Free Radical Annelation in the Synthesis of Bicyclic β-Lactams. 4.[1] Exo vs. Endo Cyclizations in the Construction of the (±)-1-Oxacepham and (±)-1-Oxahomocepham Systems

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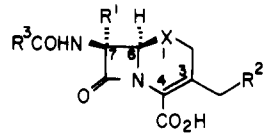
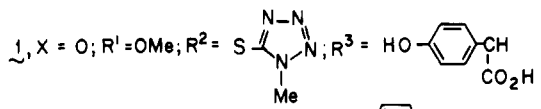
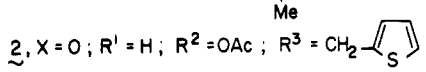
The (±)-1-oxacephams **38** and **39**, (±)-1-oxahomocephams **26** and **27**, and their didehydro derivatives **32**, **33**, **37**, **40**, and **41** have been synthesized from appropriately substituted nonfused β-lactams. The key reaction in these syntheses is a regiochemically controlled intramolecular addition of alkenyl and alkynyl free radicals of types **30** and **44**, respectively.

The long-standing postulate that β-lactams which do not derive from the molecular nuclei of the penicillins or of the cephalosporins may be useful in the treatment of bacterial infections which do not respond to the classical β-lactam antibiotics has been recently proved by the introduction of two new drugs into the medical practice. One of these drugs, the 1-oxacephem derivative **1**[2] constitutes

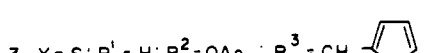




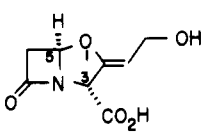
1, X = O; R' = OMe; R² = ; R³ =



2, X = O; R' = H; R² = OAc; R³ =



3, X = S; R' = H; R² = OAc; R³ =



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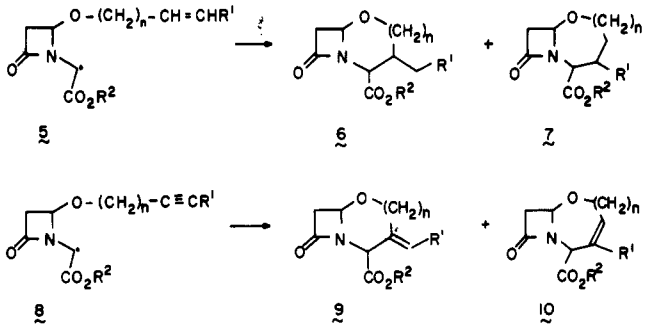
the first example of a synthetic β-lactam antibiotic having an unnatural ring system to be used in medicine. Its development followed the important finding that (±)-1-oxacephalothin **2**, which was prepared by total synthesis, exhibits antibacterial activity comparable to that of cephalothin **3**.[3] The other drug contains clavulanic acid (**4**), a recently discovered naturally occurring β-lactamase inhibitor,[4] as a synergist to a conventional penicillin.[5] The chemistry and the syntheses of oxacephalosporins, clavulanic acid, and related oxabicyclo β-lactams have been recently reviewed.[2,6,7] We now report on a new method for the synthesis of oxabicyclo β-lactams of types **6**, **7**, **9**, and **10** in which $n = 1$ (see Scheme I).

Since β-lactam antibiotics are highly susceptible to nucleophilic reagents, a synthetic plan which involves the completion of the bicyclic molecular backbone by a free radical rather than by an ionic reaction was designed. Our strategy is based on the synthesis of nonfused β-lactams

Scheme I



n = 0 or 1

which may be induced to generate free radicals of type **5** or **8**. Free radicals **5** may cyclize to saturated oxabicyclo β-lactams of type **6** and/or **7**, and free radicals **8** may annelate to unsaturated oxabicyclo β-lactams of type **9** and/or **10**. The versatility of this approach depends, to a large extent, on the efficiency of the annelation and on the possibility of controlling the regiospecificity of addition of the free radical center to the multiple bond. In the present paper annelation of compounds **5** and **8**, in which $n = 1$, leading to oxacephams and/or oxahomocephams is discussed.[1]

As an unambiguous method to generate the desired free radicals **5** and **8**, we chose the reaction between the corresponding chlorides **14** and tri-*n*-butylstannane.[8] The chlorolactams **14** were prepared from the readily available 4-acetoxy-2-azetidinone (**11**)[9] by a known methodology.[10,11] The zinc acetate catalyzed substitution of the acetoxy

† Department of Organic Chemistry.
‡ Department of Structural Chemistry.

(1) Preliminary reports: (a) Bachi, M. D.; Hoornaert, C. "Abstracts of Papers", 2nd European Symposium on Organic Chemistry, Stresa, Italy, 1981; p 284. (b) Bachi, M. D.; Hoornaert, C. *Tetrahedron Lett.* **1981**, *22*, 2689. (c) Bachi, M. D.; Hoornaert, C. *Ibid.* **1981**, *22*, 2693. (d) Bachi, M. D.; Hoornaert, C. *Ibid.* **1982**, *23*, 2505.
(2) Otsuka, H.; Nagata, W.; Yoshioka, M.; Narisada, M.; Yoshida, T.; Harada, Y.; Yamada, H. *Med. Res. Rev.* **1981**, *1*, 217.
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(6) Cooper, R. D. G. In "Topics in Antibiotic Chemistry"; Sammes, P. G., Ed.; Ellis Horwood: Chichester, 1980; Vol. 3, p 39.
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(8) It is generally accepted that the reduction of halides by organotin hydrides proceeds by a free-radical chain mechanism, see: Kuivila, H. G. *Synthesis* **1970**, 499 and references cited therein.
(9) Clauss, K.; Grimm, D.; Prossell, G. *Justus Liebigs Ann. Chem.* **1974**, 539.
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(11) Branch, C. L.; Nayler, J. H. C.; Pearson, M. J. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1450.

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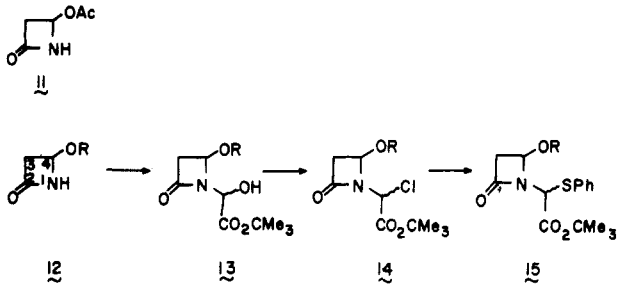


11

12 13 14 15

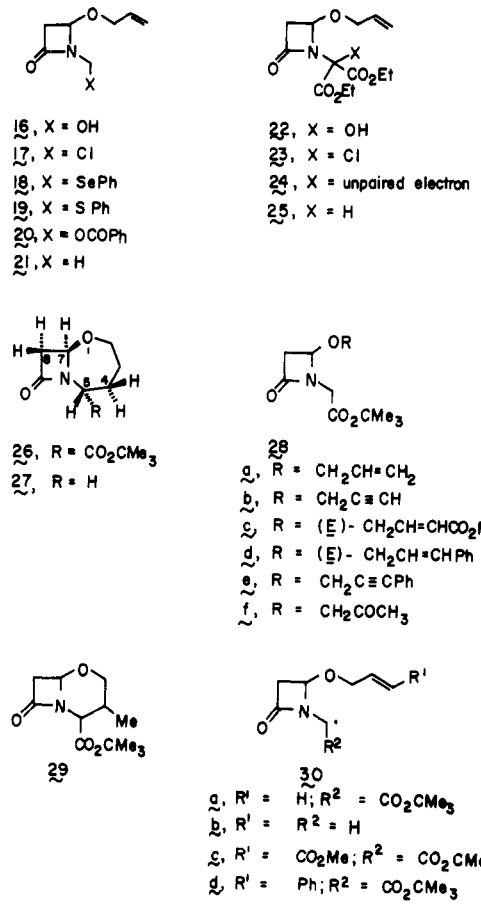
a, R = $CH_2CH=CH_2$
b, R = $CH_2C\equiv CH$
c, R = (E)- $CH_2CH=CHCO_2Me$
d, R = (E)- $CH_2CH=CHPh$
e, R = $CH_2C\equiv CPh$

group in 11 by the appropriate alkenyloxy or alkynyloxy groups gave the 4-alkoxy-2-azetidinones **12** which were condensed with *tert*-butyl glyoxylate to afford a mixture of the epimeric α-hydroxy esters **13**. Treatment of **13** with thionyl chloride and 2,6-lutidine gave the α-chloro esters **14**. The chloro lactams **17** and **23** (Chart I) which were also required for this study were similarly obtained from the corresponding carbinols **16** and **22**, readily prepared by the condensation of **12a** respectively with formaldehyde or with diethyl 2-oxomalonate. Since the chloro lactams appeared unstable during attempted purifications by chromatography, they were used in their crude form immediately after their preparation. For characterization they were converted into the corresponding more stable phenylthio derivatives **15** or **19** in a phase-transfer reaction with benzenethiol (NaOH, C_6H_6, H_2O, n-Bu_4NBr). In a similar way the phenyl selenide **18** was obtained from **17** and phenylselenol. The benzoyloxy-derivative **20** was prepared by benzoylation of **17** with benzoyl chloride. The phenyl selenide **18**, the phenyl sulfide **19**, and the benzoate **20** were needed for their evaluation as possible more stable substitutes to the sensitive chloride in the free radical generation process. Indeed, they proved to be stable during chromatography on silica gel and on storage at 5 °C.

Unless otherwise stated, the experiments for free radical annelation with the chloroazetidinones **14a–e**, **17**, and **23** with the sulfides **15** and **19**, with the selenide **18**, and with the benzoate **20** were performed under the following conditions. A 0.02 M solution of the free radical precursor in benzene with 1.1 equiv of n-Bu_3SnH and 2–4 mol % of azobis(isobutyronitrile) (AIBN) was boiled under argon for 44 h.

Treatment of a diastereomeric mixture of the ethylenic chloro lactam **14a** with tri-n-butylstannane under these standard conditions afforded the 1-oxahomocepham **26** (47%) and the nonfused reduced product **28a** (22%). The other possible annelation product **29** was not obtained. Evidently the bicyclic β-lactam **26** was formed through the intermediacy of the free radical **30a** by endo addition to the double bond. This pathway differs from the few previously reported cyclizations of 6-heptenyl radicals which gave exclusively, or predominantly, the products deriving from the exo-addition mode.[12-15] Since the regioselectivity of cyclization may depend inter alia on the

Chart I



16, X = OH
17, X = Cl
18, X = SePh
19, X = S Ph
20, X = OCOPh
21, X = H

22, X = OH
23, X = Cl
24, X = unpaired electron
25, X = H

26, R = CO_2CMe_3
27, R = H

28
a, R = $CH_2CH=CH_2$
b, R = $CH_2C\equiv CH$
c, R = (E)- $CH_2CH=CHCO_2Me$
d, R = (E)- $CH_2CH=CHPh$
e, R = $CH_2C\equiv CPh$
f, R = CH_2COCH_3

29

30
a, R' = H; R^2 = CO_2CMe_3
b, R' = R^2 = H
c, R' = CO_2Me; R^2 = CO_2CMe_3
d, R' = Ph; R^2 = CO_2CMe_3

stability of the free radicals,[16] the reaction courses taken by *N*-alkyl radicals of 4-(allyloxy)-2-azetidinone in which the free radical center is less or more stabilized than in **30a** were examined. It was found that the *N*-chloromethyl derivative **17** is converted under the standard conditions into 1-oxahomocepham (**27**, 34%) and the nonfused β-lactam **21** (31%). Although the primary free radical **30b** is expected to be more reactive than the secondary free radical **30a**, which is flanked by a pair of capto-dative[17] substituents, they seem to follow the same reaction pattern. Attempts to annelate the chloromalonate derivative **23** through the presumably more stabilized tertiary free radical **24** resulted in the cleavage of the β-lactam ring to give the unsaturated amide **31** (38%; Chart II) accompanied by the nonfused lactam **25** (20%). No annelation product was detected. The cleavage of the 1,4-bond in β-lactams, although not very common, has been reported to occur under various reaction conditions[18-20] and does not necessarily involve a free-radical mechanism.

The potential use of phenylseleno, phenylthio, and benzoyloxy functionalities as substitutes to the chlorine atom for the generation of free radicals of type **30** was examined with the β-lactams **17–20**. The results displayed in Table I show that under the aforementioned standard conditions the reactions of the phenyl selenide **18** and of the phenyl sulfide **19** with tri-n-butylstannane take a similar course to that of the reaction of the chloro deriv-

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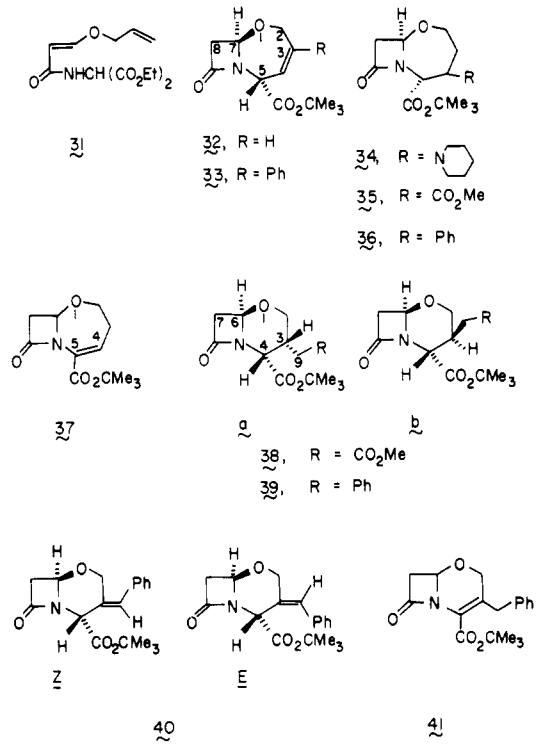
(13) Brandney, M. A. M.; Forbes, A. D.; Wood, J. *J. Chem. Soc., Perkin Trans. 2* **1973**, 1655.
(14) Beckwith, A. L. J.; Moad, G. *J. Chem. Soc., Chem. Commun.* **1974**, 472.
(15) Bakuzis, P.; Campos, O. O. S.; Bakuzis, M. L. F. *J. Org. Chem.* **1976**, *41*, 3261.
(16) Julia, M. *Acc. Chem. Res.* **1971**, *4*, 386.
(17) Viehe, H. G.; Merenyi, R.; Stella, L.; Janousek, Z. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 917.
(18) Manhas, M. S.; Amin, S. G.; Bose, A. K. *Heterocycles* **1976**, *5*, 669.
(19) Bachi, M. D.; Goldberg, O. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1184.
(20) Kametani, T.; Honda, T.; Sasaki, J.; Terasawa, H.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1884.

Table I. Yields of Products from the Reactions of Compounds 17-20 with 1.1 Equiv of n-Bu_3SnH and 2-4 Mol % of AIBN in Benzene

entry	X in 17-20	concn, mM	temp, °C	time, h	ratio[a] of 27/21	yield,[b] % 27	21	SM[d]
1	Cl	20	80	44	1.3:1	34	31	
2	Cl	5	80	44	9:1	57		
3	Cl	5	80	96	9:1	56		
4	SeC_6H_5	20	80	44	1.4:1	38	27	
5	SC_6H_5	20	15[c]	44		22	42	
6	SC_6H_5	20	80	44	1.3:1	41	30	
7	SC_6H_5	20	140	44	1.5:1	40	24	
8	SC_6H_5	5	80	44		37		37
9	SC_6H_5	5	80	120	9:1	56		17
10	$OCOC_6H_5$	20	80	44		0	0	98

[a] Ratio estimated from the NMR of the crude product. [b] Yield of product isolated by column chromatography over silica gel (EtOAc-hexane). [c] The reaction mixture was irradiated with four 40-W sunlamps. [d] Recovered starting material.

Chart II



ative 17 (entries 1, 4, and 6), giving about the same ratio of annelated to unannelated products **27** and **21**, respectively. These results indicate the involvement of a common free radical intermediate, **30b**. On the other hand, an attempt to generate the free radical **30b** from the (benzoyloxy)methyl derivative **20** was unsuccessful (entry 10), leaving the starting material unchanged. Apparently the generation of free radicals from benzoic acid esters requires more severe conditions.[22] In line with the reported trend for free radical cyclizations,[16,21] the annelation of the chloro and phenylthio derivatives was found to be favored by increasing the dilution (entries 2, 3, and 9) and, to a lesser extent, by raising the temperature (entries 5–7), the reaction of the phenylthio derivative proceeding somewhat more slowly.

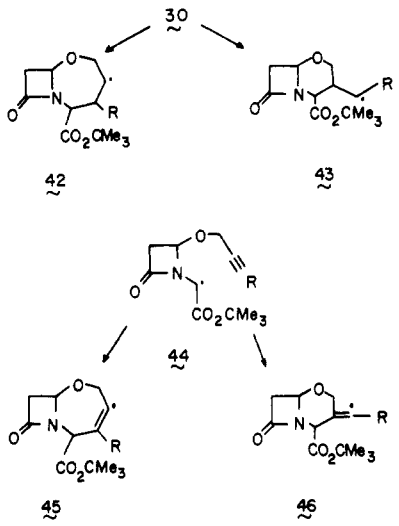
The reaction of the acetylenic chloro lactam **14b** and tri-n-butylstannane under the standard conditions afforded a 2:1 mixture of the nonfused β-lactam **28b** and the 1-oxahomoceph-3-em **32** (49%), as well as a small amount (ca. 3%) of the 3-phenyl-1-oxahomoceph-3-em **33**. While part of **28b** crystallized out of the mixture of **28b** and **32**, quantitative separation by chromatography was unsuccessful. The acetylenic β-lactam **28b** was therefore converted into the more polar acetonyloxy derivative **28f**, thus, enabling a chromatographic separation. On treatment of the mixture of **28b** and **32** with $HgCl_2$ in piperidine, followed by an aqueous workup,[11] the 4-propargyloxy β-lactam **28b** was converted into the acetonyloxy β-lactam **28f** while the 1-oxahomoceph-3-em **32** was converted into the piperidine adduct **34**. Reasonabely, this piperidyl derivative resulted from a piperidine-catalyzed isomerization of **32** into the 1-oxahomoceph-4-em **37** followed by 1,4-addition of the secondary amine to the α,β-unsaturated ester system. The unsaturated bicyclic β-lactam **37** was regenerated quantitatively from **34** by elimination of piperidine during preparative TLC over silica gel. The 1-oxahomoceph-4-em **37** was also obtained from **32** by treatment with pyridine. The isolation of the 1-oxahomoceph-3-em **32** was eventually achieved by performing the hydration of the triple bond in **28b** under conditions which do not induce double bond migration in **32**. Thus, treatment of the mixture of **28b** and **32** with $HgSO_4$ and dilute aqueous sulfuric acid in boiling methanol[23] afforded, after chromatography, the 1-oxahomoceph-3-em **32**.

Access to the 1-oxacepham and 1-oxacephem systems required the diversion of the annelation course from the observed endo-addition mode, yielding a seven-membered ring, to the exo-addition mode, leading to a six-membered ring. The nature of the factors which may contribute to the regioselectivity of ring closure through intramolecular free radical addition to a multiple bond has been discussed in several reviews.[16,24-26] These factors, which are of thermochemical, polar, steric, and stereoelectronic origin, may act in the same or in opposite directions. As the stereoelectronic element is expected to encourage the exo-addition mode,[25,26] it was reasoned that substitution of the double bond in **30a** by a group R^1 which is capable of delocalizing the free spin will result in an additional contribution to this intrinsic tendency also on account of the three other elements. The annelation through the intermediacy of the free radicals **30c** and **30d** was therefore studied.

Treatment of the diastereomeric mixture of the chloro lactam **14c** with tributylstannane under the standard

(21) Walling, C.; Cioffari, A. *J. Am. Chem. Soc.* **1972**, *94*, 6059, 6064.
(22) Khoo, L. E.; Lee, H. H. *Tetrahedron Lett.* **1968**, 4351.
(23) Harris, M. D.; McMillan, I.; Nayler, J. H. C.; Osborn, W. F.; Pearson, M.; Southgate, R. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1612.
(24) Julia, M.; Descoins, C.; Baillarge, M.; Jacquet, B.; Uguen, D.; Groeger, F. A. *Tetrahedron* **1975**, *31*, 1737.
(25) Beckwith, A. L. J.; Ingold, K. U. In "Rearrangements in Ground and Excited States"; de Mayo, P., Ed.; Academic Press: 1980, Vol. 1, p 161.
(26) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073.

Scheme II



conditions afforded the 1-oxacepham **38** (68%) as a 3.3:1 mixture (by NMR), respectively, of the two epimers **38a** and **38b** from which the first was crystallized out. An additional product consisted of a mixture (by NMR) of the nonfused β-lactam **28c** (ca. 16% overall) and a bicyclic β-lactam to which structure **35** was tentatively assigned (ca. 4% overall). Similarly, the chloro lactam **14d** afforded the 3-benzyl-1-oxacepham **39** (68%) as a 1:1 mixture (by NMR) of the epimers **39a** and **39b**, from which the former was crystallized out, and the nonfused β-lactam **28d** (10%). The formation of the 1-oxahomocepham **36** was not observed. After having solved the problem of regiochemical control, the annelation was performed under the standard conditions with the phenylacetylene chloro lactam **14e** which afforded the 3-benzylidene-1-oxacepham **40** (64%) as a 1.3:1 mixture, respectively, of the *E* and *Z* isomers and the nonfused β-lactam **28e** (18%).

Hydrogenation of **40** in the presence of 5% Pd/C gave the 1-oxacepham **39** (72%, two epimers), identical with the product of annelation of the cinnamyloxy chloro lactam **14d**, albeit in a different epimeric ratio.

To convert the 3-benzylidene-1-oxacepham **40** into the 1-oxaceph-3-em **41** a sample containing a mixture of the *E* and *Z* isomers was treated with 4-(dimethylamino)-pyridine (40 h, room temperature). Under these conditions only the *Z* isomer of **40** underwent migration of the double bond from the exocyclic position into conjugation with the ester group to give *tert*-butyl 3-benzyl-1-oxaceph-3-em-4-carboxylate (**41**, 76%), while the *E* isomer of **40** was recovered almost quantitatively.

It has been shown that ethylenic and acetylenic β-lactam *N*-alkyl radicals of type **30** and **44** (Scheme II) can be readily generated from various precursors and that these free radicals undergo cyclization to bicyclic β-lactams. When the multiple bond in **30** and in **44** occupies a terminal position (R = H) the cyclization proceeds exclusively through the endo-addition mode, yielding the corresponding bicyclic free radicals **42** and **45**. Although these intermediates are usually reduced to their end products by a hydrogen-transfer reaction, the rather reactive vinyl radical **45** (R = H) undergoes, in parallel, also an aromatic substitution reaction on benzene, which was used as a solvent, to give, as a minor product, the phenyl derivative **33**. The annelation of free radicals of type **30** or **44** was diverted to the exo-addition mode by formally substituting the hydrogen atom of the terminal multiple bond by a methoxycarbonyl group (R = CO_2Me) or by a phenyl group (R = Ph). The bicyclic free radical **43** is obtained as a

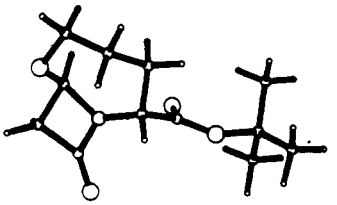


Figure 1. Drawing of *tert*-butyl (±)-1-oxahomocepham-5α-carboxylate (**26**).

mixture of two epimers at position 3. The vinylic radical **46** affords in the hydrogen transfer reaction a mixture of the *E* and the *Z* isomers of **40**.

The structural and stereochemical assignments[27] of the annelation products were based mainly on the analysis of their 270-MHz ^1H NMR spectra which included pertinent homonuclei decoupling by double irradiation and the measurement of the nuclear Overhauser effect (NOE) for the establishment of the double bond geometry of the two isomers of **40**. These data are described in detail in the Experimental Section. Noteworthy is the zig–zag coupling across five bonds (^5J) which is observed in the spectra of some of the bicyclic β-lactams. Thus, the 5-H signal for the 1-oxahomocepham **26** appears as a doublet of doublets with slightly broad signals at δ 4.23 ($J_{5\beta,4\alpha}$ = 8.8 Hz, $J_{5\beta,4\beta}$ = 4.4 Hz). The broadening of these signals is due to a long-range coupling with the 8β-proton. Indeed, the signal for the 8β-proton appears as a doublet of an apparent triplet, resolved by double irradiation to δ 2.83 ($J_{8\beta,8\alpha}$ = 14.7 Hz, $J_{8\beta,7\alpha}$ = 1.4 Hz, $J_{8\beta,5\beta}$ = 1.2 Hz). Only the $^5J_{8\beta,5\beta}$ was observed, and the corresponding $^5J_{8\alpha,5\beta}$ was not detected. In the spectrum of the unsubstituted 1-oxahomocepham (**27**) all the possible zig–zag $^5J_{5,8}$ couplings for the four protons were observed. The $^5J_{5,8}$ coupling was not observed at all in the spectra of the 1-oxahomoceph-3-ems **32** and **33**, and neither was the corresponding $^5J_{4,7}$ coupling seen in the spectra of the 1-oxacephams **38**–**40**. The occurrence of a similar ^5J coupling has been previously reported for a few other bicyclic β-lactams.[28]

Structure **26** was further confirmed by an X-ray crystallographic analysis. Figure 1 exhibits a view of the molecule in which the seven-membered ring attains a twisted-chain conformation with a *tert*-butyloxycarbonyl group in a pseudoequatorial α configuration.[27] The displacement of the nitrogen atom from the plane passing through the atoms C-5, C-7, and C-9 is insignificant (0.03 Å). The OC–N bond length is 1.35 Å which is a characteristic value for unstrained β-lactams.[29]

Experimental Section

IR spectra were recorded with a Perkin-Elmer 237 apparatus. ^1H NMR spectra were recorded on a 80-MHz Varian FT-80A instrument, except for the 270-MHz spectra which were recorded on a Brucker WH-270 spectrometer. The signal assignments in the 270-MHz spectra were supported by appropriate decoupling. Low- and high-resolution mass spectra were recorded on a Varian MaT-731 (double focusing) apparatus. Melting points were measured by using a Fisher-Johns heating plate and are uncorrected. Column chromatographies were performed on Merck silica

(27) All compounds are racemic. All structural formulas and stereochemical designations refer to the enantiomer related to clavulanic acid (**4**).

(28) (a) Demarco, P. V.; Nagarajan, R. In "Cephalosporins and Penicillins"; Flynn, E. H., Ed.; Academic Press: New York and London, 1972; p 311. (b) Spry, D. O. *Tetrahedron Lett.* **1973**, 165. (c) Aratani, M.; Hagiwara, D.; Takeno, H.; Hemmi, K.; Hashimoto, M. *J. Org. Chem.* **1980**, *45*, 3682. (d) Bachi, M. D.; Breiman, R.; Meshulam, H. *J. Org. Chem.*, in press.

(29) Sweet, R. M. In "Cephalosporins and Penicillins"; Flynn, E. H., Ed.; Academic Press: New York and London, 1972; p 280.

gel 60 (70–230 mesh), and flash chromatographies[30] were performed with Merck silica gel 60 (230–400 mesh). Analytical TLC was carried out on Merck 0.25-mm silica gel 60 plates.

4-(Allyloxy)-2-azetidinone (12a). A stirred mixture of 4-acetoxy-2-azetidinone (11;[9] 5.2 g, 40 mmol), finely powdered $Zn(OAc)_2 \cdot 2H_2O$ (4.4 g, 20 mmol), and allyl alcohol (14 mL, 200 mmol) in dry benzene (80 mL) was boiled for 20 h in a Dean–Stark separator. The residue obtained after filtration and evaporation of the cooled reaction mixture, was chromatographed over a silica gel column (EtOAc–hexane) to give the (allyloxy)azetidinone **12a**: 3.9 g (76%); R_f 0.25 (EtOAc–hexane, 4:1); IR ($CHCl_3$) 3420, 1780 cm^{-1}; NMR ($CDCl_3$) δ 2.94 (ddd, J = 15.1, 1.8, 0.7 Hz, 3β-CH), 3.09 (ddd, J = 15.1, 3.6, 2.5 Hz, 3α-CH), 4.05 (br d, J = 5.5 Hz, OCH_2CH), 5.10 (dd, J = 3.6, 1.8 Hz, 4α-CH), 5.15–5.43 (m, $CH{=}CH_2$), 5.71–6.18 (m, $CH_2CH{=}CH_2$), 6.93 (br, NH); after addition of D_2O 2.94 (dd, J = 15.1, 1.8 Hz, 3.09 (dd, J = 15.1, 3.6 Hz, 6.93 absent.

4-(Propargyloxy)-2-azetidinone (12b).[11] A stirred mixture of 11 (5.2 g, 40 mmol), propargyl alcohol (12 mL, 200 mmol), and $Zn(OAc)_2 \cdot 2H_2O$ (4.4 g, 20 mmol) in dry benzene (80 mL) was boiled for 20 h in a Dean–Stark separator and then worked up as described for **12a** to give 4-(propargyloxy)-2-azetidinone (**12b**): 2.8 g (56%); mp 40–41 °C (from toluene) (lit.[11] mp 35–36 °C); IR ($CHCl_3$) 3420, 3310, 1775 cm^{-1}; NMR ($CDCl_3$) δ 2.50 (t, J = 2.4 Hz, $CH_2C{\equiv}CH$), 3.00 (ddd, J = 15.1, 1.7, 0.8 Hz, 3β-CH), 3.14 (ddd, J = 15.1, 3.6, 2.5 Hz, 3α-CH), 4.25 (d, J = 2.4 Hz, $OCH_2{\equiv}CH$), 5.23 (dd, J = 3.6, 1.7 Hz, 4α-CH), 6.77 (br m, NH); after addition of D_2O 3.00 (dd, J = 15.1, 1.7 Hz), 3.14 (dd, J = 15.1, 3.6 Hz), 6.77 absent.

4-[[(*E*)-3-(Methoxycarbonyl)prop-2-enyl]oxy]-2-azetidinone (12c). A stirred mixture of 11 (655 mg, 5 mmol), methyl (*E*)-4-hydroxybut-2-enoate[31] (600 mg, 5.1 mmol), and $Zn(OAc)_2 \cdot 2H_2O$ (600 mg, 2.7 mmol) in dry benzene (10 mL) was boiled for 21 h in a Dean–Stark separator and then worked up as described for **12a** to give the title compound **12c**: 670 mg (73%); mp 69–70 °C (from CH_2Cl_2–hexane), IR ($CHCl_3$) 3400, 1775, 1720, 1665 cm^{-1}; NMR ($CDCl_3$) δ 2.92 (ddd, J = 15.2, 1.8, 0.6 Hz, 3β-CH), 3.09 (ddd, J = 15.2, 3.6, 2.7 Hz, 3α-CH), 3.75 (s, OMe), 4.22 (dd, J = 4.3, 2.0 Hz, $OCH_2CH{=}CH$), 5.14 (dd, J = 3.6, 1.8 Hz, 4α-CH), 6.11 (dt, J = 15.8, 2.0 Hz, $CH_2CH{=}CHCO_2$), 6.94 (dt, J = 15.8, 4.3 Hz, $CH_2CH{=}CHCO_2$, superimposed on br m of NH); after addition of D_2O 2.92 (dd, J = 15.2, 1.8 Hz), 3.09 (dd, J = 15.2, 3.6 Hz), br m at 6.94 absent. Anal. Calcd for $C_8H_{11}NO_4$: C, 51.88; H, 5.99; N, 7.56. Found: C, 51.98; H, 6.13; N, 7.61.

4-(Cinnamyloxy)-2-azetidinone (12d). A stirred mixture of 11 (651 mg, 5 mmol), cinnamyl alcohol (764 mg, 5.7 mmol), and $Zn(OAc)_2 \cdot 2H_2O$ (600 mg, 2.7 mmol) in dry benzene (10 mL) was boiled for 23 h in a Dean–Stark separator and then worked up as described for **12a** to give the 4-(cinnamyloxy)azetidinone **12d**: 390 mg (38%); mp 90–92 °C (from CH_2Cl_2–hexane); IR (CCl_4) 3410, 1770 cm^{-1}; NMR ($CDCl_3$) δ 2.98 (ddd, J = 15.1, 1.9, 0.9 Hz, 3β-CH), 3.12 (ddd, J = 15.1, 3.5, 1.9 Hz, 3α-CH), 4.23 (dd, J = 5.7, 0.7 Hz, $OCH_2CH{=}CH$), 5.16 (dd, J = 3.5, 1.9 Hz, 4α-CH), 6.26 (dt, J = 16, 5.7 Hz, $CH_2CH{=}CHPh$), 6.48 (br d, J = 16 Hz, $CH{=}CHPh$), 7.42–7.29 (m, Ph); high-resolution mass spectrum, calcd for $C_{12}H_{13}NO_2$ m/e 203.0946, found m/e 203.0928; m/e 203 (M^+), 161 ($M^+ - CH_2{=}C{=}O$), 134 ($PhCH{=}CHCH_2OH$), 70 ($M^+ - PhCH{=}CHCH_2O$). Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.45; N, 6.89. Found: C, 70.87; H, 6.44, N, 7.07.

4-[(3-Phenylprop-2-ynyl)oxy]-2-azetidinone (12e). A stirred solution of 3-phenylprop-2-ynyl alcohol[32] (847 mg, 6.4 mmol) in dry benzene (8 mL) was boiled in a Dean–Stark separator for 30 min. A solution of 11 (778 mg, 6 mmol) in dry benzene (4 mL) and $Zn(OAc)_2 \cdot 2H_2O$ (660 mg, 3 mmol) were added, and the reaction mixture was boiled for an additional 24 h and then worked up as described for **12a** to give the title compound **12e**: 846 mg (70%); mp 51–54 °C; IR ($CHCl_3$) 3410, 1775 cm^{-1}; NMR ($CDCl_3$) δ 3.03 (ddd, J = 15.1, 1.8, 0.9 Hz, 3β-CH), 3.16 (ddd, J = 15.1, 3.5, 2.4 Hz, 3α-CH), 4.47 (s, $OCH_2C{\equiv}CPh$), 5.30 (dd, J = 3.5, 1.8 Hz, 4α-CH), 6.66 (br m, NH); 7.36 (m, Ph); after exchange with D_2O 3.03 (dd, J = 15.1, 1.8 Hz), 3.16 (dd, J = 15.1, 3.5 Hz), 6.66 absent; high-resolution mass spectrum, calcd for $C_{12}H_{11}NO_2$ m/e 201.0789, found m/e 201.0771; m/e 201 (M^+), 159 ($M^+ - CH_2{=}C{=}O$), 115 ($C_9H_7^+$).

***tert*-Butyl [4-(Allyloxy)-2-oxoazetidin-1-yl]chloroacetate (14a) and *tert*-Butyl (4-(Allyloxy)-2-oxoazetidin-1-yl)(phenylthio)acetate (15a).** A solution of 4-(allyloxy)-2-azetidinone (**12a**; 636 mg, 5 mmol) and *tert*-butyl glyoxylate monohydrate (2.15 g, 15 mmol) in dry toluene (25 mL) was boiled for 4 h in a Dean–Stark separator. The residue obtained after evaporation [55 °C (0.3 mmHg)] of the cooled solution was chromatographed over silica gel columns (hexane, EtOAc) to give the hydroxy ester **13a**: 990 mg (77%, mixture of two isomers); R_f 0.46 and 0.50 (EtOAc–hexane, 3:1); IR (CCl_4) 3500 (br), 1785, 1740 cm^{-1}; NMR ($CDCl_3$) δ 1.50 (s) and 1.53 (s) (9 H), 2.89–3.03 (m, 2 H), 3.77–4.17 (br m, 3 H, 1 H exchangable with D_2O), 5.11–5.39 (m, 4 H), 5.59–6.07 (m, 1 H). To a solution of **13a** (514 mg, 2 mmol) in dry tetrahydrofuran (20 mL) at −15 °C, under argon, was added 2,6-lutidine (460 mg) followed by thionyl chloride (370 mg). After being stirred for 1 h at −15 °C, the reaction mixture was evaporated, and the residue was triturated with dry benzene (20 mL) under argon and filtered. The filtrate was evaporated to give the chloro ester **14a**: 555 mg; dark brown oil. The chloro ester **14a** was redissolved in dry benzene (10 mL) and filtered again, and more benzene was added to make a total volume of 25 mL. This solution was used immediately, either for the free-radical annelation (vide infra) or for conversion into the sulfide **15a**.

A solution of **14a** (277 mg, ca. 1 mmol) in benzene (12.5 mL) was virorously shaken with a solution of thiophenol (0.22 g, 2 mmol) and *tetra-n*-butylammonium bromide (15 mg) in 1 N aqueous NaOH (6 mL) for 10 min at 10 °C. The reaction mixture was then diluted with benzene (10 mL), and the organic layer was washed with cold water and brine, dried ($MgSO_4$), and evaporated. The residue was chromatographed over silica gel (EtOAc–hexane) to give the sulfide **15a**: 169 mg (mixture of two isomers); R_f 0.40 (EtOAc–hexane 1:2); IR (CCl_4) 1775, 1740 cm^{-1}; NMR ($CDCl_3$) δ 1.44 (s) and 1.47 (s) ($OCMe_3$), 2.68–3.25 (m, 3-CH_2), 4.11–4.40 (m, $OCH_2CH{=}CH_2$), 5.11–5.50 (m, $CH_2CH{=}CH_2$ and 4-CH), 5.57 (s) and 5.73 (s) NCHSPh), 5.79–6.12 (m, $CH_2CH{=}CH_2$), 7.35 (m) and 7.55 (m) SPh; high-resolution mass spectrum, calcd for $C_{13}H_{14}NO_2S$ m/e 248.0729, found m/e 248.0745; m/e 248 ($M^+ - CO_2CMe_3$), 240 ($M^+ - SC_6H_5$).

***tert*-Butyl [4-(Propargyloxy)-2-oxoazetidin-1-yl]chloroacetate (14b) and *tert*-Butyl [4-(Propargyloxy)-2-oxoazetidin-1-yl](phenylthio)acetate (15b).** A solution of 4-(propargyloxy)-2-azetidinone (**12b**; 753 mg, 6 mmol) and *tert*-butyl glyoxalate monohydrate (2.7 g, 18 mmol) in dry benzene (40 mL) was boiled for 5 h in a Dean–Stark separator and then worked up as described for the preparation of **13a** to give the hydroxy ester **13b**: 1.20 g (78%, mixture of two isomers); R_f 0.41 and 0.46 (EtOAc–hexane, 3:1); IR (CCl_4) 3500, 3310, 1780, 1740 cm^{-1}; NMR ($CDCl_3$) δ 1.50 (s) and 1.53 (s) ($OCMe_3$), 2.47 (t, J = 2.4 Hz) and 2.49 (t, J = 2.4 Hz) ($CH_2C{\equiv}CH$), 3.07 (m, 3-CH_2), 4.19 (d, J = 2.4 Hz) and 4.31 (d, J = 2.4 Hz) ($OCH_2C{\equiv}CH$), 5.16 (br s) and 5.23 (br s) (NCHOH), 5.31 (dd, J = 3.5, 2.0 Hz, 4-CH). To a solution of **13b** (384 mg, 1.5 mmol) in dry tetrahydrofuran (15 mL) at −15 °C, under argon, were sequentially added 2,6-lutidine (370 mg) and thionyl chloride (310 mg). After being stirred for 80 min, the reaction mixture was worked up as described for the preparation of **14a** to give **14b**: 411 mg; dark brown oil. A sample of one isomer of **14b** was obtained by flash chromatography on silica gel (EtOAc–hexane): NMR ($CDCl_3$) δ 1.52 (s, $OCMe_3$), 2.51 (t, J = 2.5 Hz, $OCH_2C{\equiv}CH$), 3.08 (dd, J = 15.0, 2.1 Hz, 3β-CH), 3.21 (dd, J = 15.0, 4.0 Hz, 3α-CH), 4.47 (d, J = 2.5 Hz, $OCH_2C{\equiv}CH$), 5.76 (dd, J = 4.0, 2.1 Hz, 4α-CH), 5.93 (s, NCHCl).

A solution of **14b** (100 mg, ca. 0.39 mmol) in benzene (7 mL) was added to a cold (ice–water) solution of thiophenol (110 mg, 1 mmol) and *tetra-n*-butylammonium bromide (5 mg) in 1 N aqueous NaOH. The cold mixture was vigorously shaken for 10 min and then worked up as described above for the preparation of **15a** to give the phenylthio ester **15b**: 92 mg (mixture of two isomers); R_f 0.37 (EtOAc–hexane, 1:2), IR (CCl_4) 3310, 1780, 1740 cm^{-1}; NMR ($CDCl_3$) δ 1.45 (s) and 1.48 (s) ($OCMe_3$), 2.47 (t, J = 2.4 Hz) and 2.49 (t, J = 2.4 Hz) (C≡CH), 2.77–3.28 (m, 3-CH_2), 4.32–4.52 (m, $OCH_2C{\equiv}CH$), 5.30 (m) and 5.61 (dd, J = 3.9, 1.9 Hz) (4-CH), 5.57 (s) and 5.71 (s) (NCHSPh), 7.35 (m, 3 H), 7.54 (m, 2 H); high-resolution mass spectrum, calcd for $C_{18}H_{21}NO_4S$

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m/e 347.1190, found *m/e* 347.1226; *m/e* 347 (M^+), 246 ($M^+ - CO_2CMe_3$), 182 ($M^+ - SPh - CH_2{=}CMe_2$).

***tert*-Butyl [4-[[(*E*)-3-(Methoxycarbonyl)prop-2-enyl]oxy]-2-oxoazetidin-1-yl]chloroacetate (14c).** A solution of 4-[[(*E*)-3-(methoxycarbonyl)prop-2-enyl]oxy]-2-azetidinone (**12c**; 372 mg, 2 mmol) and *tert*-butyl glyoxalate monohydrate (908 mg, 6 mmol) in dry benzene (20 mL) was boiled for 5 h in a Dean–Stark separator and then worked up as described for the preparation of **13a** to give **13c**: 497 mg (79%, mixture of two isomers); R_f 0.33 and 0.41 (EtOAc–hexane, 3:1); IR (CCl_4) 1780, 1725, 1665 cm^{-1}; NMR ($CDCl_3$) δ 1.49 (s) and 1.52 (s) ($OCMe_3$), 2.93–3.08 (m, 3-CH_2), 3.75 (s, OMe), 4.19–4.36 (m, $OCH_2CH{=}CH$), 5.16–5.30 (m, 4-CH and NCHOH), 6.10 (m, visible $J \simeq 16$ Hz, $CH{=}CH_2CO_2$), 6.75–7.12 (m, $CH_2CH{=}CHCO_2$). To a solution of **13c** (244 mg, 0.76 mmol) in dry tetrahydrofuran (10 mL) at −15 °C, under argon, was added 2,6-lutidine (0.17 g) followed by thionyl chloride (0.14 g). The reaction mixture was stirred for 1 h at −15 °C and then evaporated. The residue was triturated in benzene (10 mL) under argon, filtered, and evaporated. The residue was redissolved in benzene (10 mL) and filtered again, and the orange-yellow filtrate containing the chloro ester **14c** was diluted with more benzene to a total volume of 25 mL. This solution was used immediately for the free radical annelation (vide infra).

***tert*-Butyl [4-(Cinnamyloxy)-2-oxoazetidin-1-yl]chloroacetate (14d) and *tert*-Butyl [4-(Cinnamyloxy)-2-oxoazetidin-1-yl](phenylthio)acetate (15d).** A solution of 4-(cinnamyloxy)-2-azetidinone (**12d**; 311 mg, 1.5 mmol) and *tert*-butyl glyoxalate monohydrate (685 mg, 4.6 mmol) in dry benzene (15 mL) was boiled for 3 h in a Dean–Stark separator and then worked up as described for the preparation of **13a** to give the hydroxyester **13d**: 346 mg (73%, two isomers); R_f 0.51 and 0.53 (EtOAc); IR (CCl_4) 3500, 1780, 1745 cm^{-1}; NMR ($CDCl_3$) δ 1.51 (s) and 1.52 (s) (9 H), 2.70–3.24 (m, 2 H), 3.80 (d, J = 7.1 Hz) and 3.95 (d, J = 6.3 Hz) (2 H), 4.18 (m) and 4.28 (m) (2 H), 5.13–5.30 (m, 1 H), 5.98–6.76 (m, 2 H), 7.32 (m, 5 H). To a solution of **13d** (334 mg, 1 mmol) in dry tetrahydrofuran (10 mL) at −15 °C under argon were sequentially added 2,6-lutidine (0.22 g) and thionyl chloride (0.20 g). After being stirred for 1 h at −15 °C, the reaction mixture was worked up as described for the preparation of **14c** to give a solution of the chloro ester **14d** in benzene (25 mL).

Half of this solution was used for the free radical annelation (vide infra). The other half was vigorously stirred for 30 min under argon at 5–10 °C with a mixture of thiophenol (0.12 g), *tetra-n*-butylammonium bromide (8 mg), and 1 N NaOH (4 mL). A workup as described for the preparation of **15a** afforded the sulfide **15d**: 143 mg (mixture of two isomers); R_f 0.45 (EtOAc–hexane, 1:1); NMR ($CDCl_3$) δ 1.45 (s) and 1.48 (s) ($OCMe_3$), 2.73–3.25 (m, 3-CH_2), 4.29–4.72 (m, $OCH_2CH{=}CHPh$), 5.23 (m) and 5.57 (m, 4-CH), 5.60 (s) and 5.76 (s, NCHS), 6.03–6.44 (m, $CH{=}CHPh$), 6.65 (d, J = 16.0 Hz, $CH{=}CHPh$), 7.33 (m, 2 Ph); IR (CCl_4), 1775, 1745 cm^{-1}; high-resolution mass spectrum, calcd for $C_{24}H_{27}NO_4S$ *m/e* 425.1660, found *m/e* 425.1701; *m/e* 425 (M^+), 383 ($M^+ - H_2C{=}C{=}O$), 369 ($M^+ - H_2C{=}CMe_2$), 316 ($M^+ - SPh$).

***tert*-Butyl [4-[(3-Phenylprop-2-ynyl)oxy]-2-oxoazetidin-1-yl]chloroacetate (14e).** A solution of 4-[(3-phenylprop-2-ynyl)oxy]-2-azetidinone (**12e**; 603 mg, 3 mmol) and *tert*-butyl glyoxalate dihydrate (1.36 g, 9 mmol) in dry benzene (20 mL) was boiled in a Dean–Stark separator for 16 h. The solvent was then evaporated, and the residue was chromatographed over silica gel (EtOAc–hexane) to give the hydroxy ester **13e**: 860 mg (86%, mixture of two isomers); R_f 0.42 and 0.46 (EtOAc–hexane, 2:1); IR (CCl_4) 3490, 1780, 1735 cm^{-1}; mass spectrum, *m/e* 331 (M^+), 289 ($M^+ - CH_2{=}C{=}O$), 275 ($M^+ - CH_2{=}CMe_2$), 233 ($M^+ - CH_2{=}CMe_2 - CH_2{=}C{=}O$). To a solution of **13e** (267 mg, 0.8 mmol) in dry tetrahydrofuran (10 mL) at −15 °C under argon were sequentially added 2,6-lutidine (190 mg) and thionyl chloride (150 mg). After being stirred for 75 min at −15 °C, the reaction mixture was worked up as described for the preparation of **14c** to give the chloro ester **14e**, 278 mg.

***N*-(Chloromethyl)-4-(allyloxy)-2-azetidinone (17), *N*-[(Phenylseleno)methyl]-4-(allyloxy)-2-azetidinone (18), *N*-[(Phenylthio)methyl]-4-(allyloxy)-2-azetidinone (19), and *N*-[(Benzoyloxy)methyl]-4-(allyloxy)-2-azetidinone (20).** A mixture of 4-(allyloxy)-2-azetidinone (1.27 g, 10 mmol) and paraformaldehyde (600 mg, 20 mmol) was stirred at 115 °C for 2 h under argon. Chromatography of the product over silica gel (EtOAc–hexane) afforded the *N*-(hydroxymethyl)azetidinone **16**: 1.47 (96%); R_f 0.24 (EtOAc–hexane, 3:1); IR (CCl_4) 3440 (br), 1770 br cm^{-1}; NMR ($CDCl_3$) δ 2.91 (dd, J = 15.2, 1.8 Hz, 3β-CH), 3.06 (dd, J = 15.2, 3.6 Hz, 3α-CH), 3.29 (br s, CH_2OH), 4.15 (d, J = 5.3 Hz, $OCH_2CH{=}CH_2$), 4.62 and 4.77 (AB q, J = 11.7 Hz, NCH_2O), 5.07–5.38 (m, $OCH_2CH{=}CH_2$, 4-CH), 5.63–6.14 (m, $OCH_2CH{=}CH_2$). To a solution of **16** (319 mg, 2 mmol) in dry tetrahydrofuran (15 mL) at −15 °C, under argon, were sequentially added 2,6-lutidine (460 mg) and thionyl chloride (370 mg). After being stirred for 60 min at −15 °C the reaction mixture was worked up as described for the preparation of **14c** to give a solution of the (chloromethyl)azetidinone **17** in benzene (25 mL).

A mixture of 8.3 mL of this solution (0.66 mmol of **17**) and a solution of thiophenol (235 mg) and *tetra-n*-butylammonium bromide (15 mg) in 1 *N* NaOH (3 mL) was vigorously shaken, under argon, at 5–10 °C for 15 min and worked up as described for the preparation of **15a** to give *N*-[(phenylthio)methyl]-4-(allyloxy)-2-azetidinone (**19**), 110 mg. A similar result was obtained on tenfold scaling up; R_f 0.48 (EtOAc–hexane, 2:1); IR (CCl_4) 1775 cm^{-1}; NMR ($CDCl_3$) δ 2.81–2.99 (m, 2 H), 4.04 (m, 2 H, visible J = 5.2 Hz), 4.32 (dd, 1 H, J = 14.5, 0.7 Hz), 4.95 (d, 1 H, J = 14.5 Hz), 5.0–5.4 (m, 3 H), 5.66–6.12 (m, 1 H), 7.20–7.54 (m, 5 H); high-resolution mass spectrum, calcd for $C_{13}H_{15}NO_2S$ *m/e* 249.0823, found *m/e* 249.0853; *m/e* 249 (M^+), 192 ($M^+ - CH_2{=}CHCH_2O$), 165 ($PhSCH_2N{=}C{=}O$), 140 ($M^+ - PhS$).

A solution of the *N*-(chloromethyl)-2-azetidinone **17** (ca. 4 mmol, prepared as described above from 635 mg of **16**) and benzeneselenol (ca. 6 mmol, prepared by reduction of 936 mg of diphenyldiselenide)[33] in benzene (60 mL) was mixed, under argon, with a solution of tetra-*n*-butylammonium bromide (80 mg) in 1 N NaOH (20 mL) at 5–10 °C. The reaction mixture was vigorously stirred for 30 min, the layers were separated, the aqueous phase was extracted with benzene, and the combined organic fractions were washed with water and brine, dried ($MgSO_4$), and evaporated. The residue was chromatographed over silica gel (EtOAc–hexane) to give the phenyl selenide **18**: 762 mg; R_f 0.33 (EtOAc–hexane, 1:1); IR (CCl_4) 1775 cm^{-1}; NMR ($CDCl_3$) δ 2.83–2.89 (m, 3-CH_2), 3.98 (m, visible J = 5.3 Hz, $OCH_2CH{=}CH_2$), 4.37 (dd, J = 13.0, 0.7 Hz) and 5.02 (d, J = 13.0 Hz) (NCH_2Ph), 5.03 (dd, J = 3.4, 4-CH), 5.08–5.34 (m, $CH{=}CH_2$), 5.57–6.05 (m, $CH{=}CH_2$), 7.17–7.66 (m, Ph); high-resolution mass spectrum, calcd for $C_{13}H_{15}NO_2Se$ *m/e* 297.0267, found *m/e* 297.0283; *m/e* 297 (M^+), 140 ($M^+ - SePh$).

***N*-[(Benzoyloxy)methyl]-4-(allyloxy)-2-azetidinone (20).** To a solution of *N*-(hydroxymethyl)azetidinone **16** (473 mg, 3 mmol) in dry CH_2Cl_2 (10 mL) was added, under argon at −20 °C, 2,6-lutidine (0.65 g, 6 mmol) followed by a solution of benzoyl chloride (420 mg, 3 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred for an additional 1 h at −20 °C and 14 h at −5 °C. More CH_2Cl_2 (10 mL) was added, and the mixture was washed with cold 0.5 N HCl, water, and brine, dried ($MgSO_4$), and evaporated. Chromatography of the residue over a silica gel column afforded the benzoyl ester **20**: 510 mg (65%); mp 38–39 °C, IR (CCl_4) 1785, 1720 cm^{-1}; NMR ($CDCl_3$) δ 2.99 (dd, J = 15.3, 1.9 Hz, 3β-CH), 3.11 (dd, J = 15.3, 3.7 Hz, 3α-CH), 4.19–4.29 (m, $OCH_2CH{=}CH_2$), 5.11–5.42 (m, 4-CH, $OCH_2CH{=}CH_2$), 5.42 (s, NCH_2OCO), 5.62–6.16 (m, $OCH_2CH{=}CH_2$), 7.32–7.54 (m), 7.89–8.09 (m, Ph); high-resolution mass spectrum, calcd for $C_{14}H_{15}NO_4$ *m/e* 261.1001, found *m/e* 261.1016; *m/e* 261 (M^+), 219 ($M^+ - H_2C{=}C{=}O$), 156 ($M^+ - PhCO$), 140 ($M^+ - PhCO_2$).

Diethyl [4-(Allyloxy)-2-oxoazetidin-1-yl]chloromalonate (23). A solution of 4-(allyloxy)-2-azetidinone (**12a**; 385 mg, 3 mmol) and diethyl mesoxalate (1.54 g, 8.8 mmol) in dry toluene (15 mL) was boiled in a Dean–Stark separator for 3 h. The residue obtained after removal of the solvent and excess diethyl mesoxalate [at 60 °C (0.2 mmHg)] was chromatographed over silica gel (hexane–EtOAc–EtOH) to give the hydroxy malonate **22**: 799 mg (88%); R_f 0.24 (hexane–EtOAc–EtOH, 7:2:1); IR (CCl_4) 3490, 1785, 1755 cm^{-1}; NMR ($CDCl_3$) δ 1.32 (t, J = 7.0 Hz, OCH_2CH_3), 2.95 (dd, J = 15.2, 2.0 Hz, 3β-CH), 3.10 (dd, J = 15.2, 3.8 Hz, 3α-CH), 4.10 (br d, J = 5.3 Hz, $OCH_2CH{=}CH_2$), 4.32 (q, J = 7.1 Hz) and 4.34 (q, J = 7.1 Hz) (2 OCH_2CH_3), 4.73 (s, NCOH), 5.07-5.36 (m, $OCH_2CH{=}CH_2$), 5.59 (dd, J = 3.8, 2.0 Hz, 4-CH),

(33) Salmond, W. G.; Barta, M. A.; Cain, A. M.; Sobala, M. C. *Tetrahedron Lett.* **1977**, 1683.

5.64–6.08 (m, $OCH_2CH{=}CH_2$). To a solution of the hydroxy malonate **22** (211 mg, 0.7 mmol) in dry tetrahydrofuran (10 mL), at −15 °C under argon were sequentially added 2,6-lutidine (170 mg) and thionyl chloride (135 mg). The reaction mixture was stirred for 80 min at −15 °C and then worked up as described for the preparation of **14a** to give the chloromalonate **23**: 226 mg; dark brown oil.

Free Radical Reactions. Unless otherwise indicated, the following standard procedure was employed for the generation of free radicals from their precursors **14a–e**, **17-20**, and **23** and for the workup of the reaction products. A solution of a freshly prepared free radical precursor (e.g., 2 mmol) in dry benzene (e.g., 25 mL) was added under argon to a solution of tri-*n*-butylstannane[34] (1.1 equiv, 2.2 mmol) and azobis(isobutyronitrile) (0.02–0.04 equiv, 0.06 mmol) in dry benzene, and the total volume was made up to give a 0.02 M solution of the free radical precursor (e.g., 100 mL). The reaction mixture was boiled under reflux for 44 h and then evaporated. The residue was dissolved in dry acetonitrile (e.g., 30 mL) and washed with dry hexane (e.g., 5 × 10 mL).[35] The acetonitrile layer was evaporated, and the reaction products were separated by chromatography. Since crude chlorides **14a–e**, **17**, and **23** were used, calculations with these compounds were made on the assumption of 100% conversion of **13a–e** → **14a–e**, **16** → **17**, and **22** → **23**. Yields in this section do therefore represent two steps: **13a–e** → **14a–e** → products, **16** → **17** → products, and **22** → **23** → products.

Annelation of 14a. Standard treatment of **14a** (2 mmol) afforded the following after chromatography on silica gel (EtOAc–hexane). (a) The nonfused β-lactam **28a**: 107 mg (22%); R_f 0.43 (EtOAc–hexane, 1:1); IR (CCl_4) 1780, 1745 cm^{-1}; NMR ($CDCl_3$) δ 1.47 (s, $OCMe_3$), 2.90 (br d, J = 15.1 Hz, 3β-CH), 3.11 (dd, J = 15.1, 3.6 Hz, 3α-CH), 3.65 (br d, J = 18 Hz) and 4.13 (d, J = 18 Hz) (NCH_2CO_2), 4.09 (d m, J = 5.2 Hz, $OCH_2CH{=}CH_2$), 5.12–5.40 (m, $CH{=}CH_2$ and 4α-CH), 5.67–6.08 (m, $OCH_2CH{=}CH_2$); mass spectrum, m/e 199 ($M^+ - CH_2{=}C{=}O$), 168 ($M^+ - OCMe_3$), 157 ($O{=}C{=}NCH_2CO_2CMe_3$), 140 ($M^+ - CO_2CMe_3$). (b) *tert*-Butyl (±)-1-oxahomocepham-5α-carboxylate (**26**): 226 mg (47%); mp 59–60 °C (from hexane); IR (CCl_4) 1775, 1740 cm^{-1}, NMR (270 MHz, $CDCl_3$) δ 1.46 (s, $OCMe_3$), 1.90 (m, 3-CH_2 and 4α-CH), 2.33 (m, 4β-CH), 2.83 (ddd, J = 14.7, 1.4, 1.2 Hz, 8β-CH), 3.17 (dd, J = 14.7, 3.8 Hz, 8α-CH), 3.58 (m, visible J_{gem} = 12.4 Hz) and 4.11 (m, visible J_{gem} = 12.4 Hz) (2-CH_2), 4.23 (dd, J = 8.8, 4.4 Hz, 5β-CH), 5.29 (dd, J = 3.8, 1.4 Hz, 7α-CH); high-resolution mass spectrum, calcd for $C_8H_{11}NO_4$ m/e 185.0687, found m/e 185.0657; m/e 185 ($M^+ - CH_2{=}CMe_2$), 140 ($M^+ - CO_2CMe_3$), 98 ($M^+ - CO_2CMe_3 - CH_2{=}C{=}O$). Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.81. Found: C, 59.65; H, 7.90; N, 5.76.

X-ray Diffraction Analysis of *tert*-Butyl (±)-1-Oxahomocepham-5α-carboxylate (26). Single crystals of the title compound were monoclinic, space group $P2_1/n$, with a = 10.984 (1) Å, b = 9.951 (1) Å, c = 13.544 (1) Å, β = 69.04 (1)°, V = 1382.31 $Å^3$, d_{calcd} = 1.16 g cm^{-3}, and d_{meas} = 1.16 g cm^{-3} for Z = 4 ($C_{12}H_{19}NO_4$, M_r = 241.28). A total of 3208 reflections were measured up to $\theta \leq 27°$ with an Enraf-Nonius CAD-4 diffractometer (Mo Kα radiation, graphite monochromator). The measured intensities were processed in the usual way, yielding 2524 unique reflections. A total of 1979 structure amplitudes with $F_o > 3\sigma(F_o)$ were used for structure solution and refinement. The structure was solved by means of direct methods.[36] All hydrogens were located from a difference Fourier map. At the last stage of refinement, nonhydrogen atoms were refined with anisotropic temperature factors (isotropic for hydrogens). The terminal values of R and R_w were 0.06 and 0.07, respectively. The difference Fourier map at this stage shows no significant features.

Annelation of 14b, Isomerization of 32 to 37, and Purification of 32. Standard treatment of **14b** (1.5 mmol) afforded the following after flash chromatography on silica gel (EtOAc–hexane, 1:1.3). (a) *tert*-Butyl 3-phenyl-1-oxahomoceph-3-em-5-carboxylate (**33**): 13 mg (2.7%); mp 107–109 °C; R_f (0.48 (EtOAc–hexane, 1:1); IR (CCl_4) 1775, 1740 cm^{-1}; NMR ($CDCl_3$)δ 1.49 (s, $OCMe_3$), 2.98 (dd, J = 15.0, 1.3 Hz, 8β-CH), 3.22 (dd, J = 15.0, 3.5 Hz, 8α-CH), 4.60 and 4.74 (br AB q, J = 14.8 Hz, 2-CH_2), 5.22 (br d, J = 5.4 Hz, 5-CH), 5.75 (dd, J = 3.5, 1.3 Hz, 7α-CH), 5.85 (d, J = 5.4 Hz, 4-CH), 7.29 (br s, Ph); high-resolution mass spectrum, calcd for $C_{18}H_{21}NO_4$ m/e 315.1470, found m/e 315.1449; m/e 315 (M^+), 259 ($M^+ - CH_2{=}CMe_2$), 214 ($M^+ - CO_2CMe_3$), 186 ($M^+ - CO_2CMe_3 - CO$), 172 ($M^+ - CO_2CMe_3 - CH_2{=}C{=}O$). (b) A 2:1 mixture (175 mg, 49%) respectively of *tert*-butyl [4-(propargyloxy)-2-oxoazetidin-1-yl]acetate (**28b**) and *tert*-butyl 1-oxahomoceph-3-em-5-carboxylate (**32**); R_f 0.32 (EtOAc–hexane, 1:1). Crystallization from Et_2O–hexane at −20 °C afforded a pure sample of **28b**: IR (CCl_4) 3300, 1780, 1740 cm^{-1}; NMR ($CDCl_3$) 1.47 (s, $OCMe_3$), 2.48 (t, J = 2.4 Hz, $CH_2C{\equiv}CH$), 3.02 (br d, J = 15.0 Hz, 3β-CH), 3.14 (dd, J = 15.0, 3.6 Hz, 3α-CH), 3.75 and 4.11 (AB q, J = 18 Hz, NCH_2CO_2), 4.26 (d, J = 2.4 Hz, $OCH_2C{\equiv}CH$), 5.38 (dd, J = 3.6, 1.7 Hz, 4α-CH); mass spectrum, m/e 197 ($M^+ - CH_2{=}C{=}O$), 166 ($M^+ - OCMe_3$), 139 ($M^+ - CH_2{=}CMe_2 - CO_2$), 138 ($M^+ - CO_2CMe_3$).

A mixture of **28b** and **32** (2:1, respectively; 124 mg, 0.52 mmol) was stirred with $HgCl_2$ (184 mg, 0.68 mmol) in piperidine (5 mL) for 1 h at room temperature and then evaporated. The residue was taken up with a mixture of water and EtOAc (1:1), stirred for 5 min, and then filtered through Celite. The organic layer was washed with brine, dried, and evaporated. Chromatography of the residue over silica gel (EtOAc–hexane) afforded the following. (a) Crude *tert*-butyl 4-piperidyl-1-oxahomocepham-5-carboxylate (**34**): 52 mg; R_f 0.30 (EtOAc–hexane, 1:1); high-resolution mass spectrum, calcd for $C_{17}H_{28}N_2O_4$ m/e 324.2048, found m/e 324.2055; m/e 324 (M^+), 268 ($M^+ - CH_2{=}CMe_2$), 223 ($M^+ - CO_2CMe_3$). Preparative TLC on a silica gel plate (four elutions with EtOAc–hexane, 1:2) afforded *tert*-butyl 1-oxahomoceph-4-em-5-carboxylate **37**: 24 mg; mp 102–103 °C; IR (CCl_4) 1790, 1720, 1645 cm^{-1}; UV (EtOH) λ_{max} 242 (ε 9330); NMR (270 MHz, $CDCl_3$) δ 1.50 (s, $OCMe_3$), 2.36 (dddd, J = 17.5, 8.0, 3.6, 1.5 Hz) and 2.61 (m, visible J = 17.5, 12.0, 4.0 Hz) (3-CH_2), 2.87 (dd, J = 15.2, 1.7 Hz, 8β-CH), 3.23 (dd, J = 15.2, 4.0 Hz, 8α-CH), 3.33 (m, visible J = 12.0, 1.5 Hz) and 4.09 (m, visible J = 12.0, 3.8 Hz) (2-CH_2), 4.94 (dd, J = 4.0, 1.7 Hz, 7α-CH), 6.50 (dd, J = 8.0, 4.0 Hz, 4-CH); high-resolution mass spectrum, calcd for $C_{12}H_{17}NO_4$ m/e 239.1157, found m/e 239.1157; m/e 239 (M^+), 183 ($M^+ - CH_2{=}CMe_2$), 166 ($M^+ - OCMe_3$), 141 ($M^+ - CH_2{=}CMe_2 - CH_2{=}C{=}O$), 138 ($M^+ - CO_2CMe_3$). (b) *tert*-Butyl [4-(acetonyloxy)-2-oxoazetidin-1-yl]acetate (**28f**): 36 mg; R_f 0.22 (EtOAc–hexane, 2:1); IR (CCl_4) 1780, 1740 cm^{-1}; NMR ($CDCl_3$) δ 1.46 (s, $OCMe_3$), 2.14 (s, COMe), 2.97 (br d, J = 15.1 Hz, 3β-CH), 3.13 (dd, J = 15.1, 3.6 Hz, 3α-CH), 3.79 and 4.07 (AB q, J = 18 Hz NCH_2CO_2H), 4.22 (s, OCH_2CO), 5.32 (dd, J = 3.6, 1.7 Hz, 4α-CH).

A mixture of **28b** and **32** (1.3:1, respectively; 105 mg, 0.44 mmol) in methanol (3.5 mL) and water (0.3 mL) was added to a saturated solution of $HgSO_4$ in 10% H_2SO_4 (5 mL). After the mixture was boiled under reflux for 1 h, EtOAc (5 mL) was added, and the reaction mixture was filtered through Celite. The organic layer was washed with water and brine, dried ($MgSO_4$), and evaporated. Chromatography of the residue over silica gel (EtOAc–hexane) afforded the following: (a) *tert*-Butyl 1-oxahomoceph-3-em-5-carboxylate (**32**): 29 mg; IR (CCl_4) 1775, 1740 cm^{-1}; NMR (270 MHz, $CDCl_3$) δ 1.47 (s, $OCMe_3$), 2.87 (dd, J = 15.0, 1.4 Hz, 8β-CH), 3.20 (dd, J = 15.0, 3.6 Hz, 8α-CH), 4.27 (m, visible J_{gem} = 16.5 Hz) and 4.41 (m, visible J_{gem} = 16.5 Hz) (2-CH_2), 5.06 (br, s, 5-CH), 5.47 (dd, J = 3.6, 1.4, 7α-CH), 5.74 (m, 3-CH and 4-CH); high-resolution mass specltrum, calcd for $C_7H_8NO_2$ m/e 138.0555, found m/e 138.0542; m/e 138 ($M^+ - CO_2CMe_3$), 96 ($M^+ - CO_2CMe_3 - CH_2{=}C{=}O$). (b) *tert*-butyl [4-(acetonyloxy)-2-oxoazetidin-1-yl]acetate (**28f**; see above).

Annelation of 14c. Standard treatment of **14c** (0.76 mmol) afforded the following after chromatography on silica gel (EtOAc–hexane). (a) *tert*-Butyl 3-[(methoxycarbonyl)methyl]-1-oxacepham-4α-carboxylate (**38**): 156 mg (68%); R_f 0.48 (EtOAc–hexane, 1:1), 3.3:1 mixture (by NMR), respectively, of the two 3-C epimers **38a** and **38b**. Crystallization from Et_2O–hexane afforded **38a**: mp 86–87 °C; IR (CCl_4) 1785, 1745, 1730 cm^{-1}; NMR (270 MHz, $CDCl_3$) δ 1.47 (s, $OCMe_3$), 2.16 (dd, J = 17.2, 7.0 Hz, 9-CH), 2.28 (dd, J = 17.2, 8.6 Hz, 9′-CH), 2.63 (m, 3β-CH), 2.83 (dd, J = 15.0, 0.8 Hz, 7β-CH), 3.18 (dd, J = 15.0, 3.2 Hz, 7α-CH), 3.71 (s, OMe), 3.82 (dd, J = 12.0, 11.2 Hz, 2α-CH), 3.87 (dd, J = 12.0, 4.3 Hz, 2β-CH), 4.63 (d, J = 6.3 Hz, 4β-CH), 5.33 (dd, J

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= 3.2 0.8 Hz, 6α-CH); high-resolution mass spectrum, calcd for $C_{13}H_{21}NO_5$ 271.1419, found *m/e* 271.1410; *m/e* 271 ($M^+ - CO$), 243 ($M^+ - CH_2{=}CMe_2$), 226 ($M^+ - OCMe_3$), 225 ($M^+ - HOCMe_3$), 215 ($M^+ - CH_2{=}CMe_2 - CO$), 199 ($M^+ - CH_2{=}CMe_2 - CO_2$), 198 ($M^+ - CO_2CMe_3$), 156 ($M^+ - CO_2CMe_3 - H_2C{=}C{=}O$). Anal. Calcd for $C_{14}H_{21}NO_6$: C, 56.17; H, 7.07; N, 4.68. Found: C, 56.38; H, 7.12; N, 4.75. NMR of **38b**, obtained by substraction of the spectrum of **38a** from that of the mixture (270 MHz, $CDCl_3$): δ 1.44 (s, $OCMe_3$), 2.39 (m, visible *J* = 7 Hz, 3α-CH), 2.62 (dd, *J* = 17.2, 6.9 Hz, 9-CH), 2.76 (dd, *J* = 17.2, 8.6 Hz, 9′-CH), 2.90 (dd, *J* = 15.1, 0.9 Hz, 7β-CH), 3.24 (dd, *J* = 15.1, 3.1, Hz, 7α-CH), 3.71 (s, OMe), 3.94 (br s, 2-CH_2), 4.32 (s, 4β-CH), 5.20 (dd, *J* = 3.1, 0.9 Hz, 6α-CH). (b) A 4:1 mixture (by NMR) of the nonfused β-lactam **28** and the 1-oxahomocepham **35**: 45 mg (20%); R_f 0.22 (EtOAc–hexane, 1:1); NMR (270 MHz, $CDCl_3$) for **28c** δ 1.46 (s, $OCMe_3$), 2.88 (br d, *J* = 15.2 Hz, 3β-CH), 3.11 (dd, *J* = 15.2, 3.6 Hz, 3α-CH), 3.60 and 4.10 (AB q, *J* = 17.8, NCH_2CO_2), 3.75 (s, OMe), 4.25 (dd, *J* = 4.3, 1.9 Hz, $OCH_2CH{=}C$), 5.33 (dd, *J* = 3.8, 1.8 Hz, 4α-CH), 6.12 (dt, *J* = 15.7, 1.9 Hz, $CH_2CH{=}CHCO_2$), 6.90 (dt, *J* = 15.7, 4.2 Hz, $CH_2CH{=}CHCO_2$); for **35** (tentative) δ 1.44 (s, $OCMe_3$), 2.77 (d, *J* = 15.2 Hz, 8β-CH), 3.15 (dd, *J* = 15.2, 3.7 Hz, 8α-CH), 3.73 (s, OMe), 4.83 (d, *J* = 5 Hz, 5β-CH), 5.42 (br d, *J* = 3.7 Hz, 7α-CH).

Annelation of 14d. Standard treatment of **14d** (0.5 mmol) followed by preparative TLC on silica gel plates (EtOAc–hexane, 1:1.5) afforded the following. (a) *tert*-Butyl 3-benzyl-1-oxacepham-4α-carboxylate (**39**; 108 mg, 68%) as a 1:1 mixture (by NMR) of the two 3-C epimers **39a** and **39b**. Crystallization from Et_2O–hexane afforded **39a**: mp 121–122 °C; IR (CCl_4) 1780, 1735 cm^{-1}; NMR (270 MHz, $CDCl_3$) δ 1.52 (s, $OCMe_3$), 2.25 (dd, *J* = 13.8, 7.5 Hz, 9-CH), 2.37 (m, 3β-CH), 2.76 (dd, *J* = 15.0, 0.7 Hz, 7β-CH), 2.77 (dd, *J* = 13.8, 6.0 Hz, 9′-CH), 3.14 (dd, *J* = 15.0, 3.2 Hz, 7α-CH), 3.75 (dd, *J* = 12.0, 3.6 Hz, 2β-CH), 3.90 (apparent t, *J* = 11.7 Hz, 2α-CH), 4.51 (d, *J* = 5.6 Hz, 4β-CH), 5.28 (dd, *J* = 3.2, 0.7 Hz, 6α-CH), 7.15–7.34 (m, Ph); high-resolution mass spectrum, calcd for $C_{14}H_{15}NO_4$ *m/e* 261.1001, found *m/e* 261.1024; *m/e* 261 ($M^+ - CH_2{=}CMe_2$), 216 ($M^+ - CO_2CMe_3$), 174 ($M^+ - CO_2CMe_3 - H_2C{=}C{=}O$). Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.31; N, 4.41. Found: C, 68.36; H, 7.39; N, 4.36. NMR (270 MHz, $CDCl_3$) of **39b** (obtained by substraction of the spectrum of **39a** from that of the mixture): δ 1.44 (s, $OCMe_3$), 2.08 (br t, *J* = 8.6 Hz, 3α-CH), 2.85 (dd, *J* = 13.8, 8.6 Hz, 9-CH), 2.95 (dd, *J* = 13.8, 8.6 Hz, 9′-CH), 2.98 (dd, *J* = 15.1, 0.9 Hz, 7β-CH), 3.24 (dd, *J* = 15.1, 3.2 Hz, 7α-CH), 3.81 (br d, *J* = 13.8 Hz, 2-CH), 3.86 (dd, *J* = 13.8, 2.1 Hz, 2′-CH), 4.25 (s, 4β-CH), 5.20 (m, 6α-CH), 7.15–7.34 (m, Ph). (b) *tert*-Butyl [4-(cinnamyloxy)-2-oxoazetidin-1-yl]acetate (**28d**): 17 mg (10%); R_f 0.24 (EtOAc-hexane, 1:1.5); IR (CCl_4) 1780, 1740 cm^{-1}; NMR ($CDCl_3$) δ 1.42 (s, $OCMe_3$), 2.95 (br d, *J* = 15 Hz, 3β-CH), 3.15 (dd, *J* = 14.9, 3.6 Hz, 3α-CH), 3.67 (br d, *J* = 18 Hz) and 4.15 (d, *J* = 18 Hz) (NCH_2CO_2), 4.26 (br d, *J* = 5.7 Hz, $OCH_2CH{=}C$), 5.35 (dd, *J* = 3.6, 1.7 Hz, 4α-CH), 6.40 (dt, *J* = 16, 5.7 Hz, $OCH_2CH{=}CH$), 6.62 (br d, *J* = 16 Hz, $CH_2CH{=}CHPh$), 7.34 (m, Ph).

Annelation of 14e. Standard treatment of **14e** (0.8 mmol) afforded the following after chromatography over silica gel (EtOAc–hexane). (a) *tert*-Butyl 3-benzylidene-1-oxacepham-4α-carboxylate (**40**) as a 1.3:1 mixture (NMR), respectively, of the *E* and *Z* isomers: 162 mg (64%); R_f 0.47 (EtOAc–hexane, 1:1); IR (CCl_4) 1780, 1735 cm^{-1}; high-resolution mass spectrum, calcd for $C_{14}H_{12}NO_3$ *m/e* 242.0817, found *m/e* 242.0838; *m/e* 242 ($M^+ - OCMe_3$), 214 ($M^+ - CO_2CMe_3$), 200 ($M^+ - OCMe_3 - H_2C{=}C{=}O$), 172 ($M^+ - CO_2CMe_3 - H_2C{=}C{=}O$); the low-resolution mass spectrum shows a weak peak at *m/e* 315 (M^+). For isolation of the pure *E* isomer of **40**, see the section on the isomerization of **40**. (*E*)-**40**: mp 117–118 °C (hexane); NMR (270 MHz, $CDCl_3$) δ 1.45 (s, $OCMe_3$), 2.85 (dd, *J* = 15, 0.8 Hz, 7β-CH), 3.16 (dd, *J* = 15, 3.5 Hz, 7α-CH), 4.32 (d, *J* = 12.6 Hz) and 4.57 (d, *J* = 12.6 Hz) (2-CH_2), 5.37 (s, 4β-CH), 5.40 (dd, *J* = 3.5, 0.8 Hz, 6α-CH), 6.69 (s, C=CHPh), 7.38 (m, Ph); nuclear Overhauser effect: irradiation of the 2-CH_2 protons resulted in an increase of ca. 15% of the intensity of the signal of the vinylic proton. Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.80; H, 6.83; N, 4.10. NMR (270 MHz, $CDCl_3$) of (*Z*)-**40** (obtained by substraction of the spectrum of (*E*)-**40** from that of the mixture): δ 1.45 (s, $OCMe_3$), 2.85 (dd, *J* = 15, 0.8 Hz, 7β-CH), 3.20 (dd, *J* = 15, 3.5 Hz, 7α-CH), 4.37 (d, *J* = 13.7 Hz) and 4.83 (d, *J* = 13.7 Hz), 2-CH_2), 4.95 (s, 4β-CH), 5.34 (dd, *J* = 3.5, 0.8 Hz, 6α-CH), 6.77 (s, C=CHPh), 7.38 (m, Ph). (b) The nonfused β-lactam **28e**: 41 mg (16%); R_f 0.37 (EtOAc–hexane, 1:1); IR (CCl_4) 1780, 1740 cm^{-1}; NMR ($CDCl_3$) δ 1.42 (s, $OCMe_3$), 3.14 (br d, *J* = 15 Hz, 3β-CH), 3.28 (dd, *J* = 15, 3.5 Hz, 3α-CH), 3.80 and 4.14 (AB q, *J* = 18 Hz, NCH_2CO_2), 4.49 (s, $OCH_2C{\equiv}C$), 5.45 (dd, *J* = 3.5, 1.8 Hz, 4α-CH), 7.29–7.43 (m, Ph); mass spectrum, *m/e* 315 (M^+), 273 ($M^+ - CH_2{=}C{=}O$), 157 ($O{=}C{=}NCH_2CO_2CMe_3$).

Hydrogenation of 40. A solution of **40** (71 mg, 1.3:1 mixture of the corresponding *E* and *Z* isomers) in EtOH (4 mL) was shaken with 5% Pd/C (100 mg) under hydrogen (4 atm) for 24 h. The mixture was centrifuged, filtered, and evaporated to give *tert*-butyl 3-benzyl-1-oxacepham-4-carboxylate (**39**): 52 mg; an 85:15 mixture (NMR), respectively, of the epimers **39a** and **39b**. Crystallization from hexane gave **39a** (38 mg; mp 121 °C) identical with the compound obtained by the annelation of **14d**.

Isomerization of (*Z*)-40 and Separation of (*E*)-40. A solution of **40** [63 mg, consisting of 0.087 mmol of (*Z*)-**40** and 0.113 mmol of (*E*)-**40**] and *p*-(dimethylamino)pyridine (13 mg, 0.1 mmol) in CH_2Cl_2 (1 mL) was allowed to evaporate under a stream of argon and kept at room temperature for 40 h. Preparative silica gel TLC (double elution with EtOAc–hexane, 1:3) afforded the following. (a) *tert*-Butyl 3-benzyl-1-oxacepham-4-carboxylate (**41**): 21 mg [76% conversion based on (*Z*)-**40**]; mp 102–103 °C; IR (CCl_4) 1795, 1720, 1640 cm^{-1}; UV (EtOH) λ_{max} 258 (ε 10 940); NMR ($CDCl_3$) δ 1.54 (s, $OCMe_3$), 2.87 (dd, *J* = 15.6, 1.1 Hz, 7β-CH), 3.29 (dd, *J* = 15.6, 3.6 Hz, 7α-CH), 3.59 and 3.96 (AB q, *J* = 14.9 Hz, CH_2Ph), 4.19 (s, 2-CH_2), 4.94 (dd, *J* = 3.6, 1.1 Hz, 6α-CH), 7.25 (s, Ph); high-resolution mass spectrum, calcd for $C_{14}H_{13}NO_4$ *m/e* 259.0845, found *m/e* 259.0867; *m/e* 259 ($M^+ - H_2C{=}CMe_2$), 231 ($M^+ - H_2C{=}CMe_2 - CO$), 217 ($M^+ - H_2C{=}CMe_2 - CO - H_2C{=}C{=}O$). Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.45; H, 6.80; N, 4.33. (b) *tert*-Butyl (*E*)-3-benzylidene-1-oxacepham-4-carboxylate ((*E*)-**40**): 30 mg (84% recovery); for physical data see Annelation of **14e**.

Annelation of 17–19. *N*-(Chloromethyl)-4-(allyloxy)-2-azetidinone (**17**), *N*-[(phenylseleno)methyl]-4-(allyloxy)-2-azetidinone (**18**), and *N*-[(phenylthio)methyl]-4-(allyloxy)-2-azetidinone (**19**) were treated with tri-*n*-butylstannane and AIBN under the standard conditions or as otherwise specified in Table I to give the following after flash chromatography on silica gel (EtOAc–hexane, 3:1). (a) 1-Oxahomocepham (**27**): R_f 0.16 (EtOAc); IR (CCl_4) 1770 cm^{-1}; NMR (270 MHz, $CDCl_3$) δ 1.76 (m) and 1.94 (m) (3-CH_2 and 4-CH_2), 2.77 [m, visible *J* = 14.8 Hz (resolved by decoupling to dddd, *J* = 14.8, 1.4, 0.9, 0.9 Hz), 8β-CH], 3.04 (dddd, *J* = 14.8, 3.6, 1.5, 0.6 Hz, 8α-CH), 3.28 (m, visible *J* = 12.8, 2.7 Hz) and 3.43 (ddd, *J* = 12.8, 11.0, 2.9 Hz) (5-CH_2), 3.51 (ddd, *J* = 12.8, 9.5, 2.3 Hz and 4.04 (dd, *J* = 12.8, 4.0 Hz) (2-CH_2), 5.07 (dd, *J* = 3.6, 1.4 Hz, 7α-CH); high-resolution mass spectrum, calcd for $C_7H_{11}NO_2$ 141.0789, found *m/e* 141.0754; *m/e* 141 (M^+), 113 ($M^+ - CO$), 99 ($M^+ - H_2C{=}C{=}O$). (b) *N*-Methyl-4-(allyloxy)-2-azetidinone (**21**): R_f 0.25 (EtOAc); IR (CCl_4) 1770 cm^{-1}; NMR ($CDCl_3$) δ 2.7–3.1 (m, NMe, 3-CH_2), 4.09 (m, visible *J* = 5.3 Hz, $OCH_2CH{=}CH_2$), 4.96 (dd, *J* = 3.3, 1.6 Hz, 4-CH), 5.1–5.4 (m, $CH_2CH{=}CH_2$), 5.7–6.2 (m, $OCH_2CH{=}CH_2$); mass spectrum, *m/e* 141 (M^+), 113 ($M^+ - CO$), 99 ($M^+ - CH_2{=}C{=}O$), 84 ($M^+ - MeN{=}C{=}O$ and/or $M^+ - CH_2{=}CHCH_2O$).

The yields of the products of these reactions are displayed in Table I.

Reaction with the Chloromalonate 23. Standard treatment of diethyl [4-(allyloxy)-2-oxoazetidin-1-yl]chloromalonate (**23**, 0.7 mmol) afforded the following after preparative TLC (four elutions with EtOAc–hexane, 1:2). (a) The amide **31**: 68 mg (34%); R_f 0.30 (EtOAc–hexane, 1:1), mp 79–81 °C (toluene–petroleum ether); IR ($CHCl_3$) 1775, 1740, 1675, 1615 cm^{-1}; NMR (270 MHz, $CDCl_3$) δ 1.29 (t, *J* = 7.1 Hz, 2 CH_2CH_3), 4.28 (m, 2-CH_2CH_3), 4.34 (br d, *J* = 5.4 Hz, $OCH_2CH{=}CH$), 5.18 [d, *J* = 6.7 Hz, $NHCH(CO_2)_2$], 5.28 (d, *J* = 12.2, $COCH{=}CHO$), 5.22–5.34 (m, $CH_2CH{=}CH_2$), 5.78–5.93 (m, $CH_2CH{=}CH_2$), 6.25 (br d, *J* = 6.7 Hz, NH), 7.54 (d, *J* = 12.2 Hz, $CH{=}CHO$); mass spectrum, calcd for $C_{13}H_{19}NO_6$ *m/e* 285.1222, found *m/e* 285.1230; *m/e* 285 (M^+), 240 ($M^+ - OEt$), 212 ($M^+ - CO_2Et$), 111 ($M^+ - NHCH(CO_2Et)_2$). (b) Diethyl (4-(allyloxy)-2-oxoazetidin-1-yl)malonate (**25**): 40 mg (20%); R_f 0.27 (EtOAc–hexane, 1:1); NMR ($CDCl_3$) δ 1.30 (t, *J* = 7.1 Hz, 2 CH_2CH_3), 2.97 (dd, *J* = 15.0, 1.9 Hz, 3β-CH), 3.13 (dd, *J* = 15.0, 3.7 Hz, 3α-CH), 4.03–4.39 (m, visible *J* = 7.1 Hz, 2 CH_2CH_3 and

$OCH_2CH{=}CH_2$), 5.04–5.36 [m, $CH_2CH{=}CH_2$ and $NCH(CO_2)_2$], 5.52 (dd, J = 3.7, 1.9 Hz, 4α-CH), 5.62–6.09 (m, $CH_2CH{=}CH_2$).

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Registry No. 11, 64804-09-7; **12a**, 85082-38-8; **12b**, 85082-39-9; **12c**, 85082-40-2; **12d**, 85082-41-3; **12e**, 85082-42-4; **13a** (isomer 1), 85082-43-5; **13a** (isomer 2), 85082-44-6; **13b** (isomer 1), 85082-45-7; **13b** (isomer 2), 85082-46-8; **13c** (isomer 1), 85082-47-9; **13c** (isomer 2), 85082-48-0; **13d** (isomer 1), 85082-49-1; **13d** (isomer 2), 85082-50-4; **13e** (isomer 1), 85082-51-5; **13e** (isomer 2), 85082-52-6; **14a** (isomer 1), 85082-53-7; **14a** (isomer 2), 85082-54-8; **14b** (isomer 1), 85082-55-9; **14b** (isomer 2), 85082-56-0; **14c** (isomer 1), 85082-57-1; **14c** (isomer 2), 85082-58-2; **14d** (isomer 1), 85082-59-3; **14d** (isomer 2), 85082-60-6; **14e** (isomer 1), 85082-61-7; **14e** (isomer 2), 85082-62-8; **15a** (isomer 1), 85082-63-9; **15a** (isomer 2), 85082-64-0; **15b** (isomer 1), 85082-65-1; **15b** (isomer 2), 85082-66-2; **15d** (isomer 1), 85082-67-3; **15d** (isomer 2), 85082-68-4; **16**, 85068-05-9; **17**, 85068-06-0; **18**, 85068-07-1; **19**, 85068-08-2; **20**, 85068-09-3; **21**, 85068-10-6; **22**, 85068-11-7; **23**, 85068-12-8; **25**, 85068-13-9; **26**, 85068-14-0; **27**, 85068-15-1; **28a**, 85068-16-2; **28b**, 85068-17-3; **28c**, 85068-18-4; **28d**, 85068-19-5; **28f**, 85068-20-8; **31**, 85068-21-9; **32**, 85068-22-0; **33**, 85068-23-1; **34**, 85068-24-2; **35**, 79196-76-2; **37**, 85068-25-3; **38a**, 85114-74-5; **38b**, 85114-75-6; **39a**, 85114-76-7; **39b**, 85114-77-8; (*E*)-**40**, 85114-78-9; (*Z*)-**40**, 85114-79-0; **41**, 85068-26-4; methyl (*E*)-4-hydroxybut-2-enoate, 29576-13-4; 3-phenylprop-2-ynyl alcohol, 1504-58-1; *tert*-butyl glyoxylate, 7633-32-1; thiophenol, 108-98-5; benzeneselenol, 645-96-5; diethyl mesoxalate, 609-09-6.

Supplementary Material Available: A drawing and tables containing atom coordinates, anisotropic temperature factors, hydrogen atom coordinates, bond lengths, and bond angles of *tert*-butyl (±)-1-oxahomocepham-5α-carboxylate (**26**) (5 pages). Ordering information is given on any current masthead page.

Electronic Control of Stereoselectivity. 18. Stereospecific Capture of Electrophiles by 9-Isopropylidenebicyclo[4.2.1]nona-2,4,7-triene[1]

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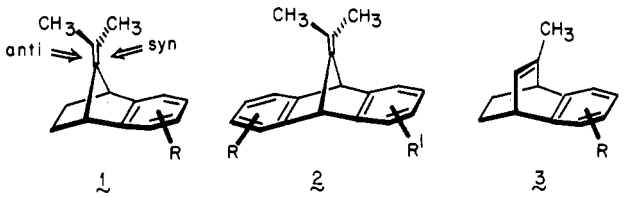
The stereochemistry of addition of several weak electrophiles to the exocyclic double bond of the title compound (**4**) has been determined. Anti stereoselectivity was seen to operate exclusively in every example. The product structures were established by a combination of NMR spectroscopy, independent synthesis of the epimer, and (in one instance) X-ray crystallographic analysis. The causative factors that appear to underlie kinetically favored electrophilic attack in the indicated direction are discussed.

While 9-isopropylidenebenzonorbornenes (**1**) preferably



1 **2** **3**

enter into bonding from the anti direction with weakly electrophilic reagents,[2,3] strong electrophiles are captured with remarkably exclusive syn π-facial stereoselectivity.[3,4] Dissimilar functional groups in otherwise more symmetrical 11-isopropylidenedibenzonorbornadienes (**2**) are likewise capable of modulating stereoselection when lesser reactive agents are involved.[5] This may well be a consequence of the importance of long-range homoaromatic involvement by the aryl rings in the corresponding transition states.[3,6] Since comparable through-space coupling is nonoperational in benzobicyclo[2.2.2]octadienes (**3**), stereoelectronic control is seen neither in these systems[7] nor their dibenzo counterparts.[8] The experimental data relating to the more powerful electrophiles correlate most reasonably with initial π-complexation to the aromatic rings, thus constituting a special case of guided electrophilic capture.[5]

The presumed existence of a direct link between π-facial stereoselectivity and the development of extended positive-charge stabilization in **1** and **2**, at least when such reagents as *m*-chloroperbenzoic acid, *N*-bromosuccinimide, *N*-methyltriazolinedione, singlet oxygen, and dichlorocarbene are involved, has prompted the present investigation. The question at issue was whether electrophile stereoselection could be utilized as an experimental tool

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