(d, 5-CH, J = 5.9 Hz, 1 H), 7.31 (s, Ph H, 5 H), 7.60 (s, py 6-H, 1 H); IR (neat) 1730, 1670, 1635, 1450, 1125 cm^{-1}; MS, m/e 631 (M^+, 0.4), 585 ($M^+ - CH_2OCH_3$, 1), 218 (100). Anal. Calcd for $C_{32}H_{45}H_3O_{10}$: C, 60.84; H, 7.18; N, 6.65. Found: C, 61.06; H, 7.05; N, 6.47.

3-Oxazolinylpyridine 30. As previously reported,[16] to a stirred solution of **10** (5 g, 19.7 mmol) in THF (50 mL) was added t-BuOK (2.43 g, 21.7 mmol), followed by MeI (2.92 g, 19.7 mmol) in THF (10 mL) at 25 °C. The mixture was stirred for 5 h, followed by evaporation in vacuo to give a residue, which was dissolved in CH_2Cl_2, washed with aqueous $NaHCO_3$ (10%), dried over anhydrous $MgSO_4$, evaporated in vacuo, and column chromatographed by eluting with EtOAc/C_6H_{12} to give (95%) **30** as an oil: 5.28 g; ^1H NMR δ 3.44 (s, OCH_3, 3 H), 3.67 (m, OCH_2, 2 H), 4.34 (m, 4-CH, 1 H), 5.52 (d, 5-CH, J = 7.0 Hz, 1 H), 7.30–7.44 (m, py 5-H, 1 H), 7.36 (s, Ph H, 5 H), 8.30 (ddd, py 4-H, $J_{4,5}$ = 7.8 Hz, $J_{4,2} = J_{4,6}$ = 2.0 Hz, 1 H), 8.73 (dd, py 6-H, $J_{6,5}$ = 4.6 Hz, $J_{6,4}$ = 2 Hz, 1 H), 9.24 (dd, py 2-H, $J_{2,4}$ = 2.0 Hz, $J_{2,5}$ = 1.4 Hz, 1 H).

Reduction of α,α,α-Trifluoroacetophenone (TFA) with *N*-Metallo-1,4-dihydropyridine 31. As described by Meyers,[14a] to a stirred solution of **30** (268 mg, 1.0 mmol) in THF (10 mL) was added MeMgBr (0.4 mL; 2.5 M in ether, 1.0 mmol), and the mixture was stirred an additional 30 min, to which a second equivalent of MeMgBr (0.40 mL; 2.5 M in ether, 1.0 mmol) was added. A solution TFA (2 equiv, 0.2 mmol) in THF (3 mL) was added in one portion at 0 °C, and then the mixture was slowly warmed to 55 °C. After 5 h, the H_2O (1 mL) was added. The mixture was concentrated in vacuo, dissolved in CH_2Cl_2 (20 mL), washed with aqueous $NaHCO_3$ (10%, 10mL), dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo to give a residue, which was column chromatographed (Al_2O_3) by eluting with EtOAc/C_6H_{12} (1:1) to give two major fractions:

Fraction A was a mixture of two components which were separated (ThLC, C_6H_6) to give **32** (93% with respect to **30**) as an oil: 164 mg; bp 93 °C (15 mm) [lit.[31] bp 99–105 °C (17 mm); $[\alpha]^{20}_D$ +13.4° (c 0.91, C_6H_6)]; ^1H NMR δ 2.45 (br s, OH, 1 H), 4.93 (q, CH, $J_{H,F}$ = 6.8 Hz, 1 H), 7.25–7.50 (m, Ph H, 5 H). Alcohol **32** was analyzed by polarimetry:[30] $[\alpha]^{25}_D$ +1.39° (c 1.80, C_6H_6), corresponding to an enantiomeric bias of 54.5:45.5 S/R (% ee = 10.4). The second component was **34**: ^1H NMR δ 1.79 (q, CH_3, $J_{H,F}$ = 1.5 Hz, 3 H), 2.71 (br s, OH), 7.4–7.6 (m, Ph H, 5 H).

Fraction B gave (95%) the 4-methylpyridine **33**[16] as an oil: 268 mg; ^1H NMR δ 2.62 (s, py CH_3, 3 H), 3.42 (s, OCH_3, 3 H), 3.68 (m, OCH_2, 2 H), 4.30 (m, 4-CH, 1 H), 5.48 (d, 5-CH, J = 6.4 Hz, 1 H), 7.16 (d, py 5-H, J = 5.0 Hz, 1 H), 8.91 (d, py 6-H, J = 5.0 Hz, 1 H), 8.98 (s, py 2-H, 1 H).

Reduction of α,α,α-Trifluoroacetophenone with the Lariat 26. To a portion of the THF solution of **26**, described above (16 mL; ~0.475 mmol of **26**), was added TFA (0.86 mmol) in THF (2 mL) in one portion. The reaction was allowed to proceed as above (with **31**), and after standard workup, alcohol **32** (74 mg, ~49%) was recovered along with **34** (243 mg, 1.28 mmol) and lariat **28** (125 mg, ~26% yield). Purified alcohol **32**, as above, was analyzed by polarimetry: $[\alpha]^{25}_D$ +0.67° (c 1.54, C_6H_6), corresponding to an enantiomeric bias of only 52.5:47.5 S/R (% ee = 5).

Reduction of 24b with $LiAlH_4$. To a stirred solution of **24b** (100 mg, 0.18 mmol) in THF at 25 °C was added $LiAlH_4$ (100 mg). The solution was warmed to 60–65 °C and then stirred an additional 24 h. A H_2O/THF (50:50, 10 mL) mixture was added, and then the THF was evaporated in vacuo. The residue was treated with aqueous $NaHCO_3$ (10%, 20 mL), extracted with CH_2Cl_2, dried over anhydrous $MgSO_4$, concentrated in vacuo, and chromatographed (ThLC) by eluting with $CHCl_3$/EtOH (1:1) to give the desired product **22b** (5 mg, 5%), unchanged **24b** (25 mg, 26%), and numerous unidentified decomposition products.

Acknowledgment. We acknowledge the partial support by the National Institutes of Health and the National Science Foundation for funds to purchase our NMR spectrometer and the timely comments of Professor George W. Gokel.

(31) (a) Jurczak, J.; Konowal, A.; Krawczyk, Z. *Synthesis* **1977**, 258. (b) Peters, H. M.; Feigl, D. M.; Mosher, H. S. *J. Org. Chem.* **1968**, *33*, 4245.

Useful Chemistry of 3-(1-Methylethylidene)-4-acetoxy-2-azetidinone: A Formal Synthesis of (±)-Asparenomycin C

John D. Buynak,* M. Narayana Rao, Hassan Pajouhesh, Ramalakshmi Yegna Chandrasekaran, and Kenneth Finn

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

Patrice de Meester and Shirley C. Chu

Department of Electrical Engineering, Southern Methodist University, Dallas, Texas 75275

Received April 23, 1985

3-(1-Methylethylidene)-4-acetoxy-2-azetidinone (**5**) was prepared from the addition of chlorosulfonyl isocyanate to 1-acetoxy-3-methylbuta-1,2-diene. Isolated as a stable crystalline solid, this material is a versatile intermediate and is used in a formal synthesis of (±)-asparenomycin C. The double bond can participate in a number of useful reactions including allylic halogenation, hydrogenation, and addition of hypochlorous acid. The 4-acetate can be easily substituted by oxygen, sulfur, and carbon nucleophiles. 3-Alkylidene-4-(phenylthio)-2-azetidinones are easily reduced by $(n\text{-Bu})_3SnH$ in the presence of AIBN.

Some strains of bacteria can defend themselves from conventional β-lactam antibiotics through the use of a defensive enzyme known as β-lactamase.[1] There are, in fact, several types of β-lactamase,[2] and much work has lately focused on determining the mechanism of action of these enzymes as well as on developing effective β-lactamase inhibitors.[3] While clavulanic acid and thienamycin

(1) For a review of β-lactamases, see: Sykes, R. B.; Bush, K. In "Chemistry and Biology of β-Lactam Antibiotics"; Morin, R. B., Gorman, M., Eds.; Academic Press: New York, 1982; Vol. 3.

(2) For a leading reference, see: Knott-Hunziker, V.; Petursson, S.; Waley, S. G.; Jaurin, B.; Grundstrom, T. *Biochem. J.* **1982**, *207*, 315.

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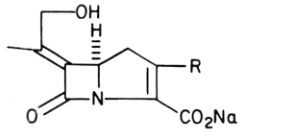
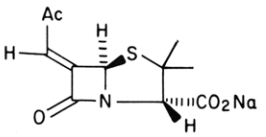
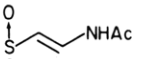
are the best known inhibitors, several extremely active compounds possess an α-alkylidene side chain on the β-lactam unit. Included in this class, sometimes called the "ene-type" β-lactam antibiotics, are the asparenomycins[4] (1), Ro 15-1903[5] (2), and 6-[(*Z*)-methoxymethylene]-penicillanic acid[6] (3).

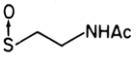


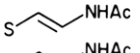
1

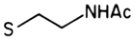


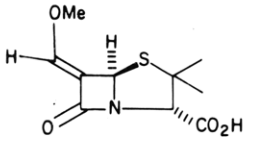
2

a, asparenomycin A; R = 

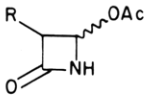
b, asparenomycin B; R = 

c, asparenomycin C; R = 

d, 6643-X; R = 



3

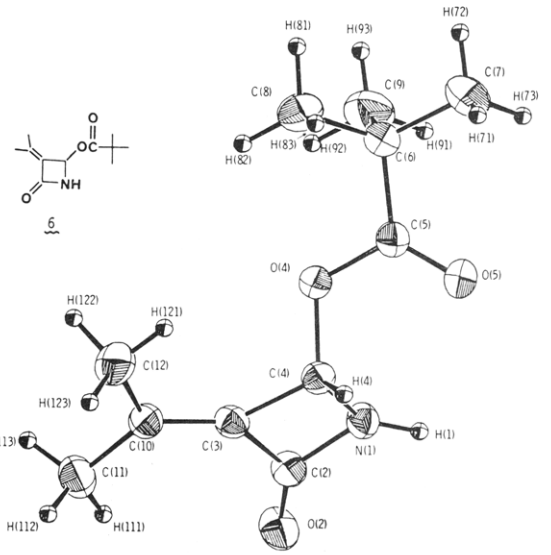


4

We recently initiated a program designed to explore the addition of chlorosulfonyl isocyanate (CSI) to functionalized alkenes with the goal of preparing useful intermediates for the synthesis of the carbapenems and other antibiotics. In particular, we were seeking to prepare intermediates of general structural type 4, where R could be easily transformed into a synthetically useful side chain. The 4-acetoxy substituent is known to be easily substituted by nucleophiles[7] and is of demonstrated synthetic utility.

Among the side chains considered to be synthetically useful were alkylidene groups, which not only serve as integral features of several important antibiotics, but also should be readily amenable to a variety of synthetic transformations. The olefinic substrates for the CSI addition thus became allenyl acetates,[8] some of which are readily available from silver-catalyzed rearrangement of the corresponding propargylic acetates.[9]

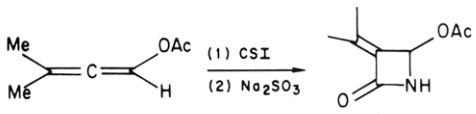
The addition of CSI to 1-acetoxy-3-methyl-1,2-butadiene,[9] followed by treatment with Na_2SO_3, produced an oily substance which rapidly decomposed when allowed to warm to room temperature. We found, however, that if



6

Figure 1. Crystal structure of **6**.

the ethereal extract was carefully titurated with hexane before it became concentrated, 4-acetoxy-3-(1-methylethylidene)-2-azetidinone (**5**) could be isolated in 22% yield. The crystalline material (mp 92 °C) can be stored

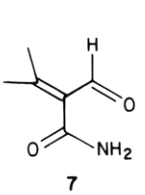


5

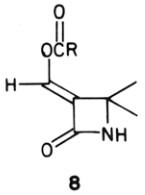
for at least several months at −20 °C. The decomposition observed on concentration is apparently due to the presence of undefined impurities.

An X-ray crystal structure of the corresponding pivalate **6** (prepared via CSI addition to the allenyl pivalate) is shown in Figure 1. Relevant crystal data are given as supplementary material. Of interest is the coplanarity of the azetidinone moiety, indicating resonance interaction of the carbonyl carbon with both the exocyclic double bond and the nitrogen lone pair. Indeed, we have found that this α-alkylidene–β-lactam bond is neither unusually susceptible to cleavage of the amide carbon nitrogen bond or to conjugate addition (vide infra).

The modest yield of **5** is partially a result of the workup procedure. Reduction of the sulfonyl chloride was performed by treatment with Na_2SO_3 in the presence of excess K_2HPO_4 as reported for similar systems. We found, however, that when an ethereal solution of the product azetidinone **5** was subjected to these conditions for 3 h at room temperature, less than 30% of the material could be recovered. Attempts to improve the yield by varying the workup time and temperature and by using other procedures have thus far proved unsuccessful. On the basis of known reactions of 4-acetoxyazetidinone, the products are most likely amido aldehyde **7** and its bisulfite adduct. We



7



8

also observed that **5** is partially destroyed by column chromatography (SiO_2). Despite repeated attempts, we

(3) For a discussion of the possible mechanics of action of β-lactamase inhibitors, see: (a) Daston, C. J.; Knowles, J. R. *Biochemistry* **1982**, *21*, 2857. (b) Charnas, R. L.; Knowles, J. R. *Biochemistry* **1981**, *20*, 2732. (c) Fischer, J.; Belasco, J. G.; Khosla, S.; Knowles, J. R. *Biochemistry* **1980**, *19*, 2895. (d) Charnas, R. L.; Fischer, J.; Knowles, J. R. *Biochemistry* **1978**, *17*, 2185. (e) Knott-Hunziker, V.; Petursson, S.; Waley, S. G.; Jaurin, B.; Grundstrom, T. *Biochem. J.* **1982**, *207*, 315. (f) Cohen, S. A.; Pratt, R. F. *Biochemistry* **1980**, *17*, 3996. (g) Brenner, D. G.; Knowles, J. R. *Biochemistry* **1984**, *23*, 5833. (h) Brenner, D. G.; Knowles, J. R. *Biochemistry* **1984**, *23*, 5839.

(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.; Takanashi, Y.; Kozuki, S.; Hattori, T.; Kondo, E.; Tanaka, K. *J. Antibiot.* **1982**, *35*, 15. (c) Tsuji, N.; Nagashima, K.; Kobayashi, 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.

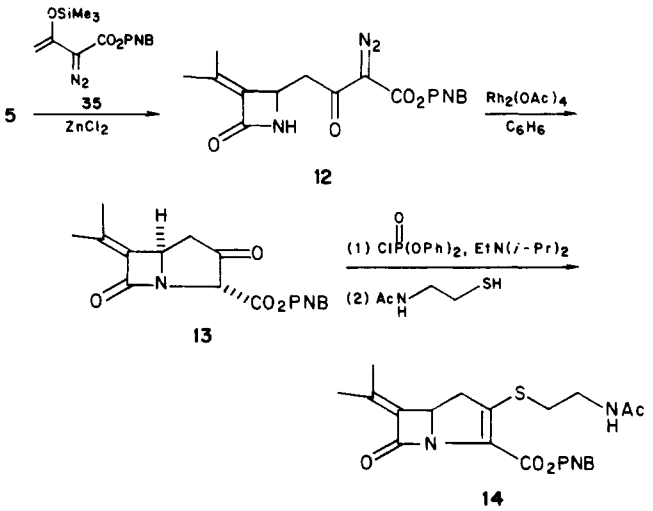
(6) Brenner, D. G. *J. Org. Chem.* **1985**, *50*, 18.

(7) Clauss, K.; Grim, D.; Prossel, G. *Justus Liebigs Ann. Chem.* **1974**, 539.

(8) For another example of the addition of CSI to allenes, see: Moriconi, E. J.; Kelly, J. F. *J. Org. Chem.* **1968**, *33*, 3036.

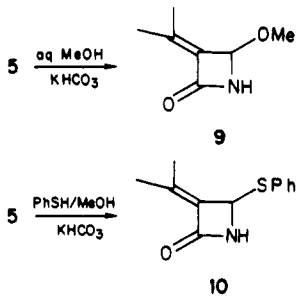
(9) Oelberg, D. G.; Schiavelli, M. D. *J. Org. Chem.* **1977**, *42*, 1804 and references cited therein.

Scheme I



could not isolate any of the isomeric product 8 from reaction of either the allenyl acetate or the allenyl pivalate.

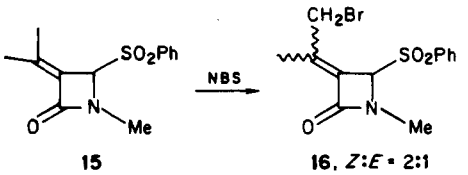
A variety of nucleophiles will substitute the acetate. Reaction with methanolic $KHCO_3$ produces 4-methoxy-2-azetidinone (9) within 10 min, and reaction with thiophenoxide produces the sulfide 10. We were particularly interested in the preparation of the carbapenems and thus sought to use one of the known methods for replacement of the acetate with a carbon nucleophile.



Treatment of 5 with the trimethylsilyl enol ether of *p*-nitrobenzyl α-diazoacetoacetate 11 in the presence of zinc chloride[10] produced the α-diazo-β-keto ester 12, which could be cyclized by treatment with rhodium acetate[11] in refluxing benzene to the bicyclic keto ester 13. Activation of the carbonyl, followed by treatment with *N*-acetylcysteamine, produced the *p*-nitrobenzyl ester of deshydroxy 6643-X (14) as shown in Scheme I.

Since the asparenomycin antibiotics possess an α-(hydroxymethyl)ethylidene side chain, we sought to develop an efficient procedure for allylic functionalization. We had earlier demonstrated[12] that the sulfone 15 could be allylically halogenated by treatment with NBS to produce a 2:1 mixture of (*Z*)- and (*E*)-allylic bromides 16, respectively. These materials could then be transformed into the allylic alcohols by heating in aqueous dioxane in the presence of $NaHCO_3$.

Unfortunately, all attempts to prepare a suitably protected derivative of keto ester 13 failed, and we were forced to introduce this functionality at an earlier stage. We

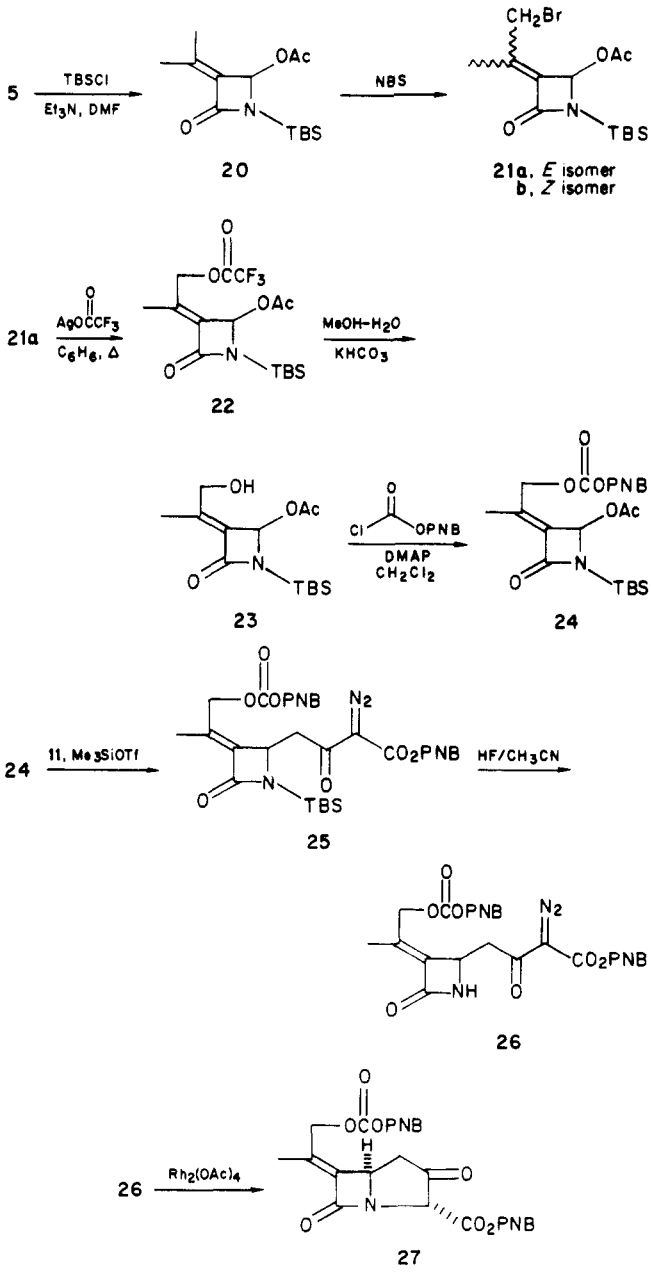


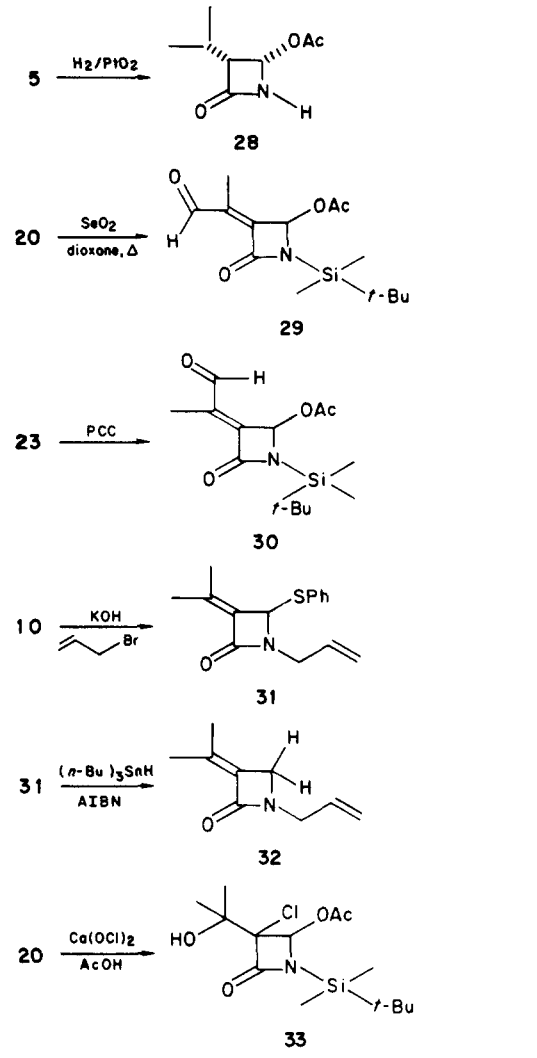
found that acetate 5 could be trimethylsilylated and brominated with NBS to produce a 1:1 mixture of *E* and *Z* bromides 17a and 17b. This mixture could then be desilylated and reacted with trimethylsilyl enol ether 11 in the presence of zinc chloride to yield α-diazo-β-keto esters 18a and 18b in 40% yield. Attempts to carry out the coupling with the *N*-trimethylsilyl bromides 17a and 17b or to improve the yield via the use of other zinc halides were unsuccessful. A more convenient procedure utilized Barrett's[13] method of treating the *N*-(trimethylsilyl)azetidinones with the trimethylsilyl enol ether 11 in the presence of a catalytic amount of trimethylsilyl triflate. This method allowed the preparation of the keto esters 18 (*E* and *Z* isomers in a 1.2:1 ratio) in 41% overall yield. 18a, albeit somewhat thermally unstable, could be separated and cyclized to bicyclic keto ester as shown in Scheme II. Neither 19 nor 18a could be cleanly hydrolyzed to the corresponding alcohol under a variety of conditions.

It was thus decided that the hydrolysis would have to occur at an early stage of the synthesis. This was not an inviting prospect due to the aforementioned sensitivity of the acetate 5 toward hydroxylic reagents. We found that protection of the nitrogen with the *tert*-butyldimethylsilyl group lent more base stability to the compound. The allylic bromides obtained therefrom were stable to column chromatography and the *E* (21a) and *Z* (21b) isomers could be separated. Hydrolysis of 21a could not be achieved in the usual manner ($NaHCO_3$/aq dioxane, KNO_2/DMF, $NaOCOCF_3$/DMF) but was finally accomplished by treating it with silver trifluoroacetate[14] in refluxing benzene followed by treatment with $KHCO_3$/MeOH. The free hydroxyl group of 23 was readily protected by treatment with *p*-nitrobenzyl chloroformate in the presence of DMAP. Reaction with 11 in the presence of Me_3SiOTf produced 25, which could be isolated as such or directly treated with HF/acetonitrile to produce 26 in 77% yield. 26 was cyclized by treatment with rhodium acetate to produce bicyclic keto ester 27. Compounds 26 and 27 have been synthesized by Ohno and co-workers[15] via a different route and have been transformed into asparenomycin C. Our spectra agree precisely with those obtained from him. This work thus constitutes a formal synthesis of the antibiotic.

We have also explored a number of synthetically intriguing transformations of acetate 5. Hydrogenation (PtO_2) at 30 psi yields the *cis*-4-acetoxy-3-isopropyl-2-azetidinone 28. Treatment of 20 with selenium dioxide[16] in dry dioxane (10 min, reflux) yields exclusively the *Z* aldehyde 29. The mechanism may involve coordination of the selenium with the carbonyl oxygen. Oxidation of alcohol 23 with pyridinium chlorochromate[17] provided the

(10) Reider, P. J.; Rayford, R.; Grabowski, E. J. J. *Tetrahedron Lett.* **1982**, *23*, 379.
(11) Ratcliffe, R. W.; Salzmann, T. N.; Christensen, B. G. *Tetrahedron Lett.* **1980**, 21, 31.
(12) Buynak, J. D.; Pajouhesh, H.; Lively, D. L.; Ramalakshmi, Y. *J. Chem. Soc., Chem. Commun.* **1984**, 948.
(13) Attrill, R. P.; Barrett, A. G. M.; Quayle, P.; Westhuizen, J.; Betts, M. G. *J. Org. Chem.* **1984**, *49*, 1679.
(14) Wong, H. N. G.; Sondheimer, F.; Goodin, R.; Brestow, R. *Tetrahedron Lett.* **1976**, 2715.
(15) Okano, K.; Kyotani, Y.; Ishihama, H.; Kobayashi, S.; Ohno, M. *J. Am. Chem. Soc.* **1983**, *105*, 7186.
(16) For a review of SeO_2 oxidations, see: Rabjohn, N. In "Organic Reactions"; Wiley: New York, 1976; Vol. 24, p 261.





E aldehyde for comparison. **30** is not isomerized to **29** by treatment with SeO_2 in refluxing dioxane. Treatment of allyl sulfide **31** with tributyltin hydride in the presence of AIBN initiator[18] yielded the reduced *N*-allyl compound **32**. Treatment of **20** with hypochlorous acid[19] produced chlorohydrin **33**. This material does not appear to be a mixture of diastereomers by ^{13}C or ^{1}H NMR. The assignment of stereochemistry in this compound is very difficult in the absence of the other diastereomer for comparison. We tend to favor the structure with Cl and OAc trans, based on least-hindered approach to the double bond.

In summary, **5** is a versatile intermediate for the preparation of a wide range of β-lactams. It can be prepared in modest yield from readily available materials. In addition to using **5** to accomplish a formal synthesis of asparenomycin C, we have demonstrated a number of useful transformations of this class of compounds.

Experimental Section

Melting points are uncorrected. NMR spectra were recorded on a Perkin-Elmer R32 (90 MHz) or an IBM/Bruker WP-200SY (200 MHz) instrument. Elemental analyses were carried out by Canadian Microanalytical Service Ltd. (Vancouver, B.C.).

All glassware was thoroughly dried in an oven and cooled in a desiccator. All reactions were performed under argon with a balloon being used to maintain positive pressure. Ether was distilled from $LiAlH_4$ prior to use. CH_2Cl_2, C_6H_6, CH_3CN, Et_3N, EtOAc, and $(i\text{-}Pr)_2NEt$ were distilled from CaH_2. DMF was treated with BaO and distilled at 5 mm of pressure. Chlorosulfonyl isocyanate, *p*-nitrobenzyl alcohol, *p*-nitrobenzyl chloroformate, CCl_4 (spectroqual), 4-(dimethylamino)pyridine, SeO_2, $Ca(OCl)_2$ (technical grade), pyridinium chlorochromate, and $Rh_2(OAc)_4$ were purchased from Aldrich Chemical Co. and used without further purification. Me_3SiOTf, Me_3SiCl, and $t\text{-}BuMe_2SiCl$ were purchased from Petrarch Systems Inc. AgO_2CCF_3 and $AgClO_4$ were purchased from Alfa Products. *p*-Nitrobenzyl 2-diaza-3-oxobutanoate was prepared from *p*-nitrobenzyl acetoacetate according to the procedure of Regitz.[20] $(n\text{-}Bu)_3SnH$ was prepared from $[(n\text{-}Bu)_3Sn]_2O$ according to the published procedure.[21] Flash chromatography[22] was performed with silica gel 60 (230–400 mesh) (Merck) purchased from EM Science.

4-Acetoxy-3-(1-methylethylidene)-2-azetidinone (5). In a dry two-necked flask, equipped with magnetic stirrer, low-temperature thermometer, and nitrogen inlet, was placed a solution

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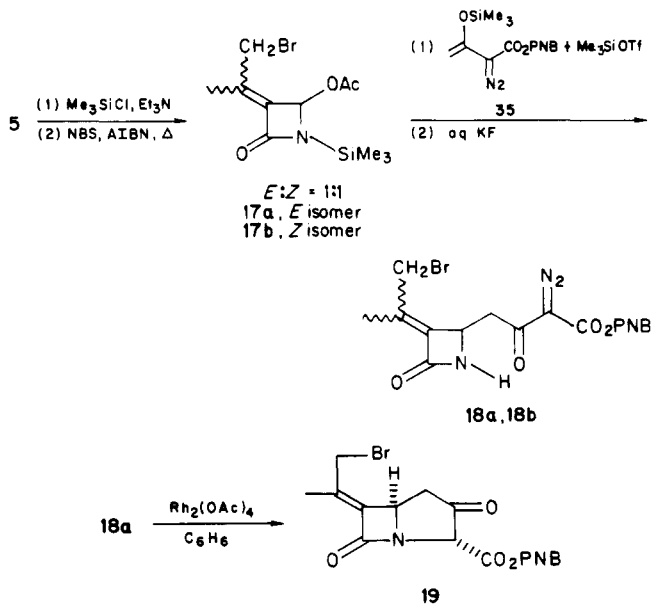
Scheme II



of 73 g (0.578 mol) of 1-acetoxy-3-methyl-1,2-butadiene[9] in 70 mL anhydrous ether. While the mixture was cooled to −70 °C, a solution of 84 g (51.7 mL, 0.594 mol) of chlorosulfonyl isocyanate in 80 mL ether was added via cannula. The reaction was then removed from the cooling bath and the temperature allowed to rise to −2 °C. Caution: If the temperature of the reaction is allowed to rise above +5 °C, a strongly exothermic reaction ensues which cannot be controlled. The reaction temperature was carefully kept between −2 and −6 °C by intermittent immersion in the cooling bath. Because of its initial exothermicity, the reaction requires a great deal of cooling during the first 30 min. After 1.5 h at this temperature, the reaction mixture was cooled to −20 °C, and the contents were transferred (via cannula) to a rapidly stirred two-phase solution of 103 g of Na_2SO_3, 260 g of K_2HPO_4, 800 mL of water, and 800 mL of ether chilled at 0 °C. The solution was rapidly stirred at 0 °C for 30 min and then at room temperature for 1.5 h. The ether layer was then separated and the aqueous portion extracted with ether. The combined ether layers were washed with brine, dried over Na_2SO_4 and concentrated to a volume of 50 mL while keeping the temperature at or below 25 °C. Then approximately 150 mL of hexane was added to precipitate the product, which was filtered and washed again with cold hexane. A second crop of crystals were obtained by adding more hexane to the filtrate, and the solid was dried in vacuo to yield 22 g (23%) of **5** as a white solid: mp 90–92 °C; IR ($CHCl_3$) 3440, 1780, 1745, 1545, 1230, 980 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 1.79 (s, 3 H), 2.06 (s, 3 H), 2.10 (s, 3 H), 6.18 (s, 1 H), 6.97 (br s, 1 H); ^{13}C NMR δ 19.5, 20.2, 26.1, 38.5, 77.2, 132.9, 139.9, 164.0, 178.6. Anal. Calcd for $C_8H_{11}NO_3$: C, 56.80; H, 6.55; N, 8.28. Found: C, 56.79; H, 6.54; N, 8.25.

4-[(2,2-Dimethylpropanoyl)oxy]-3-(1-methylethylidene)-2-azetidinone (6). This material was prepared in the same manner used for **5**: yield, 11%; mp 106–108 °C; IR (CCl_4) 3430, 2970, 1750, 1720, 1260, 1140, 980 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 1.21 (s, 9 H), 1.79 (s, 3 H), 2.06 (s, 3 H), 6.16 (s, 1 H), 7.18 (br s, 1 H); ^{13}C NMR δ 19.5, 20.1, 26.6, 38.5, 77.1, 132.9, 139.9, 164.0, 178.6. Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.34; H, 7.98; N, 6.47. Crystal structure: Colorless needles were grown by slow evaporation of hexane solution. The data were collected on a Syntex $P2_1$ Automatic Diffractometer. The structure was solved by direct methods and refined by full-matrix least squares. Pertinent data can be found in Tables I and II in the supplementary material.

4-Methoxy-3-(1-methylethylidene)-2-azetidinone (9). To a solution of $KHCO_3$ (0.100 g, 1.0 mmol) in 10 mL of a 4/1 (v/v) mixture of methanol/water was added **5** (0.10 g, 0.59 mmol), and the solution was allowed to stir for 2 h at room temperature. The reaction mixture was then poured into 100 mL of water and extracted with ether (3 × 50 mL). The combined ether layers were then washed with water, brine, and dried over $MgSO_4$ to yield a viscous oil, which was crystallized (ether/hexane) to produce **9** as a white solid (70 mg, 84%): mp 57–59 °C; IR (CCl_4) 3730, 1745, 1440, 1370, 1330, 1265, 1110 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 1.79 (s, 3 H), 2.05 (s, 3 H), 3.30 (s, 3 H), 5.56 (s, 1 H), 7.30 (br s, 1 H). Anal. Calcd for $C_7H_{11}NO_2$: C, 59.56; H, 7.85; N, 9.92. Found: C, 59.45; H, 7.86; N, 9.86.

3-(1-Methylethylidene)-4-(phenylthio)-2-azetidinone (10). K_2CO_3 (1.80 g, 13 mmol) was added to a solution of thiophenol (1.46 mL, 14.2 mmol) in 40 mL of methanol while cooling to 0 °C. **5** (2.0 g, 11.8 mmol) was then added in one portion and the reaction placed under inert atmosphere and stirred at 0 °C for 30 min. The reaction was then poured into 200 mL of saturated aqueous NaCl and extracted (3 × 70 mL) with CH_2Cl_2. The combined organics were dried (Na_2SO_4) and concentrated in vacuo, and the resultant yellow oil was purified by flash chromatography (SiO_2, 20% EtOAc/CH_2Cl_2) to yield **10**, 1.65 g (64%), as white crystals: mp 115–117 °C; IR ($CHCl_3$) 3430, 1745, 1440, 1370, 1330, 1265, 1110, 950, 910, 860, 830 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 1.89 (s, 3 H), 1.98 (s, 3 H), 5.36 (s, 1 H), 6.96 (br s, 1 H), 7.23–7.53 (m, 5 H); ^{13}C NMR δ 19.7, 20.3, 61.7, 128.1, 128.8, 131.3, 133.3, 140.0, 164.1. Anal. Calcd for $C_{12}H_{13}NOS$: C, 65.72; H, 5.97; N, 6.39. Found: C, 66.09; H, 5.96; N, 6.46.

***p*-Nitrobenzyl 2-Diazo-3-[(trimethylsilyl)oxy]but-3-enoate (11).** To a solution of *p*-nitrobenzyl 2-diaza-3-oxobutanoate (65.0 g, 0.247 mol) and triethylamine (44.0 mL, 0.316 mol) in 350 mL of dry CCl_4 was added trimethylsilyl triflate (61.1 mL, 0.316 mol) while cooling in an ice bath. The reaction was allowed to warm to room temperature and stir overnight. The reaction was then poured into a dry separatory funnel and the bottom layer concentrated in vacuo to yield 68 g (82%) of **11** as an orange solid, which was used without further purification. This material typically contained 10% of the keto ester by NMR. Prolonged storage of this material is difficult. It can be kept for several months in a tightly sealed container, in a desiccator, at −20 °C: ^1H NMR ($CDCl_3$, 90 MHz) δ 0.16 (s, 9 H), 4.20 (d, J = 2 Hz, 1 H), 4.90 (d, J = 2 Hz, 1 H), 5.24 (s, 2 H), 7.44 (d, J = 8.0 Hz, 2 H), 8.10 (d, J = 8.0 Hz, 2 H).

3-(1-Methylethylidene)-4-[3-(((*p*-nitrobenzyl)oxy)carbonyl)-3-diazo-2-oxopropyl]-2-azetidinone (12). Zinc chloride (0.681 g, 5.0 mmol) was heated in vacuo to remove moisture. Then it was suspended in 30 mL of CH_2Cl_2 and chilled to −23 °C. In rapid succession, 1.69 g (10.0 mmol) of **5** and 6.15 g (20.0 mmol) of **11** were added, and the reaction was stirred at −23 °C for 1 h. Then the reaction was diluted with 200 mL of ethyl acetate, and the combined organics were washed with saturated $NaHCO_3$ and brine. After drying over $MgSO_4$, the solution was concentrated in vacuo to produce a yellowish white solid. Purification by flash chromatography (20% EtOAc/CH_2Cl_2, SiO_2) produced 1.39 g (37%) of **12** as a viscous oil: IR ($CHCl_3$) 3440, 3000, 2150, 1720, 1640, 1520, 1380, 1345, 1295, 1120, 905 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.75 (s, 3 H), 2.02 (s, 3 H), 2.96 (dd, J = 10.0, 17.7 Hz, 1 H), 3.53 (d, J = 17.7 Hz, 1 H), 4.40 (d, J = 10.0 Hz, 1 H), 5.41 (s, 2 H), 7.03 (s, 1 H), 7.59 (d, J = 8.5 Hz), 8.29 (d, J = 8.5 Hz). Anal. Calcd for $C_{17}H_{16}N_4O_6$: C, 54.83; H, 4.34; N, 15.05. Found: C, 54.69; H, 4.35; N, 14.85.

***p*-Nitrobenzyl 6-(1-Methylethylidene)-1-azabicyclo[3.2.0]heptane-3,7-dione-2-carboxylate (13).** To a solution of 8.0 g (22.0 mmol) of **12** in 150 mL of dry benzene was added 0.05 g of $Rh_2(OAc)_4$ and the flask thoroughly degassed. The solution was heated to reflux for 30 min, cooled, and concentrated and the product purified by flash chromatography (CH_2Cl_2, SiO_2) to yield 6.5 g (86%) of **13** as a white solid: mp 138–140 °C; IR ($CHCl_3$) 1740, 1520, 1330, 1270, 1160, 1100, 970, 840 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.75 (s, 3 H), 2.02 (s, 3 H), 2.34 (dd, J = 7.9, 19.0 Hz, 1 H), 2.78 (dd, J = 7.0, 19 Hz, 1 H), 4.49 (dd, J = 7.0, 7.9 Hz, 1 H), 4.62 (s, 2 H), 5.12, 5.19, 5.24, and 5.31 (4 line AB, J = 13.3 Hz, 2 H), 7.45 (d, J = 8.2 Hz, 2 H), 8.13 (d, J = 8.2 Hz, 2 H). Anal. Calcd for $C_{17}H_{16}N_2O_6$: C, 59.30; H, 4.68; N, 8.14. Found: C, 59.31; H, 4.63; N, 8.09.

***p*-Nitrobenzyl 3-[(2-Acetamidoethanyl)thio]-6-(1-methylethylidene)-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (14).** Diisopropylethylamine (0.825 mL, 4.71 mmol) and 0.975 mL (4.71 mmol) of diphenyl chlorophosphate were added to a solution of 1.63 g (4.74 mmol) of keto ester **13** in 61 mL of dry acetonitrile while cooling to 0 °C. After the mixture was stirred at 0 °C for 1 h, 0.825 mL (4.71 mmol) of diiso-

propylethylamine and 0.558 g (4.68 mmol) of *N*-acetylcysteamine were added. The solution was stirred at 0 °C for 2 h, then another 0.825 mL of diisopropylethylamine and 0.558 g of *N*-acetylcysteamine were added, and the reaction was allowed to stand at −20 °C overnight. The precipitated product was collected by filtration of the solution, washed with anhydrous ether, and dried under vacuum to yield 1.5 g (71%) of **14** as a white solid: mp 178–180 °C; IR ($CHCl_3$) 3450, 3000, 1750, 1660, 1510, 1345, 1270, 1170, 1110, 970, 850 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.85 (s, 3 H), 1.99 (s, 3 H), 2.12 (s, 3 H), 2.80–3.18 (m, 3 H), 3.25–3.50 (m, 3 H), 4.75 (t, J = 8 Hz, 1 H), 5.26 (d, J = 14 Hz, 1 H), 5.55 (d, J = 14 Hz, 1 H), 6.00 (br s, 1 H), 7.70 (d, J = 8 Hz, 2 H), 8.24 (d, J = 8 Hz, 2 H). Anal. Calcd for $C_{21}H_{23}N_3O_6S$; C, 56.65; H, 5.21; N, 9.43. Found: C, 55.90; H, 5.23; N, 9.18.

4-Acetoxy-3-[(*E*)-2-bromo-1-methylethylidene]-1-(trimethylsilyl)-2-azetidinone (17a) and 4-Acetoxy-3-[(*Z*)-2-bromo-1-methylethylidene]-1-(trimethylsilyl)-2-azetidinone (17b). A solution of 8.00 g (47.3 mmol) of **5** in 132 mL of dry THF was treated with 25.9 mL (186 mmol) of triethylamine and 23.6 mL (186 mmol) of trimethylsilyl chloride while cooling to 0 °C. The reaction was allowed to stir at 0 °C for 2 h, then the precipitated solid removed by suction filtration, and the solvent removed in vacuo. CCl_4 (30 mL) was added to the yellow oil thus obtained, the solution again filtered, and the solvent removed in vacuo. 4-Acetoxy-3-(1-methylethylidene)-1-(trimethylsilyl)-2-azetidinone (9.60 g, 84%) was thus obtained as an oil, which was not further purified: IR (neat) 2960, 1735, 1370, 1260, 1220, 1180, 1090, 850 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 0.25 (s, 9 H), 1.71 (s, 3 H), 2.00 (s, 3 H), 2.04 (s, 3 H), 6.47 (br s, 1 H); ^{13}C NMR δ −1.5, 19.2, 19.7, 20.5, 78.1, 134.6, 138.4, 167.1, 169.9.

A solution of 6.0 g (24.9 mmol) of crude *N*-trimethylsilylated azetidinone in 110 mL of CCl_4 was treated with 4.88 g (27.4 mmol) of NBS and 0.35 g (2.57 mmol) of AIBN. The flask was then thoroughly degassed and the solution heated to reflux for 30 min. The flask was cooled in an ice bath and the precipitated succinimide removed by vacuum filtration. Concentration yielded 7.5 g of a 1:1 mixture of **17a** and **17b** as a brown oil, which was not further purified: IR (neat, mixture of isomers) 2960, 1750, 1440, 1380, 1305, 1260, 1230, 1185, 1095, 1005, 850 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz, mixture of isomers) δ 0.25 (18 H, s, both Me_3Si), 1.85 (3 H, s, allylic CH_3 of **17b**), 2.10 (6 H, s, acetate of both), 2.14 (3 H, s, allylic CH_3 of **17a**), 3.70, 3.82, 3.88, and 4.00 (4 line AB, 2 H, J = 10 Hz, CH_2Br of **17a**), 4.32 (br s, 2 H, CH_2Br of **17b**), 6.52 (br s, 2 H, CH of both).

3-[(*E*)-2-Bromo-1-methylethylidene]-4-[3-(((*p*-nitrobenzyl)oxy)carbonyl)-3-diazo-2-oxopropyl]-2-azetidinone (18a). A solution of 1.0 g (4.15 mmol) of the crude bromides **17a** and **17b** and 1.67 g (4.98 mmol) of **11** in 20 mL of dry CH_2Cl_2 was cooled to −78 °C and treated with 2.0 mL of a 1% (v/v) solution of Me_3SiOTf in CH_2Cl_2. After being stirred 15 min at that temperature, the reaction was allowed to warm to room temperature over a 20-min period and stirred at that temperature for an additional 30 min. A 5% (w/v) aqueous solution of KF (40 mL) was then added and the reaction stirred for 15–20 min. The layers were separated, the aqueous layer was extracted (2 × 50 mL) with CH_2Cl_2, and the combined organics were dried ($MgSO_4$) and concentrated to yield a thick yellow oil. Further purification by flash chromatography (20% EtOAc/CH_2Cl_2, SiO_2) yielded 0.44 g of **18a**, mp 133–135 °C dec, and 0.37 g of **18b**, mp 118–120 °C dec (46% yield overall from **5**).

18a: IR ($CHCl_3$) 3440, 2150, 1740, 1715, 1640, 1520, 1380, 1350, 1290, 1120, 850 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.20 (s, 3 H), 3.03 (dd, J = 18, 10 Hz, 1 H), 3.61, (dd, J = 18, 2 Hz, 1 H), 3.86, 3.85 (AB q, J = 10 Hz, 2 H), 4.54 (dd, J = 10, 2 Hz, 1 H), 5.39 (s, 2 H), 6.42 (s, 1 H), 7.56 (d, J = 8 Hz, 2 H), 8.28 (d, J = 8 Hz, 2 H); ^{13}C NMR δ 16.4, 31.6, 44.3, 51.3, 65.6, 124.0, 128.8, 135.1, 139.2, 141.9, 148.1, 160.6, 163.1, 189.5. Anal. Calcd for $C_{17}H_{15}BrN_4O_6$: C, 45.24; H, 3.36; N, 12.42. Found: C, 45.29; H, 3.39; N, 12.35.

18b: IR ($CHCl_3$) 3440, 2150, 1745, 1710, 1650, 1520, 1380, 1350, 1295, 1120, 910, 850 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.89 (s, 3 H), 3.00 (dd, J = 18, 10 Hz, 1 H), 3.53 (dd, J = 18, 2 Hz, 1 H), 4.39 (s, 2 H), 4.45 (br d, J = 10 Hz), 5.39 (s, 2 H), 7.02 (br s, 1 H), 7.57 (d, J = 8 Hz, 2 H), 8.24 (d, J = 8 Hz, 2 H).

***p*-Nitrobenzyl 6-[(*E*)-2-Bromo-1-methylethylidene]-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (19).** The procedure is the same as for the cyclization of **12**. The product proved to be unstable to column chromatography. The best purification method involved dissolving the product in 5% EtOAc/CH_2Cl_2 and filtering through a small plug of silica gel. In this way, a 81% yield of **19**, mp 129–131 °C dec, could be obtained: IR ($CHCl_3$) 3030, 2950, 1750, 1605, 1525, 1350, 1270, 1175, 1110, 1070, 980, 850 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.21 (s, 3 H), 2.53 (dd, J = 19, 7 Hz, 1 H), 2.90 (dd, J = 19, 7 Hz, 1 H), 3.85, 3.83 (AB q, J = 10 Hz, 2 H), 4.68 (t, J = 7 Hz, 1 H), 4.70 (s, 1 H), 5.33 and 5.25 (AB q, J = 13 Hz, 2 H), 7.25 (d, J = 9 Hz, 2 H), 8.22 (d, J = 9 Hz, 2 H); ^{13}C NMR δ 17.8, 29.8, 39.3, 55.8, 63.5, 66.3, 123.9, 128.4, 139.7, 140.3, 141.9, 148.0, 165.1, 167.1, 206.1. Anal. Calcd for $C_{17}H_{15}BrN_2O_6$: C, 48.24; H, 3.58; N, 6.62. Found: C, 48.02; H, 3.63; N, 6.56.

4-Acetoxy-1-(*tert*-butyldimethylsilyl)-3-(1-methylethylidene)-2-azetidinone (20). A solution of 1.0 g (5.92 mmol) of **5** in 17 mL of dry DMF was treated with 2.0 mL (14.2 mmol) of triethylamine and 2.14 g (14.2 mmol) of *tert*-butyldimethylsilyl chloride while cooling to 0 °C. The reaction was allowed to stir at 0 °C for 2 h, poured into 150 mL of H_2O, and extracted with ether (3×). The combined organics were washed with water (4×), washed with brine (1×), dried over $MgSO_4$, and concentrated to yield an orange liquid. This material was further purified to produce 1.0 g (60%) of pure **20** as a colorless oil: IR (neat) 1750, 1730, 1465, 1450, 1375, 1300, 1230, 1180, 1095, 1000, 840, 680 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 0.23 (s, 6 H), 0.97 (s, 9 H), 1.72 (s, 3 H), 2.03 (s, 3 H), 2.08 (s, 3 H), 6.63 (s, 1 H); ^{13}C NMR δ −6.4, −6.3, 17.9, 19.5, 20.1, 20.8, 25.7, 78.6, 134.7, 138.8, 167.6, 169.9.

4-Acetoxy-3-[(*E*)-2-bromo-1-methylethylidene]-1-(*tert*-butyldimethylsilyl)-2-azetidinone (21a) and 4-Acetoxy-3-[(*Z*)-2-bromo-1-methylethylidene]-1-(*tert*-butyldimethylsilyl)-2-azetidinone (21b). A solution of 3.00 g (10.6 mmol) of **20** in 50 mL of CCl_4 was treated with 2.08 g (11.69 mmol) of NBS and 0.03 g of AIBN. The flask was thoroughly degassed and the solution heated to reflux for 30 min. The reaction mixture was then cooled to 0 °C, suction filtered, and concentrated and the product purified by flash chromatography (50% CH_2Cl_2/hexane, SiO_2) to yield 1.5 g of *E* isomer **21a** and 1.5 g of *Z* isomer **21b** (78% yield overall).

21a: IR (film) 1750, 1470, 1435, 1375, 1300, 1230, 1185, 1095, 1005, 840, 740, 675 cm^{-1}; ^1H NMR ($CDCl_3$ 90 MHz) δ 0.20 (s, 6 H), 0.92 (s, 9 H), 2.06 (s, 3 H), 2.09 (s, 3 H), 3.75, 3.90 (AB q, J = 10 Hz, 2 H), 6.60 (s, 1 H). Anal. Calcd for $C_{14}H_{24}BrNO_3Si$: C, 46.40; H, 6.69; N, 3.87. Found: C, 46.47; H, 6.69; N, 3.82.

21b: IR (film) 1745, 1470, 1440, 1375, 1300, 1260, 1225, 1120, 1095, 1005, 840, 735, 675 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 0.20 (s, 6 H), 0.93 (s, 9 H), 1.83 (s, 3 H), 2.06 (s, 3 H), 4.30 (s, 2 H), 6.60 (s, 1 H).

4-Acetoxy-1-(*tert*-butyldimethylsilyl)-3-(2-hydroxy-1-methylethylidene)-2-azetidinone (23). A solution of 2.2 g (6.09 mmol) of **21a** and 1.61 g (7.29 mmol) of silver trifluoroacetate in 50 mL of benzene was placed under nitrogen and heated to reflux for 1 h. The solution was then allowed to cool to room temperature and filtered and the filtrate concentrated in vacuo to yield 2.16 g (90%) of oily trifluoroacetate **22**, which was not further purified but was directly hydrolyzed: ^1H NMR ($CDCl_3$, 90 MHz) δ 0.20 (s, 6 H), 0.91 (s, 9 H), 2.05 (br s, 6 H), 4.75 and 4.80 (AB q, J = 12 Hz, 2 H), 6.64 (br s, 1 H).

Trifluoroacetate **22** (2.16 g, 5.46 mmol) was added to a solution of 2.20 g (21.97 mmol) of $KHCO_3$ and 8.8 mL of H_2O in 35 mL of methanol. The solution was allowed to stir at room temperature for 30 min, then poured into brine, and extracted with ether (3×). The combined organics were dried over $MgSO_4$, concentrated, and purified by flash chromatography (20% EtOAc/CH_2Cl_2, SiO_2) to yield 1.4 g (85%) alcohol **23** as an oil: IR (film) 3470, 1750, 1730, 1470, 1445, 1375, 1300, 1230, 1170, 1095, 1000, 840, 825, 680 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.19 (s, 3 H), 0.20 (s, 3 H), 0.92 (s, 9 H), 1.97 (s, 3 H), 2.04 (s, 3 H), 4.11 (s, 2 H), 6.74 (s, 1 H); ^{13}C NMR δ −6.5, −6.4, 14.3, 17.8, 20.7, 25.5, 63.3, 78.6, 133.6, 140.9, 168.2, 169.9.

4-Acetoxy-1-(*tert*-butyldimethylsilyl)-3-[(*E*)-1-methyl-2-((((*p*-nitrobenzyl)oxy)carbonyl)oxy)ethylidene]-2-azetidinone (24). A solution of 0.410 g (1.37 mmol) of alcohol **23** in 8 mL of CH_2Cl_2 was treated with 0.205 g (1.68 mmol) of (dimethylamino)pyridine and 0.355 g (1.65 mmol) of *p*-nitrobenzyl chloroformate while cooling to 0 °C. The reaction was stirred

at this temperature for 45 min, then washed with saturated bicarbonate, dried ($MgSO_4$), concentrated, and purified by flash chromatography (5% EtOAc/CH_2Cl_2, SiO_2) to yield 0.596 g (91%) of **24** as a colorless oil: IR (film) 1740, 1600, 1520, 1460, 1350, 1260, 1180, 1090, 1000, 960, 840 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.21 (s, 3 H), 0.22 (s, 3 H), 0.92 (s, 9 H), 2.01 (s, 3 H), 2.04 (s, 3 H), 4.59 and 4.66 (AB q, J = 14 Hz, 2 H), 5.23 (s, 2 H), 6.68 (s, 1 H), 7.54 (d, J = 9 Hz, 2 H), 8.22 (d, J = 9 Hz, 2 H). Anal. Calcd for $C_{22}H_{30}N_2O_8Si$: C, 55.20; H, 6.33; N, 5.85. Found: C, 54.50; H, 6.20; N, 5.55.

1-(*tert*-Butyldimethylsilyl)-3-[(*E*)-1-methyl-2-((((*p*-nitrobenzyl)oxy)carbonyl)oxy)ethylidene]-4-[3-(((*p*-nitrobenzyl)oxy)carbonyl)-3-diazo-2-oxopropyl]-2-azetidinone (25) and 3-[(*E*)-1-Methyl-2-((((*p*-nitrobenzyl)oxy)carbonyl)oxy)ethylidene]-4-[3-(((*p*-nitrobenzyl)oxy)carbonyl)-3-diazo-2-oxopropyl]-2-azetidinone (26). A solution of 0.100 g (0.21 mmol) of acetate **24** and 0.084 g (0.25 mmol) of **11** in 2.0 mL of dry CH_2Cl_2 were treated with a 0.2 mL of a 1% (v/v) solution of Me_3SiOTf in dry CH_2Cl_2 while cooling to −78 °C. The reaction mixture was stirred at this temperature for 15 min and then allowed to stir at room temperature for 1 h. It was then washed with saturated $NaHCO_3$, concentrated, and purified by flash chromatography (5–40% EtOAc/CH_2Cl_2, SiO_2) to yield 0.033 g (0.058 mmol) of **25** and 0.055 (0.081 mmol) of **26** (62% yield overall) as oils.

25: IR (film) 2975, 2940, 2875, 2150, 1720, 1650, 1610, 1520, 1450, 1380, 1355, 1330, 1230, 1160, 1110, 1050, 990, 840, 820 cm^{-1}; ^1H NMR ($CDCl_3$ 90 MHz) δ 0.15 (s, 3 H), 0.22 (s, 3 H), 0.93 (s, 9 H), 2.01 (s, 3 H), 3.36 (d, J = 4 Hz, 2 H), 4.60 (s, 2 H), 4.73 (br t, J = 4 Hz, 1 H), 5.21 (s, 2 H), 5.34 (s, 2 H), 7.53 (d, J = 8 Hz, 2 H), 8.23 (d, J = 8 Hz, 2 H).

26: IR (film) 3440, 2975, 2875, 2150, 1745, 1720, 1650, 1610, 1520, 1440, 1380, 1350, 1270, 1125, 1035, 1000, 910, 855 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.04 (3 H, s), 3.02 (dd, J = 18, 10 Hz, 1 H), 3.58 (dd, J = 18, 3 Hz, 1 H), 4.48 (m, 1 H), 4.59 and 4.62 (AB q, J = 14 Hz, 2 H), 5.22 (s, 2 H), 5.29 and 5.30 (AB q, J = 12 Hz), 7.47 (d, J = 8 Hz, 4 H), 8.23 (d, J = 8 Hz, 2 H), 8.24 (d, J = 8 Hz, 2 H).

3-[(*E*)-1-Methyl-2-((((*p*-nitrobenzyl)oxy)carbonyl)oxy)ethylidene]-4-[3-(((*p*-nitrobenzyl)oxy)carbonyl)-3-diazo-2-oxopropyl]-2-azetidinone (26). To a solution of 0.2 mL of 48% aqueous HF in 3.8 mL of acetonitrile was added 94.4 mg (0.139 mmol) of **25**. The reaction was allowed to stir at room temperature for 15 min, then poured into 100 mL 5% $KHCO_3$, and extracted with CH_2Cl_2 (3 × 25 mL). The combined organics were dried over Na_2SO_4, concentrated in vacuo, and further purified by flash chromatography (20% EtOAc/CH_2Cl_2) to yield 74.1 mg (94%) of **26** as a white solid: mp 80–82 °C; IR and NMR reported above.

***p*-Nitrobenzyl 6-[(*E*)-1-Methyl-2-((((*p*-nitrobenzyl)oxy)carbonyl)oxy)ethylidene]-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (27).** A solution of 0.050 g (0.088 mmol) of azetidinone **26** in 5.0 mL of benzene was treated with 1 mg of $Rh_2(OAc)_4$ and the solution heated to reflux under N_2 for 20 min. The solution was then allowed to cool to room temperature, filtered, and concentrated in vacuo to yield 0.040 g (85%) of bicyclic keto ester **27** as a yellow oil, which crystallized when titurated with $CHCl_3$; mp 150–152 °C. This material was unstable toward further purification by column chromatography: IR ($CHCl_3$) 2960, 1750, 1600, 1520, 1440, 1350, 1295, 1275, 1255, 1235, 1220, 1170, 1110, 975, 850 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.05 (s, 3 H), 2.45 (dd, J = 19, 7 Hz, 1 H), 2.80 (dd, J = 19, 7 Hz, 1 H), 4.61 (t, J = 7 Hz, 1 H), 4.70 (s, 1 H), 4.70 and 4.74 (AB q, J = 16 Hz, 2 H), 5.24 (s, 2 H), 5.24 and 5.29 (AB q, J = 13 Hz, 2 H), 7.50 (d, J = 8 Hz, 4 H), 8.17 (d, J = 8 Hz, 2 H), 8.18 (d, J = 8 Hz, 2 H); ^{13}C NMR δ 15.5, 40.6, 56.9, 64.1, 66.2, 68.3, 68.6, 123.9, 124, 128.3, 128.7, 137.2, 137.6, 141.6, 142.0, 147.9, 148.1, 154.1, 165.3, 168.3, 206.7.

***cis*-4-Acetoxy-3-(1-methylethyl)-2-azetidinone (28).** A slurry of 300 mg of **5** (1.77 mmol) and 100 mg of PtO_2 in 10 mL of EtOAc were shaken on a Parr hydrogenator at 30 psi for 12 h. The solution was then concentrated and purified by flash chromatography (10% EtOAc/CH_2Cl_2) to yield 200 mg (66% yield) of **28** as an oil: IR (film) 3425, 2975, 2940, 2880, 1750, 1720, 1460, 1360, 1220, 1060, 1010, 905 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 0.98 (d, J = 7 Hz, 3 H), 1.16 (d, J = 7 Hz, 3 H), 2.11 (s, 3 H), 2.20 (m, 1 H), 3.06 (br d, J = 10 Hz), 5.87 (d, J = 4 Hz, 1 H), 7.20 (br s, 1 H); ^{13}C NMR δ 20.0, 20.8, 21.4, 25.4, 61.7, 75.3, 169.1, 171.1.

(*Z*)-4-Acetoxy-1-(*tert*-butyldimethylsilyl)-3-(1-methyl-2-oxoethylidene)-2-azetidinone (29). SeO_2 (0.189 g, 1.70 mmol) was added to a solution of 0.40 g (1.42 mmol) of acetate **20** in 20 mL of dry dioxane. The flask was placed under N_2 and heated to reflux for 30 min. It was then cooled to room temperature and concentrated and the product purified by flash chromatography (CH_2Cl_2, SiO_2) to yield 0.20 g (48%) of pure aldehyde **29** as an oil: IR (film) 2995, 2860, 1745, 1690, 1465, 1375, 1305, 1260, 1220, 1180, 1090, 1000, 840, 670 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 0.22 (s, 6 H), 0.91 (s, 9 H), 1.72 (s, 3 H), 2.07 (s, 3 H), 6.76 (s, 1 H), 10.68 (s, 1 H). Anal. Calcd for $C_{14}H_{23}NO_4Si$: C, 56.52; H, 7.81; N, 4.71. Found: C, 56.71; H, 7.91; N, 4.68.

(*E*)-4-Acetoxy-1-(*tert*-butyldimethylsilyl)-3-(1-methyl-2-oxoethylidene)-2-azetidinone (30). To a solution of 0.050 g (0.167 mmol) of alcohol **23** in 1 mL of dry CH_2Cl_2 was added a suspension of 0.054 g (0.251 mmol) of pyridinium chlorochromate (PCC) in 1 mL of CH_2Cl_2. The reaction mixture was stirred at room temperature for 30 min, diluted with 10 mL ether, filtered through silica gel, and concentrated to yield 0.03 g (60%) of aldehyde **30** as a white solid: mp 43–45 °C; IR ($CHCl_3$) 2930, 2850, 1730, 1675, 1360, 1300, 1250, 1160, 1080, 1000 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 0.21 (s, 6 H), 0.91 (s, 9 H), 2.01 (s, 3 H), 2.04 (s, 3 H), 6.97 (s, 1 H), 9.77 (s, 1 H). Anal. Calcd for $C_{14}H_{23}NO_4Si$: C, 56.52; H, 7.77; N, 4.70. Found: C, 56.59; H, 7.77; N, 4.70.

3-(1-Methylethylidene)-1-(2-propenyl)-4-(phenylthio)-2-azetidinone (31). Powdered KOH (0.288 g, 5.13 mmol) was added to a solution of 0.300 g (1.37 mmol) of sulfide **10** in 6 mL of allyl bromide. The solution was allowed to stir overnight, poured into 100 mL of water, and extracted (2×) with ether. The combined ether layers were dried over $MgSO_4$ and concentrated in vacuo, and the product was purified by flash chromatography to yield 0.170 g (48%) of **31** as a white solid: mp 38–39 °C; IR (film) 3060, 2980, 2910, 1720, 1630, 1575, 1430, 1380, 1280, 1240, 1190, 1060, 1030, 985, 920, 890, 850, 800, 740, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 1.91 (s, 3 H), 1.99 (s, 3 H), 3.75 (dd, J = 16, 8 Hz, 1 H), 4.27 (br d, J = 16 Hz, 1 H), 5.17 (d, J = 18 Hz, 1 H), 5.21 (d, J = 10 Hz, 1 H), 5.39 (s, 1 H), 5.58–6.05 (m, 1 H), 7.30–7.60 (m, 5 H).

3-(1-Methylethylidene)-1-(2-propenyl)-2-azetidinone (32). A solution of 0.05 g (0.193 mmol) of sulfide **31** in 2 mL of dry toluene was placed under N_2 and heated at a bath temperature of 90 °C. A second solution of 0.090 g (0.308 mmol) of $(n\text{-}Bu)_3SnH$ and 0.006 g (0.04 mmol) of AIBN was added dropwise over the course of 30 min. The reaction was allowed to stir at this temperature for an additional 1.5 h, then concentrated in vacuo, and purified by column chromatography to yield 0.028 g (97%) of **32** as an oil: IR (film) 3000, 2950, 2920, 2890, 1728, 1445, 1390, 1370, 1280, 1220, 1150, 1115, 1070, 990, 930, 840 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 1.65 (s, 3 H), 2.00 (s, 3 H), 3.60 (s, 2 H), 3.88 (d, J = 6 Hz, 2 H), 5.16 (d, J = 10 Hz, 1 H), 5.18 (d, J = 15 Hz, 1 H), 5.50–6.00 (m, 1 H).

***trans*-4-Acetoxy-3-chloro-3-(1-hydroxy-1-methylethyl)-1-(*tert*-butyldimethylsilyl)-2-azetidinone (33).** Glacial acetic acid (124 μL, 2.17 mmol) was added to a solution of 164 mg (1.15 mmol) of $Ca(OCl)_2$ (technical grade) in 2.0 mL of H_2O while stirring at room temperature. Then 253 mg (0.89 mmol) of the acetate **20** was added in one portion and the reaction allowed to stir at room temperature for 45 min. The reaction mixture was then poured into 20 mL of 5% $NaHCO_3$ and extracted with CH_2Cl_2 (2 × 10 mL). The combined organics were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash chromatography (10% EtOAc/CH_2Cl_2) to yield 0.100 g of **33** (34%) as a colorless oil: IR (film) 3500, 2940, 2860, 1720, 1470, 1370, 1320, 1260, 1200, 1120, 1070, 1010, 965, 935, 880, 845, 790, 735, 695, 675 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.18 (s, 6 H), 0.90 (s, 9 H), 1.32 (s, 3 H), 1.40 (s, 3 H), 2.08 (s, 3 H), 2.56 (s, 1 H), 6.26 (s, 1 H); ^{13}C NMR δ −6.4, −6.3, 18.2, 21.0, 25.1, 25.7, 26.0, 72.4, 80.8, 84.6, 167.7, 168.7. Anal. Calcd for $C_{14}H_{26}ClNO_4Si$: C, 50.06; H, 7.80; N, 4.17. Found: C, 49.70; H, 7.60; N, 4.19.

Acknowledgment. This investigation was supported by the Robert A. Welch Foundation and the donors of the Petroleum Research Fund, administered by the American Chemical Society. We thank the Chemistry Department

of Southern Methodist University for Lazenbee Postdoctoral Fellowships to M.N.R. and H.P. and Southern Methodist University for a teaching assistantship to R.Y.C. We also thank Dr. F. Dinnino and Dr. P. J. Reider (Merck, Sharp, and Dohme) for helpful discussions and Dr. M. Ohno (University of Tokyo) for providing us with copies of his spectra (corresponding to our compounds **26** and **27**).

Supplementary Material Available: Tables of bond lengths and angles, a list of anisotropic temperature factors for the non-hydrogen atoms, atomic coordinates, and crystal structure data (5 pages). Ordering information is given on any current masthead page.

Studies Related to the Robinson Transposition Reaction[1]

R. J. Pariza and P. L. Fuchs*

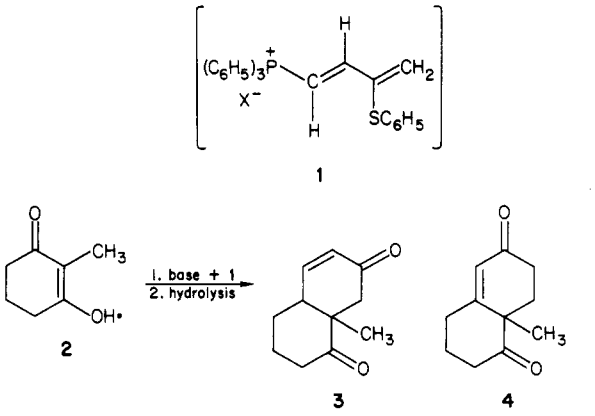
Department of Chemistry, Purdue University, West Lafayette, Indiana 47907

Received April 28, 1984

The formation and reactivity of 1,4-dichloro-2-(thio-substituted)-2-butenes is explored, leading to a new bis(phosphonium) salt, **18**. **18** may be used as a reagent to effect a functionalized four-carbon annulation sequence, analogous to the well-known Robinson annulation, but yielding enones that are transposed relative to the standard regiochemistry. Some mechanistic studies on the formation of **18** are described, along with trapping studies during the annulation process and various hydrolysis conditions for the resulting dienyl sulfides. Extensive use is made of ^{13}C and ^{31}P NMR and high-field ^{1}H NMR.

In our efforts to develop synthetic strategies applicable to quassinoid syntheses,[1,2] a reagent, **1**, was conceived which could be used to effect a four-carbon annulation reaction, yielding, after hydrolysis, an enone similar to the result of the widely used Robinson annulation reaction,[5] but transposed regiochemically, as shown in Scheme I. The desired product (**3**) from **1** and 2-methyl-1,3-cyclohexanedione (**2**) would resemble the well-known Wieland–Miescher ketone **4**, and indeed could conceivably be made from it using one of many known carbonyl transposition sequences.[4] Furthermore, the idea of a 1,4-nucleophilic addition to a dienylphosphonium salt is not new, but was demonstrated by Buchi and Pawlak[3a] and Fuchs[3b] several years ago. Martin and Desai[6] used (2-ethoxy-1,3-pentadienyl)triphenylphosphonium iodide to presumably generate unstable masked enones that were directly hydrolyzed to methyl-substituted enones with the standard Robinson[5] regiochemistry. Other reactions leading to ylides, via nucleophilic addition to vinylphosphonium salts, and cyclopropyl- and cyclobutylphosphonium salts have been used to form inter- and intramolecular products.[8] These reactions complement the usual way of generating an ylide: deprotonation of an adjacent carbon. Darling et al.[9] obtained products resulting from the conjugate addition of enolates to butadienylphosphonates, but these

Scheme I



adducts failed to undergo the intramolecular Wadsworth–Emmons[10] reaction. It is known that such reactions require an additional electron-withdrawing substituent to be successful.[11]

We have successfully produced a reagent which nicely fulfills the requirements of the Robinson transposition reaction.[12a] The reactions which are described are clean and can confidently be performed on a laboratory scale. The application of this strategy to the synthesis of bruceantin or other quassinoid compounds has not proven feasible, so alternate chemistry, ironically enough utilizing a standard Robinson sequence, was developed.[12b]

Results and Discussion

The initial attempt at preparation of reagent **1** was based upon the previously observed reaction of 2-thiophenylbutadiene[7a] (**5**) with triphenylphosphonium tetrafluoro-

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