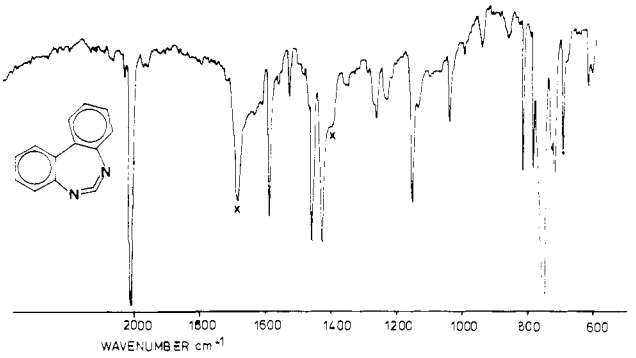

Figure 2. Infrared spectrum of dibenzo[*d*,*f*]-1,3-diazacyclohepta-1,2,4,6-tetraene at −196 °C. Bands marked X are due to impurities.

In view of these results, the stable intermediate in the interconversion of 2-pyridylnitrenes (eq 1) should now be formulated as the carbodiimide **11**, rather than the carbene **1**. The question whether **1** is formed at all, or whether it is in thermal equilibrium with **11** in the gas phase, cannot be answered at this time.[14]

The identification of the stable intermediate as the carbodiimide **11** receives strong support from the observation of a common intermediate in the pyrolyses of tetrazolo[5,1-*a*]isoquinoline (**14**) and tetrazolo[1,5-*a*]quinoline (**15**) (Scheme II). Sublimation of these compounds at or above 150 °C gave the previously unknown azides **16** and **17**, respectively, identified by their IR spectra at −196 °C and by the fact that they reverted to **14** and **15**, respectively, when warmed to −10 to 0 °C [**16**: IR 2140 (s), 2120 (s), 1350 (s) cm^{-1}. **17**: IR 2130 (vs), 2110 (s), 1330 (s) cm^{-1}]. The intensities of the azide absorptions increased with the pyrolysis temperature until ca. 380 °C, when a new and strong absorption at 2000 cm^{-1} appeared. The latter absorption increased in intensity till ca. 500 °C; the azide absorptions decreased over the same temperature interval. Above 500 °C, the 2000-cm^{-1} band started disappearing again, and new nitrile absorptions at 2225–2250 cm^{-1} appeared in its place. The latter absorptions remained unchanged at room temperature, and isolation and chromatographic separation of the material allowed their assignment to the two nitriles **22** and **23**, which had been identified previously.[4]

An optimal pyrolysis temperature for the observation of the 2000-cm^{-1} absorption was found at 490 °C. Under these conditions, only traces of the azides (**16** or **17**) remained, and only weak bands due to the end products **22** and **23** were present. The spectra recorded at −196 °C, following pyrolysis of either **14** or **15** at 490 °C, were identical, and we therefore assign them to a common intermediate, the carbodiimide **19**. When the matrix was warmed to ca. −55 °C, the carbodiimide band at 2000 cm^{-1} disappeared, and the nitriles **22** and **23** did *not* appear. Instead, a new compound, $C_{18}H_{12}N_4$, corresponding to a dimer of **19** was isolated. The two dimers formed from **14** and **15** were identical.[15]

These observations are summarized and interpreted in Scheme II. The formation of the common intermediate **19** demonstrates that both 1-isoquinolylnitrene (**18**) and 2-quinolylnitrene (**20**) undergo ring expansion under rather mild conditions, i.e., the activation energies cannot be significantly higher than those required for thermolysis of the azides **16** and **17**. It would be difficult to interpret the observed spectra in terms of the fused azirines **24** and **25** (Scheme II). These molecules would be expected neither to absorb at 2000 cm^{-1} nor to have identical IR spectra, or to give identical dimers. Furthermore, **24** and **25** are predicted to be unstable relative to the triplet nitrenes **18** and **20**,[16] and force-field–SCF calculations on the all-carbon analogues indicated that the heat of formation of **24** is 17 kcal/mol higher than that of **25**.[17] We therefore reinforce our original conclusion[6] that the seven-membered ring intermediates are more stable than the bicyclic azirines.

Since annelated benzene rings appeared to stabilize the cyclic carbodiimides, 9-azidophenanthridine (**26**) was also investigated.

26 27

26 was obtained by pyrolysis of tetrazolophenanthridine at 150–300 °C. At 490 °C, this azide had entirely disappeared, and an almost pure sample of the carbodiimide **27** was obtained, characterized by a strong absorption at 2010 cm^{-1} (Figure 2). **27** was stable in the solid state until ca. −40 °C, where rapid dimerization to a colorless, crystalline material occurred.[15] Pyrolyses of **26** at higher temperatures (700–800 °C) resulted in the formation of 4- and 9-cyanocarbazoles as previously described.[4,5]

In conclusion, we have shown that heteroarylnitrenes rearrange to diazacycloheptatetraenes in the gas phase under relatively mild conditions. The diazacycloheptatetraenes are remarkably stable and can even be prepared in quantity by deposition at −196 °C. These results open the possibility of a new chemistry of cyclic carbodiimides and related compounds.

(13) Harder, R.; Wentrup, C. *J. Am. Chem. Soc.* **1976**, *98*, 1259.

(14) (a) It is relevant to note that the chemistry of the all-carbon analogue of **1**, cycloheptatrienylidene, is usually rationalized in terms of carbene character, although indications of an equilibrium with cycloheptatetraene have appeared.[14b] Quantum-chemical calculations indicate that cycloheptatetraene is the most stable or even exclusive structure in this system.[14c] (b) Jones, W. M. *Acc. Chem. Res.* **1977**, *10*, 353–359. Mayor, C.; Jones, W. M. *J. Org. Chem.* **1978**, *43*, 4498–4502. (c) Tyner, R. L.; Jones, W. M.; Ohrn, Y.; Sabin, J. R. *J. Am. Chem. Soc.* **1974**, *96*, 3765–3769. Dewar, M. J. S.; Landman, D. *Ibid.* **1977**, *99*, 6179–6182.

(15) The X-ray structures of the dimers of **19** and **27** will be reported in the full paper. The dimer of **27** is a normal carbodiimide dimer, consisting of two units of **27** joined by an almost square four-membered ring. We thank Dr. W. Massa for the structure determination.

(16) See ref 10, 196–199.

(17) Lindner, H. J.; Wentrup, C., to be published.

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Received March 24, 1980

A Stereocontrolled Synthesis of (+)-Thienamycin

Sir:

The recent discovery of thienamycin (**1**)[1] and related, naturally occurring, carbapenem antibiotics has provided impetus for considerable synthetic activity due to both the novel chemical structure[1,2] and the unprecedented and highly desirable antibiotic

(1) *Thienamycin.* Isolation: J. S. Kahan, F. M. Kahan, R. Goegelman, S. A. Currie, M. Jackson, E. O. Stapley, T. W. Miller, D. Hendlin, S. Mochales, S. Hernandez, and H. B. Woodruff, 16th Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL, 1976, Abstr. 227; J. S. Kahan, F. M. Kahan, R. Goegelman, S. A. Currie, M. Jackson, E. O. Stapley, T. W. Miller, A. K. Miller, D. Hendlin, S. Mochales, S. Hernandez, H. B. Woodruff, and J. Birnbaum, *J. Antibiot.*, **32**, 1 (1979). Structure: G. Albers-Schonberg, B. H. Arison, E. Kaczka, F. M. Kahan, J. S. Kahan, B. Lago, W. M. Maiese, R. E. Rhodes, and J. L. Smith, 16th Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL, 1976, Abstr. 229; G. Albers-Schonberg, B. H. Arison, O. D. Hensens, J. Hirshfield, K. Hoogsteen, E. A. Kaczka, R. E. Rhodes, J. S. Kahan, F. M. Kahan, R. W. Ratcliffe, E. Walton, L. J. Ruswinkle, R. B. Morin, and B. G. Christensen, *J. Am. Chem. Soc.*, **100**, 6491 (1978). Biological Activity: H. Kropp, J. S. Kahan, F. M. Kahan, J. Sundelof, G. Darland, and J. Birnbaum, 16th Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL, 1976, Abstr. 228; F. P. Tally, N. V. Jacobus, and S. L. Gorbach, *Antimicrob. Agents Chemother.*, **14**, 436 (1978); S. S. Weaver, G. P. Bodey, and B. M. LeBlanc, *ibid.*, **15**, 518 (1979).

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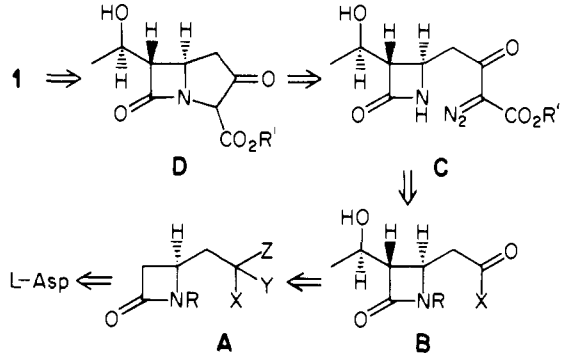
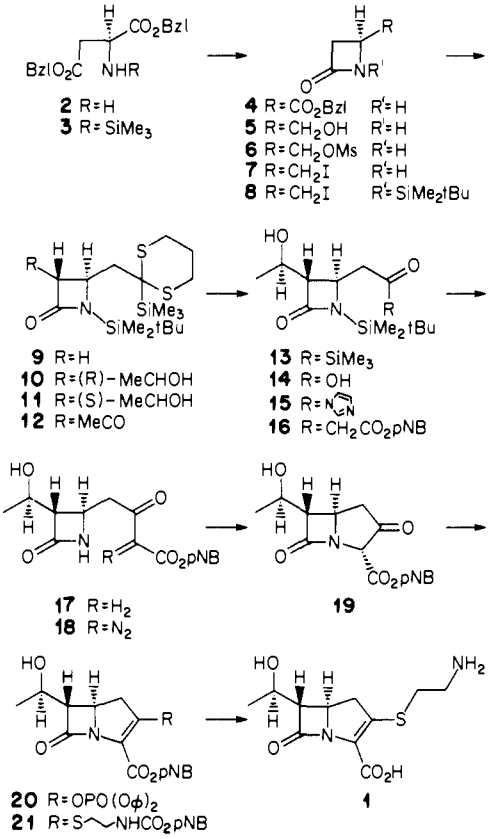
Scheme I



Scheme II



properties associated with this class of compounds.[1,2] Previous synthetic routes to thienamycin[3] and simpler analogues[4] have yielded racemic compounds and have relied on the formation of the C2–C3[5] bond as the penultimate step in the construction of the bicyclic ring system. We now report a stereocontrolled synthesis of (+)-thienamycin which employs a highly efficient carbene insertion reaction to produce the bicyclic nucleus by formation of the N–C3 bond.[6]

The evolution of the synthetic strategy ultimately employed for our approach to thienamycin was guided by three important considerations: (1) the chemical lability of the intact carbapenem nucleus, which suggested that construction of the bicyclic system be delayed until as late as possible in the synthetic sequence; (2) the desire to add both the cysteamine and the hydroxyethyl side chains onto preformed ring systems, thereby allowing facile preparation of analogues involving replacement of these groups; and (3) the desire to develop a chiral, stereocontrolled synthesis. With these considerations in mind, we formulated the general strategy outlined in retrosynthetic form in Scheme I.

Decomposition of diazo keto ester C and insertion of the resulting carbene into the azetidinone N–H bond would provide a mild, neutral route to bicyclic keto ester D, which, upon addition of cysteamine and net elimination of water, would provide the fully functionalized thienamycin ring system. The keto ester portion of C could be elaborated from an acyl derivative B, which in turn would be derived from a masked carboxylate A. Since intermediate A contains only one acidic center, stereocontrolled introduction of the hydroxyethyl group could be effected at this stage via the use of the enolate derived from A. Finally, elaboration of the azetidinone A from readily available and inexpensive L-aspartic acid would lead to thienamycin having the correct absolute configuration.

The initial problem to be addressed in the execution of Scheme I was the cyclization of aspartic acid to an appropriate azetidinone starting material. Although the literature is replete with examples of the cyclization of β-amino acids and esters to azetidinones,[7] in most cases the substrates are relatively simple with no potentially interfering substituents. For our purposes, a Grignard-mediated cyclization of an N-silylated aspartate diester seemed most promising.[8] Thus, dibenzyl aspartate **2**[9] was monosilylated (Me_3SiCl, Et_3N, Et_2O, 0 °C) to give compound **3** which, after filtration to remove the triethylammonium hydrochloride, was treated with *tert*-butylmagnesium chloride (1.0 equiv., 0 °C). After standing overnight at room temperature, the reaction mixture was hydrolyzed (2 N HCl saturated with NH_4Cl) to give chiral azetidinone ester **4** in 65–70% yield.[10]

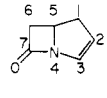
Reduction of **4** to alcohol **5** proceeded smoothly by using excess sodium borohydride in methanol.[11] Compound **5** was converted to mesylate **6** (CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0 °C) and subsequently to iodide **7** (NaI, acetone, Δ), which was N-protected as the *tert*-butyl(dimethylsilyl) derivative **8** (*tert*-$BuMe_2SiCl$, Et_3N,

(2) (a) *Epithienamycins.* Isolation and Structure: P. J. Cassidy, E. O. Stapley, R. Goegelman, T. W. Miller, B. Arison, G. Albers-Schonberg, S. B. Zimmerman, and J. Birnbaum, 17th Interscience Conference on Antimicrobial Agents and Chemotherapy, New York, 1977, Abstr. 81. (b) *Olivanic Acids.* Isolation and Structure: A. G. Brown, D. F. Corbett, A. J. Eglington, and T. T. Howarth, *J. Chem. Soc., Chem. Commun.*, 523 (1977); D. F. Corbett, A. J. Eglington, and T. T. Howarth, *ibid.*, 953 (1977); D. Butterworth, M. Cole, G. Hornscomb, and G. N. Robinson, *J. Antibiot.*, **32**, 287 (1979); J. D. Hood, S. J. Box, and M. S. Verrall, *ibid.*, **32**, 295 (1979). (c) *PS-5.* Isolation: K. Okamura, S. Hirata, A. Koki, K. Hori, N. Shibamoto, Y. Okumura, M. Okabe, R. Okamoto, K. Kouno, Y. Fukagawa, Y. Shimanchi, T. Ishikura, and J. Lein, *ibid.*, **32**, 262 (1979). Structure: K. Okamura, S. Hirata, Y. Okumura, Y. Fukagawa, Y. Shimanchi, K. Kouno, T. Ishikura, and J. Lein, *ibid.*, **31**, 480 (1978). Biological Activity: M. Sakamoto, H. Iguchi, K. Okamura, S. Hori, Y. Fukagawa, T. Ishikura, and J. Lein, *ibid.*, **32**, 280 (1979). (d) *MC696-SY2A.* K. Maeda, S. Takahashi, M. Sezaki, K. Iinuma, H. Naganawa, S. Kondo, M. Ohno, and H. Umezawa, *ibid.*, **30**, 770 (1977).

(3) D. B. R. Johnston, S. M. Schmitt, F. A. Bouffard, and B. G. Christensen, *J. Am. Chem. Soc.*, **100**, 313 (1978).

(4) (a) L. D. Cama and B. G. Christensen, *J. Am. Chem. Soc.*, **100**, 8006 (1978); (b) R. J. Ponsfred, P. M. Roberts, and R. Southgate, *J. Chem. Soc., Chem. Commun.*, 847 (1979); (c) A. J. G. Baxter, K. H. Dickinson, P. M. Roberts, T. C. Smale, and R. Southgate, *ibid.*, 236 (1979); (d) T. Kametami, S. Huang, and M. Ihara, *Heterocycles*, **12**, 1189 (1979); (e) For a related approach involving a synthesis from penicillin, see: H. Ononue, M. Narisada, S. Uyeo, H. Matsumura, K. Okada, T. Yano, and W. Nagata, *Tetrahedron Lett.* 3867 (1979).

(5) The numbering system employed for the carbapenem nucleus i is as shown below.



i

(6) A similar approach was used to construct the oxapenam ring system: L. D. Cama and B. G. Christensen, *Tetrahedron Lett.*, 4233 (1978).

(7) For recent reviews, see: A. K. Mukerjee and R. C. Srivastava, *Synthesis*, 327 (1973); N. S. Isaacs, *Chem. Soc. Rev.*, **5**, 181 (1976).

(8) The cyclization of *O,N*-bis(trimethylsilyl)-β-amino acids has been reported: L. Birkofer and J. Schramm, *Justus Liebigs Ann. Chem.*, 2195 (1975).

(9) L. Zervas, M. Winitz, and J. P. Greenstein, *J. Org. Chem.*, **22**, 1515 (1957).

(10) A sample of **4** was debenzylated (H_2, Pd/C, EtOH) and hydrolyzed (6 N HCl, 100 °C) to L-aspartic acid hydrochloride, which retained >97% of the original optical activity, thus indicating that racemization had not occurred under the cyclization conditions.

(11) See: W. F. Huffman, K. G. Holden, T. F. Buckley, J. G. Gleason, and L. Wu, *J. Am. Chem. Soc.*, **99**, 2352 (1977), and ref 10 cited therein.

DMF). The overall yield of **8** from L-aspartic acid was ca. 50%, and the sequence could conveniently be carried out on molar scale.

Reaction of **8** with 2-lithio-2-(trimethylsilyl)-1,3-dithiane[12] (THF, -78°C) gave the substituted dithiane derivative **9** in 70-80% yield. Direct aldol condensation of the enolate derived from **9** (LDA, THF, -78 °C) with excess acetaldehyde[13] gave a 97% yield of an approximately 1:1 mixture of the desired trans-*R* isomer **10** and the trans-*S* epimer **11**. A small amount (<5%) of the cis-*R* isomer was also isolated. In order to achieve stereocontrol in the preparation of **10**, an alternate approach was examined. Direct acylation of **9** (2 equiv. of LDA, THF, -78 °C, inverse quench into 2.0 equiv of *N*-acetylimidazole, THF, -78 °C)[14] provided acetyl compound **12** in 82% yield on the basis of recovered **9**. Alternatively, the mixture of isomers produced in the aldol reaction could be oxidized to **12** (TFAA-Me_2SO/Et_3N, CH_2Cl_2, -78 °C)[15] in 88% yield. In both cases, only one isomer of **12** could be detected, and this was assigned the thermodynamically preferred trans stereochemistry on the basis of the small (2.1 Hz) coupling constant between the azetidinone ring protons. Reduction of **12** with excess K-Selectride (KI, ether, 25 °C) gave an 87% yield of a 9:1 mixture of **10** and **11**. Thus, by this method, the stereocenters at C5 and C6 are completely specific, with the C8 center 90% controlled. Compounds **10** and **11** are readily separable at this point, and the undesired hydroxyethyl isomer **11** can be recycled by reoxidation to **12**.

Compound **10** is readily converted into carboxylic acid **14** (Scheme I, intermediate B) via a two-step process. Hydrolysis of **10** ($HgCl_2$, HgO, aqueous CH_3OH, Δ)[12] provided silyl ketone **13** in 93% yield. Warming **13** with a small excess of hydrogen peroxide in aqueous methanol gave carboxylic acid **14** in 76% yield after crystallization. The required keto ester chain was homologated by using a slight modification of the method recently reported by Masamune.[16] Thus, **14** was converted to imidazolide **15** (carbonyl diimidazole, THF, room temperature), which was treated in situ with the magnesium salt of the mono *p*-nitrobenzyl ester of malonic acid (THF, room temperature) to provide keto ester **16** in 86% yield. Brief treatment of **16** with methanolic HCl effected removal of the N-silyl protecting group to give **17** in >90% yield.[17] The desired cyclization precursor **18** was prepared in 90% yield by diazo exchange with *p*-carboxybenzenesulfonyl azide (Et_3N, CH_3CN, 0-20 °C).[18]

Previous model work[19] had shown rhodium(II) acetate to be the catalyst of choice for the carbenoid-mediated cyclization of diazo azetidinones such as **18**. In the present case, thermolysis of **18** at ca. 80 °C in benzene or toluene containing a catalytic amount of rhodium(II) acetate (substrate/catalyst ca. 1000:1) smoothly produced bicyclic keto ester **19** in essentially quantitative yield. To our knowledge, this is the most efficient method yet devised to construct a highly strained and reactive bicyclic β-lactam.

The final phase of the synthesis was accomplished by activating the keto ester of **19** by conversion to vinyl phosphate **20** (ClP(O)$(OPh)_2$, catalytic DMAP, *i*-Pr_2NEt, CH_3CN, 0 °C). Although this material could be isolated and carried on in a separate step, it was more convenient to directly treat it in situ with *N*-[[(*p*-nitrobenzyl)oxy]carbonyl]cysteamine[3] (*i*-Pr_2NEt, CH_3CN, -5 °C) to provide the bis-protected thienamycin derivative **21** in 70% overall yield. Catalytic hydrogenation of **21** (H_2, 40 psi, 10% Pd/C) gave **1** identical in all respects with natural thienamycin.

The use of the above general route for the preparation of thienamycin analogues will be reported in due course.

Acknowledgment. We thank Dr. C. Shunk for the preparation of numerous starting materials; J. Smith, H. Flynn, and Dr. B. Arison for mass spectral and 300-MHz NMR measurements; J. P. Gilbert and staff for microanalytical determinations; and J. Kahan for antibacterial assays.

Supplementary Material Available: Physical constants, optical rotations, infrared and proton magnetic resonance spectra for compounds **4**, **8**, **10**, **12**, **14**, **18**, **19**, and **21** (2 pages). Ordering information is given on any current masthead page.

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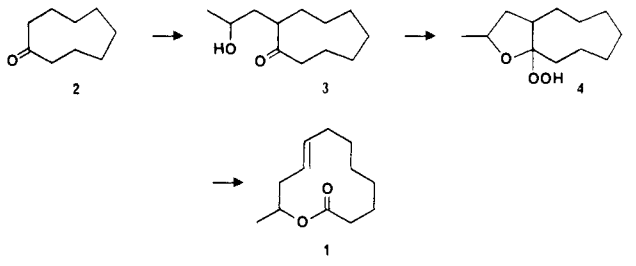
Fragmentation Reactions of α-Alkoxy Hydroperoxides and Application to the Synthesis of the Macrolide (±)-Recifeiolide

Sir:

As part of an investigation into the generation and synthetic usefulness of α-alkoxy hydroperoxides, we have studied new applications of the metal ion catalyzed fragmentation reactions of peroxides. Although a great deal is known about the mechanism of these reactions due to the elegant work of Kochi,[1] very few synthetic applications have been reported. We report our initial efforts which have led to a very short and efficient synthesis of (±)-recifeiolide (**1**), a naturally occurring macrolide isolated from the fungus *Cephalosporium recifei*.[2,3]

We have found that monoalkylation of the lithium enolate of cyclononanone with propylene oxide could be cleanly effected at -78 °C by the addition of 2.4 equiv of $AlMe_3$ to give the keto alcohol **3**[4-6] (80% yield, 96% based on recovered **2**). Treatment



(12) (a) A. G. Brook, J. M. Duff, P. F. Jones, and N. R. Davis, *J. Am. Chem. Soc.*, **89**, 431 (1968); (b) E. J. Corey, D. Seebach, and R. Freedman, *ibid.*, **89**, 434 (1968).

(13) The procedure used for this reaction was analogous to that reported in ref 3. The configurations of the various hydroxyethyl isomers were established by comparison of spectra to those of related compounds of unambiguous structure. See: F. A. Bouffard, D. B. R. Johnston, and B. G. Christensen, *J. Org. Chem.*, **45**, 1130 (1980).

(14) For a related example, see: S. L. Hartzell and M. W. Rathke, *Tetrahedron Lett.*, 2757 (1976).

(15) S. L. Huang, K. Omura, and D. Swern, *Synthesis*, 297 (1978); K. Omura and D. Swern, *J. Org. Chem.*, **41**, 3329 (1976).

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

(17) The Merck Process Research Department has prepared compound **17** in racemic form via an alternate synthetic route which is potentially amenable to the production of thienamycin on a commercial scale; see: D. G. Melillo, I. Shinkai, K. M. Ryan, T. M. H. Liu, and M. Sletzinger, *Tetrahedron Lett.*, **21**, 2783 (1980). Both approaches employ similar strategy for the ultimate conversion of **17** to thienamycin.

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

(19) R. W. Ratcliffe, T. N. Salzmann, and B. G. Christensen, *Tetrahedron Lett.*, 31 (1980).

(1) For a review, see: J. K. Kochi, "Free Radicals", Wiley-Interscience, New York, 1973, Vol. 1, Chapter 11, Vol. 2, Chapter 23.

(2) (a) R. F. Vesonder, F. H. Stodola, L. J. Wickerham, J. J. Ellis, and W. K. Rohwedder, *Can. J. Chem.*, **49**, 2029 (1971); (b) R. F. Vesonder, F. H. Stodola, and W. K. Rohwedder, *Can. J. Biochem.*, **50**, 363 (1972).

(3) For previous syntheses, see: E. J. Corey, P. Ulrich, and J. M. Fitzpatrick, *J. Am. Chem. Soc.*, **98**, 222 (1976); H. Gerlach, K. Oertle, and A. Thalmann, *Helv. Chim. Acta*, **59**, 755 (1976); K. Narasaka, M. Yamaguchi, and T. Mukaiyama, *Chem. Lett.*, 959 (1977); K. Utimoto, K. Uchida, M. Yamaya, and H. Nozaki, *Tetrahedron. Lett.*, 3641 (1977); B. M. Trost and T. R. Verhoeven, *ibid.*, 2775 (1978).

(4) Satisfactory spectroscopic data [^1H NMR, IR, mass spectrum (MS)] were obtained for all compounds. All experimental procedures and spectral data are included in the supplementary material.

0002-7863/80/1502-6163$01.00/0