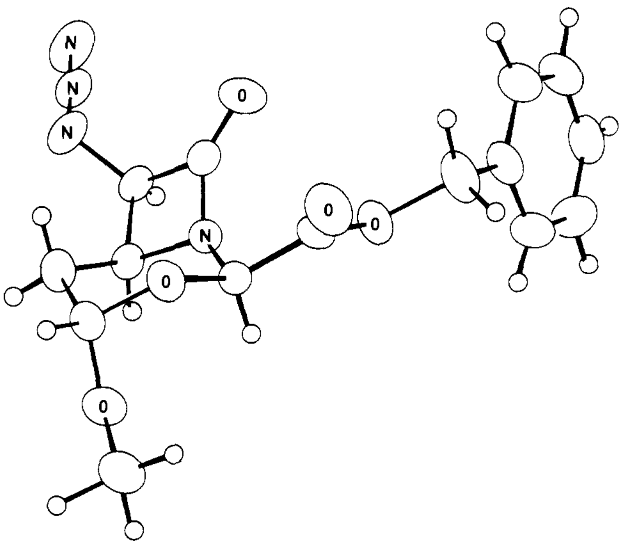


Figure 1. The X-ray crystallographic structure of **10b**.

Table II. Structural Characteristics of 3-Oxacephalosporin and Representative β-Lactam Antibiotics[a]

compd	sum of bond angles about nitrogen, deg	distance of N atom from plane of three substituents, Å	β-lactam bond Length, Å
10b	350.5	0.24	1.360
cephaloridine	350.7	0.24	1.382
cephalosporin C	345	0.32	1.385
penicillin V	337	0.40	1.46
Δ^2-cephem	359.3	0.06	1.355

[a] Data for standards were abstracted from ref 16.

The observation of potent antibacterial activity for 4:6 bicyclic β-lactams lacking unsaturation in the six-membered ring was quite unexpected and would appear to be of considerable theoretical importance. A number of groups have reported the synthesis of saturated 4:6 bicyclic β-lactams,[12] including a 2-oxa-3-ethoxy-1-dethiacepham (**19**).[12d] None, however, possessed significant antibacterial activity. The absence of biological activity for these nuclear analogues has been ascribed to the lack of sufficient strain in the bicyclic ring system.[13] In addition, the assigned configuration of the carboxylic acid in both biologically active isomers **12** and **13** is opposite to that of the naturally occurring penicillins. To provide further information about strain and to determine unambiguously the stereochemistry of this novel ring system, an X-ray crystallographic study of **10b** was undertaken.[14] The results of this analysis are summarized in Table II and the molecular geometry is illustrated in Figure 1. In the crystal state, the six-membered ring exists in a chair conformation with the carboxyl group in an equatorial conformation and the methoxy group axial, as predicted above. The β-lactam nitrogen is not planar, but is 0.24 Å above the plane defined by the β-lactam carbonyl, C-2, and the bridgehead carbon. This deformation, which significantly increases the reactivity of the β-lactam, presumably results from fusion of the second ring. The magnitude of the deformation is similar to that observed for active cephalosporins and is significantly greater than the inactive Δ^2-cephalosporin isomers.[15,16] The observed spatial relationship between the carboxylic acid and β-lactam group is very similar to that seen in the active Δ^3-cephalosporins.[15] This would suggest that the relative positions of these groups and not the configuration of the carboxyl may be important for enzyme recognition and antibacterial activity.

The lack of antibacterial activity of the demethoxy analogue **18** suggests that the methoxyl group contributes significantly to biological activity. In the crystal state, the methoxy group does not appear to be sterically crowded and it is therefore unlikely that the observed effect is purely of steric origin. However, from the available data, it is not possible to ascertain if the methoxyl group merely serves to increase the strain and hence the reactivity of the β-lactam, or if further fragmentation to a reactive species following enzymatic cleavage of the β-lactam is important in imparting the observed potent antibacterial activity.

Acknowledgment. We are grateful to Drs. W. Huffman and H. Rapoport for helpful discussions during the course of this work, S. Fagan and K. Erhard for the preparation of important intermediates, and J. Guarini for the antibacterial results reported in this paper.

References and Notes

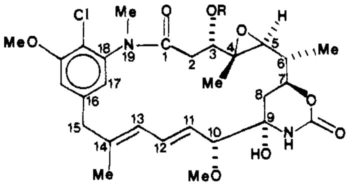
(1) For part 5 in this series, see J. Finkelstein, K. G. Holden, and C. D. Perchonock, *Tetrahedron Lett.*, 1629 (1978).
(2) J. L. Strominger, P. M. Blumberg, H. Suginaka, J. Umbreit, and G. G. Wickus, *Proc. R. Soc. London, Ser. B*, **179**, 369 (1971), J. L. Strominger, *Harvey Lect.*, **64**, 1979 (1970).
(3) D. J. Tipper and J. L. Strominger, *Proc. Natl. Acad. Sci. U.S.A.*, **54**, 1133 (1965).
(4) W. F. Huffman, K. G. Holden, T. F. Buckley, J. G. Gleason, and L. Wu, *J. Am. Chem. Soc.*, **99**, 2352 (1977).
(5) R. M. Jacobson, *Tetrahedron Lett.*, 3215 (1974).
(6) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis", Interscience, New York, 1967, p 154.
(7) The observation of an upfield shift in the ^{1}H NMR of H-2 in **10a** relative to **11** is consistent with the assigned stereochemistry. See, for example, E. G. Brain, A. J. Eglington, J. H. C. Nayler, N. F. Osborne, R. Southgate, and P. Tolliday, *J. Chem. Soc., Perkin Trans. 1*, 2479 (1977).
(8) The observation of a significant proportion of the 1,3-diaxial product points to a remarkably strong anomeric effect in this ring system.
(9) Satisfactory elemental analyses were obtained for **2, 3, 10a, 10b, 12, 13,** and **14.** All other compounds were characterized by spectroscopic methods.
(10) The antibacterial activities of **14, 15,** and **18** were compared in a disk assay vs. *B. subtilis* at drug concentration of 100 and 500 μg/mL.
(11) J. G. Gleason and P. Siler, unpublished results. The synthesis of this and other 3-hetero-1-dethiacephams will be described elsewhere.
(12) See, for example, (a) G. Lowe, *Chem Ind.* (*London*), 459 (1975); (b) R. B. Woodward, *Pharm. J.*, **205**, 562 (1970), S. Kukolja, *J. Am. Chem. Soc.*, **94**, 7590 (1972); (c) E. Van Heyningen and L. K. Ahern, *J. Med. Chem.*, **11**, 933 (1968); (d) T. W. Doyle, B. Belleau, B. Y. Luh, C. F. Ferrari, and M. P. Cunningham, *Can. J. Chem.*, **55**, 468 (1977). (e) The sulfur and nitrogen analogues of **18** did not possess useful biological activity (W. F. Huffman and R. Hall, unpublished results).
(13) (a) G. Lowe, *Chem. Ind.* (*London*), 459 (1975); (b) M. Gorman and C. W. Ryan in "Cephalosporins and Penicillins; Chemistry and Biology", E. H. Flynn, Ed., Academic Press, New York, 1972, Chapter 12.
(14) Compound **10b** was prepared from **8** by thermal addition of benzyl glyoxylate (toluene, 90 °C), chromatographic separation of isomers and cyclization (*p*-TsOH, 4-Å sieves, CH_2Cl_2, room temperature). Reduction, acylation with phenoxyacetyl chloride and hydrogenolysis afforded exclusively **12.** Single crystals of **10b** were obtained by crystallization from methylene chloride–ether.
(15) R. M. Sweet and L. F. Dahl, *J. Am. Chem. Soc.*, **92**, 5489 (1970).
(16) R. M. Sweet in ref 13b, Chapter 7.

John G. Gleason,* T. F. Buckley, Kenneth G. Holden
D. Boles Bryan, P. Siler
Research & Development Division
Smith Kline & French Laboratories
Philadelphia, Pennsylvania 19101

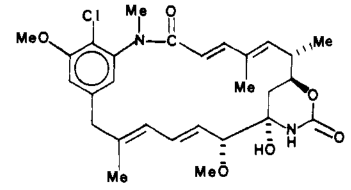
Received March 19, 1979

Progress toward the Total Synthesis of Maytansinoids. Synthesis of (±)-4,5-Deoxymaysine (*N*-Methylmaysenine)

Sir:

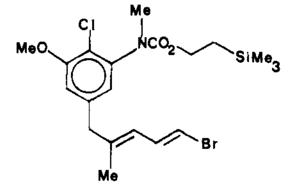


1, R = $\overset{O}{\overset{\|}{C}}$-CH(CH$_3$)N(CH$_3$)$\overset{O}{\overset{\|}{C}}CH_3$

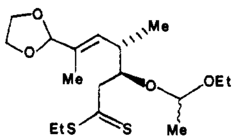


(±)-**2**

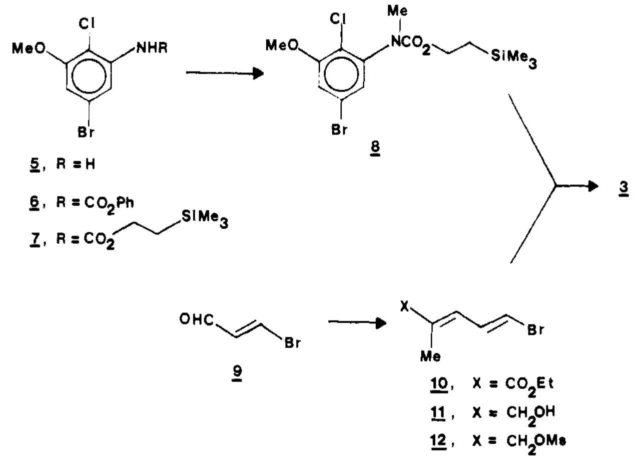
The extensive efforts by a number of laboratories[1] to reach the antitumor macrocycle, maytansine (**1**) have appeared in the past five years. Recently, Corey[2] has reported the first successful synthesis of a maytansinoid, (±)-*N*-methylmaysenine (4,5-deoxymaysine, **2**). We describe our own total synthesis of **2**, which we anticipate to represent a general route to other maytansinoids. The synthetic strategy leading to **2** was based upon a convergent scheme involving the key intermediates **3** and **4** which were prepared with a high degree of stereoselectivity in multigram quantities. The *E,E* aromatic diene **3** was acquired from the tetrasubstituted benzene **5**[3] which was transformed into the phenylurethane **6** (PhOCOCl, pyridine) and then to the silylurethane **7** with β-(trimethylsilyl)ethanol[4] (0–25 °C, THF, *t*-BuOK). Without purification, the latter was treated with *t*-BuOK–MeI furnishing **8** (80% from **5**).[5] The diene moiety in **3** was constructed from β-bromoacrolein **9**[6] which was homologated to the pure *E,E*-diene ester **10** (80%) using ethyl α-diethoxyphosphonopropionate (*t*-BuOK, −78 °C, THF). Reduction with diisobutylaluminum hydride (0 °C, hexane) gave **11** (98%, oil)[7] which was treated with excess methanesulfonyl chloride (Et_3N, CH_2Cl_2, −25 °C) to give the mesylate **12** and used immediately to couple with **8** (*n*-BuLi, −78 °C, $C_3H_7C{\equiv}CCu\cdot[(Me_2N)_3P]_2$,[8] Et_2O, −78 °C) providing the bromodiene **3** in 40–45% yield after purification by medium-pressure liquid chromatography (mp 61 °C).[9]



3



4



The second key intermediate **4** was obtained from the unsaturated aldehyde **13.**[10] Removal of the tetrahydropyranyl ether (5% HCl-THF, (1:1), 100%) to the hydroxy aldehyde **14** was followed by acylation (CH_3COCl, pyridine, CH_2Cl_2, 0 °C, 95%) to the ester **15**, which was transformed into the ethylene ketal (ethylene glycol, pyridinium tosylate, benzene) and hydrolyzed (K_2CO_3-MeOH) to the hydroxy ketal **16**