A New Approach to Substituted Arene Oxides. Total Synthesis of Senepoxide and Seneol[1]

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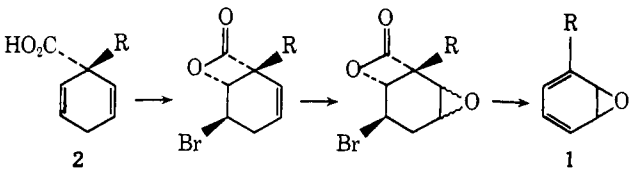
Abstract: A novel approach to 3-substituted benzene epoxides is described based on the consecutive elimination of HBr and CO_2 under mild conditions from cyclohexane-bromo-β-lactone epoxides. The method accommodates a variety of substituents which can be attached to the six-membered ring by the alkylation of dilithio 1,4-dihydrobenzoate. The resulting 1-substituted-1,4-dihydrobenzoic acids undergo exclusive halo-β-lactonization when dissolved in sodium bicarbonate solution and treated with bromine. Oxidation of the alkene bond in substances **3a, 3b, 3c, 3d, 3e,** and **3f** with CF_3CO_3H smoothly furnishes the corresponding epoxides, usually as stereoisomeric mixtures. The effect of angular substituents on the rate and stereochemistry of epoxidation is discussed and a heretofore unnoticed side reaction of peroxytrifluoroacetic acid is described. Dehydrobromination of **10b, 11b, 10d, 11d** and **10f** followed by thermal decarboxylation leads to the corresponding arene oxides **1** in good yield. The utility of **1d** in a total synthesis of the shikimate-derived metabolites senepoxide and seneol is described.

Introduction

Since the early discoveries by Boyland and Levi that polycyclic aromatic hydrocarbons undergo biological oxidation to their corresponding dihydroarene epoxides,[3,4] a major research effort has helped unravel the chemistry and pharmacology of these reactive species.[5-9] Our own interest in the chemistry of 3-substituted benzene epoxides originated with an intent to explore biomimetic schemes for the total synthesis of arene oxide derived natural products. One approach to gliotoxin might, for example, employ a derivative or equivalent of 2′,3′-oxidophenylalanine (**1i**).[10] On another front, our laboratory recently set forth a proposal invoking arene oxides **1d** or **1h** to account for the origin in nature of a family of highly oxidized cyclohexane derivatives including crotepoxide, senepoxide, and pipoxide.[11] To test these ideas we required a general preparation of the structures **1** illustrated below.

The essence of our plan germinated with the observation that olefinic bromo-β-lactones such as **3** undergo rapid dehydrobromination and extrusion of CO_2 to produce benzene or other substituted aromatics.[12] If the double bond in **3** could be epoxidized, a similar elaboration of the latent conjugated diene in **4** might furnish **1.** The regiospecific alkylation of 1,4-dihydrobenzoic acid[13] promised access to 1-substituted 1,4-dihydrobenzoic acids **2** and thence to a variety of 3-substituted arene oxides **1.**



2 **3** **4** **1**

a, R = H
b, R = CH_3
c, R = CH_2OH
d, R = CH_2OCOPh
e, R = CH_2OCOCF_3
f, R = CH_2CO_2Et
g, R = CH_2Ph

1d, R = CH_2OCOPh
1h, R = CO_2R'
1i, R = CH_2CHCO_2H (with NH_2)

This article presents a full account of our studies which have implemented this scheme as a new and general route to arene oxide structures. Moreover, its utility is illustrated by a successful total synthesis of the shikimate-derived metabolites senepoxide and seneol from **1d.**[14]

Synthesis of 1-Substituted 1,4-Dihydrobenzoic Acids. In 1961 Plieninger and Ege[13] reported that 1,4-dihydrobenzoic acid **2a** formed a dianion with potassium amide in liquid ammonia which could be alkylated with benzyl chloride or chloroacetic acid to form exclusively 1-substituted 1,4-dihydrobenzoates. We have found it more convenient to employ lithium diisopropylamide (2.0–2.1 equiv) as base in THF at −10 °C and using a variety of electrophiles (1.5 equiv), including formaldehyde, have observed equally regiospecific alkylations. Table I summarizes our results.

All alkylations proceed with a fading of the red-orange dianion color upon addition of each electrophile. Several attempts at the carbomethoxylation of **2a** were unsuccessful in producing a half-malonate ester. This substance apparently decarboxylated quite readily upon neutralization of the reaction mixture, thus furnishing only methyl dihydrobenzoate.

The starting material for all these experiments, 1,4-dihydrobenzoic acid **2a,** was made by sodium–ammonia–ethanol reduction of benzoic acid according to an established *Organic Syntheses* preparation.[15] We have performed this experiment many times on up to 80-g scale and since it is a widely used procedure wish to record a worthwhile experimental improvement. Unless the bulk of ethanol solvent was removed during workup *before* acidification of the reaction mixture, substantial quantities of ethyl dihydrobenzoate were formed at the expense of the desired acid. By simply evaporating the alcohol, our yields of product after distillation routinely became 90–92% in such large-scale preparations.

Lactonization of 1-Substituted 1,4-Dihydrobenzoates. Barnett and Needham reported in 1975 that bromination of a sodium 1,4-dihydrobenzoate salt in bicarbonate solution led to a four- or five-membered lactone, depending upon the substitution pattern of the ring-sp^2 carbons.[16] The unsubstituted parent **2a** thus formed only the bicyclic *trans*-bromo-β-lactone **3a** in 42% yield, probably by a concerted bromonium ion cyclization. We have subjected the series of 1-alkylated dihydrobenzoates (Table I) lacking olefinic substituents to identical reaction conditions and observed, as expected, that they afforded only four-membered lactones. The excellent yields obtained (Table II) were in marked contrast to the behavior of **2a** itself.

When β-lactones were formed in such halocyclizations they were generally kinetic products.[17] This was the case with **3a,** which, upon distillation, underwent ring expansion and concomitant bromine migration to the thermodynamically more stable trans bromo-γ-lactone **6a,** albeit in low yield. A number of the alkylated β-lactones depicted in Table II exhibited similar behavior; merely warming them in a Kugelrohr apparatus (130 °C, 3 h) produced the ring-expanded products **6** in good yield.

An isomeric family of cis bromolactones **7** arose when the

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Table I. Alkylation of Dilithio-1,4-dihydrobenzoate

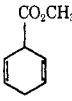
alkylating agent	time (temp, °C)	product (yield, %)
CH_3I	1 h (−10)	**2b**, R = CH_3 (83)
CH_2O	20 min (−10)	**2c**, R = CH_2OH (85–90)
$ClCO_2CH_3$	20 min (−78)	 (60)
$BrCH_2CO_2Et$	1.5 h (−78)	**2f**, R = CH_2CO_2Et (34)
$BrCH_2Ph$	3 h (0)	**2g**, R = CH_2Ph (87)

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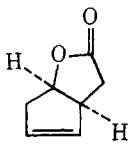
Table II. Lactones from 1-Substituted 1,4-Dihydrobenzoates

dihydrobenzoate	β-lactone (yield, %)	trans γ-lactone (yield, %)	cis γ-lactone (yield, %)
2a	**3a** (42)	 **6a**, R = H (5-10)	 **7a**, R = H (40) (ref 19)
2b	**3b** (78)	**6b** (70)	**7b** (38)
2c	**3c** (85)	**6c** (81)	**7c** (65)
	3d[a] (97)		
2f	**3f** (64)		**7f** (25)
2g	**3g** (63)		

[a] Prepared by benzoylation of **3c** (95% yield).

above sequence of operations on dihydrobenzoic acid was inverted. Bromination of free **2a** dissolved in CCl_4 afforded a mixture of trans dibromides. When aqueous sodium bicarbonate was added, the major dibromocarboxylate underwent internal S_N2 cyclization, producing cis bromo-γ-lactone **7a** as the only neutral product.[18,19] This interesting variation, shown in Table II to be a general phenomenon, additionally points to the considerable utility of halolactonization processes in preparative organic chemistry.

Epoxidation of Unsaturated Bromo-β-lactones. Substituent Effects in the 7-Oxabicyclo[4.2.0]oct-2-en-8-one Network. Geometric considerations raised interesting questions about the approach of reagents to the disubstituted olefinic bond in this fused bicyclic ring system. As a consequence of the cis ring juncture one might expect the exo face (anti to lactone) to be more accessible to an incoming electrophile. On the other hand, cis-fused 5,5 systems such as γ-lactone **8** formed preponderant amounts of the endo oxide **9** in a highly solvent dependent re-



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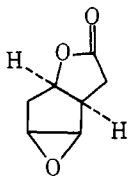

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action with peracetic acid.[20] Since we knew of no epoxidation studies in bicyclic[4.2.0]lactones, we decided to initiate a systematic survey of the substances at hand.

From preliminary experiments with **3a** it quickly became clear that the double bond in our bicyclic lactone systems was completely inert to most common oxirane-forming reagents. Neither **3a** nor **3c** was epoxidized after prolonged exposure at elevated temperatures[21] to *m*-chloroperoxybenzoic acid and each was recovered unchanged from $Mo(CO)_6$- or VO(acac)$_2$-catalyzed oxidation with *tert*-butyl hydroperoxide. This behavior of **3c** was, at first, surprising in view of Sharpless' demonstration[22] that an allylic or homoallylic hydroxyl group markedly accelerated such transition metal assisted oxidations. However, Dreiding models illustrated that the remote disposition of OH and C=C groups in **3c** made anchimeric assistance difficult in this system. Another dramatic indication of the inertness of the double bond in **3c** was its failure to add bromine, even in hot $CHCl_3$ solution.

Table III. Epoxidation of Olefinic β-Lactones Using CF_3CO_3H

			ratio **10**:**11** (yield, %)
3a[a]	**10a**	**11a**	7.7:1 (85)
3b	**10b**	**11b**	2.5:1 (92)
3c	**10c**	**11c**	3:1 (75)
3d	**10d**	**11d**	2.6:1 (81)
3e	**10e**	**11e**	3:1[b] (90)[c]
3f	**10f**		(83)

[a] Except where noted all oxidations were carried out using 5 equiv of CF_3CO_3H buffered with 10 equiv of anhydrous Na_2HPO_4 at room temperature. [b] This experiment was carried out in boiling $ClCH_2CH_2Cl$. [c] Yield based on recovered starting material.

Peroxytrifluoroacetic acid is an especially powerful oxidant which has found broad utility in epoxidizing electron-deficient olefins.[23] When the parent β-lactone **3a** was treated with buffered solutions of CF_3CO_3H (5 equiv) in CH_2Cl_2 or $ClCH_2CH_2Cl$ for 2 h at room temperature, a 7.7:1 mixture of stereoisomeric epoxylactones **10a** and **11a** was produced in 85% yield. The two solid isomers were readily separated by a combination of fractional crystallization and chromatography and we assigned structure **10a** to the major product. Although even 270-MHz NMR spectra were too complex for unambiguous interpretations, support for the designated assignments came from the epoxidation of methylated homologue **3b** where, under identical conditions, a 2.5:1 ratio of stereoisomers resulted (90% yield). Presumably the substitution of methyl for hydrogen at the ring fusion impeded β-epoxidation leading to a smaller proportionate amount of **10b**. Our survey of peracid reactions on substituted oxabicyclo[4.2.0]octenone systems is summarized in Table III.

We expected hydroxymethyl-β-lactone **3c** to exhibit characteristics similar to **3b** in its reaction with peracid. Since models suggested minimal anchimeric assistance by the OH group in **3c**, the angular substituent should sterically hinder oxidation from the β direction and perhaps exert an overall weakly retarding inductive effect on epoxidation. In line with prediction, a simple competition experiment revealed that **3c** was oxidized 0.80 times as fast as **3b**. However, we were surprised to discover that trifluoroacetylation of the alcohol functional groups had also occurred. Thus when pure **3c** was oxidized for 5 h at room temperature, a mixture of two epoxytrifluoroacetates **10e** and **11e** was obtained along with about 10% of unreacted alkene. This alkene had TLC characteristics different from those of **3c** and prolonged exposure to peracid failed to epoxidize it. When the crude product mixture was chromatographed on a silica gel column, the trifluoroacetates were cleaved and the isomeric epoxy alcohols **10c** and **11c** were eluted in a ratio of 3:1 (overall yield). Unreacted alkene was always recovered from chromatography as starting material **3c**.

This unexpected esterification apparently constituted the first indication that hydroxyl groups could be trifluoroacetylated by CF_3CO_3H. We have recently tested the generality of this method and reported that upon exposure to the peracid, a variety of alcohols did form trifluoroacetates in good yield.[24] Control experiments ruled out trifluoroacetic acid (TFA) or

its anhydride as the active reagent. In accordance with a simple Fischer esterification mechanism, strong proton donors such as TFA itself catalyzed the reaction. A recent compendium[25] listed numerous unsaturated compounds (including alcohols) which have been epoxidized with CF_3CO_3H. However, no mention was made of this side reaction, probably because crude products in many instances were inadvertently hydrolyzed during workup or chromatography.

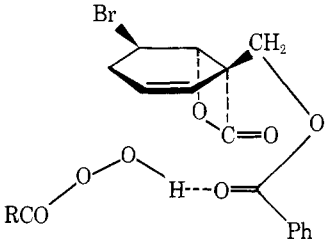
Since the epoxidation of **3c** was complicated by a competing esterification, we decided to unravel the overall process by investigating the oxidation of olefinic trifluoroacetate **3e.** This substance, prepared from **3c** using TFA anhydride, was identical with the peracid-resistant alkene noted as a by-product in the oxidation of **3c.** Consistent with this observation, **3e** produced no epoxides whatsoever even when exposed to 5 equiv of buffered peracid at room temperature for up to 24 h. We therefore concluded with assurance that while a slow esterification of **3c** competed with epoxidation, the 3:1 ratio of **10c** and **11c** truly represented the oxidation products at the double bond of **3c** with peroxytrifluoroacetic acid.

Although inert at room temperature, **3e** did react slowly in boiling 1,2-dichloroethane with peroxytrifluoroacetic acid (83 °C, 55% complete after 19 h) and also afforded a 3:1 ratio of epoxides **10e** and **11e.** The larger volume occupied by the trifluoroacetate group in **3e** as well as its strong inductively withdrawing character are factors most likely responsible for the sluggish reactivity of this substrate.

As with **3e,** we had expected that the inductive effect of the added benzoyl group in **3d** combined with its considerable size would markedly deactivate the alkene bond relative to **3c.** In fact, the reaction of **3d** with CF_3CO_3H was complete in 8 h at room temperature and led to a mixture (ratio 2.6:1) of epoxybenzoates **10d** and **11d** in high yield. Authentic samples of these benzoates were prepared from **10c** and **11c** in order to correlate new product structures. Since the very bulky β substituent should have retarded epoxidation by blocking access to the double bond, the unexpected reactivity of **10d** can only be explained by invoking some compensatory rate-promoting function for the benzoate ester.

Concurrent with our oxidation studies, Cerefice and Fields reported experiments showing that in the absence of unusual steric or conformational effects, the carbonyl oxygen of esters could participate as a hydrogen bond acceptor in the syn epoxidation of adjacent double bonds.[26] Among its many important consequences, this paper clarified Henbest's early observation that the epoxidation of allylic acetates furnished more of the cis isomer than could be rationalized by steric considerations only.[27,28] This phenomenon also accounted for the stereospecific epoxidation of dihydrophthalate esters.[29,30]

Because the ester side chain in **3d** extended an oxygen two atoms further than the alcohol group of **3c,** the benzoate carbonyl became ideally suited for hydrogen bonding with an approaching molecule of peracid as shown in **12.** Moreover,



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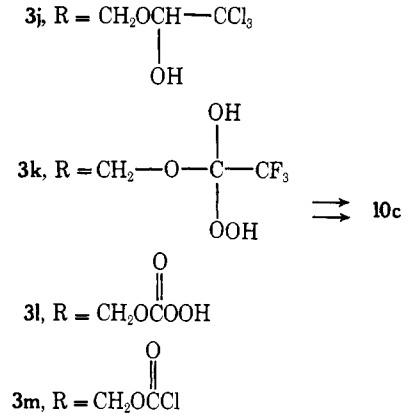
trifluoroacetate **3e** would not be expected to exert an analogous syn-directive influence since its electron-deficient carbonyl constitutes an extremely poor hydrogen bond acceptor. Epoxidation of ethyl ester **3f** was also relatively rapid (3 h, room temperature) and seemed to give a single product which decomposed during careful column chromatography.

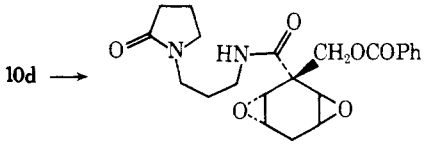
Encouraged by the possibility of anchimerically assisted epoxidations, we tried to design a substituent for the ring junction of **3c** which would induce a completely stereospecific epoxidation. Three worth noting are shown below.



Addition of pure, dry chloral (1 equiv) to **3c** furnished hemiacetal **3j** as a stable solid, mp 150–152 °C. Although this substance effectively presented a powerful coordinating group in the vicinity of the double bond, its reaction with peracid produced no recognizable products except for recovered starting material. Structures like peroxy ether **3k** have not heretofore been characterized; nevertheless they could, in principle, serve as epoxidizing agents akin to the peroxyimidic[31] and peroxycarbamic[32,33] acids. Fischer esterification of **3c** with CF_3CO_3H likely produces **3k** as an intermediate which collapses in concerted fashion to *syn*-epoxytrifluoroacetate **10e.** The same tetrahedral intermediate might arise from the reaction of olefinic trifluoroacetate **3e** with H_2O_2; however, we could engender no epoxidation of **3e** by combining these two substances in any proportion under a variety of conditions. Finally we planned to synthesize peroxycarbonic acid **31** and study its decomposition. Reaction of **3c** with phosgene in dichloroethane–pyridine smoothly furnished chloroformate **3m,** but when subjected to H_2O_2 under neutral anhydrous conditions, **3m** reverted only to **3c.**

Arene Oxides from Bromo-β-lactone Epoxides. In the case of unepoxidized bromolactones such as **3a,** dehydrohalogenation had been accomplished using triethylamine or one of the amidine bases, DBN and DBU.[12] Those olefinic lactones, which should more readily lose HBr than their epoxy-containing counterparts, sometimes formed high molecular weight by-products incorporating DBN or DBU residues. We felt that this acylation of so-called "nonnucleophilic bases"[34] by reactive β-lactone intermediates might pose a more serious problem during relatively slow eliminations.

Epoxylactone **10d** could be stirred overnight in pyridine or triethylamine without change. It was likewise unaffected in THF solution with potassium *tert*-butoxide at 0 °C, although it decomposed slowly when this reaction mixture was warmed to 40 °C. Upon exposure to DBN (1–2 equiv) in $CHCl_3$, the β-lactone in **10d** was ruptured by nucleophilic attack to form



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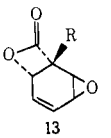
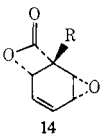
a product tentatively identified by mass spectral and NMR analysis as **15** (mol wt 414 g/mol).

Substituting DBU for DBN and changing the solvent to benzene (5 h, room temperature) greatly improved matters and

Table IV. Elimination of HBr and CO_2 from Bromo-β-lactone Epoxides

epoxylactone	−HBr →	intermediate	−CO_2 →	arene oxide (yield, %)
10a				
11a				
10b		 13b, R = CH_3 13	(87)	**1b** (56)
11b		 14b, R = CH_3 14		**1b**
10e, 11e				
10d		**13d**, R = CH_2O-COPh		**1d** (90)
11d		**14d**, R = CH_2O-COPh		**1d**
10f		**13f**, R = CH_2C-O_2Et		**1f** (75-85)

made it possible to isolate the desired olefinic epoxylactone **13d** in excellent yield after careful aqueous workup. Despite the fact that this compound was extremely acid sensitive and could not be purified, NMR spectra of unpurified samples were quite clear-cut and very characteristic. Most notable was the eight-line first-order ABMX pattern for the two vinylic hydrogens. When dissolved in benzene and heated at reflux for 2 h, **13d** underwent spontaneous decarboxylation to form (2′,3′-epoxybenzyl)benzoate **1d** contaminated with minor amounts of the derived phenol (*o*-hydroxybenzyl)benzoate. This by-product could be completely suppressed by carrying out both the dehydrobromination and decarboxylation reactions in dry, ammonia-washed glassware. Table IV presents the results we have obtained with various arene epoxide precursors, including two stereoisomeric pairs.

Epoxide **1d** proved to be inordinately stable. It could be stored for months in the freezer and purified, if necessary, by column chromatography on activity IV alumina or silica gel. It even survived exposure to solutions of ammonia in $CHCl_3$ at room temperature without appreciable destruction. At present, the factors responsible for such uncharacteristic stability are not well understood.

The same arene oxide could as well be obtained from stereoisomeric β-lactone **11d.** Dehydrobromination of **11d** took place as before with DBU in benzene, only more slowly (complete after 8 h at 10 °C). This difference in rates was consistent with stereochemical assignments since the transition state for trans 1,2-elimination in **11d** required removal of the hydrogen syn to the oxirane ring. Workup of **14d** below room temperature showed it to be contaminated with substantial amounts of **1d,** indicating that decarboxylation of the cis olefinic epoxylactone occurred more rapidly than in the corresponding trans isomer **13d.** Additional experiments demonstrated this to be a general phenomenon.

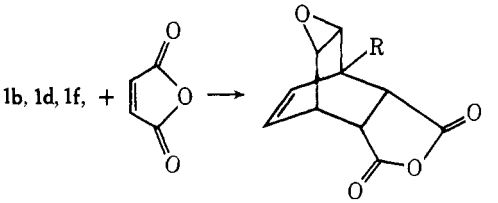
We were unable to prepare the parent substance, benzene epoxide, from **10e** or **11e.** When these epoxylactones were separately subjected to DBU-C_6H_6 or triethylamine at 60-80 °C, a thick, white precipitate appeared exhibiting polymeric properties. The absence of an angular substituent may cause this deleterious outcome because the β-lactone would be more vulnerable to nucleophilic attack, either before or after HBr elimination.[34]

Methylated β-lactones **10b** and **11b** posed a critical test for our methodology. The derived epoxide **11b** of toluene is one of the least stable arene oxides known since alkyl substitution at unoxygenated ring positions promotes the rate of isomerization to phenols.[9] Our success is unmasking **1b** from the above-mentioned precursors required the strictest attention to detail; for instance, all reaction vessels *and attendant glassware including NMR tubes* had to be carefully washed with ammonia and oven dried for optimum yields. By taking such precautions, epoxylactone **10b** could be subjected to DBU in benzene and the disappearance of starting material monitored by TLC. Cold aqueous NaCl workup with a pH 4 water wash cleanly afforded **13b,** contaminated with only the faintest trace of *o*-cresol. The NMR spectrum of **13b,** like that of **13d,** revealed the characteristic eight-line pattern for its vinyl hydrogens. To obtain the best spectra of toluene epoxide, a C_6D_6 solution of **13b** under argon was heated in an NMR tube and its spectrum monitored hourly. Time for the decarboxylation varied from 3 to 5 h.

The same overall reaction sequence also furnished toluene oxide **1b** from epoxylactone **11b.** In line with previous experience, **11b** underwent a slower dehydrobromination than did its isomer **10b;** however, the intermediate olefin **14b** spontaneously lost CO_2 at room temperature to form arene oxide. The aqueous workup used to remove DBU by-products tended to decompose **1b,** so that for preparative purposes, precursor **10b** was preferred.

Attempted elimination of the mixture of trifluoroacetates **10e** and **11e** gave a complex distribution of products having a strong amide carbonyl absorption in the infrared. In one additional test of its capability, this arene oxide methodology was applied to the synthesis of **1f.** Bromolactone **10f** produced a relatively stable alkene **13f** upon dehydrohalogenation, a fact which lent further support to the assigned β-epoxide stereochemistry. Decarboxylation of **13f** led to **1f** without complication.

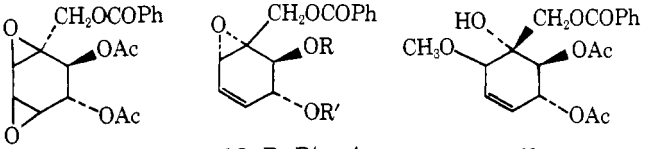
To provide unambiguous proof of structure for the new arene oxides-oxepins, **1b, 1d,** and **1f** were characterized in the form



16b, R = CH_3
d, R = CH_2OCOPh
f, R = CH_2CO_2Et

of their Diels-Alder adducts with maleic anhydride.

Synthesis of Senepoxide and Seneol. Arene oxide **1d,** or its congener **1h,** may be a biosynthetic intermediate between isochorismic acid and the secondary metabolites crotepoxide **17,**[35] senepoxide **18,**[36] seneol **19,**[36] and pipoxide **20.**[11,37] With



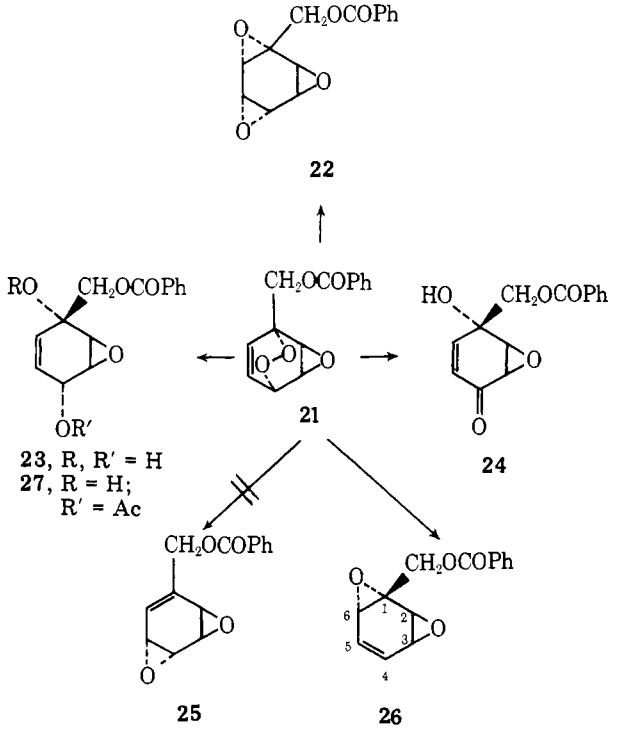
17 **18**, R, R′ = Ac; **20**, R = COPh; R′ = H **19**

1d in hand, we first decided to explore oxidative routes leading to **17** and **18** which might be compatible with physiological conditions in the plant.

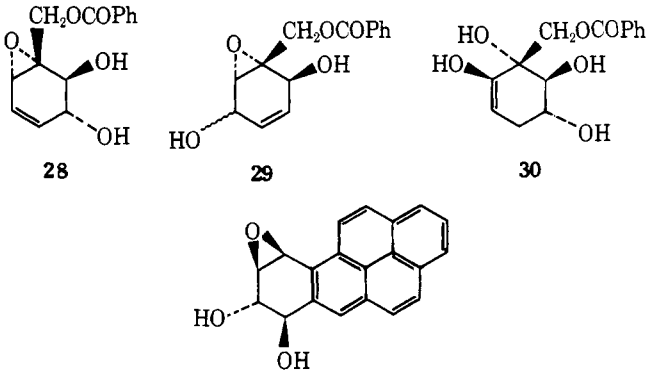
Molecular oxygen represents a principal biological oxidant

and chlorophyll-sensitized photooxygenation of **1d** furnished the crystalline trans endoperoxy epoxide **21** in 60–80% yield. This substance smoothly rearranged in benzene at reflux to trioxide **22.** Both **21** and **22** might serve as precursors to crotepoxide but are at a higher oxidation state than is required for senepoxide. Since the direct monoepoxidation of **1d** with *m*-chloroperoxybenzoic acid afforded only the rearranged phenol (*o*-hydroxybenzyl)benzoate, the reactions of endoperoxide **21** with reducing agents were examined. Thiourea in methanol quantitatively transformed **21** to diol **23**[38] whereas dimethyl sulfide, like pyridine, largely caused fragmentation leading to hydroxy enone **24.**

The desired deoxygenation of **21** was successfully accomplished with trivalent phosphorus compounds. Either triphenylphosphine or trimethyl phosphite in benzene produced trans diepoxide **26** from **21** in yields of 30 and 88%, respectively, uncontaminated with the corresponding positional isomer **25.**[39]



The final conversion of **26** to senepoxide necessitated a selective, acid-catalyzed trans opening of the $\Delta^{2,3}$ epoxide ring. In planning this step we had relied on some early studies by Kupchan with crotepoxide showing that the trisubstituted $\Delta^{6,1}$ oxirane in **17** was inordinately resistant to mineral acids.[35] In fact the hydrolysis of **26** proved to be highly solvent and acid dependent: with either 1 equiv of HOAc in boiling $CHCl_3$ or upon heating in 1:3 HOAc–CH_2Cl_2, **26** furnished **27,** the product of conjugate opening, in over 60% yield. The structure of **27** was confirmed by acetylation (Ac_2O, pyridine, 4-dimethylaminopyridine) to afford a diacetate identical with a sample of peracetylated **23.** Upon exposure of **26** to NaOAc–HOAc a complex mixture of products arose. The preponderance of these displayed no epoxide but several acetate resonances in the NMR spectrum. Low material recovery plagued the alumina-catalyzed hydration of **26** according to the method of Posner[40] and only trace amounts of the desired trans 1,2-diol **28** could be detected. Optimum conditions for selective opening of the 2,3-oxide in **26** utilized 1:1 THF–10% aqueous HOAc whereupon **28** was formed in 32% yield along with 1,4-diol **29** (21%) and tetraol **30** (21%). The surprisingly competitive opening of both epoxide rings in this experiment led us to investigate it more carefully. Control experiments showed that the $\Delta^{1,6}$ epoxide in pure **28** was much more rapidly hydrolyzed



than it was in **26.** Thus, one could account for essentially all of the tetraol arising from **26** by an ordered stepwise process **26** → **28** → **30** where anchimeric assistance by the 3α-hydroxyl in diol epoxide **28** accelerated cleavage of the trisubstituted epoxide. Such behavior of **28** is reminiscent of diol epoxide **31** produced by the hepatic oxidation of benzo[*a*]pyrene. The pronounced electrophilicity of the epoxide in **31** is thought to be responsible for benzpyrene's carcinogenic properties.[41]

After column chromatography, diol **28** was obtained pure and, when acetylated, led to *dl*-senepoxide **18.** Our sample had the same melting point as previously prepared synthetic racemic material and IR, NMR, and TLC characteristics identical with those of naturally occurring **18** kindly provided by Mme. Judith Polonsky (CNRS, Gif-sur-Yvette, France). Additional evidence for the structure of **18** came from its acid-catalyzed methanolysis ($HClO_4$) which produced *dl*-seneol **19,** a metabolite of senepoxide in *Uvaria catocarpa.*[36]

Experimental Section

Melting points were determined using a Thomas-Hoover Unimelt instrument and are uncorrected. NMR spectra of deuteriochloroform solutions were recorded on a Varian A-60A or EM-390 spectrometer relative to an internal tetramethylsilane standard. IR spectra were determined on a Perkin-Elmer 137 spectrophotometer. Mass spectra were carried out using a computerized AEI MS-902 instrument. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Unless otherwise noted, all reactions were performed under N_2 in flame-dried or oven-dried (overnight at 105 °C) glassware. All air- and moisture-sensitive solutions were transferred or dispensed using oven-dried hypodermic syringes. Ethereal solvents were distilled under N_2 from $LiAlH_4$. All starting materials and reagents were commercial products and used as supplied.

Synthesis of 1-Methyl-1,4-dihydrobenzoic Acid (2b) from 1,4-Dihydrobenzoic Acid Using LDA. A solution of diisopropylamine (Aldrich, 3.42 g, 33.8 mmol) in THF (50 mL) was cooled to −10 °C in a 250-mL round-bottom three-necked flask. To it was added *n*-butyllithium (Ventron, 14.3 mL of a 2.37 M solution in hexane, 33.8 mmol) and when the internal temperature returned to −10 °C, a solution of 1,4-dihydrobenzoic acid (2.0 g, 16.1 mmol) in THF (25 mL) was introduced slowly over 30 min to produce the characteristic orange-brown dianion color. Then CH_3I (1.50 mL, 24 mmol) was added by syringe; the color faded immediately and the temperature rose to 10 °C. The reaction mixture was stirred for 1 h at room temperature, then water added (50 mL). After the bulk of the THF was evaporated, the aqueous layer was extracted twice with ether and the ether layers were discarded. With concentrated HCl the aqueous layer was brought to pH 2 (precipitate) and extracted five times with ether (500 mL total). The combined extracts were washed with 10% $Na_2S_2O_3$ and saturated NaCl, dried ($MgSO_4$), and concentrated to a yellow oil. Kugelrohr distillation afforded 1.838 g (83%) of **2b:** bp 110–120 °C (0.2 mm); NMR δ 5.4–5.6 (m, 4 H, vinyl), 2.50 (broad s, 2 H, allylic), 1.28 (s, 3 H, methyl); IR λ_{max} ($CHCl_3$) 5.79 μ.

Synthesis of 1-Hydroxymethyl-1,4-dihydrobenzoic Acid (2c). A solution of LDA in THF (150 mL) at −10 °C was prepared as above in a 500-mL round-bottom three-necked flask from diisopropylamine

(26.8 mL, 0.189 mol) and *n*-BuLi (76.5 mL of a 2.37 M hexane solution). Dihydrobenzoic acid (11.19 g, 0.09 mol) in THF (50 mL) was added, then the −10 °C flask was fitted with a short gas inlet tube connected to a 50-mL filter flask containing paraformaldehyde (4.05 g, 0.135 mol). The paraformaldehyde was heated in a 140 °C oil bath under a slow stream of N_2 which carried monomeric HCHO directly into the vortex of the rapidly stirred dianion solution. Upon completion of addition the deep red color had faded to pale yellow and water (100 mL) was added. The bulk of THF was removed on the rotary evaporator and the pH of the aqueous residue adjusted to 8–9 using concentrated HCl. After three ether washings (discarded) the aqueous layer was acidified to pH 2–3 and extracted with ether (2 × 250 mL). The aqueous layer was then saturated with NaCl and extracted again with ether (2 × 100 mL). The combined ether extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated to yield 12.65 g (91%) of yellow oil which was almost pure by NMR. Upon trituration with hexane, 10.27 g of crystals was deposited. A small portion was recrystallized from benzene–hexane to afford needles of **2c:** mp 97–99 °C; NMR δ 5.7–6.2 (m, 4 H, vinyl), 3.72 (s, 2 H, CH_2O), 2.75 (broad s, 2 H, allylic); IR λ_{max} ($CHCl_3$) 5.88 μ.

Anal. ($C_8H_{10}O_3$) C, H.

Bromolactonization of 1-Methyl-1,4-dihydrobenzoic Acid (2b). Synthesis of 3b. To a vigorously stirred solution of acid **2b** (1.0 g, 7.24 mmol) in saturated aqueous $NaHCO_3$ (25 mL) was added a solution of Br_2 in CH_2Cl_2 (36.2 mL of a 0.20 M solution, 1.0 equiv) which rapidly decolorized. After 10 min the organic layer was separated and the aqueous phase extracted once with 75 mL of CH_2Cl_2. The combined organics were washed with H_2O, dried over $MgSO_4$, filtered, and concentrated to an oil. Crystallization from hexane yielded 1.22 g (78%) of white crystals: mp 85–87 °C; NMR δ 6.05 (m, 1 H, vinyl), 5.69 (d, 1 H, J = 10.8 Hz, vinyl), 4.72 (d, 1 H, J = 3 Hz, CHO), 4.54 (m, 1 H, CHBr), 2.70 (m, 2 H, allyl), 1.48 (s, 3 H, methyl); IR λ_{max} ($CHCl_3$) 5.48 μ.

Anal. ($C_8H_9BrO_2$) C, H.

Isomerization of β-Lactone 3b to Trans Bromo-γ-lactone 6b. A sample of **3b** (0.320 g, 1.47 mmol) was heated in a Kugelrohr oven for 3 h at 130 °C, then distilled at aspirator pressure to afford 0.224 g (70%) of white solid: mp 65–70 °C; NMR δ 5.6–5.9 (m, 1 H, vinyl), 5.2–5.45 (m, 1 H, vinyl), 4.75 (broad m, 1 H, CHO), 4.29 (dd, 1 H, J = 5, 1.1 Hz, CHBr), 2.6 (m, 2 H, allyl), 1.34 (s, 3 H, methyl); IR λ_{max} (film) 5.60 μ.

Formation of Cis Bromo-γ-lactone 7b from 2b. Acid **2b** (0.666 g, 5.0 mmol) was dissolved in CCl_4 and to it was added a solution of Br_2 in CCl_4 (2.3 mL of a 2.15 M solution, 1.0 equiv) with ice cooling. The resulting colorless organic solution was taken up in a pipet and added dropwise to a rapidly stirred saturated aqueous $NaHCO_3$ solution (50 mL). After 2 h, stirring was stopped and the reaction mixture allowed to stand overnight. The CCl_4 layer was decanted and the aqueous phase extracted once with $CHCl_3$. The combined chlorocarbon layers were dried ($MgSO_4$) and concentrated to yield a white solid, mp 53–58 °C. One recrystallization from petroleum ether afforded 0.375 g (38%) of crystals: mp 71–71.5 °C; NMR δ 5.62 (m, 2 H, vinyl), 4.80 (complex m, 1 H, CHO), 4.34 (s, 1 H, CHBr), 2.55 (m, 2 H, allyl), 1.43 (s, 3 H, methyl); IR λ_{max} ($CHCl_3$) 5.60 μ.

Bromolactonization of 1-Hydroxymethyl-1,4-dihydrobenzoic Acid (2c). Synthesis of 3c. Acid **2c** (5.0 g, 32.5 mmol) was suspended in distilled water (100 mL) and powdered $NaHCO_3$ was added (1.5 equiv, 4.14 g). To the resulting solution was added Br_2 in CCl_4 (15.2 mL of a 2.15 M solution) with rapid stirring. Upon completion of addition, faint traces of residual Br_2 were discharged with 10% $Na_2S_2O_3$ and the layers separated. The aqueous layer was extracted (3 × 50 mL) with $CHCl_3$ and the combined chlorocarbon extracts were washed with 10% $Na_2S_2O_3$ and water and dried ($MgSO_4$). Concentration afforded 6.82 g (94%) of oil which solidified on standing: mp 50–55 °C; NMR δ 6.10 (m, 1 H, vinyl), 5.62 (d, 1 H, J = 10 Hz, vinyl), 5.14 (d, 1 H, J = 3 Hz, CHO), 4.56 (m, 1 H, CHBr), 3.78, 4.10 (AB quartet, 2 H, J = 11 Hz, CH_2O), 2.75 (m, 2 H, allyl); IR λ_{max} 2.88, 5.48 μ.

Anal. ($C_8H_9BrO_3$) C, H.

Isomerization of 3c to Trans Bromo-γ-lactone 6c. β-Lactone **3c** (0.134 g, 0.61 mmol) was heated in a Kugelrohr oven at 130 °C for 1 h, then the volatile material distilled at 0.1 mmHg to afford 0.110 g (81%) of γ-lactone **6c:** NMR δ 5.7–6.1 (m, 1 H, vinyl), 5.48 (broad d, 1 H, J = 10 Hz, vinyl), 4.75 (m, 1 H, CHO), 4.08, 3.73 (AB quartet, 2 H, J = 12 Hz), 2.5–2.7 (m, 2 H, allyl); IR λ_{max} 5.62 μ.

Formation of Cis Bromo-γ-lactone 7c from 2c. Using the same procedure described above for **7b,** acid **2c** (0.150 g, 0.97 mmol) was treated with Br_2 (0.05 mL) in $CHCl_3$ (5 mL), then cyclized in aqueous $NaHCO_3$ solution to furnish 0.148 g (65%) of pure γ-lactone **7c** as a colorless oil: NMR δ 6.10 (m, 1 H, vinyl), 5.88 (broad d, 1 H, J = 10 Hz, vinyl), 4.88 (m, 1 H, CHO), 4.45 (s, 1 H, CHBr), 4.15, 3.90 (AB quartet, 2 H, J = 12 Hz, CH_2O), 2.62 (m, 1 H, allyl), 2.34 (m, 1 H, allyl); IR λ_{max} (film) 2.90, 5.63 μ.

Anal. ($C_8H_9BrO_3$) C, H.

Benzoylation of 3c. Preparation of 3d. Pyridine (1.95 mL, 24.2 mmol) was added to a 0 °C solution of benzoyl chloride (distilled, 1.41 mL, 12.1 mmol) in CH_2Cl_2 (5 mL) followed by alcohol **3c** (1.88 g, 8.06 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was allowed to reach room temperature and stir overnight. The bulk of CH_2Cl_2 was removed under reduced pressure, the residue taken up in THF (15 mL), and excess aqueous $NaHCO_3$ added. After stirring for 8 h, the THF was removed and the residue extracted (3 × 25 mL) with $CHCl_3$. The combined extracts were washed with 5% HCl and 5% $NaHCO_3$, dried ($MgSO_4$), filtered, and concentrated to an oil (2.63 g, 97%) which crystallized on standing, mp 77–87 °C. This material was pure enough for most purposes but could be recrystallized from CCl_4 to obtain an analytical sample (76%): mp 103–104 °C [Note: the melting point previously reported for this substance (119–122 °C, ref 12) was a typographical error]; NMR δ 8.10, 7.50 (2 m, 5 H, benzoate), 6.05–6.30 (m, 1 H, vinyl), 5.78 (broad d, 1 H, J = 11 Hz, vinyl), 5.08 (d, 1 H, J = 3 Hz, CHO), 4.62)m, 1 H, CHBr), 4.74, 4.57 (AB quartet, 2 H, J = 12 Hz, CH_2OR), 2.75 (broad m, 2 H, allyl); IR λ_{max} ($CHCl_3$) 5.44, 5.80 μ.

Anal. ($C_{15}H_{13}BrO_4$) C, H.

Bromolactonization of 1-Carbethoxymethyl-1,4-dihydrobenzoic Acid (2f). Preparation of 3f. Acid **2f** (0.150 g, 0.71 mmol) was dissolved in water (5 mL) containing $NaHCO_3$ (0.18 g) and treated with Br_2 (0.36 mL of a 2.0 M solution in CCl_4, 1.0 equiv). Upon completion of addition the layers were separated and the aqueous phase was extracted twice with CH_2Cl_2. The chlorocarbon extracts were combined, washed with brine, dried ($MgSO_4$), and evaporated to furnish 0.184 g (89%) of almost pure product. Chromatography on Brinkmann silica gel (8 g) using $CHCl_3$ afforded 0.131 g (64%) of pure **3f:** NMR δ 5.95–6.25 (m, 1 H, vinyl), 5.64 (broad d, 1 H, J = 11 Hz, vinyl), 5.05 (d, 1 H, J = 3 Hz, CHO), 4.56 (m, 1 H, CHBr), 4.20 (q, 2 H, J = 7.5 Hz, CH_2CH_3), 3.05, 2.82 (AB quartet, 2 H, J = 18 Hz, CH_2CO), 2.72 (m, 2 H, allylic), 1.29 (t, 3 H, J = 7.5, methyl); IR λ_{max} ($CHCl_3$) 5.49, 5.80 μ.

Synthesis of 3g by Bromolactonization of 1-Benzyl-1,4-dihydrobenzoic Acid (2g). To a stirred solution of acid **2g** (1.30 g, 6.1 mmol) in saturated $NaHCO_3$ (75 mL) was added Br_2 in CH_2Cl_2 (30.4 mL of a 0.2 M solution). When decolorization was complete the layers were separated and the aqueous phase was extracted (3 × 75 mL) with CH_2Cl_2. The combined organics were washed with 5% $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated to yield 1.128 g (63%) of oil: NMR δ 7.1–7.2 (m, 5 H), 5.5–6.0 (m, 2 H, vinyl), 4.55 (d, 1 H, J = 3 Hz, CHO), 4.39 (m, 1 H, CHBr), 3.27, 2.91 (AB quartet, 2 H, J = 15 Hz, benzyl), 2.60 (m, 2 H, allyl); IR λ_{max} ($CHCl_3$) 5.50 μ.

General Procedure for Preparing Peroxytrifluoroacetic Acid. To epoxidize 10 mmol of alkene, the following preparation of peracid is representative.

A one-necked 250-mL round-bottom flask equipped with 1-in. magnetic stir bar and $CaSO_4$ drying tube was charged with CH_2Cl_2 (100 mL) and anhydrous Na_2HPO_4 (Mallinckrodt, 1.42 g, 120 mmol). [Note: commerical samples of this buffer must be rigorously dried by heating at 200–220 °C to a constant weight, then stored in a desiccator.] The suspension was cooled to 0 °C and trifluoroacetic anhydride added (10.5 g, 7.1 mL, 50 mmol). Ten minutes later, 90% H_2O_2 (FMC Corp., 1.68 mL, 60 mmol) was added carefully dropwise using a syringe with a Teflon needle. The ice bath was removed and the suspension stirred for 1.5 h at room temperature, by which time IR analysis showed that all the anhydride had been consumed.

Reaction of 3a with CF_3CO_3H. Preparation of 10a and 11a. Using the general procedure described above, a buffered suspension of CF_3CO_3H was prepared from $(CF_3CO)_2O$ (10.45 mL, 74 mmol), 90% H_2O_2 (2.50 mL), Na_2HPO_4 (21 g), and CH_2Cl_2 (75 mL). To it was added a solution of lactone **3a** (3.0 g, 14.8 mmol) in CH_2Cl_2 (25 mL) and the reaction mixture stirred for 2 h at room temperature. Water (50 mL) was added and after the layers were separated the aqueous phase was extracted (2 × 75 mL) with $CHCl_3$. The combined organic layers were washed with 10% $NaHSO_3$ and 5% $NaHCO_3$, dried ($MgSO_4$), and concentrated to an oil (3 g); TLC in 1:1 ether–

hexane showed only two products having R_f 0.44 (minor) and 0.23 (major). Trituration of the crude oil with ether produced crystals (0.10 g) of the minor product. The supernatant was purified by column chromatography on silica gel (ICN, 150 g). Elution with 2:3 ether-hexane afforded an additional 0.216 g (total yield 9%) of **11a:** mp 149–150 °C; NMR δ 4.78 (dd, 1 H, J = 6, 2.4 Hz, CHO), 4.25–4.40 (m, 2 H, CHBr, CHCO), 3.40 (broad s, 2 H, epoxide), 2.75 (m, 2 H, $-CH_2-$); IR λ_{max} ($CHCl_3$) 5.45 μ. Continued elution of the column afforded 2.43 g (75%) of **10a:** mp 68–69 °C (ether); NMR δ 4.74 (t, 1 H, J = 6.9 Hz, CHO), 4.10–4.40 (complex m, 2 H, CHBr, CHCO), 3.32–3.52 (m, 2 H, epoxide), 2.69, 2.35 (16-line ABMX pattern, 2 H, J_{AB} = 15, J_{AM} = 1.5, J_{AX} = 11.4, J_{BM} = 3, J_{BX} = 5.4 Hz, $-CH_2-$); IR λ_{max} ($CHCl_3$) 5.45 μ.

Reaction of 3b with CF_3CO_3H. Preparation of 10b and 11b. Peroxytrifluoroacetic acid was prepared as above from $(CF_3CO)_2O$ (7.95 mL, 57.2 mmol), 90% H_2O_2 (1.92 mL, 68.6 mmol), Na_2HPO_4 (16.2 g), and CH_2Cl_2 (50 mL). To it was added a solution of **3b** (2.459 g, 11.4 mmol) in CH_2Cl_2 (15 mL), the reaction mixture stirred for 2 h at room temperature, then water (60 mL) added to dissolve the inorganic salts. The layers were separated and the aqueous phase was extracted (2 × 50 mL) with $CHCl_3$. The combined organic extracts were washed with 10% $NaHSO_3$ and brine, dried ($MgSO_4$), and concentrated to a crude oil (2.6 g). TLC in $CHCl_3$ showed two products having R_f 0.43 (minor) and 0.38 (major). Column chromatography on silica (Brinkmann, 60 g) eluting with 5:1 hexane–ethyl acetate first afforded **11b** (0.67 g, 25%): mp 137–139 °C dec (from benzene); NMR δ 4.65 (broad s, 1 H, CHO), 4.35 (broad s, 1 H, CHBr), 3.51, 3.31 (2 broad s, 2 H, epoxide), 2.79 (broad s, 2 H, $-CH_2-$), 1.75 (s, 3 H, methyl); IR λ_{max} 5.47 μ.

Continued elution afforded the more polar isomer **10b** (1.69 g, 65%): mp 114–115 °C dec (from ether-hexane); NMR δ ($CDCl_3$) 4.42 (d, 1 H, J = 2.5 Hz, CHO), 4.35 (m, 1 H, CHBr), 3.35 (broad m, 1 H, epoxide), 3.14 (d, 1 H, J = 5 Hz, epoxide), 2.2–2.0 (complex m, 2 H, $-CH_2-$), 1.61 (s, 3 H, methyl); NMR δ (C_6D_6) 4.00–4.33 (complex overlapping m, 2 H, CHO, CHBr), 2.63 (s, 2 H, epoxy), 1.9–2.2 (2 m, 1 H), 1.4–1.8 (m, 1 H), 1.04 (s, 3 H, methyl); IR λ_{max} 5.45 μ.

Reaction of 3c with CF_3CO_3H. Preparation of 10c and 11c. Peroxytrifluoroacetic acid was prepared as above using $(CF_3CO)_2O$ (0.75 mL), 90% H_2O_2 (0.20 mL), Na_2HPO_4 (1.82 g), and CH_2Cl_2 (10 mL). To it was added **3c** (0.250 g, 1.07 mmol) and the reaction mixture stirred for 4.5 h at room temperature. Water (10 mL) was added, then 1 M $Na_2S_2O_3$ until a starch–iodide test registered negative (1 mL). After shaking, the layers were separated and the aqueous phase extracted (3 × 10 mL) with CH_2Cl_2. The combined organic layers were washed with $NaHCO_3$ (10 mL), dried (Na_2SO_4), and concentrated to a viscous oil (0.297 g). NMR analysis revealed residual vinyl peaks and the IR spectrum showed a strong trifluoroacetate ester absorption at 5.60 μ. Although three spots were evident on TLC analysis of the crude reaction mixture (3:1 hexane–ethyl acetate), no starting **3c** was present. One spot (R_f 0.30) was identical with an authentic sample of **3e,** prepared from **3c** using $(CF_3CO)_2O$.

Anal. ($C_{10}H_8BrF_3O_4$) C, H.

Chromatography on silica gel (Brinkmann, 15 g) eluting with 4:1 $CHCl_3$–ether first afforded **3c** (0.022 g, 9%). Continued elution gave the minor isomer **11c** (0.46 g, 19%): mp 125–127 °C ($CHCl_3$); NMR δ 4.99 (d, 1 H, J = 3 Hz, CHO), 4.40 (m, 1 H, CHBr), 4.23, 4.07 (AB quartet, 2 H, J = 13.5 Hz, CH_2OH), 3.49 (m, 1 H, epoxide), 3.31 (d, 1 H, J = 3.8 Hz, epoxide), 2.88 (m, 2 H, $-CH_2-$); IR λ_{max} (film) 2.86, 5.50 μ.

Anal. ($C_8H_9BrO_4$) C, H.

Further elution gave 0.137 g (56%) of **10c:** mp 68–70 °C (CH_2Cl_2–CCl_4); NMR δ 4.79 (d, 1 H, J = 6 Hz, CHO), 4.38 (m, 1 H, CHBr), 4.16, 3.97 (AB quartet, 2 H, J = 11 Hz, CH_2OH), 3.38 (m, 1 H, epoxide), 3.23 (d, 1 H, J = 4 Hz, epoxide), 2.55 (m, 2 H, $-CH_2-$); IR λ_{max} (film) 2.75, 5.50 μ.

Anal. ($C_8H_9BrO_4$) C, H.

Reaction of 3d with CF_3CO_3H. Preparation of 10d and 11d. Peroxytrifluoroacetic acid was prepared as above using $(CF_3CO)_2O$ (69 mmol, 14.5 g, 9.8 mL), 90% H_2O_2 (89.7 mmol, 2.5 mL), Na_2HPO_4 (anhydrous, 23.5 g), and CH_2Cl_2 (140 mL in a 500-mL three-neck flask fitted with drying tube and overhead stirring motor. Lactone **3d** (4.62 g, 13.8 mmol) was added and the mixture stirred at room temperature overnight. Water (200 mL) was added and stirring continued until the salts dissolved. The layers were separated and the aqueous layer was extracted (3 × 50 mL) with CH_2Cl_2. The combined CH_2Cl_2 extracts were washed with saturated $NaHSO_3$ (100 mL) and saturated $NaHCO_3$ (100 mL) and dried over Na_2SO_4. Concentration of the solution afforded 5.37 g of viscous oil. Crystallization from CCl_4 afforded 2.55 g (52%) of epoxide **10d:** mp 122–124 °C after recrystallization from CCl_4; NMR ($CDCl_3$) δ 8.08 (m, 2 H, aromatic), 7.54 (m, 3 H, aromatic), 4.81 (d, 1 H, -CHBr) 3.93 (m, 2 H, epoxide), 2.55 (m, 2 H, $-CH_2-$); IR λ_{max} ($CHCl_3$) 5.45, 5.81 μ. Column chromatography of the supernatant on silica gel (ICN, 270 g) with 5:1 hexane–ethyl acetate afforded 1.10 g (23%) of the minor isomer **11d:** mp 94.5–96 °C (ether); NMR δ 8.09, 7.55 (2 m, 5 H, aromatic), 4.95 (d, 1 H, J = 3 Hz, CHO), 4.79 (s, 2 H, $-CH_2O$-COPh), 4.39 (m, 1 H, -CHBr–), 3.48 (m, 1 H, epoxide), 3.40 (d, 1 H, J = 4 Hz, epoxide), 2.80 (m, 2 H, $-CH_2-$); IR λ_{max} ($CHCl_3$) 5.48, 5.82 μ.

Anal. ($C_{15}H_{13}BrO_5$) C, H.

Continued elution afforded more (0.315 g, 6%) of the major isomer **10d.**

Anal. ($C_{15}H_{13}BrO_5$) C, H.

Reaction of 3e with CF_3CO_3H. Preparation of 10e and 11e. Using 1,2-dichloroethane (3 mL) instead of CH_2Cl_2, peroxytrifluoroacetic acid was prepared by the standard procedure from $(CF_3CO)_2O$ (0.21 mL), 90% H_2O_2 (0.05 mL), and Na_2HPO_4 (0.52 g). After addition of solid **3e** (0.100 g, 0.30 mmol, mp 68–71 °C) the mixture was heated at reflux for 19 h. After cooling, water (3 mL) was added and the layers were separated. The organic phase was diluted with CH_2Cl_2 and washed with saturated $NaHSO_3$ (2 mL), then dried (Na_2SO_4). Concentration afforded 0.071 g of a viscous oil. NMR analysis indicated that the epoxidation was 55% complete. Slow filtration through silica gel (3.5 g) eluting with 4:1 $CHCl_3$–ether afforded 0.066 g of epoxy alcohols **10e** and **11e.** LC analysis (μ-Bondapak, flow rate 1 mL/min, 45:55 CH_3CN–H_2O, UV detector at 205 nm) indicated a 3:1 ratio of **10e** to **11e** having retention times of 5.0 and 4.5 min, respectively.

Formation of 10f by Epoxidation of 3f with CF_3CO_3H. A suspension of buffered CF_3CO_3H was prepared as described above using $(CF_3CO)_2O$ (5.22 mL, 36.5 mmol), H_2O_2 (1.32 mL), Na_2HPO_4 (10.47 g), and $ClCH_2CH_2Cl$ (75 mL). To it was added a solution of **3f** (2.13 g, 7.37 mmol) in $ClCH_2CH_2Cl$ (40 mL) and the mixture stirred for 3 h at room temperature before workup. Water (50 mL) was added and the layers were separated. The usual workup afforded 1.86 g (83%) of almost pure **10f** as an oil. Column chromatography on silica gel (Brinkmann, 100 g) using $CHCl_3$ afforded a pure sample (1.11 g, 50%): NMR δ 4.75 (d, 1 H, J = 5 Hz, CHO), 4.0–4.4 (m, 3 H, CHBr, $-CH_2CH_3$), 3.35 (m, 1 H, epoxide), 3.21 (d, 1 H, J = 4 Hz, epoxide), 3.00 (s, 2 H, CH_2CO), 2.50–2.85 (m, 2 H, $-CH_2-$), 1.30 (t, 3 H, J = 7 Hz, $-CH_3$); IR λ_{max} 5.45, 5.79 μ.

Reaction of Epoxylactone 10b with DBU. Synthesis of Toluene 2,3-Epoxide 1b. A 25-mL round-bottom flask with stir bar rinsed with 28% NH_4OH and dried overnight in a 145 °C oven was charged with **10b** (0.100 g, 0.43 mmol) in dry benzene (10 mL) and stirred under a $CaSO_4$ drying tube. To it was added DBU (Aldrich, 76 μL, 0.52 mmol, 1.2 equiv) by syringe and the reaction monitored by TLC. A fine precipitate of DBU·HBr began to appear within 15 min and after 3 h more DBU (0.3 equiv, 18 μL) was added. After 7 h no trace of starting material (R_f 0.52, $CHCl_3$) could be detected, only a new spot at R_f 0.45 and DBU at the origin. The reaction mixture was cooled to 10 °C, then pipetted into ice-cold, half-saturated aqueous NaCl (10 mL) whose pH had been adjusted to 4 using 1% HCl. A second 10-mL washing tested acid so the benzene extract was washed with cold 5% $NaHCO_3$, dried (Na_2SO_4) in an Erlenmeyer flask, and filtered into a 25-mL pear-shaped flask. (Note: both flasks were NH_3 washed and oven dried.) Removal of the solvent (0 °C, rotary evaporator) afforded 0.057 g of olefinic lactone **13b** (87%) as an oil: NMR δ (C_6D_6, NH_3-washed tube) 6.04 (dd, 1 H, J = 10.5, 3 Hz, vinyl), 5.74 (dd, 1 H, J = 10.5, 4.6 Hz, vinyl), 4.08 (d, 1 H, J = 4.6 Hz, CHO), 2.8–2.92 (m, 2 H, epoxide), 1.13 (s, 3 H, methyl); IR λ_{max} (film) 5.48 μ.

The above-mentioned NMR sample (0.057 g in 0.5 mL of C_6D_6) was immersed in a 93 °C oil bath under argon and its spectrum monitored periodically. Arene oxide **1b** began to appear immediately and its formation was complete after 5 h: NMR δ (C_6D_6) 5.8–6.2 (complex m, 3 H), 4.30, 4.45 (2 m, 2 H), 1.80 (s, 3 H, methyl). A trace of *o*-cresol was also formed (NMR δ 2.32, CH_3). Careful evaporation of the benzene at 0 °C afforded **1b** as an oil (0.030 g, 65% from **10b**).

In a duplicate experiment, maleic anhydride (sublimed, 0.037 g, 0.37 mmol) was added to the C_6D_6 solution of **1b** described above and the NMR tube heated for 5 h at 93 °C. After cooling and diluting with $CHCl_3$ (10 mL), the organic layer was washed successively with pH 4 brine, pH 9 brine, and water. Drying (Na_2SO_4) and concentration afforded 0.014 g (16% of theoretical, from **10b**) of the cycloadduct **16b:** NMR δ (C_6D_6) 5.30–5.55 (m, 2 H, vinyl), 3.0 (m, 1 H), 2.60 (m, 1 H), 2.2–2.3 (m, 2 H), 1.99 (d, 1 H, J = 10 Hz), 1.44 (s, 3 H, methyl); IR λ_{max} ($CHCl_3$) 5.45 (weak), 5.62 μ (strong).

Reaction of Lactone Benzoate 10d with DBN. Formation of 15. An ice-cold solution of **10d** (0.100 g, 0.283 mmol) in $CHCl_3$ (2 mL) was treated with DBN (Aldrich, 0.07 mL, 2.0 equiv). After 5 h, water (5 mL) was added and the layers were separated. The $CHCl_3$ phase was washed (2 × 5 mL) with cold 5% HCl and once with 5% $NaHCO_3$, dried (Na_2SO_4), and concentrated to afford 0.113 g of yellow oil. Using column chromatography on silica gel (Brinkmann, 2 g), the most polar product (R_f 0.12 in 9:1 ether–methanol) was eluted to furnish 0.033 g: NMR δ 7.3–8.2 (m, 5 H, benzoate), 4.85 (s, 2 H, CH_2O), 3.1–3.5 (complex m, 10 H, 3 CH_2 N + epoxides), 1.6–2.7 (complex m, 8 H, isolated CH_2's); IR λ_{max} 2.90, 5.81, 6.0 μ; mass spectrum (CI, isobutane) 415 (M + 1), 416 (M + 2), 123 (base peak, benzoic acid). These data are consistent with bisamide **15.**

Reaction of 10d with DBU. Synthesis of 13d and (2,3-Epoxybenzyl)benzoate 1d. When this procedure was performed on small scale (0.1–0.5 g), a 90% yield of arene oxide was obtained. The following experiment describes the formation of preparatively useful quantities of **1d** without isolating **13d.**

A 100-mL round-bottom three-necked flask and stir bar, rinsed with 28% NH_4OH and dried overnight at 145 °C, was charged with **10d** (5.97 g, 16.9 mmol) in dry benzene (30 mL). The flask was fitted with addition funnel and reflux condenser, purged with N_2, and heated to reflux. A solution of DBU (2.5 mL, 16.9 mmol) in benzene (10 mL) was added dropwise over 0.5 h. Within 5 min the solution turned yellow and began to darken; a fine precipitate of DBU·HBr appeared. Heating was continued for an additional 0.5 h. The mixture was cooled, filtered, washed twice with water (100 mL) and once with brine (100 mL), dried (Na_2SO_4), and concentrated to a dark oil. Chromatography on alumina (Woelm, activity IV, 80 g) with benzene afforded **1d** 2.20 g, 57%) as a yellow oil: NMR δ (C_6D_6) 8.13, 7.12 (2 m, 5 H, benzoate), 5.62–6.17 (complex m, 3 H), 4.75 (s, 2 H, CH_2O), 4.32, 4.48 (2 m, 2 H); IR λ_{max} (film) 5.80 μ; UV λ_{max} (isooctane) 281 nm (sh, ϵ 3700), 273, 267 (4500, no minimum), 247 (minimum), 228 (14 700); λ_{max} (95% ethanol) 267 (5100), 250 (minimum), 231 (13 600).

With maleic anhydride, **1d** formed a cycloadduct **16d** in boiling benzene: NMR δ 8.13, 7.13 (5 H, benzoate), 5.32–5.45 (m, 2 H, vinyl), 4.85, 4.62 (AB quartet, 2 H, CH_2OCO–), 2.40–3.10 (complex m, 3 H), 2.33 (s, 1 H), 2.30 (s, 1 H); IR λ_{max} ($CHCl_3$) 5.45 (weak), 5.65, 5.83 μ. The adduct was characterized as its dimethyl ester obtained by hydrolysis (K_2CO_3–H_2O–THF) and diazomethane treatment: mp 107–109 °C (CCl_4–hexane); NMR δ 8.05, 7.45 (2 m, 5 H, benzoate), 6.12, 5.82 (ABX, 2 H, J = 6, 9 Hz), 4.60 (broad s, 2 H, –CH_2OCO–), 3.59 (s, 3 H), 3.54 (s, 3 H), 3.15–3.42 (m, 5 H); IR λ_{max} ($CHCl_3$) 5.78, 5.82 μ.

Anal. ($C_{20}H_{20}O_7$) C, H.

To isolate the intermediate olefin **13d,** the dehydrobromination must be run at room temperature for 5 h. After DBU·HBr was filtered, the benzene solution was washed with half-saturated aqueous NaCl whose pH had been adjusted to 4 (1% HCl), then with 5% $NaHCO_3$ and brine, and dried (Na_2SO_4). Concentration afforded **13d:** mp 82 °C dec; NMR δ (C_6D_6) 8.10, 7.15 (2 m, 5 H, benzoate), 5.95 (dd, 1 H, J = 10.5, 3.5 Hz, vinyl), 5.65 (dd, 1 H, J = 10.5, 4.5 Hz, vinyl), 4.11–4.59 (complex m, 3 H), 3.02, 3.82 (2 m, 2 H, epoxide); IR λ_{max} 5.48 μ.

Preparation of Arene Oxide 1f from Lactone 10f. Using the procedure described above for **10b,** a solution of **10f** (0.100 g, 0.33 mmol) in benzene (10 mL) was treated with DBU (147 μL, 3.0 equiv) and stirred for 19 h at room temperature. The reaction mixture was washed with ice-cold brine, 1% HCl, and 5% $NaHCO_3$, then the organic layer was dried ($MgSO_4$) and concentrated at room temperature to afford 0.090 g of **13f** containing some benzene: NMR δ (C_6D_6) 6.05 (dd, 1 H, J = 10.5, 3 Hz, vinyl), 5.74 (dd, 1 H, J = 10.5, 4.5 Hz, vinyl), 4.50 (d, 1 H, J = 4.5 Hz, CHO), 3.85 (q, 2 H, J = 7.5 Hz), 3.08, 2.95 (2 m, 2 H, epoxide), 2.56 (s, 2 H, CH_2CO), 0.95 (t, 3 H, J = 7.5 Hz, methyl); IR λ_{max} ($CHCl_3$) 5.47, 5.79 μ.

The NMR tube containing **13f** in C_6D_6 (0.5 mL) was heated for 1 h at 50 °C, then at 70 °C for 4 h, by which time spectral analysis indicated that formation of **1f** was complete: NMR δ (C_6D_6) 5.7–6.0 (m, 3 H), 4.25, 4.38 (2 m, 2 H), 3.86 (q, 2 H, J = 7.5 Hz), 2.92 (s, 2 H, CH_2CO), 0.95 (t, 3 H, J = 7.5 Hz, CH_3). The NMR spectrum also showed the presence of ~5% of the corresponding *o*-phenol.

This NMR sample was diluted to 5 mL with benzene and heated at reflux with maleic anhydride (sublimed, 0.048 g, 1.5 equiv) for 3 h under N_2. The reaction mixture was further diluted to 30 mL with benzene, washed (3 × 5 mL) with water and once with brine, dried ($MgSO_4$), and concentrated to afford 0.078 g (85%) of almost pure solid. One recrystallization from CCl_4 produced crystals of **16f** (0.030 g, 33% from **10f**): mp 137.5–138.5 °C; NMR δ 5.65–6.05 (m, 2 H, vinyl), 4.25 (q, 2 H, J = 7.5 Hz), 3.29–3.71 (complex m, 5 H), 3.15 (s, 2 H, CH_2CO), 1.26 (t, 3 H, J = 7.5 Hz, methyl); IR λ_{max} (Nujol) 5.47 (weak), 5.60 (strong), 5.80 μ (strong); mass spectrum *m/e* 278 (M), 279 (M + 1), 233 (base).

Anal. ($C_{14}H_{14}O_6$) C, H.

Photooxygenation of 1d. Synthesis of Endoperoxide 21 and Trioxide 22. Oxygen was bubbled through a 0 °C solution of **1d** (2.24 g, 9.8 mmol) and hematoporphyrin (Sigma, 0.020 g) in EtOH–$CHCl_3$ (3:1, 40 mL) with irradiation from a sunlamp (General Electric, 275-W). When the reaction was judged complete by TLC monitoring, the reaction mixture was concentrated at room temperature and the residue filtered through alumina (Woelm, activity IV, 10 g) using $CHCl_3$. Concentration of the filtrate and trituration with ice-cold EtOH afforded 1.12 g (44%) of **21** as a white powder, mp 86.5–87 °C. Chromatography of the supernatant residue (Brinkmann silica, 50 g, 4:1 hexane–EtOAc) furnished an additional 0.56 g of **21** for a total isolated yield of 60%: NMR δ 8.10, 7.53 (2 m, 5 H, benzoate), 6.38 (m, 2 H, vinyl), 5.10 (m, 1 H, CHO_2), 4.79, 4.63 (AB quartet, 2 H, J = 12 Hz), 3.69 (m, 2 H, epoxides); IR λ_{max} ($CHCl_3$) 5.81 μ.

On boiling in dry benzene for 5–6 h, **21** rearranged to **22** in quantitative yield: mp 132–133 °C (CH_3OH); NMR δ 8.10, 7.49 (2 m, 5 H, benzoate), 4.74, 4.40 (AB quartet, 2 H, J = 12 Hz), 3.52, 3.43 (broad s, m, 5 H, epoxides); IR λ_{max} ($CHCl_3$) 5.80, 7.90 μ; mass spectrum *m/e* 260 (M^+), 105 (base).

Anal. ($C_{14}H_{12}O_5$) C, H.

Reduction of 21 with Trimethyl Phosphite. Preparation of 26. Trimethyl phosphite (0.99 g, 8.24 mmol) was added to a solution of **21** (1.07 g, 4.12 mmol) in benzene (40 mL) and after 1 h the reaction was complete (TLC monitoring). Thirty percent H_2O_2 (20 mL) was added, the layers were separated, and the organic phase was washed three times with water, once with $NaHSO_3$, and with brine and dried (Na_2SO_4). Concentration, then trituration with ether, afforded 1.11 g of solid **26,** mp 67–68 °C, which was not further purified: NMR δ 8.09, 7.51 (2 m, 5 H, benzoate), 6.09 (m, 2 H, vinyl), 4.75, 4.38 (AB quartet, 2 H, J = 12.5 Hz), 3.88 (dd, 1 H, J = 4.2, 0.9 Hz, epoxide), 3.18 (m, 2 H, epoxide); IR λ_{max} ($CHCl_3$) 5.81, 7.88 μ; mass spectrum (CI, isobutane) 245 (M + 1), 123 (base).

Hydrolysis of 26 in HOAc–THF–H_2O. Preparation of 28. A solution of **26** (0.551 g, 2.26 mmol) in THF (5 mL) was treated with 10% aqueous HOAc (5 mL) and stirred at room temperature for 30 h. The pH was adjusted to 7–8 with powdered $NaHCO_3$, and the reaction mixture was saturated with NaCl and extracted (3 × 15 mL) with EtOAc. The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), and concentrated to an oil (0.63 g). Column chromatography (25 g of silica, 2:98 CH_3OH–$CHCl_3$) afforded 0.132 g (32%) of **28:** R_f 0.40 (2:98 CH_3OH–$CHCl_3$); NMR δ 8.13, 7.58 (2 m, 5 H, benzoate), 6.30 (m, 2 H, vinyl), 5.15, 4.21 (AB quartet, 2 H, J = 13.5 Hz), 4.45–4.28 (m, 1 H, C*H*OH), 4.25–3.90 (m, 1 H, C*H*OH), 3.48 (m, 1 H, epoxide), 3.20, 2.30 (2 d, each 1 H, exchange with D_2O); IR λ_{max} (film) 2.88, 5.80, 7.88 μ.

Also eluted was 0.116 g (21%) of the 1,4-diol **29** (R_f 0.16) and 0.133 g (21%) of tetraol **30** (R_f 0.08).

Synthesis of Senepoxide 19 from 28. To a solution of **28** (0.069 g, 0.26 mmol) and 4-dimethylaminopyridine (trace) in Et_3N (1 mL) at 0 °C was added acetic anhydride (0.1 mL, 1.05 mmol). After 2 h, during which the reaction mixture slowly warmed to room temperature, CH_3OH (10 drops) and $CHCl_3$ (25 mL) were added and then the solution was washed twice with 5% HCl (15 mL) and once with $NaHCO_3$ and dried (Na_2SO_4). Concentration and filtration of the residue through a pipetful of silica gel afforded 0.088 g (98%) of *dl*-senepoxide, mp 97–98 °C (CH_3OH) having TLC characteristics and NMR and IR spectra identical with those of an authentic sample.[36]

Anal. ($C_{18}H_{18}O_7$) C, H.

Treatment of senepoxide (0.022 g) with $HClO_4$ (2 drops) in CH_3OH (10 mL) for 3 h according to Polonsky[36] afforded *dl*-seneol **19** whose NMR spectrum and behavior on TLC exactly matched those of the natural product.

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Structure and Absolute Configuration of Thienamycin

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Abstract: The structure and stereochemistry of the potent new β-lactam antibiotic thienamycin were determined as shown in formula **22.**

Thienamycin (**1**) was discovered in fermentation broths of the soil microorganism *Streptomyces cattleya*.[1] It is a novel β-lactam antibiotic[2] of exceptional antibacterial potency and spectrum including activity against *Pseudomonas* and β-lactamase producing species.[3] Since its first publication in the patent literature[4] several closely related structures have been recognized.[5-7] Recently, the first total synthesis of the antibiotic has been reported.[8] In the first part of this paper we describe the chemical and spectroscopic observations which first led to the elucidation of the new structure. In the second part we discuss the relative and absolute stereochemistry at the three chiral centers of thienamycin.

Structure of Theinamycin

Thienamycin is a zwitterionic compound with an acidic dissociation constant of ca. 3.1. Broad infrared absorption at ca. 1580 cm^{-1} is characteristic of a carboxylate anion and a sharper band at 1765 cm^{-1} is reminiscent of the β-lactam carbonyl absorption of cephalosporins and cephamycins.[9,10] The characteristic ultraviolet absorption maximum at 296–297 nm (ε 7900) in the pH range from 4 to 8 shifts to 309 nm at pH 2 and can be abolished together with biological activity by treating the antibiotic with hydroxylamine at neutral pH. ^1H and ^{13}C NMR signals of thienamycin are listed in Table I. The elemental composition $C_{11}H_{16}N_2O_4S$, mol wt 272, was deduced from field-desorption mass spectra of the antibiotic (MH^+ 273) and from high-resolution mass spectra of the derivatives **2** and **3** (Scheme I). These derivatives were first prepared when only small amounts of partially purified antibiotic were available. For each of them several spectra were averaged to obtain the most accurate *m/e* values. The resulting data sets ruled out alternative compositions which have similar fractional masses. Subsequently, the assignments were confirmed by measurements on and derivatization of the purified antibiotic. Molecular weight determination by ultracentrifugation, sulfur analysis by energy dispersive X-ray fluorescence,

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