the α,β-unsaturated ketone **6** (30% H_2O_2, 10% NaOH, MeOH) gave exclusively a single product. As the β side of the double bond of **6** is highly hindered, the reagent should attack from the α side, producing thus the α-epoxide **7:** 82% yield; mp 117–118 °C; IR ($CHCl_3$) 3590, 3460, 1695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.54 (1 H, d, J = 12 Hz), 3.66 (1 H, d, J = 13 Hz), 4.24 (1 H, d, J = 13 Hz), 4.50 (1 H, d, J = 12 Hz). Formation of the allyl alcohol **8** (mp 137–138 °C; IR ($CHCl_3$) 3470 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.86 (1 H, br)) was effected by the reductive cleavage of **7** using 100% $NH_2NH_2{\cdot}H_2O$[7] (90 °C for 5 min, then 120 °C for 15 min).

The crucial point of the present synthesis is in the strategy for the selective and effective protection of three different alcohols present in **8.** A selective protection of C-8 CH_2OH was first required. The crude **8** was, without purification, treated with t-$BuMe_2SiCl$[8] in DMF in the presence of imidazole to give the monosilyl ether **9** (oil; IR ($CHCl_3$) 3420 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.81 (1 H, br)) as a sole product in 55% overall yield from **7,** which shows that this bulky reagent could recognize a slight difference between two primary alcohols in **8.** The protection of vicinal alcohols in **9** should be achieved using a protective group stable to acid but sensitive to base because an acid-catalyzed selective deprotection of the above introduced silyl group is required in the next step. A carbonate protecting group[9] was presumed to be ideally suited for this purpose; thus **9** was converted into the corresponding carbonate **10** (100% yield; mp 59–60 °C; IR ($CHCl_3$) 1785 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.17 (2 H, s), 4.32 (1 H, d, J = 9 Hz), 4.75 (1 H, d, J = 9 Hz), 6.05 (1 H, br)) by refluxing in benzene with N,N'-carbonyldiimidazole. Here **10** was treated with camphorsulfonic acid[10] in methanol affording the allyl alcohol **11** (100% yield; mp 146–149 °C; IR ($CHCl_3$) 3600, 3400, 1785 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.19 (2 H, s), 4.36 (1 H, d, J = 9 Hz), 4.71 (1 H, d, J = 9 Hz), 6.15 (1 H, dd, J = 5, 2 Hz)), the carbonate group being retained as expected. Jones oxidation[11] of **11** gave the enal **12:** 100% yield; mp 133–135 °C; IR ($CHCl_3$) 1790, 1695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.34 (1 H, d, J = 9 Hz), 4.62 (1 H, d, J = 9 Hz), 7.21 (1 H, dd, J = 5, 2 Hz), 9.40 (1 H, s). The aldehyde **12** was converted into the acetal **13** (1,3-propanediol, p-TsOH, benzene, reflux): 97% yield; mp 167–168 °C; IR ($CHCl_3$) 1780 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.30 (1 H, d, J = 9 Hz), 5.04 (1 H, s), 5.12 (1 H, d, J = 9 Hz), 6.31 (1 H, dd, J = 5, 2 Hz). The carbonate group present in **13** was then cleaved by base treatment (10% NaOH–dioxane–H_2O (3:10:5), room temperature) to give the glycol acetal **14:** 98% yield; mp 99–100 °C; IR ($CHCl_3$) 3500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.14 (1 H, s), 6.23 (1H, br). This compound **14** was assumed to be quite sensitive to acids since it involves a labile allyl alcohol moiety; in addition its primary alcohol is located in a position which could assist in the acid-catalyzed cleavage of the cyclic acetal group; and in fact, **14** gives several spots on TLC when exposed to acid (p-TsOH, benzene).[12] Therefore, conversion of the glycol into the α-hydroxy aldehyde should be conducted under neutral or basic conditions. After several attempts,[13] this difficulty was overcome by use of the Moffatt oxidation.[14] The desired α-hydroxy aldehyde **15** (mp 114–116 °C; IR ($CHCl_3$) 3480, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.84 (1 H, s), 6.31 (1 H, br), 9.77 (1 H, d, J = 1 Hz)) was obtained in 73% yield by standard procedures (excess Me_2SO, Py (1.4 equiv), CF_3CO_2H (0.5 equiv), DCC (3 equiv), benzene, room temperature). Acid hydrolysis (p-TsOH, acetone, room temperature) of **15** gave (±)-warburganal (**1,** mp 111–112 °C) in quantitative yield. The spectral data (IR, NMR, mass spectra) were identical with those of the natural product.[15]

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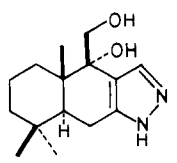
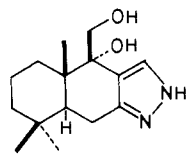


i



ii

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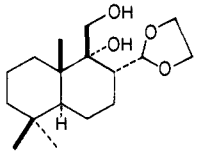

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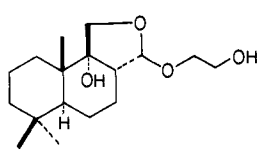

iv

(13) The corresponding ethylene acetal derivative gave less satisfactory result (33% yield). Moreover, the Corey's procedure for the oxidation of α-glycol used in gibberellin A_3 synthesis (Me_2SO, $(CCl_3CO)_2O$, followed by Et_3N treatment) (E. J. Corey, R. L. Danheiser, S. Chandrasekaran, P. Siret, G. E. Keck, and J.-L. Gras, *J. Am. Chem. Soc.*, **100,** 8031 (1978); see also, K. Omura, A. K. Sharma, and D. Swern, *J. Org. Chem.*, **41,** 957 (1976); S. L. Huang, K. Omura, and D. Swern, *ibid.*, **41,** 3329 (1976)) gave **15** in only 7% yield, although the model compound iii afforded the corresponding aldehyde in much better yield (59%).
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(15) The authors express their gratitude to Professor K. Nakanishi, Columbia University, for the generous donation of the authentic sample of natural warburganal.

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Synthesis of Mokupalide

Sir:

Recently, Yunker and Scheuer reported the isolation of three unusual hexaprenes from a Pacific marine sponge.[1] These

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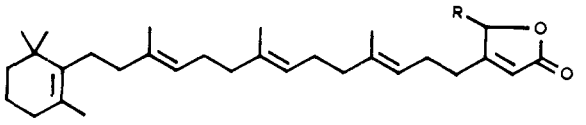
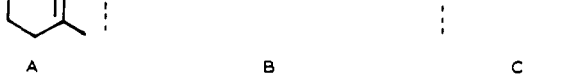


1, R = H
2, R = OH
3, R = OAc

compounds were found to have structures **1**–**3**, which represent a new type of C_{30} isoprenoid containing a novel arrangement of six isoprene units linked head-to-tail. The parent compound **1** was named mokupalide, and we wish to report a stereoselective synthesis of mokupalide.

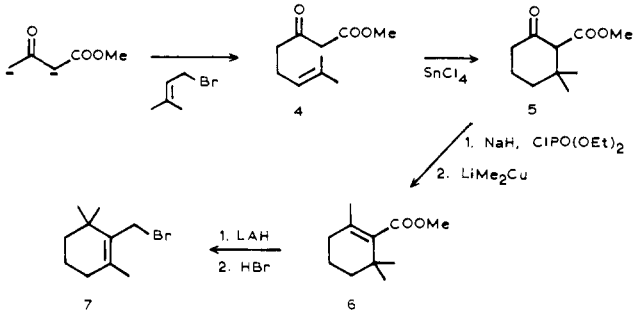
A cursory analysis of structure **1** points to the importance of controlling the stereochemistry of the three isolated trisubstituted double bonds and developing an efficient plan to construct this unusual carbon framework. We chose to divide the molecule into three separate units—A, B, and C—as shown below, and we constructed our synthetic route on these two crucial CC bond formations. In addition, we were intrigued by the potential application of β-keto esters (acetogenins) to synthesize terpenes.[2]



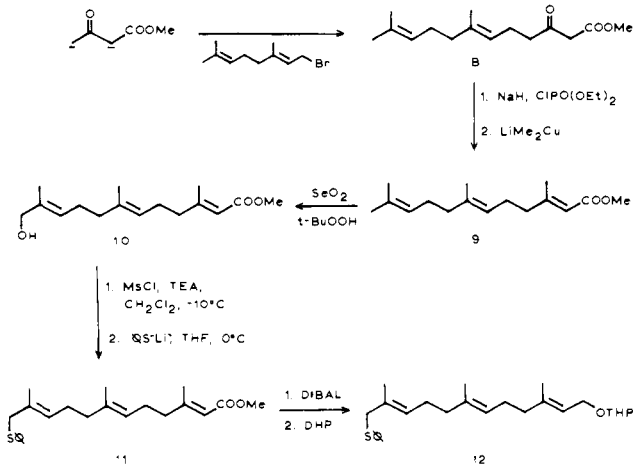
A B C

Unit A was synthesized as shown in Scheme I. The dianion of methyl acetoacetate[3] was alkylated with dimethylallyl bromide (THF, 0 °C, 85%). The resulting olefinic β-keto ester **4**[4] was cyclized (CH_2Cl_2, 25 °C) with a number of Lewis acids, of which stannic chloride[5] proved most efficient, yielding 2-carboxymethyl-3,3-dimethylcyclohexanone (**5**) in up to 97% yield. Then in an application of our new alkene synthesis,[6] the β-keto ester was converted into the corresponding enol phosphate[7] (NaH, $ClPO(OEt)_2$, Et_2O, 0 °C), which was coupled with lithium dimethylcuprate (Et_2O, −78 → −23 °C) to yield the α,β-unsaturated ester **6** in 85–92% yield from **5**. The ester **6** was reduced ($LiAlH_4$, Et_2O, reflux, 92–98%), and the resulting alcohol was converted into the allylic bromide **7** using the two-phase procedure of van Tamelen et al.[8] (48% HBr–pentane, 0 °C, 75–80%).

Scheme I. Synthesis of 2-Bromomethyl-1,3,3-trimethylcyclohexene (7)

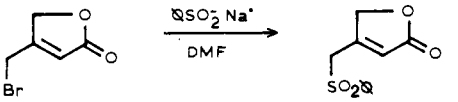


Scheme II, Synthesis of Thioether **12**



The thioether **12** related to unit B was prepared according to the route in Scheme II. The dianion of methyl acetoacetate[3] was alkylated with geranyl bromide (THF, 0 °C) in up to 95% yield to give **8**.[5] This acyclic β-keto ester **8** was stereoselectively converted into the (*Z*)-enol phosphate (NaH, $ClPO(OEt)_2$, Et_2O, 0 °C), which was coupled with lithium dimethylcuprate (Et_2O, −78 → 47 °C) to give (*all-E*)-methyl farnesoate (**9**) in >90% yield and >98% stereoselectivity. The terminal methyl group of **9** was oxidized with *tert*-butyl hydroperoxide and SeO_2[9] (CH_2Cl_2, 10 °C, 38%) to produce alcohol **10.** The allylic alcohol **10** was converted (75–90%) into the thioether **11** via the mesylate of **10.** Finally, the ester **11** was reduced (DIBAL, Et_2O, −23 °C), and the resulting alcohol was protected as the tetrahydropyranyl ether (DHP, TsOH, CH_2Cl_2, 25 °C) to produce **12** in 95% yield for the two steps.

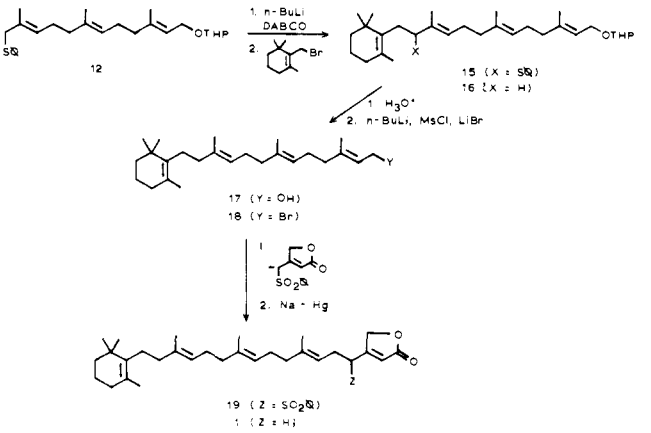
Unit C is embodied in the sulfone **14** that was prepared from 3-bromomethyl-2-butenolide (**13**),[10] which on treatment with



sodium benzenesulfinate (DMF, 25 °C) produced the sulfone **14** in 85% yield. The synthesis was completed by assembling the three subunits as shown in Scheme III. The anion from **12** (*n*-BuLi, DABCO, THF, −23 °C) was alkylated with the allylic bromide **7** (THF, −23 → 0 °C) to give the coupled product **15,** which was hydrogenolyzed[11] (Ni-B, EtOH, 25 °C) to give the polyolefinic ether **16** in 65–70% yield from **12.** The tetrahydropyranyl ether was cleaved (TsOH, MeOH, 25 °C) and the resulting alcohol **17** was quantitatively converted into the crude bromide **18** (*n*-BuLi, MsCl, LiBr, Et_2O, −78 → 25 °C).[12] Bromide **18** was alkylated with the anion from sulfone **14** (NaH, DMF, 25 °C) to give the *all-E* product **19** in almost 60% yield from alcohol **17.** Finally, the sulfone group in **19** was hydrogenolyzed[13] (6% Na–Hg, MeOH, −10 °C, 80–82%) to give mokupalide (**1**). The synthetic product had spectral data (NMR, IR, and MS) identical with that of the natural material.[14]

This synthesis exemplifies the utility of the enol phosphate–cuprate coupling method[6] to generate cyclic and acyclic α,β-unsaturated esters. Furthermore, the method is stereo-

Scheme III. Synthesis of Mokupalide (1)



selective in the case of acyclic esters and can be used in conjunction with the alkylation of the dianion of methyl acetoacetate[3] to stereoselectively introduce isoprene units in a synthetic sequence.[15]

Supplementary Material Available: IR and ^1H NMR spectra and analytical data for compounds **4–8**, **10–12**, and **14–19** (2 pages). Ordering information is given on any current masthead page.

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(14) We are grateful to Professor Scheuer and Dr. Yunker for copies of the spectra of mokupalide (**1**) and for a sample of acetoxymokupalide (**3**).
(15) We are grateful to the National Research Council of Canada for financial support of this work.

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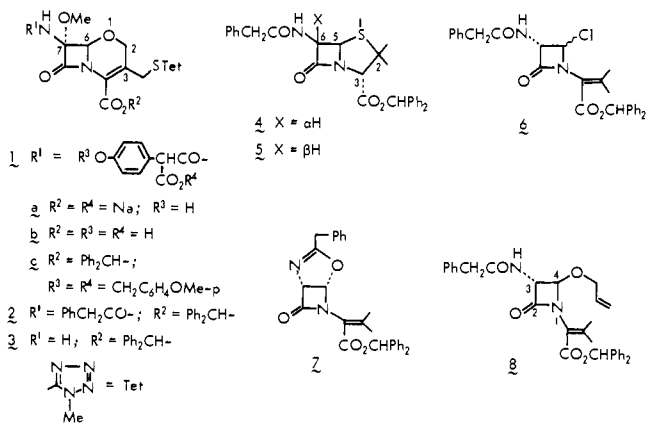
Stereocontrolled Synthesis of 7α-Methoxy-1-oxacephems from 6-Epipenicillin G[1]

Sir:

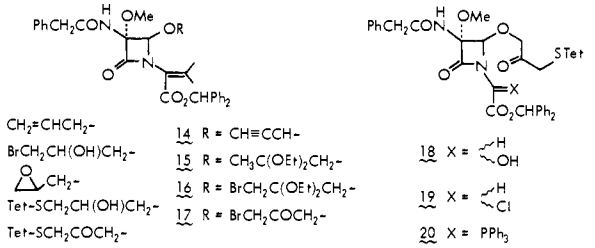
We have recently demonstrated that 7α-methoxy-1-oxacephem[2] antibiotic **1a** shows potent antibacterial activity against Gram-negative microorganisms including β-lactamase-producing resistant strains, pathogenic anaerobic bacteria, and *Pseudomonas* species.[3]

The 1-oxacephem syntheses studied to date in our and other laboratories are unsatisfactory for large-scale preparation of this clinically useful antibiotic because of either poor stereoselectivity in introduction of the 1-oxa functionality[4] or multisteps necessary for improving the stereoselectivity.[1b] Thus, a more efficient and practical route to this important material, **1a**, was desired urgently.

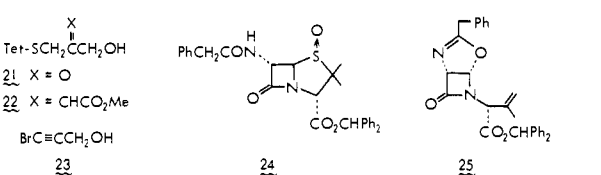


We now report here a new, stereocontrolled, and obviously more practical synthesis of 7β-amino-7α-methoxy-1-oxacephem-4-carboxylate (**3**), which can be easily converted into the antibiotic **1a**, from 6-epipenicillin (**5**).

Treatment of penicillin G diphenylmethyl ester (**4**) with BSA-DBN[5] in CH_2Cl_2 at 0 °C gave a highly crystalline 6-epi derivative **5**, mp 191–192 °C, in 60% yield. Compound **5** was converted into epioxazoline (**7**),[6] mp 104.5–106 °C, in 60% yield by a "one-pot" procedure involving chlorination in CH_2Cl_2 with Cl_2 at −20 °C to seco chloride **6** and cyclization with aqueous NaOH in the presence of a phase-transfer catalyst (n-$Bu_4N^+Cl^-$). Epioxazoline (**7**) dissolved in allyl alcohol was treated with a catalytic amount of CF_3SO_3H[7] at 25 °C to afford stereospecifically[8] *trans*-allyl ether (**8**), mp 108–109.5 °C, in >80% yield.[9] Completely stereoselective introduction of a methoxy group at the 3α position of azetidinone **8** was nicely effected by a method using 1.5 equiv each of t-BuOCl and a methanolic $LiOCH_3$ solution in CH_2Cl_2 at −30 °C followed by Zn/AcOH treatment, giving **9**, mp 70–72 °C, in 80% yield.[10] Compound **9** was transformed into the 7α-methoxy-1-oxacephem **2** in 34% overall yield by a modification of the procedure[3,4a] that we have recently developed. Thus, **9** was converted into the epoxide **11** via bromohydrin **10** (NBS, aqueous Me_2SO, 20 °C, t-BuOK). Epoxide cleavage ((1-methyl-1H-tetrazole-5-thiol, n-BuLi (catalytic), THF, 20 °C)) to **12** followed by Jones oxidation provided **13**. Ozonolysis of **13** followed by direct reduction of the resulting ozonide with Zn/AcOH in CH_2Cl_2 at −15 °C gave an epimeric mixture of alcohols **18**. Chlorination ($SOCl_2$, pyridine, CH_2Cl_2, −18 °C) to epimeric chlorides **19** and subsequent treatment with PPh_3 in refluxing CH_2Cl_2 gave ylide **20**. Intramolecular Wittig reaction in refluxing dioxane gave 7β-phenylacetamido-7α-methoxy-1-oxacephem (**2**), mp 172–173 °C, in good yield.



In search of a more efficient route, the following transformations were examined. Methoxypropargyl ether **14**, prepared by reaction of **7** with propargyl alcohol and subsequent methoxylation in a way similar to that described for preparing **9**, was converted (EtOH–$CH(OEt)_3$, HgO (catalytic), reflux) into ketal **15**. Bromination to **16**, hydrolysis to **17**, and substitution by the process developed in our laboratories[1b] afforded ketone **13**. Although the overall yield of **13** from **7** was comparable with that obtained from the above route, use of HgO was considered to be disadvantageous. In order to reduce the number of synthetic steps, reaction of epioxazoline (**7**) with some properly functionalized alcohols, **21**, **22**, and **23**, was also investigated, but the yields of the resulting ethers were so low that they offset the advantage of the fewer reaction steps.



Very recently a convenient, efficient preparation of iso-

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