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.

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(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

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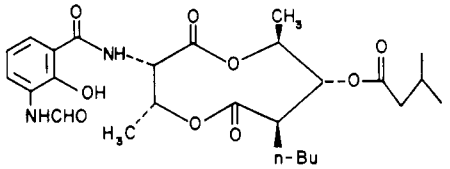
Antimycin A_3 (**13**),[1] a unique unsymmetrical nine-membered dilactone isolated from a number of *Streptomyces* strains,[2] exhibits



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

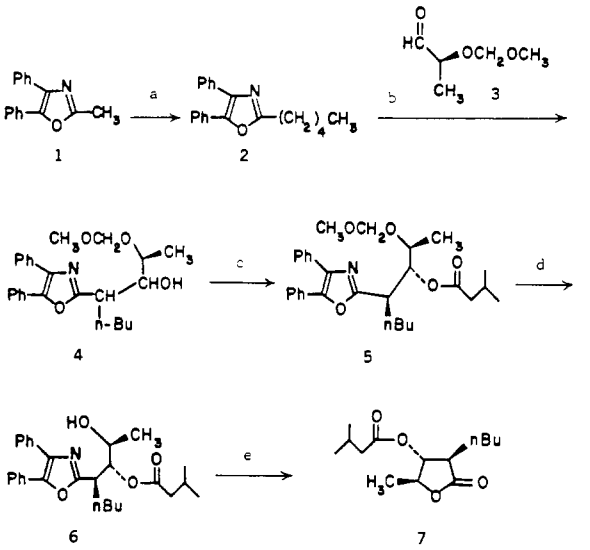
(1) (a) For isolation of antimycin A_3, see: Lockwood, J. L.; Leben, C.; Keitt, G. W. *Phytopathology* **1954**, *44*, 438 and references therein. (b) For structural determination, see: Kinoshita, M.; Aburaki, S.; Umezawa, S. *J. Antibiot.* **1972**, *25*, 373 and references therein.

(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.

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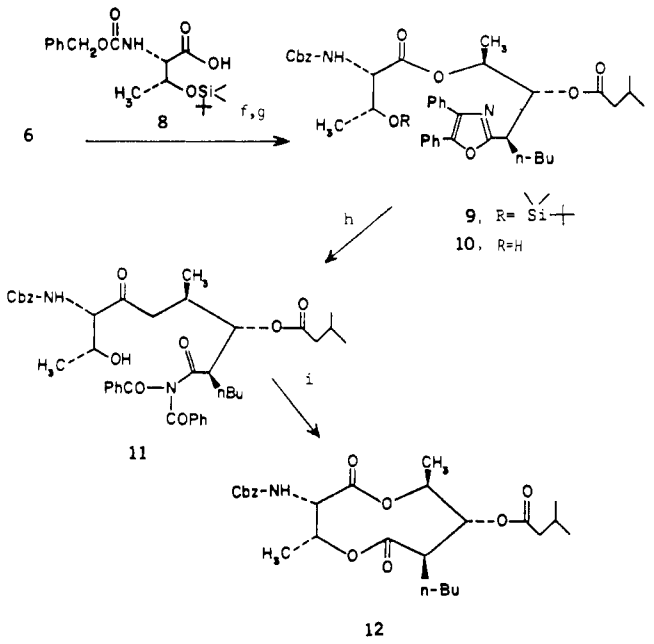
Scheme II[a]



[a] (f) DCC, DMAP, CH_2Cl_2; (g) n-Bu_4NF, THF, 0 °C; (h) $^1O_2$, CH_2Cl_2, Sensitox, 25 °C, 3 h; (i) pyridinium p-toluenesulfonate, xylenes, Δ.

(58%). The mixture **4a-d** was then acylated with isovaleryl chloride in pyridine, forming the corresponding esters **5a-d**[15] (74%). From the ester mixture, which was more easily separated on a larger scale by chromatography than **4a-d**, it was possible to obtain stereoisomer **5**, having the natural configuration, as the major diastereomeric component.[9] Deprotection was achieved with boton trifluoride etherate and thiophenol[10] affording the hydroxy oxazole **6**[15] (57%).

At this stage of our work, we were able to establish the absolute stereochemistry of **6** by converting it to (+)-blastmycinone (**7**)[2,11] (Scheme I), a product of mild saponification[12] of antimycin A_3 (**13**). This was accomplished by photooxygenation of **6** (Sensitox, CH_2Cl_2, 25 °C, 3 h), forming **7** (35%) as the sole isolable lactone species.

Continuing the synthesis, stereoisomer **6** was then condensed with the *N*-carbobenzoxy-L-threonine derivative **8**[13] (DCC, DMAP, CH_2Cl_2)[14] to give ester **9**[15] (95%). In this esterification process, the latent carboxylate in the molecule remained well protected within the oxazole framework. The *tert*-butyldimethylsilyl ether was then removed (n-Bu_4NF, THF, 0 °C), yielding the ω-hydroxy oxazole **10**[15] (64%). Dye-sensitized photooxygenation of **10** (Sensitox, CH_2Cl_2, 25 °C, 3 h) led cleanly to the activated triamide **11**, which was dissolved in xylenes and added slowly to a refluxing solution of pyridinium p-toluenesulfonate in xylenes. Under these conditions of buffered acid catalysis, the desired nine-membered dilactone **12** was isolated (20%) (Scheme II).

Compound **12** exhibited physical and spectroscopic properties (melting point, $[\alpha]^{22}_D$, IR, high-resolution MS) in complete accord with those values reported by M. Kinoshita.[3] In addition, the 100-MHz ^1H NMR spectrum of **12** was indistinguishable from the spectrum of authentic dilactone kindly provided by M. Kinoshita. The final steps in the conversion of compound **12** to (+)-antimycin A_3 (**13**)[3] have previously been reported by Kinoshita,[3] and our work thus constitutes a formal synthesis of the naturally occurring macrolide. The construction of the medium-ring dilactone system in **12** by this method further illustrates the applicability of the oxazole-triamide rearrangement to the formation of macrolides.

(15) Satisfactory IR, ^1H NMR, elemental analyses, and/or high-resolution mass spectra were obtained.

(16) Polymer-bound Rose Bengal, available commercially from Hydron Laboratories, New Brunswick, NJ.

Acknowledgment. This work was supported by NIH Grant GM-13854. The support of the NSF/NMR Northeast Regional Facility at Yale University (Grant CHE-7916210) is acknowledged. We thank Dr. M. Kinoshita, Keio University, Yokohama, for spectroscopic data on (±)-blastmycinone (**7**) and the dilactone **12** and Dr. William Murray, Ortho Pharmaceuticals, for assistance in determining the 100-MHz NMR spectra of **12**.

An Extremely Efficient Method for One-Pot, Three-Component, 2 + 2 + 2 Construction of Functionalized Cyclohexenes

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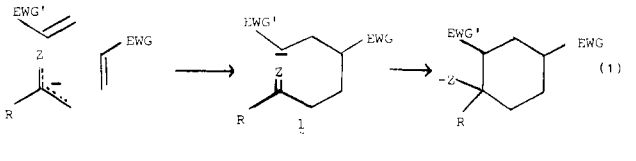
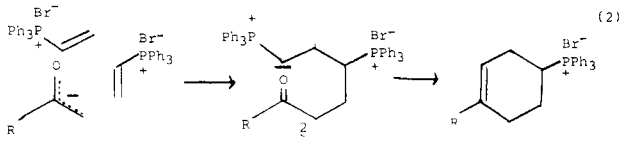
Formation of more than one carbon-carbon bond in a reaction vessel allows rapid and efficient conversion of simpler into structurally more complex organic molecules. Such very fundamental and popular operations as Diels-Alder cycloadditions[1] and Robinson annulations[2] attest to the great importance of multiple C-C bond-forming processes in rapid and efficient construction of cyclohexene structural units from two simpler components.[3] We envisioned that formation in one pot of *three* carbon-carbon bonds producing a six-membered carbocycle should be possible via sequential *Mi*chael-*Mi*chael-*ri*ng *c*losure (MIMIRC) reactions as illustrated in general by eq 1 (Z = O or NR); polymerization



(1)



(2)

of the Michael acceptor should be interrupted by the anticipated cyclization of reactive intermediate **1**.[4,5] This communication describes the development[6] of this idea in the form of a powerful method for connecting three separate two-carbon units in an efficient 2 + 2 + 2 construction of some phosphorus-substituted cyclohexenes (eq 2); the annulation sequence is consummated by an intramolecular Wittig reaction of intermediate keto ylide **2**.

(1) (a) Kloetzel, M. C. *Org. React.* **1948**, *4*, 1. (b) Holmes, H. L. *Ibid.* **1948**, *4*, 60. (c) Butz, L. W.; Rytina, A. W. *Ibid.* **1949**, *5*, 136. (d) Wasserman, A. "Diels-Alder Reactions"; Elsevier Publishing Co.: New York, 1965. (e) Wollweber, H. "Diels-Alder Reakton"; Georg Thieme Verlag: Stuttgart, 1972. (f) Bonjouklian, R.; Ruden, R. A. *J. Org. Chem.*, **1977**, *42*, 4095.

(2) House, H. O. "Modern Synthetic Reactions", 2nd ed.; Benjamin: New York, 1972; pp 606-611, 621-623.

(3) Other important multiple C-C bond-forming reactions include the following: (a) Robinson-Schopf synthesis of tropane alkaloids by a series of Mannich condensations (four C-C bonds are formed in one pot) (Robinson, R. *J. Chem. Soc.* **1917**, *111*, 762, 876. Schopf, C. *Angew. Chem.* **1937**, *50*, 779, 797). (b) Stevens alkaloid synthesis (three C-C bonds in one pot (Stevens, R. V. *J. Chem. Soc., Chem. Commun.* **1983**, 1425). (c) Gadek, T. R.; Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 802.

(4) For our first example of the validity of this concept, see: Posner, G. H.; Mallamo, J. P.; Black, A. *Tetrahedron* **1981**, *37*, 3921.

(5) For other examples of one-pot MIMIRC reactions, see: (a) Cory, R. M.; Chan, D. M. T. *Tetrahedron Lett.* **1975**, 4441. (b) Spitzner, D.; Engler, A.; Liese, T.; Splettstosser, G.; Meizere, A. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 791. (c) Fouchet, B.; Joucha, M.; Messager, J. C.; Toupet, L. *J. Chem. Soc., Chem. Commun.* **1982**, 858. (d) Danishefsky, S.; Chackalamannil, S.; Silvestri, M. *J. Org. Chem.* **1983**, *48*, 3615. (e) Danishefsky, S.; Harrison, P.; Silvestri, M.; Segmuller, B. *Ibid.* **1984**, *49*, 1319.

(6) The first example of this process is due to: Cory, R. M.; Chan, D. M. T.; Nagrub, Y. M. A.; Rastall, M. H.; Renneboog, R. M. *J. Org. Chem.* **1980**, *45*, 1852.

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