Sulfur-free penicillin derivatives. VII. Multiple functionalization of 2-azetidinyl-3-methyl-2-butenoates

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The title compounds, substituted with chlorine in the 4′-position and with phthalimido, 2,2,2-trichloroethoxycarbonylamino, or phenoxycarbonylamino in the 3′-position of the azetidinone ring, have been converted to bis-allylic formates via bromination of both methyl groups with excess *N*-bromosuccinimide, and displacement of both bromines by formate ions in methylene chloride solvent. The diformates react smoothly with a deficit of a boron halide to form *E*/*Z* mixtures of halogeno-formates, in which the *E*-isomer predominates. Depending on the 3′-azetidinyl substituent, these halogeno-formates undergo a second displacement with acetate either with retention of olefinic geometry or inversion of olefinic geometry. The mechanisms of these reactions are discussed, along with further transformations leading to hydroxylactones, halogenolactones, halogenohydrins, and other compounds. Examination of the proton magnetic resonance spectra of twenty-one compounds reveals that methylene protons *cis* to the β-lactam nitrogen atom of a methyl 2-azetidinyl-2-butenoate are found at higher field than methylene protons *cis* to the methoxycarbonyl group. This observation appears to provide a more reliable criterion for the assignment of configuration to geometrical isomers than one based on the magnitude of the chemical shift nonequivalence of the *E* and *Z* methylene protons.

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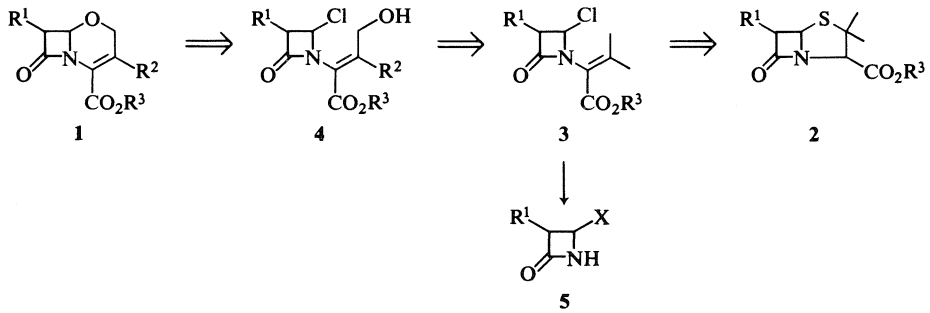
Le composé mentionné dans le titre portant une chlore en position 4′ et un groupe phtalimido, trichloro-2,2,2 éthoxycarbonylamino ou phénoxycarbonylamino en position 3′ du cycle azétidinone, soumis à une bromation des groupes méthyles au moyen d'un excès de *N*-bromosuccinimide suivie par déplacement des bromes par des ions formiates dans le chlorure de méthylène, conduit aux formiates bis-allyliques. Les diformiates réagissent avec un défaut d'halogènure de bore en donnant les mélanges *E*/*Z* d'halogénoformiates dans lesquels l'isomère *E* est majoritaire. Dépendant du substituant en position 3′ du cycle azétidinyle, ces halogénoformiates, en présence d'un acétate, subissent une deuxième réaction de déplacement avec rétention ou inversion de la géométrie de l'oléfine. On discute des mécanismes de ces réactions ainsi que des transformation plus poussées qui conduisent à des hydroxylactones, des halogénolactones, des halohydrines et à d'autres composés. Les spectres de rmn du ^{1}H de vingt et un composés révèlent que les protons méthyléniques en position 6 par rapport à l'atome d'azote du β-lactame du azétidinyl-2 butène-2 oate de méthyle, sont déplacés vers les champs forts par rapport aux protons méthyléniques en position *cis* du groupe méthoxycarbonyle. Ces observations semblent fournir des critères plus surs, que ceux fondés sur l'ordre de grandeur de la non équivalence des déplacements chimiques des protons méthyliques des isomères *E* et *Z*, pour déterminer la configuration des isomères géométriques.

[Traduit par le journal]

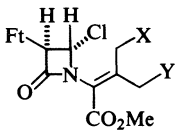
The first synthesis of a 1-oxacephem (**1**; $R^2 = CH_3$) from a penicillin precursor (**2**) was achieved by the sequence shown retrosynthetically in Scheme 1 (1). This approach became feasible following the development of routes from penicillins to the chloroazetidinones **3** (2, 3), and the observation that displacement of chlorine from such compounds proceeds without rupture of the β-lactam ring (2, 4, 5).

Numerous syntheses of 1-oxacephems from β-lactam natural products have since appeared in the literature (6), and two rather different strategies have evolved. One, as in Scheme 1, retains the isoprenoid moiety attached to the azetidinyl nitrogen of **3** and cognate 3-methyl-2-butenoates or 3-methyl-3-butenoates. An advantage of this approach is that these compounds possess the complete carbon skeleton of the target molecule so that,

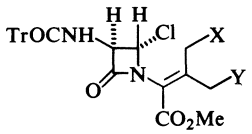


SCHEME 1

0008-4042/82/020144-10$01.00/0


(Ft = phthalimido)

6


(TrOC = Cl_3CCH_2OCO)

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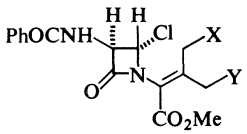

(PhOC = PhOCO)

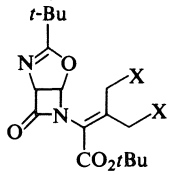
8

a X = Y = OCHO
b X = Y = Br
c X = Br; Y = H
d X = H; Y = Br
e X = H; Y = OCHO
f X = OCHO; Y = H
g X = Y = Cl
h X = OCHO; Y = Br
i X = Br; Y = OCHO
j X = OH; Y = Br
k X = OTHP; Y = Br
l X = O-*tert*-butyldimethylsilyl; Y = Br
m X = OCHO; Y = Cl
n X = Cl; Y = OCHO
o X = OH; Y = Cl
p X = OAc; Y = OCHO
q X = OCHO; Y = OAc
r X = OH; Y = OAc

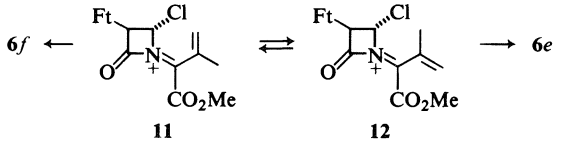
in principle, the oxacephem ring system can be reached by an oxidation and a ring closure. An alternative strategy employs methodology first devised by Woodward *et al.* (7). This approach begins with the removal of the butenoate moiety (**3** → **5**) (8); a new ring is then reconstructed by a multistep process (7). The particular advantage of this strategy is that it has allowed the ready laboratory synthesis and biological evaluation of a wide range of bicyclic systems (see, for example, ref. 9). A disadvantage is that the existing multistep sequences cannot be implemented economically on an industrial scale (10).

This paper is concerned with the elaboration of routes to compounds of type **4**, in which $R^2 \neq CH_3$, by functionalization of a 2-azetidinylbutenoate. Important intermediates in these sequences are the diformates **6***a*–**8***a*. A compound of this type (**9**) has been obtained by Campbell *et al.* (11) from the reaction of **10** with formate ions under phase transfer conditions. However, removal of the formate groups with bicarbonate led to loss of the β-lactam ring and concomitant rearrangement to a 1,5-oxazocine. In the present work the diformates **6***a*–**8***a* have been prepared, by a different procedure, from the dibromo precursors **6***b*–**8***b* and have been found to be convertible to the desired compounds **4** ($R^2 \neq CH_3$) under appropriate reaction conditions.

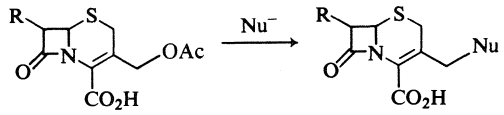
In an earlier investigation of the displacement of bromine from **6***c* and **6***d* (12), it was observed that a 1:1 mixture of these monobromides is converted in over 90% isolated yield to a 2:1 mixture of *E* (**6***e*) and *Z* (**6***f*) formates, using tetramethylguanidinium formate in chloroform solvent at room temperature. Under the same conditions, **6***a* was not obtained from the dibromide **6***b*. It has now been found that simply changing the solvent from chloroform to methylene chloride allows the isolation of **6***a* in 21–28% yield, using tetramethylguanidinium formate at −10°C, and in 42–47% yield using tetra-*n*-butylammonium formate at room temperature. Similar conditions were employed to prepare **7***a* and **8***a*.


9 X = OCHO
10 X = Br

The recovery of a 2:1 mixture of **6***e* and **6***f* from the 1:1 mixture of **6***c* and **6***d* suggested (12) that both geometrical isomers react via the same intermediate, **11** (⇄ **12**), addition of formate to **11** leading to the *Z* isomer, and addition to **12** leading to the *E* isomer. There is precedent for such an elimination–addition pathway in the mechanism proposed for the process **13** → **14** (13). However, it should be noted that the latter reaction proceeds only in hydroxylic solvents, and does not occur with oxygen nucleophiles, in contrast to the observations of ref. 12.

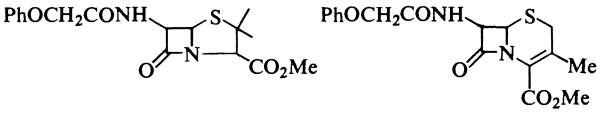

11 **12**

It is known that the pyramidality of the β-lactam nitrogen atom decreases in the order penicillin > cephalosporin > monocyclic azetidinones. This trend is seen in the solid state (14), and is reflected (15, 16) in the different β-lactam carbonyl stretching frequencies of these compounds (**15**: 1790 cm^{-1}; **16**: 1785 cm^{-1}; unfused β-lactams: < 1760 cm^{-1}).



13 14

The azetidinones of type **3** exhibit carbonyl absorption in the range 1773–1779 cm^{-1} (17), suggesting a more nearly planar geometry at the β-lactam nitrogen than in a Δ^3-cephem. Such a geometrical change can lead to an increase in the HOMO–LUMO interaction (18) between the nitrogen lone pair and the allylic halide systems of **6***c* and **6***d*, and thereby facilitate ionization to **11** (**12**).



15 16

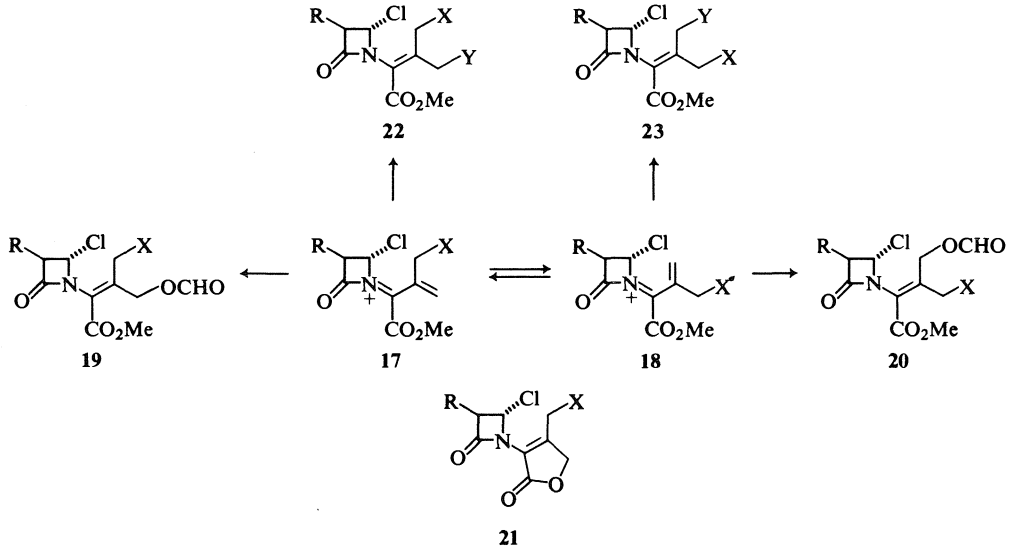
It was thought that the conversion of a dibromide to a diformate might proceed analogously, via **17** (**18**) (X = Br), leading to a mixture of the bromoformates **19** and **20** at an intermediate stage, but such compounds could not be isolated from any of the reactions of **6***b*–**8***b*. These multiply-functionalized butenoates were, however, accessible from the reactions of the diformates with boron halides.

Exploratory experiments with the phthalimido compound **6***a* revealed that one mol-equiv. of boron tribromide regenerated the dibromide **6***b* in quantitative yield; use of boron trichloride led to the dichloride **6***g*. With 0.6 mol-equiv. of boron tribromide, **6***a* was converted in 75% yield to a 2:1 mixture of the bromo-formates **6***h* and **6***i*, from which the major isomer **6***h*, mp 135.0–137.0°C, could be isolated in pure form. The assignment of the *E* configuration to this compound is based on the finding that deformylation under acidic conditions (HCl–MeOH–CH_2Cl_2) leads to the bromohydrin **6***j*, convertible to the tetrahydropyranyl ether **6***k* and the *tert*-butyldimethylsilyl ether **6***l*. Under the same deformylation conditions the minor isomer **6***i* was converted to the bromolactone **21** (R = Ft; X = Br), and the diformate **6***a* afforded the hydroxylactone **21** (R = Ft; X = OH). The hydroxylactone was convertible to the bromolactone upon further treatment with boron tribromide. The tetrahydropyranyl and *tert*-butyldimethylsilyl derivatives were also prepared.

With 0.6 mol-equiv. of boron trichloride, **6***a* gave, in 68% yield, a 3:1 mixture of the isomeric chloro-formates **6***m* and **6***n*, the assignment of configuration again being based on the deformylation of **6***m* to the chlorohydrin **6***o*, and of **6***n* to the chlorolactone **21** (R = Ft; X = Cl).

The sequences just described proved to be compatible with the TrOC (**7***a*) and PhOC (**8***a*) side chains. Deformylation of **7***a* and **8***a* led to **21** (R = TrOCNH; X = OH) (quantitative) and **21** (R = PhOCNH; X = OH) (91%), respectively. Boron tribromide afforded a separable 4:1 mixture of **7***h* and **7***i* (61%) from **7***a*, and a 4:1 mixture of **8***h* and **8***i* (61%) from **8***a*.

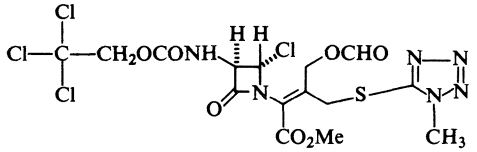
Thus, in the replacement of formate by halogen, as in the earlier replacement of halogen by formate (12), the *E*-geometrical isomer (**6***h*, **6***m*, **7***h*, **8***h*) is formed preferentially. However, despite their stereochemical similarities, the two reactions appear to proceed via different mechanisms. Indeed, that as many as three different mechanistic pathways may



22 23 19 17 18 20 21

exist for the displacement of one allylic substituent by another in such compounds became apparent when the bromo-formates **6***h*, **7***h*, and **7***i* were allowed to react with tetraethylammonium acetate, to form acetoxyformates.

In the phthalimido series, this reaction proceeded *with inversion of olefinic geometry* to yield **6***p* (60%), with no trace of the geometrical isomer **6***q*. On the other hand, both TrOC compounds underwent displacement by acetate *with retention of olefinic geometry*. Thus, **7***h* afforded **7***q*, and **7***i* afforded **7***p*. In each case, the configurations of the acetoxyformates were established by deformylation experiments: **6***p* and **7***p* were converted to the acetoxylactones **21** (R = Ft, TrOC; X = OAc), but **7***q* gave the acetoxyhydrin **7***r*. The bromo-formate **7***h* was also converted to the mercaptomethyltetrazole derivative **24**, with mercaptomethyltetrazole in dimethylformamide solvent. Deformylation afforded the alcohol **25**, which appears to be a useful intermediate for further work.



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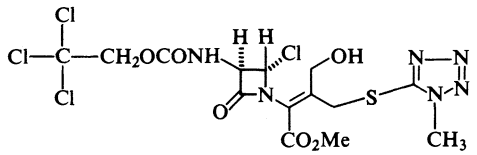

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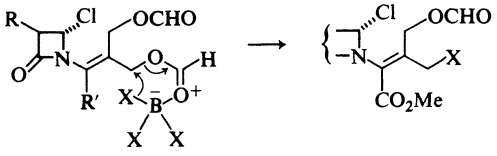
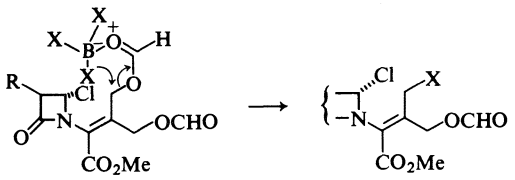
If the reaction of a diformate with boron tribromide and the reaction of a bromo-formate with a nucleophile both proceed via the elimination–addition pathway postulated earlier, then the same cationic species (**17** ⇄ **18**) (X = OCHO) must intervene in both cases. Since both reactions are conducted in methylene chloride solvent and at similar temperatures (−15° to 0°C), the partitioning of the intermediate (**17** → **22**; **18** → **23**) should not depend greatly on the nature of the entering nucleophile Y.

This behaviour is not observed in the phthalimido series, since **6***a* is converted preferentially to the *E*-bromoformate **6***h*, but **6***h* is, in turn, converted to the *Z*-acetoxyformate **6***p*. The expected behaviour is also not observed in the TrOC series, since the geometrical isomers **7***h* and **7***i* give different products upon reaction with acetate, and **7***h* is converted exclusively to **24** upon treatment with mercaptomethyltetrazole.

The most reasonable interpretation of these observations is that the displacement of bromine in the TrOC series proceeds via an S_N2 process and, in the phthalimido series, via the cationic intermediates **17** and **18** (X = OCHO).[1] The replacement of formate by halogen, using a boron halide, then requires a third mechanism; it is suggested that this is the S_Ni process depicted in **26** and **27**.



26 (R′ = CO_2Me)



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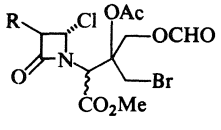
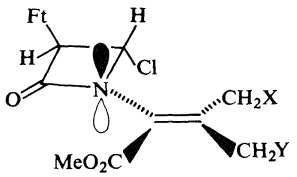
Inspection of molecular models reveals a possible conformational origin for the mechanistic difference between the phthalimido and TrOC compounds. The azetidinyl nitrogen lone pair will participate optimally in the ionization of the allylic bromine when this lone pair is oriented perpendicular to the 2-butenoate moiety (cf. **28**). Such a conformation can be achieved without difficulty in the phthalimido series. However, in the TrOC series, a hydrogen bond can exist between the TrOC N—H and the carbonyl oxygen of the ester group (cf. **29**). The resulting 90° rotation of the butenoate moiety will greatly diminish orbital interaction between the nitrogen lone pair and the allylic system.

In a recent publication dealing with compounds of type **30**, the Farmitalia group have observed (19) that, for certain combinations of E and Z, the

[1]A multistep process, involving Michael addition of acetate to the conjugated ester to form **i**, followed by displacement of bromine and elimination of acetate, might also be proposed. This seems unlikely for three reasons: (*i*) we have been unable to observe conjugate addition to compounds of type **3** under a variety of conditions; (*ii*) the β-elimination of acetate is expected (1) to lead to a mixture of geometrical isomers; (*iii*) the reaction mixture contains no source of protons to complete the conjugate addition.



i



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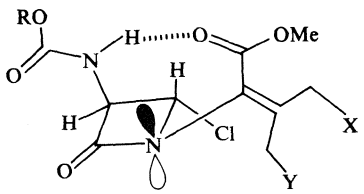

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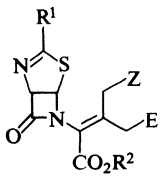
methylene protons of the CH_2E moiety exhibit a larger chemical shift nonequivalence than those of the CH_2Z moiety, and suggest that this observation may be useful for the assignment of configurations to such double bond isomers. Using stereochemical assignments apparently based on the generalizations of Martin and Martin (20, 21) for the proton chemical shifts of the methyl groups of compounds of type CH_3—CZ=CY—COX, a 0.28–0.36 ppm chemical shift difference was observed for E = Br, SPh and Z = H; and a 0.0–0.09 ppm chemical shift difference was observed for Z = Br, SPh and E = H. No chemical shift nonequivalence was observed when one of E or Z was OMe, O-*t*-Bu or OAc. For example, the bromoacetates **30** (E = Br, Z = OAc) and **30** (E = OAc, Z = Br) each showed singlets for both methylene groups. Although these latter compounds are described separately, it is not clear from the published data how the configurations were assigned.



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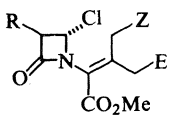

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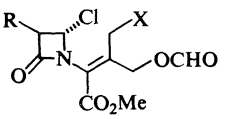

32

The present work has led to a large number of compounds of type **31** of known stereochemistry about the double bond. It has, therefore, been possible to examine in some detail the generality of the earlier proposal concerning the use of chemical shift nonequivalence for configurational assignments. Table 1 summarizes the data for twenty-one compounds. In all cases where $Z \neq E$, δ^Z_{av} is found at higher field than δ^E_{av}. This observation has been used to assign the δ^E_{av} and δ^Z_{av} resonances to compounds in which Z = E, and also to the various acetoxyformates.

Only three compounds (**6***a*, **7***p*, and **7***r*) show no chemical shift nonequivalence in either of the methylene groups. Where nonequivalence is observed, thirteen compounds exhibit greater nonequivalence in CH_2E, in agreement with the Farmitalia observations. Five compounds, corresponding to structure **32** (X = Br, Cl, OAc), show the opposite behavior.

Since the reasons for the observed chemical shift nonequivalence of the diastereotopic methylene protons of these complex compounds are not known, the present results suggest that the magnitude of such nonequivalence is not a reliable criterion for the assignment of configuration. It may be more useful to base assignments on the finding that δ^Z_{av} is at higher field than δ^E_{av}. This result is consistent with the data of Table 2 of ref. 20, if it is supposed that the methoxycarbonyl group of **31** has a greater effect on δ_{av} than the β-lactam nitrogen.

TABLE 1. Chemical shift data for the CH_2Z and CH_2E protons of compounds **31**[a,b]

Compound	Z	$\delta^{Z\,c}_{av}$	Δδ	E	$\delta^{E\,c}_{av}$	Δδ
6*a*	OCHO	5.23	0	OCHO	5.57	0
6*b*	Br	4.52	0.19	Br	4.79	0.31
6*g*	Cl	4.55	0.15	Cl	4.80	0.18
6*h*	OCHO	5.17	0	Br	4.73	0.27
6*i*	Br	4.56	0.17	OCHO	5.53	0
6*j*	OH	4.43	0	Br	4.64	0.17
6*m*	OCHO	5.07	0	Cl	4.72	0.12
6*n*	Cl	4.45	0.17	OCHO	5.37	0
6*o*	OH	4.41	0	Cl	4.69	0.14
6*p*	OAc	5.01	0.23	OCHO	5.13	0
7*a*	OCHO	4.97	0	OCHO	5.24	0.14
7*b*	Br	4.33	0	Br	4.62	0.17
7*h*	OCHO	5.02	0	Br	4.54	0.14
7*i*	Br	4.27	0.16	OCHO	5.32	0
7*p*	OAc	4.87	0	OCHO	5.23	0
7*q*	OCHO	4.93	0	OAc	5.15	0.13
7*r*	OH	4.83	0	OAc	5.15	0
8*a*	OCHO	4.97	0	OCHO	5.23	>0[d]
8*b*	Br	4.30	0	Br	4.63	0.19
8*h*	OCHO	4.92	0	Br	4.49	0.17
8*i*	Br	4.19	0.17	OCHO	5.23	0

[a]All spectra were recorded on a Varian EM360 spectrometer in $CDCl_3$ solvent.
[b]Chemical shifts are given in ppm relative to internal TMS.
[c]Refers to the position of the singlet, where a singlet was observed, or to the centre of the AB quartet.
[d]A broad singlet was observed in this case.

Experimental

General experimental procedures have been described previously (17). The ^{1}Hmr spectra were recorded on a Varian EM360 spectrometer; infrared (ir) spectra were taken on a Perkin Elmer 180 instrument. Analyses are by Galbraith Laboratories, Knoxville, TN.

Preparation of **6**a

To a solution of **6***b* (2.35 g, 4.52 mmol) in methylene chloride (5 mL) was added, during 30 min, a solution of tetra-*n*-butylammonium formate (3.73 g, 13.56 mmol) in methylene chloride (20 mL). The reaction mixture was stirred for 48 h under nitrogen at room temperature and was then diluted with 10% acetone–hexane (10 mL) and chromatographed on silica gel. Graded elution with acetone–hexane afforded 919 mg (45%) of the diformate **6***a* as a pale yellow foam; ir ($CHCl_3$): 1795, 1775, 1735 cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 3.87 (3H, s), 5.00 (2H, s), 5.23 (2H, s), 5.57 (1H, d, 2 Hz), 6.23 (1H, d, 2 Hz), 7.73 (4H, d), 7.97 (2H, s). *Anal.* calcd. for $C_{19}H_{15}N_2O_9Cl$: C 50.62, H 3.35, N 6.22; found: C 50.37, H 3.46, N 6.18.

Hydrolysis of **6**a *to the hydroxylactone* ***21*** *(R = Ft; X = OH)*

The diformate **6***a* (102 mg, 0.226 mmol) was dissolved in methylene chloride (4 mL), and *N* methanolic hydrogen chloride (0.2 mL) was added. The reaction mixture was stirred at 25°C for 2 h, and the solvent was then removed. The residue (89 mg) was a pale yellow foam, which appeared homogeneous on tlc. It was purified by plc (silica gel, acetone–hexane, 2:3) to give 79 mg (96%) of **21** (R = Ft; X = OH); ir ($CHCl_3$): 1790, 1770, 1725 cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 3.00 (1H, br s, exch D_2O), 4.54, 4.81 (2H, ABq, J = 16 Hz), 4.95 (2H, s), 5.53 (1H, d, 2 Hz), 6.57 (1H, d, 2 Hz), 7.68 (4H, br s).

Conversion of **6**a *to* **6**b *with excess boron tribromide*

To an ice-cold solution of the diformate **6***a* (52 mg, 0.115 mmol) in methylene chloride (3 mL) was added an ice-cold solution of boron tribromide (30 mg, 0.116 mmol) in methylene chloride (0.25 mL). The solution was stirred at 0°C for 1.5 h and then poured onto ice-cold brine (20 mL) and the layers separated. The aqueous layer was extracted with chloroform (3 × 40 mL) and the combined organic layers were washed with brine (2 × 5 mL), dried ($MgSO_4$), and evaporated to give 59 mg (100%) of **6***b* as a colourless foam. The ^{1}Hmr spectrum of the product was identical with that of authentic material.

Reaction of **6**a *with 0.5 mol-equiv. of boron tribromide*

To an ice-cold solution of the diformate (304 mg, 0.675 mmol) in methylene chloride (5 mL) was added dropwise, with stirring, a solution of boron tribromide (86 mg, 0.34 mmol) in methylene chloride (0.8 mL). Stirring was continued for 1.5 h at 0°C, and the solution was then poured onto ice-cold 5% sodium bicarbonate. The layers were separated and the aqueous layer was extracted with methylene chloride (3 × 60 mL). The combined organic layers were washed with brine (3 × 10 mL), dried (Na_2SO_4), and evaporated to a colourless foam (322 mg). This was purified by plc (silica gel, acetone–hexane, 1:4) to give three products. The leading band was **6***b* (25 mg). The middle band was a 79:21 mixture of **6***h* and **6***i* (245 mg, 75%). Separation and characterization of these two compounds is described in the following experiment.

Preparation of **6**a *and* **6**i

To an ice-cold solution of **6***a* (937 mg, 2.08 mmol) in methylene chloride (10 mL) was added, dropwise under a nitrogen atmosphere, a solution of boron tribromide (321 mg, 1.28 mmol, 0.61 mol-equiv.) in methylene chloride (6 mL). The mixture was stirred for 1.5 h at 0°C and then poured into a large excess of saturated ice-cold sodium bicarbonate. Isolation as described above afforded a crude product which was chromatographed on silica gel. Elution with 1% acetone in hexane afforded successively the dibromide **6***b* (trace), **6***h* (343 mg, 34%), **6***i* (176 mg, 17%), unreacted **6***a* (trace), and an unidentified compound. Compound **6***h*: mp 135.0–137.0°C; ir ($CHCl_3$): 1800, 1780, 1730 cm^{-1}; ^{1}Hmr ($CDCl_3$) δ: 4.00 (3H, s), 4.59, 4.86 (2H, ABq, 10 Hz), 5.17 (2H, s), 5.67 (1H, d, 2 Hz), 6.35 (1H, d, 2 Hz), 7.90 (4H, br s), 8.17 (1H, s). *Anal.* calcd. for $C_{18}H_{14}N_2O_7BrCl$: C 44.51, H 2.91, N 5.77, Br 16.45, Cl 7.30; found: C 44.37, H 3.02, N 5.74, Br 16.47, Cl, 7.47. Compound **6***i*: foam; ^{1}Hmr ($CDCl_3$) δ, 4.05 (3H, s), 4.47, 4.64 (2H, ABq, 10 Hz), 5.53 (2H, s), 5.76 (1H, d, 2 Hz), 6.47 (1H, d, 2 Hz), 8.03 (4H, br s), 8.27 (1H, s).

Conversion of **6**a *to* **6**g, **6**m, *and* **6**n *with boron trichloride*

To an ice-cold solution of **6***a* (131 mg, 0.29 mmol) in methylene chloride (4 mL) was added 0.2 mL of a *M* solution of boron trichloride in methylene chloride (0.70 mol-equiv.). The resulting solution was stirred for 2 h at 0°C and then poured into ice-cold 5% sodium bicarbonate. The aqueous layer was extracted with methylene chloride (3 × 50 mL), and the combined organic extracts were washed with brine (2 × 20 mL), dried (Na_2SO_4), and evaporated to 133 mg of a foam. This was purified by plc (silica gel, 30% acetone in hexane) to give three products: the dichloride **6***g* (8 mg, 6%); ^{1}Hmr ($CDCl_3$) δ: 3.93 (3H, s), 4.47, 4.62 (2H, ABq, 12 Hz), 4.71, 4.89 (2H, ABq, 12 Hz), 5.65 (1H, d, 2 Hz), 6.25 (1H, d, 2 Hz), 7.83 (4H, d); and a 3:1 mixture of **6***m* and **6***n* (84 mg, 68%). Compound **6***m*: ^{1}Hmr ($CDCl_3$) δ: 3.93 (3H, s), 4.66, 4.78 (2H, ABq, 12 Hz), 5.07 (2H, br s), 5.61 (1H, d, 2 Hz), 6.27 (1H, d, 2 Hz), 7.80 (4H, d), 8.10 (1H, s). Compound **6***n*: ^{1}Hmr ($CDCl_3$) δ: 3.91 (3H, s), 4.36, 4.53 (2H, ABq, 11 Hz), 5.37 (2H, s), 5.61 (1H, d, 2 Hz), 6.27 (1H, d, 2 Hz), 7.80 (4H, d), 8.10 (1H, s).

Hydrolysis of **6**h *to the bromohydrin* **6**j

The bromo-formate **6***h* (87 mg, 0.18 mmol) in methylene chloride (4 mL) was cooled to 0°C, and 0.2 mL of 3.2 *M* methanolic hydrogen chloride was added. The resulting solution was stored at 0°C for 1.5 h and then poured onto ice-cold 2.5% potassium bicarbonate (20 mL). The aqueous phase was extracted with methylene chloride (3 × 50 mL), and the combined organic layers were then washed with brine (2 × 20 mL), water (2 × 20 mL), dried (Na_2SO_4), and evaporated. The crude product, 73 mg of a nearly colourless foam, was purified by plc on silica gel buffered at pH 7.65 with boric acid – borax. Five developments with 20% acetone in hexane yielded 45 mg of **6***j*; ^{1}Hmr ($CDCl_3$) δ: 2.87 (1H, br s, exch D_2O), 3.92 (3H, s), 4.43 (2H, s), 4.55, 4.72 (2H, ABq, 10 Hz), 5.60 (1H, d, 1.8 Hz), 6.27 (1H, d, 1.8 Hz), 7.83 (4H, d).

Hydrolysis of **6**m *to the chlorohydrin* **6**o

The chloro-formate **6***m* (53 mg, 0.12 mmol) in methylene chloride (3 mL) was cooled to 0°C and 0.15 mL of *N* methanolic hydrogen chloride was added. The resulting solution was stored for 2 h at 0°C, and then worked up as described above for **6***j* to give the chlorohydrin **6***o*, 49 mg; ^{1}Hmr ($CDCl_3$) δ: 2.87 (1H, br s, exch D_2O), 3.90 (3H, s), 4.41 (2H, s), 4.62, 4.76 (2H, ABq, 12 Hz), 5.60 (1H, d, 1.8 Hz), 6.23 (1H, d, 1.8 Hz), 7.77 (4H, s).

Hydrolysis of **6**i *to the bromolactone* ***21*** *(R = Ft; X = Br)*

The bromo-formate **6***i* (59 mg, 0.122 mmol) in methylene chloride (3 mL) was cooled to 0°C and 0.15 mL of 3.2 *M* methanolic hydrogen chloride was added. The resulting solution was stored at 0°C for 1.5 h, and the product was then isolated as described above, 35 mg; ^{1}Hmr ($CDCl_3$) δ: 4.41, 4.72 (2H, ABq, 12 Hz), 5.00 (2H, s), 5.67 (1H, d, 2 Hz), 6.70 (1H, d, 2 Hz), 7.87 (4H, d).

Conversion of ***21*** *(R = Ft; X = OH) to* ***21*** *(R = Ft; X = Br)*

The hydroxylactone, prepared by deformylation of **6***a* (92 mg, 0.2 mmol), was dissolved in methylene chloride (3.5 mL) and, at 0°C, boron tribromide (0.1 mL) was added. The resulting solution was stirred at 0°C for 48 h and the product was then isolated in the usual manner to yield 80 mg (94% from **6***a*) of the bromolactone, identical to the material described above.

Tetrahydropyranylation of ***21*** *(R = Ft; X = OH)*

The hydroxylactone (86 mg) (prepared from 104 mg, 0.23 mmol of **6***a*) was dissolved in dry tetrahydrofuran (5 mL). To this solution were added freshly purified dihydropyran (0.5 mL) and boron trifluoride etherate (0.2 mL). The resulting solution was stirred for 2 h at room temperature and was then poured into ice-cold 5% sodium bicarbonate (20 mL). The mixture was extracted with chloroform (3 × 40 mL), and the combined organic extracts were washed with brine (2 × 20 mL), dried (Na_2SO_4), and evaporated to give the crude product as an oil. This was purified by plc (silica gel, acetone–hexane, 2:3) to yield the tetrahydropyranyl ether **21** (R = Ft; X = OTHP), 97 mg (94% from **6***a*); ^{1}Hmr ($CDCl_3$) δ: 1.65 (6H, m), 3.67 (2H, m), 4.59, 4.79 (2H, br ABq, 12 Hz), 4.83 (1H, br, s), 5.00 (2H, br s), 5.60 (1H, d, 2 Hz), 6.67 (1H, d, 2 Hz), 7.80 (4H, d).

Silylation of ***21*** *(R = Ft; X = OH)*

The hydroxylactone (72 mg), prepared from **6***a* (86 mg, 0.19 mmol), was dissolved in dimethylformamide (2.5 mL), and the solution was treated successively with imidazole (30 mg, 0.44 mmol) and *tert*-butyldimethylchlorosilane (30 mg, 0.2 mmol). The reaction mixture was stirred for 1 h at room temperature, and the solvent was then removed under reduced pressure at 40–45°C. The residue was purified by plc (silica gel, 20% acetone in hexane) to yield 60 mg (65% from **6***a*) of the *tert*-butyldimethylsilyl ether; ^{1}Hmr ($CDCl_3$) δ: 0.13 (6H, s), 0.92 (9H, s), 4.74, 4.98 (2H, ABq, 17 Hz), 4.93 (2H, s), 5.55 (1H, d, 2 Hz), 6.60 (1H, d, 2 Hz), 7.73 (4H, d).

Tetrahydropyranylation of the bromohydrin **6**j

The bromohydrin **6***j* (56 mg, 0.12 mmol) was dissolved in methylene chloride (5 mL) and to this solution were added dihydropyran (0.5 mL) and anhydrous *p*-toluenesulfonic acid (2 mg). The mixture was stirred at room temperature for 50 min and was then poured onto ice-cold 5% sodium bicarbonate (30 mL). Extraction with chloroform (3 × 40 mL), followed by washing of the chloroform extracts with brine (2 × 20 mL), drying (Na_2SO_4), and evaporation yielded 79 mg of an oil. This was purified by plc (silica gel, 30% acetone in hexane, two developments) to give the tetrahydropyranyl ether **6***k* (36 mg, 55%); ^{1}Hmr ($CDCl_3$) δ: 1.68 (6H, m), 3.73 (2H, m), 3.90 (3H, s), 4.40, 4.64 (2H, ABq, 14 Hz), 4.52 (1H, s), 4.72 (2H, s), 5.57 (1H, d, 2 Hz), 6.25 (1H, d, 2 Hz), 7.97 (4H, d).

Conversion of the bromo-formate **6**h *to the acetoxyformate* **6***p*

A solution of the bromo-formate **6***h* (137 mg, 0.28 mmol) in methylene chloride (4.5 mL) was cooled to −15°C and, under nitrogen, tetraethylammonium acetate (65 mg, 0.34 mmol) was added. The reaction mixture was stirred at −15°C for 18 h and then at 0°C for 24 h. It was then poured into ice-cold brine (20 mL), the layers were separated, and the aqueous layer was extracted with methylene chloride (3 × 60 mL). The combined organic extracts were washed with brine (2 × 20 mL), dried (Na_2SO_4), and evaporated to 114 mg of a pale yellow foam. This was purified by plc (silica gel, acetone–hexane, 3:7) to give 79 mg (60%) of the acetoxyformate **6***p*; ^{1}Hmr ($CDCl_3$) δ: 2.07 (3H, s), 3.87 (3H, s), 4.89, 5.12 (2H, ABq, 12 Hz), 5.13 (2H, s), 5.53 (1H, d, 2 Hz), 6.20 (1H, d, 2 Hz), 7.72 (4H, d), 7.97 (1H, s).

The acetoxyformate (79 mg, 0.172 mmol) was dissolved in methylene chloride (3 mL) and, at 0°C under nitrogen, *N* methanolic hydrogen chloride (0.17 mL) was added. The solution was stored at 0°C for 3 h and the solvent was then removed under reduced pressure. The residue was purified by plc (silica gel, acetone–hexane, 2:3, two developments) to give the acetoxylactone **21** (R = Ft; X = OAc), 59 mg (90%); ^{1}Hmr ($CDCl_3$) δ: 2.10 (3H, s), 4.87 (2H, s), 5.20 (2H, s), 5.55 (1H, d, 2 Hz), 6.58 (1H, d, 2 Hz), 7.70 (4H, br s).

Preparation of ***3*** *(R^1 = TrOC; R^3 = CH_3)*

A solution of methyl 6-trichloroethoxycarbonylaminopenicillanate (68.4 g, 0.168 mol) in methylene chloride (600 mL) was cooled to −78°C, and a precooled (−78°C) solution of chlorine (23.9 g, 0.336 mol) in methylene chloride (47 mL) was added dropwise, with stirring. Stirring was continued for 1 h at −78°C, and the reaction mixture was then brought to room temperature. Evaporation of the solvent under reduced pressure afforded a pale yellow foam, which crystallized upon trituration with ice-cold ether. The chloroazetidinone was collected, and washed with ice-cold ether: 48.7 g (70%), mp 139–140°C; ^{1}Hmr ($CDCl_3$) δ: 2.03 (3H, s), 2.30 (3H, s), 3.80 (3H, s), 4.77 (2H, s), 4.93 (1H, dd, 2, 8 Hz), 5.83 (1H, br s), 6.47 (1H, br d, 8 Hz).

Preparation of ***7***b

To a suspension of **3** (R^1 = TrOC; R^3 = CH_3) (49 g, 0.12 mol), in carbon tetrachloride (450 mL), were added *N*-bromosuccinimide (47 g, 0.264 mol) and benzoyl peroxide (0.5 g). The mixture was brought to rapid reflux, under nitrogen, and was then irradiated for 3 h over a Sylvania No. 2 Superflood lamp, cooled to room temperature, and filtered to remove succinimide. The filtrate was washed successively with ice-cold 5% sodium bisulfite (2 × 50 mL) and ice-cold brine (2 × 50 mL), and dried ($MgSO_4$). Evaporation afforded 72.2 g of **7***b* (100%) as a pale yellow foam which could be used directly in further reactions; ^{1}Hmr ($CDCl_3$) δ: 3.90 (3H, s), 4.33 (2H, s), 4.53, 4.70 (2H, ABq, 10 Hz), 4.77 (2H, s), 4.90 (1H, dd, 2, 8 Hz), 6.00 (1H, d, 2 Hz), 6.53 (1H, d, 8 Hz).

Preparation of ***7***a

A solution of **7***b* (2.107 g, 3.72 mmol) in chloroform (20 mL) was cooled to 0°C and, under nitrogen, treated dropwise during 5 min with a solution of tetramethylguanidinium formate (2.576 g, 16 mmol) in chloroform (8 mL). Stirring was continued for 30 min at 0°C and then overnight at room temperature. The reaction mixture was poured onto ice-cold brine (50 mL), and the layers were separated. The aqueous layer was extracted with methylene chloride (3 × 40 mL). The combined organic layers were washed with brine (3 × 20 mL), dried (Na_2SO_4), and evaporated to give the crude product as a light brown foam. Purification on silica gel (10% acetone in hexane) afforded 483 mg (26%) of **7***a* as a pale yellow foam; ^{1}Hmr ($CDCl_3$) δ: 3.90 (3H, s), 4.77 (2H, s), 4.90 (1H, dd, 2, 8 Hz), 4.97 (2H, s), 5.17, 5.31 (2H, ABq, 12 Hz), 6.00 (1H, d, 2 Hz), 6.37 (1H, d, 8 Hz), 8.10 (2H, s). *Anal.* calcd. for $C_{14}H_{14}N_2O_9Cl_4$: C 33.89, H 2.84, N 5.65; found: C 33.53, H 2.82, N 5.86.

Hydrolysis of **7**a

The diformate (250 mg, 0.5 mmol) was dissolved in methylene chloride (6 mL), the solution was cooled to 0°C, and methanolic hydrogen chloride (1 mL of a 2 *M* solution, 2 mmol) was added. The reaction mixture was stirred for 1 h at 0°C by which time the starting material had disappeared. The solvent was removed under reduced pressure, and the product was taken up in methylene chloride (20 mL) and washed with cold brine (1 × 20 mL), dried (Na_2SO_4), and evaporated to give **21** (R = TrOC; X = OH) as a white foam which appeared homogeneous by tlc, 202 mg (100%); ^{1}Hmr (CD_3COCD_3) δ: 4.17 (1H, br s, exch D_2O), 4.71, 4.86 (2H, ABq, 18 Hz), 4.90 (2H, s), 5.10 (2H, s), 5.10 (1H, dd, 2, 8 Hz), 6.47 (1H, d, 2 Hz), 7.90 (1H, d, 8 Hz).

Conversion of 7a *to* 7h *and* 7i

An ice-cold solution of **7*a*** (3.394 g, 6.84 mmol) in methylene chloride (40 mL) was treated dropwise, under nitrogen, with a solution of boron tribromide (1.025 g, 4.09 mmol) in methylene chloride (10 mL). The addition required 15 min, and stirring was continued at 0°C for an additional 30 min. The solution was then poured onto ice-cold 2.5% potassium bicarbonate and, after shaking, the layers were separated. The aqueous layer was extracted with methylene chloride (3 × 50 mL) and the combined organic extracts were washed with brine (2 × 10 mL) and dried (Na_2SO_4). Evaporation left a pale yellow foam, 3.515 g, which was subjected to silica gel chromatography. Elution with 15% acetone–hexane yielded three fractions. The first was the dibromide **7*b*** (418 mg, 11%); the second was a mixture of **7*h*** and **7*i*** (2.217 g, 61%), and the third fraction was unreacted **7*a*** (315 mg, 9%).

Separation of 7h *and* 7i

The above mixture of geometrical isomers (2.2 g) was rechromatographed on silica gel using 20% ethyl acetate in hexane as eluent. This afforded pure **7*h*** (1.6 g) and **7*i*** (0.4 g). For compound **7*h***, ^{1}Hmr ($CDCl_3$) δ: 3.88 (3H, s), 4.47, 4.61 (2H, ABq, 11 Hz), 4.75 (2H, s), 4.88 (1H, dd, 2, 7 Hz), 5.02 (2H, s), 5.95 (1H, d, 2 Hz), 6.34 (1H, d, 7 Hz), 8.05 (1H, s). *Anal.* calcd. for $C_{13}H_{13}N_2O_7BrCl_4$: C 29.40, H 2.46, N 5.28; found: C 29.65, H 2.54, N 4.80. For compound **7*i***, ^{1}Hmr ($CDCl_3$) δ: 3.88 (3H, s), 4.19, 4.35 (2H, ABq, 10 Hz), 4.73 (2H, s), 4.98 (1H, dd, 2, 6 Hz), 5.32 (2H, s), 5.98 (1H, d, 2 Hz), 6.05 (1H, d, 6 Hz), 8.05 (1H, s).

Conversion of 7h *to the acetoxyformate* 7q

A solution of tetramethylguanidinium acetate (300 mg, 1.73 mmol) in chloroform (5 mL) was cooled to 0°C and, with stirring, treated all at once with a solution of the bromo-formate **7*h*** (265 mg, 0.5 mmol) in chloroform (3 mL). Stirring was continued for 1 h at 0°C and then at room temperature for 5 h. The mixture was then poured onto ice-cold brine (50 mL), the layers were separated, and the aqueous layer washed with methylene chloride (3 × 40 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated to a light brown foam (239 mg). Purification by plc (silica gel, ethyl acetate – hexane, 3:7) afforded recovered **7*h*** (40 mg) and the acetoxyformate **7*q*** (57 mg, 25%) as a colourless foam; ^{1}Hmr ($CDCl_3$) δ: 2.08 (3H, s), 3.88 (3H, s), 4.75 (2H, s), 4.88 (1H, dd, 2, 7 Hz), 4.93 (2H, s), 5.04, 5.17 (2H, ABq, 14 Hz), 5.97 (1H, d, 2 Hz), 6.27 (1H, d, 7 Hz), 8.08 (1H, s).

Hydrolysis of 7q *to the acetoxyhydrin* 7r

A solution of the acetoxyformate **7*q*** (57 mg, 0.11 mmol) in methylene chloride (3 mL) was cooled to 0°C and treated with 2 *M* methanolic hydrogen chloride (0.1 mL). The resulting solution was stirred for 1 h at 0°C and was then evaporated to dryness to give a product which retained the methyl ester and acetate groups, but had lost the formate group; ^{1}Hmr ($CDCl_3$) δ: 2.10 (3H, s), 3.63 (1H, br s, exch D_2O), 3.83 (3H, s), 4.70 (2H, s), 4.83 (2H, s), 5.15 (2H, s), 5.16 (1H, dd, 2, 6 Hz), 6.38 (1H, d, 2 Hz), 6.38 (1H, d, 6 Hz).

Conversion of 7i *to the acetoxyformate* 7p

The bromo-formate **7*i*** (217 mg, 0.41 mmol) was dissolved in chloroform (3 mL) and the solution was added to an ice-cold solution of tetrabutylammonium acetate (223 mg, 0.74 mmol) in chloroform (3 mL). The resulting solution was stirred at 0°C for 3 h under nitrogen, and then at room temperature for 22 h. It was then poured onto ice-cold brine (30 mL), the layers were separated, and the aqueous layer was washed with methylene chloride (3 × 40 mL). The combined organic extracts were washed with brine (2 × 20 mL), dried (Na_2SO_4), and evaporated. The resulting material was purified by plc (silica gel, ethyl acetate – hexane, 3:7, three developments) to give 100 mg (48%) of the acetoxyformate **7*p***; ^{1}Hmr ($CDCl_3$) δ: 2.10 (3H, s), 3.90 (3H, s), 4.80 (2H, s), 4.87 (2H, s), 4.97 (1H, dd, 2, 6 Hz), 5.23 (2H, s), 5.97 (1H, d, 2 Hz), 6.52 (1H, d, 6 Hz), 8.03 (1H, s).

Hydrolysis of 7p *to the lactone* ***21*** *(R = TrOC; X = OAc)*

The acetoxyformate **7*p*** (100 mg, 0.20 mmol) was dissolved in methylene chloride (4 mL), the solution was cooled to 0°C, and methanolic hydrogen chloride (1 mL of a 0.8 *M* solution) was added. The resulting solution was stirred for 1.5 h, an additional 0.5 mL of *M* methanolic hydrogen chloride was added, and stirring was continued for 0.5 h. The reaction mixture was poured into cold 2.5% potassium bicarbonate (30 mL) and the layers were separated. The aqueous layer was extracted with methylene chloride (3 × 40 mL) and the combined organic extracts were washed with brine (2 × 20 mL), dried (Na_2SO_4), and evaporated to give the acetoxylactone as a colourless foam (74 mg, 83%), homogeneous by tlc; ^{1}Hmr ($CDCl_3$) δ: 2.13 (3H, s), 4.77 (2H, s), 4.90 (2H, s), 4.95 (1H, dd, 2, 6 Hz), 5.17 (2H, s), 6.38 (1H, d, 2 Hz), 6.57 (1H, d, 6 Hz).

Preparation of ***24***

The bromoformate **7*h*** (133 mg, 0.25 mmol) was dissolved in dimethylformamide (6 mL), mercaptomethyltetrazole (35 mg, 0.30 mmol) was added, and the solution was stirred overnight at room temperature. The reaction mixture was then poured into ice-cold water (50 mL) and extracted with ethyl acetate (2 × 30 mL). This extract was washed successively with water (4 × 10 mL), saturated sodium bicarbonate (1 × 10 mL), and brine (1 × 10 mL), dried and evaporated to yield **24** as a colourless foam, homogeneous on tlc (125 mg, 91% yield); ^{1}Hmr ($CDCl_3$) δ: 3.88 (3H, s), 3.95 (3H, s), 4.39, 4.71 (2H, ABq, 14 Hz), 4.75 (2H, s), 4.93 (1H, dd, 2, 8 Hz), 4.98 (2H, br s), 5.95 (1H, d, 2 Hz), 6.67 (1H, d, 8 Hz), 8.03 (1H, s).

Preparation of ***25***

Deformylation of **24** in the usual manner afforded **25**; ^{1}Hmr ($CDCl_3$) δ: 3.45 (1H, br s, exch D_2O), 3.88 (3H, s), 3.98 (3H, s), 4.45 (2H, s), 4.62 (2H, s), 4.77 (2H, s), 4.90 (1H, dd, 2, 8 Hz), 6.02 (1H, d, 2 Hz), 6.95 (1H, d, 8 Hz).

Preparation of ***8***a

A slurry of 6-aminopenicillanic acid (21.6 g, 0.1 mol) in water (250 mL) was cooled to 0–5°C, and 2 *N* potassium hydroxide was added dropwise until a clear solution was obtained, and the pH was 7.5. This solution was diluted with tetrahydrofuran (200 mL). Then a solution of phenyl chloroformate (23.5 g, 19.1 mL, 0.15 mol) in dry tetrahydrofuran (40 mL) was added dropwise, with stirring at 5–10°C and simultaneous addition of 2 *N* potassium hydroxide to maintain the pH in the range 7–8. The turbid reaction mixture was extracted with ethyl acetate (2 × 300 mL), and this extract was discarded. The aqueous layer was layered with ethyl acetate (300 mL), the system cooled to 5–10°C and, with stirring, the pH was adjusted to 1 with concentrated hydrochloric acid. The layers were separated, the aqueous layer extracted with ethyl acetate (3 × 150 mL), and the combined organic extracts were washed with saturated brine, dried ($MgSO_4$), and evaporated to yield phenoxycarbonylaminopenicillanic acid (31 g, 92%), as a crisp white foam; ^{1}Hmr ($CDCl_3$) δ: 1.60 (3H, s), 1.70 (3H, s), 4.47 (1H, s), 5.40–5.87 (2H, m), 6.00 (1H, br d, 10 Hz), 7.23 (5H, m). Methyl ester: ^{1}Hmr ($CDCl_3$) δ: 1.53 (3H, s), 1.67 (3H, s), 3.77 (3H, s), 4.45 (1H, s), 5.38–5.70 (2H, m), 6.12 (1H, br d, 10 Hz), 7.20 (5H, m).

To the methyl ester (7.973 g, 22.78 mmol) in methylene chloride (40 mL) at −78°C was added, in one portion, a precooled solution of chlorine (3.234 g, 45.56 mmol) in methylene chloride (20 mL). The reaction mixture was stirred at −78°C for 1 h, warmed to room temperature, and evaporated. Chroma-

tography of the resulting foam (silica gel, 10–30% ethyl acetate – hexane) gave pure **3** (R^1 = PhOC; R^3 = CH_3) (5.867 g, 73%) as a colourless foam; ^{1}Hmr ($CDCl_3$) δ: 2.00 (3H, s), 2.27 (3H, s), 3.73 (3H, s), 4.93 (1H, dd, 1.5, 8 Hz), 5.83 (1H, d, 1.5 Hz), 6.30 (1H, d, 8 Hz), 7.20 (5H, m). *Anal.* calcd. for $C_{16}H_{17}N_2O_5Cl$: C 54.47, H 4.86, N 7.94; found: C 54.18, H 4.95, N 7.62.

To a solution of **3** (R^1 = PhOC; R^3 = CH_3) (2.466 g, 7 mmol), in carbon tetrachloride (25 mL), were added *N*-bromosuccinimide (2.550 g, 14.2 mmol) and benzoyl peroxide (50 mg). Bromination was performed for 15 min, and the product isolated in the usual manner as a light brown foam (3.534 g). Chromatography on silica gel (ethyl acetate – hexane, 3:7) afforded pure ***8b*** (2.446 g, 68%) as a colourless foam; ^{1}Hmr ($CDCl_3$) δ: 3.85 (3H, s), 4.30 (2H, s), 4.53, 4.72 (2H, ABq, 10.5 Hz), 4.87 (1H, dd, 1.5, 8 Hz), 6.03 (1H, d, 1.5 Hz), 6.10 (1H, d, 8 Hz), 7.22 (5H, m). The dibromide (3.060 g, 6 mmol) was dissolved in chloroform (25 mL), the solution was cooled to 0°C and, under nitrogen, a solution of tetramethylguanidinium formate (4.0 g, 24.84 mmol) in chloroform (15 mL) was added dropwise during 5 min. The resulting solution was stirred at 0°C for 30 min and then at room temperature for 15 h. It was then poured onto a mixture of ice and water and the layers were separated. The aqueous layer was washed with methylene chloride (3 × 40 mL) and the combined organic layers were washed with saturated brine (2 × 10 mL), dried (Na_2SO_4), and evaporated to a pale brown foam (2.30 g). The diformate ***8a*** was isolated by chromatography on silica gel (10–20% acetone–hexane); 689 mg (26%); ^{1}Hmr ($CDCl_3$) δ: 3.87 (3H, s), 4.88 (1H, dd, 1.8, 8 Hz), 4.97 (2H, s) 5.23 (2H, br s), 6.05 (1H, d, 1.8 Hz), 6.23 (1H, d, 8 Hz), 7.27 (5H, m), 8.10 (2H, s).

Hydrolysis of ***8***a

A solution of ***8a*** (214 mg, 0.49 mmol) in methylene chloride (5 mL) was cooled to −10°C, and methanolic hydrogen chloride (2 mL, 29 mg/mL, 1.59 mmol) was added. The solution was allowed to stand overnight, by which time the starting material had disappeared and a single product had formed (tlc, silica gel, acetone–hexane, 3:1). The solvent was removed under reduced pressure and the residual light yellow foam was chromatographed on silica gel (30% acetone in hexane) to yield **21** (R = PhOC; X = OH), 157 mg (91%) as a colourless foam; ^{1}Hmr ($CDCl_3$) δ: 3.50 (1H, br s, exch D_2O), 4.38, 4.68 (2H, ABq, 16 Hz), 4.85 (2H, br s), 4.95 (1H, dd, 1.8, 8 Hz), 6.32 (1H, d, 1.8 Hz), 6.48 (1H, d, 8 Hz), 7.17 (5H, m).

Conversion of ***8***a *to* ***8***h *and* ***8***i

The diformate (184 mg, 0.42 mmol) was dissolved in methylene chloride (4 mL), and the solution was cooled to 0°C, under nitrogen. Then a solution of boron tribromide (61 mg, 0.24 mmol, 0.57 mol-equiv.) in methylene chloride (0.5 mL) was added dropwise during 5 min. The reaction mixture was stirred for 1 h at 0°C and was then poured onto ice-cold 2.5% potassium bicarbonate (20 mL). The layers were separated, and the aqueous layer was extracted with methylene chloride (3 × 40 mL). The combined organic extracts were washed with saturated brine (2 × 20 mL), dried (Na_2SO_4), and evaporated to give the crude product (188 mg) as a yellow foam. This was purified by plc (silica gel, 40% acetone–hexane) to give three bands. The leading band (10 mg) was identified as the dibromide ***8b***, and the trailing band (30 mg) was unreacted diformate. The middle band, 102 mg (61%, based on recovered starting material), was the mixture of ***8h*** and ***8i***, in the ratio 4:1. For ***8h***, ^{1}Hmr ($CDCl_3$) δ: 3.77 (3H, s), 4.40, 4.57 (2H, ABq, 10 Hz), 4.78 (1H, dd, 2, 8 Hz), 4.92 (2H, s), 5.92 (1H, d, 2 Hz), 6.23 (1H, d, 8 Hz), 7.10 (5H, m), 7.90 (1H, s). For ***8i***, ^{1}Hmr ($CDCl_3$) δ: 3.67 (3H, s), 4.10, 4.27 (2H, ABq, 10 Hz), 4.78 (1H, dd, 2, 8 Hz), 5.23 (2H, s), 5.92 (1H, d, 2 Hz), 6.23 (1H, d, 8 Hz), 7.10 (5H, m), 7.90 (1H, s).

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