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 ^{1}H 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.

References and Notes

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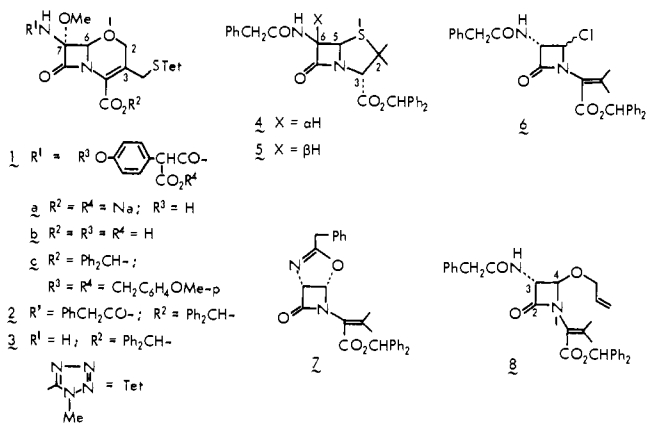
Stereocontrolled Synthesis of 7α-Methoxy-1-oxacephems from 6-Epipenicillin G[1]

Sir:

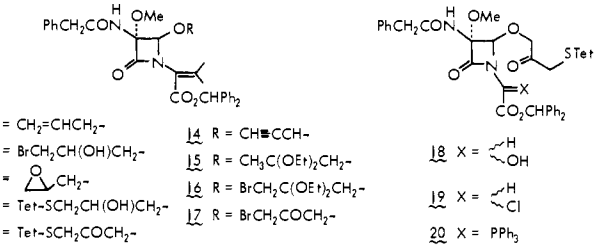
We have recently demonstrated that 7α-methoxy-1-oxacephem[2] antibiotic **1a** shows potent antibacterial activity against Gram-negative microorganisms including β-lactamase-producing resistant strains, pathogenic anaerobic bacteria, and *Pseudomonas* species.[3]

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.

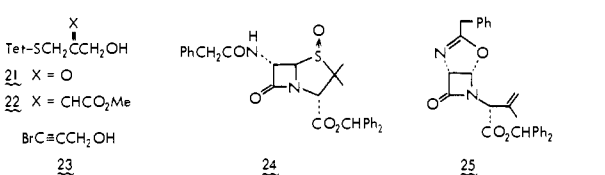


We now report here a new, stereocontrolled, and obviously more practical synthesis of 7β-amino-7α-methoxy-1-oxacephem-4-carboxylate (**3**), which can be easily converted into the antibiotic **1a,** from 6-epipenicillin (**5**).

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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propenylepioxazoline (**25**) from 6-epipenicillin sulfoxide (**24**) was reported from our laboratories.[11] Since treatment of **25** with Et_3N gave isopropylideneepioxazoline (**7**) in quantitative yield and epimerization of penicillin sulfoxides at position 6 is more facile than that of penicillins,[5] the overall yield of epioxazoline **7** from penicillin G ester **4** has now become ~60% making the present synthetic route advantageous.

The last crucial problem in our synthesis is transformation of compound **2** having the fundamental skeleton of antibiotic **1a** to the methoxy amine nucleus **3** without epimerization at C-7; it is well known that the side-chain cleavage of a thia analogue (cephamycin-type compound) gives an undesired, thermodynamically stable 7α-amino-7β-methoxy epimer as a major product.[12] With the expectation that probable hydrogen bonding between the oxygen atom at position 1 and the 7β-amino group would stabilize the 1-oxa product **3**, compound **2** was subjected to side-chain cleavage (PCl_5, pyridine, CH_2Cl_2; MeOH; Et_2NH;[13] 3–10 °C) to give the 7α-methoxy amine **3**, mp 164–165.5 °C (from CH_2Cl_2–MeOH), in 54% yield, accompanied by an unappreciable amount of the 7β-methoxy epimer.

Conversion of **3** into the antibiotic **1** can be easily achieved, as reported in our previous paper,[3] by acylation with 2-[4-[(4-methoxybenzyl)oxy]phenyl]-2-[[(4-methoxybenzyl)-oxy]carbonyl]acetyl chloride and pyridine, deprotection of diester **1c** with trifluoroacetic acid or $AlCl_3$ in the presence of anisole, and treatment of the resulting diacid **1b** with sodium hexanoate.[14]

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(7) Use of cosolvents (CH_2Cl_2, benzene, etc.) and/or other acids (BF_3·ether, TsOH, MsOH, etc.) gave less satisfactory results.

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(14) The structure assignments of new compounds were supported by their IR and NMR data. Correct combustion analyses were obtained for all the crystalline compounds whose melting points (uncorrected) were given.

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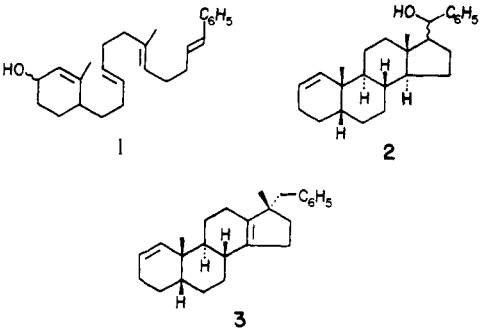
Biomimetic Polyene Cyclizations.[1] Trapping of the Resultant Carbocation by an Internal Nucleophile

Sir:

The idea expressed in the title, besides having possible biogenetic implications,[2] is attractive because good control of cyclizations may be expected with substrates containing built-in nucleophiles that can be intramolecularly delivered only to that site destined for termination of the process.[3] The present paper discloses the results of our first study along these lines, involving the use of an internal nucleophile in conjunction with a styryl terminator.

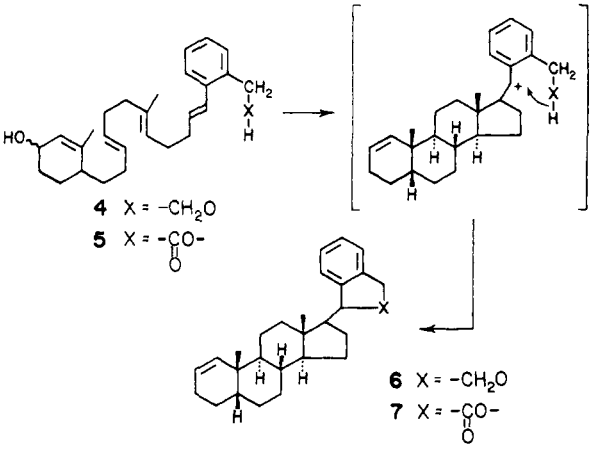
An appropriately positioned styryl group has certain advantages as a terminator of polyene cyclizations because it not only participates regiospecifically to form directly the five-membered D ring of the steroid nucleus,[4] but it reacts in a highly stereoselective manner to give the C/D trans (natural) configuration,[5] as illustrated in the conversion **1** → **2**.[4] On the



other hand, the tetracyclic benzylic cation (formula **2** with a plus charge in place of OH) is highly susceptible to both polymerization and backbone rearrangement (to form **3**) which are the major reactions observed except under carefully controlled conditions.[6] The problem is exacerbated in cyclizations conducted in nonnucleophilic media, which provide no readily accessible means of trapping the aforementioned benzylic cation. Thus treatment of **1** with stannic chloride in methylene chloride gives mainly polymers, while, under conditions of high dilution, up to 50% yields of **3** can be isolated from the mixture. We were therefore prompted to explore the use of an internal nucleophile with this system, anticipating the transformation suggested in Scheme I.

Substrate **4** was prepared by a convergent synthesis as depicted in Scheme II. Thus the alcohol **10**[11a,12,13] was derived from the isochroman **8** in eight steps in an overall yield of 36%.[14] Collins oxidation of **10** afforded the aldehyde **11** in 86% yield.[12,13] The polyenic thioketal **13** was obtained by a Wittig–Schlosser condensation[15,16] of **11** and the known phos-

Scheme I



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