intensity) 190 (M^+, 100), 161 (34), 81 (28).

(Z)-5-Methyl-3-(phenylthio)-1,3-hexadiene (5c): IR (neat) 3120, 1640, 1600, 1495, 1480, 1460, 1000, 930, 760, 710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (6 H, d, J = 7.0 Hz), 3.10 (1 H, m), 5.00 (1 H, dd, J = 10.0, 1.5 Hz), 5.50 (1 H, dd, J = 17.0, 1.5 Hz), 6.05 (1 H, d, J = 9.0 Hz), 6.35 (1 H, dd, J = 17.0, 10.0 Hz), 7.16 (5 H, m); MS, m/z 204 (M^+, 100), 95 (49). Anal. Calcd for $C_{13}H_{16}S$: C, 76.42; H, 7.89. Found: C, 76.33; H, 7.85.

(Z)-5-Phenyl-3-(phenylthio)-1,3-pentadiene (5d): IR (neat) 3070, 1620, 1600, 1580, 1490, 1480, 1450, 1430, 975, 910, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.80 (2 H, d, J = 7.4 Hz), 5.07 (1 H, d, J = 10.5 Hz), 5.61 (1 H, d, J = 16.8 Hz), 6.37-6.43 (2 H, m), 7.05-7.28 (10 H, m); ^{13}C NMR ($CDCl_3$) δ 36.72 (t), 116.89 (t), 125.21 (d), 126.23 (d), 127.25 (d), 128.53 (d), 128.57 (d), 128.79 (d), 132.21 (s), 136.23 (s), 136.81 (d), 139.42 (s), 142.12 (d); MS, m/z (relative intensity) 252 (M^+, 100), 161 (22), 143 (56).

Acknowledgment. We thank Dr. T. S. Chou for helpful discussions and the National Science Council of the Republic of China for financial support.

Intramolecular Electrophilic Additions to Olefins in Organic Syntheses. Stereoselective Synthesis of 3,4-Substituted β-Lactams by Bromine-Induced Oxidative Cyclization of *O*-Acyl β,γ-Unsaturated Hydroxamic Acid Derivatives

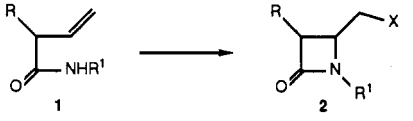
G. Rajendra and Marvin J. Miller*†

Department of Chemistry, University of Notre Dame, Notre Dame, Indiana 46556

Received June 1, 1987

A mild, efficient, and stereoselective preparation of 3,4-disubstituted β-lactams is described. The method involves treatment of *O*-acyl β,γ-unsaturated hydroxamic acids with bromine in mildly basic aqueous acetonitrile at 0 °C. The resulting rapid reaction provides the β-lactams cleanly and stereoselectively in very good yields. The α-substituent has a profound affect on the stereochemical outcome of the reaction. α-Alkyl substituents induce preferential formation of the trans β-lactams, whereas a Cbz-protected α-amino substituent promotes formation of the cis β-lactam as the major product. These results are especially significant since most biologically active α-amino-substituted bicyclic β-lactams are cis substituted and many α-alkylated bicyclic β-lactams are trans substituted. These are also among the first examples to demonstrate the effect of α-substituents on electrophilic cyclizations to four-membered rings. The results are consistent with and help generalize some of the recently proposed theoretical considerations related to other electrophilic addition reactions.

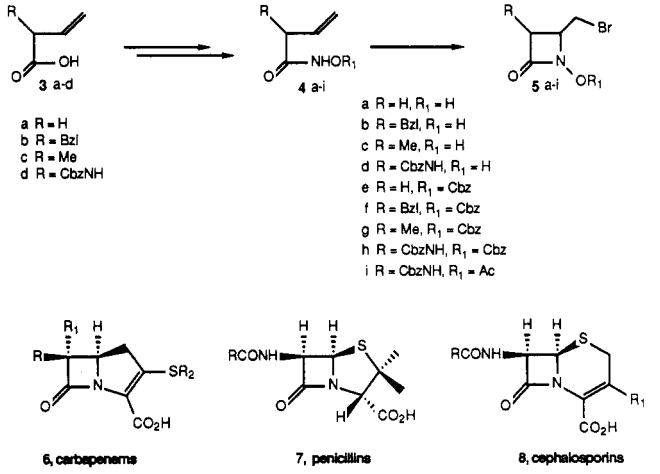
Electrophile-promoted additions to olefins are among the most fundamental and versatile tools in organic synthesis. Recent experimental and theoretical studies have contributed significantly to the understanding of the origin of the stereoselectivity observed during the electrophilic addition to chiral alkenes.[1,2] The stereoselective synthesis of functionalized five- and six-membered heterocyclic ring systems by such oxidative additions has been especially notable.[1,3] However, relatively few examples of oxidative additions to form four-membered rings have been reported.[4-6] The utility of 4-(halomethyl)-2-azetidinones **2** for the synthesis of nuclear analogues of penicillins and cephalosporins,[7a] carbapenems,[7b] and functionalized monocyclic β-lactam antibiotics[7c] made consideration of the oxidative cyclization of the corresponding β,γ-unsaturated amides **1** very attractive (eq 1).



(1)

On the basis of Ganem's precedent,[5a] which indicated that the low pK of the carboxamide group of β,γ-unsaturated *N*-tosylamides **1** (R^1 = Ts) promoted bromine-induced oxidative cyclizations to β-lactams, we recently developed an efficient oxidative cyclization of α-unsubstituted β,γ-unsaturated *O*-acyl hydroxamates to the corresponding α-unsubstituted 4-(bromomethyl) *N*-hydroxy-β-lactams (Scheme I; R = H, R^1 = acyl).[6] However, neither the earlier work on the tosylamide cyclizations nor our preliminary results on the oxidative cyclization of

Scheme I



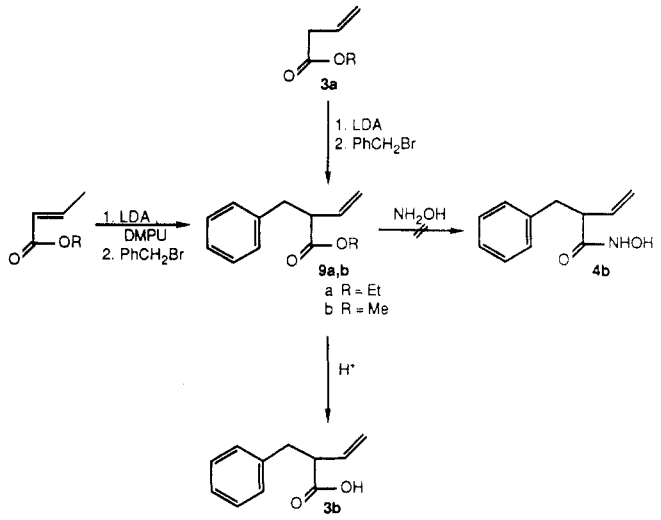
†Recipient of an NIH Research Career Development Award (1983-1988).

(1) (a) Chamberlin, A. R.; Mulholland, Jr., R. L.; Scott, D. K.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 672 and references therein. (b) Kahn, S. D.; Rau, C. F.; Chamberlin, A. R.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 650. (c) Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 666. (d) Chemberlin, A. R.; Dezube, M.; Dussault, P.; McMills, M. C. *J. Am. Chem. Soc.* **1983**, *105*, 5819. (e) Chamberlin, A. R.; Dezube, M.; Dessault, P. *Tetrahedron Lett.* **1981**, *22*, 4611.

(2) (a) Houk, K. N.; Paddon-Row, M. N.; Gordon, N. G.; Wu, Y. D.; Brown, F. K.; Spellmeyer, D. C.; Metz, J. T.; Li, Y.; Loncharich, R. J. *Science (Washington, D.C.)* **1986**, *231*, 1108 and references therein. (b) Houk, K. N.; Wu, Y. D.; Moses, S. R. *J. Am. Chem. Soc.* **1986**, *108*, 2754. (c) Houk, K. N.; Moses, S. R.; Wu, Y.-D.; Rondon, N. G.; Jager, V.; Schohe, R.; Fronczek, F. R. *J. Am. Chem. Soc.* **1984**, *106*, 3880 and references therein. (d) Houk, K. N.; Rondon, N. G.; Wu, Y.-D.; Metz, J. T.; Paddon-Row, M. N. *Tetrahedron* **1984**, *40*, 2257.

0022-3263/87/1952-4471$01.50/0

Scheme II



hydroxamates fully addressed the stereochemical consequences of incorporating α-substituents (R, Scheme I) into the cyclization precursors.[8] Since the most effective β-lactam antibiotics contain alkyl, substituted alkyl, or substituted amino groups at this corresponding α-position, we decided to study the stereochemical effects of various α-substituents on the oxidative cyclization of our hydroxamates. The results reported here indicate that the stereochemical outcome of the oxidative cyclization of α-substituted β,γ-unsaturated hydroxamates (Scheme I) is highly dependent on the nature of the α substituent.

Results

Many of the recently discovered carbapenem antibiotics (**6**) are trans substituted[9] with alkyl or substituted alkyl substituents α to the β-lactam carbonyl, but the more classic penicillins (**7**) and cephalosporins (**8**) are cis substituted[10] with amide groups. Thus, examples of both α-alkyl- and protected α-amino-substituted substrates **4** were studied. The benzyl and methyl groups were chosen as representative α-alkyl substituents, since the former was anticipated to facilitate subsequent chromatographic isolation and spectral characterization, while the latter was to provide the minimum alkyl steric influence for study of α-substituent effects. A carbobenzyloxy (Cbz) protected amino group was the choice for studies of the effect of an α-amino substituent, since the Cbz group is easily replaced with many different physiologically active side chains of active β-lactam antibiotics. These choices required preparation of the α-substituted β,γ-unsaturated carboxylic acids **3b** (R = CH_2Ph), **3c** (R = CH_3), and **3d** (R = CbzNH) from which the desired hydroxamates **4** could be derived as before (Scheme I).[6]

Our initial attempt to prepare α-benzylvinylacetic acid (**3b**) is illustrated in Scheme II. Deconjugative alkylation[11] of ethyl crotonate **8** with benzyl bromide (LDA/THF/DMPU[12]) proceeded as expected to provide the desired racemic ethyl α-benzylvinylacetate (**9a**) in good yield. Alternatively, alkylation of methyl vinylacetate with benzyl bromide provided the corresponding methyl ester **9b**. Attempted direct hydroxaminolysis of esters **9a** and **9b** failed to produce desired hydroxamate **4b** when mild conditions (NH_2OH·HCl/$NaHCO_3$/aqueous THF), which would avoid double-bond isomerization of **9a,b**, were used. Recovery of starting esters **9a,b** under these initial conditions encouraged attempts with stronger bases. However, only isomerized (conjugated) starting materials and products were then obtained. Our earlier success with the conversion of acid chlorides into hydroxamic acids[6] prompted us to attempt simple hydrolysis of **9a** and **9b** to the corresponding acid **3b** and then proceed through the acid chloride to **4b**. Again, all basic hydrolytic attempts failed to provide the β,γ-unsaturated acid **3b**, but mild acid hydrolysis of the methyl ester **9b** was successful. Direct preparation of the desired acid **3b** by an alternate route was also explored.

Literature precedent[13] for the direct α-alkylation of dianions derived from α,β- and β,γ-unsaturated carboxylic acids with allyl bromide encouraged us to try a similar approach. Indeed, separate formation of the dianions of both crotonic acid and vinylacetic acid (**3a**) followed by treatment with benzyl bromide provided the desired α-benzylvinylacetic acid (**3b**, Scheme III). However, the yield of **3b** was higher (55%) when vinylacetic acid was used. Reaction of **3b** with oxalyl chloride gave acid chloride **10**, which upon direct treatment with hydroxylamine provided desired hydroxamic acid **4b** in 86% overall yield from **3b**. Acylation of **4b** with (benzyloxy)carbonyl chloride[6] gave *O*-carbobenzyloxy α-benzylvinylacetohydroxamate (**4f**),[14] which was directly treated with bromine and potassium carbonate in aqueous acetonitrile to provide the expected trans β-lactam *trans*-**5f** in 75% overall yield from hydroxamate **4b**. The trans substitution of **5f** was clearly demonstrated by the charcteristic small (J = 2.4 Hz) coupling constant between the α- and β-protons on the ring. No trace of the cis β-lactam was detected in either the crude or chromatographically purified product.

The stereospecific nature of the oxidative cyclization of α-benzylhydroxamate **4f** provided further incentive to

(3) (a) Staninets, V. I.; Shilov, E. A. *Russ. Chem. Rev. (Engl. Transl.)* **1971**, *40*, 272. (b) Dowle, M. D.; Davis, D. I. *Chem. Soc. Rev.* **1979**, 171. (c) Bartlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: Orlando, FL, 1984; Vol. 3, Chapter 6, p 411. (d) Tamaru, Y.; Mizutani, M.; Furukawa, Y.; Kawamura, S.-i.; Yoshida, Z-i.; Yanagi, K.; Minobe, M. *J. Am. Chem. Soc.* **1984**, *106*, 1079. (e) Tamaru, Y.; Kawamura, S.-i.; Yoshida, S.-i. *Tetrahedron Lett.* **1985**, *26*, 2885. (f) Tamaru, Y.; Kawamura, S.; Tanaka, K.; Yoshida, Z. *Heterocycles* **1985**, *23*, 192. (g) Williams, D. R.; White, F. H. *Tetrahedron Lett.* **1986**, *27*, 2195.

(4) For oxdative cyclizations to β-lactones, see: Barnett, W. E.; McKenna, J. *Tetrahedron Lett.* **1971**, 2595. (b) Barnett, W. E.; Sohn, W. H. *J. Chem. Soc., Chem. Commun.* **1972**, 472. (c) Barnett, W. E.; Sohn, W. H. *Tetrahedron Lett.* **1972**, 1777.

(5) (a) Biloski, A. J.; Wood, R. D.; Ganem, B. *J. Am. Chem. Soc.* **1982**, *104*, 3233. (b) Ihara, M.; Haga, Y.; Yonekura, M.; Ohsawa, T.; Fukumoto, K.; Kametani, T. *J. Am. Chem. Soc.* **1983**, *105*, 7345.

(6) Rajendra, G.; Miller, M. J. *Tetrahedron Lett.* **1985**, *26*, 5385.

(7) (a) Huffman, W. F.; Holden, K. G.; Buckley, T. F., III; Gleason, J. G.; Wu, L. *J. Am. Chem. Soc.* **1977**, *99*, 2352. (b) Salzmann, T. N.; Ratcliffe, R. W.; Christensen, B. G.; Bouffard, F. A. *J. Am. Chem. Soc.* **1980**, *102*, 6161. (c) Miller, M. J.; Bajwa, J. S.; Mattingly, P. G.; Peterson, K. *J. Org. Chem.* **1982**, *47*, 4928.

(8) Ganem's report[5a] included one example, a dihydrobenzoyl derivative leading to a cis-fused bicyclic β-lactam, as might be expected. However, no examples were reported that did not incorporate a second ring.

(9) Kametani, T.; Fukumoto, K.; Ihara, M. *Heterocycles* **1982**, *17*, 463.

(10) Morin, R. B., Gorman, M., Eds.; *Chemistry and Biology of β-Lactam Antibiotics*; Academic: New York, 1982; Vol. 1–3.

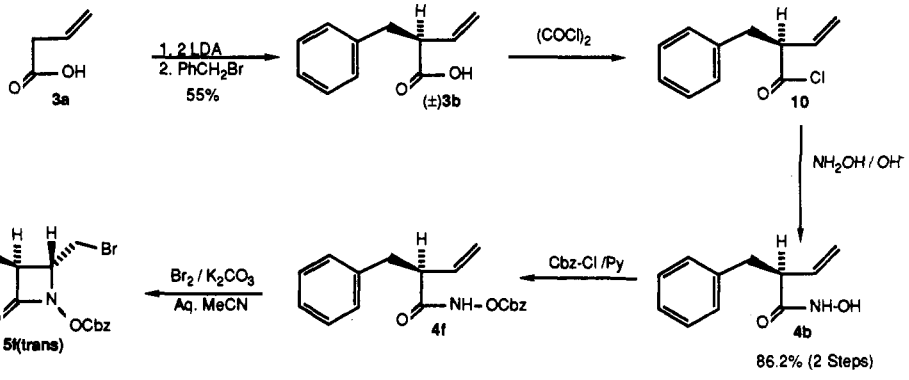
(11) Hermann, J. L.; Kieczykowski, G. R.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, 2433.

(12) Mukhopadhyay, T.; Seebach, D. *Helv. Chim. Acta* **1982**, *65*, 385.

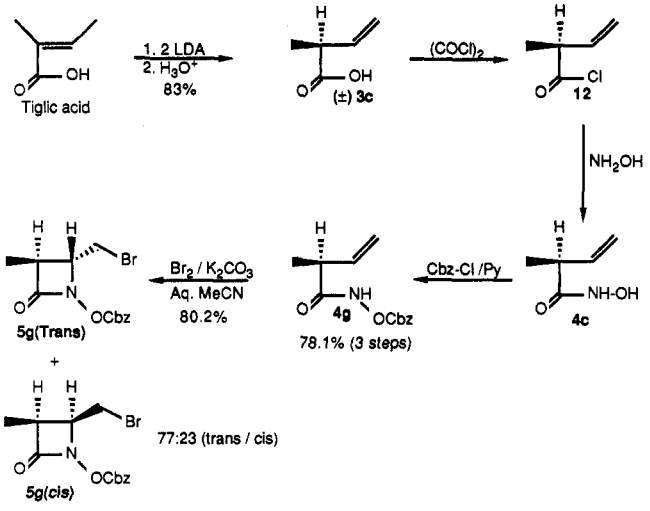
(13) Katzenellenbogen, J. A.; Crumrine, A. L. *J. Am. Chem. Soc.* **1976**, *98*, 4925.

(14) Many of the *O*-Cbz hydroxamate derivatives reported here and elsewhere underwent partial to extensive decomposition during chromatography on silica gel. Hence, crystallization, whenever possible, was the preferred way to purify these compounds. On the other hand, when crystallization failed the crude product (generally ≥95% pure) could be subjected to oxidative cyclization without any detrimental effects. Purification at the β-lactam stage in such instances resulted in better overall yields

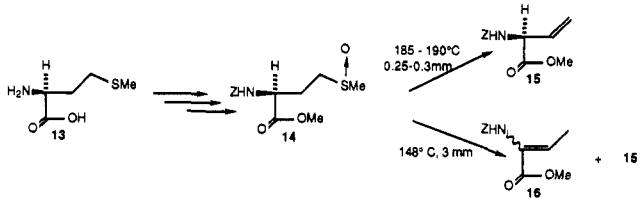
Scheme III



Scheme IV



Scheme V



study the cyclization of the sterically less demanding α-methyl analogue **4g**. The synthesis of *O*-carbobenzyloxy 2-methylvinylacetohydroxamate (**4g**) is outlined in Scheme IV. Commercially available tiglic acid (**11**) was converted into 2-methylvinylacetic acid (**3c**) in 83% yield by kinetic quenching of the corresponding dianion. Acid **3c** was then treated with oxalyl chloride to provide acid chloride **12**. Hydroxaminolysis of crude **12** followed by acylation of the resulting hydroxamic acid **4c** with CbzCl furnished the desired cyclization precursor **4g** in 78% recrystallized yield for the three-step process (**3c** → **4g**). Compound **4g** was then subjected to the usual[6] bromine-induced oxidative cyclization conditions. However, in contrast to the previous case, this reaction provided a diastereomeric mixture of β-lactams *trans*-**5g** and *cis*-**5g** in 80% isolated yield. Although the mixture was chromatographically homogeneous, ^{1}H NMR analysis of the product mixture clearly distinguished the diastereomers and indicated a 77:23 trans to cis ratio (J_{trans} = 2.5 Hz, J_{cis} = 5.95 Hz). Thus, although the methyl group had a less dramatic affect on the stereoselectivity of the cyclization process, the trend of trans product dominance was still maintained.

The stereoselective nature of the oxidative cyclization of α-alkyl β,γ-unsaturated hydroxamates **4f** and **4g** prompted further study of the cyclization of α-heteroatom-substituted hydroxamates, especially the previously mentioned amine derivatives. Although no definitive study of such reactions to form four-membered rings by oxidative additions has been reported, analogy to halolactonizations and related reactions[1] suggested that the allylic heteroatom might alter the stereochemical outcome of the cyclization. Thus, potentially the cyclization of substituted α-amino β,γ-unsaturated hydroxamic acids would provide very important cis-substituted β-lactams with α-amino substituents.

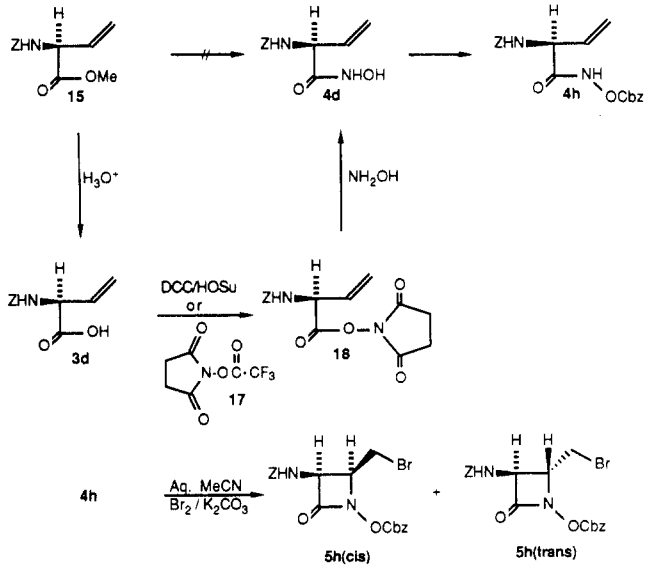
The key starting material for this study was an appropriately protected (Cbz) L-vinylglycine (**3d**). Hanessian[15] and Rapoport[16] reported preparatively useful syntheses of L-vinylglycine from L-glutamic acid and L-methionine, respectively. The glutamic acid route[15] was initially utilized, but in our hands, the key oxidative decarboxylations proceeded in poor yields and large-scale reactions were hampered by the need to use excess amounts of freshly prepared lead tetraacetate. These results prompted us to try the alternate synthesis of vinylacetic acid from methionine.[16]

As shown in Scheme V, L-methionine (**13**) was suitably protected and oxidized with sodium periodate to sulfoxide **14**. However, repeated attempts to pyrolize **14** under the initially reported conditions[16a] failed to produce the desired vinylglycine derivative **15** cleanly. Instead, double-bond migration to conjugated dehydroamino acid **16** predominated. Alternatively, pyrolysis in refluxing DMSO (185–190 °C, 1 h) worked well, but isolation of the desired product **15** was hampered by difficulties in complete removal of DMSO and its decomposition products during workup. Eventual use of Rapoport's more recently reported modified pyrolysis procedure[16b] worked quite well with a few of our own modifications, which are described in the Experimental Section. Direct access to multigram quantities of protected vinylglycine **15** allowed us to consider its conversion to a substrate for our oxidative cyclization studies.

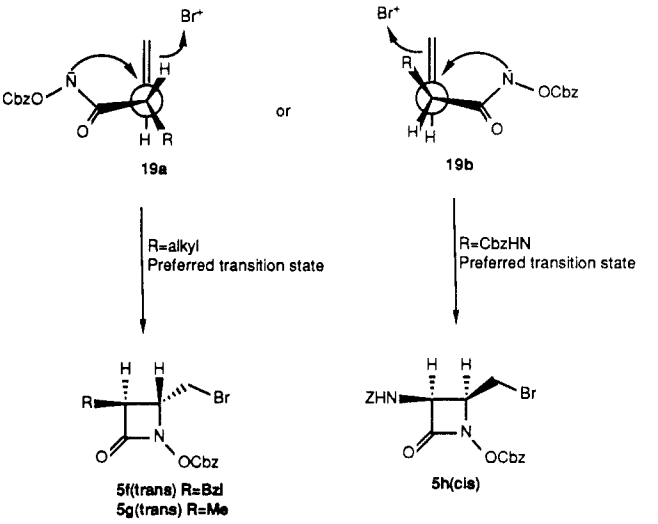
Again, attempts to form hydroxamic acid **4d** by direct hydroxaminolysis of ester **15** generated the conjugated isomer instead. Alternative routes to **4d** were more successful (Scheme VI). Careful acidic hydrolysis of methyl ester **15** produced free acid **3d** in 87% yield. Preparation of *N*-hydroxysuccinimide ester **18** with dicyclohexylcarbodiimide (DCC) and *N*-hydroxysuccinimide (HOSu) proceeded as expected. Unfortunately, crystallization and chromatographic attempts to purify **18** from dicyclo-

(15) Hanessian, S.; Sahoo, S. P. *Tetrahedron Lett.* **1984**, *25*, 1425.
(16) (a) Ardakam, A. A.; Rapoport, H. *J. Org. Chem.* **1980**, *45*, 4917. (b) Shaw, K. J.; Luly, J. R.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 4515.

Scheme VI



Scheme VII



hexylurea resulted in extensive isomerization of the essential double bond. Although material only slightly contaminated with DCU could be obtained and successfully used in subsequent reactions, this situation was not ideal. However, treatment of **3d** with *O*-(trifluoroacetyl)-*N*-hydroxysuccinimide (**17**)[17] provided **18** in good yield and in acceptably pure form (contaminated with only about 1–2% double-bond-isomerized side product). Subsequent treatment of **18** with hydroxylamine provided desired hydroxamic acid **4d** in 72% recrystallized yield. Acylation with (benzyloxy)carbonyl chloride gave the desired substituted hydroxamic acid **4h** in 90% yield after recrystallization. Bromine-induced oxidative cyclization of **4h** provided a 75–80% yield of a mixture of the cis and trans β-lactams *cis*-**5h** and *trans*-**5h** in a 7:3 ratio. Most interesting was that the major and easily crystallized isomer was *cis*-**5h**. Although the *O*-Cbz-substituted hydroxamates are preferred,[6] we decided to also briefly study the effect of changes of the *O*-acyl group of the hydroxamate substrate. Oxidative cyclization of *O*-acyl hydroxamate **4i** provided a similar ratio (64:36) of *cis*-**5i** and *trans*-**5i**. These results contrast directly with those obtained from the cyclization of the α-alkylated β,γ-unsaturated hydroxamates **4f** and **4g**, which favored the formation of trans β-lactams. The significance of these results deserve further emphasis since most biologically active α-amino-substituted bicyclic β-lactams are cis substituted and many α-alkylated bicyclic β-lactams are trans substituted.

Discussion

Oxidative cyclizations of unsaturated systems are becoming increasingly useful in heterocyclic syntheses. A variety of electrophiles, including phenylselenyl halides, mercury salts, halogens, and *N*-haloimide derivatives, have been used to induce cyclizations to five- and six-membered rings under both kinetic and thermodynamic conditions with moderate to excellent regio- and stereoselectivity.[1-3] However, no extensive studies had been reported on the course of acyclic stereoselection of similar oxidative cyclizations to four-membered rings.[4-6] The studies on the oxidative cyclization of the β,γ-unsaturated hydroxamates to β-lactams reported here and earlier[5,6] help fill this gap. The cyclization conditions are quite similar to those previously used for many kinetically controlled electrophilic additions to olefins.[1-3] Detailed mechanisms for the cyclizations described here are not known. In fact, several alternatives to direct electrophilic addition to the olefin are possible. For example, reaction of the bromine with the hydroxamate nitrogen before or during electrophilic addition to the olefin cannot be ruled out. However, the stereochemical consequences can be predicted by using transition-state structures (Scheme VII) similar to those considered by Hehre and Chamberlin[1a] and Houk[2] for other inter- and intramolecular electrophilic additions. Thus, structure **19a** (Scheme VII) should correspond to a preferred transition state for oxidative cyclization of α-alkyl-substituted β,γ-unsaturated hydroxamates and produce the trans β-lactam as the major product. Alternatively, heteroatom-induced change in the stereochemistry of the cyclization is consistent with the suggestion[1,2] that the preferred transition state for α-heteroatom-substituted systems resembles **19b**.

In conclusion, we have demonstrated that oxidative cyclizations can be used to form substituted four-membered rings stereoselectively. The specific examples reported here further illustrate the potential of this route for the preparation of important β-lactams with stereochemical control dependent upon the choice of substituents on the unsaturated starting materials. Related studies are planned that may allow for the more exclusive formation of cis β-lactams with α-heteroatom-containing groups.[18] Incorporation of a variety of substituents in other positions will also be used to explore the scope of this type of oxidative cyclization.[19]

Experimental Section

General Comments. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra (IR) were recorded on Perkin-Elmer 727B and 1420 spectrometers. Nuclear magnetic resonance (NMR) spectra were recorded on Varian EM 390 (90-MHz), Magnachem A200 (200-MHz), or Nicolet NB300 (300-MHz) spectrometers. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane (TMS). Mass spectra were obtained with AEI

(17) Sadakibara, S.; Inukai, N. *Bull. Chem. Soc. Jpn.* **1964**, *37*, 1231.

(18) Increasing cis selectivity during oxidative cyclizations to larger rings by changing heteroatom substituents has precedent. See: Wang, Y.-F.; Izawa, T.; Kobayashi, S.; Ohno, M. *J. Am. Chem. Soc.* **1982**, *104*, 6465.

(19) Oxidative cyclization studies of various γ-substituted derivatives of *O*-carbobenzyloxy vinylacetohydroxamates have been submitted for publication.

Scientific Apparatus MS 902, Du Pont DP102, or Finnigan Mat Model 8234 spectrometers. FD and FAB mass spectra were obtained by Dr. John Occolowitz at Eli Lilly and Co. Elemental analyses were performed by MHW Laboratories, Phoenix, AZ. Thin-layer chromatography (TLC) was performed on Merck aluminum-backed 0.2-mm precoated silica gel plates. Common commercial solvents were glass distilled prior to use in chromatography or reaction workup. Reagent-grade solvents were used in reactions and were further purified and dried by standard procedures. All reactions requiring anhydrous conditions were carried out under a nitrogen atmosphere.

2-Benzylvinylacetic Acid (3b). A solution of diisopropylamine (3.38 mL, 24.12 mmol, 205 mol %) in THF was cooled to 0 °C. *n*-Butyllithium (15 mL, 1.58 M in hexanes, 23.8 mmol, 202 mol %) was added, with stirring, under an atmosphere of N_2. After the mixture was stirred for 10 min, a solution of vinyl acetic acid (**3a**; 1.0 mL, 11.77 mmol, 100 mol %) in 10 mL of THF was added slowly over a period of 15 min. The resulting mixture was stirred at 0 °C for 45 min to obtain a deep yellow solution. Benzyl bromide (neat, 1.43 mL, 12.00 mmol, 102 mol %) was added, whereupon the reaction mixture immediately turned colorless. After 30 min at 0 °C and 15 min at room temperature, the pH of the solution was adjusted to 2.5 with 4 N HCl. The organic phase was separated. The aqueous layer was saturated with solid NaCl and extracted with ethyl acetate (4 × 50 mL). The organic layers were combined and extracted with 5% aqueous $NaHCO_3$ solution (300 mol %). Again the pH was adjusted to 2.5, and the solution was back-extracted with ethyl acetate (5 × 40 mL) after saturation with solid NaCl. The combined organic layers were dried over anhydrous $MgSO_4$ and filtered. Removal of solvents under reduced pressure followed by chromatography on silica gel (10 → 20% ethyl acetate/hexanes) yielded the product as a colorless oil (1.14 g, 55% yield): ^{1}H NMR (200 MHz, $CDCl_3$/TMS) δ 2.72–3.18 (ddd, 2 H), 3.22–3.38 (br q, 1 H), 5–5.18 (m, 2 H), 5.7–5.94 (m, 1 H), 7.03–7.33 (m, 5 H), 11.6–11.8 (br, 1 H); ^{13}C NMR ^{1}H decoupled (A 200, neat, TMS) δ 38.10, 51.89, 118.02, 126.54, 128.41, 129.08, 134.82, 138.30, 180.28; IR (thin film) 3600–2400 (v br), 1708 cm^{-1}; mass spectrum (FAB/thioglycerol) *m/e* 177 (M + 1), 132 (M + 1 − CO_2H). Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.88; H, 6.93.

2-Benzylvinylacetohydroxamic Acid (4b). 2-Benzylvinylacetic acid (**3b**; 2.1 g, 11.92 mmol, 100 mol %) was placed in a dry flask fitted with a drying tube and cooled to 0 °C. Oxalyl chloride (1.14 mL, 13.11 mmol, 110 mol %) was added, and the reaction mixture was stirred for 20 h, allowing the ice bath to warm to room temperature over the period, to obtain acid chloride **10** as a pale yellow oil: ^{1}H NMR ($CDCl_3$/TMS, 90 MHz) δ 2.76–3.07 (m, 2 H), 3.23–3.9 (q, 1 H), 5.06–5.43 (m, 2 H), 5.63–6.10 (m, 1 H), 7.28 (s, 5 H); IR (thin film) 1795 cm^{-1}. A solution of KOH (1.563 g, 24.55 mmol, 88.15% assay, 206 mol %) in anhydrous reagent-grade MeOH (25 mL) and a solution of NH_2OH·HCl (0.8614 g, 12.39 mmol, 104 mol %) also in anhydrous MeOH (25 mL) were prepared separately and mixed together at 0 °C. After the resultant mixture was stirred at 0 °C for 10 min under N_2, acid chloride **10**, dissolved in 15 mL of dry THF, was added rapidly. The resulting mixture was stirred at 0 °C for 15 min and at room temperature for 2 h. Most of the MeOH was removed under reduced pressure. The residue was diluted with 50 mL of distilled water, and the pH was adjusted to 3.5 with 2 N HCl. The solution was saturated with solid NaCl and extracted with ethyl acetate (5 × 50 mL). The combined organic layers were washed once with brine and dried over anhydrous $MgSO_4$. Filtration followed by removal of solvents under reduced pressure left an off-white solid residue that was crystallized from MeOH/ethyl acetate/hexanes to obtain the product as fine white needle-shaped crystals (two crops, 1.96 g, 86.2% yield): mp 128.5–129.5 °C; ^{1}H NMR (300 MHz, acetone-d_6/TMS) δ 2.6–2.87 (m, 1 H), 2.9–3.2 (m, 2 H), 5.0–5.1 (m, 2 H), 5.83–6.0 (m, 1 H), 7.05–7.3 (m, 5 H), 8.4–8.6 (br, 1 H); mass spectrum (DCI/isobutane) *m/e* 193 (M + 2), 192 (M + 1, intensity 100%), 191 (M$^+$), 176 (M + 1−16), 131, 91. Anal. Calcd for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.64; N, 11.19. Found: C, 57.66; H, 5.52; N, 11.39.

***O*-Carbobenzyloxy 2-Benzylvinylacetohydroxamate (4f).** Hydroxamic acid **4b** (0.75 g, 3.92 mmol, 100 mol %) was dissolved in dry THF (50 mL, 0.08 M) and cooled to 0 °C. Pyridine (0.33 mL, 4.12 mml, 105 mol %) was added and stirred for 5 min, followed by CbzCl (neat, 0.59 mL, 3.92 mmol 95% purity, 100 mol %). A white precipitate formed immediately. The reaction mixture was further stirred for 30 min and then transferred to a separatory funnel with 150 mL of ethyl acetate/hexanes (1:1). The organic phase was washed with 0.5 M HCl (2 × 25 mL) and brine and dried over anhydrous $MgSO_4$. Filtration followed by removal of solvents under aspirator pressure yielded the crude product as a colorless oil in quantitative yield. The crude product was >95% pure by NMR and could be used in the subsequent reaction without further purification. For analytical reasons, a sample of the product (0.64 g) was purified by chromatography on silica gel (10 → 18% ethyl acetate in hexanes) to obtain the pure product as a colorless oil (0.426 g, 66.9% yield; the lower yield after chromatography was the result of the decomposition of the product during chromatography); ^{1}H NMR (200 MHz, chloroform-*d*/TMS) δ 2.75–2.95 (m, 1 H), 3.05–3.28 (m, 2 H), 5.20 (s, 2 H), 5.00–5.03 (m, 2 H), 5.75–5.95 (m, 1 H), 7.1–7.3 (m, 5 H), 7.34 (s, 5 H), 9.93 (br, 1 H); ^{13}C NMR ^{1}H decoupled (A 200, chloroform-d/TMS) δ 37.82, 49.50, 71.23, 118.40, 126.33, 128.25, 128.32, 128.52, 128.66, 129.17, 134.23, 134.86, 138.24, 154.07, 171.59; IR (thin film) 3150 (br), 1797, 1688 cm^{-1}; mass spectrum (FD) *m/e* 326 (M + 1), 325 (M$^+$), 281 (−CO_2), 131, 108, 91.

Oxidative Cyclization of *O*-Carbobenzyloxy 2-Benzylvinylacetohydroxamate (4f). Compound **4f** (0.3058 g, 0.94 mmol, 95% purity, 100 mol %) was dissolved in MeCN (19 mL, 0.05 M), and the resultant mixture was cooled to 0 °C with an ice bath. Potassium carbonate (0.143 g, 1.03 mmol, 110 mol %) followed by water (2.4 mL) was added, and the mixture was stirred vigorously for 2 min. It was essential that vigorous stirring was maintained throughout the reaction. A solution of bromine (55.4 μL, 1.08 mmol, 100 mol %) in MeCN (5 mL) was added dropwise over a period of 8 min. Following 2 min of stirring after the addition of bromine, the reaction mixture was transferred to a separatory funnel with 150 mL of 1:1 ethyl acetate/hexanes. The solution was washed with water (25 mL), 10% aqueous Na_2SO_3 (2 × 20 mL), and brine and dried over anhydrous $MgSO_4$. Filtration followed by removal of solvents under reduced pressure yielded the product as a pale yellow oil. It was purified by chromatography on silica gel (8 → 10% ethyl acetate in hexanes) to obtain pure *trans*-**5f** as a colorless oil (0.285 g, 75% yield for two steps): ^{1}H NMR (300 MHz, chloroform-*d*/TMS) δ 2.9–3.25 (m, 3 H), 3.28–3.5 (ddd, 2 H, *J* = 10.9, 5.8, 5.9 Hz), 4.05–4.15 (m, 1 H, *J* = 5.85, 5.81, 2.4 Hz), 5.24 (s, 2 H), 7.15–7.45 (m, 10 H); ^{13}C NMR ^{1}H decoupled (NB 300, chloroform-*d*/TMS) δ 30.18, 33.79, 52.86, 64.08, 71.97, 127.03, 128.61, 128.72, 128.81, 129.12, 133.57, 137.04, 153.38, 165.17 (two of the aromatic carbons apparently resonated at the frequency); IR (thin film) 1805, 1785 cm^{-1}; mass spectrum (FAB/thioglycerol) *m/e* 406 (M + 3), 403 (M − 1), 132 (C_9H_8O). Anal. Calcd for $C_{19}H_{18}BrNO_4$: C, 56.45; H, 4.49; N, 3.46. Found: C, 56.21; H, 4.56; N, 3.55.

2-Methylvinylacetic Acid (3c). This compound has been previously prepared from crotylmagnesium bromide and CO_2.[20] However, we have found the following deconjugative procedure to be more general.[19]

A solution of diisopropylamine (15.1 mL, 0.108 mol, 220 mol %) in THF (50 mL) was cooled to −78 °C. *n*-BuLi (65 mL, 1.58 M/hexanes, 0.103 mol, 210 mol %) was added. The resulting mixture was stirred for 20 min to obtain a pale yellow solution. A solution of tiglic acid (5 g, 0.049 mol, 100 mol %) in THF (30 mL) was added to the rapidly stirred solution of lithium diisopropylamide (LDA) over a period of 30 min. The bath temperature was maintained between −40 and −20 °C during the addition. The resulting yellow solution was stirred at room temperature for 1 h and then poured into a vigorously stirred ice-cold solution of 3 M HCl (120 mL). The organic layer was separated, and the aqueous layer was saturated with solid NaCl and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and filtered. The solvents were removed under reduced pressure to obtain the crude product as a yellow oil. It was then purified by reduced pressure distillation (bp 89–91 °C, bath temperature 95–99 °C, pressure 15 mm) to provide the pure product as a colorless oil (4.06 g, 82.9% yield).

(20) Lane, J. F.; Roberts, J. D.; Young, W. G. *J. Am. Chem. Soc.* **1944**, *66*, 543.

***O*-Carbobenzyloxy 2-Methylvinylacetohydroxamate (4g).** 2-Methylvinylacetic acid (6.0 g, 59.9 mmol) was converted into its acid chloride by treatment with oxalyl chloride (neat, 5.7 mL, 65.32 mmol, 109 mol %, 0 °C to room temperature, 57 h). The acid chloride in turn was converted into the product via the hydroxamic acid by the same procedure explained for the preparation of *O*-carbobenzyloxy 2-benzylvinylacetohydroxamate (**4f**). The crude product was obtained as a white solid and was crystallized from CH_2Cl_2/hexanes to obtain the pure product as white needle-shaped crystals (11.66 g, two crops, combined yield 78.1%). These crystals were unusually hydroscopic, and a reliable melting point was not obtained. Although the mother liquor still contained a considerable amount of the product, a third crystallization failed. ^{1}H NMR (200 MHz, chloroform-*d*/TMS) δ 1.3 (d, 3 H, J = 7.8 Hz), 3.0–3.2 (m, 1 H), 5.13–5.36 (m, 2 H, superimposed on s, 2 H), 5.78–6.0 (m, 1 H), 7.37 (s, 5 H), 9–9.4 (br s, 1 H); mass spectrum (DCl/isobutane) m/e 251 (M + 2), 250 (M + 1), 207 (M + 2 – CO_2), 206 (M + 1 – CO_2). Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.64. Found: C, 62.53; H, 6.13; N, 5.74.

Oxidative Cyclization of *O*-Carbobenzyloxy 2-Methylvinylacetohydroxamate (4g) to β-Lactam 5g. *O*-Carbobenzyloxy 2-methylvinylacetohydroxamate (**4g**; 0.275 g, 1.1 mmol, 100 mol %) was dissolved in MeCN (15 mL) and cooled to 0 °C. Potassium carbonate (0.16 mmol, 105 mol %) followed by water (2 mL) was added, and the reaction mixture was stirred vigorously for 1 min. A solution of bromine (61.2 μL, 1.21 mmol, 110 mol %) in MeCN (5 mL, final concentration of the substrate in the reaction mixture) was added. The reaction mixture was diluted with 100 mL of ether, washed with water (25 mL), 10% aqueous Na_2SO_3 (25 mL), and brine and dried over $MgSO_4$. Filtration followed by removal of solvents under reduced pressure yielded a very pale yellow oil. Purification by chromatography on silica gel (15 → 20% ethyl acetate in hexanes) yielded 0.263 g of a white solid, which was a mixture of cis and trans β-lactams **5g** (3:7). *cis*-**5g**: ^{1}H NMR (300 MHz, $CDCl_3$ reference at δ 7.24) δ 1.26 (d, 3 H, J = 7.42 Hz), 3.29 (m, 1 H, J = 7.4, *5.95* Hz), 3.33–3.58 (the high-field end is partially buried under the methylene protons of the trans product, m, 2 H, J = 6.5, 7.6, 10.6 Hz), 4.31–4.4 (m, 1 H, J = 6.5, 7.6, *5.95* Hz), 5.21 (s, 2 H), 7.34 (s, 5 H); IR 1795, 1775, 1220 cm^{-1}. *trans*-**5g**: ^{1}H NMR (300 MHz, $CDCl_3$ reference at δ 7.24) δ 1.36 (d, 3 H, J = 7.3 Hz), 2.78–2.89 (d of q, 1 H, J = 7.3, *2.5* Hz), 3.41–3.62 (ddd, 2 H, J = 10.64, 5.40, 7.17 Hz), 3.88 (m, 1 H), 5.208 (s, 2 H), 7.40 (s, 5 H); IR 1795, 1775, 1220 cm^{-1}; mass spectrum (DCI/isobutane) m/e 331 (M + 4), 330 (M + 3), 329 (M + 2), 328 (M + 1), 286 (M – 3 – 44), 284 (M + 2 – 44), 274 (M + 3 – C_3H_4O), 272 (M + 1 – C_3H_4O), 130, 228, 196, 194. Anal. Calcd for $C_{13}H_{14}BrNO_4$: C, 62.64; H, 6.07; N, 5.64. Found: C, 62.53; H, 6.13; N, 5.74.

Pyrolysis of the Sulfoxide 14 to Vinylglycine Derivative 15.[16] Sulfoxide **14** (5–10 g, 16–30 mmol) was placed in a round-bottom flask (providing a surface area of 30–55 cm^2/g of the sulfoxide) as a solution in ethyl acetate [20–25% (w/w) ethyl acetate/sulfoxide] so as to give a fluid enough solution to be transferred by a pipet. The flask was then placed in a preheated Kugelrohr apparatus (temperature of the air bath 185–190 °C). Very rapid oscillation of the flask was initiated, and the pressure was immediately brought down to 0.25–0.3 mm. After about 1–1.5 h, the product was collected from the receiver and purified by chromatography on silica gel (5 → 8% ethyl acetate in hexanes) to obtain pure product **15**[16] as an almost colorless oil in 55–62% yield.

Selective Hydrolysis of Methyl *N*-Carbobenzyloxyvinylglycinate (15) to *N*-Carbobenzyloxyvinylglycine (3d). Compound **15** (12.5 g, 50.14 mmol) was dissolved in 100 mL of glacial acetic acid, and 100 mL of 1 M HCl was added to obtain a cloudy yellow solution (~0.25 M). It was gently refluxed for 1 h, and the resulting clear pale yellow solution was allowed to cool down to room temperature. Most of the solvents were removed under reduced pressure, and the residue was transferred to a separatory funnel with 400 mL of ethyl acetate. The organic layer was washed with water (6 × 30 mL) and brine and dried over anhydrous $MgSO_4$. Filtration followed by removal of solvents gave a pale yellow solid that was crystallized from ethyl acetate/hexanes to obtain the product as white flaky crystals (two crops combined, 10.25 g, 86.9% yield): mp 130–131 °C; ^{1}H NMR (300 MHz, acetone-d_6/TMS) δ 4.9–5.0 (br m, 1 H), 5.12 (s, 2 H), 5.23–5.48 (m, 2 H), 5.95–6.10 (m, 1 H), 7.25–7.45 (m, 5 H); ^{13}C NMR ^{1}H decoupled (NB 300, chloroform-*d* reference at δ 77.00) δ 38.01, 51.75, 118.25, 126.44, 128.29, 128.95, 134.53, 138.14, 179.91 (the carbamate carbonyl was not seen under the experimental conditions); mass spectrum (FD) m/e 237 (M + 2), 236 (M + 1), 235 (M$^+$), 190. Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.38; H, 5.67; N, 6.04.

Preparation of Hydroxamic Acid 4d. *N*-Carbobenzyloxyvinylglycine (**3d**; 3.00 g, 12.75 mmol, 100 mol %) and *O*-(trifluoroacetyl)-*N*-hydroxysuccinimide[17] (3.365 g, 15.94 mmol, 125 mol %) were placed in a dry flask under N_2, and the flask was cooled to 0 °C (ice bath). Dry THF (100 mL, 0.13 M) was added, and the resulting clear colorless solution was stirred for 5 min. Pyridine (1.14 mL, 14.03 mmol, 110 mol %) was added and stirred for 5 h, allowing the ice bath to reach room temperature over the period. The reaction mixture was then transferred to a separatory funnel. Ether (150 mL) and hexanes (150 mL) were added, and the organic layer was washed successively with 50 mL each of water, 0.5 M HCl, water, 2% aqueous $NaHCO_3$, water, and brine. The organic phase was dried over $MgSO_4$ and filtered, and the solvents were removed under reduced pressure to obtain active ester **18** as a viscous colorless oil, which was used immediately without further purification: ^{1}H NMR (90 MHz, $CDCl_3$/TMS) δ 2.78 (s, 4 H), 5.06–5.70 (m, 6 H), 5.83–6.27 (m, 1 H), 7.45 (s, 5 H).

Active ester **18** was dissolved in 100 mL of 50% aqueous THF (0.3 M). NH_2OH·HCl (2.66 g, 38.28 mmol, 300 mol %) followed by $NaHCO_3$ (2.95 g, 35.11 mol, 275 mol %) was added. The resulting cloudy solution was stirred at room temperature for 3.5 h, and the solution was adjusted to pH 3.5 with 2 M HCl. The organic layer was separated. The aqueous layer was saturated with solid NaCl and extracted with ethyl acetate (75 mL). The combined organic layers were diluted with 75 mL of hexanes and washed with water (4 × 50 mL) and brine and finally dried over $MgSO_4$. Filtration followed by removal of solvents under reduced pressure yielded a pale yellow solid residue. The residue was dissolved in a minimum amount of MeOH. Ethyl acetate (75 mL) was added, followed by hexanes until the solution was faintly cloudy. After 5 h at room temperature and overnight at 0 °C, pure product **4d** was obtained as white needle-shaped crystals (two crops combined to give 2.30 g, 71.9% yield): mp 118–120 °C; ^{1}H NMR (300 MHz, acetone-d_6/TMS) δ 4.7–4.8 (t, 1 H), 5.08 (s, 2 H), 5.15–5.45 [dd, 2 H, J = 17.1 (trans), 10.2 (cis) Hz], 5.87–6.02 (m, 1 H), 6.6–6.7 (br d, 1 H), 7.25–7.42 (m, 5 H), 8.34 (br s, 1 H); IR (KBr) 3650–2500 (v br), 1690, 1625 cm^{-1}. Anal. Calcd for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.64; N, 11.19. Found: C, 57.66; H, 5.52; N, 11.39.

Acylation of Hydroxamic Acid 4d with CbzCl To Provide 4h. Hydroxamic acid **4d** (1.86, 7.43 mmol, 100 mol %) was dissolved in dry THF (75 mL, 0.1 M) and cooled to 0 °C. Pyridine (0.63 mL, 7.8 mmol, 105 mol %) was added, and the reaction mixture was stirred for 5 min. CbzCl (neat, 1.12 mL, 7.43 mmol, 95% purity, 100 mol %) was added dropwise. An immediate formation of a white precipate took place. The reaction was monitored by TLC (1:1 ethyl acetate/hexanes). When all of the starting material had disappeared (15 min), the reaction mixture was transferred to a separatory funnel with 200 mL of ether and washed with water (2 × 40 mL), 0.5 M HCl (2 × 40 mL), and brine and dried over $MgSO_4$. Filtration followed by removal of solvents under reduced pressure (keeping the bath temperature ≤25–28 °C) yielded a colorless oil. Recrystallization from CH_2Cl_2/hexanes provided pure product **4h** as white needle-shaped crystals (2.56 from two crops, 89.6% yield): mp 95–96 °C; ^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ 4.83–4.93 (br, 1 H), 5.10 (s, 2 H), 5.24 (s, 2 H), 5.28–5.48 (m, 2 H), 5.6–5.7 (br d, 1 H), 5.83–5.98 (m, 1 H), 7.33 (s, 5 H), 7.36 (s, 5 H), 9.8–10 (br, 1 H); mass spectrum (FD) m/e 385 (M + 1), 384 (M$^+$), 190. Anal. Calcd for $C_{20}H_{20}N_2O_6$: C, 62.49; H, 5.24; N, 7.29. Found: C, 62.39; H, 5.24; N, 7.32.

Oxidative Cyclization of 4h to β-Lactams *cis*-5h and *trans*-5h. Compound **4h** (0.4 g, 1.04 mmol, 100 mol %) was dissolved in 40 mL of MeCN and cooled with an ice bath. Potassium carbonate (0.15 g, 1.1 mmol, 105 mol %) followed by water (2.5 mL) was added. The reaction mixture was vigorously stirred for 1 min, and the vigorous stirring was maintained throughout the reaction. A solution of bromine (110 mol %) in MeCN (12 mL) was added over a period of 5 min. After 2 min, the reaction

mixture was subjected to a reductive aqueous workup with Na_2SO_3 as in the above experiments to obtain the crude product (mixture of cis and trans β-lactams) as a pale yellow oil. Purification by chromatography on silica gel (ethyl acetate/hexanes) followed by crystallization from methylene chloride/hexanes yielded pure cis product *cis*-**5h** as white crystals (52%). However, the trans product was contaminated with some cis product. The combined yield of the products was 89.9%. *cis*-**5h**: mp 95–97 °C; ^{1}H NMR (300 MHz, chloroform-*d*) δ 3.35–3.6 (m, 2 H), 4.45–4.58 (m, 1 H), 5.15 (s, 2 H), 5.1–5.25 (m, 1 H), 5.27 (s, 2 H), 5.73–5.87 (br d, 1 H), 7.3–7.45 (2 s, 10 H); IR 1818, 1790, 1725 cm^{-1}. Anal. Calcd for $C_{20}H_{19}BrN_2O_6$: C, 51.85; H, 4.13; N, 6.05. Found: C, 51.66; H, 4.17; N, 6.16.

Acylation of Hydroxamic Acid 4d with Acetyl Chloride To Form 4i. Hydroxamic acid **4d** (0.70 g, 2.8 mmol, 100 mol %) was dissolved in dry THF (28 mL, 0.1 M), and the solution was cooled to 0 °C. Pyridine (0.24 mL, 2.94 mmol, 105 mol %) was added followed by acetyl chloride (0.21 mL, 2.94 mmol, 105 mol %) 5 min later. A white precipitate formed immediately. After being stirred for 10 min, the reaction mixture was transferred to a separatory funnel with 150 mL of ether, washed successively with 30 mL each of water, 0.5 M HCl, and brine, and dried over $MgSO_4$. Filtration, followed by removal of the solvent under aspirator pressure, yielded product **4i** as a white solid of almost pure product. An analytically pure sample was obtained by crystallization from MeOH/ether/hexanes (white needle-shaped crystals, 86% yield): mp 119–122 °C ^{1}H NMR (300 MHz, chloroform-*d*/TMS) δ 2.182 (s, 3 H) (s, 3 H), 4.88–5.03 (br, 1 H), 5.10 (s, 2 H), 5.28–5.5 [dd, 2 H, *J* = 17.1 (trans), 10.2 (cis) Hz], 5.75–5.85 (br d, 1 H), 5.83 (br d, 1 H), 5.83–6.0 (m, 1 H), 7.33 (s, 5 H); IR ($CDCl_3$) 3275, 3200, 1720–1685 cm^{-1} (br, overlapping carbonyls). Anal. Calcd for $C_{14}H_{16}N_2O_5$: C, 57.53; H, 5.52; N, 9.58. Found: C, 57.53; H, 5.59; N, 9.63.

Oxidative Cyclization of *O*-Acetyl *N*-Carbobenzyloxy-L-vinylglycinehydroxamate (4i). The hydroxamate derivative (**4i**; 0.2 g, 0.68 mmol, 100 mol %) was dissolved in 30 mL of MeCN at room temperature. Potassium carbonate (0.999 g, 0.72 mmol, 105 mol %) followed by water (6.8 mL) was added, and the mixture was vigorously stirred for 1 min. A solution of bromine (38.6 μL, 0.75 mmol) in MeCN (4 mL) was added to the reaction mixture over a period of 3 min (vigorous stirring was maintained throughout the reaction). After 1 min more of stirring, the reaction mixture was transferred to a separatory funnel with 100 mL of ether. The ethereal layer was washed successively with 25 mL each of water, 10% aqueous sodium thiosulfate, and brine, dried over $MgSO_4$, and filtered. Removal of solvents yielded a white solid residue (0.20 g), which was a mixture of cis and trans products (64:36 as determined from the crude NMR spectrum). The cis product (94 mg) was obtained in almost pure form by a single crystallization from acetone/$CHCl_3$/hexanes: mp 161.5–163.5 °C dec; ^{1}H NMR (300 MHz, acetone-d_6/TMS) δ 2.2 (s, 3 H), 3.5–3.8 (ddd, 2 H, *J* = 10.5, 7.5, 6.3 Hz), 4.48–4.6 (br q, *J* = 6.3, 7.5, *5.4* Hz), 5.140 (s, 2 H), 5.25–5.33 (dd, 1 H, *J* = *5.4*, 9.45 Hz), 7.23–7.35 (m, 5 H).

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Stereospecific Total Synthesis of 9-Aminoanthracyclines: (+)-9-Amino-9-deoxydaunomycin and Related Compounds

Kikuo Ishizumi,* Naohito Ohashi, and Norihiko Tanno

Research Laboratories, Research and Development Division, Sumitomo Pharmaceuticals Company, Ltd., Konohana, Osaka, Japan

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9-Amino-9-deoxydaunomycin and related compounds, in which the hydroxyl group at the 9-position of daunomycin is replaced by an amino group, have been synthesized. Asymmetry was introduced into the synthetic sequence for the AB synthon by resolution of the intermediate amino ester or acetamido acid to afford (*R*)-(−)-2-acetyl-2-acetamido-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene, which was converted to the tetracyclic amido ketones by Friedel–Crafts acylation with phthalic anhydride or its 3-methoxy derivative. The resulting regioisomers 4- and 1-methoxy compounds were separated, after methylation and selective demethylation, by crystallization and preparative TLC. The required introduction of the C7-hydroxyl function proceeded stereospecifically via a three-step reaction sequence involving formation of an oxazine compound. The silver trifluoromethane assisted glycosidation of the resulting aglycons with 2-deoxy-3,4-di-*O*-acetyl-D-*erythro*-pentopyranosyl bromide or *N*,*O*-bis(trifluoroacetyl)daunosaminyl chloride, followed by alkaline hydrolysis afforded the target glycosides. The work reported herein comprises an efficient, practical synthesis of 9-amino-9-deoxydaunomycin and its analogues with the same stereochemistry as in the naturally occurring anthracyclines.

The clinically important antitumor antibiotics daunomycin (**1**) and adriamycin (**2**) are believed to exert their primary effect by blocking DNA function by means of drug–DNA binding intercalations.[1] Recent X-ray crystallographic study of daunomycin intercalated into a self-complementary DNA fragment has pointed out that the C9-OH in ring A interacts through hydrogen bonding with the DNA base pairs and provides an anchoring function. It was suggested that modifications of the anchor function may change the manner in which the anthracycline interacts with the DNA and thereby change its activity against different types of tumors.[2] Here, we report a practical total synthesis of the new anthracyclines 9-amino-9-deoxydaunomycin (**3**) and related compounds in which the hydroxyl group at the 9-position of daunomycin (**1**) is replaced by an amino group.

Our synthetic plan leading to the aglycons is shown in Scheme I and is analogous to Wong's scheme for the synthesis of daunomycinone.[3]

(1) Neidle, S. *Topics in Antibiotic Chemistry*; Sammes, P. G., Ed.; Halsted: New York, 1978; Vol. 2.

(2) Quiglry, G. J.; Wang, A.; Ughetto, G.; van der Marel, G.; van Boom, J.; Rich, A. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 7204.

(3) Wong, C. M.; Schwenk, R.; Popien, D.; Ho, T.-L. *Can. J. Chem.* **1973**, *51*, 466.

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