Nuclear analogs of β-lactam antibiotics. VIII. Synthesis of 3-acetoxymethyl-Δ^3-*O*-2-isocephems[1]

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The synthesis of 7β-(-2′-thienylacetamido)-3-acetoxymethyl-Δ^3-*O*-2-isocephem-4-carboxylic acid (**17**) is described. Thus treatment of enol mesylate **3***a* or triflate **3***b* with triethylamine gave the allene **4** which gave the diiodide upon treatment with iodine. The diiodide gave benzyl 7β-azido-3-acetoxymethyl-Δ^3-*O*-2-isocephem-4-carboxylate (**12**) on treatment with potassium acetate in DMF. Hydrogenolysis of **12** gave the amino acid **16** which was converted to **17** upon treatment with 2-thienylacetyl chloride. Resolution of **17** into its optical antipodes was carried out. The antibiotic activities of racemic **17** and each antipode is compared to that of cephalothin. Antibiotic activity was found to reside in the dextrorotatory isomer.

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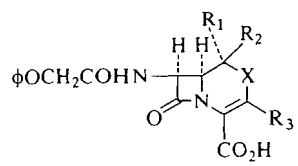
On décrit la synthèse de l'acide (thiényl-2′ acétamido-7β) acétoxyméthyl-3 Δ^3-*O*-isocéphem-2 carboxylique-4 (**17**). Ainsi le traitement du mésylate énolique **3***a* ou triflate **3***b* par la triéthylamine conduit à l'allène **4** qui fournit le dérivé diiodé par réaction avec l'iode. Le diiodure conduit à l'azido-7β acétoxyméthyl-3 Δ^3-*O*-isocéphem-2 carboxylate-4 de benzyle (**12**) par réaction avec l'acétate de potassium dans le DMF. L'hydrogénolyse de **12** fournit l'acide aminé **16** qui peut être transformé en **17** par réaction avec le chlorure de thiényl-2 acétyle. La résolution de **17** en antipodes optiques a été réalisée. On compare les activités antibiotiques du **17** racémique et de chacun de ses antipodes avec celles de la céphalothine. On a trouvé que l'isomère dextrorotatoire possède l'activité antibiotique.

[Traduit par le journal]

Recent reports from a number of laboratories attest to the continuing interest in β-lactam antibiotics with modified nuclei, both from natural sources and by total synthesis (2). In the earlier papers of this series we have described the syntheses of a number of nuclear analogs of the cephalosporins **1***a–m* in which the sulfur at the 1 position has been replaced by a carbon atom and the carbon atom at the 2 position by a hetero atom. In each of these cases the substituent at position 3 was hydrogen, methyl, or aralkyl. In view of the pronounced improvement of activity observed when the 3 substituent is acetoxy methyl in the natural series, we desired an entry into these systems as well. In this paper we should like to report the synthesis of the 3-acetoxymethyl-*O*-2-isocephem system **1***n*.[4]



	X	R_1	R_2	R_3
a	O	H	H	H
b	O	H	H	CH_3
c	O	H	H	$CH_2\phi$
d	O	H	H	$(CH_2)_2\phi$
e	O	CH_3	H	CH_3
f	O	H	CH_3	CH_3
g	O	— O	—	CH_3
h	NCH_3	H	H	CH_3
i	NCO_2Et	H	H	CH_3
j	S	H	H	CH_3
k	S	H	H	CH_3
l	SO	H	H	CH_3
m	SO_2	H	H	CH_3
n	O	H	H	CH_2OAc

Our initial attempts to prepare the 3-substituted methyl systems by free radical bromination of the methyl group using either bromine or NBS under a variety of conditions failed completely as did a

[1]For Part VII of this series see ref. 1.

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[4]For a review of some of the earlier literature on nuclear modifications of β-lactams and an explanation of the trivial nomenclature used throughout this series, see ref. 3.

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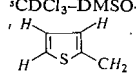
TABLE 1. Nuclear magnetic resonance spectra[a]

Compound	Aromatic protons			AR—CH_2	CH_3	Other
3*b*[d]	7.32(s, 5H)	4.91(d) $J = 5$	—	5.24(s)	2.89(s) 2.83(s)[c] 2.47(s) 2.25(s)[e]	4.3(m, 3H)[b]
4	7.30(s, 5H)	4.92(d) $J = 4.5$	—	5.18(s)	2.92(s)[c]	5.65(s, 2H)[f] 4.40(m, 3H)[b]
7 and **8***b*	7.30(s, 5H)	—	—	5.21(s)	2.91(s)[c]	4.0–5.0(m, 6H)[g]
7 and **8***a*	7.20(s, 5H)			5.13(s)	2.91(s)[c]	4.2–5.2(m, 6H)[g]
7 and **8***d*	7.35(s, 5H)	—	—	5.21(s)	2.92(s)[c] 2.49(s)[j] 2.47(s)[j]	4.2–5.3(m, 4H)[h] 2.42(br, 2H)[i]
11	7.42(s, 5H)	—	—	5.37(s)	—	7.02(d, 1H, $J = 3$) 6.80(d, 1H, $J = 3$)
12	7.40(bs, 5H)	5.20(m)	4.60(m)	5.27(s)	2.05(s)[l]	5.09(s, 2H)[k] 3.5–4.1(m, 2H)[m]
13	7.50(s, 5H)	—	—	5.35(s)	2.08(s)[l]	5.15(s, 2H)[k] 1.63(bs, 2H)[n] 4.9–4.6, 4.2–3.7(4H, m)
14	6.8–7.7(m, 10H)	5.62(dd) $J_1 = 7$ $J_2 = 5$	—	5.33(s)	2.05(s)[l]	5.15(s, 2H)[k] 4.56(s, 2H)[o] 3.8–4.6(m, 3H)
15[q]	6.9–7.6(m, 5H)	5.77(m)	—	—	2.07(s)[l]	5.06(s, 2H)[k] 4.65(s, 2H)[o] 3.6–4.6(m, 3H)
16[r]		5.32(d)	—	—	2.17(s)[l]	5.20(s, 2H)[k] 4.0–5.0(m, 3H) 4.90(b, 2–3H)[n]
17[s]	6.9 and 7.3[t] (m, 3H)	5.55(dd) $J_1 = 8$ $J_2 = 4.5$	—	—	2.02(s)[l]	4.96(s, 2H)[k] 3.70(s, 2H)[f] 8.75(d, $J = 8$, 1H)[u] 4.50(d, 1H, $J = 6$)[p] 3.6–4.1(m, 2H)

[a]All spectra were recorded on a Varian A-60A at 60 MHz in $CDCl_3$ unless otherwise noted. Shifts are in δ and couplings are in Hz.
[b]CH—CH_2OMes.
[c]SO_2CH_3.
[d]Two isomers 1:5 ratio.
[e]  .
[f] .
[g]H-3, H-4, CH_2—OMes, CH_2Br(or I).
[h]H-3, H-4 + CH_2—OMes.
[i]CH_2Cl.
[j]SCH_3.
[k]CH_2OAc.
[l]CH_3C.
[m]—CH_2—O—.
[n]NH_2.
[o]ϕOCH—.
[p]Either $H_{1\alpha}$ or $H_{1\beta}$.
[q]DMSO-d_6.
[r]D_2O–DMSO-d_6.
[s]$CDCl_3$–DMSO-d_6.
[t] 
[u]NH.

number of other attempts to oxidize the 3-methyl group. The fortuitous observation that the enol mesylate **3** could be converted in high yields to the allene **4** eventually provided an entry into the desired 3-acetoxymethyl-*O*-2-isocephems (Scheme 1). Thus in the preparation of **3***a* (4) it was noticed that if an excess of triethylamine was used in the reaction of the enol **2** (5) with mesyl chloride and the reaction mixture was allowed to stand at room temperature, the bismesylate disappeared and a new olefinic signal appeared at 5.65 δ in the nmr spectrum which was assigned to the allenic protons in **4** (Table 1). A by-product of this reaction was the *O*-2-isocephem **6** which was formed in variable yields. We speculate

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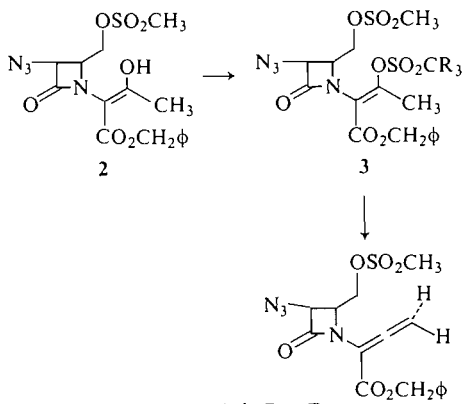
that **6** was formed by fragmentation of the initially formed mesylate to give **5** which under the reaction conditions cyclized to yield **6** (Scheme 2). To avoid this side reaction it was decided to prepare **4** via the triflate **3***b* rather than the mesylate **3***a*. Thus treatment of **2** with triflic anhydride (6) in the presence of triethylamine at $-10°C$ gave, after work-up, **3***b* as a mixture of geometric isomers in 71% yield.

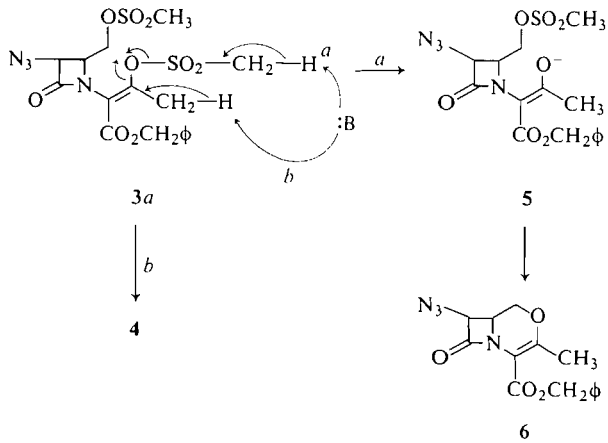
Stang and Hargrove (7) have reported the conversion of vinyl triflates to allenes in low to moderate yields by treatment of the triflates at 100°C in quinoline. In the case of **3***b* the conversion to **4** proceeded in high yield (>90%) under mild conditions. Treatment of **3***b* in methylene chloride at 0°C with 1 equiv. of triethylamine and letting the solution come to 23°C over 15 min gave a virtually quantitative yield of allene. Although the allene could be isolated it proved to be relatively unstable and was usually used immediately in the subsequent step. The observation of facile allene formation in our case represents an extension of Stang and Hargrove's original work (7) to vinyl triflates derived from β-keto esters and may well provide access to other members of this elusive class of compounds.



SCHEME 1

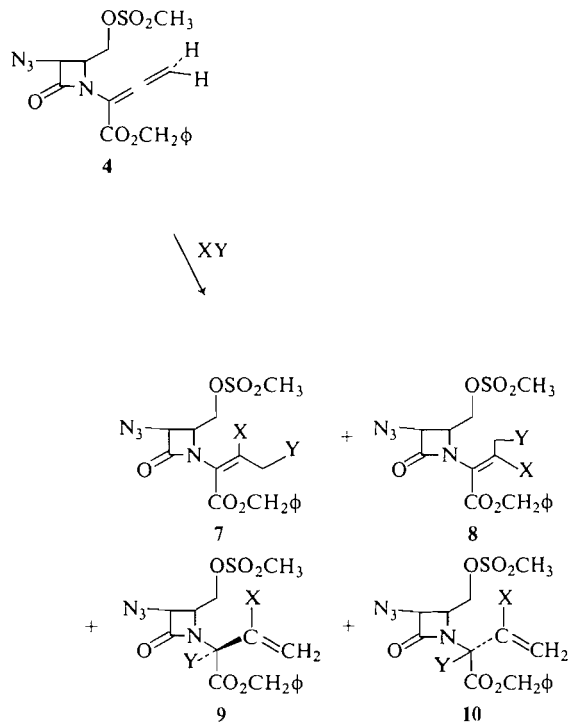
A priori a number of ways to convert the allene **4** to the desired 3-methyl-substituted-*O*-2-isocephems might be envisioned. Electrophilic addition to the allene might well be expected to give products at the right level of oxidation. Accordingly, the halogenation of **4** was examined. In principle one would expect to obtain as many as four possible products from the reaction (8) arising from the four possible allylic cations which might be generated (Scheme 3).

Treatment of **4** with 1 equiv. of chlorine in methylene chloride gave a mixture of products. The product mixture exhibited olefinic signals in the nmr at 6.23 and 5.83 δ as sets of doublets, and singlets at 4.74 and 4.27 δ. These have been assigned



SCHEME 2

to **9***c* and **10***c*, and **7***c* and **8***c*, respectively, and are in an approximate ratio of 1:1:1:1. In view of the complexity of the mixture, further work using chlorination was abandoned. We next turned our attention to bromination of **4**. Treatment of **4** with 1 equiv. of bromine led to a mixture of dibromides. Chromatography of the mixture on silica gel gave a



7 ⟶ 10 *a* X = I = Y
b X = Br = Y
c X = Cl = Y
d X = SMe Y = Cl

SCHEME 3

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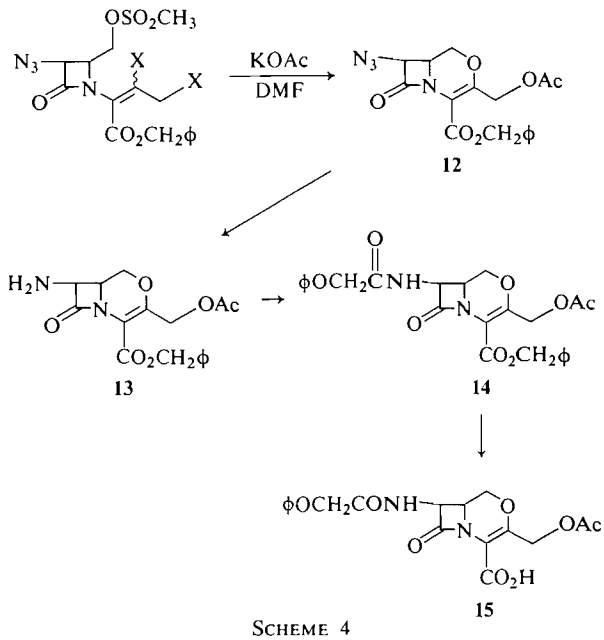
mixture of the desired dibromides **7***b* and **8***b*[5] in 45% yield.

Treatment of **4** with a solution of iodine in methylene chloride gave the diiodides **7***a* and **8***a* analytically pure in 91% yield. In addition to the above halogenations, attempts were also made to react the allene with a number of other electrophiles such as 2,4-dinitrobenzenesulfenyl chloride, isobutanesulfenyl chloride, methane sulfenyl chloride, *tert*-butyl hypochlorite, sodium hypochlorite, hydrogen peroxide, potassium permanganate, and peracids. For the most part these experiments yielded only polymer. In the case of methanesulfenyl chloride (9) a low yield of an adduct (32%) identified as a mixture of **7***d* and **8***d* by its spectral characteristics was obtained. The uv maximum at 307 nm (ε 7700) was especially diagnostic of the sulfur atom bound at the central atom of the allene (1).[6]

With the dibromides (**7***b* and **8***b*) and diiodides (**7***a* and **8***a*) in hand the conversion of these to the *O*-2-isocephem system was examined next. Thus treatment of either the diiodide or the dibromide with an excess of potassium acetate in dimethylformamide gave the desired intermediate **12** in 35–60% yields (Scheme 4). Although the yield of **12** from the dibromides was higher, the overall yield from the allene was greater using the diiodide. It should also be noted that it was possible to go from the enol **2** to the 3-acetoxymethyl-*O*-2-isocephem **12** without the necessity of isolating the intermediates. Presumably compound **12** arose via displacement of the terminal iodide or bromide by acetate, Michael addition of acetate to the double bond with halide elimination,



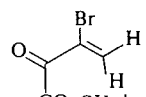
SCHEME 4

hydrolysis of the vinyl acetate to give the enolate, and finally ring closure of enolate. The sequence in which the displacement steps occur is unclear. Attempts to selectively displace the allylic halide failed. The structure of **12** was supported by its elemental analysis, ir and nmr spectra, and by subsequent conversions.

Reduction of **12** using hydrogen sulfide – triethylamine gave the amine **13** in 60% yield. Treatment of **13** with *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (10) (EEDQ) and phenoxyacetic acid gave the amide **14** in 69% yield. Hydrogenolysis of **14** yielded the desired 7β-(phenoxyacetamido)-3-acetoxymethyl-Δ^3-*O*-2-isocephem-4-carboxylic acid (Scheme 4). Compound **15** showed antibiotic activity greater than that observed for the 3-methyl analog.

To provide a comparison of the antibiotic activity of a 2-isocephem with a commercially available cephalosporin, the synthesis of a cephalothin analog was attempted next. Thus hydrogenation of the azido ester **12** over palladium gave a near quantitative yield of the crude amino acid **16** as its hydrochloride salt. Suspension of this salt in aqueous sodium bicarbonate followed by addition of 2-thienylacetyl chloride (11) gave after work-up the racemic 7β-(2′-thienylacetamido)-3-acetoxy methyl-Δ^3-*O*-2-isocephem-4-carboxylic acid (**17**) in 51% overall yield from **12** (Scheme 5). Resolution of the racemic mixture was achieved using (+)-α-methylbenzylamine to give the dextrorotatory enantiomer and (−)-α-methylbenzylamine to give the levorotatory enantiomer. The antibiotic activities of the racemic mixture, both

[5]In addition to **7***b* and **8***b*, a small amount of a third component tentatively identified as **11** on the basis of its spectral characteristics was isolated.



11

[6]Although the products from the addition of Cl_2, Br_2, or I_2 to the allene would not permit one to distinguish between the mechanistic pathways proceeding through the allylic or vinyl cations, those from the addition of methane sulfenyl chloride to **4** do.

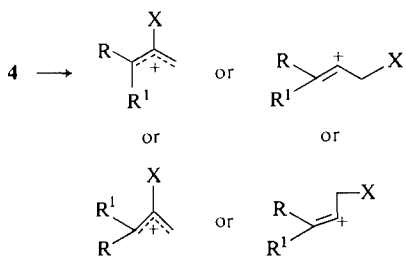


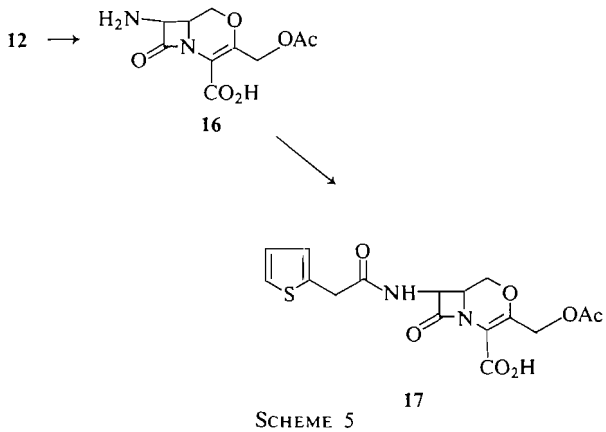
TABLE 2. Antibiotic activities[a]

Compound	*Streptococcus pneumoniae*	*Staphylococcus aureus* Smith	*Staphylococcus aureus* Meth. Res.	*Escherichia coli*	*Proteus mirabilis*
(±)-**17**	0.03	0.5	2	63	1
(+)-**17**	0.016	0.06	0.25	32	0.13
(−)-**17**	0.5	4	>125	>125	16
Cephalothin	0.08	0.16	1	63	1

[a]Expressed as MIC's (μg/ml) and determined by a two-fold serial dilution assay in Difco nutrient broth by the method of Pursiano *et al.* (12).

enantiomers, and cephalothin against a number of organisms is summarized in Table 2.

As is evident from Table 2 the activity of our cephalothin analog resides primarily in the dextrorotatory isomer (+)-**17** (13). The activity of (+)-**17** compares favorably with that of cephalothin. A more extensive discussion of the bioactivities of compounds in this series will appear elsewhere.



SCHEME 5

Experimental

The ir spectra were recorded on a Unicam Sp-200G grating, ir spectrometer. The nmr spectra were determined on a Varian A60-A spectrometer using tetramethylsilane as an internal standard. Melting points are uncorrected and were determined on a Gallenkamp melting point apparatus. The analyses were performed by Micro-Tech Laboratories, Skokie, Illinois.

Synthesis of **3**b

A solution of the enol **2** (48.0 g, 0.117 mol) in 400 ml of dichloromethane was cooled to −10°C under nitrogen and a solution of triflic anhydride (33.0 g, 0.117 mol) in 100 ml of dichloromethane was added over several minutes. A 10% solution of triethylamine in dichloromethane was added dropwise with stirring until the reaction mixture was weakly basic to p*H* paper (about 0.14 mol of triethylamine was required). The reaction solution was immediately washed with cold 10% hydrochloric acid (500 ml) followed by water (2 × 500 ml). The dichloromethane solution was dried (sodium sulfate) and filtered through 260 g of activity III silica gel. The silica gel was extracted with a further 2 L of dichloromethane. The dichloromethane was evaporated *in vacuo* from the combined extracts to give the triflate **3***b* as a yellow oil 38.3 g (71% yield) (mixture of two isomers). This material was of adequate purity for subsequent reactions. An analytical sample containing one isomer was prepared by recrystallization from ethanol, mp 57–59°C; ir (Nujol mull): 2150, 2120, 1785, 1730 cm^{-1}. *Anal.* calcd. for $C_{17}H_{17}F_3N_4O_4S_2$: C 37.67, H 3.14, N 10.33, S 11.82; found: C 37.40, H 3.12, N 10.43, S 11.73.

Preparation of **7** *and* **8**

A solution of triethylamine (1.01 g, 10 mmol) in 14 ml of dichloromethane was added with stirring to a solution of triflate **3***b* (5.42 g, 10 mmol) in 54 ml of dichloromethane at 0°C. The solution was allowed to warm to 23°C over 15 min.[7] A solution of halogen (10 mmol) in 75 ml of dichloromethane was added dropwise with stirring over 30 min. The resulting solution was washed with water (2 × 150 ml), dried (sodium sulfate), treated with activated charcoal (ca. 1 g), filtered, and the solvent was evaporated *in vacuo* to give **7** and **8** as an oil.

Diiodide 7 and **8***a* was obtained analytically pure, 5.88 g (91% yield). *Anal.* calcd. for $C_{16}H_{16}I_2N_4O_6S$: C 29.74, H 2.50, N 8.67, I 39.28, S 4.96; found: C 29.76, H 2.47, N 8.61, I 39.37, S 5.18.

Dibromide **7** and **8***b* was obtained as a mixture of isomers which could be purified by column chromatography on activity I silica gel (elution with dichloromethane) to give pure **7** and **8***b*, 2.5 g (45% yield). *Anal.* calcd. for $C_{16}H_{16}Br_2N_4O_6S$: C 34.80, H 2.92, N 10.15; found: C 35.25, H 2.97, N 10.02.

Dichloride 7 and **8***c* was obtained as a crude mixture of four isomers plus degradation products.

A by-product isolated by chromatography of the bromination reaction was tentatively identified as compound **11**: ir (mull): 1735, 1705 cm^{-1}.

Preparation of **7** *and* **8**d

The allene was prepared immediately before use in this reaction from 1.08 g (2.00 mmol) of the triflate in the usual manner.

The methanesulfenyl chloride was prepared immediately before use by the method of Douglass (9).

The allene (2.00 mmol) in 20 ml of CH_2Cl_2 was cooled to −5 to −10°C and the freshly prepared solution of MeSCl (2.00 mmol) in 3 ml of CH_2Cl_2 was added with stirring under nitrogen. After 10 min at −5°C, the solution was washed with dilute $Na_2S_2O_3$, then brine, and evaporated *in vacuo* to give a yellow oil. The oil was absorbed from CH_2Cl_2 onto 5 g of silica gel and placed (dry) on a 50 g silica gel column (activity III). The column was eluted with ether; 30 ml fractions were collected and monitored by tlc (silica, ether). Fractions showing one spot at about R_f 0.43 were combined and the solvent was evaporated *in vacuo* to give the product (306 mg, 32%

[7]The allene **4** may be isolated at this point by washing the solution with water, drying (Na_2SO_4), and evaporating the solvent *in vacuo*. The allene decomposes over several days at 0°C.

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yield) as a pale yellow oil; uv λ_{max} 309 mμ (ε 7700); (film): 2120, 1775, 1705 cm^{-1}.

Benzyl 7β-Azido-3-acetoxymethyl-Δ³-O-2-isocephem-4-carboxylate (12)

A mixture of dihalide **7** and **8***a* or *b* (10 mmol), potassium acetate (40 mmol, finely ground), dimethylformamide (50 ml), and water (0.1 ml) was stirred vigorously at 23°C for 20 h. The resulting solution was mixed with ether (250 ml) and washed with water (5 × 250 ml). The ether solution was dried (sodium sulfate) and evaporated *in vacuo* to give a brown residue. The residue was dissolved in dichloromethane and passed through 10 times its weight of activity III silica gel. The solvent was evaporated *in vacuo* and the crude product was recrystallized from benzene–hexane to give pure *O*-2-cephem **12** (35–60% yield),[8] mp 97–98°C; ir (Nujol mull): 2160, 2110, 1775, 1750, 1705, 1600 cm^{-1}. *Anal.* calcd. for $C_{17}H_{16}N_4O_6$: C 54.84, H 4.33, N 15.05; found: C 55.19, H 4.47, N 14.89.

Benzyl 7β-Amino-3-acetoxymethyl-Δ³-O-2-isocephem-4-carboxylate (13)

Hydrogen sulfide was bubbled into a solution of azide **12** (793 mg, 2.1 mmol), triethylamine (210 mg, 2.1 mmol), and dichloromethane (15 ml) for 10 min. Nitrogen was passed through the solution to remove excess hydrogen sulfide and the solvent was evaporated *in vacuo*. The residue was mixed with ether and extracted with 10% hydrochloric acid three times. The acid extract was washed with ether, made basic with sodium bicarbonate, saturated with sodium chloride, and extracted three times with dichloromethane. The dichloromethane extract was washed with saturated sodium chloride, dried (Na_2SO_4), and the solvent was evaporated *in vacuo* to give amine **13** as a colorless oil, 415 mg (60% yield); ir (film): 3400, 1775, 1745, 1715, 1620 cm^{-1}. *Anal.* calcd. for $C_{17}H_{18}N_2O_6$: C 58.95, H 5.24, N 8.09; found: C 58.39, H 5.32, N 7.95.

Benzyl 7β-(Phenoxyacetamido)-3-acetoxymethyl-Δ³-O-2-isocephem-4-carboxylate (14)

A solution of amine **13** (415 mg, 1.2 mmol), phenoxyacetic acid (183 mg, 1.2 mmol), EEDQ (325 mg, 1.3 mmol), and dichloromethane (15 ml) was stirred at 23°C for 1.5 h. The solution was washed with 10% hydrochloric acid, saturated sodium chloride, 10% sodium bicarbonate, and saturated sodium chloride (20 ml each). The resulting solution was dried (Na_2SO_4) and the solvent was evaporated *in vacuo* to give an oil. The oil was chromatographed on activity III silica gel (elution with ether). Amide **14** was obtained as colorless crystals, 400 mg (69% yield), mp 146°C; ir (Nujol mull): 3320, 1775, 1745, 1725, 1690, 1535, 1625 cm^{-1}. *Anal.* calcd. for $C_{25}H_{24}N_2O_8$: C 62.49, H 5.04, N 5.83; found: C 62.58, H 5.07, N 5.83.

7β-(Phenoxyacetamido)-3-acetoxymethyl-Δ³-O-2-isocephem-4-carboxylic Acid (15)

A mixture of ester **14** (100 mg, 0.21 mmol), 10% palladium-on-charcoal (100 mg), and tetrahydrofuran (50 ml) was hydrogenated with agitation at 23°C and 40 psi for 15 min. The catalyst was removed by filtration and the solvent was evaporated *in vacuo*. The crude product was recrystallized from ethanol to give *O*-2-cephem **15**, 50 mg (62% yield), mp 160–170°C (dec.); ir (Nujol mull): 3400–2500, 1785, 1720, 1705, 1645, 1550, 1620 cm^{-1}. *Anal.* calcd. for $C_{18}H_{18}N_2O_8$: C 55.38, H 4.65, N 7.18; found: C 55.32, H 4.88, N 7.13.

[8]Higher yields were obtained if pure dibromide was used rather than pure diiodide; however, since the yield of dibromide from allene was less than diiodide, better overall yields were obtained via the diiodide.

7β-Amino-3-acetoxymethyl-Δ³-O-2-isocephem-4-carboxylic Acid (16)

A mixture of azide **12** (5.0 g, 13.4 mmol), palladium chloride (1.2 g, 7.1 mmol), and anhydrous ethanol (300 ml) was hydrogenated with agitation at 23°C and 50 psi for 1 h. The catalyst was removed by filtration and the solvent was evaporated *in vacuo* to give the hydrochloride salt **16** as an amorphous solid, 4.2 g (100% yield). Because of its instability, the product was not purified further; ir (Nujol mull): 3400–2500, 1770, 1740–1690, 1610 cm^{-1}.

7β-(2′-Thienylacetamido)-3-acetoxymethyl-Δ³-O-2-isocephem-4-carboxylic Acid (17)

Hydrochloride salt **16** (4.2 g, 13.4 mmol) was mixed with 150 ml of water and sodium bicarbonate (7.5 g, 90 mmol) was added at 0°C. A solution of 2-thienylacetic acid chloride[9] (4.5 g, 28 mmol) in 50 ml of acetone was added with stirring to the aqueous solution. The mixture was stirred for 1 h at 0°C, then washed with ether (2 × 100 ml). The aqueous solution was acidified with 10% hydrochloric acid and extracted with dichloromethane (2 × 100 ml). The dichloromethane extract was dried (Na_2SO_4) and the solvent was evaporated *in vacuo*. The residue was crystallized by trituration with ether to give (±)-*O*-2-cephalothin **17**, 2.6 g (51% overall yield from **12**). An analytical sample was prepared by recrystallization from anhydrous ethanol, mp 182°C (dec.); uv_{max} (EtOH): 272 nm, ε 8650; ir (Nujol mull): 3300–2500, 1780, 1750, 1720, 1680, 1535, 1620 cm^{-1}. *Anal.* calcd. for $C_{16}H_{16}N_2O_4S$: C 50.52, H 4.24, N 7.37, S 8.43; found: C 50.34, H 4.41, N 7.47, S 8.45.

The acid **17** (1.0 g, 2.64 mmol) was dissolved in warm isopropyl alcohol (50 ml) and (+)-α-methylbenzylamine (0.32 g, 2.64 mmol) was added. The precipitate was collected by filtration and washed with isopropanol and ether. The precipitate was mixed with 10% hydrochloric acid and extracted with dichloromethane. The dichloromethane extract was dried (Na_2SO_4) and the solvent was evaporated *in vacuo*. The residue was crystallized by trituration with ether. The resolution procedure was repeated twice more (until material of constant rotation was obtained) to give (+)-*O*-2-cephalothin ((+)-**17**) with $[\alpha]_D$ +116° (acetone); (145 mg, 14.5% yield). The mother liquors from the above resolution were similarly treated with (−)-α-methylbenzylamine to give (−)-*O*-2-cephalothin ((−)-**17**) with $[\alpha]_D$ −115° (acetone).

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[9]The acid chloride was obtained from 2-thienyl acetic acid by stirring with oxalyl chloride for 3 h, then evaporating the excess oxalyl chloride *in vacuo* (11).

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