α-Alkylidene β-Lactams. 2. A Formal Synthesis of (±)-Carpetimycin A

John D. Buynak* and M. Narayana Rao

Department of Chemistry, Southern Methodist University, Dallas, Texas 75275

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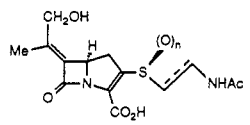
A new approach to the synthesis of the carbapenem antibiotics is described. A formal total synthesis of (±)-carpetimycin A has been accomplished. The key reaction is the addition of chlorosulfonyl isocyanate to an allenyl sulfide to produce a 3-alkylideneazetidin-2-one. The allenyl sulfide is prepared via reduction of an allenyl sulfoxide with NaI/TFAA/Et_3N. The alkylidene side chain is converted to an hydroxyalkyl group by treatment with hypobromous acid followed by reduction with $(n\text{-Bu})_3SnH$. Thus, both allenyl sulfides and α-alkylidene β-lactams are shown to be accessible and useful synthetic intermediates.

We recently undertook[1] a reinvestigation of the reaction of chlorosulfonyl isocyanate (CSI) with allenes[2] in order to explore methods for the production of synthetically useful α-alkylidene β-lactams. These ideas were spurred by recent advances in allene chemistry[3] and the discovery of the α-alkylidene β-lactam structural unit in several potent β-lactamase inhibitors, such as the asparenomycins[4] (1), Ro15-1903[5] (2), and 6-[(Z)-methoxymethylene]-penicillanic acid[6] (3). In particular, we were interested



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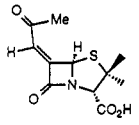

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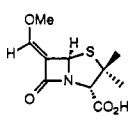

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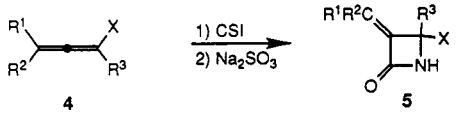
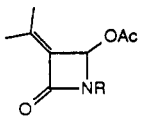
in the addition of CSI to heterosubstituted allenes of type 4, where X is oxygen or sulfur, to produce β-lactams 5 which we felt might be synthetically versatile precursors to a number of antibiotics. In an earlier work,[7] we ob-



4 5

served that the addition of CSI to 1-acetoxy-3-methylbuta-1,2-diene (generated by treatment of 3-acetoxy-3-methylbut-1-yn-3-ol with silver perchlorate) produced the versatile β-lactam 6, which we used to complete a formal total synthesis of (±)-asparenomycin C. The practical



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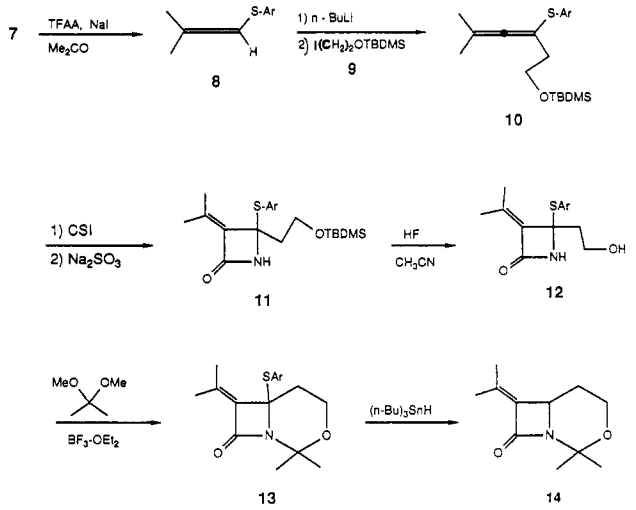
a) R = H
b) R = TBDMS

Scheme I



utility of this method, however, was limited by two factors: (1) Not surprisingly,[8] the CSI addition proceeded in low yield (23%, albeit from readily available materials). (2) The silver-catalyzed rearrangement of propargylic acetates to allenyl acetates is not a general reaction and works well only when the propargyl acetate is both a tertiary acetate and a terminal acetylene.[9] This severely restricts the number of allenyl acetates available for CSI addition and the types of side chain which can be introduced. We thus sought other allenes that might perform the same function but having a preparation that is less sensitive to small structural changes and that are capable of adding CSI in better yield.

If such allenes could be found, our second goal was to develop the chemistry of these α-alkylidene β-lactams. Typically, this functional unit is produced by elimination[10] or by olefination (both Wittig[11] and Peterson[6b,12]). Since our methodology produced this subunit early in the sequence, we were intrigued by the possibility of using the unsaturation to generate other side chains, in particular

(1) Buynak, J. D.; Pajouhesh, H.; Lively, D. L.; Ramalakshmi, Y. *J. Chem. Soc., Chem. Commun.* **1984**, 948.

(2) (a) Moriconi, E. J.; Kelly, J. F. *J. Am. Chem. Soc.* **1966**, *88*, 3657. (b) Moriconi, E. J.; Kelly, J. F. *J. Org. Chem.* **1968**, *33*, 3036.

(3) For reviews, see: (a) Pasto, D. J. *Tetrahedron* **1984**, 40, 2805. (b) Schuster, H. F.; Coppola, G. M. *Allenes in Organic Synthesis*; Wiley: New York, 1984. (c) *The Chemistry of the Allenes* Landor, S. R., Ed.; Academic: New York, 1982; Vol. 1-3. (d) *The Chemistry of Ketenes, Allenes, and Related Compounds*; Patai, S., Ed.,; Wiley: New York, 1980; Parts 1, 2.

(4) (a) Kawamura, Y.; Yasoda, Y.; Mayam, M.; Tanaka, K. *J. Antibiot.* **1982**, *35*, 10. (b) Shoji, J.; Hinoo, H.; Sakazaki, R.; Tsuji, N.; Nagashima, K.; Matsumoto, K.; Takahashi, Y.; Kozuki, S.; Hattori, T.; Kondo, E.; Tanaka, K. *J. Antibiot.* **1982**, *35*, 15. (c) Tsuji, N.; Nagashima, K.; Kobayshi, M.; Soji, J.; Kato, T.; Terui, Y.; Nakai, H.; Shiro, M. *J. Antibiot.* **1982**, *35*, 24. (d) Mukakami, K.; Doi, M.; Yoshida, T. *J. Antibiot.* **1982**, *35*, 39.

(5) Arisawa, M.; Then, R. L. *J. Antibiot.* **1982**, *35*, 1578.

(6) (a) Brenner, D. G.; Knowles, J. R. *Biochemistry* **1984**, *23*, 5839. (b) Brenner, D. G. *J. Org. Chem.* **1985**, *50*, 18.

(7) Buynak, J. D.; Rao, M. N.; Pajouhesh, H.; Chandrasekaran, R. K.; Finn, K.; de Meester, P.; Chu, S. C. *J. Org. Chem.* **1985**, *50*, 4245. (Part I of this series.)

(8) For example, the addition of CSI to vinyl acetate proceeds in 40% yield: Clauss, K.; Grimm, D.; Prossel, G. *Justus Liebigs Ann. Chem.* **1974**, 539.

(9) For studies of this reaction, see: (a) Saucy, G.; Marbet, R.; Lindlar, H.; Isler, O. *Helv. Chim. Acta* **1959**, *42*, 1945. (b) Schlossarczyk, H.; Sieber, W.; Hesse, M.; Hansen, H. J.; Schmid, H. *Helv. Chim. Acta* **1973**, *56*, 875. (c) Ramakrishan, V. T.; Narayanan, K. V.; Swaminatham, S. *Chem. Ind. (London)* **1976**, 2082. (d) Cookson, R. C.; Cramp, M. C.; Parsons, P. J. *J. Chem. Soc., Chem. Commun.* **1980**, 197. (e) Oelberg, D. G.; Schiavelli, M. D. *J. Org. Chem.* **1977**, *42*, 1804.

(10) (a) Corbett, D. F.; Eglington, A. J.; Howarth, T. T. *J. Chem. Soc., Chem. Commun.* **1977**, 953. (b) Albers-Schonberg, G.; Arison, B. H.; Hensens, O. D.; Hirshfield, J.; Hoogsteen, K.; Kaczka, E. A.; Rhodes, R. E.; Kahan, J. S.; Kahan, F. M.; Ratcliffe, R. W.; Walton, E.; Ruswinkle, L. J.; Morin, R. B.; Christensen, B. G. *J. Am. Chem. Soc.* **1978**, *100*, 6491.

(11) Sheehan, J. C.; Lo, Y. S. *J. Org. Chem.* **1973**, *38*, 3227.

(12) Okano, K.; Kyotani, Y.; Ishihama, H.; Kobayashi, S.; Ohno, M. *J. Am. Chem. Soc.* **1983**, *105*, 7186.

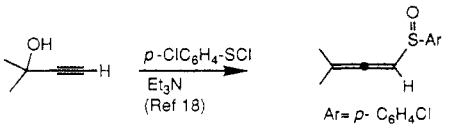
0022-3263/86/1951-1571$01.50/0

the hydroxylalkyl side chains common to many of the carbapenem antibiotics.

Results and Discussion

We envisioned that allenyl sulfides might prove to be suitable substitutes for allenyl acetates. Early work[13] had shown that some vinyl sulfides were capable of undergoing CSI addition to produce 4-(arylthio)azetidin-2-ones. Allenyl sulfides had been prepared by the base-catalyzed isomerization of propargyl thioethers,[14] by direct addition of phenylthiocopper trimethylphosphite complex to propargyl halides,[15] and by reduction of allenyl sulfoxides with P_2S_5.[16]

We favored the last procedure because of the ready availability of starting materials and the ease of handling the reagents. Thus treatment of 3-methylbut-1-yn-3-ol with *p*-chlorobenzenesulfenyl chloride[17] in the presence of triethylamine, according to the procedure of Horner,[18] produced allenyl sulfoxide **7** in 73% yield. Unfortunately,



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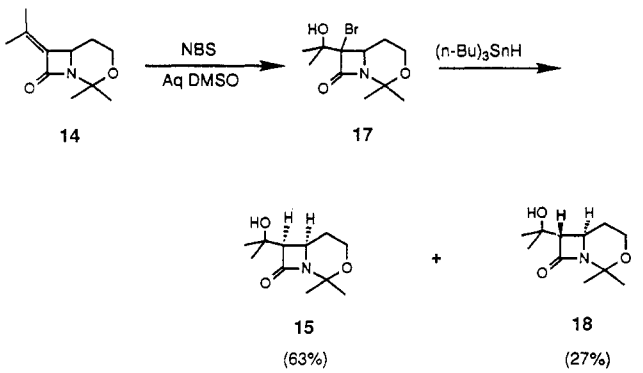
treatment of this compound with P_2S_5 and other reducing agents failed to give good yields of the desired allenyl sulfides. Reasoning that the allenyl sulfoxides, or the corresponding sulfides, might be unstable to the harsh conditions sometimes employed in these reactions, we modified the reducing medium of Oae[19] by adding triethylamine and performed the reaction at low temperature. These conditions cleanly produced allenyl sulfide **8** in 98% yield (Scheme I). Unfortunately, CSI addition to this compound gave, at best, a disappointing yield of 20%.

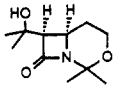
Since Moriconi[2] had obtained his best yields with tetraalkyl allenes, we wondered if replacing the hydrogen α to sulfur with an alkyl substituent would also improve our yields. Indeed, an alkyl substituent at this site (to become the 4-position of the 2-azetidinone) was required in the natural product, and placement at this stage of the synthesis might avoid a second, sometimes difficult, substitution reaction on the β-lactam. Cookson[16] and Bridges[20] have investigated the lithiation and subsequent electrophilic substitution of allenyl sulfides. The proton α to sulfur is, in most cases, readily removed and reaction with alkyl halides and carbonyl compounds proceeds in reasonable yield.

Gratifyingly, when sulfide **8** was treated with *n*-BuLi and then with iodo ether **9**, the alkylated allenyl sulfide **10** was obtained in 82% yield. Subsequent treatment with CSI, followed by reductive workup, produced β-lactam **11** in 66% yield. Earlier, we had observed that 4-acetoxy-3-(1-methylethylidene)azetidin-2-one (**6a**) was unstable to column chromatography as the free NH compound and had to be protected as the NTBDMS compound, **6b**, before such purification was possible. Sulfide **10**, however, survived column chromatography (SiO_2) nicely. In fact, we were unable to prepare the NTBDMS derivative of **11**, possibly due to steric hindrance. We thus decided to remove the protecting group from the oxygen thereby producing the relatively insoluble alcohol **12**, and protecting as the acetonide **13** (69% overall). Attempted removal of the thioaryl group with Raney nickel gave low and variable yields of bicyclic β-lactam **14**. A useful alternative was to treat **13** with tributyltin hydride in the presence of AIBN to produce **14** in quantitative yield. We have since prepared several β-lactams of this type and briefly explored their reactivity.[21]

Scheme II



We felt **14** would be the ideal compound with which to explore the reactivity of the α-alkylidene side chain. A closely related molecule, **15**, had been prepared [22] and used in a total synthesis of (±)-carpetimycin A (C-19393 H_2)[23] (**19**) (a highly potent, broad-spectrum antibiotic with β-lactamase inhibitory activity). In these cases, however,



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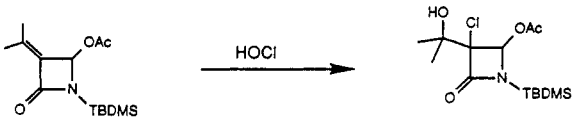
the hydroxyalkyl side chain had been generated by aldol condensation. Earlier, we had shown[7] that the α-alkylidene β-lactam **6b** could be transformed to chlorohydrin **16** (stereochemistry undetermined) on treatment with hypochlorous acid.[24,25] We assumed that if the highly sensitive



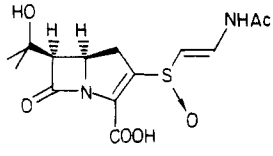
6b 16

4-acetoxy compound could undergo such a transformation, then the relatively stable **14** would certainly follow suit.

(13) Hirai, K.; Mutsuda, H.; Kishida, Y. *Chem. Pharm. Bull.* **1973**, *21*, 1090.
(14) Brandsma, L.; Wijers, H. E.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1963**, *82*, 1040.
(15) Bridges, A. J. *Tetrahedron Lett.* **1980**, *21*, 4401.
(16) Cookson, R. C.; Parsons, P. J. *J. Chem. Soc., Chem. Commun.* **1978**, 822.
(17) Harpp, D. N.; Friedlander, B. T.; Smith, R. A. *Synthesis* **1979**, 181.
(18) Horner, L.; Binder, V. *Justus Liebigs Ann. Chem.* **1972**, *757*, 33.
(19) Drabowicz, J.; Oae, S. *Synthesis* **1977**, 404.
(20) (a) Bridges, A. J.; Thomas, R. D. *J. Chem. Soc., Chem. Commun.* **1984**, 694. (b) Bridges, A. J.; Fedij, V.; Turowski, E. C. *J. Chem. Soc., Chem. Commun.* **1983**, 1093. (c) Bridges, A. J.; Thomas, R. D. *J. Chem. Soc., Chem. Commun.* **1983**, 485.
(21) Buynak, J. D.; Rao, M. N.; Chandrasekaran, R. Y.; Haley, E.; de Meester, P.; Chu, S. C. *Tetrahedron Lett.* **1985**, *26*, 5001.
(22) (a) Natsugari, H.; Matsushita, V.; Tamura, N.; Yoshioka, K.; Ochiai, M. *J. Chem. Soc., Perkin Trans. 1* **1983**, 403. (b) Aratani, M.; Hirai, H.; Sawada, K.; Yamada, A.; Hashimoto, M. *Tetrahedron Lett.* **1985**, 223.
(23) (a) Nakayama, M.; Iwasaki, A.; Kimura, S.; Mizoguchi, T.; Tanabe, S.; Murakami, A.; Wutanabe, I.; Okuchi, M.; Ito, H.; Saino, Y.; Kobayashi, F.; Mori, T. *J. Antibiot.* **1980**, *33*, 1338. (b) Imada, A.; Nozaki, Y.; Kintaka, K.; Okonogi, K.; Kitano, K.; Harada, S. *J. Antibiot.* **1980**, *33*, 1417. (c) Harada, S.; Shinagawa, S.; Nozaki, Y.; Asai, M.; Kishi, T. *J. Antibiot.* **1980**, *33*, 1425.
(24) Hegde, S. G.; Wolinsky, J. *Tetrahedron Lett.* **1981**, *22*, 5019.
(25) For a related example of electrophilic addition to an α,β-unsaturated carbonyl, see: Gouzoules, F. H.; Whitney, R. A. *Tetrahedron Lett.* **1985**, *26*, 3441.

However, treatment of **14** with hypochlorous acid under identical conditions produced a mixture of products which, when analyzed by ^1H NMR, completely lacked the relatively high-field methyl absorptions characteristic of the saturated chlorohydrin. After careful consideration of this result, we reasoned that the acetate **6b** might be capable of intramolecular stabilization of the incipient carbocation, thus providing a longer lived intermediate for nucleophilic capture. Without such stabilization, the cation might be vulnerable to other modes of decomposition. Wolinsky,[24] for example, has shown that addition of 1 equiv of hypochlorous acid to α,β-unsaturated ketones produces α-chloro-β,γ-unsaturated ketones. A possible alternative would be to use the softer electrophile Br^+ in a solvent which can, itself, help stabilize the carbocation. Indeed, treatment of **14** with NBS in wet Me_2SO[26] provided bromohydrins **17** in 60% yield (Scheme II). This material appears to be predominantly a single isomer by ^{13}C NMR, but no attempt was made to identify its stereochemistry.

Completion of the formal synthesis was effected by tributyltin hydride reduction of bromohydrin **17** to provide α-hydroxyalkyl β-lactams **15** and **18** in 63% and 27% yields, respectively. These materials were readily separated by column chromatography. As noted previously,[22] the bulky tin hydride prefers addition from the least hindered side of the radical to produce predominantly the required cis disubstituted compound. **15** was identical (NMR, TLC, IR) with a sample provided by Dr. Hashimoto, and its NMR spectra were identical with the NMR spectra provided by Dr. Natsugari.



19(*R*)-Sulfoxide

Conclusion

Allenyl sulfides are useful substitutes for allenyl acetates in the production of α-alkylidene-β-lactams via CSI addition. In these materials, the thioaryl group performs several key functions. In the form of sulfenate, it is responsible for formation of the allene itself. It activates the allene toward lithiation, thereby facilitating the preparation of a more highly substituted compound. The CSI addition could not have proceeded under such mild conditions (−20 °C) and in such a regiospecific fashion without the activating and directing effects of sulfur. Finally, it proved to be readily removable in quantitative yield, thus providing access to the biologically important ring systems.

Allenyl sulfoxides (from which the allenyl sulfides used in the present study were obtained) have found important uses in the synthesis of other natural products.[27] They are easily prepared via 2,3-sigmatropic rearrangement (which occurs below room temperature and without catalyst) of the corresponding propargylic sulfenates. This reaction can be made to occur in good to excellent yield with a wide variety of substitution patterns[18,28] (unlike the preparation of allenyl acetates). Although the CSI addition only proceeds well with tetrasubstituted allenes, the allenyl sulfides can be easily lithiated and alkylated, potentially allowing a wide variety of substitution patterns.

This work complements existing methodology by providing an additional method for the introduction of the α-hydroxyalkyl side chain, common to a number of β-lactamase inhibitors. It also provides an additional way to develop the second (non-β-lactam) portion of the bicyclic system which does not involve nucleophilic displacement on a 4-acetoxy-2-azetidinone or a preexisting bond at the 4-position. Since this substituent is put on by electrophilic substitution of the lithiated allene, this process constitutes a reversal in polarity with respect to acetate substitution and should be amenable to the preparation of a wide range of structures.

Experimental Section

Melting points were determined in open capillaries with a Mel-Temp Laboratory Devices apparatus and are uncorrected. NMR spectra were recorded on an IBM/Bruker WP-200SY instrument. Infrared spectra were recorded on a Perkin-Elmer Model 283 infrared spectrometer. Elemental analyses were carried out by Canadian Microanalytical Service Ltd. (Vancouver, B.C.). CH_2Cl_2, CH_3CN, Me_2SO, toluene, Et_3N, and THF were distilled from CaH_2. Acetone was purified by treatment with $CaSO_4$ and fractional distillation. 3-Methylbut-1-yn-3-ol, chlorosulfonyl isocyanate, $BF_3{\cdot}OEt_2$, NaI, and trifluoroacetic anhydride were purchased from Aldrich Chemical Co. and used without further purification. *p*-Chlorobenzenesulfenyl chloride was prepared by the published procedure[17] and stored at −20 °C. ICH_2CH_2OSi-*t*-$BuMe_2$ was prepared according to the method of Nicolaou.[29] $(n\text{-}Bu)_3SnH$ was prepared from $[(n\text{-}Bu)_3Sn]_2O$ according to the published procedure[30] and stored in a darkened descicator under argon at −20 °C. Flash chromatography was performed with silica gel 60 (230–440 mesh) purchased from Merck.

1-[(4-Chlorophenyl)sulfinyl]-3-methylbuta-1,2-diene (7). **7** was prepared from 3-methylbut-1-yn-3-ol according to the method of Horner.[18] Purification was accomplished by flash chromatography (SiO_2, CH_2Cl_2) to obtain **7** in 75% yield as a white solid (mp 61–63 °C): IR ($CHCl_3$) 2990, 2950, 2920, 1955, 1540, 1470, 1090, 1075, 1040, 1010, 840, 495 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.75 (d, J = 3 Hz, 3 H), 1.79 (d, J = 3 Hz, 3 H), 5.80 (sep, J = 3 Hz, 1 H), 7.30, 7.40, 7.44, 7.54 (AB q, J = 9 Hz, 4 H).

1-[(4-Chlorophenyl)thio]-3-methylbuta-1,2-diene (8). A solution of **7** (15.0 g, 66 mmol), triethylamine (41.7 mL, 300 mmol), anhydrous sodium iodide (25.4 g, 170 mmol), and 360 mL of dry acetone in a 1000-mL three-necked flask equipped with overhead stirrer was chilled to −55 °C. Trifluoroacetic anhydride (25.9 mL, 183 mmol) was then added over the course of 4 min. The bath temperature was gradually allowed to rise to −30 °C over the course of 15 min, and then the cold reaction mixture was poured into a two-phase system consisting of 300 mL of hexane, 200 mL of 5% Na_2SO_3, and 200 mL of 5% $NaHCO_3$. The separatory funnel was shaken vigorously for 2 full min, the layers were separated, and the aqueous layer was extracted twice more with hexane. The combined hexane layers were washed with water (3×) and brine (1×) and dried over Na_2SO_4. The solution was concentrated and immediately purified by flash chromatography (SiO_2, hexane) to yield 13.6 g (98%) pure **8**: IR (film) 2980, 2940, 2910, 2860, 1470, 1450, 1380, 1365, 1190, 1095, 1010, 815 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.62 (d, J = 3 Hz, 6 H), 5.80 (sep, J = 3 Hz, 1 H), 7.30 (br s, 4 H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 20.2, 83.7, 101.0, 128.8, 130.4, 132.1, 134.8, 203.2.

1-[(*tert*-Butyldimethylsilyl)oxy]-3-[(4-chlorophenyl)thio]-5-methylhexa-3,4-diene (10). *n*-Butyllithium (9.48 mL, 2.5 M, 23.7 mmol) was added dropwise to a solution of **8** (5.00 g, 23.7 mmol) in 100 mL dry THF while cooling to −78 °C. The reaction was stirred at this temperature for an additional 0.5 h and then 1-[(*tert*-butyldimethylsilyl)oxy]-2-iodoethane (6.80 g, 23.7 mmol) was added dropwise. The reaction was stirred at −78 °C for 10 min and then at 0 °C for 30 min. The reaction mixture

(26) Dalton, D. R.; Dutta, V. P.; Jones, D. C. *J. Am. Chem. Soc.* **1968**, *90*, 5498.
(27) For leading references, see: (a) Okamura, W. H.; Peter, R.; Reischl, W. *J. Am. Chem. Soc.* **1985**, *107*, 1034. (b) Okamura, W. H. *Acc. Chem. Res.* **1983**, *16*, 81.
(28) Cutting, I.; Parsons, P. J. *Tetrahedron Lett.* **1983**, *24*, 4463.
(29) Nicolaou, K. C.; Papahatjis, D. P.; Claremon, D. A.; Magolda, R. L.; Dolle, R. E. *J. Org. Chem.* **1985**, *50*, 1440. (See ref 9 of this article.)
(30) (a) Considine, W. J.; Ventura, J. J. *Chem. Ind. (London)* **1962**, 1683. (b) Kuivila, H. G. *Synthesis* **1970**, 499.

was then poured into water and extracted with ether (3×), and the ether layers were washed with water (3×) and dried (Na_2SO_4). Concentration and purification by flash chromatography produced 7.20 g (82%) of **10**: IR (film) 2950, 2920, 2855, 1470, 1255, 1100, 835, 770 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.08 (s, 6 H), 0.92 (s, 9 H), 1.68 (s, 6 H), 2.39 (t, J = 7 Hz, 2 H), 3.77 (t, J = 7 Hz, 2 H), 7.23, 7.28, 7.31, 7.36 (AB q, J = 9 Hz, 4 H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ -5.3, 18.3, 20.4, 25.9, 37.5, 61.5, 95.0, 99.1, 128.8, 131.9, 132.5, 134.1, 202.4. Anal. Calcd for $C_{19}H_{29}ClOSSi$: C, 61.83; H, 7.94. Found: C, 61.83; H, 7.88.

4-[2-((*tert*-Butyldimethylsilyl)oxy)ethyl]-4-[(4-chlorophenyl)thio]-3-(1-methylethylidene)azetidin-2-one (11). Chlorosulfonyl isocyanate (1.69 mL, 19.4 mmol) was added dropwise to a precooled (-40 °C) solution of **10** (6.80 g, 18.4 mmol) in 25 mL of anhydrous ether. The reaction was stirred at this temperature for 10 min and then at -20 °C for an additional 10 min. Then the reaction was transferred by cannula to a chilled (0 °C), rapidly stirred, two-phase system consisting of Na_2SO_3 (7.0 g, 55.5 mmol), K_2HPO_4 (17.5 g, 100 mmol), 70 mL of H_2O, and 70 mL of ether. This solution was stirred at 0 °C for 10 min and then at 23 °C for 2 h. The layers were then separated, the aqueous phase was reextracted, and the combined ether layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by flash chromatography (5% EtOAc in CH_2Cl_2, SiO_2) yielded 5.01 g (66%) of **11**: mp 54–55 °C; IR ($CHCl_3$) 3420, 3000, 2960, 2940, 2860, 1747, 1472, 1260, 1095, 838 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.06 (s, 6 H), 0.89 (s, 9 H), 1.85 (s, 6 H), 2.24–2.31 (m, 2 H), 3.72–3.87 (m, 2 H), 7.03 (br s, 1 H), 7.21, 7.25, 7.31, 7.35 (AB q, J = 9 Hz); ^{13}C NMR ($CDCl_3$, 200 MHz) δ -5.53, 18.1, 19.4, 19.6, 25.8, 39.7, 59.6, 72.5, 128.3, 128.6, 135.6, 136.5, 137.5, 138.2, 163.2.

6-[(4-Chlorophenyl)thio]-2,2-dimethyl-7-(1-methylethylidene)-8-oxo-3-oxa-1-azabicyclo[4.2.0]octane (13). HF (48%, 0.43 mL) was added to a solution of **11** (4.30 g, 10.44 mmol) and 4 mL of H_2O in 76 mL of CH_3CN. The reaction was allowed to stir at room temperature for 50 min, then poured into 5% $NaHCO_3$, and extracted with CH_2Cl_2 (3×). The combined CH_2Cl_2 layers were dried (Na_2SO_4) and concentrated in vacuo to yield 2.53 g (81%) of a somewhat insoluble white solid (**12**) which was not further characterized. To a slurry of crude **12** (2.53 g, 8.50 mmol) in 25 mL of dry CH_2Cl_2 was added 2,2-dimethoxypropane (2.09 mL, 17.0 mmol) and $BF_3{\cdot}OEt_2$ (0.11 mL, 0.89 mmol). The reaction was allowed to stir at room temperature for 45 min, then poured into 5% $NaHCO_3$, and extracted with ether (3×). The combined ether layers were washed with brine, dried (Na_2SO_4), concentrated, and purified by flash chromatography (CH_2Cl_2/SiO_2) to yield 2.42 g pure **13** (69% overall from **11**): mp 144–146 °C; IR ($CHCl_3$) 2980, 2940, 1735, 1275, 1060, 1015, 840, 800 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.61 (s, 6 H), 1.76 (s, 3 H), 1.77 (s, 3 H), 1.79–2.40 (m, 2 H), 3.80–3.86 (m, 1 H), 4.10–4.16 (m, 1 H), 7.25, 7.29, 7.34, 7.38 (AB q, J = 9 Hz, 4 H); ^{13}C NMR ($CDCl_3$, 200 MHz) 19.8 20.1, 24.8, 27.1, 34.6, 57.3, 70.7, 85.6, 128.9, 129.1, 135.5, 136.1, 138.1, 138.4, 195.1. Anal. Calcd for $C_{17}H_{20}ClNO_2S$: C, 60.43; H, 5.98; N, 4.15. Found: C, 60.58; H, 5.94; N, 4.13.

2,2-Dimethyl-7-(1-methylethylidene)-8-oxo-3-oxa-1-azabicyclo[4.2.0]octane (14). A solution of $(n\text{-}Bu)_3SnH$ (2.52 mL, 9.55 mmol) and azobisisobutyronitrile (0.16 g, 1.16 mmol) in 5 mL of toluene was added to a heated (95 °C) solution of **13** (1.58 g, 4.68 mmol) in 15 mL of toluene. The reaction mixture was kept between 95 and 100 °C for 40 min, then the solvent removed, and the crude product purified by flash chromatography (10% EtOAc/CH_2Cl_2) to yield 0.91 g (100%) pure **14**: mp 94–95 °C; IR ($CHCl_3$) 2980, 2940, 2920, 2870, 1740, 1440, 1370, 1330, 1305, 1255, 1215, 1165, 1065 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.44 (s, 3 H), 1.73 (s, 3 H), 1.79 (s, 3 H), 1.80–1.99 (m, 2 H), 2.03 (s, 3 H), 3.81 (d, J = 2 Hz, 1 H), 3.86 (t, J = 3 Hz, 1 H), 4.03 (d of d, J = 10 and 5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 19.5, 20.9, 23.2, 26.5, 29.5, 50.8, 58.2, 83.5, 135.7, 137.0, 161.3. Anal. Calcd for $C_{11}H_{17}NO_2$: C, 67.65; H, 8.79; N, 7.17. Found: C, 67.30; H, 8.75; N, 7.04.

7-Bromo-2,2-dimethyl-7-(1-hydroxy-1-methylethyl)-8-oxo-3-oxa-1-azabicyclo[4.2.0]octane (17). *N*-Bromosuccinimide (0.411 g, 2.31 mmol) was added to a solution of **14** (0.300 g, 1.54 mmol) and H_2O (0.11 mL, 6.11 mmol) in 5.0 mL of Me_2SO. The solution was allowed to stir at room temperature for 30 min and then poured into a two-phase system of water–ether. The aqueous phase was extracted (3×) with ether, and the combined ether layers were washed with water (2×) and brine (1×), dried (Na_2SO_4) and concentrated. Purification by flash chromatography (20% EtOAc in CH_2Cl_2, SiO_2) yielded 0.27 g (60%) of bromohydrin **17**, mp 108–110 °C. The bromohydrin appears to be predominantly a single diasteriomer by NMR, but no attempt was made to further purify it or identify its stereochemistry: IR ($CHCl_3$) 3580, 2980, 2930, 2870, 1750, 1570, 1055 cm^{-1}; ^1H NMR ($CDCl_3$), 200 MHz) δ 1.41 (s, 3 H), 1.45 (s, 3 H), 1.54 (s, 3 H), 1.74 (s, 3 H), 2.09–2.26 (m, 2 H), 2.19 (s, 1 H), 3.86–3.94 (m, 3 H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 22.5, 26.0, 26.3, 29.2, 51.6, 58.7, 62.4, 72.7, 78.8, 84.0, 160.7. Anal. Calcd for $C_{11}H_{18}BrNO_3$ C, 45.22; H, 6.21; N, 4.79. Found: C, 45.24; H, 6.24; N, 4.76.

Reduction of Bromohydrin 17. A solution of tributyltin hydride (0.29 mL, 1.10 mmol) and azobisisobutyronitrile (16 mg, 0.12 mmol) in 2 mL of toluene was added to a hot (95 °C) solution of bromohydrin **17** (0.160 g, 0.548 mmol) in 4 mL of toluene. The reaction was allowed to stir at this temperature for 40 min, then the solvent removed, and the product purified by flash chromatography (60% EtOAC/CH_2Cl_2). Small amounts of organotin impurities which still remained were removed by washing with pentane and, if necessary, a second column. This procedure produced **15** (63%), mp 125–126 °C, and **18** (27%), mp 103–104 °C, as white crystalline solids. Compound **15**: IR ($CHCl_3$) 3580, 2980, 2930, 2860, 1730, 1370, 1215, 1180, 805 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.29 (s, 3 H), 1.41 (s, 3 H), 1.49 (s, 3 H), 1.69 (d of d of t, J = 13, 5, 2 Hz, 1 H), 1.78 (s, 3 H), 1.96 (s, 1 H), 2.76 (d of t of d, J = 13, 11, 6 Hz, 1 H), 3.20 (d, J = 5 Hz, 1 H), 3.7–4.0 (m, 3 H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 22.4, 26.3, 26.8 27.9, 30.7, 48.4, 59.1, 62.8, 70.2, 83.2, 164.9. Anal. Calcd for $C_{11}H_{19}NO_3$: C, 61.93; H, 9.00; N, 6.57. Found: C, 61.17; H, 8.68; N, 6.43. Compound **18**: IR ($CHCl_3$) 3580, 2950, 2860, 1730, 1365, 1350, 1250, 1050 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.29 (s, 3 H), 1.38 (s, 3 H), 1.43 (s, 3 H), 1.76 (s, 3 H), 1.8–2.0 (m, 2 H), 2.10 (s, 1 H), 2.86 (d, J = 2 Hz, 1 H), 3.5–3.6 (m, 1 H), 3.8–3.9 (m, 2 H); ^{13}C NMR δ 22.6, 26.6, 26.7, 27.4, 28.0, 46.4, 58.9, 69.0, 69.2, 83.4. Anal. Calcd for $C_{11}H_{19}NO_3$: C, 61.93; H, 9.00; N, 6.57. Found: C, 61.25; H, 8.80; N, 6.37.

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