THE JOURNAL OF Organic Chemistry

VOLUME 46, NUMBER 26

DECEMBER 18, 1981

Approaches to the Synthesis of the Mitomycins. A Route to the Mitosanes Involving Activated Cyclopropanes

Samuel Danishefsky,*[1] John Regan, and Robert Doehner

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

Received July 6, 1981

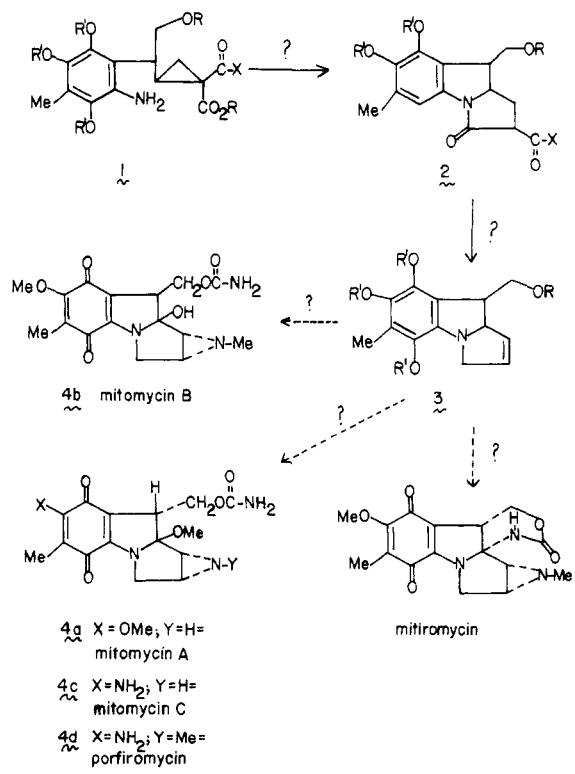
The synthesis of (9*R**,9a*S**)-9-[[(*tert*-butyldimethylsilyl)oxy]methyl]-9,9a-dihydro-5,7,8-trimethoxy-6-methyl-3*H*-pyrrolo[1,2-*a*]indole has been achieved. The key reaction involves intramolecular nucleophilic displacement of an activated cyclopropane. The modification of the electrophilicity of the diactivated cyclopropane by alteration of the geometric relationship of the carbonyl linkages with the bent bonds of the ring is an important feature of the study.

A few years ago our laboratory began an investigation into synthetic possibilities in the mitomycin area. Several objectives were defined. First, we hoped to achieve the total synthesis of, at least, some of the naturally occurring compounds. Moreover, we sought to develop a rapid entry to the general ring system, thus allowing for deep-seated structural modifications of the mitomycin skeleton. Examination of the biological consequences of such modifications might then facilitate an understanding of the mode of antitumor action of this fascinating and promising family of drugs.

Of course, the total synthesis of the natural mitomycinoids has been the object of the attentions of organic chemists since the discovery[2] of this class of compounds. The anticipated complexities associated with such an enterprise are clear upon inspection of the targets. Briefly stated, the difficulty of the problem arises from the need to deal simultaneously with the densely arrayed functionality, the high level of oxidation, the four contiguous centers of asymmetry and, above all, the unusual chemical lability of the final targets.

In fact, the only total syntheses of the naturally occurring mitomycins have been achieved by Kishi and coworkers.[3-5] The Kishi syntheses are extremely logical in their implicit analysis of the underlying problems and daring in their resultant strategy of response. Otherwise there seems little need to review here either the numerous attempts[6,7] at the total synthesis of mitomycins, their chemistry, or the spectrum of their biological activity, since

Scheme I



(1) Present address: Department of Chemistry, Yale University, New Haven, CT 06511.

(2) Lefimine, D. V.; Dann, M.; Barbatschi, F.; Hausmann, W. K.; Zbinovsky, V.; Monnikendam, P.; Adams, J.; Bohonos, N. *J. Am. Chem. Soc.* **1962**, *84*, 3184.

(3) (a) Nakatsuko, F.; Cocuzza, A. J.; Keeley, D. E.; Kishi, Y. *J. Am. Chem. Soc.* **1977**, *99*, 4835. (b) Nakatsuko, F.; Fukuyama, T.; Cocuzza, A. J.; Kishi, Y. *Ibid.* **1977**, *99*, 8115.

(4) Fukuyama, T.; Nakatsubo, F.; Cocuzza, A. J.; Kishi, Y. *Tetrahedron Lett.* **1977**, 4295.

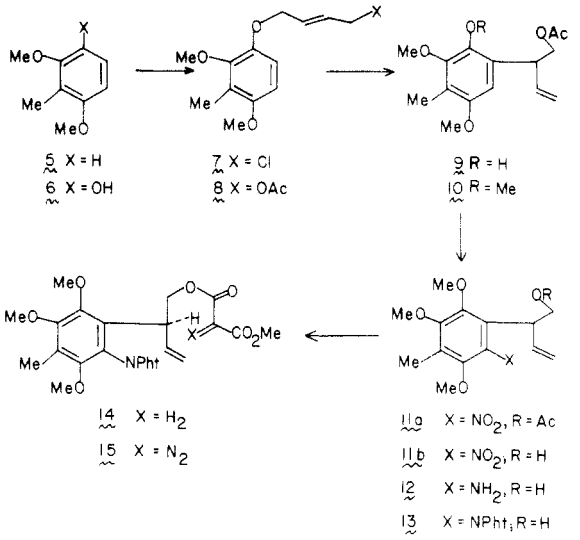
(5) Kishi, Y. *J. Nat. Prod.* **1979**, *42*, 549.

(6) Kametani, T.; Takahashi, K. *Heterocycles* **1978**, *9*, 293.

(7) Franck, R. W. *Fortschr. Chem. Org. Naturst.* **1979**, *38*, 0000.

0022-3263/81/1946-5255$01.25/0

Scheme II



these matters have been thoroughly surveyed.[8]

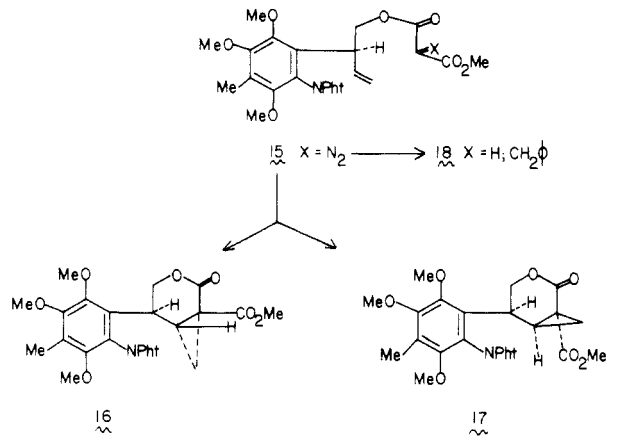
Our specific goal in this research was to achieve the synthesis of a tricyclic intermediate of the type **3** in the hope that such a structure would prove amenable toward subsequent manipulations toward some or all of the target systems, **4**. In particular it was our intention to reach series **3** through suitable functionalizations of system **2** (see Scheme I). The latter, at the planning level, would have arisen by reorganization of an activated cyclopropane of the type **1**. The chemistry of such systems and their applicability to the synthesis of natural products have been two of the concerns of our laboratory.[9a]

We had described, in communication form,[9b] the synthesis of system **2** (X = $NHNH_2$). Upon further investigation, it was found that the conversion of this version of **2** into **3** was extremely difficult. This, as well as the unacceptably low yield in reaching **2**, necessitated a substantial modification of our route, which we describe herein. In realizing this subgoal, there have been provided useful demonstrations of the interaction between geometric factors and the extent of activation of electrophilic cyclopropanes (cf. reactivity patterns of **23** vs. **35**). Ultimately, a more satisfactory synthesis of lactam ester version of **2** (i.e., X = CO_2Me; see **37**) was achieved. The conversion of such a compound into a specific variation of system **3** (R = $Si(Me)_2$-*t*-Bu; see compound **41**) is also described.

Results and Discussion

The starting material for our work was the known phenol **6** which is readily prepared from the commercially available 2,6-dimethoxytoluene (**5**; see Experimental Section). The phenyl ether **7** was obtained by the O-alkylation of **6** with 1,4-dichloro-2-butene (Scheme II). Compound **8** was obtained by "solvolysis" of **7** with sodium acetate in acetic acid. Pyrolysis of **8** in dimethylaniline resulted in a very clean Claisen rearrangement.[10] Compound **9** thus obtained was converted (sodium hydride–methyl iodide) into the trimethoxy compound **10**. Conversion of **6** → **10** could be accomplished routinely in ca. 45% yield on large scales.

Scheme III



Our next objective became the introduction of the required nitrogen functionality. In principle, this could be accomplished through the nitration of **10**. In practice, we had great difficulty in realizing the nitration of **10** under standard conditions. In addition to the desired nitro product **11a** there was obtained extensive quantities of quinone, resulting from oxidative demethylation of the "electron-rich" aromatic system.[11]

Eventually it was found that nitration, to the exclusion of oxidative demethylation, could be achieved by the reaction of **10** with mercuric acetate in nitric acid.[12] Compound **11a**, thus obtained in 66% yield, was converted to the amino compound **12** by hydrolysis and reduction. Reaction of **12** with phthalic anhydride and triethylamine in toluene gave the protected phthalimide **13**. Unfortunately, the transformation of **11** to **13** was only accomplished in 33% yield. Most of the losses were apparently sustained in the phthaloylation of the hindered amine.

In anticipation of eventual cyclopropanation,[13] compound **13** was acylated with (carbomethoxy)acetyl chloride,[14] thereby affording the "half-malonate" **14**, which was converted to **15** by standard means.[15]

Previous experiences[16] in our laboratory tended to suggest that the major cyclopropanation product of **15** would be the one in which the bulky substituent, in this case the hexasubstituted phenyl group, would emerge on the convex face of the bicyclo[4.1.0] ring system. Of course, these experiences had been gathered in synthetic studies in the pyrrolizidine alkaloid series[9,16] which involved the formation of more rigid [3.1.0] ring systems. Also, the double bond in those cases was uniformly disubstituted.[16] The yields for such internal cyclopropanations tended to be in the order of 60–70%.

Compound **15** was thermolyzed in toluene under reflux in the presence of cupric acetonylacetonate, thereby affording a 35% yield of a 5:1 mixture of the two phthalimidocyclopropanes **16** and **17** (Scheme III). In addition, there was isolated in variable yield the diastereomeric C–H insertion products **18**. Only a slight improvement in yield (42%) was realized by conducting the reaction in chloro-

(8) Remers, W. A., "The Chemistry of Antitumor Antibiotics"; Wiley-Interscience: New York, 1979; Vol. 1.

(9) (a) Danishefsky, S. *Acc. Chem. Res.* **1979**, *12*, 66. (b) Danishefsky, S.; Doehner, R. *Tetrahedron Lett.* **1977**, 3033.

(10) The phenoxy radical, generated in the limiting sense by heterolysis of the ally group, may be extensively stabilized by the two methoxy groups. This may account for the excellent quality of the Claisen rearrangement.

(11) It will be recalled that oxidative demethylation of a similar system was a deliberate step in the Kiski synthesis.[3]

(12) Stock, L. M.; Wright, T. L. *J. Org. Chem.* **1977**, *42*, 2875.

(13) Burke, S. D.; Grieco, P. A. *Org. React.* **1979**, *26*, 361.

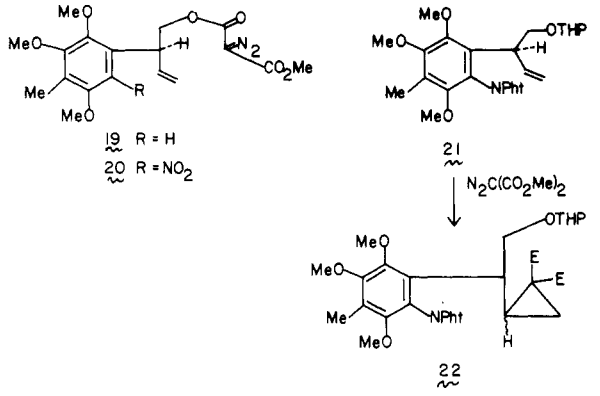
(14) Cf.: Coson, J. "Organic Syntheses"; Wiley: New York, 1955, Collect. Vol. III, p 169.

(15) Regitz, M. *Justus Liebigs Ann. Chem.* **1964**, *676*, 101.

(16) Danishefsky, S.; McKee, R.; Singh, R. K. *J. Am. Chem. Soc.* **1977**, *99*, 7711.

benzene, where intermolecular benzylic insertion would not be possible. Other changes in solvents (*tert*-butylbenzene, nitrobenzene) and catalysts (copper metal, rhodium salts[17]) provided no improvement in the yield of cyclopropanation.

Even less success was forthcoming in studying the cyclopropanation of other substrates. Indeed, attempted intramolecular reaction of **19** or **20**, easily obtained in analogous ways from **10** and **11**, respectively, afforded no detectable cyclopropane. Moreover, attempted intermolecular cyclopropanation of **21** with dimethyl diazomalonate afforded a very low yield of a 1:1 mixture of diastereomers of **22** (vide infra).

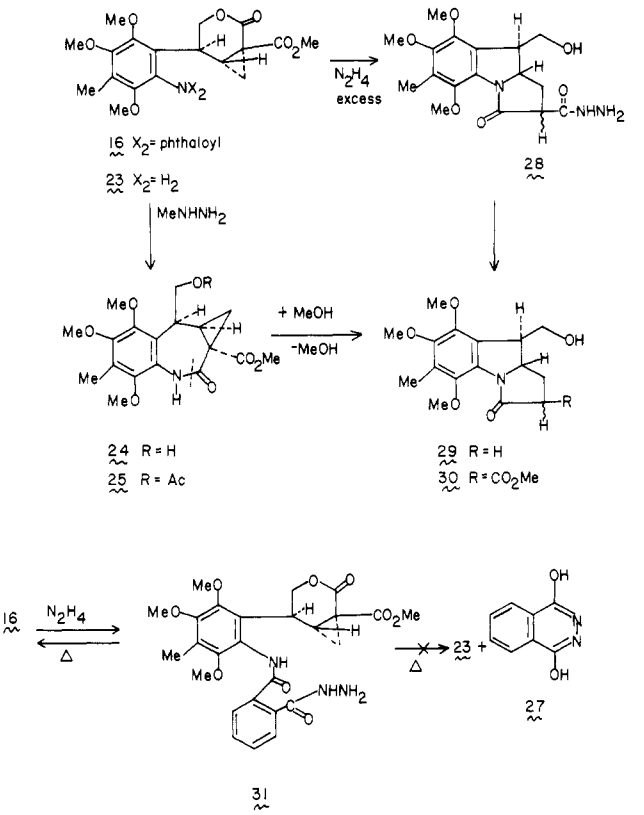


The assignment of stereochemistry to the major product (**16**) was tentative at this point. It was based largely on the precedents alluded to above. In the 250-MHz NMR spectrum of the major product, the signals from the three protons of the cyclopropane ring are all fully resolved (see Experimental Section). In the spectrum of the minor product, the corresponding protons give rise to a broad multiplet in the region δ 2.0. These data do not per se allow for the assignment of stereochemistry in the manner indicated. Subsequent correlations of compound **41**, prepared via a completely different route from that shown here,[18] strongly tend to confirm the correctness of the assignments.

We next examined the feasibility and consequences of the dephthaloylation of **16**. Reaction of **16** with 2 equiv of methylhydrazine in chloroform under reflux afforded a dephthaloylated product in 86% yield (Scheme IV). Infrared, NMR, and mass spectral analyses suggested this to be compound **24**. This assignment was fully confirmed by NMR analysis of its derived (pyridine–acetic anhydride) acetate, **25**. Apparently compound **23** is, in fact, produced on dephthaloylation. However, the ability of the carbonyl group of the lactone to function as an acylating agent transcends that of the activated cyclopropane to act as an alkylating agent. This was a surprising result since in our previous work in the pyrrolizidine series, and indeed in a model system closely related to **23**, the reverse tendency prevailed.[15,16,19]

In a parallel series of experiments, the action of excess hydrazine on **16** was examined. With roughly stoichiometric equivalents of hydrazine, there was obtained a new product. Though its mass spectrum, m/e 495, suggests it to be an isomer of **16**, its infrared (2.8–3.1 μm) and NMR [$CDCl_3$; δ 7.2–8.0 (4 H, br m)] spectra[20] indicated it to be the "half-cleavage" product **31**. Unfortunately, pyrolysis

Scheme IV



of **31**, carried out in an attempt to reach amino compound **23**, in fact regenerated the starting **16**.

In an attempt to achieve "complete" dephthaloylation, excess hydrazine was employed. Indeed, reaction of **16** in hot methanol with 5 equiv of hydrazine led to such a result. After filtration of the phthalhydrazide **27**, a highly polar residue was obtained. The signals in the NMR spectrum of this crude material were surprisingly broad but seemed to fall in the regions expected for compound **28**. Chromatography of this poorly behaved material on silica gel and elution with 15% methanol in benzene afforded a 20% yield of a mixture of epimers which, upon trituration with ether, gave a solid material melting from 160 to 165 °C. The infrared, NMR, and high-resolution mass spectra of this substance are all supportive of its being **28**.[21]

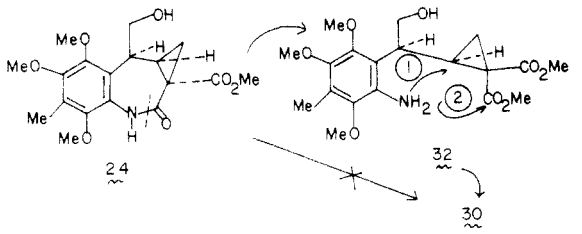
Unfortunately, in our hands compound **28** did not prove to be amenable to efficient elaboration toward the target systems. Many attempts to achieve deacylation of the extraneous hydrazinocarbonyl function by vigorous acidic and basic hydrolysis also resulted in opening of the lactam ring with the formation of highly water soluble products. Attempts to deal with the presumed bicyclic amino acid corresponding to **29** by esterification and cyclization gave vanishingly low yields of a compound presumed to be **29** by comparison of its infrared and TLC, properties with those of material obtained in another way (vide infra). Again, in poor yield we could achieve (methanol–chloral[22]) the transformation of **28** to the more manageable mixture of methyl ester epimers **30**.

A slightly improved route to the tricyclic esters **30** was realized by the methanolysis of **24**. The reaction was carried out in methanol containing a catalytic amount of sodium methoxide in a sealed tube at 135 °C. The predominant material received was, in fact, recovered starting

(17) Hubert, A. J.; Noels, A. F.; Anciaux, A. J.; Teyssie, P. *Synthesis* **1976**, 600.
(18) Berman, E., Yale University, private communication.
(19) Danishefsky, S.; Doehner, R. *Tetrahedron Lett.* **1977**, 3031.
(20) The NMR spectra of **13–16** revealed a symmetrical pattern for the phthalimido protons. However, **31** showed protons having an unsymmetrical character.
(21) For experimental details describing these transformations see the Ph.D. dissertation of R.D., University of Pittsburgh, Pittsburgh, PA, 1978.
(22) Kametani, T.; Umezawa, O. *Chem. Pharm. Bull.*, **1966**, *14*, 369.

material. However, in ca. 20% yield there could be obtained the lactam esters **30**. Also from this reaction there could be isolated traces of **29**, apparently arising from the decarbomethoxylation of **30**. As noted above, the TLC and NMR properties of **29** obtained via hydrazide **28** were the same as those of the material obtained in this fashion via **24**.

Although from a synthetic standpoint we never mastered the conditions required to bring about a high yield conversion of **24** to **30**, the mechanism of this transformation is of some interest. No experiments were performed in this connection. Nevertheless, we would regard the "direct" conversion (cf. arrows **24** → **30**) as unlikely. It is recog-



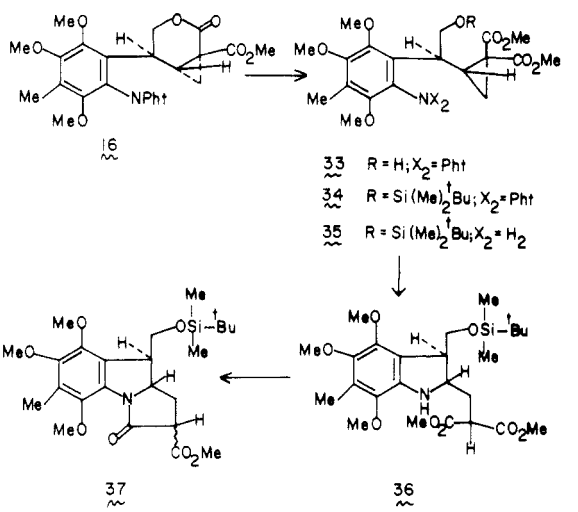
nized that this direct process corresponds to a front-side displacement on the activated cyclopropane. A more likely pathway would appear to involve methanolysis of the lactam to afford the hydroxy diester **32**. The latter could then participate in the usual pyrrolizidine-forming process of activated cyclopropanes.[9]

Following these failures to produce ample amounts of compound **29** or **30**, it was reasoned that greater success might be achieved if the lactone ring of starting material **16** could be opened prior to release of the amino group. Two considerations guided this initiative. First, it was hoped that in a diester such as **35**, the reactivity of the cyclopropane functionality might be greater since the relevant π orbitals of both carbonyl groups[9] are now well-disposed to activate the cyclopropane. By contrast, in system **23** the π system of the lactone carbonyl linkage is approximately orthogonal to the "spiro mode"[9] bond of the cyclopropane. Accordingly, it could be hoped that in **35**, as opposed to **23**, alkylation by the activated cyclopropane would predominate over acylation. Furthermore, it was anticipated that removal of the amino function from a precursor such as **33** or **34** could be more selectively accomplished than was the case from a precursor such as **16** where competitive acylation of the hydrazino nucleophile by the strained lactone had created additional complications.

Accordingly, lactone **16** was treated with methanol under reflux in the presence of a catalytic amount of camphorsulfonic acid. There was thus obtained the hydroxydiester **33**, mp 160–165 °C (Scheme V). The hydroxyl group could be protected as an OTHP derivative, thereby giving rise to one of the components of the mixture, **22** (NMR analysis), whose preparation in a nonstereospecific way via **21** was described above. More satisfactorily, the hydroxyl group was protected as its *tert*-butyldimethylsilyl ether, giving **34**: mp 132–133 °C; 87% yield.

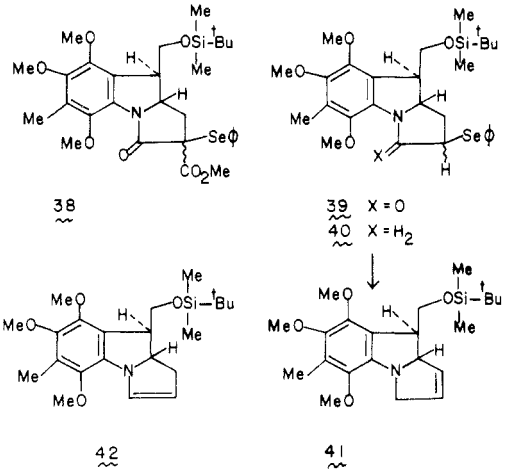
On the basis of our results in the lactone series, compound **34** was subjected to the action of methylhydrazine in methanol under reflux. After 80 h there was obtained an 81% yield of **36**. With the intermediate **36** well characterized and firmly in hand, we could now determine that its cyclization to a tricyclic lactam was far from an automatic matter. This was accomplished preparatively in 58% yield by thermolysis of **36** in toluene in the presence of camphorsulfonic acid. Hence the transformation of the major phthalimidocyclopropane to the manageable lactam

Scheme V



esters **37** could be accomplished in 30–35% yield. The NMR spectrum of **37** thus obtained was very similar to that of the hydroxy compound **30** which was obtained both from **24** and **38** (vide supra).

We then sought to exploit the β-dicarbonyl functionality to introduce a phenylseleno function α to the lactam center. This could be conveniently accomplished with sodium hydride and phenylselenenyl chloride. There were obtained (77% yield) the diastereomeric phenylselenenyl esters **38**, mp 126–127 °C. Hydrolysis (KOH–THF, 0 °C) of **38** followed by decarboxylation (toluene, reflux, 60 min) afforded the diastereomeric lactam selenide epimers **39**. The now extraneous lactam carbonyl group underwent smooth reduction with borane–THF to afford (83% yield) the selenide diastereomers **40**.



The stage was set for the crucial elimination reaction. To the best of our knowledge there were no precedents describing the elimination of structurally analogous phenylseleno pyrrolidines. Our reliance was placed on rather less precise precedents from the experiments of Sharpless.[23] A trend could be discerned which suggested that in the elimination of α-heterosubstituted selenoxides there might be expected a preponderance of the allylic, rather than the vinylic, heterosubstituted system.

Happily, reaction of **40** with hydrogen peroxide afforded, by oxidative elimination, the long desired type **3** (vide supra) system in the form of its *tert*-butyldimethylsilyl derivative **41**. We could detect none of the alternate en-

(23) Sharpless, K. B.; Lauer, R. F. *J. Org. Chem.* **1974**, *39*, 429.

amine product **42**. Of course, since the yield of homogeneous **41** was only 55% and since **42** might well be a highly labile system, we cannot rule out the possibility of competition in the elimination step.

Overall then, the ester β-dicarbonyl functionality of lactam ester of **35** was converted to the desired $\Delta^{1,2}$ system **41** in a 20% yield over five steps. The yield of this compound from the readily available phthalmido diazoester is ca. 2%. The results of continuing experiments aimed at synthesis in the mitomycin area will be disclosed shortly.

Experimental Section[24]

4-Chloro-1-[(2,4-dimethoxy-3-methylphenyl)oxy]but-2-ene (7). To 60 g (1.25 mol) of pentane-washed 50% NaH in 300 mL of DMF at 0 °C under nitrogen was added a solution of 200 g (1.19 mol) of 2,4-dimethoxy-3-methylphenol (**6**)[25] in 1 L of DMF over a period of 1 h. Stirring was continued for an additional 1 h, whereupon 500 mL (4.7 mol) of *trans*-1,4-dichlorobut-2-ene was added. The mixture was heated at 100 °C for 15 h. The reaction mixture was cooled, diluted with ether, and washed with water and brine. The organic layer was dried, and the volatiles were removed in vacuo. Excess dichlorobutene was removed with heating (not exceeding 100 °C) on a vacuum pump to afford 263 g (85.7%) of ether **7**: NMR δ ($CDCl_3$) 6.64 (1 H, d, J = 9 Hz), 6.43 (1 H, d, J = 9 Hz), 5.95 (2 H, m), 4.47 (2 H, m), 4.03 (2 H, m), 3.77 (3 H, s), 3.73 (3 H, s), 2.13 (3 H, s); mass spectrum, m/e 256 (P). Anal. Calcd for $C_{13}H_{17}O_3Cl$: C, 60.79; H, 6.67. Found: C, 60.59; H, 6.85.

4-Acetoxy-1-[(2,4-dimethoxy-3-methylphenyl)oxy]but-2-ene (8). To 263 g (1.02 mol) of **7** was added 210 g (2.5 mol) anhydrous sodium acetate in 1.1 L of acetic acid. This mixture was heated under reflux for 14 h. The cooled solution was diluted with 1 L of ether, washed with ten 1-L portions of water, saturated sodium bicarbonate, and brine, and then dried over anhydrous $MgSO_4$. Solvent removal afforded 255 g (0.91 mol) of crude ether **8**: NMR δ ($CDCl_3$) 6.71 (1 H, d, J = 9 Hz), 6.47 (1 H, d, J = 9 Hz), 5.98 (2 H, m), 4.55 (4 H, m), 3.80 (3 H, s), 3.75 (3 H, s), 2.15 (3 H, s), 2.05 (3 H, s); IR ($CHCl_3$) $\bar{\nu}_{max}$ 1730 cm^{-1}; mass spectrum, m/e 280 (P). Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.14; H, 7.21.

4-Acetoxy-3-(2-hydroxy-3,5-dimethoxy-4-methylphenyl)-but-1-ene (9). Crude ether **8** was mixed with 255 mL of *N,N*-dimethylaniline and heated at 200 °C for 1 h. The cooled solution was diluted with 1 L of chloroform and washed with six 500-mL portions of 10% HCl, followed by saturated sodium bicarbonate. Drying over anhydrous $MgSO_4$ and vacuum distillation gave 153 g of phenol **9** in 45% overall yield from **6**: bp 135–160 °C (0.1 mm); NMR δ ($CDCl_3$) 6.37 (1 H, s), 6.37–5.80 (1 H, m), 5.58 (1 H, s), 5.28–4.88 (2 H, m), 4.47–3.74 (3 H, m), 3.73 (6 H, s), 2.13 (3 H, s), 2.00 (3 H, s); IR ($CHCl_3$) $\bar{\nu}_{max}$ 3500, 1748 cm^{-1}; mass spectrum, m/e 280 (P). Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.37; H, 7.25.

4-Acetoxy-3-(2,3,5-trimethoxy-4-methylphenyl)but-1-ene (10). To 26.1 g (0.54 mol) of pentane-washed 50% NaH in 340 mL of DMF at 0 °C was added 138 g (0.493 mol) of phenol **9** in 680 mL of DMF over 1 h. Stirring was continued for an additional 0.5 hours, whereupon 34 mL of methyl iodide (0.54 mol) was added. The reaction was stirred at room temperature for 19 h, diluted with 1.5 L of chloroform, washed with seven 2-L portions of water and with brine, and dried. Solvent removal afforded the theoretical amount of **10** as an oil: NMR δ ($CDCl_3$) 6.42 (1 H, s), 6.40–5.80 (1 H, m), 5.38–5.00 (2 H, m), 4.53–4.05 (3 H, m), 3.83 (9 H, s), 2.12 (3 H, s), 2.02 (3 H, s); IR ($CHCl_3$) $\bar{\nu}_{max}$ 1745 cm^{-1}; mass spectrum, m/e 294 (P). Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.09; H, 7.63.

3-(2,3,5-Trimethoxy-4-methyl-6-nitrophenyl)but-1-en-4-ol (11b). A mixture of 56 g (0.190 mol) of **10** and 1.54 g (4.83 mmol) of mercuric acetate in 550 mL of acetic acid and 1650 mL of acetic anhydride was heated at 90 °C for 15 min. The solution was cooled to 2 °C in an ice bath, and 80 g of 90% HNO_3 was added dropwise over 30 min. The reaction was stirred an additional 30 min at 2 °C and then poured onto a mixture of 1 L of chloroform and 2 L of ice–water. The organic layer was separated and washed with four 2-L portions of cold 5% NaOH, with water, and with brine. The solution was dried, and the volatiles were removed in vacuo. The residue was dissolved in 300 mL of methanol. To the cooled solution was added dropwise a solution of 100 g of NaOH in 100 mL each of water and methanol. The solution was stirred at room temperature for 19 h. The cooled solution was acidified with concentrated HCl and extracted with chloroform. The organic layers were combined, washed with saturated sodium bicarbonate, and dried. The volatiles were removed, and the residue was chromatographed on 730 g of silica gel with 3:1 hexane–ethyl acetate and 7:3 hexane–ethyl acetate as eluants to afford 37.6 g (66.5%) of **11b**: NMR δ ($CDCl_3$) 6.35–5.80 (1 H, m), 5.30–4.92 (2 H, m), 4.08–3.42 (12 H, m, containing 3 s (3 H each) at 3.85, 3.82, and 3.78), 2.20 (3 H, s), 1.81 (1 H, br s); IR ($CHCl_3$) $\bar{\nu}_{max}$ 3500, 1515 cm^{-1}; mass spectrum, m/e 297 (P). Anal. Calcd for $C_{14}H_{19}NO_6$: C, 56.56; H, 6.44. Found: C, 56.71; H, 6.54.

3-(2,3,5-Trimethoxy-4-methyl-6-phthalimidophenyl)but-1-en-4-ol (13). To 35 g (0.118 mol) of **11b** dissolved in 200 mL of methanol was added 200 mL of concentrated HCl. The solution was rapidly stirred in a round-bottomed flask equipped with a condenser. To the mixture was added 56 g (0.85 mol) of zinc dust over a 25-min period at such a rate as to maintain vigorous reaction. Upon completion of the zinc addition, the reaction was stirred an additional 2 h. Excess metal was filtered and washed with 10% HCl. The combined filtrates were extracted once with chloroform. The aqueous layer was cooled in an ice bath and made basic with 1 L of 20% aqueous potassium hydroxide. The aqueous suspension was extracted with chloroform; the extracts were combined with the prebasificiation extract, washed with water and brine, and dried. Solvent removal gave 28.8 g of an oil. This material was mixed with 24 g (0.162 mol) of phthalic anhydride and 3 mL of triethylamine in 400 mL of toluene. This mixture was heated at reflux under a water separator for 2 h. Silica gel chromatography using 2:1 hexane–acetone as the eluant followed by crystallization from ether afforded 15.76 g of **13** in 33.5% overall yield from **11b**: mp 144–145 °C; NMR δ ($CDCl_3$) 8.00–7.58 (4 H, m), 6.32–5.78 (1 H, m), 5.08–4.77 (2 H, m), 4.02–3.32 (12 H, m, containing 3 s (3 H each) at 3.87, 3.83, and 3.52), 2.32–2.12 (4 H, m, containing a singlet (3 H) at 2.20); IR ($CHCl_3$) $\bar{\nu}_{max}$ 3500, 1786, 1739 cm^{-1}; mass spectrum, m/e 397 (P). Anal. Calcd for $C_{22}H_{23}NO_6$: C, 66.49; H, 5.83; N, 3.52. Found: C, 66.39; H, 5.83; N, 3.48.

Methyl [3-(2,3,5-Trimethoxy-4-methyl-6-phthalimidophenyl)but-1-en-4-yl]malonate (14). To 0.500 g (1.26 mmol) of **13** dissolved in 0.5 mL each of ether and pyridine, cooled to 0 °C under nitrogen, was added 240 mg (1.76 mmol) of (carbomethoxy)acetyl chloride in a dropwise manner. After being stirred at 0 °C for 90 min, the reaction mixture was diluted with 2 mL of ether. To this was added 160 mg (1.17 mmol) of (carbomethoxy)acetyl chloride in two portions over a 3-h period. After the mixture was stirred a total of 5 h, the reaction was quenched by the addition of ether and water. The organic layer was washed with 2% HCl, saturated sodium bicarbonate, water, and brine. Drying and solvent removal was followed by chromatography on silica gel with 7:3 hexane–ethyl acetate as the eluant. This process afforded 540 mg (86%) of **14** as an oil: NMR δ ($CDCl_3$) 8.00–7.55 (4 H, m), 6.28–5.68 (1 H, m), 5.20–4.75 (2 H, m), 4.58–4.20 (2 H, m), 3.95–3.47 (13 H, m, containing 4 s (3 H each) at 3.85, 3.81, 3.61, and 3.51), 3.29 (2 H, s), 2.20 (3 H, s); IR ($CHCl_3$) $\bar{\nu}_{max}$ 1725 cm^{-1}; mass spectrum, m/e 497 (P). Anal. Calcd for $C_{26}H_{27}NO_9$: C, 62.77; H, 5.47; N, 2.82. Found: C, 62.52; H, 5.60; N, 2.71.

Methyl 3-(2,3,5-Trimethoxy-4-methyl-6-phthalimidophenyl)but-1-en-4-yl Diazomalonate (15). A solution of 13.31 g (26.8 mmol) of **14**, 5.83 g (29.6 mmol) of tosyl azide, and 4.11 mL of triethylamine in 65 mL of acetonitrile was stirred at room temperature under nitrogen for 20 h. The reaction was diluted with 500 mL of ether and washed with two 350-mL portions of

(24) Melting points are uncorrected. Infrared spectra were obtained on Perkin-Elmer 137 or 247 spectrophotometers. NMR spectra were measured in the indicated solvents with tetramethylsilane as an internal standard. Chemical shifts are reported in parts per million (δ) from the Me_4Si resonance. High-resolution mass spectra were obtained on a Varian MAT CH-5 instrument by the direct-inlet method and by using a peak matcher. Combustion analyses were conducted by Galbraith Laboratories, Inc.

(25) Royer, R.; Demerseman, P.; Laval-Jeantet, A.-M.; Rossignol, J.-F.; Cheutin, A. *Bull. Soc. Chim. Fr.* **1968**, 1026.

cold 8% aqueous KOH, two 350-mL portions of cold 2% aqueous KOH, 350 mL of water, and brine. The dried solution was stripped of its volatiles and triturated with pentane to afford 11.15 g (80%) of **15**: mp 153–155 °C; NMR δ ($CDCl_3$) 8.13–7.73 (4 H, m), 6.38–5.83 (1 H, m), 5.18–4.47 (4 H, m), 4.00–3.45 (13 H, m, containing 4 s (3 H each) at 3.93, 3.87, 3.80, and 3.58), 2.23 (3 H, s); IR ($CHCl_3$) $\bar{\nu}_{max}$ 2128, 1786, 1748, 1730 cm^{-1}; mass spectrum, *m/e* 523 (P). Anal. Calcd for $C_{26}H_{25}N_3O_9$: C, 59.65; H, 4.81; N, 8.03. Found: C, 59.81; H, 4.96; N, 7.87.

Preparation of Lactone Cyclopropanes 16 and 17. A solution of **15** (0.400 g, 0.765 mmol) and $Cu(acac)_2$ in 4 mL of chlorobenzene (distilled from NaH) was heated at 125 °C for 1 h and cooled to room temperature. Chromatography on silica gel (50 g) with 33% ethyl acetate in hexanes as the eluant afforded 0.1328 g (35%) of **16** as the less polar isomer [mp 242–243 °C (from ether)], and 26.6 mg (7%) of **17** as the more polar isomer, mp 244–245 °C (from benzene–pentane).

Less polar isomer: NMR δ ($CDCl_3$) 8.00–7.65 (4 H, m), 4.71 (1 H, dd, *J* = 10.60, 10.60 Hz), 4.11 (1 H, dd, *J* = 4.96, 10.60 Hz), 3.93 (3 H, s), 3.85 (3 H, s), 3.77 (3 H, s), 3.57 (3 H, s), 2.82 (1 H, ddd, *J* = 5.43, 5.56, 9.01 Hz), 2.36 (1 H, ddd, *J* = 4.96, 5.43, 10.60 Hz), 2.25 (3 H, s), 1.98 (1 H, dd, *J* = 5.56, 9.01 Hz), 1.10 (1 H, dd, *J* = 5.56, 5.56 Hz); IR ($CHCl_3$) $\bar{\nu}_{max}$ 1775, 1725 cm^{-1}; mass spectrum, *m/e* 495 (P). Anal. Calcd for $C_{26}H_{25}NO_9$: C, 63.03; H, 5.09; N, 2.83. Found: C, 63.25; H, 5.20; N, 2.79.

More polar isomer: NMR δ ($CDCl_3$) 8.00–7.65 (4 H, m), 4.48 (1 H, dd, *J* = 11.25, 11.25 Hz), 4.14 (1 H, m), 4.00–3.45 (13 H, m, containing 4 s (3 H each) at 3.90, 3.81, 3.67, and 3.50), 3.35–1.95 (6 H, m, containing a singlet (3 H) at 3.28); IR ($CHCl_3$) $\bar{\nu}_{max}$ 1775, 1760, 1725 cm^{-1}; mass spectrum, *m/e* 495 (P). Anal. Calcd for $C_{26}H_{25}NO_9$: C, 63.03; H, 5.09; N, 2.83. Found: C, 63.25; H, 5.20; N, 2.73.

Preparation of Benzazepin-2-one 24. A solution of 160 mg (0.323 mmol) of **16** in 2.0 mL of chloroform containing 34.3 μL (0.64 mmol) of methylhydrazine was heated 70 °C for 18 h. The cooled mixture was filtered, and the filtrate was placed on a 20-g silica gel column. The column was eluted with 2:1 ethyl acetate–benzene, and the fractions containing the product were stripped of their volatiles. The residue was redissolved in chloroform, the mixture was filtered, and the volatiles were removed to afford 101 mg (86%) of **24** as an oil.

For spectral purposes, compound **24** was acetylated with acetic anhydride and pyridine to afford the corresponding acetate, **25**: NMR δ ($CDCl_3$) 7.59 (1 H, br s), 4.44–3.96 (3 H, m), 3.85 (3 H, s), 3.83 (3 H, s) 3.75 (3 H, s), 3.64 (3 H, s), 2.18 (3 H, s), 1.98 (3 H, s), 1.96–1.20 (3 H, m); IR ($CHCl_3$) $\bar{\nu}_{max}$ 3400, 1748, 1742, 1678 cm^{-1}; mass spectrum, *m/e* 407 (P). Anal. Calcd for $C_{20}H_{25}NO_8$: C, 58.96; H, 6.19; N, 3.44. Found: C, 59.14; H, 6.47; N, 3.54.

Dimethyl (*R)-2-[(*R**)-α-(Hydroxymethyl)-2,3,5-trimethoxy-4-methyl-6-phthalimidobenzyl]-1,1-cyclopropanedicarboxylate (33).** A solution of **16** (0.4351 g, 0.879 mmol) and camphorsulfonic acid (40 mg, 0.172 mmol) in 90 mL of absolute methanol was heated under reflux for 4 h. The cooled solution was concentrated in vacuo and the residue chromatographed on silica gel (40 g). Elution with 25% ethyl acetate in hexanes afforded 0.4050 g (87%) of hydroxy diester **33**: mp 160–161 °C; NMR δ ($CDCl_3$) 7.95 (4 H, m), 4.00–3.75 (8 H, m, containing 2 s (3 H each) at 3.97 and 3.90), 3.70 (3 H, s), 3.57 (3 H, s), 3.29 (3 H, s), 2.35 (2 H, m), 2.24 (3 H, s), 1.25 (2 H, m); IR ($CHCl_3$) $\bar{\nu}_{max}$ 3490, 1710 cm^{-1}; mass spectrum, *m/e* 527 (P), calcd for $C_{27}H_{29}NO_{10}$ 527.1791, found 527.1803.

Dimethyl (*R)-2-[(*R**)-α-[(*tert*-Butyldimethylsiloxy)methyl]-2,3,5-trimethoxy-4-methyl-6-phthalimidobenzyl]-1,1-cyclopropanedicarboxylate (34).** A solution of **33** (0.3359 g, 0.637 mmol), *tert*-butyldimethylchlorosilane (0.9559 g, 6.37 mmol), 4-pyrrolidinopyridine (60 mg, 0.405 mmol), 2 mL of triethylamine (distilled from CaH_2), and 25 mL of methylene chloride (distilled from CaH_2) was stirred at room temperature under nitrogen for 12 h. The solution was washed twice with 3% H_2SO_4, H_2O, and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on 25 g of silica gel. Elution with 50% ethyl acetate in hexanes afforded 0.3783 g (87%) of the silyl ether **34**: mp 132–133 °C; ^1H NMR δ ($CDCl_3$) 7.94 (4 H, m), 4.10–3.50 (14 H, m, containing 4 s (3 H each) at 3.88, 3.83, 3.63, and 3.53), 3.13 (3 H, br s), 2.52 (1 H, m), 1.90 (3 H, s), 1.26 (2 H, m), 0.81 (9 H, s), 0.05 (6 H, s); ^{13}C NMR δ (C_6H_6) 170.75, 169.19, 168.54, 153.99, 153.08, 149.83, 149.18, 134.37, 133.72, 132.94, 131.25, 130.08, 126.83, 125.92, 124.10, 122.02, 66.53, 61.34, 60.68, 59.77, 52.37, 36.25, 32.23, 26.64, 19.10, 10.26. -4.94; IR ($CHCl_3$) $\bar{\nu}_{max}$ 1715 cm^{-1}; mass spectrum, *m/e* 641 (P), calcd for $C_{29}H_{34}NO_{10}Si$ 584.1952, found 584.1955.

Dimethyl [[(2*R,3*S**)-3-[(*tert*-Butyldimethylsiloxy)methyl]-4,5,7-trimethoxy-6-methyl-2-indolinyl]methyl]malonate (36).** A solution of **34** (0.5018 g, (0.783 mmol), methyl hydrazine (freshly distilled from BaO; 54.1 μL, 1.02 mmol), and 2.7 mL of $CHCl_3$ (distilled from CaH_2) was heated under reflux for 19 h, whereupon 54.1 μL of methylhydrazine was added. Heating was continued for 29 h, and an additional 27.1 μL of methyl hydrazine was added. The solution was heated at reflux for 12 h, cooled, filtered, and concentrated in vacuo. The residue chromatographed on silica gel (20 g). The material obtained upon elution with 33% ethyl acetate in hexanes was dissolved in 5 mL of absolute MeOH. The solution was heated at reflux for 20 h and concentrated in vacuo. Chromatography of the residue on silica gel (20 g) with 33% ethyl acetate in hexanes as the eluant afforded 0.3249 g (81%) of dihydroindole **36**: NMR δ ($CDCl_3$) 4.03, (1 H, dd, *J* = 4, 10 Hz), 3.80–3.50 (18 H, m, containing 5 s (3 H each) at 3.84, 3.75, 3.74, 3.73, and 3.69), 3.23 (1 H, m), 2.35–2.05 (5 H, m, containing a singlet (3 H) at 2.14); IR ($CHCl_3$) $\bar{\nu}_{max}$ 3390, 1730 cm^{-1}; mass spectrum, *m/e* 511 (P), calcd for $C_{25}H_{42}NO_8Si$ 511.2601, found 511.2588.

Methyl (9*R,9a*S**)-9-[(*tert*-Butyldimethylsiloxy)methyl]-2,3,9,9a-tetrahydro-5,7,8-trimethoxy-6-methyl-3-oxo-1*H*-pyrrolo[1,2-*a*]indole-2-carboxylate (37).** A solution of **36** (0.2894 g, 0.566 mmol), and a camphorsulfonic acid (29 mg, 0.125 mmol) in 3.6 mL of toluene (distilled from CaH_2) was heated under reflux for 1 h, cooled, and concentrated in vacuo. Rapid chromatography on 20 g of silica gel with 50% ethyl acetate in hexanes as the eluant afforded 0.1566 g (58%) of lactam ester **37**: NMR δ ($CDCl_3$) 4.80–4.20 (1 H, m), 4.00 (1 H, m), 3.85–3.30 (15 H, m, containing 3 s at 3.80 (6 H), 3.78 (3 H), 3.76 (3 H)), 2.70–2.40 (2 H, m), 2.16 (3 H, s), 0.90 (9 H, s), 0.05 (6 H, s); IR ($CHCl_3$) ν_{max} 1730, 1700 cm^{-1}; mass spectrum, *m/e* 479 (P), calcd for $C_{24}H_{37}NO_7Si$ 479.2339, found 479.2339.

Methyl (9*R,9a*S**)-9-[*tert*-Butyldimethylsiloxy)methyl]-2,3,9,9a-tetrahydro-5,7,8-trimethoxy-6-methyl-3-oxo-2-(phenylselenyl)-1*H*-pyrrolo[1,2-*a*]indole-2-carboxylate (38).** A suspension of NaH (50%, pentane washed; 29.6 mg, 0.617 mmol) in 1.2 mL of anhydrous tetrahydrofuran (THF) was stirred under nitrogen at 0 °C. The slurry was treated dropwise with a solution of **37** (0.2468 g, 0.5141 mmol) in 3.2 mL of anhydrous THF. After the addition was complete, the mixture was stirred 20 min, whereupon a solution of phenylselenyl chloride (0.1279 g, 0.6683 mmol) in 1.2 mL of anhydrous THF was added in a single portion. After the mixture was stirred 10 min, the reaction was quenched with saturated $NaHCO_3$ and ether. The aqueous layer was extracted once with ether, and the combined organic layers were washed with H_2O and brine and dried ($MgSO_4$). Evaporation of the volatiles in vacuo and chromatography of the residue on silica gel (20 g) with 33% ethyl acetate in hexanes as the eluant afforded 0.2526 g (77%) of selenide **38**, mp 126–127 °C. More polar epimer: NMR δ (CCl_4) 7.80–7.20 (5 H, m), 4.30 (1 H, m), 3.74 (3 H, s), 3.69 (6 H, s), 3.64 (3 H, s) 3.30 (2 H, m), 3.00–2.20 (2 H, m), 2.08 (3 H, s), 0.90 (9 H, s), 0.05 (3 H, s), 0.04 (3 H, s); IR ($CHCl_3$) $\bar{\nu}_{max}$ 1700 cm^{-1}. Less polar epimer: NMR δ (CCl_4) 7.80–7.20 (5 H, m), 4.25 (1 H, m), 3.80–3.40 (15 H, m, containing 2 s at 3.77 (3 H) and 3.72 (9 H), 3.30–2.80 (2 H, m), 2.17 (3 H, s), 0.90 (9 H, s), 0.05 (6 H, s); IR ($CHCl_3$) $\bar{\nu}_{max}$ 1705 cm^{-1}. Mixture of epimers: mass spectrum, *m/e* 635 (P), calcd for $C_{30}H_{41}NO_7SeSi$ 635.1818, found 635.1812.

(9*R,9a*S**)-9-[(*tert*-Butyldimethylsiloxy)methyl]-2,3,9,9a-tetrahydro-5,7,8-trimethoxy-6-methyl-3-oxo-2-(phenylselenyl)-1*H*-pyrrolo[1,2-*a*]indole (39).** A solution of **38** (0.2251 g, 0.354 mmol) in 5 mL of THF and 10 mL of 10% aqueous KOH was stirred at room temperature for 3 h, cooled to 0 °C with an ice bath, acidified with concentrated H_2SO_4, saturated with sodium chloride, and extracted thoroughly with $CHCl_3$. The combined organic layers were washed with H_2O and brine and dried ($MgSO_4$). The solvent was removed in vacuo, and the residue was dissolved in 4 mL of toluene (distilled from CaH_2), heated at reflux for 60 min, cooled, and concentrated in vacuo. Chromatography on 15 g of silica gel with 20% ethyl acetate in

hexanes as the eluant afforded 0.1468 g (72%) of lactam selenide **39**. Mor polar epimer: NMR δ (CCl_4) 7.80–7.10 (5 H, m), 4.50–4.00 (1 H, m), 3.80–3.60 (10 H m, containing 2 s at 3.72 (3 H) and 3.70 (6 H), 3.40 (2 H, m), 2.45 (2 H, m), 2.10 (3 H, s), 0.90 (9 H, s), 0.05 (6 H, s); IR ($CHCl_3$) ν_{max} 1690 cm^{-1}. Less polar epimer: NMR δ (CCl_4) 7.80–7.10 (5 H, m), 4.25 (2 H, m), 3.80–3.60 (12 H, m, containing 2 s at 3.79 (3 H) and 3.72 (6 H), 3.30–2.50 (2 H, m), 2.13 (3 H, s), 0.90 (9 H, s), 0.05 (3 H, s), 0.04 (3 H, 5); IR ($CHCl_3$) ν_{max} 1690 cm^{-1}. Mixture of epimers: mass spectrum *m/e* 577 (P), calcd for $C_{28}H_{39}NO_5SeSi$ 577.1763, found 577.1771.

(9*R,9a*S**)-9-[(*tert*-Butyldimethylsiloxy)methyl]-2,3,9,9a-tetrahydro-5,7,8-trimethoxy-6-methyl-2-(phenylselenyl)-1*H*-pyrrolo[1,2-*a*]indole (40).** To a solution of **39** (0.1257 g, 0.217 mmol) in 6 mL of anhydrous THF was added 0.9 mL of 1 M BH_3–THF dropwise. The solution was then heated under reflux for 60 min, cooled with an ice bath, quenched with 1 mL of 10% aqueous H_2SO_4, and neutralized with 3 mL of 10% aqueous KOH, and most of the THF was evaporated in vacuo at room temperature. The residual solution was extracted thoroughly with ether. The combined organic layers were washed with brine and dried ($MgSO_4$). The volatiles were evaporated in vacuo, and the residue was chromatographed on 10 g of silica gel. Elution with 33% ethyl acetate in hexanes afforded 0.1014 g (83%) of amine **40**: NMR δ (CCl_4) 7.70–7.10 (5 H, m), 4.30–3.10 (15 H, m, containing 2 s (3 H each) at 3.70 and 3.59), 2.20–1.80 (5 H, m), 0.90 (4.5 H, s), 0.87 (4.5 H, s), 0.05 (6 H, m); IR ($CHCl_3$) ν_{max} 2930, 2850 cm^{-1}; mass spectrum *m/e* 563 (P).

(9*R,9a*S**)-[(*tert*-Butyldimethylsiloxy)methyl]-9,9a-dihydro-5,7,8-trimethoxy-6-methyl-3*H*-pyrrolo[1,2-*a*]indole (41).** To a solution of **40** (85.8 mg, 0.152 mmol) in 0.8 mL of THF at 0 °C was added 30% H_2O_2 (15.5 μL, 0.152 mmol). After the mixture was stirred for 60 min the reaction was warmed to room temperature, and 20 mg of $NaHCO_3$ was added. Stirring was continued for 60 min. The mixture was quenched with 100 μL of saturated $Na_2S_2O_3$, and most of the THF was evaporated at room temperature in vacuo. The residual mixture was diluted with ether and saturated $NaHCO_3$. The organic layer was washed with brine and dried ($MgSO_4$). Concentration in vacuo at room temperature and chromatography of the residue on alumina (activity grade 1) with 11% ethyl acetate in hexanes as the eluant afforded 33.8 mg (55%) of olefin **41**: NMR δ ($CDCl_3$) 5.82 (2 H, s), 4.80 (1 H, m), 4.20–4.00 (3 H, m), 3.84 (3 H, s), 3.81 (3 H, s), 3.77 (3 H, s), 3.57 (2 H, m), 2.17 (3 H, s), 0.93 (9 H, s), 0.12 (3 H, s), 0.09 (3 H, s); IR ($CHCl_3$) ν_{max} 2930, 2850 cm^{-1}; mass spectrum, *m/e* 405 (P), calcd for $C_{22}H_{35}NO_4Si$ 405.2335, found 405.2313.

Acknowledgment. This research was supported by a grant from the National Institute of Health (CA-12107-13-16).

Registry No. **6**, 19676-67-6; **7**, 79421-11-7; **8**, 79421-12-8; **9**, 65480-96-8; **10**, 65480-97-9; **11b**, 65481-00-7; **13**, 65481-02-9; **14**, 65481-03-0; **15**, 65481-04-1; **16**, 79465-33-1; **17**, 79465-34-2; **24**, 79421-13-9; **25**, 79421-14-0; **33**, 79421-15-1; **34**, 79421-16-2; **36**, 79421-17-3; **37**, 79421-18-4; **38** (isomer 1), 79435-69-1; **38** (isomer 2), 79465-96-6; **39** (isomer 1), 79421-19-5; **39** (isomer 2), 79465-35-3; **40**, 79421-20-8; **41**, 79421-21-9; *trans*-1,4-dichlorobut-2-ene, 110-57-6; (carbomethoxy)acetyl chloride, 37517-81-0.

Decomposition of *endo*- and *exo*-(2-Norbornyl)formyl *p*-Chlorobenzoyl Peroxides

Cheves Walling,* Robert R. W. Humphreys, John P. Sloan, and Traci Miller

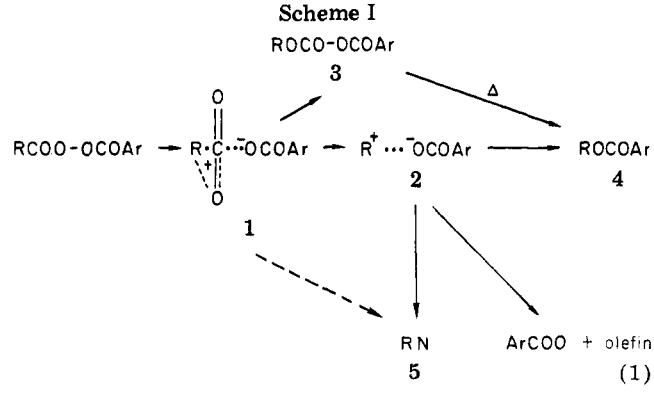
Department of Chemistry, University of Utah, Salt Lake City, Utah 84112

Received August 18, 1981

The subject peroxides undergo first-order decomposition in several solvents with rates increasing moderately with solvent polarity and endo/exo rates in a ratio of 1:10–100. Carboxyl inversion product, ROCOOCOAr, and other "polar" products are formed with no evidence for significant free-radical production. Products from an *exo*-peroxide have exclusively exo configurations, but carboxyl inversion product from endo peroxide contains small amounts of exo isomer. In acetic acid, 2-norbornyl acetate is a major product, with an endo/exo ratio of 14:86 from the *endo*-peroxide. Optically active *exo*-peroxide in acetic acid gives *exo*-2-norbornyl acetate with 6% net retention of configuration. The results are discussed in terms of successive ion pairs and carboxyl inversion product arising early on the reaction path and other products later.

Diacyl peroxides, RCO–O_2–COAr [R = *sec*- or *tert*-alkyl or benzyl and Ar = negatively substituted phenyl group (*m*-ClPh has been most investigated)], undergo a relatively rapid first-order decomposition, with little or no evidence for free-radical production.[1-5] In inert solvents the major product is usually the carboxyl inversion product or mixed aroyl carbonic anhydride (RO–CO–O–COAr), but ester (ROCOAr) or acid (ArCOOH) plus olefin may be formed as well.[6] In nucleophilic solvents, solvent is captured, e.g., to yield imides ($CH_3CONRCOAr$)[2,5] in acetonitrile, acetate esters[5] ($ROCOCH_3$) in acetic acid, and ethers or alcohol (ROH) in the presence of alcohols[5] or water.[4]

Scheme I



The reactions increase moderately in rate with solvent ionizing power and are generally considered to involve ion-pair intermediates. A plausible formulation is as shown in Scheme I.

(1) Denney, D. B.; Sherman, N. *J. Org. Chem.* **1965**, *30*, 3760–3761.
(2) Walling, C.; Waits, H. P.; Milovanovic, J.; Pappiaonnou, C. G. *J. Am. Chem. Soc.* **1970**, *92*, 4927–4932.
(3) Taylor, K. G.; Gorindan, C. K.; Kaelin, M. S. *J. Am. Chem. Soc.* **1979**, *101*, 2091–2099.
(4) Linhardt, R. J.; Murr, B. L. *Tetrahedron Lett.* **1979**, 1007–1010.
(5) Walling, C.; Sloan, J. P. *J. Am. Chem. Soc.* **1979**, *101*, 7679–7683.
(6) Such products, along with varying amounts of radical products, are, in general, observed in peroxides showing "two-bond" scission. For a general discussion see: Koenig, T. In "Free Radicals"; Kochi, J. K., Ed.; Wiley: New York, 1973; Vol. 1, pp 136–137. It has been proposed that both radical and ionic products are produced through a common rate-determining transition state.[2]

0022-3263/81/1946-5261$01.25/0