ature under Ar with 20 mL of dry hexane; the extract was cooled to −70 °C and filtered under Ar. Concentration of the filtrate gave 1.27 g (68%) of **1** as an air-sensitive orange oil contaminated with small amounts of hydrocarbon impurities. Further purification was achieved by vacuum distillation, giving 0.81 g (43%) of a pale yellow oil: bp 130 °C (0.01 kPa); ^{1}H NMR [$(CD_2)_4O$] (vs. Me_4Si) δ 7.85 (d of d, 1, $J_{2,3}$ = 7.9, $J_{2,4}$ = 1.6 Hz, C_2H), 7.62 (d of d, 1, $J_{4,3}$ = 6.9, $J_{4,2}$ = 1.7 Hz, C_4H), 7.44 (d of d, 1, $J_{3,2} \approx J_{3,4} \approx 7$ Hz, C_3H), 1.02 (s, 6, Me); ^{13}C NMR (vs. Me_4Si) δ 137.8, 134.3, 132.5, 130.8, 125.6, 14.5 (br); ^{11}B NMR (vs. BF_3·OEt_2) δ + 79; mass spectrum,[14] *m/z* (relative intensity) 208 (100, M^+), 193 (26), 177 (44), 168 (60), 153 (75); high-resolution mass spectrum calcd for $^{12}C_{14}{}^1H_{18}{}^{11}B_2$ 208.1589, found 208.1600.

When a sample of **1** was treated with excess KH suspended in $(CH_2)_4O$ or $(CD_2)_4O$, a borohydride was obtained as evidenced by upfield shifts of the ^{1}H and ^{11}B NMR signals. It was isolated by evaporating the solvent from the supernatant solution and crystallization of the residue in CH_2Cl_2. Anal. Calcd for $C_{14}H_{19}B_2K$: C, 67.80; H, 7.72; B, 8.72; K, 15.76. Found: C, 67.65; H, 7.78; B, 8.54; K, 15.58. The resulting solid adduct displayed a very broad IR band at 2065 cm^{-1} and an ^{11}B NMR signal at +4 ppm, indicative of a bridged monohydride structure.[15] (The ^{1}H NMR peaks were centered at 7.1 and 0.0 ppm vs. Me_4Si.) Recrystallization of the solid from dioxane gave single crystals whose structure was determined[16] by X-ray diffraction (see Figure 1). The calculated structure verified that the adduct was in fact a bridged hydride. The two B–H bond lengths are 1.20 (5) and 1.49 (5) Å, while the B–H–B bond angle is 142 (4) °. These values are consistent with previously reported data for $B_2(C_4H_8)_2H_3^-$ as well as with a theoretical calculation[17] on $B_2H_7^-$. The B–H bond lengths in **1**·KH are somewhat longer than the experimentally determined[18] bridging bond lengths in $B_2H_7^-$. Otherwise, the formation of **1**·KH appears to involve less strain and the loss of fewer degrees of freedom than does the formation of previously described bridged borohydrides.

Compounds **1** abstracted hydride from a variety of triorganoborohydrides, including triphenylborohydride,[19] dimethyl-1-naphthylborohydride,[20] and the monohydride of the bis(borane)[21] from the reaction of butadiene with 2 equiv of 9-borabicyclononane. Thus, hydride anion is strongly chelated by **1**, forming a complex of unusual thermodynamic stability. (This behavior is reminiscent of that of **2** with monoammonium salts, leading us to propose that **1** be trivially named "hydride sponge".) The complex is kinetically stable as well, failing to reduce benzaldehyde in $(CH_2)_4O$ solution over 18 h at 60 °C. In an additional experiment, hydride was removed from bis(cyclopentadienyl)zirconium chloride hydride by **1**, which suggests **1** as a nondestructive reagent for detecting and sequestering hydride in organometallic systems.[22]

The behavior of **1** in the presence of anhydrous fluoride donors indicates that **1** forms a bridged adduct with fluoride as well. This adduct is characterized by a ^{1}H NMR doublet at 0.06 ppm (J_{HF} = 19 Hz) and a broad ^{19}F NMR signal at 195 ppm upfield from $CFCl_3$. On the other hand, **1** seems to interact weakly with chloride and bromide.

Further investigations of the physical organic chemistry of 1,8-diborylnaphthalenes are in progress. In addition, the 1,8-diborylnaphthyl unit may be useful as a building block in assembling anion binders containing several boranyl substituents, whose boron atoms are definitely spaced.

Supplementary Material Available: A listing of atomic positional and thermal parameters [K][$C_{14}H_{19}B_2$·$3O_2C_4H_8$ (7 pages). Ordering information is given on any current masthead page.

(14) We warmly thank W. P. Reents and A. M. Mujsce for obtaining the mass spectral data.

(15) Nöth, H.; Wrackmeyer, B. "Nuclear Magnetic Resonance Spectroscopy of Boron Compounds"; Springer-Verlag: New York, 1978.

(16) The X-ray structure was determined by Dr. C. S. Day of Crystalytics Co., Lincoln, NE. The crystals were orthorhombic, space group *Pbca*-D_{2h}^{15}, a = 16.343 (4) Å, b = 21.683 (5) Å, c = 17.183 (4) Å, $\alpha = \beta = \gamma = 90°$, V = 6089 (2) Å^3, and Z = 8. The structure was refined to R = 0.057 and R_w = 0.052 by using 1492 independent reflections of Cu Kα radiation, λ = 1.54184 Å, 2θ between 3.0° and 105.1°, and T = 20 °C. Additional details will be published at a later date.

(17) Raghavachari, K.; Schleyer, P. v. R; Spitznagel, G. W. *J. Am. Chem. Soc.* **1983**, *105*, 5917–5918.

(18) Shore, S. G.; Lawrence, S. H.; Watkins, M. I.; Bau, R. *J. Am. Chem. Soc.* **1982**, *104*, 7669–7670.

(19) Burlitch, J. M.; Burk, J. H.; Leonowicz, M. E.; Hughes, R. E. *Inorg. Chem.* **1979**, *18*, 1702–1709.

(20) Prepared from 1-lithionaphthalene and Me_2BOEt, bp 110 °C (0.03 kPa).

(21) Brown, H. C.; Pai, G. G.; Naik, R. G. *J. Org. Chem.* **1984**, *49*, 1072–1078.

(22) The hydridic character of organometallic hydrides is a topic of great current interest. See, for example: Bursten, B. E.; Gatter, M. G. *Organometallics* **1984**, *3*, 895–899.

The Total Synthesis of Quinocarcinol Methyl Ester†

Samuel J. Danishefsky,* Peter J. Harrison,
Robert R. Webb II, and Brian T. O'Neill

Department of Chemistry, Yale University
New Haven, Connecticut 06511

Received August 24, 1984

Takahashi and Tomita recently reported the isolation of two new antitumor antibiotics, quinocarcinol (**1**) and quinocarcin (**2**), from *Streptomyces melanovinaceus*.[1] These structures[2] invite comparison with another compound of similar biological behavior, naphthyridinomycin (**3**).[3,4] Given the congruence of naphthyridinomycin in its quinoidal segment with antibiotics such as the mitomycins,[5a] saframycin,[5b] and renieromycin,[5c] it might well have been conjectured that this substructure is critical for biological capability. However, the apparently potent activity of the quinocarcins would tend to suggest that the hexahydroiminoazepinoisoquinoline ring system, bearing a hydroxymethyl group at the 5-position, may house much of the antibiotic function.

Our interest in the recently discovered quinocarcins evolved from a long-term pursuit directed to the total synthesis of naphthyridinomycin. A strategy that resulted in a tetracyclic subunit, epimeric with that present in compound **3**, has recently been disclosed.[6] With some rather considerable modification this blueprint provided the basis for a synthetic attack on the quinocarcins. An account of experiments that led to the first total synthesis of quinocarcinol (**1**) is provided herein.

The first subtarget was the vinylisoquinolinol **13**. A new sequence to reach this ring system was devised.[7] Commercially available *m*-hydroxybenzaldehyde (**4**) was allylated (sodium hydride, allyl bromide, 93%) to afford **5**.[8b] Claisen rearrangement (*N*,*N*-dimethylaniline, 230 °C) gave, not unexpectedly,[9a] a pre-

† This paper is dedicated to Professor Peter Yates on the occasion of his 60th birthday.

(1) (a) Tomita, F.; Takahashi, K.; Shimizu, K. *J. Antibiot.* **1983**, *36*, 463. (b) Takahashi, K.; Tomita, F. *J. Antibiot.* **1983**, *36*, 468.

(2) Hirayama, N.; Shirahata, K. *J. Chem. Soc., Perkin Trans. 2*, **1983**, 1705.

(3) Sygusch, J.; Bussi, F.; Hanessian, S.; Kluepfel, D. *Tetrahedron Lett.* **1974**, 4021. Correct structural drawing is shown in: *Tetrahedron Lett.* **1975**, No. *3*, (errata).

(4) Kluepfel, D.; Baker, H. A.; Piattoni, G.; Sehgal, S. N.; Sidorowicz, A.; Singh, K.; Vezina, C. *J. Antibiot.* **1975**, *28*, 497. Kluepfel, D.; Sehgal, S. N.; Vezina, C. U.S. Patent 4 003 902; *Chem. Abstr.* **1977**, *86*, 119256*d*.

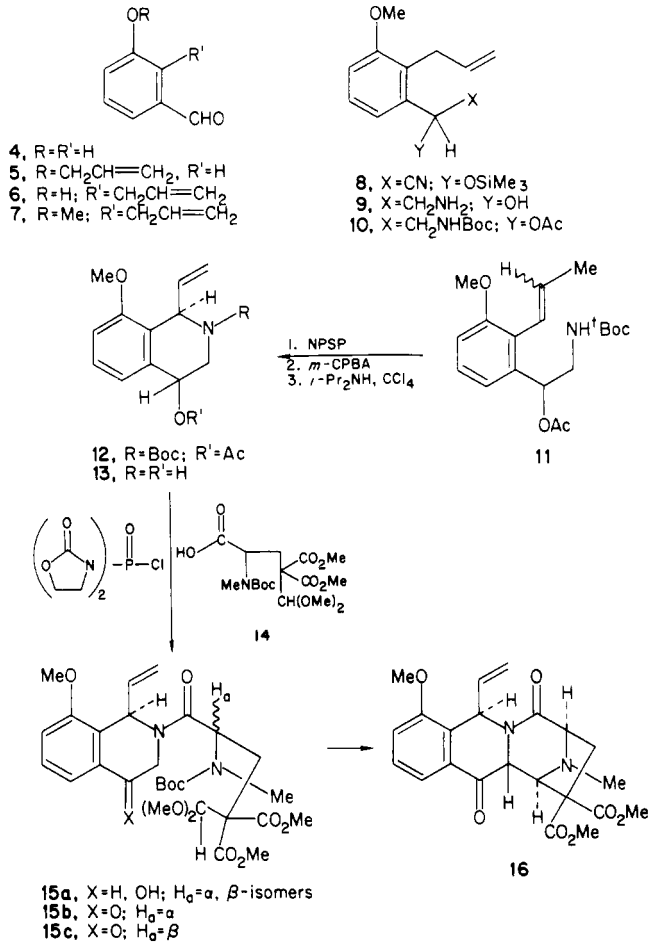
(5) (a) Franck, R. W. *Fortschr. Chem. Org. Naturst.* **1979**, *38*, 1. (b) Fukuyama, T.; Sachleben, R. A. *J. Am. Chem. Soc.* **1982**, *104*, 4957. (c) Frincke, J. M.; Faulkner, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 265.

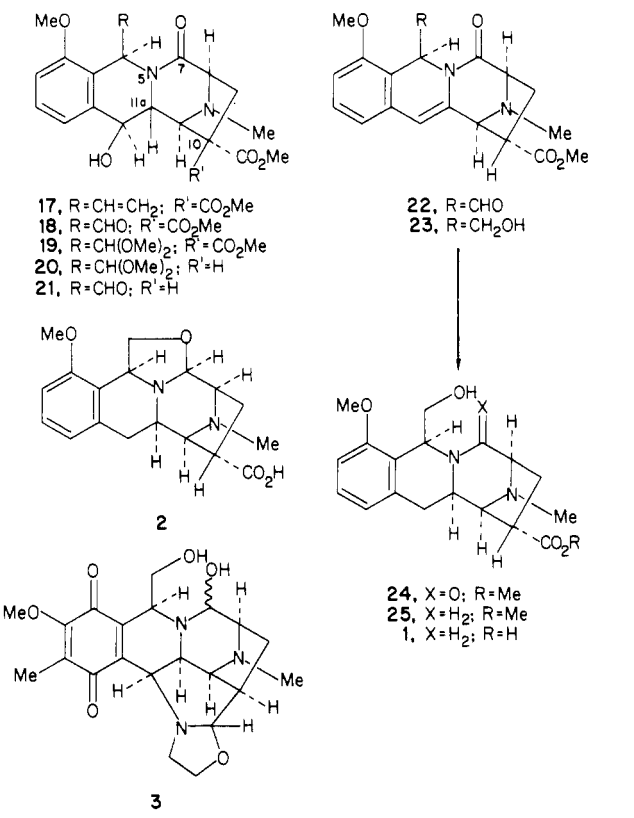
(6) (a) Danishefsky, S.; O'Neill, B. T.; Taniyama, E.; Vaughan, K. *Tetrahedron Lett.*, in press. (b) Danishefsky, S.; O'Neill, B. T.; Springer, J. P. *Tetrahedron Lett.*, in press.

(7) The modified Pomerantz–Fritsch approach used in the model case[6a] proved inapplicable in this case, in that it seems to require an activated aromatic ring (cf.: Euerby, M. R.; Waigh, R. D. *J. Chem. Soc, Chem. Commun.* **1984**, 127).

(8) (a) This compound was characterized by its NMR, infrared, and mass spectral properties. (b) This compound was characterized by its NMR, infrared, and mass spectral properties, as well as by combustion analysis.

0002-7863/85/1507-1421$01.50/0





ponderance[9b] of the 1,2,3-isomer **6**,[8b] which, upon methylation (sodium hydride, methyl iodide), afforded an 84% yield of **7**.[8a] Reaction of the latter with trimethylsilyl cyanide (KCN; 18-crown-6) gave compound **8**,[8a] which, upon reduction with lithium aluminum hydride, afforded the amino alcohol **9**,[8b] mp 91–93 °C. Sequential acylations, first with $(t\text{-BuOCO})_2O$ followed by acetic anhydride–triethylamine–4-(dimethylamino)pyridine, gave a 68% yield (overall from **7**) of Boc acetate **10**[8b] as a single crystalline compound, mp 106–108 °C. Conversion of the allyl group to a 3.5:1 mixture of *E*/*Z* isomers **11** was accomplished in quantitative (crude) yield through the agency of $PdCl_2$·$(MeCN)_2$ in methanol.[10]

The tetrahydroisoquinoline ring system was established[11a] by the reaction of **11** with the Nicolaou reagent, *N*-phenylselenophthalimide,[11b] in the presence of camphorsulfonic acid. Treatment of the resultant product with *m*-chloroperoxybenzoic acid, followed by heating in the presence of diisopropylamine, afforded a 50% overall yield (from **11**) of the racemic vinyl compound **12**,[8a] as a single diastereomer (TLC, 250-MHz NMR) of unassigned relative configuration.[12] Removal of the Boc and acetyl groups was smoothly accomplished by sequential treatment of **12** with trifluoroacetic acid followed by potassium carbonate in methanol to afford racemic **13**,[8b] mp 130–131 °C (configuration unassigned).

Compound **13** coupled with the racemic differentiated γ-carboxyglutamate derivative **14**[6a] under the conditions of Palomo-Coll[13] to afford a quantitative crude yield of the diastereomeric mixture **15a**. Oxidation of the latter according to the procedure of Swern[14] provided diastereomers **15b,c** (83% yield). Treatment of this mixture with BF_3·OEt_2 in chloroform under reflux gave the key tetracyclic intermediate **16**,[8b] mp 210–211 °C, in 28% yield. If it be assumed that **15b,c** is in fact a 1:1 mixture, this would correspond to a 56% yield from the *eligible* component **15b**, which has the properly "matched" (*R**,*R**) benzylic and glutamyl stereogenic centers. As in our model study,[6b] the other component, **15c**, where the centers are inappropriately matched for the synthesis of the quinocarcins, does not yield tetracyclic product.

With compound **16** in hand, there remained the requirements of conversion of the vinyl group at C_5 (quinocarcinol numbering) to a hydroxymethyl function, inversion of configuration at C_{11a}, replacement of the endo-carbomethoxy group by a hydrogen atom, and reduction of the lactam function at C_7. The program to achieve these adjustments commenced with reduction of compound **16** with zinc borohydride in methylene chloride to afford a quantitative (crude) yield of the β-alcohol **17**.[15] The vinyl group was cleaved by reaction with osmium tetroxide (catalytic) and sodium periodate in aqueous dioxane,[16] affording (84%) the hydroxy aldehyde **18**,[8b] mp 200 °C dec, which, upon reaction with trimethyl orthoformate, provided the acetal **19**,[8a] mp 211–212 °C, in 87% yield.

The critical stereoselective decarbomethoxylation was accomplished through the conditions of Krapcho (sodium cyanide–Me_2SO, 140 °C, 20 min), leading to a 75% yield of compound **20**,[8a,17] mp 199–201 °C. The acetal function was cleaved through treatment of **20** with aqueous trifluoroacetic acid, thereby pro-

(9) (a) Danishefsky, S. J.; Phillips, G. B. *Tetrahedron Lett.* **1984**, *25*, 3159. (b) A 3:1 ratio of compound **6** relative to the isomeric 1,2,4-product was produced from the Claisen rearrangement. Crystallization led to an enriched (ca. 6:1) ratio of the desired isomer. This material was carried forward in the indicated sequence. Complete removal of the undesired 1,2,4-isomer was achieved at the stage of crystallization of compound **10**.

(10) For previous use of the combination of Claisen rearrangement followed by double-bond migration to generate an *o*-propenylphenol, see: Danishefsky, S. J.; Uang, B.-J.; Quallich, G. *J. Am. Chem. Soc.* **1984**, *106*, 2453 and references therein.

(11) (a) Clive, D. L. J.; Wong, C. K.; Kiel, W. A.; Menchen, S. M. *J. Chem. Soc., Chem. Commun.* **1978**, 379. (b) Nicolaou, K. C.; Claremon, D. A.; Barnette, W. E.; Seitz, S. P. *J. Am. Chem. Soc.* **1979**, *101*, 3704.

(12) The *Z* isomer of **11** does not undergo appreciable cyclization under these conditions. It is recovered upon chromatographic purification of the crude tetrahydroisoquinoline selenide. The selenoxide elimination affords a ca. 7:1 ratio of **12** and its ethylidene isomers.

(13) Diago-Meseguer, J.; Palomo-Coll, A. L.; Fernández-Lizarbe, J. R.; Zugaza-Bilbao, A. *Synthesis* **1980**, 547.

(14) Mancuso, A. J.; Huang, S.∞L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(15) Reduction of **16** with sodium borohydride affords a 3:1 ratio of α-/β-alcohols. Conceivably the stereochemistry of the zinc borohydride reaction is governed by chelation of this metal to the tertiary nitrogen center.

(16) Pappo, R.; Allen, D. S., Jr.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478.

(17) A 10% yield of the *endo*-carbomethoxy isomer was also obtained.

viding (71%) aldehyde **21**,[8b] mp 217–218 °C. The C_{11a-12} double bond was installed by dehydration of the benzylic alcohol through the agency of the Burgess reagent, $Et_3N^+SO_2N^-CO_2Me$, in benzene under reflux,[18] to afford the enamido aldehyde **22**[8a] in 53% yield. Reduction of **22** with sodium borohydride afforded alcohol **23**[8a] in 83% yield. Reduction of the double bond of **23** through the action of hydrogen (1600 psi) on W_2 Raney nickel at 60 °C for 5 h[19] occurred cleanly from the α-face to afford (65%) 7-oxoquinocarcinol (**24**).[8a,20] Selective reduction of the lactam function of **24** was achieved through its reaction with BH_3·THF,[21] affording in 70% yield *dl*-quinocarcinol methyl ester (**25**). *The infrared, NMR (250 MHz), and mass spectra of racemic* ***25*** *prepared through total synthesis were identical with those of an authentic sample prepared by esterification of a small specimen of quinocarcinol with diazomethane.* In addition, hydrolysis of synthetic **25** (NaOH, MeOH) led to *dl*-quinocarcinol (**1**), whose NMR spectrum in methanol-d_4 matched exactly that of authentic quinocarcinol, a sample of which was kindly provided by Dr. Fusao Tomita of Tokyo Research Laboratories, Kyowa Hakko Kogya Co. Ltd.

Acknowledgment. This work was supported by PHS Grant AI16943. P.H. gratefully acknowledges financial support of the Science and Engineering Research Council (England) through a Postdoctoral Fellowship, funded in part by NATO. R.W. gratefully acknowledges a fellowship from the National Institutes of Health. NMR spectra were obtained through the auspices of the Northeast Regional NSF/NMR Facility at Yale University, which was supported by NSF Chemistry Division Grant CHE 7916210.

(18) Burgess, E. M.; Penton, H .R., Jr.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26.

(19) Similar conditions were employed by Fukuyama in his synthesis of saframycin.[5b]

(20) The reduction also produces small amounts of (±)-quinocarcinol methyl ester (**25**) as well as a diol lactam arising from reduction of the ester group of **24**.

(21) At this writing, attempts to achieve the partial reduction of the lactam of **24** to the corresponding carbinolamine, which would presumably undergo conversion to quinocarcin (**2**) methyl ester, have been unsuccessful. Similarly, attempted oxidation of **25** to produce quinocarcin (**2**) methyl ester has failed.

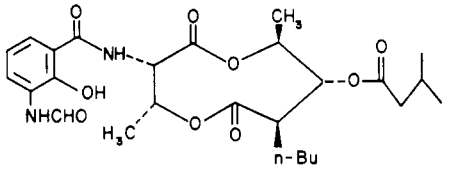
Synthesis of (+)-Antimycin A_3. Use of the Oxazole Ring in Protecting and Activating Functions

Harry H. Wasserman* and Ronald J. Gambale

Department of Chemistry, Yale University
New Haven, Connecticut 06511

Received October 5, 1984

Antimycin A_3 (**13**),[1] a unique unsymmetrical nine-membered dilactone isolated from a number of *Streptomyces* strains,[2] exhibits



both antibiotic and antifungal activity.[2] The most active among four isolated components, A_3, has been synthesized by Kinoshita[3] and Nakata.[4]

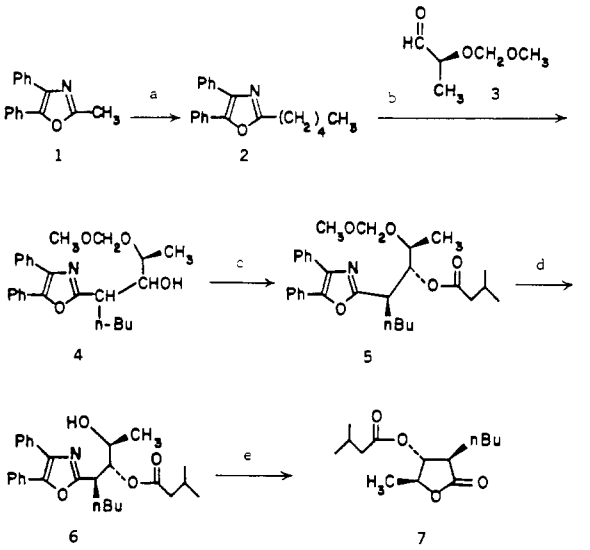
(1) (a) For isolation of antimycin A_3, see: Lockwood, J. L.; Leben, C.; Keitt, G. W. *Phytopathology* **1954**, *44*, 438 and references therein. (b) For structural determination, see: Kinoshita, M.; Aburaki, S.; Umezawa, S. *J. Antibiot.* **1972**, *25*, 373 and references therein.

(2) Liu, W.-C.; Strong, F. M. *J. Am. Chem. Soc.* **1959**, *81*, 4387.

(3) For the synthesis of anytimycin A_3 in optically active form, see: Aburaki, S.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 198 and references therein.

(4) Nakata, T.; Fukui, M.; Oishi, T. *Tetrahedron Lett.* **1983**, *24*, 2657.

Scheme I[a]



[a] (a) *n*-BuLi, *n*-BuI, −78 °C, THF; (b) *n*-BuLi, THF, −78 °C; (c) $ClCOCH_2CH(CH_3)_2$, pyridine; (d) BF_3·OEt_2, PhSH, CH_2Cl_2; (e) $^1O_2$, CH_2Cl_2, Sensitox, 25 °C, 3 h.

In previous studies,[5] we have developed a mild and efficient method of macrolide ring closure through the photooxygenation of suitably substituted 2-alkyl-4,5-diphenyloxazoles. We now report the application of this procedure to the synthesis of antimycin A_3. In this work, the stability of the oxazole unit toward acidic and basic reagents coupled with the efficient conversion to the activated triamide species avoids extra protection–deprotection–activation sequences. In addition, the ease of electrophilic addition to the 2α-methylene anion permits sequential alkylation and condensation with an appropriately protected chiral aldehyde,[6] resulting in access to the "right half" of the dilactone skeleton containing three contiguous chiral centers.

In the first phase of the synthesis, we used an oxazole substrate as the nucleus for the formation of the 2,3-*erythro*-3,4-*erythro*-2-*n*-butyl-3,4-dihydroxy segment. Thus, 2-methyl-4,5-diphenyloxazole (**1**) was alkylated with 1-iodobutane in standard fashion yielding **2** [15](93%), which was treated with *n*-butyllithium (THF, −78 °C) followed by addition of (*S*)-2-[(methoxy)methoxy]propanal[7,15] (**3**) to give a mixture of four diastereomers **4a–d**[8,15]

(5) Wasserman, H. H.; Gambale, R. J.; Pulwer, M. J. *Tetrahedron* **1981**, *37*, 4059.

(6) (a) Massad, S. K.; Hawkins, L. D.; Baker, D. C. *J. Org. Chem.* **1983**, *48*, 5180. (b) Kelly, T. R.; Kaul, P. N. *J. Org. Chem.* **1983**, *48*, 2775.

(7) Ethyl L-(+)-lactate was treated with dimethoxymethane and phosphorus pentoxide to obtain ethyl (*S*)-2-[(methoxy)methoxy]propanoate[15] (85%), $[\alpha]^{22}_D$ −88.1° (*c* 2.85, $CHCl_3$), bp 39 °C (0.35 mmHg), which was reduced (DIBALH, CH_2Cl_2, −78 °C, ref 6) to (*S*)-2-[(methoxy)methoxy]-propanal (**3**) (52%). Compound **3** was characterized as its 2,4-DNP derivative,[15] $[\alpha]^{22}_D$ −96.1° (*c* 2.00, $CHCl_3$), mp 83.0–83.5 °C.

(8) HPLC analysis (3.9 mm × 30 cm μ-Porasil column, Waters Assoc., Inc.; eluent, 92:8 hexanes/EtOAc at a flow rate of 7.0 mL/min) indicated a mixture of four diastereomers **4a–d** in 4:3:2:1 ratio (t_R 7.5, 4.5, 10.2, and 5.7 min, respectively). The major isomer **4a** was independently converted to the correct stereoisomer **5a** (isovaleryl chloride, pyridine, DMAP, 21%).

(9) The ratio of stereoisomers **5a–d** was 4:3:2:1, respectively, by isolated yields after chromatography.

(10) Kieczykowski, G. R.; Quesada, M. L.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 782.

(11) Compound **7** exhibited physical and spectroscopic properties (bp, $[\alpha]^{23}_D$, IR) in complete agreement with the values reported by M. Kinoshita,[3] In addition, the 90-MHz ^{1}H NMR spectrum was entirely consistent with a 100-MHz spectrum graciously provided by M. Kinoshita. For alternate syntheses, see: Heathcock, C. H.; Pirrung, M. C.; Lampe, J.; Buse, C. T.; Young, S. D. *J. Org. Chem.* **1981**, *46*, 2290 and references therein.

(12) Yonehara, H.; Takeuchi, S. *J. Antibiot., Ser. A* **1958**, *11*, 122, 254.

(13) *N*-Carbobenzoxy-L-threonine was treated with *tert*-butyldimethylsilyl chloride and imidazole in DMF to give **8**[15] (64%), mp 154–157 °C, $[\alpha]^{22}_D$ +10.5° (*c* 1.69, $CHCl_3$).

(14) Ziegler, F. E.; Berger, G. D. *Synth. Commun.* **1979**, *9*, 539.

0002-7863/85/1507-1423$01.50/0