134.3, 155.7, 156.5; MS m/e 345 (M^+). Anal. Calcd for $C_{22}H_{19}NO_3$: C, 76.50; H, 5.54; N, 4.06. Found: C, 76.04; H, 5.50; N, 4.11.

Oxazolidinones **20**,[25] **21**,[16] **22**,[26] and **23**[25] were identified by comparison with the authentic samples.

4-Phenyl-3-allyl-1,3-oxazolidin-2-one (24): bp 115 °C (0.1 mmHg); IR (neat) 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.21 (dd, 1 H, J = 15.4 and 8.1 Hz, one of NCH_2), 4.12-4.22 (m, 2 H, one of NCH_2 and CHN), 4.63 (t, 1 H, J = 8.8 Hz, one of CH_2O), 4.77 (dd, 1 H, J = 8.8 and 6.8 Hz, one of CH_2O), 5.04 (d, 1 H, J = 17.1 Hz, one of $=CH_2$), 5.18 (d, 1 H, J = 10.3 Hz, one of $=CH_2$), 5.66-5.76 (m, 1 H, CH=), 7.33-7.45 (m, 5 H, Ar); ^{13}NMR ($CDCl_3$) δ 44.4, 58.9, 69.6, 118.7, 126.8, 128.0, 128.9, 131.1, 137.4, 157.7; MS m/e 203 (M^+). Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.60; H, 6.56, N, 6.66.

5-Phenyl-3-allyl-1,3-oxazolidin-2-one (25): bp 115 °C (0.1 mmHg); IR (neat) 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.41 (dd, 1 H, J = 8.8 and 7.3 Hz, one of NCH_2CPh), 3.85-3.98 (m, 3 H, CH_2NCHCO), 5.21-5.27 (m, 2 H, one of $=CH_2$ and PhCHO), 5.50 (t, 1 H, J = 8.3 Hz, one of $=CH_2$), 5.74-5.84 (m, 1 H, CH=), 7.33-7.41 (m, 5 H, Ar); ^{13}C NMR ($CDCl_3$) δ 46.95, 51.79, 74.49, 118.84, 125.51, 128.81, 128.90, 131.89, 138.70, 157.71; MS m/e 203 (M^+). Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 71.02; H, 6.46; N, 6.79.

4-Methyl-4-vinyl-3-phenyl-1,3-oxazolidin-2-one (26):[3] mp 88-89 °C; IR 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.48 (s, 3 H, CH_3), 4.15 (d, 1 H, J = 8.5 Hz, one of CH_2), 4.28 (d, 1 H, J = 8.5 Hz, one of CH_2), 5.25 (d, 1 H, J = 17 Hz, one of $C=CH_2$), 5.34 (d, 1 H, J = 10.5 Hz, one of $C=CH_2$), 6.10 (dd, 1 H, J = 10.5 and 17 Hz, -CH=C), 7.20-7.38 (m, 5 H, Ar); ^{13}C NMR ($CDCl_3$) δ 21.5, 63.5, 74.2, 117.0, 126.8, 127.0, 128.9, 135.3, 139.5, 156.4; MS m/e 203 (M^+).

Acknowledgment. This work was financially supported by the Grant-in-Aid for Scientific Research No. 01850189 from the Ministry of Education, Science and Culture.

(25) Fujiwara, M.; Baba, A.; Matsuda, H. *J. Heterocycl. Chem.* **1988**, *25*, 1351.
(26) Baba, A.; Shibata, I.; Matsuda, H. *Synthesis* **1985**, 1144.

Direct Conversion of *N*-Alkoxy β-Lactams to Carbapenams: Application to the Synthesis of the Bicyclic PS-5 Keto Ester

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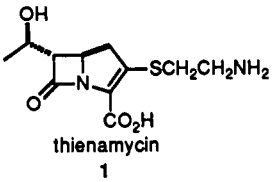
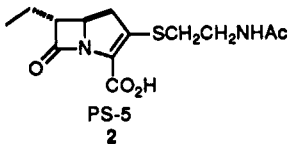
Received September 5, 1990

The synthesis and direct conversion of *N*-alkoxy β-lactams to the carbapenam ring system is described. This novel cyclization apparently proceeds by initial carbene-mediated ylide formation with concomitant rearrangement. The title reaction is applied to the construction of the methyl ester of the bicyclic β-lactam precursor of PS-5.

The carbapenem class of β-lactam antibiotics, of which thienamycin (**1**)[1] and PS-5 (**2**)[2] are representative, has received a great deal of attention from the synthetic community.[3] Recent papers have addressed enantioselective

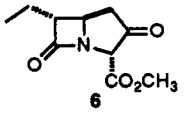


thienamycin
1



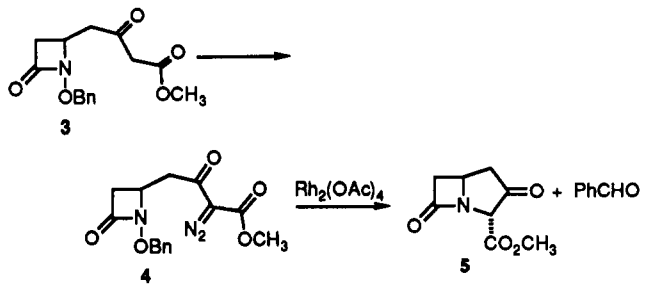
PS-5
2

syntheses[4] as well as new methods of ring construction to afford the fundamental bicyclic system.[5] It is in the latter area that we wish to report our efforts related to the synthesis of carbapenams. Since the initial disclosure of the synthesis of the *N*-benzyloxy β-lactam **3** and the direct carbene-mediated cyclization of **4** to **5** (Scheme I),[6] we have expanded the scope of this methodology to other O-alkylated β-lactams, while demonstrating direct applicability to the synthesis of the bicyclic PS-5 keto ester **6**.



6

Scheme I



The literature contains numerous examples of the rhodium-catalyzed reaction of α-diazo β-keto esters to generate carbenoid intermediates that ultimately undergo net insertion into an azetidinone N-H bond. As originally reported by the Merck group, this methodology was demonstrated in the efficient conversion of **7** to carbapenam **8** (eq 1).[7] This process has proved equally as important

7 **8**

for the synthesis of carbacephems.[8] We are presently not

(1) Kahan, J. S.; Kahan, F. M.; Goegelman, S. A.; Currie, M.; Jackson, E. O.; Stapley, T. W.; Miller, A. K.; Hendlin, D.; Mochales, S.; Hernandez, H.; Woodruff, B.; Birnbaum, J. *J. Antibiot.* **1979**, *32*, 1.
(2) Yamamoto, K.; Yoshioka, T.; Kato, Y.; Shibamoto, N.; Okamura, K.; Shimauchi, Y.; Ishikura, T. *J. Antibiot.* **1980**, *33*, 796.
(3) For general reviews, see: (a) Kametani, T.; Nagahara, T. *Heterocycles* **1987**, *25*, 729. (b) Kametani, T. *Heterocycles* **1982**, *17*, 463.
(4) (a) Evans, D. A.; Sjogren, E. B. *Tetrahedron Lett.* **1986**, *27*, 3119. (b) Evans, D. A.; Sjogren, E. B. *Tetrahedron Lett.* **1986**, *27*, 4961.
(5) Wasserman, H. H.; Han W. T. *Tetrahedron Lett.* **1984**, *25*, 3747.
(6) Williams, M. A.; Miller, M. J. *Tetrahedron Lett.* **1990**, *31*, 1807.
(7) Ratcliffe, R. W.; Salzmann, T. N.; Christensen, B. G. *Tetrahedron Lett.* **1980**, *21*, 31.
(8) (a) Bodurow, C. C.; Boyer, B. D.; Brennan, J.; Bunnell, C. A.; Burks, J. E.; Carr, M. A.; Doecke, C. W.; Eckrich, T. M.; Fisher, J. W.; Gardner, J. P.; Graves, B. J.; Hines, P.; Hoying, R. C.; Jackson, B. G.; Kinnick, M. D.; Kochert, C. D.; Lewis, J. S.; Luke, W. D.; Moore, L. L.; Morin, J. M., Jr.; Nist, R. L.; Prather, D. E.; Sparks, D. L.; Vladuchick, W. C. *Tetrahedron Lett.* **1989**, *30*, 2321. (b) Evans, D. A.; Sjogren, E. B. *Tetrahedron Lett.* **1985**, *26*, 3789. (c) Salzmann, T. N.; Ratcliffe, R. W.; Christensen, B. G. *Tetrahedron Lett.* **1980**, *21*, 1193.

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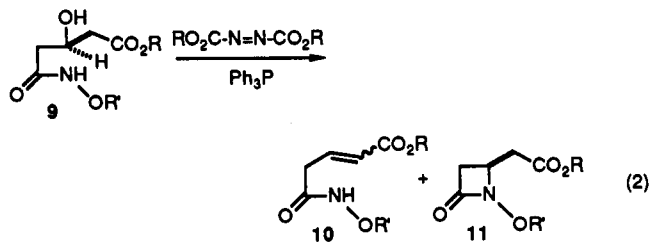
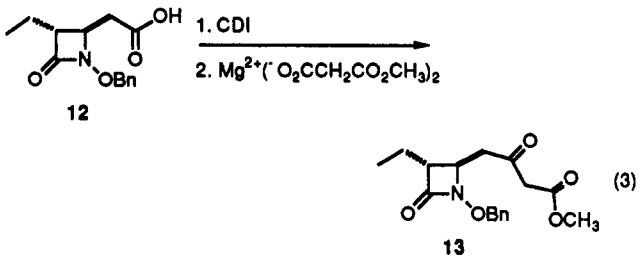
aware, however, of any related process for N-substituted azetidinones that results in the direct formation of a carbon–nitrogen bond to afford the bicyclic carbapenam ring structure.

The discovery of this novel rearrangement (4 → 5) is a direct consequence of employing the hydroxamate-mediated N–C_4 ring closure (e.g., 9 → 11, eq 2), which enables



(2)

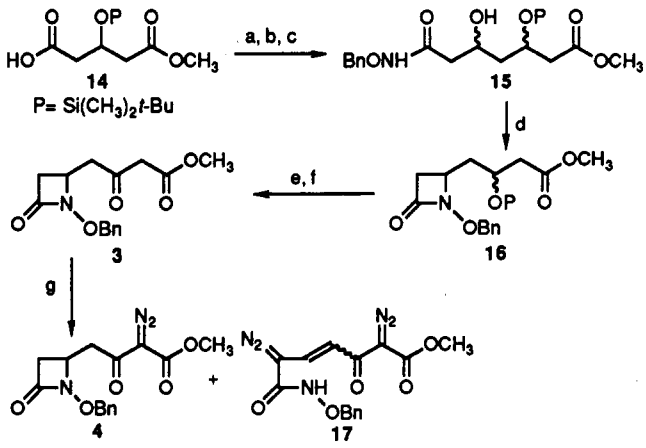
the synthesis *N*-alkoxy β-lactams.[9] This methodology was utilized in the synthesis of the key intermediate **3**, which possesses an *N*-benzyloxy β-lactam appended to the β-keto ester functionality required for diazotization to the penultimate cyclization precursor **4**. The presence these two particular structural groups necessitated specific synthetic considerations. The acylation of magnesium malonates developed by Masamune[10] is the conventional method used for β-keto ester formation in the synthesis of β-lactams, as demonstrated by the Merck group in the synthesis of thienamycin.[11] While conceptually attractive, this methodology proved problematic in the attempted conversion of **12** to **13**, which proceeded in low yield (eq 3).



(3)

Furthermore, the hydroxamate approach required additional regard for the hydroxamate precursor of **3**. While the Mitsunobu reaction does allow efficient N–C_4 closure in a variety of substrates, the presence of electron-withdrawing groups in the γ-position of β-hydroxy hydroxamates complicates the cyclization process. For example, treatment of hydroxamate **9** (eq 2) with diethyl azodicarboxylate (DEAD) and triphenylphosphine resulted in the competitive elimination to the corresponding β,γ-unsaturated hydroxamate **10** along with formation of varying amounts of β-lactam **11**.[12] Modification of the reaction conditions by substituting trialkyl or aryl phosphites for the conventionally used triphenylphosphine suppressed olefin formation, but necessitated longer reaction times and more vigorous reaction conditions. Thus, the presence of a γ-keto group in the hydroxamate precursor of **3** was anticipated to hinder cyclization. Our approach to the synthesis of **3**, therefore, was accomplished by initial construction of the entire carbon framework. Ultimate success of β-lactam ring formation from an appropriate

Scheme II[a]



[a] (a) (i) CDI, (ii) $Mg^{2+}(^{-}O_2CCH_2CO_2Bn)_2$; (b) $NaBH_4$; (c) (i) Pd–C, H_2, (ii) DCC, HOSu, $BnONH_2$; (d) DEAD, Ph_3P; (e) $Bu_4N^+F^-$, HOAc; (f) CrO_3, pyridine; (g) iPr_2NEt, *p*-carboxybenzenesulfonyl azide.

hydroxamate was achieved by employing a silyl ether as the latent β-keto group.

The synthesis of β-keto ester **3** has been detailed in a previous paper.[13] In summary (Scheme II), the mono acid ester **14** was prepared in four steps from commercially available diethyl 3-hydroxyglutarate, as dictated by literature precedent.[14] This acid was converted to the β-keto ester by the procedure of Masamune,[10] followed by $NaBH_4$ reduction of the resultant β-keto group to the β-hydroxy ester. Hydrogenolysis of the benzyl ester with hydrogen and 10% Pd–C and dicyclohexylcarbodiimide-mediated coupling of the acid with *O*-benzylhydroxylamine afforded the β-hydroxy hydroxamate **15**.[15] Cyclization of **15** under Mitsunobu conditions (DEAD, Ph_3P) gave the β-lactam **16**.[16] Deprotection of the silyl ether **16** with tetrabutylammonium fluoride[17] in the presence of an equivalent of acetic acid, followed by oxidation of the resulting alcohol with CrO_3–pyridine complex,[18] provided the ketone **3**.

The final synthetic transformation required to complete the synthesis of key substrate **4** was the introduction of the diazo moiety (Scheme II). Several diazo-transfer reagents are known for the α-diazotization of β-keto esters.[19] In general, the reagent *p*-carboxybenzenesulfonyl azide[20] was found to be suitable for this transformation, allowing simple removal of the sulfonamide byproduct by filtration. Attempted diazotization of **3** with this reagent, however, gave multicomponent mixtures when conducted with stoichiometric amounts of base at room temperature. The use of a slight excess of diisopropylethylamine (1.2

(9) (a) Miller, M. J.; Mattingly, P. G.; Morrison, M. A.; Kerwin, J. F., Jr. *J. Am. Chem. Soc.* **1980**, *102*, 7026. (b) Miller, M. J.; Mattingly, P. G. *Tetrahedron* **1983**, *39*, 2563. (c) Miller, M. J. *Acc. Chem. Res.* **1986**, *19*, 49 and references cited therein.

(10) Brooks, D. W.; Lu, L. D. L.; Masamune, S. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 72.

(11) Salzmann, T. N.; Ratcliffe, R. W.; Christensen, B. G.; Bouffard, F. A. *J. Am. Chem. Soc.* **1980**, *102*, 6161.

(12) Morrison, M. A.; Miller, M. J. *J. Org. Chem.* **1983**, *48*, 4421.

(13) Williams, M. A.; Miller, M. J. *J. Org. Chem.* **1991**, *56*, 1293.

(14) Rosen, T.; Watanabe, M.; Heathcock, C. H. *J. Org. Chem.* **1984**, *49*, 3657.

(15) Also isolated from the coupling reaction were small quantities of the corresponding six-membered ring lactone, derived from **15** by attack of the γ-hydroxyl group on the methyl ester. After recrystallization, ^{13}C NMR proved this material to be diastereomerically pure.

(16) Mitsunobu, O. *Synthesis* **1981**, 1. For application of this reagent system to β-lactam synthesis, see: Miller, M. J. *Acc. Chem. Res.* **1986**, *19*, 49 and references cited therein.

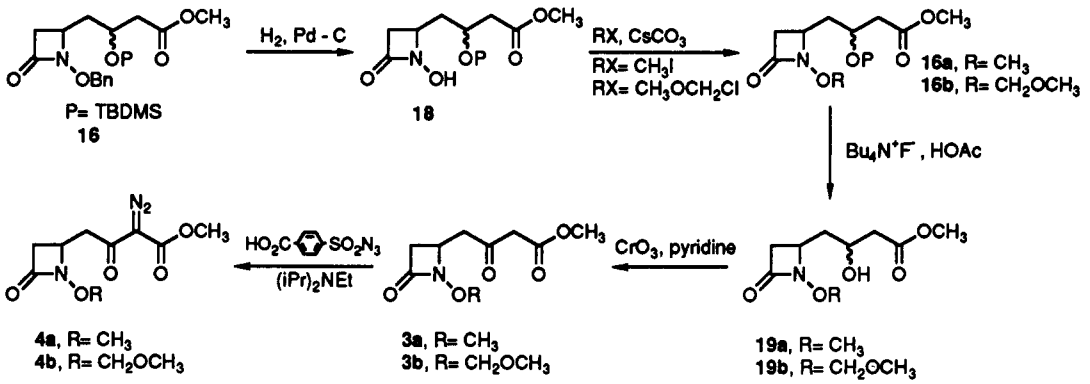
(17) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

(18) Ratcliff, R.; Rodehorst, R. *J. Org. Chem.* **1970**, *35*, 4000.

(19) (a) *p*-Toluenesulfonyl azide: Regitz, M. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 733. (b) *p*-Acetamidobenzenesulfonyl azide: Baum, J. S.; Shook, D. S. *Synth. Commun.* **1987**, *17*, 1709. (c) Mesyl azide: Taber, D. F.; Ruckle, R. E.; Hennessy, M. J. *J. Org. Chem.* **1986**, *51*, 4077. (d) Trifluoromethanesulfonyl azide: Cavender, C. J.; Shiner, V. J. *J. Org. Chem.* **1972**, *37*, 3567. (e) *p*-Dodecylbenzenesulfonyl azide: Hazen, G. G.; Weinstock, L. M.; Connell, R.; Bollinger, F. W. *Synth. Commun.* **1981**, *11*, 368.

(20) Hendrickson, J. B.; Wolf, W. A. *J. Org. Chem.* **1968**, *33*, 3610.

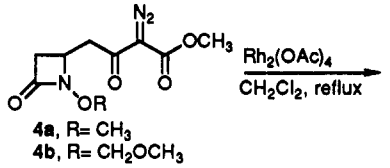
Scheme III

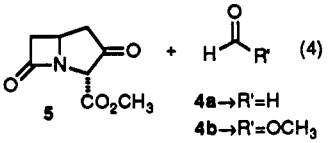


equiv) at ~−5 to −10 °C for 14 h gave the desired diazotized product **4** in 78% yield after chromatography. In addition, a small amount of chromatographically slower moving material was isolated as a bright yellow oil. Both NMR and IR data suggested that the minor component was the bis-diazo-β,γ-unsaturated hydroxamate **17**.

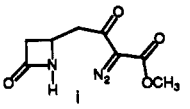
With the α-diazo β-keto ester **4** in hand, we could now address the effect of the additional *N*-alkoxy functionality on ring formation. The carbene derived from **4** could potentially provide a variety of products, based on the ability of carbenes to undergo either C–H insertion or the formation of ylide-type intermediates.[21] Treatment of **4** with catalytic quantities of rhodium acetate dimer in refluxing methylene chloride gave the carbapenam **5** directly in 37% isolated yield after silica gel chromatography, and benzaldehyde, as confirmed by TLC, HPLC, and NMR analysis of the crude reaction mixture. Comparison of **5** with authentic material[22] proved them to be identical in all respects. Analysis of the crude NMR or isolation attempts were not fruitful in the elucidation of other products. An interesting spectral anomaly was noticed on one occasion, in the ^{1}H NMR of the crude reaction mixture,[23] which indicated signals coincident with the purified carbapenam **5**, but largely consisted of other signals not characteristic of **5**. Moreover, the addition of 10 mol % of imidazole[24] to the crude NMR sample greatly simplified the spectrum, increasing the expected signals of **5** while virtually removing the predominant signals observed prior to the addition of the imidazole.[25] As one of several possible explanations for this observation, the existence of a rhodium-complexed form of the carbapenam was feasible.[26]

We wished to test further the scope of the carbene-mediated cyclization, with respect to the oxygen substituent of the *N*-alkoxy β-lactam. Alkylation of *N*-hydroxy β-lactams proceeds efficiently and cleanly with a variety of alkylating agents.[27] Thus, analogues of **4** were readily prepared (Scheme III) by debenzylation of **16** with H_2 and 10% Pd–C followed by alkylation of the resulting *N*-hydroxy β-lactam **18** with either methyl iodide or chloromethyl methyl ether in acetonitrile with $CsCO_3$ as base to provide **16a** and **16b**, respectively. The alkylated products were not purified but directly desilylated to give the alcohols **19a** (R = CH_3) and **19b** (R = CH_2OCH_3) in overall yields from **16** of 78% and 85%, respectively. In accord with the synthesis of **3**, the alcohols **19a** and **19b** were oxidized to their respective ketones (**3a**, 61%; **3b**, 75%) and subsequently subjected to diazo transfer, affording the α-diazo β-keto esters (**4a**, 83%; **4b**, 85%). Treatment of **4a** with rhodium acetate dimer in refluxing CH_2Cl_2 again formed the carbapenam **5** as verified by NMR analysis after chromatography (eq 4). In an analogous fashion, substrate **4b** gave the desired carbapenam under the same reaction conditions. A comparative assessment of the efficiency of these cyclizations was difficult, however, due to the labile nature of the bicyclic β-lactam **5**.





If the cyclizations of these analogues are operating by the same mechanism as for the cyclization of **4**, then the



(21) Doyle, M. P. *Chem. Rev.* **1986**, *86*, 919 and references therein.

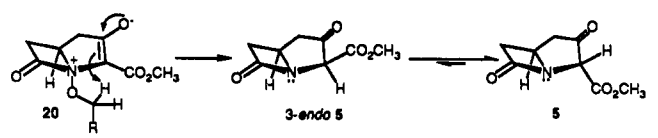
(22) (a) Compound **i** was synthesized from 4-acetoxy-2-azetidinone and the bis-trimethylsilylated dianion of methyl acetoacetate in the presence of trimethylsilyl triflate, followed by diazo transfer. Cyclization was effected with $Rh_2(OAc)_4$ in refluxing benzene to yield **5**. (b) ^{1}H NMR data were identical with previously reported data: Oida, S.; Yoshida, A.; Ohki, E. *Chem. Pharm. Bull.* **1980**, *28*, 3494.

(23) Cyclization of **4** to **5** was effected with 1.4 mol % $Rh_2(OAc)_4$ in refluxing CH_2Cl_2 over a period of 1.5 h. The solvent was removed under reduced pressure and the brown residue was placed under high vacuum (0.5 Torr, 3 h) prior to NMR analysis. NMR samples were prepared by directly dissolving this residue in $CDCl_3$ and filtration of this solution through a plug of cotton into the NMR tube.

(24) The amount of added imidazole is reported relative to the amount of diazo substrate **4**, which gave a ratio of ~7:1 imidazole/rhodium carboxylate dimer (each dimer possesses two axial coordination sites).

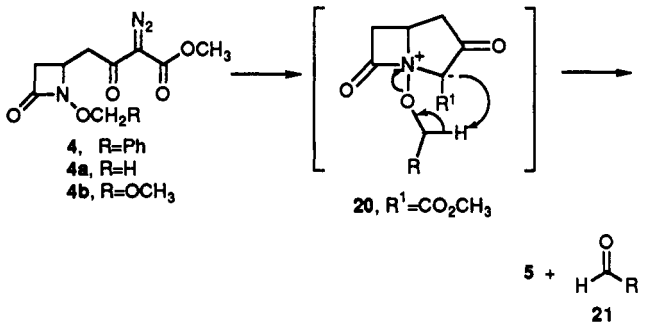
(25) The ^{1}H NMR spectra of this experiment are included in Figure 1 of the supplementary material.

(26) A reviewer has also suggested the initial formation of the endo form of **5**, which is epimerized to the more stable exo form upon exposure to imidazole. The formation of *endo*-**5** is consistent the proposed ylide intermediate **20** in which the proton is delivered to the α face. Furthermore, the observed crude ^{1}H NMR spectra from the treatment of compounds **4a** and **4b** with rhodium acetate also indicated formation of the proposed *endo*-**5**.



(27) (a) Miller, M. J.; Biswas, A.; Krook, M. A. *Tetrahedron* **1981**, *40*, 1039. (b) Woulfe, S. R.; Miller, M. J. *Tetrahedron Lett.* **1984**, *25*, 3293.

Scheme IV



expected byproducts for **4a** and **4b** would be formaldehyde and methyl formate, respectively. To verify this, the rhodium-catalyzed cyclization reactions of **4a** and **4b** were conveniently conducted in NMR tubes in $CDCl_3$ solvent at 45 °C and periodically monitored by ^1H NMR spectroscopy. In the cyclization of **4a**, a peak was detected at δ 9.7, an appropriate chemical shift for the aldehydic proton of formaldehyde. Similarly, NMR analysis of the reaction of analogue **4b** indicated the formation of methyl formate, which was unambiguously verified by the addition of authentic material to the NMR sample.

In the context of these cyclizations and their respective products, a common mechanistic picture is evident. The intermediacy of carbene–metal complexes (carbenoids) as the reactive species in the metal-catalyzed decomposition of diazo compounds has been previously established.[28] The association of the rhodium carboxylate dimer and the organic moiety in the initial carbene formation as well as in any successive intermediates that may follow cannot be ignored. One mechanistic interpretation of the experimental results, however, is provided by eventual formation of an ylide intermediate (**20**), which is not unrealistic considering the electrophilic character of carbenes (Scheme IV). The subsequence rearrangement of **20** with the oxidative expulsion of product **21** (R = H, OCH_3, Ph) can be rationalized by taking into account the lability of the N–O bond.

Having demonstrated the generality of the cyclization–rearrangement, we applied this methodology to the asymmetric synthesis of a key intermediate for the preparation of PS-5 (Scheme V). Previously, ketal **22** was synthesized in >93% diastereomeric excess, via an enantioselective aldol condensation of the boron enolate derived from chiral acylthiazolidinethione **23** with aldehyde **24**.[29] This substrate was ideally suited for further elaboration to provide the requisite diazo compound **26**. Subjecting **22** to traditional acidic hydrolysis conditions generally gave decomposition of the β-lactam ring. Attempts to effect trans-ketalization with *p*-toluenesulfonic acid in acetone were not fruitful. The use of sulfuric acid in acetic acid medium was reported to effect ketal hydrolysis in a synthesis of carbacephems.[30] In a closely related analogue, Kametani reported ketal removal with catalytic amounts of perchloric acid in methylene chloride.[31] Under these same conditions, however, significant decomposition of *N*-(benzyloxy)azetidinone **22** was observed. Aqueous formic acid or *p*-toluenesulfonic acid in THF–water was not effective in hydrolyzing ketal **22**. However, the use of 20 mol % *p*-toluenesulfonic acid in 88% formic acid allowed removal of the ketal to provide the labile keto ester **25** in 77% crude yield. The β-keto ester **25** was then directly diazotized (*p*-carboxybenzenesulfonyl azide, iPr_2NEt) to afford the diazo substrate **26** in 70% yield. Rhodium-catalyzed cyclization of **26** to the carbapenam **6** was achieved in 30% yield after silica gel chromatography. As expected, benzaldehyde was produced in this cyclization. Direct isolation of the carbapenam was performed to unambiguously confirm its formation by ^1H NMR,[32] ^{13}C NMR, and high resolution mass spectrometry. Modification of the carboxyl-protecting group of aldehyde **24** to the easily deprotected *p*-nitrobenzyl ester and application of the preceding methodology (**22** → **6**) would then afford an optically active key intermediate, which has been converted to PS-5 previously.[33]

The novel ring formation methodology presented here is compatible with the hydroxamate-mediated formation of β-lactams, enabling the *N*-alkoxy β-lactam to be cyclized directly to carbapenams without prior reduction to the N-unsubstituted β-lactam.[34] A variety of other O-alkylated systems, not explored here, may be feasible candidates for this cyclization process. This methodology may prove useful, in a broader sense, for the construction of other nitrogen-containing heterocycles.

Experimental Section

General Methods. ^1H NMR and ^{13}C NMR spectra were obtained at 300 MHz and 75 MHz, respectively, on a General Electric GN-300 spectrometer in chloroform-*d*. ^1H NMR spectra are referenced to internal tetramethylsilane at 0.00 ppm. Coupling constants (*J*) for ^1H NMR spectra are given in hertz. ^{13}C NMR spectra are referenced to the center line of the chloroform-*d* triplet at 77.00 ppm unless indicated otherwise. Mass spectra were recorded on a Finnagan MAT Model 8430 spectrometer as indicated: electron-impact ionization at 70 eV (EIMS); Chemical ionization with isobutane (CIMS); high resolution (HRMS). IR spectra were taken on a Perkin-Elmer Model 1420 spectrometer and referenced to polystyrene at 1601 cm^{-1}. Elemental analyses were determined by M-H-W Laboratories, Phoenix, AZ. Flash chromatography[35] was performed with silica gel 60, 230–400 mesh (EM Science). TLC analysis was performed on aluminum-backed silica gel 60 F_{254}, 0.2-mm plates (MCB Reagents), and visualized with UV light or ethanolic phosphomolybdic acid following by heating. Anhydrous benzene was distilled from sodium/benzophenone, while CH_2Cl_2, pyridine, and acetonitrile were distilled from calcium hydride.

Methyl 4-[1-(Benzyloxy)-2-oxo-4-azetidinyl]-α-diazo-β-ketobutyrate (4). The β-keto ester **3**[13] (667 mg, 2.29 mmol) was dissolved in acetonitrile (8 mL) and cooled to ~−10 °C (ice–salt bath), and to this solution was added *p*-carboxybenzenesulfonyl azide (572 mg, 2.52 mmol) followed by the dropwise addition of diisopropylethylamine (479 μL, 2.75 mmol) over a 5-min period (*Caution:* Although we have never encountered any problems in the use of *p*-carboxybenzenesulfonyl azide, proper care should

(28) Section II, part D, of ref 21 addresses the topic of metal–carbene complexes.

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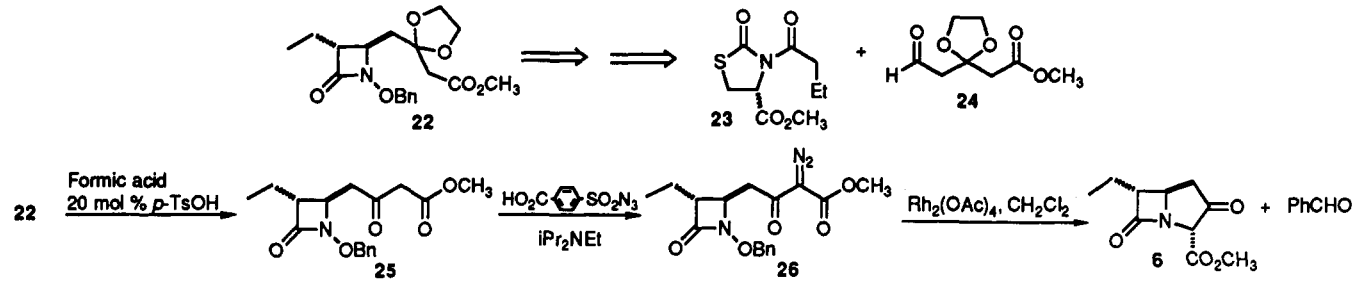
(34) Miller, M. J.; Mattingly, P. G. *J. Org. Chem.* **1980**, *45*, 410. As indicated in ref 13, however, debenzylation of **3** by catalytic hydrogenation to the *N*-hydroxy β-lactam required for N–O bond reduction results a novel intramolecular rearrangement.

(35) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

Scheme V



be exercised in handling this reagent and the diazotized products.). The reaction was stirred for 1 h at −5 to −10 °C and then capped, and the reaction flask was placed in the freezer at ~−5 °C for 12 h. The precipitated sulfonamide was removed by filtration (Celite), and the filtrate was concentrated to give a dark brown oil. The crude oil was eluted through a short column of silica (2:1 hexanes–acetone) and concentrated under reduced pressure to afford a yellow oil, which was flash chromatographed on silica gel (3:1 hexanes–acetone) to provide the diazo compound **4** (565 mg, 78%) as a yellow oil: R_f 0.45 (1:1 hexanes–acetone); IR (thin film) 3040, 2960, 2140, 1775, 1720, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.42 (dd, 1 H, J = 2.4, 13.9), 2.87 (dd, 1 H, J = 5.2, 13.9), 3.00 (dd, 1 H, J = 6.7, 17.5), 3.29 (dd, 1 H, J = 6.3, 17.5), 3.84 (s, 3 H), 4.13 (m, 1 H), 4.91 (d, 1 H, J = 10.8), 4.96 (d, 1 H, J = 10.8), 7.37 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 38.16, 42.87, 52.37, 53.03, 76.25, 77.99, 128.55, 128.89, 129.31, 135.12, 161.35, 163.98, 189.02; HRMS (CI, isobutane) calcd for MH^+ ion $C_{15}H_{16}N_3O_5$ 318.1090, found 318.1091.

Methyl 2-Oxo-1-carba-1-dethiapenam-3-carboxylate (5). The α-diazo β-keto ester **4** (60 mg, 0.19 mmol) was dissolved in dry benzene (4 mL) and evaporated under reduced pressure and was redissolved in CH_2Cl_2 (4 mL). To this solution was added $Rh_2(OAc)_4$ (0.80 mg, 1 mol %), and the reaction was refluxed for 1.25 h. The solvent was removed under reduced pressure and the resulting brown oil was placed under high vacuum (0.5 Torr, 1 h) to remove residual benzaldehyde. The crude oil was purified by flash chromatography (2:1 benzene–ethyl acetate) to give carbapenam **5** (13 mg, 37%) as a light yellow oil: R_f 0.26 (3:1 benzene–ethyl acetate); IR (CCl_4) 2960, 1785, 1775, 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.41 (dd, 1 H, J = 7.8, 18.8), 2.92 and 2.97 (dd, J = 6.8, 18.8, overlapping with dd, J = 2.1, 16.1, total 4 H), 3.66 (dd, 1 H, J = 5.0, 16.2), 3.80 (s, 3 H), 4.18 (m, 1 H), 4.71 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 41.80, 46.61, 48.44, 53.17, 64.35, 165.58, 172.36, 207.08; HRMS calcd for $C_8H_9NO_4$ 183.0532, found 183.0534.

Methyl 4-(1-Methoxy-2-oxo-4-azetidinyl)-β-hydroxybutyrate (19a). *N*-Benzyloxy β-lactam **16**[13] (600 mg, 1.47 mmol) was dissolved in ethyl acetate (5 mL), and to this was added 50 mg of 10% Pd–C. The reaction was placed under an atmosphere of H_2 using a balloon. After 6 h the reaction was incomplete, and 50 mg of 10% Pd–C in 1 mL of ethyl acetate was added. The reaction was complete after 4 additional hours. The catalyst was removed by filtration (Celite) and the solvent removed by rotary evaporation. The crude *N*-hydroxy β-lactam **18** obtained was dissolved in CH_3CN (8 mL) and cooled to 0 °C at which time $CsCO_3$ (718 mg, 2.2 mmol) was added followed by methyl iodide (200 μL, 3.2 mmol, MeI was filtered through activated alumina before use). After being stirred for 2.5 h at 0 °C, the reaction was diluted with ether (60 mL), washed with 10% citric acid, 5% $NaHCO_3$, and brine, and dried ($MgSO_4$). After filtration and removal of solvent under reduced pressure, the crude O-methylated product **16a** (474 mg) was obtained. This oil was then dissolved in THF (1 mL) and cooled to 0 °C. Acetic acid (81 μL, 1.42 mmol) was added followed by tetrabutylammonium fluoride (3.55 mL of a 1 M solution in THF, 3.55 mmol). The resulting orange solution was allowed to stir for 1 h at 0 °C and then at room temperature (~23 °C) for 14 h. The THF was evaporated under reduced pressure and the brown residue partitioned between ethyl acetate (20 mL) and water (20 mL). The aqueous layer was extracted with additional ethyl acetate (20 mL) and the combined organic extracts were washed with brine (20 mL). Upon drying ($MgSO_4$), filtration of the drying agent, and removal of solvent, 100 mg of the desired alcohol was recovered. The above extraction process was repeated once with ethyl acetate and then again with CH_2Cl_2, which afforded, after removal of solvents under reduced pressure, a mixture of product and tetrabutylammonium salts. After combination of all extracted material, 279 mg of a light brown oil was obtained, which was purified by flash chromatography on silica gel (2:1 hexanes–acetone) to afford the desilylated *N*-methoxy β-lactam **19a** (246 mg, 78% overall yield from **16**) as a yellow oil: R_f 0.33 (ethyl acetate); IR (thin film) 3440 (br), 2960, 1770, 1740 (shoulder) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.64–2.18 (series of m, total 2 H), 2.53 (m, 3 H), 2.90 and 2.93 (dd, total 1 H, J = 5.0, 14.0, diastereomeric cis C-3 β-lactam ring protons), 3.32 and 3.33 (br s, total 1 H, diastereomeric hydroxyl protons), 3.73 (s, 3 H), 3.81 and 3.82 (s, total 3 H), 4.14 and 4.24 (m, total 1 H, C-4 β-lactam ring protons); ^{13}C NMR ($CDCl_3$) δ 37.61, 38.31, 38.78, 39.50, 41.28, 41.45, 51.52, 53.89, 52.94, 63.40, 63.53, 64.97, 65.43, 163.48, 163.59, 172.22, 172.30; HRMS calcd for $C_9H_{15}NO_5$ 217.0950, found 217.0951.

Methyl 4-(1-Methoxy-2-oxo-4-azetidinyl)-β-ketobutyrate (3a). Alcohol **19a** (246 mg, 1.14 mmol) was stirred with 2 g of activated 3-Å molecular sieves in 1 mL of dry CH_2Cl_2 for 12 h prior to use in order to remove trace amounts of water. To a solution of pyridine (1.11 mL, 13.68 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added powdered CrO_3 (683 mg, 6.84 mmol). The resulting burgundy solution was then allowed to warm to room temperature, stirred for 15 min, and then cooled to 0 °C. The alcohol **19a** was added via cannula and stirred for 30 min at 0 °C, after which the reaction was warmed to room temperature. After 1 h, the reaction appeared incomplete (TLC monitor); therefore, additional CrO_3 (200 mg, 2.0 mmol) was added and the mixture was stirred 1 h. The reaction was then diluted with ether (60 mL) and filtered through Celite. Concentration of this filtrate under reduced pressure gave a brown oil, which was placed under high vacuum to remove residual pyridine. The residue was then placed on a silica gel column (2 × 15 cm) and the column was quickly eluted with ethyl acetate, collecting ~20-mL fractions. The solvent was evaporated under reduced pressure from the fractions containing product to give the β-keto ester **3a** (149 mg, 61%) as a yellow oil: R_f 0.38 (ethyl acetate); IR (thin film) 2960, 1775, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.41 (dd, 1 H, J = 2.4, 14.0), 2.91 (dd, 1 H, J = 6.4, 18.0), 2.94 (dd, 1 H, J = 5.2, 14.0), 3.13 (dd, 1 H, J = 6.6, 18.0), 3.53 (dd, AB system, 2 H), 3.75 (s, 3 H), 3.76 (s, 3 H), 4.31 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 37.78, 45.01, 48.85, 51.24, 52.18, 63.27, 163.19, 166.92, 199.67; HRMS calcd 215.0794, found 215.0792.

Methyl 4-(1-Methoxy-2-oxo-4-azetidinyl)-α-diazo-β-ketobutyrate (4a). The β-keto ester **3a** (149 mg, 0.69 mmol)) was dissolved in CH_3CN (2 mL) and cooled to −10 °C, and to this was added *p*-carboxybenzenesulfonyl azide (174 mg, 0.77 mmol) followed by the dropwise addition of diisopropylethylamine (145 μL, 0.84 mmol) over a 10-min period. The reaction was stirred for 2 h, not allowing the temperature to exceed −5 °C. The reaction was then allowed to stand in a freezer at −10 °C for 12 h. The precipitate was removed by filtration (Celite), and the filtrate was concentrated under reduced pressure to give a dark brown oil. The crude oil was eluted through a short column of silica (1:1 hexanes–acetone) and the solvent was removed under reduced pressure. The yellow oil obtained was purified by flash chromatography on silica gel (2:1 hexanes–acetone) to provide the diazo compound **4a** (139 mg, 83%) as a light yellow oil, which solidified upon standing at 0 °C overnight. An analytical sample was obtained by recrystallization from ether–hexanes: mp 55–57

°C; R_f 0.39 (1:1 hexanes–acetone); IR (KBr) 2980, 2950, 2150, 1790, 1770, 1715, 1650 cm^{-1}; IR (thin film from $CDCl_3$ solution) 2960, 2140, 1775 (br), 1720, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.47 (dd, 1 H, J = 2.4, 13.9), 2.93 (dd, 1 H, J = 5.2, 13.9), 3.13 (dd, 1 H, J = 6.6, 17.5), 3.49 (dd, 1 H, J = 6.4, 17.5), 3.79 (s, 3 H), 3.86 (s, 3 H), 4.35 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 37.91, 42.86, 51.88, 52.19, 63.49, 75.99, 161.24, 163.24, 188.79; HRMS calcd 241.0699, found 241.0700.

Methyl 4-[1-(Methoxymethyl)-2-oxo-4-azetidinyl]-β-hydroxybutyrate (19b). The silyl-protected *N*-benzyloxy β-lactam **16**[13] (986 mg, 2.37 mmol) was dissolved in ethyl acetate (10 mL), and to this solution was added 10% Pd–C (100 mg). After being placed under an atmosphere of H_2 using a balloon, the reaction was stirred for 2.5 h, at which time the catalyst was removed by filtration through Celite and the solvent was evaporated under reduced pressure. The crude *N*-hydroxy β-lactam **18** was dissolved in CH_3CN (4 mL) and cooled to 0 °C. $CsCO_3$ (1.16 g, 3.55 mmol) was added followed by the dropwise addition of chloromethyl methyl ether (260 μL, 3.31 mmol). The reaction was complete after 45 min. The reaction was then concentrated under reduced pressure to near dryness, and the residue was partitioned between ether (50 mL) and water (30 mL). The layers were separated and the aqueous layer was extracted with ether (25 mL). The combined organic layers were washed with brine and dried ($MgSO_4$), and the solvent was evaporated under reduced pressure to give crude **16b** as a light yellow oil. The alkylated product **16b** was dissolved in THF (3 mL), cooled to 0 °C, and treated with acetic acid (135 μL, 2.35 mmol) followed by tetrabutylammonium fluoride (4.74 mL of a 1 M solution in THF, 4.74 mmol). After stirring for 30 min at 0 °C and 8 h at room temperature, the THF was evaporated under reduced pressure, and the crude residue was eluted through a short column of silica with ethyl acetate. The solvent was removed under reduced pressure and the oil obtained was purified by flash chromatography on silica gel (3:1 ethyl acetate–hexanes), furnishing most fractions containing the product **19b** contaminated with a more polar material. The mixed fractions were rechromatographed (2:1 ethyl acetate–hexanes) to give the desilylated *N*-methoxymethyl β-lactam **19b** (500 mg, 85% overall yield from **16**) as an oil: R_f 0.33 (ethyl acetate); IR (thin film) 3460 (br), 2960, 1775, 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.58–2.12 (series of m, total 2 H), 2.35 (m, 3 H), 2.90 and 2.93 (dd, total 1 H, J = 5.0, 14.0, diastereomeric cis C-3 β-lactam ring protons), 3.28 and 3.29 (apparent t, total 1 H, diastereomeric hydroxyl protons), 3.53 and 3.55 (s, total 3 H), 3.73 (s, 3 H), 4.12 and 4.25 (m, total 1 H, C-4 β-lactam ring protons), 4.85 and 4.87 (dd and s respectively, total 2 H, methylene of MOM ether); ^{13}C NMR ($CDCl_3$) δ 37.86, 38.63, 38.72, 39.45, 41.30, 41.39, 51.69, 55.42, 55.58, 56.49, 56.65, 64.95, 65.48, 100.06, 100.21, 164.91, 172.55, 172.58; HRMS calcd for $C_{10}H_{17}NO_6$ 247.1056, found 247.1057.

Methyl 4-[1-(Methoxymethyl)-2-oxo-4-azetidinyl]-β-ketobutyrate (3b). The alcohol **19b** (498 mg, 2.01 mmol) was oxidized with CrO_3–pyridine complex as described for the O-methyl analogue **19a** to give the β-keto ester **3b** (371 mg, 75%) as a yellow oil: R_f 0.44 (ethyl acetate); IR (thin film) 2960, 1775, 1750 (shoulder), 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.45 (dd, 1 H, J = 2.6, 14.1), 2.90 (dd, 1 H, J = 6.9, 18.1), 3.01 (dd, 1 H, J = 5.5, 14.1), 3.20 (dd, 1 H, J = 5.8, 18.1), 3.51 (s, 3 H) overlaps with 3.52 (dd, AB system, 2 H), 3.76 (s, 3 H), 4.29 (m, 1 H), 4.76 (d, 1 H, J = 7.0), 4.86 (d, 1 H, J = 7.0); ^{13}C NMR ($CDCl_3$) δ 38.09, 45.25, 48.90, 52.14, 52.70, 56.46, 99.95, 164.46, 166.92, 199.66; HRMS calcd for $C_9H_{13}NO_5$ 215.0793, found 215.0792.

Methyl 4-[1-(Methoxymethyl)-2-oxo-4-azetidinyl]-α-diazo-β-ketobutyrate (4b). The keto ester **3b** (339 mg, 1.38 mmol) was diazotized as described for the *O*-methyl analogue **3a** and was purified by flash chromatography on silica gel (2:1 hexanes–acetone) to give the diazo compound **4b** (318 mg, 85%) as a yellow oil: R_f 0.39 (1:1 hexanes–acetone); IR (thin film) 2960, 2115, 1775, 1715, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.51 (dd, 1 H, J = 2.5, 14), 2.99 (dd, 1 H, J = 5.4, 14.0), 3.10 (dd, 1 H, J = 7.4, 17.7), 3.54 (s, 3 H), 3.57 (dd, 1 H, J = 5.7, 17.7), 3.86 (s, 3 H), 4.32 (m, 1 H), 4.80 (d, 1 H, J = 7.0), 4.89 (d, 1 H, J = 7.0); ^{13}C NMR ($CDCl_3$) δ 38.06, 42.76, 52.07, 53.11, 56.41, 75.85, 99.79, 161.08, 164.31, 188.82; HRMS calcd for $C_9H_{11}N_3O_5$ 241.0699, found 241.0700. Anal. Calcd for $C_9H_{11}N_3O_5$: C, 44.29; H, 4.83; N, 15.49. Found: C, 44.17; H, 5.21; N, 15.14.

Conversion of Diazo Substrates 4a and 4b to Carbapenam 5. The diazo substrates **4a** and **4b** were cyclized to the labile carbapenam **5** under the same conditions as described for compound **4** in comparable yields based on ^{1}H NMR analysis of the reaction mixture.

Methyl 4-[1-(Benzyloxy)-2-oxo-3(*S*)-ethyl-4(*R*)-azetidinyl]-β,β-(ethylenedioxy)butyrate (22). The ketal was prepared as described in previous paper,[29] having the following spectral data: $[\alpha]_D$ = +21.9° (*c* 1.88, $CHCl_3$); R_f 0.35 (1:1 hexanes–ethyl acetate); IR (thin film) 3040, 2970, 2880, 1765, 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.97 (t, 3 H, J = 7.5), 1.54–1.68 (m, 2 H), 2.00 (dd, 1 H, J = 8.7, 14.0), 2.37 (dd, 1 H, J = 3.9, 14.0), 2.58 (s, 2 H), 2.61 (dt, 1 H, J = 1.8, 6.6), 3.39 (ddd, 1 H, J = 1.8, 3.9, 8.7), 3.69 (s, 2 H), 3.82–4.02 (m, 4 H), 4.95 (s, 3 H), 7.30–7.50 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 10.87, 21.07, 39.03, 42.42, 51.73, 53.43, 59.01, 64.75, 64.77, 77.88, 107.46, 128.38, 128.67, 129.15, 135.22, 166.66, 169.19; HRMS calcd for $C_{19}H_{25}NO_6$ 363.1682, found 363.1683.

Methyl 4-[1-(Benzyloxy)-2-oxo-3(*S*)-ethyl-4(*R*)-azetidinyl]-β-ketobutyrate (25). Ketal **22** (298 mg, 0.82 mmol) was dissolved in 2 mL of 88% formic acid, to this solution was added *p*-toluenesulfonic acid (31 mg, 0.16 mmol, 20 mol %), and the reaction was stirred at room temperature for 9 h. At this time an aliquot (150 μL) was removed and partitioned between 5% $NaHCO_3$ and CH_2Cl_2. The organic layer was separated and dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. NMR analysis of this aliquot indicated that the reaction was complete. The remaining reaction solution (having stirred an additional hour) was then evaporated under reduced pressure to remove the formic acid. The residue obtained was partitioned between 5% $NaHCO_3$ (20 mL) and CH_2Cl_2 (10 mL). The aqueous layer was extracted with additional CH_2Cl_2 (3 × 10 mL) and all organic extracts were combined, washed with brine (10 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the crude β-keto ester **25** (200 mg, 77%) as a pale yellow oil. This material was of sufficient purity for characterization and was used directly in the next step without any further purification: R_f 0.41 (1:1 hexanes–ethyl acetate); IR (thin film) 3040, 2960, 1770, 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 3 H), 1.67 (m, 2 H), 2.48 (apparent dt, J = 2.0, 7.0), 2.66 (dd, 1 H, J = 7.0, 17.9), 2.84 (dd, 1 H, J = 6.0, 17.9), 3.41 (dd, AB system, 2 H), 3.70 and 3.73 (m overlapping with s, 4 H), 4.88 (d, 1 H, J = 11.0), 4.93 (d, 1 H, J = 11.0), 7.38 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 10.99, 21.11, 44.80, 49.09, 52.35, 52.93, 58.02, 77.73, 128.49, 128.94, 129.42, 135.02, 166.10, 166.96, 199.74; EIMS *m/z* 319 (M^+), 254, 222, 204, 91; HRMS calcd for $C_{17}H_{21}NO_5$ 319.1420, found 319.1419.

Methyl 4-[1-(Benzyloxy)-2-oxo-3(*S*)-ethyl-4(*R*)-azetidinyl]-α-diazo-β-ketobutyrate (26). The crude β-keto ester **25** (200 mg, 0.63 mmol) was dissolved in acetonitrile (2 mL) and cooled to ~−5 °C (ice–salt bath), and to this solution was added *p*-carboxybenzenesulfonyl azide (150 mg, 0.66 mmol) followed by the dropwise addition of diisopropylethylamine (120 μL, 0.69 mmol) over a 10-min period. Upon addition of the amine, the reaction mixture was homogeneous, with subsequent formation of a white solid after 30 min. The reaction mixture was stirred an additional 30 min at −5 °C and then capped and placed in a freezer at −5 °C for 15 h. At this time additional azide (15 mg) and diisopropylethylamine (12 μL) were added, and the reaction stirred at 0 °C for 3 h. The precipitate was removed by filtration, and the solvent was removed under reduced pressure to yield a brown oil, which was chromatographed on silica gel (3:1 hexanes–acetone) to give the α-diazo β-keto ester **26** (152 mg, 70%) as a light yellow oil: R_f 0.50 (1:1 hexanes–acetone): IR (thin film) 3040, 2970, 2140, 1775, 1720, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 3 H, J = 7.4), 1.60–1.80 (m, 2 H), 2.55 (ddd, 1 H, J = 2.1, 6.4, 7.4), 3.01 (dd, 1 H, J = 6.5, 17.4), 3.32 (dd, 1 H, J = 6.4, 17.4), 3.80 and 3.84 (dt, J = 2.1, 6.5, overlapping with s, 4 H), 4.91 (d, 1 H, J = 10.9), 4.95 (d, 1 H, J = 10.9), 7.34–7.44 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 11.10, 21.14, 42.60, 52.27, 52.47, 58.69, 76.10, 77.77, 128.80, 129.31, 135.07, 161.27, 166.08, 189.05; CIMS *m/z* 346 (MH^+). Anal. Calcd for $C_{17}H_{19}N_3O_5$: C, 59.12; H, 5.55; N, 12.17. Found: C, 58.79; H, 5.59; N, 11.81.

Methyl (7*R*)-2-Oxo-6(*R*)-ethyl-1-carba-1-dethiapenam-3-carboxylate (6). The α-diazo β-keto ester **26** (100 mg, 0.29 mmol) was dissolved in dry benzene (5 mL), and the solvent was evaporated under reduced pressure. The oil was redissolved in dry CH_2Cl_2 (5.5 mL). Rhodium acetate dimer (1.28 mg, 1 mol %)

was added and the solution was refluxed for 2 h. The solvent was evaporated under reduced pressure followed by high vacuum (0.1 Torr, 45 min) to afford a brown oil. The crude residue was flash chromatographed on silica gel (4:1 benzene–ethyl acetate) to give the carbapenam **6** (18 mg, 30%) as a pale yellow oil: R_f 0.33 (4:1 benzene–ethyl acetate); IR (thin film) 2970, 2880, 1760 (br) cm^{-1}, (CCl_4) 1775, 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.13 (t, 3 H, J = 7.4), 1.86–2.05 (m, 2 H), 2.44 (dd, 1 H, J = 7.6, 18.9), 2.90 (ddd, 1 H, J = 0.69, 6.9, 18.9), 3.12 (ddd, 1 H, J = 2.0, 6.9, 8.1), 3.80 (s, 3 H), 3.90 (ddd, 1 H, J = 2.0, 7.0, 7.5), 4.69 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 11.53, 22.17, 41.41, 53.11, 53.85, 62.59, 64.00, 165.70, 174.85, 207.40; EIMS m/z 211, 179, 151, 141, 114, 96, 69; HRMS calcd for $C_{10}H_{13}NO_4$ 211.0844, found 211.0842.

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Supplementary Material Available: ^1H and ^{13}C NMR spectra for **3**, **3a**, **3b**, **4**, **4a**, **4b**, **5**, **6**, **19a**, **19b**, **22**, **25**, and **26** (27 pages). Ordering information is given on any current masthead page.

A Friedel–Crafts Cyclization Approach toward Cephalotaxine

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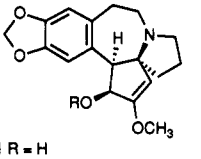
The 1-azaspiro[4.4]nonane portion **11** of cephalotaxine was prepared via an intramolecular S_N2' substitution reaction followed by ozonolysis; condensation of **11** with the aromatic portion **13** gave compound **15**; a Friedel–Crafts cyclization of **15** in polyphosphoric acid smoothly afforded the cephalotaxine skeleton **16**. A single-crystal X-ray analysis of the HCl salt of **16** confirmed the structure of **16**.

Cephalotaxine (**1**), the major alkaloid of *C. harringtonia*, has a unique skeleton with an unusual 1-azaspiro[4.4]nonane moiety fused to a benzazepine system.[1] The simple ester derivatives of **1** including harringtonine (**2**), homoharringtonine (**3**), isoharringtonine (**4**), and deoxyharringtonine (**5**) were shown to exhibit significant antileukemia activity.[2] Due to this potential pharmacological activity and its unique structural features, cephalotaxine (**1**) has been a target of many synthetic efforts. Among them several elegant total syntheses of **1** have been achieved.[3] Recently many novel synthetic entries[4] to the cephalotaxine alkaloid have been reported which prompted us to disclose our efforts aimed at a practical route for cephalotaxine ring synthesis. In this paper, we report our efficient approach to the cephalotaxine skeleton **16** via an intramolecular Friedel–Crafts cyclization reaction.



1 R = H
(-)-Cephalotaxine

2 R = $(CH_3)_2C(OH)CH_2CH_2C(OH)(CH_2CO_2CH_3)CO$-
(-)-Harringtonine

3 R = $(CH_3)_2C(OH)CH_2CH_2CH_2C(OH)(CH_2CO_2CH_3)CO$-
(-)-Homoharringtonine

4 R = $(CH_3)_2CHCH_2CH_2$-C(OH)-CO-
$CH(OH)CO_2CH_3$
(-)-Isoharringtonine

5 R = $(CH_3)_2CHCH_2CH_2C(OH)(CH_2CO_2CH_3)CO$-
(-)-Deoxyharringtonine

The bicyclic lactam **6**, prepared previously in our laboratory,[5] was treated with di-*tert*-butyl dicarbonate, triethylamine, and 4-(dimethylamino)pyridine[6] to give the protected lactam **7** (94%). Reaction of **7** with 2.2 equiv of methyllithium gave the carbinol **8**. Crude **8** was then treated with a catalytic amount of *p*-toluenesulfonic acid in dichloromethane at room temperature to afford the spiro compound **9** (75% overall yield from **7**) via an intramolecular S_N2' substitution reaction (5-*exo*-*trig*[7]). Cleavage of the exo-cyclic double bond of **9** by ozonolysis gave **10** (96%). Removal of the *tert*-butoxycarbonyl group of **10** by trifluoroacetic acid produced **11**. Reaction of crude **11** immediately with *p*-(nitrophenyl)sulfonyl ester **12** afforded **14** (72%). Attempted Friedel–Crafts cyclization of **14** with various acid catalysts to close the seven-membered ring failed. Therefore, the spiroamino ketone **11** was then condensed with the *p*-nitrophenylsulfonyl ester **13** with a dimethoxyphenyl group to give compound

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