Selective in the case of acyclic esters and can be used in conjunction with the alkylation of the dianion of methyl acetooacetate to stereoselectively introduce isoprene units in a synthetic sequence. 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.

References and Notes

4. All compounds were characterized by IR, NMR, and MS data, and either elemental analysis or high-resolution mass spectral data.
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).
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Stereocontrolled Synthesis of 7α-Methoxy-1-oxacephems from 6-Epipenicillin G

Sir:

We have recently demonstrated that 7α-methoxy-1-oxacephem antibiotic 1a shows potent antibacterial activity against Gram-negative microorganisms including β-lactamase-producing resistant strains, pathogenic anaerobic bacteria, and Pseudomonas species. The 1-oxacephem synthases 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 or multiplicity of steps necessary for improving the stereoselectivity. 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-DBN2 in CH2Cl2 at 0 °C gave a highly crystalline 6-epi derivative 5, mp 191-192 °C, in 60% yield. Compound 5 was converted into epoxazoline (7), mp 104.5-106 °C, in 60% yield by a "one-pot" procedure involving chlorination in CH2Cl2 with Cl2 at −20 °C to secocloride 6 and cyclization with aqueous NaOH in the presence of a phase-transfer catalyst (n-Bu4NCl+). Epoxazoline (7) dissolved in allyl alcohol was treated with a catalytic amount of CF3SO3H at 25 °C to afford stereospecifically trans-allyl ether (8), mp 108-109.5 °C, in >80% yield. Completely stereoselective introduction of a methoxy group at the 3α position of azetidine 8 was nicely effected by a method using 1.5 equiv of t-BuOCl and a methanolic LiOHCH3 solution in CH2Cl2 at −30 °C followed by Zn/ArCOH treatment, giving 9, mp 70-72 °C, in 80% yield. Compound 9 was transformed into the 7α-methoxy-1-oxacephem 2 in 34% overall yield by a modification of the procedure1-6 that we have recently developed. Thus, 9 was converted into the epoxide 11 via bromohydrin 10 (NBS, aqueous Me2SO, 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. Ozoneolysis of 13 followed by direct reduction of the resulting ozonide with Zn/ArCOH in CH2Cl2 at −15 °C gave an epimeric mixture of alcohols 18. Chlorination (SOCl2, pyridine, CH2Cl2, −18 °C) to epimeric chlorides 19 and subsequent treatment with PPh3 in refluxing CH2Cl2 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 methoxilation in a way similar to that described for preparing 9, was converted (EtOH-CH(EtO)2H, H2O (catalytic), reflux) into ketal 15. Bromination to 16, hydrolysis to 17, and substitution by the process developed in our laboratories10 afforded ketone 13. Although the overall yield of 13 from 7 was comparable with that obtained from the above route, use of H2O was considered to be disadvantageous. In order to reduce the number of synthetic steps, reaction of epoxazoline (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-
oxazoline (25) from 6-epipenicillin sulfoxide (24) was reported from our laboratories.6 Since treatment of 25 with Et3N gave isopropylideneoxazoline (7) in quantitative yield and epimerization of penicillin sulfoxides at position 6 is more facile than that of penicillins,6 the overall yield of epoxazoline 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-amin-7β-methoxy epimer as a major product.1 With the expectation that probably hydrogen bonding between the oxygen atom at position 8 and the 7β-amino group would stabilize the 1-oxa product, compound 2 was subjected to side-chain cleavage (PCls, pyridine, CH2Cl2; MeOH; Et3NHCl;3 3–10 °C) to give the 7α-methoxy amine 3, mp 164–165.5 °C (from CH2Cl2-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 hexanoate. I

other hand, the tetracyclic benzyl 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 benzyl 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 1011,12,13 was derived from the isochromon B 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 thiolactone 13 was obtained by a Wittig-Schlosser condensation5,10 of 11 and the known phosphine.