gel; 10% EtOAc/hexane + 25% EtOAc/hexane) yielded starting material (10 mg, 0.045 mmol) and a mixture (4.5:1) of the enol phosphates **19** and **20** (125 mg, 0.35 mmol, 78% yield). A solution of the enol phosphates (202 mg, 0.57 mmol) and *t*-BuOH (403 mg, 5.4 mmol) in THF (4 mL) was added dropwise to a solution of lithium metal (55 mg, 7.92 mmol) in dry refluxing methylamine (10 mL). The mixture was stirred for 30 min, after which the reaction was quenched with solid sodium benzoate and then saturated aqueous NH_4Cl. The solution was allowed to warm to room temperature and the methylamine allowed to evaporate. The remaining solution was diluted with pentane and washed with 10% HCl, saturated $NaHCO_3$, and saturated NaCl. The organic layer was dried over $NaSO_4$ and filtered through a small amount of silica gel. The solvent was then removed cautiously on a rotary evaporator. A 4.5:1 mixture of silphinene (**1**) and isosilphinene (**21**) was obtained (115 mg, 0.56 mmol, 99% yield). Pure silphinene was isolated by column chromatography on 15% $AgNO_3$/silica gel eluted with 2% benzene/hexane. The NMR spectrum of the synthetic silphinene was identical with that of a comparison spectrum of authentic silphinene provided by Professor D. D. Sternbach.

Silphinene (**1**): ^1H NMR (250 MHz, $CDCl_3$) 0.82 (d, J = 6.0 Hz, 3 H), 0.93 (s, 3 H), 0.99 (s, 3 H), 1.08 (s, 3 H), 1.14-1.36 (band, 3 H), 1.67 (AB, 2 H), 1.77-2.08 (band, 3 H), 2.19 (ddd, J = 13.6 Hz, 2.4 Hz, 2.4 Hz, 1 H), 2.49 (ddd, J = 13.6 Hz, 2.4 Hz, 2.4 Hz, 1 H), 5.46 (m, 1 H), 5.60 (m, 1 H); ^{13}C NMR (200 MHz, $CDCl_3$) 16.43, 26.65, 27.40, 27.64, 30.95, 37.43, 38.58, 38.36, 49.22, 50.95, 58.33, 63.73, 72.83, 125.36, 138.41 Isosilphinene (2): ^1H NMR (250 MHz, $CDCl_3$) 0.87 (s, 3 H), 0.98 (s, 3 H), 0.99 (d, J = 6.0 Hz, 3 H), 1.02 (s, 3 H), 1.09-1.45 (band, 3 H), 1.58 (AB, 2 H), 1.61-1.97 (band, 3 H), 2.06 (d, J = 13.6 Hz, 1 H), 2.67 (d, 13.6 Hz, 1 H), 5.50 (s, 2 H,). ^{13}C NMR (200 MHz, $CDCl_3$) 17.04, 23.42, 26.97, 27.20, 27.93, 32.28, 37.00, 38.63, 41.12, 53.95, 57.87, 64.19, 67.92, 126.03, 142.62.

Acknowledgment. We gratefully acknowledge financial support from the National Institutes of Health (AI-20283), the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the University of North Carolina for a Junior Faculty Development Award to M.T.C. Thanks are due to Lori D. Bredon and Dr. David H. Harris for assistance in recording 250-MHz NMR spectra. We also thank Professor Daniel D. Sternbach for providing authentic spectra of silphinene for comparison purposes.

Cationic Cyclopentaannelation: An Efficient Methylenomycin Synthesis

Marcus A. Tius,* Donald P. Astrab, Abdul H. Fauq, Jean-Bernard Ousset, and Sanjay Trehan

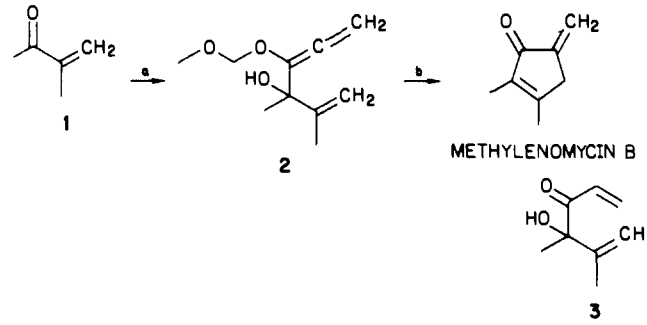
Contribution from the Department of Chemistry, University of Hawaii, Honolulu, Hawaii 96822.
Received September 23, 1985

Abstract: A cationic cyclopentaannelation reaction which was discovered in our laboratories has been used for an extremely short and efficient synthesis of some methylenomycins. Methylenomycin B was prepared in two steps. (±)-Desepoxy-4,5-didehydromethylenomycin A and (±)-desdihydroxy-4,5-didehydroxanthocidin have also been prepared in order to demonstrate the scope and the efficiency of this unusual cyclization.

Cyclopentanoid antibiotics have been the focus of considerable synthetic activity in recent years. The isolation of methylenomycins A and B from a streptomycete strain and the elucidation of their structure in 1974[1] were followed by disclosure of their synthesis by several groups.[2] Xanthocidin, the most densely functionalized member of this class of compounds and a highly unstable molecule, was prepared by Smith through a very ingenious route in 1983.[3] The interest that the methylenomycins have elicited is due to their unusual structure and their promising profile of antibiotic and antineoplastic activity. Methylenomycin A is effective against Lewis lung carcinoma in mice.[4] Methylenomycin A and methylenomycin B are active against Gram-positive and Gram-negative bacteria and are cytotoxic in vitro in the KB assay.[1,5]

A cationic cyclopentaannelation reaction which was discovered in our laboratories[6] appeared to offer an extremely direct method

Scheme I.[a] Synthesis of Methylenomycin B



[a] (a) 4 equiv of α-lithio-α-(methoxymethyl)allene, THF/ether (1:1) -78 °C, 88%; (b) 3 equiv of $(CF_3CO)_2O$, 5 equiv of 2,6-lutidine, CH_2Cl_2, -20 °C, 74%.

(1) Methylenomycins A and B were isolated from a strain of *Streptomyces violaceoruber*: Haneishi, T.; Kitahara, N.; Takiguchi, Y.; Arai, M.; Sugawara, S. *J. Antibiot.* **1974**, *27*, 386-392. Haneishi, T.; Terahara, A.; Arai, M.; Hata, T.; Tamura, C. *Ibid.* **1974**, *27*, 393-399. Desepoxy-4,5-didehydromethylenomycin A was isolated from *Streptomyces coelicolor* A3(2): Hornemann, U.; Hopwood, D. A. *Tetrahedron Lett.* **1978**, 2977-2978.

(2) (a) Jernow, J.; Tautz, W.; Rosen, P.; Williams, T. H. *J. Org. Chem.* **1979**, *44*, 4212-4213. (b) Newton, R. F.; Reynolds, D. P.; Eyre, T. *Synth. Commun.* **1981**, *11*, 527-532. (c) Takahashi, Y.; Kosugi, H.; Uda, H. *J. Chem. Soc., Chem. Commun.* **1982**, 469-497. (d) Billington, D. C.; Pauson, P. L. *Organometallics* **1982**, *1*, 1560-1561. (e) Strunz, G. M.; Lal, G. S. *Can. J. Chem.* **1982**, *60*, 2528-2530. (f) Siwapinyoyos, T.; Thebtaranonth, Y. *J. Org. Chem.* **1982**, *47*, 598-599. (g) Doutheau, A.; Sartoretti, J.; Gore, J. *Tetrahedron* **1983**, *39*, 3059-3065. (h) Negishi, E.; Miller, J. A. *J. Am. Chem. Soc.* **1983**, *105*, 6761-6763. (i) Mikolajczyk, M.; Balczewski, P. *Synthesis* **1984**, 691-694. (j) Pohmakotr, M.; Chancharunee, S. *Tetrahedron Lett.* **1984**, 4141-4144. (k) Cameron, A. G.; Hewson, A. T.; Osammor, M. I. *Tetrahedron Lett.* **1984**, 2267-2270. (l) Scarborough, R. M., Jr.; Smith, A. B., III. *J. Am. Chem. Soc.* **1977**, *99*, 7085-7087. (m) Scarborough, R. M., Jr.; Toder, B. H.; Smith, A. B., III. *J. Am. Chem. Soc.* **1980**, *102*, 3904-3913. (n) Jernow, J.; Tautz, W.; Rosen, P.; Blount, J. F. *J. Org. Chem.* **1979**, *44*, 4210-4212. (o) Takahashi, Y.; Isobe, K.; Hagiwara, H.; Kosugi, H.; Uda, H. *J. Chem. Soc., Chem. Commun.* **1981**, 714-715. (p) Koreeda, M.; Chen, Y. P. L. *Tetrahedron Lett.* **1981**, 15-18. (q) Boschelli, D.; Scarborough, R. M., Jr.; Smith, A. B., III. *Tetrahedron Lett.* **1981**, 19-22.

(3) Smith, A. B., III; Boschelli, D. *J. Org. Chem.* **1983**, *48*, 1217-1226.

(4) Terahara, A.; Haneishi, T.; Arai, M. *Heterocycles* **1979**, *13*, 353-361.

(5) Tius, M. A.; Patterson, G. M. L.; Astrab, D. P. *J. Antibiot.* **1985**, *38*, 1061-1067.

0002-7863/86/1508-3438$01.50/0

for the preparation of substituted α-methylene cyclopentanones from acyclic precursors. In the discussion which follows it is shown that the cyclopentaannelation reaction is broadly applicable to the total synthesis of methylenomycins.

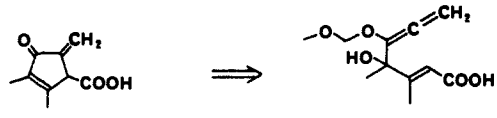
Methylenomycin B

The cationic cyclopentaannelation reaction is ideally suited for the preparation of methylenomycin B, the simplest of the methylenomycins,[7] as the five-membered ring bearing the exo methylene group is generated directly by means of the cationic cyclization. Addition of the α-lithio anion of allenyl methoxymethyl ether to a solution of 3-methyl-3-buten-2-one in ether–THF (1:1) furnished **2** in 88% yield (Scheme I). Treatment of **2** with a variety of Lewis acids, including boron trifluoride etherate, failed to produce more than traces of methylenomycin B. The major reaction product was enone **3** which was derived from the hydrolysis of the enol ether. The hydrolytically sensitive allene functionality placed limits on the conditions which may be employed for the cyclization. Success was finally realized when Denmark's conditions for conducting Nazarov reactions were applied to **2**.[8] Treatment of a solution of **2** in dichloromethane at 0 °C with 0.5 equiv of anhydrous ferric chloride produced methylenomycin B in 48% yield.[7] The yield for the cyclization was raised to 74% through systematic investigations of other Lewis acids which revealed that the best reagent for the cyclization was a mixture of trifluoroacetic anhydride and 2,6-lutidine.

The preparation of methylenomycin B through the cationic cyclization was extremely efficient. A simple experimental procedure was employed which required no intermediate purifications and which allowed significant quantities of synthetic material to be prepared rapidly. It is worth noting that 800 mg of methylenomycin B were prepared in 1 day by a single worker. The success with methylenomycin B led us to a synthesis of (±)-desepoxy-4,5-didehydromethylenomycin A.

(±)-Desepoxy-4,5-didehydromethylenomycin A

The second synthetic target with which to demonstrate the utility of the cationic cyclopentaannelation differed from methylenomycin B only in having a carboxylic acid appended to the five-membered ring. The retrosynthesis led to open-chain compound **4**. The synthesis of **4** or of the corresponding methyl ester was anticipated to be straightforward; however, the presence of

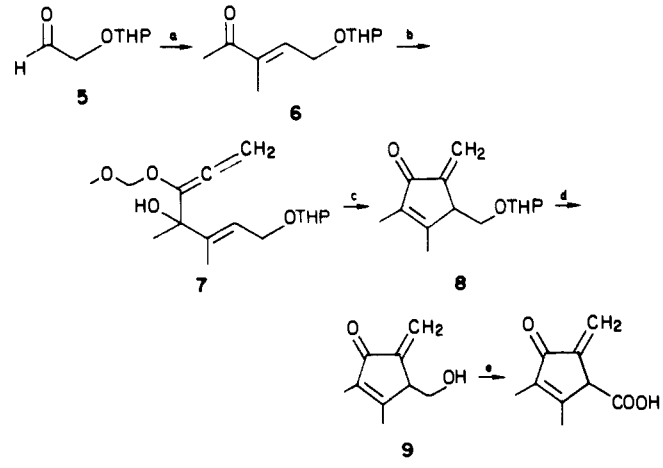


DESEPOXY-4,5-DIDEHYDROMETHYLENOMYCIN A **4**

an electron-withdrawing group was expected to inhibit the cyclization. Therefore a carboxylic acid equivalent was incorporated into the substrate for the cyclization. Protected hydroxyacetaldehyde **5** was the starting material for the first of the two syntheses of (±)-desepoxy-4,5-didehydromethylenomycin A which were developed. Ozonolysis of allyl tetrahydropyranyl ether produced **5** which was converted in 62% yield to enone **6** by treatment in THF with the lithio anion of diethyl 2-oxo-1-methylpropylphosphonate (Scheme II). The Horner–Emmons reaction was highly stereoselective, and none of the *Z* isomer was detected by ^{1}H NMR at 300 MHz. Condensation of **6** with the α-lithio anion of allenyl methoxymethyl ether produced **7** in 76% yield.

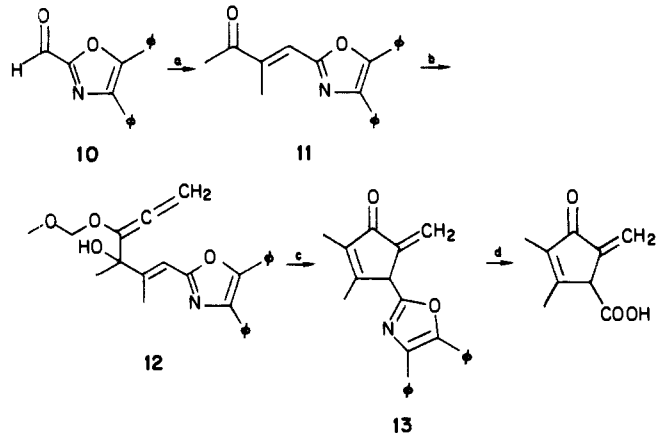
Several unsuccessful attempts to cyclize **7** were made. Ferric chloride and boron trifluoride etherate produced **8** in 50% and ca. 15% yields, respectively, but the reactions were difficult to reproduce. Optimal conditions were found when a solution of **7** in THF was treated at −25 °C with triethylamine followed by methanesulfonyl chloride and the mixture was allowed to warm to 24 °C. When these conditions were used, **8** was formed reproducibly in 50% yield. Hydrolytic removal of the protecting group was followed by oxidation of the primary alcohol to the carboxylic acid with freshly prepared Jones reagent.

Scheme II.[a] Synthesis of Desepoxy-4,5-didehydromethylenomycin A



[a] (a) 1.2 equiv of diethyl 2-oxo-1-methylpropylphosphonate, 1.2 equiv of LDA, 0 °C, 62%; (b) 4 equiv of α-lithio-α-(methoxymethyl)-allene, THF/ether (1:1), −78 °C 76%; (c) 4 equiv of CH_3SO_2Cl, 7 equiv of triethylamine, THF, −25 to 0 °C, 50%; (d) 5% aqueous HCl, THF, 25 °C, 93%; (e) Jones reagent, acetone, 0 °C, 72%.

Scheme III.[a] Alternative Synthesis of Desepoxy-4,5-didehydromethylenomycin A



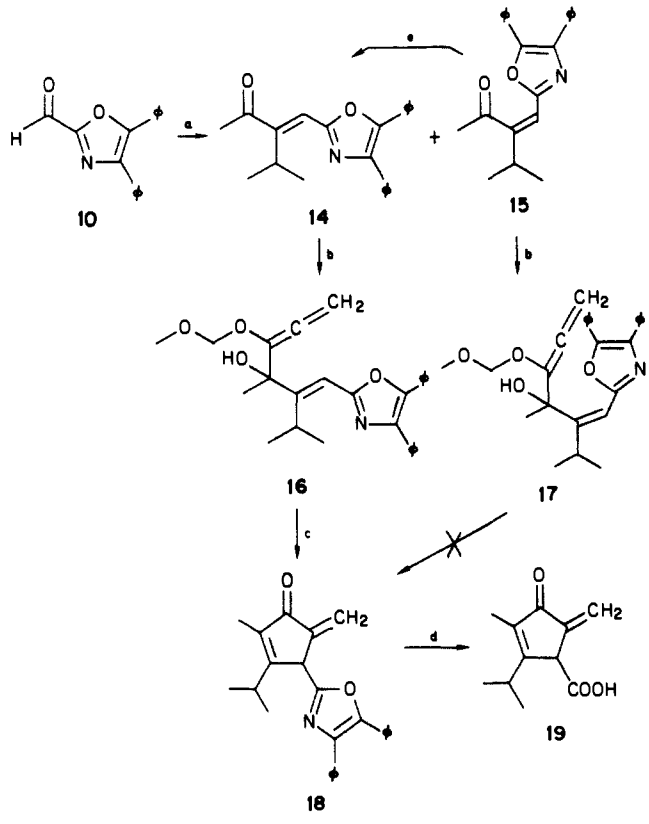
[a] (a) 1.2 equiv of diethyl 2-oxo-1-methylpropylphosphonate, 1.2 equiv of LDA, −78 to 0 °C, 85%; (b) 4 equiv of α-lithio-α-(methoxymethyl)allene, THF/ether (1:1), −78 °C, 95%; (c) 5 equiv of $(CF_3C-O)_2O$, 5 equiv of 2,6-lutidine, CH_2Cl_2, −25 °C, 50–70%; (d) $^1O_2$, $ClCH_2CH_2Cl$, 25 °C, 50–60%.

An alternative synthesis of (±)-desepoxy-4,5-didehydromethylenomycin A was also developed. 2-Formyl-4,5-diphenyloxazole (**10**)[9] was condensed with diethyl 2-oxo-1-methylpropylphosphonate to produce enone **11** as a single geometric isomer (Scheme III). Enone **11** was converted to **12** with the α-lithio anion of allenyl methoxymethyl ether in 95% yield. Treatment of a solution of **12** in acetonitrile or dichloromethane with trifluoroacetic anhydride and 2,6-lutidine at 20 °C led to cyclized product in 65% yield. Lewis acids failed to catalyze the cyclization, probably because of competing complex formation with the heterocyclic nitrogen.[10] The diphenyloxazole group was

(6) Tius, M. A.; Astrab, D. P. *Tetrahedron Lett.* **1984**, 1539–1542.
(7) A less efficient synthesis of methylenomycin B is described in ref 5.
(8) Denmark, S. E.; Jones, T. K. *J. Am. Chem. Soc.* **1982**, *104*, 2642–2645.

(9) 2-Formyl-4,5-diphenyloxazole was prepared in four steps from commercially available 2-methyl-4,5-diphenyloxazole in 55% overall yield: (i) *N*-bromosuccinimide, dibenzoyl peroxide, carbon tetrachloride; (ii) potassium acetate, *N,N*-dimethylformamide; (iii) potassium carbonate, methanol; (iv) dimethyl sulfoxide, oxalyl chloride, triethylamine, dichloromethane.
(10) The trifluoroacetic anhydride–2,6-lutidine reagent system was devised specifically for the transformation of **12** into **13** but has been demonstrated to be more broadly applicable.

Scheme IV.[a] Synthesis of Desdihydroxy-4,5-didehydroxanthocidin



[a] (a) 1.2 equiv of diethyl 2-oxo-1-isopropylphosphonate, 1.2 equiv of LDA, −78 to 0 °C, 74%; (b) 4 equiv of α-lithio-α-(methoxymethyl)-allene, THF/ether (1:1), −78 °C, 86% for **16**, 84% for **17**; (c) 5 equiv of $(CF_3CO)_2O$, 5 equiv of 2,6-lutidine, CH_2Cl_2, −25 °C, 72%; (d) $^1O_2$, $ClCH_2CH_2Cl$, 25 °C, 55–60%; (e) I_2, PhH, reflux.

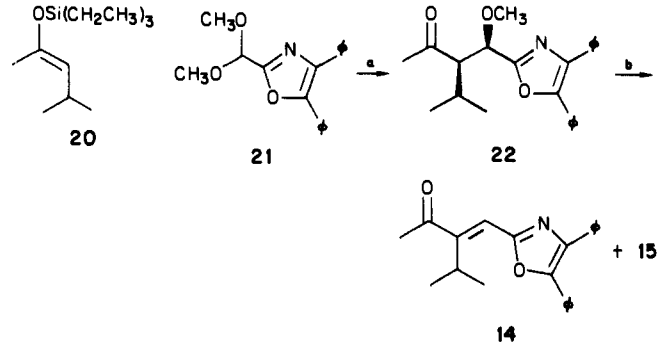
developed by Wasserman as a masked carboxyl group, and its use in total synthesis has been reported.[11] It proved to be a particularly useful group in the present instance, because it facilitated the cyclization reaction by stabilizing the cationic intermediate, in addition to serving as a latent carboxyl function. The diphenyloxazole present in **13**, having served its purpose, was converted to the carboxylate in 60% yield by reaction with singlet oxygen. Both methods produced (±)-desepoxy-4,5-didehydromethylenomycin A which was identical by spectroscopic comparison (^{1}H NMR, IR, MS) with material which was prepared by Prof. Amos Smith.[2q]

The efficacy of the cationic cyclopentaannelation for the synthesis of (±)-desepoxy-4,5-didehydromethylenomycin A had been demonstrated, so a synthesis of (±)-desdihydroxy-4,5-didehydroxanthocidin (**19**) was undertaken.[3]

(±)-Desdihydroxy-4,5-didehydroxanthocidin (19)

The structure of **19**, the presumed biosynthetic precursor to xanthocidin,[3] differed trivially from (±)-desepoxy-4,5-didehydromethylenomycin A, having an isopropyl group in place of a methyl at the enone β carbon. Nevertheless, this seemingly minor difference necessitated a change in the synthetic plan. The precursor to cyclization was prepared according to the protocol which had been developed for (±)-desepoxy-4,5-didehydromethylenomycin A. Condensation of **10** with diethyl 2-oxo-1-isopropylphosphonate led to a 1:3 mixture of *E* and *Z* isomers **14** and **15** (Scheme IV). The two isomers were readily distinguished by the chemical shift of the vinyl hydrogen (δ 6.93 for **14**, δ 6.18 for **15**). Their separation by chromatographic methods

Scheme V.[a] Alternative Synthesis of **14**



[a] (a) Catalyst TMSOTf, CH_2Cl_2, −78 to 25 °C, 60%; (b) 2 equiv of DBU, 3-Å molecular sieves, CH_2Cl_2/CH_2CN (1:1), reflux, 60% of **14**, 15% of **15**.

was tedious but could be accomplished by flash chromatography on silver nitrate impregnated silica gel. The addition of the α-lithio anion of allenyl methoxymethyl ether to **14** and **15** produced **16** and **17**, respectively. Whereas the cyclization of **16** to **18** with trifluoroacetic anhydride and 2,6-lutidine took place in 72% yield, **17** failed to cyclize under these conditions presumably because the cation which was derived from the solvolysis of the trifluoroacetate of **17** was prevented from achieving planarity by the diphenyloxazole which is directed syn to the allene. Steric effects here would be expected to inhibit conrotatory electrocyclization, and decomposition to a variety of products took place. Treatment of **18** with singlet oxygen produced **19**, the presumed biosynthetic precursor of xanthocidin which was identical by spectroscopic comparison (^{1}H NMR, IR, MS) with material which was prepared by Prof. Amos Smith.[3]

In order to make more efficient use of the starting materials, an attempt was made to isomerize the undesired *Z* isomer **15** to the *E* isomer **14**. Heating a benzene solution of **15** to reflux for 12 h in the presence of a catalytic amount of iodine resulted in a 1:1 mixture of **14** and **15** which were separated. The recycling scheme greatly increased the efficiency of the synthesis; however, a practical route to **14** would be more convenient. The isomer problem was overcome by making use of a Lewis acid-catalyzed aldol reaction. Mesityl oxide was converted in quantitative yield to **20** (as a single geometric isomer) by treatment with triethylsilane and Wilkinson's catalyst (Scheme V).[12] The condensation of **20** with dimethyl acetal **21** in the presence of trimethylsilyl triflate as the catalyst gave methoxy ketone **22** in 60% yield as a 10:1 mixture of erythro and threo isomers. The stereochemistry of the addition is in accord with previous results and has been rationalized by postulating an extended transition state.[13] Heating a solution of **22** in dichloromethane with 1,8-diazabicyclo-[5.4.0]undec-7-ene led to **14** in 60% yield along with 15% of *Z* isomer **15**.[14] The aldol route to **14** made the synthesis of **19** extremely expeditious.

Conclusion

A serendipitous discovery in our laboratory has been exploited to develop an extremely efficient synthesis of racemic methylenomycins. The utility of the method has been demonstrated by preparing three natural products. A series of methylenomycin analogues has been prepared, and their antibacterial and cytotoxic properties have been screened.[5] A limitation of the method became apparent during the synthesis of **19**. Only the adducts of the α-lithio anion of allenyl methoxymethyl ether with (*E*)-enones underwent the cationic cyclization. Since the basic structural unit of the methylenomycins is present in a number of interesting natural products, further studies to delineate the full scope of this

(11) Wasserman, H. H.; Gambale, R. J. *J. Am. Chem. Soc.* **1985**, *107*, 1423–1424. Pridgen, L. N.; Shilcrat, S. C.; Lantos, I. *Tetrahedron Lett.* **1984**, 2835–2838. For a review see: Wasserman, H. H.; Lipshutz, B. H. In *Singlet Oxygen*; Wasserman, H. H.; Murray, R. W., Eds.; Academic Press: New York, 1979; Chapter 9.

(12) Ojima, I; Nihonyanagi, M.; Kogure, T.; Kumagai, M.; Horiuchi, S.; Nakatsugawa, K. *J. Organomet. Chem.* **1975**, *94*, 449–461.

(13) Murata, S.; Suzuki, M.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 3248–3249.

(14) Ishida, A.; Mukaiyama, T. *Chem. Lett.* **1975**, 1167–1170.

reaction will be carried out. Some observations concerning the mechanism, tacitly assumed to be a conrotatory 4π process, will be reported in due course.

Experimental Section

Preparation of Enones: General Procedure. To 1.2 mmol of a 0.3 M solution of lithium diisopropylamide (LDA) was added a solution of 1.2 $CDCl_3$) of diethyl 2-oxo-1-alkylpropanephosphonate in 0.5 mL of THF at −78 °C. The reaction mixture was stirred for 1 h at −78 °C. The temperature of the solution was raised to 0 °C, and 1.0 mmol of a solution of aldehyde in 1 mL of THF was added by cannula. Stirring was continued for an additional hour. The reaction was quenched by the addition of 0.1 N aqueous HCl. Following ether extraction (3 × 10 mL), the organic phase was washed sequentially with water and brine and was dried over $MgSO_4$. The dry organic extract was filtered and was concentrated. The residue was purified by flash chromatograpy. The yield for the reaction varied between 62% and 84%.

(*E*)-3-Methyl-5-[(2-tetrahydropyranyl)oxy]pent-3-en-2-one (6) was prepared from 144 mg (1.0 mmol) of (2-tetrahydropyranyl)acetaldehyde and 250 mg (1.2 mmol) of diethyl 2-oxo-1-methylpropanephosphonate. The product was obtained in 62% yield (123 mg) as a single isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.62 (dd, J = 5.3, 5.9 Hz, 1 H), 4.60 (m, 1 H), 4.41 (ABq, J = 5.3, 14.8 Hz, 1 H), 4.15 (ABq, J = 5.9, 14.8 Hz, 1 H), 3.90–3.80 (m, 1 H), 3.55–3.40 (m, 1 H), 2.30 (s, 3 H), 1.80 (s, 3 H), 1.90–1.60 (m, 6 H); IR (neat) 2950, 2860, 1672 cm^{-1}.

(*E*)-3-Methyl-4-(4,5-diphenyloxazol-2-yl)but-3-en-2-one (11) was prepared from 250 mg (1.0 mmol) of 2-formyl-4,5-diphenyloxazole and 253 mg (1.2 mmol) of diethyl 2-oxo-1-methylpropanephosphonate. The product was obtained in 85% yield (256 mg) as a single isomer (yellow crystals, mp 89–91 °C): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (m, 4 H), 7.39 (m, 6 H), 7.30 (s, 1 H), 2.49 (s, 3 H), 2.41 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.24, 158.56, 146.57, 142.32, 137.58, 131.93, 129.05, 128.74, 128.60, 128.48, 128.26, 127.98, 126.57, 122.70, 25.90, 13.33; IR (CH_2Cl_2) 2998, 1670, 1637, 1604, 1589, 1535, 1504, 1479, 1444, 1365, 1336, 1277, 1234, 1190, 1113, 1070, 1028 cm^{-1}; mass spectrum, m/e 304 (M^+ + 1), 303 (M^+), 260 (M^+ − $COCH_3$), 198, (100%), 165, 129, 115, 105, 91, 77; exact mass calcd for $C_{20}H_{17}NO_2$ 303.1273, found 303.1259. Anal. Calcd for $C_{20}H_{17}NO_2$: C, 79.19; H, 5.65; N, 4.62. Found: C, 78.91; H, 5.62; N, 4.59.

3-Isopropyl-4-(4,5-diphenyloxazol-2-yl)but-3-en-2-one [(*E*)-14,(*Z*)-15] was prepared from 250 mg (1.0 mmol) of 2-formyl-4,5-diphenyloxazole and 283 mg (1.2 mmol) of diethyl 2-oxo-1-isopropylpropanephosphonate. The product was obtained in 74% yield (245 mg) as a 3:1 mixture of Z and E isomers. **14**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61–7.48 (m, 4 H), 7.32–7.15 (m, 6 H), 6.93 (s, 1 H), 3.93–3.88 (m, 1 H), 2.35 (s, 3 H), 1.24 (d, J = 7.0 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.17, 157.93, 152.97, 131.87, 128.91, 128.67, 128.58, 128.51, 128.35, 127.88, 126.46, 126.25, 120.56, 109.47, 28.56, 28.08, 21.04, 20.45; IR (neat) 2346, 1701, 766, 692 cm^{-1}; mass spectrum, m/e 332 (M^+ + 1), 331 (M^+), 288 (M^+ − $COCH_3$), 226 (100%), 165; exact mass calcd for $C_{22}H_{21}NO_2$ 331.1577, found 331.1572. Anal. Calcd for $C_{22}H_{21}NO_2$: C, 79.73; H, 6.39; N, 4.23. Found: C, 79.64; H, 6.40; N, 4.23. **15**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58–7.46 (m, 4 H), 7.32–7.17 (m, 6 H), 6.18 (s, 1 H), 2.67–2.61 (m, 1 H), 2.40 (s, 3 H), 1.14–1.12 (d, J = 6.9 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.51, 157.54, 157.38, 145.62, 136.51, 132.02, 129.12, 128.92, 128.60, 128.41, 128.15, 127.78, 126.26, 109.44, 32.99, 31.01, 21.10, 21.04; IR (neat) 2346, 1701, 766, 692 cm^{-1}; mass spectrum, m/e 332 (M^+ + 1), 331 (M^+), 288 (M^+ − $COCH_3$), 226 (100%), 165; exact mass calcd for $C_{22}H_{21}NO_2$ 331.1577, found 331.1572. Anal. Calcd for $C_{22}H_{21}NO_2$: C, 79.73; H, 6.39; N, 4.23. Found: C, 79.64; H, 6.40; N, 4.23.

Addition of the Lithio Anion of Allenyl Methoxymethyl Ether: General Procedure. A solution of 4.0 mmol on *n*-butyllithium in 10 mL of a 1:1 mixture of ether and THF was treated at −78 °C with 500 mg (5.0 mmol) of allenyl methoxymethyl ether. After 30 min a solution of 1 mmol of the enone in 10 mL of the same solvent mixture was added by cannula to the rapidly stirring lithioallene solution at −78 °C. The progress of the reaction was followed by thin-layer chromatography. After 5 min the reaction was quenched by addition of 5 mL of water. Upon warming to room temperature, the reaction mixture was partitioned between ether and water. The ethereal layer was washed with water and brine and was dried ($MgSO_4$). Evaporation of the solvent under reduced pressure followed by flash chromatography on silica gel produced the products as oils.

2,3-Dimethyl-3-hydroxy-4-[(methoxymethyl)oxy]-1,4,5-hexatriene (2) was prepared from 84 mg (1.0 mmol) of 3-methyl-3-buten-2-one in 88% yield (162 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.53 (s, 2 H), 5.16 (m, 1 H), 4.92 (m, 1 H), 4.83 (ABq, J = 6.1 Hz, 1 H), 4.81 (ABq, J = 6.1 Hz, 2 H), 3.39 (s, 3 H), 2.54 (br s, 1 H), 1.75 (dd, J = 0.72, 1.4 Hz, 3 H), 1.36 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ 196.49, 148.65, 133.08, 110.07, 93.84, 90.97, 74.63, 55.34, 24.44, 18.47; IR (neat) 3495, 2926, 1958, 1655, 1454 cm^{-1}; mass spectrum, m/e 185 (M^+ + 1), 184 (M^+), 166 (M^+ − H_2O), 123 (M^+ − CH_3OCH_2O), 85 (C_5H_9O, 100%).

3,4-Dimethyl-4-hydroxy-5-[(methoxymethyl)oxy]-1-[2-tetrahydropyranyl)oxy]-2,5,6-heptatriene (7) was prepared from 185 mg (1.0 mmol) of 3-methyl-5-[(2-tetrahydropyranyl)oxy]-3-penten-2-one (**6**) in 76% yield (225 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.85 (t, J = 7.0 Hz, 1 H), 5.55 (s, 2 H), 4.90–4.80 (m, 2 H), 4.65 (s, 1 H), 4.30 (dd, J = 15.0, 7.0 Hz, 1 H), 3.90–3.80 (m, 1 H), 3.60–3.45 (m, 1 H), 3.40 (s, 3 H), 1.90–1.50 (m, 6 H), 1.70 (s, 3 H), 1.40 (s, 3 H); IR (neat) 3490, 1958 cm^{-1}.

2,3-Dimethyl-3-hydroxy-4-[(methoxymethyl)oxy]-1-(4,5-diphenyloxazol-2-yl)-1,4,5-hexatriene (12) was prepared from 303 mg (1.0 mmol) of (*E*)-3-methyl-4-(4,5-diphenyloxazol-2-yl)-3-buten-2-one (**11**) in 95% yield (382 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (m, 4 H), 7.40 (m, 6 H), 6.79 (s, 1 H), 5.60 (s, 2 H), 4.84 (s, 2 H), 3.39 (s, 3 H), 2.88 (s, 1 H), 2.31 (s, 3 H), 1.45 (s, 3 H); IR (neat) 3429, 2951, 1956, 1653, 1603, 1543, 1500, 1442, 1371, 1327, 1151, 1116, 1059 cm^{-1}; mass spectrum, m/e 404 (M^+ + 1), 403 (M^+), 358, 348, 342, 341, 328, 316, 304, 286, 260, 249, 198, 193, 165, 45 (100%); exact mass calcd. for $C_{25}H_{25}NO_4$ 403.1758, found 403.1784.

2-Isopropyl-3-methyl-3-hydroxy-4-[(methoxymethyl)oxy]-1-(4,5-diphenyloxazol-2-yl)-1,4,5-hexatriene (16) was prepared from 331 mg (1.0 mmol) of (*E*)-3-isopropyl-4-(4,5-diphenyloxazol-2-yl)-3-buten-2-one (**14**) in 86% yield (369 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67–7.56 (m, 4 H), 7.39–7.29 (m, 6 H), 6.34 (s, 1 H), 5.50 (s, 2 H), 4.86 (s, 2 H), 3.39 (s, 3 H), 1.63 (s, 3 H), 1.25 (d, J = 2.0 Hz, 3 H), 1.18 (d, J = 2.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.96, 160.33, 159.22, 144.77, 137.63, 136.29, 132.65, 132.55, 128.96, 128.53, 128.35, 128.26, 128.01, 127.84, 127.61, 126.65, 126.35, 110.15, 94.86, 92.27, 77.27, 76.98, 56.83, 29.51, 25.08, 20.39, 20.12; IR (neat) 3429, 2951, 1956, 1654, 1603, 1542, 1500, 1442, 1370, 1327, 1059 cm^{-1}; mass spectrum, m/e 432 (M^+ + 1), 431 (M^+), 386 (M^+ − CH_3OCH_2), 376, 332, 315, 300, 249, 165, 45 (100%). The Z isomer of **17** was prepared from 331 mg (1.0 mmol) of **15** in 84% yield (361 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.75 (s, 1 H), 7.69–7.57 (m, 4 H), 7.39–7.29 (m, 6 H), 5.50 (s, 2 H), 4.86 (s, 2 H), 3.39 (s, 3 H), 1.63 (s, 3 H), 1.20 (d, J = 2.1 Hz, 3 H), 1.18 (d, J = 2.0 Hz, 3 H); IR (neat) 3429, 2952, 1957, 1654, 1603, 1542 cm^{-1}; mass spectrum, m/e 432 (M^+ + 1), 431 (M^+), 386 (M^+ − CH_3OCH_2), 376, 332, 315, 300, 249, 165, 45 (100%).

Cyclization with 2,6-Lutidine and Trifluoroacetic Anhydride: General Procedure. To a solution of 1.0 mmol of the tertiary alcohol and 5.0 mmol of 2,6-lutidine in 15 mL of dichloromethane or acetonitrile was added trifluoroacetic anhydride (3–5 mmol) at −20 °C dropwise over a period of 15–30 min. The reaction was monitored by thin-layer chromatography. After 5–10 min, the reaction was quenched at −20 °C with 3 mL of water. The product was extracted into ether. The ethereal layer was washed with water and brine and was dried ($MgSO_4$). Filtration followed by evaporation of the solvent furnished a residue which was purified by flash chromatography on silica gel.

Methylenomycin B was prepared by treating a solution of 1 g (5.4 mmol, 1.0 equiv) of 2,3-dimethyl-3-hydroxy-4-[(methoxymethyl)oxy]-1,4,5-hexatriene (**2**) in 16 mL of dichloromethane containing 3.1 mL of 2,6-lutidine (27 mmol, 5 equiv) with 2.3 mL (16.3 mmol, 3 equiv) of trifluoroacetic anhydride in 74% yield (490 mg). The product after flash chromatography was obtained as a pale-yellow oil which crystallized in the refrigerator (mp 4 °C): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.02 (m, J = 1.0 Hz, 1 H), 5.32 (m, J = 1.5 Hz, 1 H), 3.05 (br s, 2 H), 2.04 (m, J = 1.0 Hz, 3 H), 1.78 (m, J = 1.0 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ 194.79, 194.79, 162.30, 142.35, 138.18, 114.11, 36.59, 15.90, 8.28; IR (neat) 1690, 1660, 1625 cm^{-1}; mass spectrum, m/e 122 (M^+), 107 (M^+ − CH_3), 93, 86, 84, 79 (100%); exact mass calcd for $C_8H_{10}O$ 122.0723, found 122.0732. When $FeCl_3$ was used to catalyze the cyclization of **2**, in addition to methylenomycin **B**, enone **3** was formed in 40% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.66 (dd, J = 17.2, 10.2 Hz, 1 H), 6.46 (dd, J = 17.2, 2.0 Hz, 1 H), 5.74 (dd, J = 10.2, 2.0 Hz, 1 H), 5.18 (s, 1 H), 5.07 (s, 1 H), 4.16 (br s, 1 H), 1.58 (s, 3 H), 1.46 (s, 3 H); IR (neat) 3450, 2950, 1700, 1650, 1450, 1350 cm^{-1}; mass spectrum, m/e 140 (M^+), 125 (M^+ − CH_3), 97, 85, 57, 49 (100%).

Cyclopentenone 13 was prepared from 138 mg (0.34 mmol, 1 equiv) of **12**, 183 mg (1.7 mmol, 5 equiv) of 2.6-lutidine, and 0.24 mL of trifluoroacetic anhydride (1.7 mmol, 5 equiv) in 65% yield (76 mg) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (m, 4 H), 7.35 (m, 6 H), 6.22 (s, 1 H), 5.54 (s, 1 H), 4.70 (br s, 1 H), 2.13 (s, 3 H), 1.89 (s. 3 H); IR (neat) 2950, 1699, 1667, 1634, 1562, 1498, 1443, 1395, 1331 cm^{-1}; mass spectrum, m/e 342 (M^+ + 1), 341 (M^+), 312, 236, 208, 165, 77 (100%); exact mass calcd for $C_{23}H_{19}NO_2$ 341.1410, found 341.1416.

Cyclopentenone 18 was prepared from 240 mg (0.55 mmol, 1 equiv) of **16**, 298 mg (2.8 mmol, 5 equiv) of 2,6-lutidine, and 0.39 mL of trifluoroacetic anhydride (2.8 mmol, 5 equiv) in 72% yield (156 mg) as

pale-yellow crystals: mp 109–112 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64–7.61 (m, 2 H), 7.49–7.46 (m, 2 H), 7.40–7.30 (m, 6 H), 6.20 (s, 1 H), 5.48 (s, 1 H), 4.89 (s, 1 H), 3.1 (m, 1 H), 1.93 (s, 3 H), 1.20 (d, J = 6.8 Hz, 3 H), 0.95 (d, J = 7.1 Hz, 3 H); IR (neat) 2971, 1697, 1661, 1620, 1498, 1445, 1392 cm^{-1}; mass spectrum, m/e 371 (M^+ + 2), 370 (M^+ + 1), 369 (M^+), 354 ($M^+ - CH_3$), 326, 165, 77, 43 (100%); exact mass calcd for $C_{25}H_{23}NO_2$ 369.1746, found 369.1729. Anal. Calcd for $C_{25}H_{23}NO_2$: C, 81.27; H, 6.27; N, 3.79. Found: C, 80.98; H, 6.26; N, 3.79.

Photooxidation: General Procedure. A solution of 0.15 mmol of the oxazolylcyclopentaenone in 10 mL of dichloroethane into which a small quantity (ca. 1 mg) of Sensitox had been added was irradiated with a 500-W tungsten lamp as oxygen was bubbled through the mixture. The progress of the reaction was monitored by thin-layer chromatography. When the reaction was complete, the solution was filtered through Celite, and the solvent was evaporated. The crude product was dissolved in 2 mL of THF, and an equal volume of saturated aqueous Na_2CO_3 was added. The two-phase mixture was stirred for 20 min and was extracted with ether (2 × 2 mL). The aqueous layer was acidified with 10% aqueous HCl and was extracted with ethyl acetate (2 × 3 mL). The organic extract was dried (Na_2SO_4), and the solvent was evaporated. The residual oil was purified by flash chromatography on silica gel, eluting successively with ethyl acetate, 1:1 ethyl acetate/acetone, acetone, and 1:9 water/acetone.

(±)-Desepoxy-4,5-didehydromethylenomycin A was prepared from 240 mg (0.7 mmol) of **13** in 60% yield (70 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.20 (s, 1 H), 5.65 (s, 1 H), 4.10 (s, 1 H), 2.13 (s, 3 H), 1.85 (s, 3 H); IR (neat) 3485, 2926, 1736, 1695, 1624 cm^{-1}; mass spectrum, m/e 166 (M^+), 122 ($M^+ - CO_2$), 121 ($M^+ - CO_2H$), 45, 43 (100%); exact mass calcd for $C_9H_{10}O_3$ 166.0638, found 166.0630.

(±)-Desdihydroxy-4,5-didehydroxanthocidin (19) was prepared from 50 mg (0.15 mmol) of **18** in 60% yield (17 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.15 (s, 1 H), 5.55 (s, 1 H), 4.19 (s, 1 H), 3.05 (m, 1 H), 1.87 (s, 3 H), 1.22 (t, J = 6 Hz, 6 H); IR (neat) 3480, 1734, 1697 cm^{-1}; mass spectrum, m/e 194 (M^+), 166 (M^+ − CO), 149 (M^+ − COOH), 43 (100%); calcd for $C_{11}H_{14}O_3$ 194.0929, found 194.0942.

Alternative Synthesis of (±)-Desepoxy-4,5-didehydromethylenomycin A: Cyclization. A solution of 100 mg (0.33 mmol) of **7** in 3 mL of dry THF was treated at −25 °C with 0.33 mL (2.34 mmol, 7 equiv) of triethylamine followed by 0.11 mL (1.34 mmol, 4 equiv) of methanesulfonyl chloride. The solution was allowed to warm to room temperature overnight and was quenched with 2 mL of water. The reaction mixture was extracted with dichloromethane (2 × 2 mL), and the organic extract was dried (Na_2SO_4). The solvent was evaporated, and the residue was purified by flash chromatography on silica gel. Cyclized product **8** was obtained in 50% yield (40 mg) as a mixture of diastereomers: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.06 and 6.04 (s, 1 H), 5.46 and 5.45 (s, 1 H), 4.60–4.56 (m, 1 H), 4.00–3.30 (m, 5 H), 2.07 (s, 3 H), 1.77 (s, 3 H), 1.73–1.40 (m, 6 H); IR (neat) 2950, 2875, 1695, 1632 cm^{-1}; mass spectrum, m/e 236 (M^+), 122, 85 (100%).

Hydrolysis of the Tetrahydropyranyl Group. A solution of 100 mg (0.42 mmol, 1 equiv) of **8** in 3 mL of a 1:1 mixture of THF and 5% aqueous HCl was stirred at room temperature overnight. The THF was evaporated from the mixture, and the residue was extracted with dichloromethane (2 × 2 mL). The organic extract was dried (Na_2SO_4), and the solvent was evaporated. The residue was purified by flash chromatography on silica gel. Alcohol **9** was obtained in 93% yield (60 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.17 (s, 1 H), 5.40 (s, 1 H), 4.00–3.70 (m, 3 H), 2.04 (s, 3 H), 1.52 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.08, 165.38, 143.42, 139.41, 115.42, 62.32, 48.99, 14.82, 8.26; IR (neat) 3450, 3080, 2940, 1690, 1630 cm^{-1}; mass spectrum, m/e 152 (M^+), 134 ($M^+ - H_2O$), 122 (100%), 121.

Oxidation of the Alcohol. A solution of 50 mg of **9** (0.33 mmol, 1.0 equiv) in 2 mL of acetone was treated at 0 °C with freshly prepared Jones reagent until a persistent orange color was observed. The progress of the reaction was monitored by thin-layer chromatography. After nearly 2 h the reaction mixture was extracted with dichloromethane (2 × 2 mL). The organic extract was dried (Na_2SO_4), and the solvent was evaporated. The residue was purified by flash chromatography on silica gel. (±)-Desepoxy-4,5-didehydromethylenomycin A was obtained in 72% yield (39 mg).

Alternative Procedure for the Preparation of 14: Aldol Condensation of 20 with 21. To a solution of 400 mg (1.35 mmol, 1 equiv) of acetal **21** in 15 mL of dry dichloromethane was added 0.13 mL of a 0.1 M solution of trimethylsilyl trifluoromethanesulfonate in dichloromethane. The reaction mixture was cooled to −78 °C, and 0.60 mL (2.7 mmol, 2.0 equiv) of triethylsilyl enol ether **20** in 5 mL of dichloromethane was added. The solution was stirred at −78 °C for 8 h and was allowed to warm to room temperature. The reaction was quenched with water, and the product was extracted into dichloromethane, was washed with water and brine, and was dried ($MgSO_4$). The solvent was evaporated, and the residue was purified by flash chromatography on silica gel to give a 10:1 mixture of *erythro*-**22** and the threo isomer in 60% yield (294 mg). The isomers were not separated but were taken on to the elimination step: ^{1}H NMR (300 MHz, C_6D_6) δ 7.90 (d, J = 7.8 Hz, 2 H), 7.66 (d, J = 6.8 Hz, 2 H), 7.23–7.1 (m, 6 H), 4.90 (d, J = 9.8 Hz, 1 H), 3.52 (dd, J = 4.7, 9.8 Hz, 1 H), 3.30 (s, 3 H), 2.34 (m, 1 H), 2.10 (s, 3 H), 1.08 (d, J = 6.8 Hz, 3 H), 1.03 (d, J = 7.1 Hz, 3 H); IR (neat) 2972, 1703, 1609, 1505, 1440, 768, 683 cm^{-1}; mass spectrum, m/e 364 (M^+ + 1), 363 (M^+), 348 ($M^+ - CH_3$), 331 ($M^+ - CH_3OH$), 320 ($M^+ - CH_3CO$), 306, 290, 289, 288, 165, 43 (100%).

Elimination of Methanol from 22. A solution of 500 mg (1.37 mmol, 1.0 equiv) of methoxy ketone **22** and its threo isomer in 15 mL of dichloromethane was treated with 5 mL of a dichloromethane solution of 420 mg of DBU (2.75 mmol, 2.0 equiv). Molecular sieves (3 Å, 500 mg) were added, and the mixture was heated to a gentle reflux for 4 h. The reaction mixture was poured onto 10 mL of ice-cold brine and 20 mL of 1 N aqueous HCl. The solution was extracted with ether and was washed with water and brine. The organic phase was dried ($MgSO_4$), and the solvent was evaporated. The product was purified by flash chromatography on silica gel. A 4:1 mixture of *E* and *Z* isomers **14** and **15** was obtained in 75% yield (353 mg).

Acknowledgement is made to the National Science Foundation, CHE-84-03495, for generous support. NSF Grant CHE-81-00240 supported the purchase of the 300-MHz NMR spectrometer. We thank Prof. Amos B. Smith, III, for generously supplying us with spectra of the final products.

Supplementary Material Available: Experimental procedures and experimental data for diethyl 2-oxo-1-alkylpropanephosphonates and oxazolealdehyde **26** (2 pages). Ordering information is given on any current masthead page.