Table IV. Decarboxylation of Pivalic Acid (1.46×10^{-2} M) and Phenylacetic Acid-*1*-^{14}C (1.46×10^{-2} M) at 74.3 ± 0.10 °C[a]

time (min)	total CO_2 (mol × 10^4)	cpm	active CO_2 (mol × 10^4)	inactive CO_2 (mol × 10^4)	k^I/k^{II}
22.0	0.253	25173	0.214	0.039	0.165
28.0	0.328	32687	0.278	0.050	0.157
31.1	0.363	35916	0.306	0.057	0.160
35.5	0.427	42064	0.358	0.069	0.163
41.8	0.501	48742	0.414	0.087	0.169
70.0	0.757	72520	0.614	0.137	0.150
14 days	1.892	110500	0.965	0.927	
		average	k^I/k^{II} =	0.161 ± 0.005	

[a] Pivalic acid (0.985×10^{-4} mol); phenylacetic acid-*1*-^{14}C (0.953×10^{-4} mol); potassium peroxydisulfate (3.70×10^{-4} mol).

Table V. Products from the Reaction of Phenylacetic Acid (2.94×10^{-2} M) and Potassium Peroxydisulfate (5.70×10^{-2} M) at 74.3 × 0.10 °C[a]

product	mol × 10^4	% of phenylacetic acid
CO_2	5.73	100
toluene	0.057	1.49
benzaldehyde	0.178	4.42
bibenzyl	0.412	10.86
polymer (0.51 g)		

[a] Phenylacetic acid (5.73×10^{-4} mol, 0.078 g); potassium peroxydisulfate (11.13×10^{-4} mol).

number of counts/min (cpm) recorded on the scintillation counter. This linear relation was used to relate the activity observed to the amount of radioactive gas evolved in the competitive decarboxylation reactions.

The reactions when carried out to 20 kinetic half-lives gave quantitative yields of labeled and unlabeled carbon dioxide. The purity of the gas was confirmed by mass spectroscopic analysis.

A typical kinetic run is given in Table IV.

Product Analysis from the Decarboxylation of Phenylacetic Acid. Aqueous solutions which were 2.94×10^{-2} M in phenylacetic acid, 5.8×10^{-2} M in potassium hydroxide, and 3.80 × 10^{-2} in potassium peroxydisulfate were placed in break seals, degassed, sealed, and thermostated at 74.3 °C. The decarboxylation reactions were carried to infinity (20 h). After the completion of the reaction, the CO_2 was measured after acidification. The reaction mixture was saturated with potassium bromide, and the organic material was extracted repeatedly with ether. The ethereal solution was separated, leaving a yellow solid suspended in the aqueous layer.

Analysis of the ethereal solution was carried on by GLPC using a 10 ft × $^1/_8$ in. SE-30, 5% on 60/80 Chromosorb W column on a Varian Aerograph Model 600-D with a flame ionization detector. Freon-112 was added as an external standard.

The insoluble polymeric material suspended in the aqueous layer was separated by centrifugation and repeatedly washed with water, and the solid was dried over P_2O_5 at reduced pressure. The polymer was insoluble in the common organic solvents (*n*-pentane, benzene, toluene, carbon tetrachloride, methylene chloride, chloroform, methyl alcohol, and ethyl alcohol). It dissolved in dimethyl formamide and dimethyl sulfoxide. The average molecular weight of the polymer was 1400 and the elemental analysis showed, C, 63.26; H, 4.31; O, 20.19; S, 2.33. An approximate molecular formula for the polymer was calculated to be $C_{72}H_{60}O_{17}S_1$. The IR spectrum showed a strong hydroxyl band (3340 cm^{-1}) and a weak carboxyl band (1700 cm^{-1}). A typical analysis is shown in Table V.

Acknowledgment. We thank Professor Cheves Walling for his helpful criticism of this manuscript. We also thank the Natural Sciences and Engineering Research Council of Canada and the University of Alberta for their generous support of this work.

Registry No. *o*-$MeC_6H_4CH_2CO_2H$, 644-36-0; *p*-$MeC_6H_4CH_2CO_2H$, 622-47-9; *p*-$MeOC_6H_4CH_2CO_2H$, 104-01-8; *p*-$PhOC_6H_4CH_2CO_2H$, 6328-74-1; $PhCH_2CO_2H$, 103-82-2; *p*-$BrC_6H_4CH_2CO_2H$, 1878-68-8; *m*-$BrC_6H_4CH_2CO_2H$, 1878-67-7; *p*-$ClC_6H_4CH_2CO_2H$, 1878-66-6; *m*-$ClC_6H_4CH_2CO_2H$, 1878-65-5; *m*-$FC_6H_4CH_2CO_2H$, 4771-80-6; 1-cyclohexene-3-carboxylic acid, 4771-80-6; pivalic acid, 75-98-9; cyclohexanecarboxylic acid, 98-89-5; isobutyric acid, 79-31-2; ethyl *o*-tolylacetate, 40291-39-2; α-methyl-*o*-tolylacetic acid, 62835-95-4; α-methyl-*p*-tolylacetic acid, 938-94-3; potassium peroxydisulfate, 7727-21-1; diphenylacetic acid, 117-34-0; triphenylacetic acid, 595-91-5; mandelic acid, 90-64-2; α,α-dimethylphenylacetic acid, 826-55-1.

β-Lactam Annulation Using (Phenylthio)nitromethane

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2-[(Phenylthio)carbonyl]-1-azabicyclo[4.2.0]octan-8-one (**8a**), 2-[(phenylthio)carbonyl]-1-azabicyclo[3.2.0]-heptan-7-one (**10a**), 2-[(phenylthio)carbonyl]-4-oxa-1-azabicyclo[3.2.0]heptan-7-one (**19a**), 3,3-dimethyl-2-[(phenylthio)carbonyl]-4-oxa-1-azabicyclo[3.2.0]heptan-7-one (**19c**), and 3-[[(*tert*-butyldimethylsilyl)oxy]-methyl]-2-[(phenylthio)carbonyl]-5-oxa-1-azabicyclo[4.2.0]oct-2-en-8-one (**26**) were prepared in good overall yields from the monocyclic β-lactam aldehydes **6c**, **6g**, **18b**, **18f**, and **24d**. The key process in this novel annulation was the condensation reaction of the aldehydes **6c**, **6g**, **18b**, **18f**, and **24d** with (phenylthio)nitromethane (1) followed by cyclization of the resultant (*Z*)-nitroalkenes **6e**, **6i**, **18d**, **18h**, and **24f** with tetrabutylammonium fluoride followed by ozone. These studies unequivocally establish (phenylthio)nitromethane (1) as a versatile reagent for the construction of the carbapenam, carbacepham, oxapenam, and oxacephem frameworks. These units occur in diverse β-lactam antibiotics and β-lactamase inhibitors.

Recently we had occasion to study (phenylthio)nitromethane (**1**)[1,2] as a convenient reagent for the homologation of aldehydes to produce α-substituted phenylthio esters.[3] Thus, for example, acetaldehyde was reacted with **1**, catalyzed by potassium *tert*-butoxide in THF and *tert*-butyl alcohol, followed by dehydration with methanesulfonyl

(1) Bordwell, F. G.; Bartmess, J. E. *J. Org. Chem.* **1978**, *43*, 3101.
(2) Miyashita, M.; Kumazawa, T.; Yoshikoshi, A. *J. Chem. Soc., Chem. Commun.* **1978**, 362.
(3) Banks, B. J.; Barrett, A. G. M.; Russell, M. A. *J. Chem. Soc. Chem. Commun.* **1984**, 670. Barrett, A. G. M.; Graboski, G. G.; Russell, M. A. *J. Org. Chem.* **1986**, *51*, 1012.

0022-3263/87/1952-4693$01.50/0

Chart I

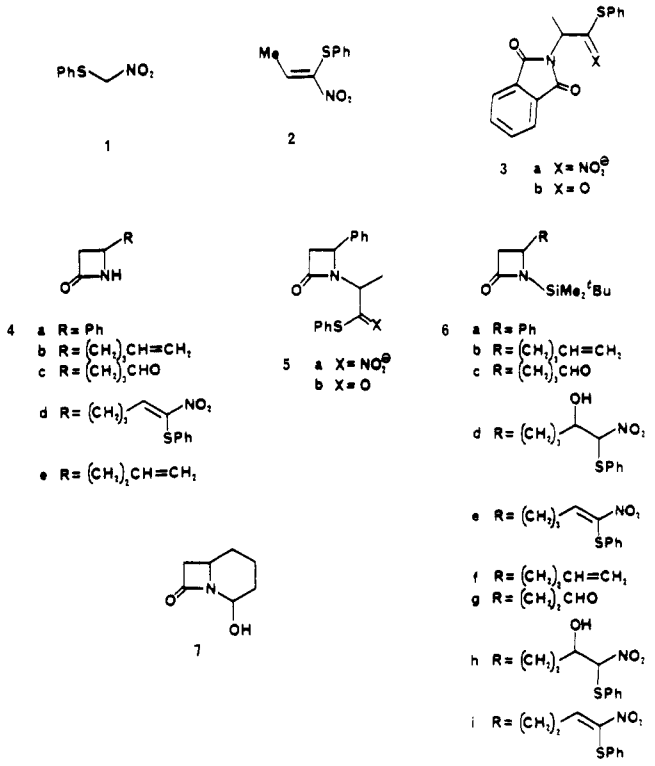
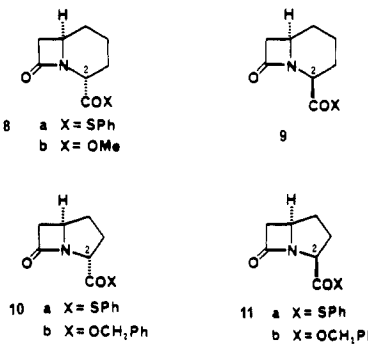


Chart II



chloride and triethylamine[2] to produce the (*Z*)-nitroalkene[4] **2** (≥89%). In DMF solution **2** smoothly reacted with potassium phthalimide to produce **3a**.[5] This was not isolated but was directly oxidized in situ with ozone, according to the McMurry procedure,[6] to provide the phenyl thio ester **3b** (68%). The reaction was shown to be useful for diverse nucleophiles, and thus we sought to explore the possibility of using 1-nitro-1-(phenylthio)alkenes in β-lactam synthesis.[7] Since β-lactams are outstanding antibacterial agents, novel concise chemistry for their elaboration is constantly being sought. Herein we report experimental details that unequivocally establish the generality of the nitroalkene Michael addition in bicyclic β-lactam synthesis. Shibuya has very elegantly demonstrated that simple terminal nitroalkenes can be employed in carbapenem synthesis.[8] Additionally, more recently, Hanessian has utilized 1,1-bis(alkylthio)nitroalkene intermediates in penem construction.[9]

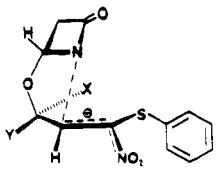
Results and Discussion

(Phenylthio)nitromethane (1) was prepared either from (phenylthio)acetic acid by nitration of the derived dianion with propyl nitrate[10] or from the reaction of benzenesulfenyl chloride with nitromethane monoanion.[11] On a large scale the second procedure, due to Seebach, was more convenient and far superior. The derived nitroalkene **2**[3] reacted smoothly with 4-phenyl-2-azetidinone (**4a**)[12] in the presence of base to produce the nitronate **5a**. This was not isolated but was directly ozonolyzed in situ[6] to produce the β-lactam phenyl thio ester **5b** as a mixture of diastereoisomers (1:1.3). In the optimum reaction (41%), potassium *tert*-butoxide in *tert*-butyl alcohol and DMF was used to mediate the nitroalkene addition step. Clearly such a base protocol was causing problems due to the lability of the β-lactam ring. As an alternative we sought to examine fluoride anion mediated desilylation chemistry[13] to trigger the β-lactam N-alkylation. Thus 1-(*tert*-butyldimethylsilyl)-4-phenyl-2-azetidinone (**6a**) was chosen as the starting material. The addition of tetrabutylammonium fluoride in THF to a mixture of **6a** and **2** in dichloromethane at −30 °C and ozonolysis at −78 °C gave **5b** in superior yield (75%). Having established these mild conditions for the conversion of **4a** into **5b**, we sought to extend the chemistry to bicyclic systems.

Synthesis of the Carbapenam and Carbacepham Framework. The formal [2 + 2] cycloaddition reaction of 1,6-heptadiene with chlorosulfonyl isocyanate[14] gave, on sodium sulfite workup, the 4-pentenyl-substituted β-lactam **4b** in 49% yield. This was directly protected by using *tert*-butylchlorodimethylsilane and ethyldiisopropylamine[13] to produce **6b** (99%). Subsequent ozonolysis, with a dimethyl sulfide workup,[15] gave the aldehyde **6c** (97%) as a colorless oil. Clearly in our approach to the carbacepham famework the silyl group had a dual functionality. First, it prevented premature cyclization in that β-lactam aldehydes related to **4c** exist as the cyclized carbinolamine isomer **7**. Second, the β-lactam N-centered anion was easily released at the nitroalkene stage, thereby initiating the required annulation. Henry reaction of aldehyde **6c** with (phenylthio)nitromethane (1) was most effeciently carried out by using a catalytic quantity of potassium *tert*-butoxide in *tert*-butyl alcohol and THF at 0 °C. Under these conditions, product **6d** was formed as a mixture of diastereoisomers in 81% yield without competitive desilylation or β-lactam cleavage. Dehydration of the mixed diastereoisomers **6d** using the Miyashita reaction conditions[2,10] gave the nitroalkene **6e** (81%) as a single geometric isomer. This was unequivocally assigned the *Z* geometry based on the chemical shift[16] of the vinyl proton in the NMR spectrum [δ 7.6 (t, 1 H, *J* = 7.5 Hz)]. Clearly this geometric preference reflects thermodynamic control

(4) For recent review of nitroalkene chemistry, see: Barrett, A. G. M.; Graboski, G. G. *Chem. Rev.* **1986**, *86*, 751. Varma, R. S.; Kabalka, G. W. *Heterocycles* **1986**, *24*, 2645.
(5) All structures refer to racemic modifications.
(6) McMurry, J. E.; Melton, J.; Padgett, H. *J. Org. Chem.* **1974**, *39*, 259.
(7) For a preliminary communication of results, see: Barrett, A. G. M.; Graboski, G. G.; Russell, M. A. *J. Org. Chem.* **1985**, *50*, 2603.
(8) Shibuya, M.; Kuretani, M.; Kubota, S. *Tetrahedron Lett.* **1981**, *22*, 4453.
(9) Hanessian, S.; Bedeschi, A.; Battistini, C.; Mongeli, N. *J. Am. Chem. Soc.* **1985**, *107*, 1438.
(10) Miyashita, M.; Kumazawa, T.; Yoshikoshi, A. *J. Org. Chem.* **1980**, *45*, 2945.
(11) Seebach, D.; Lehr, F. *Helv. Chim. Acta* **1979**, *62*, 2239.
(12) Graf, R. *Liebigs Ann. Chem.* **1963**, *661*, 111.
(13) For the use of the *tert*-butyldimethylsilyl protecting group in β-lactam chemistry, see: Christensen, B. G.; Salzmann, T. H.; Ratcliffe, R. W. *Eur. Pat. Appl.* 1980, 7973; *Chem. Abstr.* **1980**, *93*, 71548r.
(14) Rasmussen, J. K.; Hassner, A. *Chem. Rev.* **1976**, *76*, 389.
(15) Pappas, J. J.; Keaveney, W. P.; Gancher, E.; Berger, M. *Tetrahedron Lett.* **1966**, 4273.
(16) For example, see: Denmark, S. E.; Dappen, M. S.; Cramer, C. J. *J. Am. Chem. Soc.* **1986**, *108*, 1306.

Chart III



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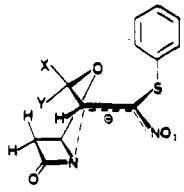

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in the E_{1cb} elimination[17] of the intermediate β-nitro methanesulfonate.

The nitroalkene **6e** was cyclized to produce the carbacepham framework by two distinct procedures. Thus, reaction of **6e** with dilute hydrogen fluoride–pyridine[18] in dichloromethane gave crude **4d** in 78% yield. This materal was not purified. Direct reaction wtih potassium *tert*-butoxide in THF and *tert*-butyl alcohol, followed by ozonolysis in situ, gave the corresponding isomeric carbacephams **8a** and **9** (73%) as two easily separable diastereoisomers (1:1.3). Alternatively the nitroalkene **6e** was directly cyclized by using tetrabutylammonium fluoride in THF at −55 °C,[19] followed by ozonolysis in situ at −78 °C, to provide **8a** and **9** (1:3.3; 83%). In this one-pot cyclization, careful temperature control was essential for success. At lower temperatures desilylation and cyclization were slow. At higher temperatures degradation was extensive. The two isomers **8a** and **9** were readily distinguished by their respective NMR spectra and by interconversion (vide infra). The less polar minor isomer **8a** was unequivocally assigned the 2*R*(*S*),6*R*(*S*) relative stereochemistry principally on the basis of the chemical shift and coupling constants for the C-2 proton [δ 4.64 (br d, 1 H, J = 6.6 Hz)]. Kametani reported that the corresponding ester **8b** showed the following C-2H NMR characteristics [δ 4.50 (br d, 1 H, J = 6.5 Hz)].[20] In the major, more polar isomer **9** the C-2H was observed at higher field [δ 3.94 (m, 1 H)]. As a confirmation of stereochemistry the major isomer **9** was reacted with ethyldiisopropylamine in THF to produce the more stable exo isomer **8a** (98%). Clearly in this chemistry (phenylthio)nitromethane (**1**) is a convenient reagent for the conversion of aldehyde **6c** into the carbacepham framework.[21]

The known β-lactam **4e**[22] was converted into the carbapenams **10a** and **11a** by using identical chemistry. Although the nitroalkene intermediate **6i** was extensively decomposed with hydrogen fluoride–pyridine, it was smoothly cyclized by using tetrabutylammonium fluoride followed by direct ozonolysis in situ to produce the inseparable mixture of isomeric carbapenams **10a** and **11a** (1:2.5) in 83% yield. The sterochemistry of the products was assigned by comparison with the ^{1}H NMR spectra for the known benzyl esters **10b** and **11b**.[22] Clearly (phenylthio)(nitromethane (**1**) is additionally useful for a concise synthesis of the carbapenam framework.[23]

Synthesis of the Oxapenam Skeleton. In principal the nitroalkene methodology should be applicable to hetero-substituted bicyclic β-lactams including oxapenams and oxacephems. There is, however, the possibility that the precursor nitroalkenes **12** would fragment (arrows on **12**) rather than ring-close. We considered that this reaction was unlikely since related nucleophilic displacement reactions of **13** to provide **14** are generally slow. The analogy is direct since the conversion of **13** into **14** most probably involves an elimination, readdition mechanism and the intermediacy of **15**[24] or its conjugate acid. Thus, undesirable fragmentation reactions should not occur at the low bicyclization temperature. 4-Acetoxy-2-azetidinone (**16**)[25] was converted into the known[26] ether **17a** by displacement with allyl alcohol. This material was N-silylated (95%) and the resultant alkene **18a** converted into the nitroalkene **18d** (44% overall). In this case it was found advantageous to carry out the Henry reaction using a mixed potassium *tert*-butoxide and aluminum tri-*tert*-butoxide catalyst. This modification resulted in a faster, cleaner reaction. Reaction of the nitroalkene **18d** with tetrabutylammonium fluoride and ozone gave the readily separable oxapenams **19a** (23%) and **20a** (33%). The assignment of stereochemistry in these products was unequivocally established by NMR spectroscopy and, in particular, the chemical shifts for the C-2 and C-5 protons [^{1}H NMR δ **19a** 5.46 (dd, 1 H, J = 3, <1 Hz), 4.74 (dd, 1 H, J = 8, 6 Hz); **20a** 5.20 (dd, 1 H, J = 3.2, <1 Hz) 4.48 (dd, 1 H, J = 8.4, 3.0 Hz)]. These values were in full agreement with literature data[27] for the related benzyl esters **19b** and **20b** [^{1}H NMR δ **19b** 5.26 (d, 1 H, J = 3 Hz), 4.56 (dd, 1 H, J = 7.6, 6.3 Hz); **20b** 5.09 (d, 1 H, J = 3 Hz), 4.09 (dd, 1 H, J = 6.4, 4.5 Hz)]. In this analogy the relative chemical shifts[27] of both the C-2H and C-5H are diagnostic of stereochemistry. Additionally the major kinetic product **20a** was cleanly isomerized by using ethyldiisopropylamine to produce only the exo phenyl thio ester **19a**.

The oxapenam study was extended to the synthesis of the dimethyl analogue **19c**. The related methyl ester **19d** is a known β-lactamase inhibitor.[28] Thus acetate **16** was condensed with 2-methyl-3-buten-2-ol in the presence of zinc acetate[29] to provide the ether **17b** (53%). This β-lactam was transformed into the (*Z*)-nitroalkene **18h** (52% overall). Cyclization in the usual way gave the oxapenams

(17) For an example, see: Berndt, A. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 613.

(18) Wasserman, H. H.; Han, W. T. *J. Am. Chem. Soc.* **1985**, *107*, 1444.

(19) Blaszczak, L. C. (Lilly Research Laboratories), unpulished observations. We thank Dr. Blaszczak for advice on low temperature desilylation.

(20) Kametani, T.; Honda, T. *Heterocycles* **1982**, *19*, 1861.

(21) Derivatives of the 1-aza-8-oxobicyclo[4.2.0]octane-2-carboxylic acid ring system are reported elsewhere. For examples, see: Hatanaka, M.; Ishimaru, T. *Tetrahedron Lett.* **1983**, *24*, 4837. Greengrass, C. W.; Hoople, D. W. T.; Nobbs, M. S. *Ibid.* **1982**, *23*, 2419. Wasserman, H. H.; Han, W. T. *Ibid.* **1984**, *25*, 3743. Uyeo, S.; Ona, H. *Chem. Pharm. Bull.* **1980**, *28*, 1578.

(22) Bateson, J. H.; Baxter, A. J. G.; Roberts, P. M.; Smale, T. C.; Southgate, R. *J. Chem. Soc., Perkin Trans. 1* **1981**, 3242.

(23) Derivatives of the 1-aza-7-oxobicyclo[3.2.0]heptane-2-carboxylic acid ring system are reported elsewhere. For examples, see: Berryhill, S. R.; Price, T.; Rosenblum, M. *J. Org. Chem.* **1983**, *48*, 158. Miyashita, M.; Chida, N.; Yoshikoshi, A. *J. Chem. Soc., Chem. Commun.* **1984**, 195. Bateson, J. H.; Roberts, P. M.; Smale, T. C.; Southgate, R. *Ibid.* **1980**, 185. Shibuya, M.; Kuretani M.; Kubota, S. *Tetrahedron* **1982**, *38*, 2659. Karady, S.; Amato, J. S.; Reamer, R. A.; Weinstock, L. M. *J. Am. Chem. Soc.* **1981**, *103*, 6765. Hatanaka, M.; Nitta, H.; Ishimaru, T. *Tetrahedron Lett.* **1984**, *25*, 2387. Reider, P. J.; Grabowski, E. J. J. *Ibid.* **1982**, *23*, 2293. Shibuya, M.; Kubota, S. *Ibid.* **1981**, *22*, 3611. Hatanaka, M.; Yamamoto, Y.; Nitta, H.; Ishimaru, T. *Ibid.* **1981**, *22*, 3883. Melillo, D. G.; Shinkai, I.; Liu, T.; Ryan, K.; Sletzinger, M. *Ibid.* **1980**, *21*, 2783. Fujimoto, K.; Iwano, Y.; Hirai, K. *Ibid.* **1984**, *25*, 1151. Ratcliffe, R. W.; Salzmann, T. N.; Christensen, B. G. *Ibid.* **1980**, *21*, 31. Foxton, M. W.; Mearman, R. C.; Newall, C. E.; Ward, P. *Ibid.* **1981**, *22*, 2497. Yoshioka, T.; Watanabe, A.; Isshiki, K.; Fukagawa, Y.; Ishikura, T. *Ibid.* **1986**, *27*, 4335. Evans, D. A.; Sjogren, E. B. *Ibid.* **1986**, *27*, 4961. Kametani, T.; Honda, T.; Nakayama, A.; Sasakai, Y.; Mochizuki, T.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2228.

(24) Although there is no direct evidence in favor of **15** (but see Ueda, Y.; Maynard, S. C. *Tetrahedron Lett.* **1985**, *26*, 6309), its intermediacy in displacement reactions is fully consistent with the stereochemistry of reaction; for example see ref 25.

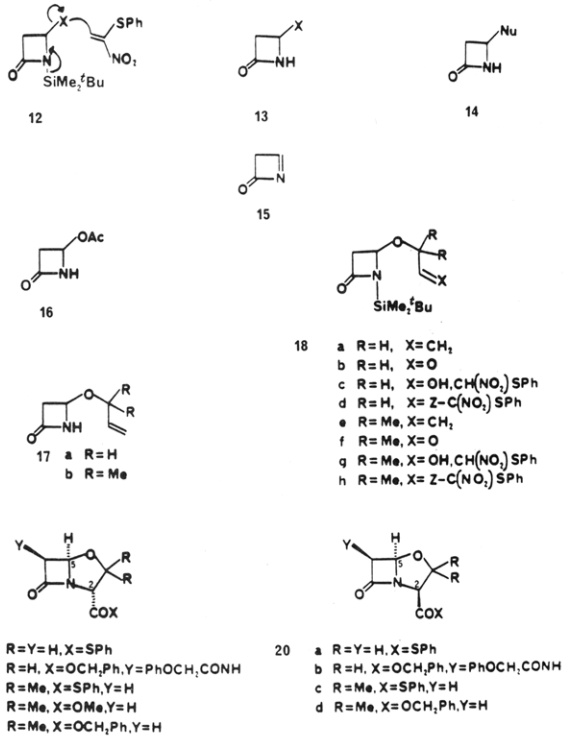
(25) Clauss, K.; Grimm, D.; Prossel, G. *Liebigs Ann. Chem.* **1974**, 539.

(26) Bachi, M. D.; Frolow, F.; Hoornaert, C. *J. Org. Chem.* **1983**, *48*, 1841.

(27) Cama, L. D.; Christensen, B. G. *Tetrahedron Lett.* **1978**, 4233.

(28) Kobayashi, T.; Iwano, Y.; Hirai, K. *Chem. Pharm. Bull.* **1978**, *26*, 1761.

Chart IV



19c (65%) and **20c** (14%). The stereochemistry of the two products was unambiguously established by comparisons of the NMR spectra with data reported for the related benzyl esters **19e** and **20d**.[29] Clearly the kinetic preference in the cyclization of the nitroalkene **18h**, which favors the exo product **19c**, is in contrast to the cyclization biases of nitroalkenes **6e**, **6i**, and **18d**. This will be discussed further below.

Synthesis of the Oxacephem Framework. In order to prepare an oxacephem using the (phenylthio)nitromethane (1) chemistry, it is necessary to elaborate the heavily substituted nitroalkene **21**, to ring-close this material to product **22**, and to subsequently eliminate HX. Acetate **16**[25] was condensed with 2-methylene-1,3-propanediol[30] with zinc acetate catalysis[29] to produce **23** (86%). Double N,O[13,31]-protection of this material with *tert*-butylchlorodimethylsilane and subsequent ozonolysis gave the ketone **24b** (70%). Vinylmagnesium bromide reacted regiospecifically with **24b** to produce the allylic alcohol **24c** (95%). In this reaction, competitive attack of the Grignard reagent on the less electrophilic β-lactam carbonyl was not a problem. For characterization purposes, product **24c** was recrystallized and the experimental data refer to the crystalline single diastereoisomer. In subsequent transformations, the chromatographically homogeneous mixture of diastereoisomers was employed. Ozonolysis of **24c** gave the corresponding α-hydroxy aldehyde **24d** (95%). Again, recrystallization gave a single isomer although subsequent transformations were carried out with the diastereoisomeric mixture. The aldehyde **24d** smoothly, albeit slowly, reacted with (phenylthio)nitromethane (1) to provide the Henry adduct **24e** (62%). Allowing for unreacted aldehyde **24d** (28%), the conversion to provide **24e** proceeded in acceptable yield (86%). The product **24e** was obtained as a complex mixture of diastereoisomers and was fully characterized as such. Dehydration using methanesulfonyl chloride and triethylamine gave the nitroalkene **24f** (83%) as an oily mixture of two racemic *Z* diastereoisomers. Cyclization of **24f** under standard conditions gave two phenyl thio esters **25a** (18%) and **25b** (13%). Both compounds were assigned as the required hydroxyoxacephams. The stereochemistry of the less polar major isomer **25a** was determined on the basis of an X-ray crystallographic study. The molecular structure of the compound is shown in Figure 1. The relative configuration of the more polar isomer was established by a difference nuclear Overhauser effect experiment. Thus, for **25a** irradiation of the lower field C-4 proton (δ 4.01) resulted in an enhancement of the C-6 proton (δ 5.37). Conversely, irradiation of the higher field C-4 proton (δ 3.79) resulted in an enhancement of the C-2 proton (δ 4.86). Clearly these results established that the C-6 and C-2 protons were trans, in accord with the structure determination. Furthermore, with isomer **25b**, irradiation of the lower field C-4 proton (δ 4.02) resulted in an enhancement of the C-6 proton (δ 5.28). In addition, irradiation of the higher field C-4 proton (δ 3.83) resulted in an enhancement of the C-2 proton (δ 4.69). These results are consistent with **25b** being epimeric with **25a** at C-3. As additional confirmation of this fact, irradiation of each of the two side-chain methylene protons (δ 3.76 and 3.53) in **25b** resulted in an enhancement of the C-2 proton (δ 4.69). All these results unequivocally establish the structures of the two isomers as **25a** and **25b**.

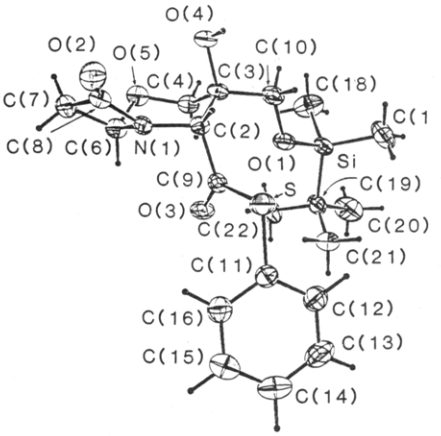


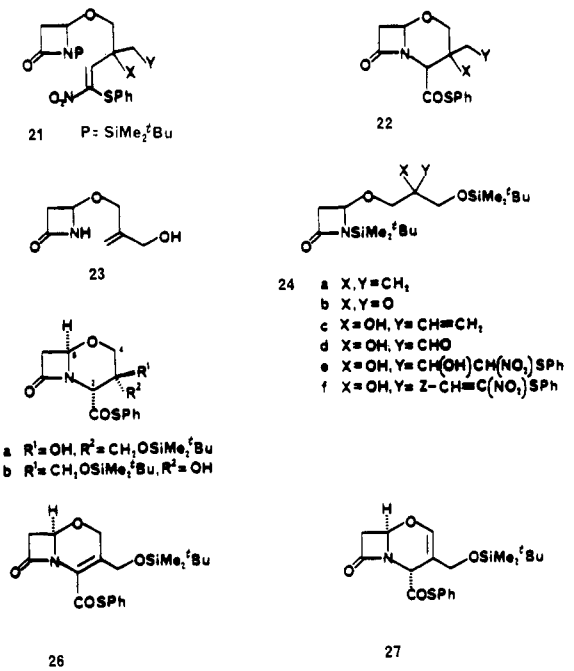
Figure 1. ORTEP diagram for hydroxyoxacepham **25a**.

The mixture of isomers **25a** and **25b** was smoothly dehydrated by reaction with methanesulfonyl chloride and triethylamine[32] to produce, as a single racemic product, the oxacephem **26** in 55% yield. The product was not contaminated by the deconjugated isomer **27**. Clearly the nitroalkene methodology is suitable for the preparation of molecules with the oxacephem skeleton.

It is important to briefly comment on the stereoselectivity of nitroalkene ring closure. It is apparent that the cyclization reactions to produce the carbacepham **8a,9**, the carbapenam **10a,11a**, and the oxapenam **19a,20a** have a small kinetic bias in favor of the endo isomers **9** (1:3.3), **11a** (1:2.5), and **20a** (1:1.4). Additionally, it is clear that cyclizations of the nitroalkenes **18h** and **24f**, both of which contain quaternary centers flanking the alkene, preferentially produce the more stable exo isomers **19c** (4.6:1) and **25** (only exo detected). It is reasonable to compare the two oxapenam cyclization reactions of the nitroalkenes **18d** and **18h**. 5-*Exo-Trig*[33] cyclization via **28** provides the endo

(29) Brown, A. G.; Corbett, D. F.; Howarth, T. T. *J. Chem. Soc., Chem. Commun.* **1977**, 359.
(30) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 3775.
(31) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
(32) For a related elimination reaction, see: Hamashima, Y.; Yoshioka, M.; Uyeo, S.; Tsuji, T.; Kikkawa, I.; Nagata, W. Ger. Offen 2 800 860, 13 July 1978; *Chem. Abstr.* **1978**, *89*, 179980g.

Chart V



isomers **20a** and **20c** whereas cyclization via **29** provides the exo epimers **19a** and **19c**. First, it is clear that in the dimethyl substrate **18h** that cyclization via **28** is disfavored by steric congestion between X and the phenylthio group (CPK models). This is consistent with an exo bias in cyclization. It is not altogether clear in the unsubstituted case (X = Y = H) why **28** is preferred over **29**. Possibly it is due to less strain during cyclization via this addition mode. In any case it is important to stress that the exo stereochemistry, which is essential for the expression of biological activity, is readily accessible either via kinetic control [**19c** and **25**] or via base-catalyzed epimerization [**8a** and **19a**].

Conclusion

It is apparent from these studies that (phenylthio)-nitromethane (**1**) is a useful reagent in β-lactam chemistry. Additionally it is important to underscore the fact that the nitroalkene methodology is highly efficient for the ring closure to produce bicyclic β-lactams using a late N-alkylation strategy. As such the method has the potential to complement the spectacular carbene insertion chemistry developed at Merck.[34]

Experimental Section

Melting points were determined on a Reichert hot stage apparatus and are uncorrected. Infrared spectra were recorded as KBr disks or films on a Sargent Welch SP3-100, Perkin-Elmer 283, or Nicolet 7199 FT instrument. ^{1}H NMR spectra were recorded on a Varian EM390A, JEOL FX270, or Varian XL-400 spectrometer using tetramethylsilane as internal standard. Mass spectra were recorded on a V-G 7070F mass spectrometer or were determined at the Midwest Center for Mass Spectrometry. Microanalyses were determined by Galbraith Laboratories, Knoxville, TN 37921. Samples for microanalyses that were oils were purified by flash chromatography, rotary evaporated, and subsequently further evaporated at ca. 0.1 mm.

Hexane, diethyl ether, and ethyl acetate were purified by distillation. THF was dried by distillation under nitrogen from potassium benzophenone ketyl. DMF, CH_2Cl_2, and Et_3N were respectively freshly distilled from CaH_2, P_4O_{10}, and Na. All reactions were carried out under dry nitrogen. Silica gel for chromatography refers to the Merck product Kieselgel 60 (Art. 9385). Thin layer chromatography was performed on Merck Kieselgel 60 F254 (Art. 5715).

(Phenylthio)nitromethane (1).[11] To a mechanically stirred solution of PhSCl (13 g) in THF (124 mL) was added a slurry of sodium nitromethane anion [from Na (2.4 g) in dry EtOH (90 mL) and $MeNO_2$ (6 g)] in less than 1 min. The solution, which turned from deep red to yellow, was partitioned between H_2O (200 mL) and CH_2Cl_2 (100 mL) by using 1 N HCl to adjust the pH of the aqueous layer to 3. The aqueous layer was further extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated to give a yellow oil which was distilled at reduced pressure to yield $PhSCH_2NO_2$ (**1**,[11] 7.0 g, 46%) as a yellow oil: bp 85–95 °C (0.050 Torr).

***N*-[1-[(Phenylthio)carbonyl]ethyl]-4-phenyl-2-azetidinone (5b). Method A.** To a mixture of 1-(*tert*-butyldimethylsilyl)-4-phenyl-2-azetidinone (**6a**)[35] (283 mg) and (*Z*)-1-nitro-1-(phenylthio)propene (**2**)[3] (198 mg) in CH_2Cl_2 (6 mL) was added Bu_4NF in THF (1.0 M; 1.08 mL) with stirring at −30 °C. After 5 min at −30 °C, the solution was further diluted with CH_2Cl_2 (40 mL) and cooled to −78 °C. Ozone was bubbled through the reaction mixture to a faint blue end point. The reaction mixture was purged with N_2 and the solution partitioned between H_2O and CH_2Cl_2. The organic layer was dried ($MgSO_4$), filtered, and evaporated to give an oil which was chromatographed on silica gel (25 g, 1:1 Et_2O/hexane as eluant) to give **5b** (236 mg, 75%) as an oil: IR 1745, 1700 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.4 (m, 10 H), 4.85 (dd, 1 H, J = 6, 2 Hz), 4.70 (q, 1 H, J = 7.5 Hz), 3.45 (dd, 1 H, J = 15, 6 Hz), 2.85 (dd, 1 H, J = 15, 2 Hz) 1.2, 1.1 (2d, 3 H, J = 7.5 Hz); mass spectrum (CI), m/e 312 (M^+ + H), 270, 199, 174, 132, 109. Anal. Calcd for $C_{18}H_{17}NO_2S$: C, 68.19; H, 5.73. Found: C, 68.32; H, 5.76.

Method B. To a solution of 4-phenyl-2-azetidinone (**4a**)[12] (66 mg) in DMF (2.0 mL) at 0 °C was added KO-*t*-Bu in *t*-BuOH (1 M; 0.45 mL). The reaction mixture was stirred at 0 °C for 10 min and cooled to −20 °C. (*Z*)-1-Nitro-1-(phenylthio)propene (**2**)[3] (87 mg) was added and stirring was continued for 20 min longer. The red-brown solution was diluted with dry MeOH (20 mL) and cooled to −78 °C, and O_3 was bubbled through the mixture until a clear, colorless solution was obtained. The reaction mixture was purged with N_2 and added to pH 7 buffer. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and evaporated to give an oil which was chromatographed to produce **5b** (57 mg, 41%).

4-(4-Pentenyl)-2-azetidinone (4b). To 1,6-heptadiene (5 mL) was added $ClSO_2NCO$ (3.2 mL) with stirring at room temperature. After 24 h, IR spectroscopy indicated the reaction was complete (lack of an adsorption at 2230 cm^{-1}). The viscous orange-yellow syrup was diluted with dry CH_2Cl_2 (80 mL) and added slowly to a vigorously stirred suspension of sodium sulfite (5 g), H_2O (100 mL), and CH_2Cl_2 (200 mL) while maintaining the pH of the stirred solution at 7–9 by the slow addition of 1 N KOH. The resulting emulsion was extracted with EtOAc, and the combined organic layers were dried ($MgSO_4$), filtered, and evaporated to yield a clear tan oil. Chromatography on silica gel (40 g, Et_2O as eluant) gave **4b** (2.51 g, 49%) as an oil: IR 3250, 1750 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 6.9 (br s, 1 H), 5.75 (m, 1 H), 5.0 (m, 2 H), 3.6 (m, 1 H), 3.1 (dd, 1 H, J = 17, 5 Hz), 2.52 (dd, 1 H, J = 17, 1 Hz), 2.1 (m, 2 H), 1.8–1.2 (m, 4 H); mass spectrum (CI), m/e 140 (M^+ + H), 98, 81. Anal. Calcd for $C_8H_{13}NO$: C, 69.01; H, 9.42; N, 10.06. Found: C, 68.90; H, 9.49; N, 10.28.

1-(*tert*-Butyldimethylsilyl)-4-(4-pentenyl)-2-azetidinone (6b). To 4-(4-pentenyl)-2-azetidinone (**4b**) (1.01 g) in dry CH_2Cl_2 (10 mL) were added *i*-Pr_2NEt (1.9 mL) and *t*-$BuMe_2SiCl$ (1.32 g) in CH_2Cl_2 (5 mL) at room temperature. The mixture was stirred for 12 h and evaporated, and the brown oily residue was chromatographed on silica gel (65 g, Et_2O as eluant) to give **6b** (1.819 g, 99%) as an oil: IR 3072, 2928, 1746 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 5.9–5.5 (m, 1 H), 5.1 (m, 1 H), 4.9 (m, 1 H), 3.6 (m, 1 H), 3.1 (dd, 1 H, J = 15, 4 Hz), 2.55 (dd, 1 H, J = 15, 2 Hz), 2.3–1.3 (m, 6 H), 1.0 (s, 9 H), 0.2 (s, 6 H); mass spectrum (CI), m/e 254

(33) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.
(34) For example, see: Salzmann, T. N.; Ratcliffe, R. W.; Christensen, B. G. *Tetrahedron Lett.* **1980**, *21*, 1193.
(35) Bergmann, H. J.; Mayrhofer, R.; Otto, H. H. *Arch. Pharm.* **1986**, *319*, 203.

($M^+ + H$), 211, 196, 154. Anal. Calcd for $C_{14}H_{27}NOSi$: C, 66.32; H, 10.76; N, 5.53. Found: C, 66.00; H, 10.64; N, 5.65.

1-(*tert*-Butyldimethylsilyl)-4-(4-oxobutyl)-2-azetidinone (6c). β-Lactam **6b** (256 mg) was dissolved in dry CH_2Cl_2 (100 mL) and cooled to −78 °C with stirring. Ozone was bubbled through the clear, colorless solution to a faint blue end point. The flask was purged with N_2 and Me_2S (5 mL) was added. The solution was warmed slowly to reflux under nitrogen for 12 h. The mixture was cooled to room temperature and evaporated. The resulting yellow oil was chromatographed on silica gel (15 g, 70% Et_2O/hexane as eluant) to give **6c** (251 mg, 97%) as a clear colorless oil: IR 2916, 2847, 1733 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 9.77 (s, 1 H), 3.48 (m, 1 H), 3.12 (dd, 1 H, J = 15, 4 Hz), 2.62 (dd, 1 H, J = 15, 2 Hz), 2.49 (t, 2 H, J = 7.3 Hz), 1.85 (m, 1 H), 1.62 (m, 2 H), 1.45 (m, 1 H), 0.97 (s, 9 H), 0.21 (s, 3 H), 0.20 (s, 3 H); mass spectrum (CI), m/e 256 ($M^+ + H$), 240, 214, 198, 156, 124. The crude material was used directly without further characterization.

1-(*tert*-Butyldimethylsilyl)-4-[4-hydroxy-5-nitro-5-(phenylthio)pentyl]-2-azetidinone (6d). $PhSCH_2NO_2$ (1) (53 mg) was dissolved in *t*-BuOH and THF (1:1 v/v; 5 mL) and cooled to 0 °C with stirring. KO-*t*-Bu in *t*-BuOH (1.0 M; 31 μL) was added dropwise, and a creamy-white suspension immediately resulted. Stirring was continued for 20 min at 0 °C and the β-lactam aldehyde **6c** (80 mg) in THF and *t*-BuOH (1:1, 2 mL) was added. The reaction mixture was stirred at −3 to 0 °C until the aldehyde was consumed (^1H NMR, 18 h). The solution was added to aqueous 1 M potassium dihydrogen phosphate buffer, the aqueous suspension was extracted with Et_2O (3 × 20 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and evaporated to give a viscous yellow oil. Chromatography on silica gel (20 g, Et_2O as eluant) gave **6d** (108 mg, 81%) as an oil: IR 3348, 1735, 1558, 1340 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.35 (m, 5 H). 5.35 (m, 1 H), 5.22 (m, 1 H), 4.10 (m, 1 H), 3.45 (m, 1 H), 3.05 (dd, 1 H, J = 15, 5 Hz), 2.50 (dd, 1 H, J = 15, 2 Hz), 2.10–1.20 (m, 6 H), 0.95 (s, 9 H), 0.15 (s, 6 H); mass spectrum, m/e $M^{\bullet+}$ absent, 407, 378, 256, 123. Anal. Calcd for $C_{20}H_{32}N_2O_4SSi$: C, 56.54; H, 7.60. Found: C, 56.80; H, 7.90.

1-(*tert*-Butyldimethylsilyl)-4-[5-nitro-5-(phenylthio)-4-(*Z*)-pentenyl]-2-azetidinone (6e). The nitro alcohol **6d** (189 mg) was dissolved in CH_2Cl_2 (15 mL) and cooled to −78 °C with stirring. To this solution were simultaneously added $MeSO_2Cl$ (104 μL) and Et_3N (185 μL). Stirring was continued at −78 °C for 5 min and the solution was warmed up to 0 °C. After 20 min, evaporation at 10 °C gave an oily brown residue. Rapid chromatography on silica gel (20 g, 1:1, Et_2O/hexane as eluant) gave **6e** (146 mg, 81%) as a bright yellow oil: IR 2950, 1733, 1570 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ 7.6 (t, 1 H, J = 7.5 Hz), 7.3 (m, 5 H), 3.45 (m, 1 H), 3.0 (m, 1 H), 2.5 (m, 1 H), 2.0–1.4 (m, 6 H), 0.9 (s, 9 H), 0.2 (s, 6 H); mass spectrum (CI), m/e 407 ($M^+ + H$), 318, 284, 246. Anal. Calcd for $C_{20}H_{30}N_2O_3SSi$: C, 59.06; H, 7.44; N, 6.89. Found: C, 58.78; H, 7.70; N, 7.17.

4-[5-Nitro-5-(phenylthio)-4(*Z*)-pentenyl]-2-azetidinone (4d). To the β-lactam **6e** (124 mg) in dry CH_2Cl_2 (25 mL) at −78 °C were added hydrogen fluoride–pyridine (Aldrich) and dry pyridine in CH_2Cl_2 (1:5:25 v:v:v; 5 mL). When the addition was complete, the yellow solution was slowly warmed up to 0 °C (1 h). After a further 2 h, the mixture was partitioned between H_2O and CH_2Cl_2. The organic layer was washed once with dilute aqueous copper sulfate, dried (Na_2SO_4), filtered, and evaporated, and the residue was chromatographed on silica gel (20 g, Et_2O as eluant) to give **4d** (70 mg, 78%) as a yellow oil: ^1H NMR (270 MHz, $CDCl_3$) δ 7.66 (t, 1 H, J = 7.9 Hz), 7.25 (m, 5 H), 5.82 (br s, 1 H), 3.59 (m, 1 H), 3.03 (m, 1 H), 2.56 (m, 3 H), 1.6 (m, 4 H). The crude product was used directly in the next transformation.

2-[(Phenylthio)carbonyl]-1-azabicyclo[4.2.0]octan-8-one (8a and 9). Method A. To a stirred solution of the nitroalkene **4d** (44 mg) in dry THF and *t*-BuOH (1:1 v/v; 2 mL) at −30 °C was added KO-*t*-Bu in *t*-BuOH (1 M; 153 μL). After being stirred for 5 min at −30 °C, the solution was diluted with dry CH_2Cl_2 (15 mL) and cooled to −78 °C. Ozone was bubbled through the mixture until the red-brown solution became clear and colorless. The flask was rapidly purged with N_2 and the solution was partitioned between H_2O and CH_2Cl_2. The organic layer was dried (Na_2SO_4), filtered, and evaporated to give an oil. Chromatography on silica gel (10 g, 1:1, Et_2O/hexane as eluant) gave **8a** and **9** (29 mg, 73%) as two separated diastereoisomers (α:β 1:1.3). The less polar (α) isomer **8a** was an oil: R_f 0.5, 1:1 Et_2O/hexane; IR 1751, 1701 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.41 (s, 5 H), 4.64 (br d, 1 H, J = 6.6 Hz), 3.77 (m, 1 H), 3.28 (dd, 1 H, J = 15.1, 5.3 Hz), 2.75 (dd, 1 H, J = 15.1, 1.9 Hz), 2.32–2.01 (m, 2 H), 1.82–1.22 (m, 4 H); mass spectrum (EI), m/e 261 ($M^{\bullet+}$), 233, 218, 123, 82. Anal. Calcd for $C_{14}H_{15}NO_2S$: C, 64.32; H, 5.80; N, 5.36. Found: C, 64.24; H, 5.90; N, 5.49. The more polar (β) isomer **9** was an oil: R_f 0.4, 1:1 Et_2O/hexane; IR 1750, 1700 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.46 (m, 2 H), 7.35 (m, 3 H), 3.94 (m, 1 H), 3.36 (m, 1 H), 3.03 (dd, 1 H, J = 14.5, 3.3 Hz), 2.57 (dd, 1 H, J = 14.5, ≤1 Hz), 2.07–1.73 (m, 4 H), 1.43–1.19 (m, 2 H); mass spectrum (EI), m/e 261 ($M^{\bullet+}$), 233, 218, 124, 82. Anal. Calcd for $C_{14}H_{15}NO_2S$: C, 64.32; H, 5.80; N, 5.36. Found: C, 64.24; H, 5.74; N, 5.33.

Method B. The nitroalkene **6e** (129 mg) was dissolved in THF (2 mL) at −55 °C and Bu_4NF in THF (1.0 M; 317 μL) was added. The solution was held at −55 °C for 5 min after the addition was complete. The brown solution was diluted with CH_2Cl_2 (45 mL) and cooled to −78 °C. Ozone was bubbled through the reaction mixture until the brown solution became clear and colorless. The solution was immediately purged with N_2 and the contents were partitioned between H_2O and CH_2Cl_2. The aqueous layer was further extracted with CH_2Cl_2 (2 × 20 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and evaporated to give an oil. Chromatography gave **8a** and **9** (82 mg, 83%) as a colorless oil. In this experiment the ratio of diastereoisomers (α:β) formed was 1:3.3.

Conversion of (2*S*(*R*),6*R*(*S*))-2-[(Phenylthio)-carbonyl]-2-azabicyclo[4.2.0]octan-8-one (9) into the 2*S*(*R*),6*S*(*R*) Diastereoisomer 8a. To pure **9** (5.1 mg) in dry THF (2.0 mL) at room temperature was added *i*-Pr_2NEt (25 μL) with stirring. The solution was warmed to 45 °C for 10 days. The resulting red mixture was chromatographed on silica gel to give the pure α epimer **8a** (5.0 mg, 98%). In the blank experiment the α-epimer **8a** was recovered unchanged on attempted isomerization with *i*-Pr_2NEt.

1-(*tert*-Butyldimethylsilyl)-4-(3-butenyl)-2-azetidinone (6f). To 4-(3-butenyl)-2-azetidinone (**4e**)[22] (1.254 g) in CH_2Cl_2 (12 mL) were added *i*-Pr_2NEt (2.6 mL) and *t*-$BuMe_2SiCl$ (1.808 g) at room temperature. The mixture was stirred for 12 h and partitioned between aqueous 1 M potassium dihydrogen phosphate (100 mL) and CH_2Cl_2. The aqueous layer was further extracted with CH_2Cl_2 (2 × 30 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and evaporated to give an oil. Chromatography on silica gel (55 g, 1:1 Et_2O/hexane as eluant) gave **6f**[36] (2.390 g, 100%) as an oil: IR 1745 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 6.0–5.7 (m, 1 H), 5.1 (m, 1 H), 5.0 (m, 1 H), 3.55 (m, 1 H), 3.15 (dd, 1 H, J = 15, 6 Hz), 2.6 (dd, 1 H, J = 15, 2 Hz), 2.2–1.4 (m, 4 H), 1.0 (s, 9 H), 0.2 (s, 6 H); mass spectrum (CI), m/e 240 ($M^+ + H$), 182, 140. Anal. Calcd for $C_{13}H_{25}NOSi$: C, 65.19; H, 10.53. Found: C, 65.57; H, 10.58.

1-(*tert*-Butyldimethylsilyl)-4-(3-oxopropyl)-2-azetidinone (6g). β-Lactam **6f** (318 mg) was dissolved in CH_2Cl_2 (20 mL) and cooled to −78 °C with stirring. Ozone was bubbled through the solution until a pale blue end point was observed. Me_2S (7 mL) was added and the mixture was warmed from −78 °C to reflux. Reflux under nitrogen was continued for 12 h. The solution was allowed to cool to room temperature and evaporated. The resultant oily residue was chromatographed on silica gel (25 g, Et_2O as eluant) to give **6g** (256 mg, 80%) as an oil: IR 1733, 1729 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 9.8 (s, 1 H), 3.6 (m, 1 H), 3.15 (dd, 1 H, J = 15, 5 Hz), 2.65–1.5 (m, 5 H), 0.95 (s, 9 H), 0.22, 0.20 (2s, 6 H); mass spectrum (CI), m/e 242 ($M^+ + H$), 216, 200, 158, 142. The aldehyde **6g** was used directly without further purification.

1-(*tert*-Butyldimethylsilyl)-4-[3-hydroxy-4-nitro-4-(phenylthio)butyl]-2-azetidinone (6h). To $PhSCH_2NO_2$ (1) (286 mg) dissolved in THF and *t*-BuOH (1:1, v/v; 10 mL) at 0 °C was added KO-*t*-Bu in *t*-BuOH (1.0 M; 170 μL). A creamy white suspension was immediately formed. The β-lactam aldehyde **6g** (394 mg) in THF and *t*-BuOH (1:1, 2 mL) was added with stirring. After 5 h at 0 °C the mixture was poured into 1 M pH 7 buffer and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL).

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The combined organic layers were dried ($MgSO_4$), filtered, and evaporated to give a yellow oil which was chromatographed on silica gel (37 g, 1:1 CH_2Cl_2/hexane as eluant) to give **6h** (598 mg, 89%) as a solid inseparable mixture of diastereoisomers. Recrystallization from EtOAc and hexane (1:10) gave an analytically pure sample: mp 89–96 °C; IR 3600–3100, 1712, 1558 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.4 (m, 5 H), 5.35 (m, 1 H), 4.1 (m, 1 H), 3.5 (m, 1 H), 3.1 (dd, 1 H, J = 15, 4 Hz), 2.55 (dd, 1 H, J = 15, 3 Hz), 2.0–1.4 (m, 5 H), 0.9 (s, 9 H), 0.21 (s, 3 H), 0.20 (s, 3 H); mass spectrum (EI), m/e $M^{\bullet+}$ absent, 393, 364, 242, 123. Anal. Calcd for $C_{19}H_{30}N_2O_4SSi$: C, 55.55; H, 7.37; N, 6.82. Found: C, 55.12; H, 7.56; N, 6.66.

1-(*tert*-Butyldimethylsilyl)-4-[4-nitro-4-(phenylthio)-3-(*Z*)-butenyl]-2-azetidinone (6i). To $MeSO_2Cl$ (0.189 mL) and Et_3N (0.38 mL) in dry CH_2Cl_2 (10 mL) at −78 °C was added dropwise **6h** (334 mg) in CH_2Cl_2 (5 mL). The reaction mixture was stirred for 20 min at −78 °C and warmed up to 0 °C over 40 min. The solvent was evaporated at −10 °C and the resultant brown oil chromatographed on silica gel (40 g, 1:1 Et_2O/hexane as eluant) to give **6i** (254 mg, 80%) as a bright yellow oil: IR 2950, 1739, 1550 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.8 (t, 1 H, J = 7 Hz), 7.4 (s, 5 H), 3.65 (m, 1 H), 3.35 (dd, 1 H, J = 15, 5 Hz), 2.8 (m, 2 H), 2.5–1.4 (m, 3 H), 1.1 (s, 9 H), 0.4 (s, 6 H). The crude nitroalkene **6i** was used directly in the next step without any further purification.

2-[(Phenylthio)carbonyl]-2-azabicyclo[3.2.0]heptan-7-one (10a and 11a). To **6i** (134 mg) dissolved in THF (3 mL) at −55 °C was added dropwise Bu_4NF in THF (1.0 M; 340 μL). After the addition was complete, the reaction mixture was diluted with CH_2Cl_2 (20 mL) and cooled to −78 °C. Ozone was bubbled through the brown solution until it became clear and colorless. The reaction mixtue was immediately purged with N_2 and the contents were partitioned between aqueous pH 7 buffer and CH_2Cl_2. The aqueous layer was further extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and evaporated to give an oil which was chromatographed on silica gel (15 g, 3:1 Et_2O/hexane as eluant) to give **10a** and **11a** (70 mg, 83%) as an inseparable pair (α:β = 1:2.5) of diastereoisomers: IR 2949, 1760, 1700 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.4 (m, 5 H), 4.53, 4.19 (2m, 1 H), 3.95, 3.72 (2m, 1 H), 3.38, 3.08 (2dd, 1 H, J = 15, 4 Hz), 2.77, 2.65 (2dd, 1 H, J = 15, 2 Hz), 2.43 (m, 2 H), 2.13 (m, 1 H), 1.75 (m, 1 H); mass spectrum (EI), m/e 247 ($M^{\bullet+}$) 159, 138, 110.

1-(*tert*-Butyldimethylsilyl)-4-(2-propenyloxy)-2-azetidinone (18a). *t*-$BuMe_2SiCl$ (1.07 g), *i*-Pr_2NEt (1.54 mL), and 4-(dimethylamino)pyridine (0.5 mg) were added to 4-(2-propenyloxy)-2-azetidinone (**17a**)[26] (0.75 g) in dry CH_2Cl_2 (25 mL). After being stirred overnight, the solution was evaporated and the residue chromatographed on silica gel (CH_2Cl_2 as eluant) to give **18a** (1.35 g, 95%) as an oil: IR 1750, 1315, 1190, 1180 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.90 (8-line m, 1 H), 5.30 (d, 1 H, J = 18 Hz), 5.20 (d, 1 H, J = 10.4 Hz), 4.98, (dd, 1 H, J = 4 <1 Hz), 4.0 (d, 2 H, J = 5.6 Hz), 3.12 (dd, 1 H, J = 16.8, 4 Hz), 2.90 (dd, 1 H, J = 16.8, <1 Hz), 0.95 (s, 9 H), 0.22 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) 170.6, 133.7, 117.1, 79.3, 67.5, 46.2, 26.2, 25.8, 18.3; mass spectrum (CI), m/e 242 (M^+ + H), 184, 158, 142. Anal. Calcd for $C_{12}H_{23}NO_2Si$: C, 59.68; H, 9.61; (M^+ + H), 242.1576. Found: C, 59.63; H, 9.30; (M^+ + H), 242.1581.

1-(*tert*-Butyldimethylsilyl)-4-(2-oxoethoxy)-2-azetidinone (18b). Ozone was bubbled through **18a** (1.76 g) in CH_2Cl_2 (25 mL) at −78 °C to a pale blue end point. The solution was purged with N_2, Me_2S (1 mL) and *t*-BuOH (0.5 mL) were added, and the mixture was stirred overnight at room temperature. Evaporation and reevaporation twice with CH_2Cl_2 (3 mL) gave an oil which was chromatographed on silica gel (1:4 EtOAc/hexane as eluant) to give **18b** (1.6 g, 95%) as a colorless oil: IR 3460, 1750–1730, 1320, 1250, 1195, 1075 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 9.70 (s, 0.5 H), 5.00 (m, 1.5 H), 4.07 (s, 1 H), 3.51 (m, 1 H), 3.18 (2dd, 1 H, J = 15, 4 Hz), 2.87 (dd, 1 H, J = 15, 2 Hz), 0.94 (s, 9 H), 0.27 (s, 3 H), 0.23 (s, 3 H); mass spectrum (CI), m/e 244 (M^+ + H), 230, 202, 184, 142. Since the aldehyde **18b** was partially hydrated as the gem diol, it was used directly without further purification.

1-(*tert*-Butyldimethylsilyl)-4-[[2-hydroxy-3-nitro-3-(phenylthio)propyl]oxy]-2-azetidinone (18c). $PhSCH_2NO_2$ (**1**)[11] (0.32 g) and $(t\text{-BuO})_3Al$ (0.05 g) were dissolved in dry THF and *t*-BuOH (1:1, 3 mL) at 0 °C. KO-*t*-Bu in THF (1 M; 0.3 mL) was added and, after stirring at 0 °C for 10 min, the aldehyde **18b** (0.46 g) in THF and *t*-BuOH (1:1, 4 mL) was added. After 3 h at 0 °C and overnight at −20 °C, the mixture was added to pH 7 buffer and extracted with CH_2Cl_2 (4 × 10 mL). The organic extract was dried (Na_2SO_4) and evaporated and the residue chromatographed on silica gel (22 g, 1:1–1:0 gradient EtOAc/hexane as eluant) to give **18c** (0.56 g, 72%) as an oil: IR 3500, 1740, 1555, 1330 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.5, 7.4 (2m, 5 H), 5.65, 5.58 (2m, 1 H), 5.00 (m, 1 H), 4.48, 4.32 (2m, 1 H), 4.0–3.6 (m, 2 H), 3.3–2.8 (m, 3 H), 0.96 (3s, 9 H), 0.27 (5s, 6 H); mass spectrum (CI), m/e 413 (M^+ + H), 366, 284, 272, 260, 244, 184, 123; high resolution mass ion measurement calcd for $C_{18}H_{28}N_2O_5SSi$ (M^+ + H) 413.1568, found (M^+ + H) 413.1568.

1-(*tert*-Butyldimethylsilyl)-4-[[3-nitro-3-(phenylthio)-2-(*Z*)-propenyl]oxy]-2-azetidinone (18d). $MeSO_2Cl$ (0.30 mL) and *i*-Pr_2NEt (0.67 mL) were added simultaneously to **18c** (0.52 g) in dry CH_2Cl_2 (10 mL) at −78 °C. After 15 min the solution was allowed to warm up to room temperature. Evaporation and chromatography on silica gel (15 g, 1:1 EtOAc/hexane as eluant) gave **18d** (0.32 g, 64%) as a yellow oil: IR 1755, 1535, 1470, 1325 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.66 (t, 1 H, J = 6 Hz), 7.35 (s, 5 H), 5.02 (dd, 1 H, J = 4, 2 Hz), 4.48 (d, 2 H, J = 6 Hz), 3.3–2.8 (m, 2 H), 0.98 (s, 9 H), 0.28 (s, 6 H).

(2*R*(*S*),5*R*(*S*))-2-[(Phenylthio)carbonyl]-4-oxa-1-azabicyclo[3.2.0]heptan-7-one (19a) and the 2*R*(*S*),5*S*(*R*) Diastereoisomer 20a. Bu_4NF in THF (1.0 M; 1.2 mL) was added to the crude nitroalkene **18d** (0.48 g) in dry THF (15 mL) at −55 °C. After 15 min the solution was cooled to −78 °C and dry CH_2Cl_2 (15 mL) added. Ozone was bubbled through the golden yellow solution to a pale yellow end point and the mixture was purged with N_2. The solution was added to pH 7 buffer and extracted with CH_2Cl_2 (4 × 10 mL). The extract was dried (Na_2SO_4) and evaporated. Chromatography of the oil on silica gel (10 g, 1:1 Et_2O/hexane as eluant) gave the less polar α-isomer **19a** (70 mg, 23%) and the β-isomer **20a** (100 mg, 33%). Recrystallization from Et_2O and hexane gave the analytically pure α-isomer **19a**: mp 86–88 °C; IR 1795, 1698, 1120 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42, 7.28 (2m, 5 H), 5.46 (dd, 1 H, J = 3, <1 Hz), 4.74 (dd, 1 H, J = 8, 6 Hz), 4.53 (dd, 1 H, J = 9, 8 Hz), 4.20 (dd, 1 H, J = 9, 6 Hz), 3.45 (dd, 1 H, J = 16.6, 3 Hz), 3.01 (dd, 1 H, J = 16.6, <1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.5, 176.2, 134.5, 129.7, 129.3, 126.7, 85.9, 74.1, 66.2, 45.1; mass spectrum (EI), m/e 249 (M^+), 207, 147, 112, 70. Anal. Calcd for $C_{12}H_{11}NO_3S$: C, 57.82; H, 4.45; ($M^{\bullet+}$), 249.0460. Found: C, 58.11; H, 4.43; ($M^{\bullet+}$) 249.0462. Recrystallization from Et_2O and hexane gave the analytically pure β-isomer **20a**: mp 101–103 °C; IR ($CHCl_3$) 1790, 1703, 1120 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49, 7.44 (2m, 5 H), 5.20 (dd, 1 H, J = 3.2, <1 Hz), 4.48 (dd, 1 H, J = 8.4, 3.0 Hz), 4.29 (dd, 1 H, J = 6, 3 Hz), 4.23 (dd, 1 H, J = 8, 6 Hz), 3.22 (dd, 1 H, J = 16.8, 3 Hz), 3.08 (dd, 1 H, J = 16.8, <1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.8, 173.1, 134.3, 129.9, 129.4, 126.2, 85.7, 74.8, 67.3, 43.9; mass spectrum (CI), m/e 249 (M^+), 147, 112, 70. Anal. Calcd for $C_{12}H_{11}NO_3S$: C, 57.82; H, 4.45; ($M^{\bullet+}$), 249.0460. Found: C, 57.37; H, 4.57; ($M^{\bullet+}$), 249.0460.

Isomerization of (2*R*(*S*),5*S*(*R*))-2-[(Phenylthio)carbonyl]-4-oxa-1-azabicyclo[3.2.0]heptan-7-one (20a) into the 2*R*(*S*),5*R*(*S*) Isomer 19a. *i*-Pr_2NEt (50 μL) was added to **20a** (15 mg) in $CDCl_3$ (0.5 mL). After 3 days at room temperature the 400-MHz NMR spectrum was consistent with clean isomerization to produce the α-isomer **19a** only.

4-[(2-Methyl-3-buten-2-yl)oxy]-2-azetidinone (17b). A mixture of 4-acetoxy-2-azetidinone (**16**)[25] (1.29 g), 2-methyl-3-buten-2-ol (2.58 g), and $Zn(OAc)_2{\cdot}2H_2O$ (1.09 g) was suspended in PhH (15 mL) and heated to reflux for 18 h with stirring. Water was removed azeotropically during the reflux by means of a Dean–Stark trap. The yellow solution was cooled to room temperature and filtered through Celite. The filtrate was concentrated by evaporation and the oily residue chromatographed on silica gel (52 g, Et_2O as eluant) to give **17b** (823 mg, 53%) as an oil: IR 3250, 2965, 1735 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.8 (br s, 1 H), 5.85 (dd, 1 H, J = 16, 12 Hz), 5.2 (m, 3 H), 3.1 (dd, 1 H, J = 16, 4 Hz), 2.8 (dd, 1 H, J = 16, ≤1 Hz), 1.32 (s, 6 H); mass spectrum (CI), m/e 156 (M^+ + H), 128, 116. Anal. Calcd for $C_8H_{13}NO_2$: C, 61.89; H, 8.45; N, 9.03. Found: C, 62.00; H, 8.44; N, 8.87.

1-(*tert*-Butyldimethylsilyl)-4-[(2-methyl-3-buten-2-yl)oxy]-2-azetidinone (18e). To **17b** (581 mg) in CH_2Cl_2 (10 mL) were added *i*-Pr_2NEt (0.979 mL), 4-(dimethylamino)pyridine (0.5 mg), and *t*-$BuMe_2SiCl$ (678 mg) at room temperature and the mixture was stirred overnight. Evaporation and chromatography of the residue on silica gel (42 g, 1:1 Et_2O/hexane as eluant) gave **18e** (980 mg, 97%) as an oil: IR 2952, 2850, 1750 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.85 (dd, 1 H, J = 17, 12.5 Hz), 5.14 (m, 2 H), 4.94 (m, 1 H), 3.10 (dd, 1 H, J = 14.5, 4 Hz), 2.77 (dd, 1 H, J = 14.5, ≤1 Hz), 1.31 (s, 3 H), 1.29 (s, 3 H), 0.95 (s, 9 H), 0.25 (s, 3 H), 0.21 (s, 3 H); mass spectrum (CI), m/e 270 (M^+ + H), 254, 242, 230, 212, 202, 184. Anal. Calcd for $C_{14}H_{27}NO_2Si$: C, 62.38; H, 10.11. Found: C, 62.10; H, 9.87.

1-(*tert*-Butyldimethylsilyl)-4-[(2-methyl-3-oxo-2-propyl)oxy]-2-azetidinone (18f). The β-lactam **18e** (753 mg) was dissolved in dry CH_2Cl_2 (25 mL) and cooled to −78 °C. Ozone was bubbled through the mixture until the solution turned pale blue. The mixture was immediately purged with N_2 and Me_2S (10 mL) was added. The solution was warmed to reflux for 8 h, cooled to room temperature, and evaporated. The resultant yellow oil was chromatographed on silica gel (20 g, Et_2O as eluant) to give **18f** (572 mg, 75%) as an oil: IR 2920, 2840, 1730, 1680 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 9.58 (s, 1 H), 5.03 (dd, 1 H, J = 3.4, 1.5 Hz), 3.24 (dd, 1 H, J = 15.1, 3.4 Hz), 2.80 (dd, 1 H, J = 15.1, 1.5 Hz), 1.33 (s, 3 H), 1.32 (s, 3 H), 0.97 (s, 9 H), 0.28 (s, 3 H), 0.25 (s, 3 H); mass spectrum (CI), m/e 272 (M^+ + H), 256, 242, 189, 142. Anal. Calcd for $C_{13}H_{25}NO_3Si$: C, 57.50; H, 9.29; N, 5.16. Found: C, 57.38; H, 9.27; N, 4.95.

1-(*tert*-Butyldimethylsilyl)-4-[[3-hydroxy-2-methyl-4-nitro-4-(phenylthio)-2-butyl]oxy]-2-azetidinone (18g). To $PhSCH_2NO_2$ (1) (484 mg) in THF and *t*-BuOH (1:1, 15 mL) at −3 °C was added KO-*t*-Bu in THF (1 M, 273 μL). After 15 min at −3 °C, the β-lactam **18f** (741 mg) in THF and *t*-BuOH (1:1, 2 mL) was added. After 48 h at −3 °C, the solution was poured into pH 7 buffer and the aqueous layer extracted with CH_2Cl_2 (4 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated to give crude **18g** (945 mg, 79%) as a yellow oil: IR 3350, 1730, 1550, 1330 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.5–7.2 (m, 5 H), 5.9–5.6 (m, 1 H), 5.2–4.9 (m, 1 H), 4.1–3.6 (m, 1 H), 3.3–2.2 (m, 3 H), 1.2 (s, 6 H), 0.9 (s, 9 H), 0.21, 0.20 (2s, 6 H); mass spectrum (CI), m/e 441 (M^+ + H), 394, 272, 184, 123. The material was used without further purification in the next step.

1-(*tert*-Butyldimethylsilyl)-4-[[(2-methyl-4-nitro-4-(phenylthio)-3(*Z*)-buten-2-yl]oxy]-2-azetidinone (18h). To $MeSO_2Cl$ (0.735 g) and Et_3N (873 μL) in dry CH_2Cl_2 (10 mL) at −78 °C was added dropwise the β-lactam **18g** (945 mg) in CH_2Cl_2 (2 mL). After 15 min at −78 °C the bright yellow solution was warmed to 0 °C. After 10 min at 0 °C, the solvent was evaporated and the light brown oily residue was immediately chromatographed on silica gel (35 g, 4:29:17 Et_2O/CH_2Cl_2/hexane as eluant) to give **18h** (815 mg, 90%) as a bright yellow oil: IR 1740, 1540, 1450, 1320 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.8 (s, 1 H), 7.4–7.2 (m, 5 H), 5.07 (m, 1 H), 3.2 (dd, 1 H, J = 15.2, 4 Hz), 2.92 (dd, 1 H, J = 15.2, 1 Hz), 1.66 (s, 3 H), 1.60 (s, 3 H), 0.98 (s, 9 H), 0.30 (s, 3 H), 0.27 (s, 3 H); mass spectrum, m/e 423, 222, 211, 184, 133. The material was used without any further purification in the next step.

3,3-Dimethyl-2-[(phenylthio)carbonyl]-4-oxa-1-azabicyclo[3.2.0]heptan-7-one (19c and 20c). To β-lactam **18h** (55 mg) in dry THF (1.0 mL) at −55 °C was added dropwise Bu_4NF in THF (1 M, 0.3 mL). The bright yellow solution turned colorless upon the complete addition of fluoride. Stirring was continued for 4 min before the solution was cooled to −78 °C and CH_2Cl_2 (12 mL) was added. Ozone was bubbled through the reaction vessel until a faint blue color appeared. The reaction mixture was purged with N_2 and partitioned between pH 7 buffer and CH_2Cl_2. The organic layer was dried ($MgSO_4$) filtered, and evaporated to give an oil which was purified on silica gel (10 g, 1:1 Et_2O/hexane as eluant) to give the two separable diastereoisomers **19c** and **20c**. The less polar isomer **19c** (23 mg, 65%) was a solid: mp 138 °C (Et_2O/hexane); IR 1785, 1700 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.4 (s, 5 H), 5.49 (dd, 1 H, J = 2.7, <1 Hz), 4.23, (s, 1 H), 3.40 (dd, 1 H, J = 16.5, 2.7 Hz), 2.96 (dd, 1 H, J = 16.5, <1 Hz), 1.57 (s, 3 H), 1.38 (s, 3 H); mass spectrum (CI), m/e 278 (M^+ + H), 250, 236, 220, 192, 140. Anal. Calcd for $C_{14}H_{15}NO_3S$: C, 60.61; H, 5.45; N, 5.05. Found: C, 60.75; H, 5.55; N, 4.96. The more polar isomer **20c** (5 mg, 14%) was a solid: mp 114 °C (Et_2O/hexane); IR 1785, 1706 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.43 (s, 5 H), 5.26 (m, 1 H), 4.00 (s, 1 H), 3.15 (m, 2 H), 1.53 (s, 3 H), 1.49 (s, 3 H); mass spectrum (CI), m/e 278 (M^+ + H), 250, 236, 220, 192, 140; high resolution mass ion measurement (CI) calcd for $C_{14}H_{15}NO_3S$ (M^+ + H) 278.0847, found (M^+ + H) 278.0845.

4-[(3-Hydroxy-2-methylenepropyl)oxy]-2-azetidinone (23). A mixture of 4-acetoxy-2-azetidinone (**16**)[25] (500 mg), $Zn(OAc)_2 \cdot 2H_2O$ (439 mg), and 2-methylene-1,3-propanediol[30] (768 mg) in PhH (50 mL) was heated to reflux with stirring for 1 h. Water was azeotropically removed during the reflux by means of a Dean–Stark apparatus. The solvent was evaporated and the yellow suspension was filtered through Celite by using EtOAc as solvent. The solvent was evaporated to give a yellow oil which was chromatographed on silica gel (25 g, EtOAc as eluant) to give **23** (527 mg, 86%) as a viscous oil: IR 3279, 2936, 2860, 1775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.05 (br s, 1 H), 5.26 (s, 1 H), 5.20 (s, 1 H), 5.08 (m, 1 H), 4.16–4.09 (m, 4 H), 3.11 (ddd, 1 H, J = 15.2, 4, 2 Hz), 2.88 (dd, 1 H, J = 15.2, 1.2 Hz), 2.45 (br s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 144.4, 113.9, 78.0, 69.3, 63.3, 45.2; mass spectrum (CI), m/e 158 (M^+ + H), 140, 99. Anal. Calcd for $C_7H_{11}NO_3$: C, 53.47; H, 7.06; N, 8.91; (M^+ + H), 158.0817. Found: C, 53.26; H, 6.86; N, 8.76; (M^+ + H), 158.0815.

1-(*tert*-Butyldimethylsilyl)-4-[[3-[(*tert*-butyldimethylsilyl)oxy]-2-methylenepropyl]oxy]-2-azetidinone (24a). To **23** (265 mg) in dry CH_2Cl_2 (15 mL) was added *i*-Pr_2NEt (654 mg) and *t*-$BuMe_2SiCl$ (636 mg) in CH_2Cl_2 (5 mL). After being stirred at room temperature for 12 h, the solution was partitioned between aqueous 1 M KH_2PO_4 and CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered, and evaporated to give an oil which was chromatographed on silica gel (20 g, 1:4 Et_2O/hexane as eluant) to give **24a** (640 mg, 100%) as a clear colorless oil: IR 1761, 1081, 890 cm^{-1}; ^1H NMR (400 MHz $CDCl_3$) δ 5.18 (s, 1 H), 5.10 (s, 1 H), 4.95 (dd, 1 H, J = 4, 1.6 Hz), 4.16 (s, 2 H), 3.99 (AB q, 2 H, J = 13 Hz), 3.11 (dd, 1 H, J = 15, 4 Hz), 2.88 (dd, J = 15, 1.6 Hz), 0.97 (s, 9 H), 0.91 (s, 9 H), 0.25 (s, 3 H), 0.24 (s, 3 H), 0.07 (s, 6 H); mass spectrum (CI), m/e (386 (M^+ + H) 328, 286, 259, 229, 184, 142. Anal. Calcd for $C_{19}H_{39}NO_3Si_2$: C, 59.15; H, 10.20; N, 3.63; (M^+ + H), 386.2547. Found: C, 59.09; H, 10.41; N, 3.83; (M^+ + H), 386.2539.

1-(*tert*-Butyldimethylsilyl)-4-[[3-[(*tert*-butyldimethylsilyl)oxy]-2-oxopropyl]oxy]-2-azetidinone (24b). β-Lactam **24a** (668 mg) was dissolved in dry CH_2Cl_2 (50 mL) at −78 °C and ozone was bubbled through the solution with stirring until a permanent pale blue color was obtained. The reaction mixture was purged with N_2, Me_2S (10 mL) was added, and the solution was warmed to room temperature under nitrogen and refluxed for 4 h. The solution was cooled to room temperature and evaporated and the resultant oil was chromatographed on silica gel (32 g, 1:1 Et_2O/hexane as eluant) to give **24b** (470 mg, 70%) as needles: mp 49.5–51 °C (Et_2O/hexane); IR 2930, 2858, 1758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.0 (dd, 1 H, J = 4, 2 Hz), 4.34 (s, 2 H), 4.28 (s, 2 H), 3.15 (dd, 1 H, J = 15.2, 4 Hz), 2.90 (dd, 1 H, J = 15.2, 2 Hz), 0.93 (s, 9 H), 0.90 (s, 9 H), 0.26 (s, 3 H), 0.25 (s, 3 H), 0.09 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206, 170, 80.3, 69.7, 68.4, 46.0; mass spectrum (CI), m/e 388 (M^+ + H), 256, 184, 142, 99. Anal. Calcd for $C_{18}H_{37}NO_4Si_2$: C, 55.74; H, 9.62; N, 3.61; (M^+ + H), 388.2339. Found: C, 55.77; H, 9.71; N, 3.64; (M^+ + H), 388.2336.

1-(*tert*-Butyldimethylsilyl)-4-[[2-[[(*tert*-butyldimethylsilyl)oxy]methyl]-2-hydroxy-3-butenyl]oxy]-2-azetidinone (24c). To **24b** (286 mg) in THF (3.5 mL) at −78 °C was added vinylmagnesium bromide in THF (1.0 M; 0.74 mL). The solution was warmed up to 0 °C and quenched by pouring into 1.0 M pH 7 buffer and extracting the aqueous layer with Et_2O (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated to give **24b** (290 mg, 95%) as a viscous oil, which solidified on standing. Recrystallization from Et_2O and hexane gave an analytically pure sample: mp 61–62 °C (needles); IR 3300, 1757, 1255, 1196, 1086, 840 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.90 (dd, 1 H, J = 17.6, 10.8 Hz), 5.44 (dd, 1 H, J = 17.5, 1.6 Hz), 5.22 (dd, 1 H, J = 10.8, 1.6 Hz), 4.92 (m, 1 H), 3.64 (d, 1 H, J = 9.6 Hz), 3.51–3.38 (m, 3 H), 3.12 (dd, 1 H, J = 14.8, 4 Hz), 2.85 (dd, 1 H, J = 14.8, <1 Hz), 2.58 (s, 1 H), 0.97 (s, 9 H), 0.90 (s,

9 H), 0.26 (s, 3 H), 0.23 (s, 3 H), 0.07 (s, 6 H); mass spectrum (CI), m/e 416 (M^+ + H), 398, 215, 184, 142. Anal. Calcd for $C_{20}H_{41}NO_4Si_2$: C, 57.76; H, 9.95; N, 3.37; (M^+ + H), 416.2654. Found: C, 57.59; H, 9.80; N, 3.23; (M^+ + H), 416.2654.

1-(*tert*-Butyldimethylsilyl)-4-[[2-[[(*tert*-butyldimethylsilyl)oxy]methyl]-2-hydroxy-3-oxopropyl]oxy]-2-azetidinone (24d). β-Lactam **24c** (190 mg) in dry CH_2Cl_2 (10 mL) was cooled to −78 °C and ozone was bubbled through the mixture until a pale blue color persisted. The flask was purged with N_2 and Me_2S (20 mL) added. The solution was refluxed for 18 h and cooled to room temperature. Evaporation gave an oil which was chromatographed on silica gel (15 g, 1:1 Et_2O/hexane) to give **24d** (185 mg, 97%) as an oil which solidified on standing. Recrystallization from Et_2O and hexane (1:15) gave an analytically pure sample: mp 76–82 °C; IR 1750, 1735, 1087 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.75 (s, 1 H), 4.96 (dd, 1 H, J = 4.0, 1.6 Hz), 3.89 (d, 1 H, J = 10.4 Hz), 3.80 (d, 1 H, J = 10 Hz), 3.66 (d, 1 H, J = 10.4 Hz), 3.57 (d, 1 H, J = 10 Hz), 3.48 (s, 1 H), 3.13 (dd, 1 H, J = 15.2, 4 Hz), 2.86 (dd, 1 H, J = 15.2, 1.6 Hz), 0.96 (s, 9 H), 0.88 (s, 9 H), 0.23 (s, 3 H), 0.22 (s, 3 H), 0.06 (s, 3 H), 0.05 (s, 3 H); mass spectrum (CI), m/e 418 (M^+ + H), 400, 286, 245, 184, 142, 115. Anal. Calcd for $C_{19}H_{39}NO_5Si_2$: C, 54.64; H, 9.41; N, 3.35; (M^+ + H), 418.2445. Found: C, 54.41; H, 9.48; N, 3.26; (M^+ + H), 418.2429.

1-(*tert*-Butyldimethylsilyl)-4-[[2-[[(*tert*-butyldimethylsilyl)oxy]methyl]-2,3-dihydroxy-4-nitro-4-(phenylthio)butyl]oxy]-2-azetidinone (24e). To $PhSCH_2NO_2$ (1) (512 mg) in THF and t-BuOH (1:1, 5 mL) at 0 °C was added KO-t-Bu in t-BuOH (1.0 M; 0.256 mL) with stirring. The solution became a creamy, white suspension. The β-lactam **24d** (1.07 g) in THF and t-BuOH (1:1, 5 mL) was added and stirring was continued at 0 °C for 24 h. The reaction mixture was added to 1 M potassium dihydrogen phosphate buffer, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated to give an oil which was chromatographed on silica gel (35 g, 1:1 Et_2O/hexane as eluant) to give **24e** (929 mg, 62%) and unreacted aldehyde **24d** (300 mg, 28%). the product **24e** was obtained as a yellow oil: IR 3300, 1733, 1559, 1320, 1255, 1085, 841, 606 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50–7.35 (m, 5 H), 6.01–5.90 (m, 1 H), 5.79–5.76 (m, 1 H), 5.0–4.9 (m, 1 H), 4.2 (m, 1 H), 4.01–3.45 (m, 5 H), 3.4–3.2 (m, 1 H), 2.95–2.80 (m, 1 H), 1.0–0.8 (3s, 18 H), 0.24 (s, 3 H), 0.21 (s, 3 H), 0.18 (s, 3 H), 0.10 (s, 3 H); mass spectrum (CI), m/e ($M^{+\cdot}$) absent, 421, 339, 240, 182, 140. Anal. Calcd for $C_{26}H_{46}N_2O_7SSi_2$: C, 53.19; H, 7.90; N, 4.77. Found: C, 52.92; H, 8.05; N, 4.51.

1-(*tert*-Butyldimethylsilyl)-4-[[2-[[(*tert*-butyldimethylsilyl)oxy]methyl]-2-hydroxy-4-nitro-4-(phenylthio)-3(*Z*)-butenyl]oxy]-2-azetidinone (24f). To the nitro alcohol **24e** (735 mg) in dry CH_2Cl_2 (10 mL) were simultaneously added $MeSO_2Cl$ (0.25 mL) and Et_3N (0.53 mL) at −78 °C with stirring. After 0.5 h the mixture was warmed up to −10 °C and stirred for 10 min. The solution was evaporated at −10 °C and the resulting bright yellow oil chromatographed on silica gel (20 g, 1:1 Et_2O/hexane as eluant) to give **24f** (592 mg, 83%) as a bright yellow oil: IR 3335, 1753, 1541, 1323 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76, 7.75 (2s, 1 H), 7.60–7.42 (m, 5 H), 5.0, 4.98 (m, 1 H), 4.27, 4.18 (2s, 1 H), 3.82–3.58 (m, 4 H), 3.15 (dd, 1 H, J = 15.6, 3.6 Hz), 2.93–2.84 (m, 1 H), 0.96 (s, 9 H), 0.91 (s, 9 H), 0.26, 0.25 (2s, 3 H), 0.24 (s, 3 H), 0.1 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 169.9, 148.4, 148.2, 144.3, 144.0, 130.8, 130.7, 130.0, 129.4, 128.3, 80.3, 80.2, 75.0, 74.9, 69.8, 69.3, 66.6, 45.9, 45.8; mass spectrum (CI), m/e 569 (M^+ + H), 408, 321, 184, 142, 111. Anal. Calcd for $C_{26}H_{44}N_2O_6SSi_2$: C, 54.87; H, 7.80; N, 4.92; (M^+ + H), 569.2537. Found: C, 54.81; H, 8.11; N, 4.82; (M^+ + H), 569.2540.

3-Hydroxy-3-[[(*tert*-butyldimethylsilyl)oxy]methyl]-2-[(phenylthio)carbonyl]-5-oxa-1-azabicyclo[4.2.0]octan-8-one (25a and 25b). To the nitroalkene **24f** (149 mg) in THF (2.0 mL) at −55 °C was added Bu_4NF in THF (1 M; 0.26 mL) with stirring. The solution was held at −55 °C for 10 min, cooled to −78 °C, and stirred for 1 h. The reaction mixture was diluted with CH_2Cl_2 (25 mL) and ozone was bubbled through the mixture to a clear pale blue end point. The mixture was purged with N_2, and the solution was partitioned between pH 7 buffer and CH_2Cl_2. The aqueous layer was further extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and evaporated to give a brown oil. Chromatography on silica gel (10 g, 1:1 Et_2O/hexane as eluant) gave **25a** and **25b** as two separate diastereoisomers. The less polar 2*R*(*S*),3*S*(*R*),6*R*(*S*) isomer **25a** (20 mg, 18%) was a crystalline solid: mp 86–88 °C (needles from EtOAc/hexane); IR 1776, 1700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (s, 5 H), 5.37 (dd, 1 H, J = 3.2, <1 Hz, 6α-*H*), 4.86 (s, 1 H, 2β-*H*), 4.01 (d, 1 H, J = 11.6 Hz, 4α-*H*), 3.82 (d, 1 H, J = 10.2 Hz, 3-C*H*), 3.79 (d, 1 H, J = 11.6 Hz, 4β-*H*), 3.65 (d, 1 H, J = 10.2 Hz, 3-C*H*), 3.26 (dd, 1 H, J = 15.2, 3.2 Hz, 7α-*H*), 3.20 (s, 1 H, O*H*), 2.87 (dd, 1 H, J = 15.2, <1 Hz, 7β-*H*), 0.98 (s, 9 H), 0.19 (s, 3 H) 0.17 (s, 3 H); mass spectrum (CI), m/e 424 (M^+ + H), 382, 314, 286, 133, 111; high resolution mass ion measurement (CI) calcd for $C_{20}H_{29}NO_5SSi$ (M^+ + H) 424.1614, found (M^+ + H) 424.1600. The more polar 2*R*(*S*),3*R*(*S*),6*R*(*S*) isomer **25b** was a solid (14 mg, 13%): mp 110–112 °C (needles from EtOAc/hexane 1:10); IR 1768, 1699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (m, 5 H), 5.28 (dd, 1 H, J = 2.8, <1 Hz, 6α-*H*), 4.69 (s, 1 H, 2β-H), 4.02 (d, 1 H, J = 12.4 Hz, 4α-*H*), 3.83 (d, 1 H, J = 12.4 Hz, 4β-*H*), 3.76 (d, 1 H, J = 10 Hz, 3-C*H*), 3.53 (d, 1 H, J = 10 Hz, 3-C*H*), 3.32 (dd, 1 H, J = 15, 3.6 Hz, 7α-*H*), 3.15 (s, 1 H, O*H*), 3.06 (dd, 1 H, J = 15, <1 Hz, 7β-*H*), 0.96 (s, 9 H), 0.09 (s, 3 H), 0.07 (s, 3 H); mass spectrum (CI), m/e 424 (M^+ + H), 382, 314, 286, 244, 133, 111; high resolution mass ion measurement (CI) calcd for $C_{20}H_{29}NO_5SSi$ (M^+ + H) 424.1614, found (M^+ + H) 424.1603.

2-[(Phenylthio)carbonyl]-3-[[(*tert*-butyldimethylsilyl)oxy]methyl]-5-oxa-1-azabicyclo[4.2.0]oct-2-en-8-one (26). To the hydroxyoxacepham **25a** and **25b** (12 mg) in dry CH_2Cl_2 (1.5 mL) at −78 °C were added $MeSO_2Cl$ (15 μL) and Et_3N (54 μL). After 15 min the solution was allowed to warm up to −20 °C and stirring was continued for 60 h. The mixture was filtered through silica gel (0.5 g) and evaporated. The resultant brown oil was chromatographed on silica gel (1:1 to 1:1 Et_2O/hexane) to give **26** (6.5 mg, 55%) as an oil: IR 1792, 1668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (m, 5 H), 5.06 (dd, 1 H, J = 4 Hz, <1 Hz), 4.68–4.49 (m, 4 H), 3.47 (dd, 1 H, J = 15.6, 4 Hz), 2.94 (dd, 1 H, J = 15.6, <1 Hz), 0.98 (s, 9 H), 0.02 (s, 6 H); mass spectrum (EI), m/e M^+ absent, 348, 296, 254, 182, 140, 110, 73; high resolution mass ion measurement calcd for $C_{16}H_{18}NO_4SSi$ (M^+ + H) 406.1509, found (M^+ + H) 406.1502.

X-ray Data Collection and Structure Determination for 25a. X-ray measurements were performed on a CAD4 diffractometrer at −80 °C using Mo Kα radiation (λ = 0.71069 Å). Crystal Data: triclinic, $P\bar{1}$, a = 9.502 (1), b = 16.905 (2), and c = 7.049 (3) Å, α = 97.29 (2)°, β = 96.36 (3)°, γ = 81.57 (1)°, V = 1106 (1) Å^3, Z = 2.

Intensity data were collected in the range $2 < \theta < 25$ from a crystal of dimension 0.45 × 0.22 × 0.10 mm using the $\omega/2\theta$ scan technique with a scan width defined by $\Delta\omega = (0.80 + 0.35 \tan \theta)$. The intensities of three standard reflections were monitored every 3 h, and no significant variation was observed throughout the data collection. The data were corrected for Lorentz and polarization effects. Of the 3891 independent reflections collected, 2177 with $I > 3\sigma(I)$ were used in the subsequent structure solution and refinement. All calculations were performed on a VAX 11/730 computer with the TEXSAN crystallographic program package.[37] The structure was solved by direct methods (MITHRIL).[38] Full-matrix least-squares refinement with anisotropic temperature factors for all non-hydrogen atoms gave the final agreement indices R = 0.035 and R_ω = 0.041. The goodness-of-fit was 1.58. The weights were of the form $w = 1/\sigma^2(F_o)$. All the H atoms were located on a Fourier difference map and refined with individual isotropic temperature factors. The final difference electron density map was featureless with the largest residual peak of 0.23 e/Å^3. The scattering factors were those taken from Cromer and Waber[39] with anomalous dispersion corrections from ref 40.

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Supplementary Material Available: Tables of atomic coordinates, thermal parameters, and bond distances and angles for hydroxyoxacepham **25a** (6 pages). Ordering information is given on any current masthead page.

Studies of the Selective O-Alkylation and Dealkylation of Flavonoids. 10. Selective Demethylation of 7-Hydroxy-3,5,8-trimethoxyflavones with Anhydrous Aluminum Halide in Acetonitrile or Ether[1]

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Demethylation of five 7-hydroxy-3,5,8-trimethoxyflavones and their acetates with anhydrous aluminum halides in acetonitrile or ether was studied and the following results were found. (1) The demethylation was apparently influenced by both solvents and afforded 5,7-dihydroxy-3,8-dimethoxyflavones in acetonitrile and 3,7-dihydroxy-5,8-dimethoxyflavones in ether as main products. (2) The demethylation with 5% w/v anhydrous aluminum bromide in acetonitrile proceeded quantitatively to give a mixture of the corresponding 5- and 3-hydroxyflavones, but that of 7-hydroxy-3,4′,5,8-tetramethoxyflavone and its acetate with 10% anhydrous aluminum chloride in acetonitrile afforded 6-acetyl-5,7-dihydroxy-3,4′,8-trimethoxyflavone as a byproduct along with the 5- and 3-hydroxyflavones. (3) The demethylation of the acetates proceeded more smoothly than that of hydroxyflavones and was superior to that of the flavones with a hydroxy group. (4) These demethylations are available for the syntheses of 3- or 5-hydroxyflavones with no substituent at 6-position.

In a previous paper, we reported a convenient method for synthesizing 3,5-dihydroxy-7,8-dimethoxyflavones from ω-(aroyloxy)-2-hydroxy-3,4,6-trimethoxyacetophenones via the corresponding 3-hydroxyflavones.[1] However, the yield of the 3-hydroxyflavones in this method is low and the improvement of the yield elevates the utility of the method. Generally, cleavage of the 5-methoxy group in 3,5-dimethoxyflavone derivatives is easier than the others. For example, the partial demethylation of 7-hydroxy-3,5,8-trimethoxyflavones **1** was employed for the synthesis of naturally occurring 5,7-dihydroxy-3,8-dimethoxyflavones **2**.[2,3] However, the demethylation of 4′,7-dihydroxy-3,5,8-trimethoxyflavone with anhydrous aluminum chloride in boiling ether does not give the corresponding 5-hydroxyflavone but gives 3,4′,7-trihydroxy-5,8-dimethoxyflavone as a main product.[4] The facts suggest that the 5- or 3-methoxy group on **1** was selectively cleaved by variation of the demethylating conditions.

Therefore, we studied the partial demethylation of 7-hydroxy-3,5,8-trimethoxyflavones **1**, and it was found that the demethylation was affected by the solvents and that the corresponding 5- or 3-hydroxyflavones were obtained as main products in acetonitrile or ether, respectively. In this paper, we report the selective demethylation of the 5- or 3-methoxy group in 3,5-dimethoxyflavones with no substituent at the 6-position and the characterization of the demethylated products.

Results and Discussion

Demethylation of 7-Hydroxy-3,4′,5,8-tetramethoxyflavone (1a) with Anhydrous Aluminum Chloride in Acetonitrile. Anhydrous aluminum chloride in acetonitrile is a most suitable demethylating reagent and the selective demethylation of the 5-methoxy group in 5,6,7-[5] and 5,7,8-trioxygenated flavones[6] affords quantitatively the corresponding 5-hydroxyflavones. Therefore, the selective demethylation of 7-hydroxy-3,5,8-trimethoxyflavones **1** was studied first.

Demethylation of 7-hydroxy-3,5,8-trimethoxyflavone (**1a**) with anhydrous aluminum chloride in acetonitrile required reaction times for 7–10 h and afforded 5,7-dihydroxy-3,4′,8-trimethoxyflavone (**2a**) as a main product, 3,7-dihydroxy-4′,5,8-trimethoxyflavone (**3a**), and 6-

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