# A Stereospecific Route to Aziridinomitosanes: The Synthesis of Novel Mitomycin Congeners

Samuel Danishefsky,\* Ellen M. Berman, Marco Ciufolini, Sarah Jane Etheredge, and Brigitte E. Segmuller

Contribution from the Department of Chemistry, Yale University, New Haven, Connecticut 06511. Received July 23, 1984

Abstract: A stereospecific route to the aziridinomitosanes is described. The key phases of the synthesis are the following: (i) the coupling of a phenol with a functionalized allylic alcohol by an adaptation of the Mitsunobu technology (see  $6 + 7 \rightarrow 8$ ); (ii) a Claisen rearrangement to establish the full side chain required for the synthesis (see  $8 \rightarrow 9$ ); (iii) a stereospecific seleno-amination-alkylation-oxidation sequence (see  $15b \rightarrow 20$ , 21 and 22); and (iv) a stereospecific aziridination sequence which begins with a concave face hydroxylation (see  $19 \rightarrow 24 \rightarrow 31$ ). The preparations of novel mitosene N-oxide derivatives (see compounds 34 and 35) as well as quinone ketal related to the 9a-deoxymitomycins (see compound 37) are also described.

The structural novelty of the mitomycins and their chemical lability constitute a formidable challenge to those who would undertake their synthesis.<sup>1,2</sup> Interest at the purely chemical level was augmented by early demonstrations, in various experimental models, of antibiotic and antitumor potential of some of these compounds.<sup>3</sup> The emergence of mitomycin C as a clinically useful anticancer chemotherapeutic resource<sup>4a,b,5</sup> promotes continuing research in this field.<sup>6,7</sup> However, in spite of the enormous amount of synthetic activity which the mitomycins have inspired, the only successful total syntheses of naturally occurring mitomycins were those described by Kishi<sup>8,9</sup> and collaborators.

Our efforts have been directed toward several goals. Of course, it was hoped to achieve a total synthesis of one or more of the naturally occurring mitomycin congeners (see structures below). Also, de novo synthesis could lead to new kinds of mitomycin analogues which would not be readily obtained by modification of the natural products themselves.

Compounds of the type c were selected as intermediary targets.

(3) Remers, W. A. "The Chemistry of Antitumor Antibiotics"; Wiley-Interscience: New York, 1979; Vol. I, p 221 ff.

(4) Remers, W. A. In "Anticancer Agents Based on Natural Product Models"; Cassady, J. M., Douros, J. D., Eds.; Academic Press: New York, 1980; p 131 ff.

(5) Lown, J. W. In "Molecular Aspects of Anticancer Drug Action"; Neidle, S., Waring, M. J., Eds.; Verlag Chemie: Weinheim, 1983; p 283 ff.

(6) For some notable contributions to this field since the review articles, see: (a) Rebek, J.; Shaber, S. H. *Heterocycles* **1981**, *16*, 1173. (b) Naruta, Y.; Nagai, N.; Maruyama, K. *Chem. Lett.* **1983**, *1383*. (c) Naruta, Y.; Arita, Y.; Nagai, N.; Uno, H.; Maruyama, K. *Ibid.* **1982**, 1859. (d) Luly, J. R.; Rapoport, H. J. Am. Chem. Soc. **1983**, *105*, 2859. (e) Luly, J. R.; Rapoport, H. J. Org. Chem. **1984**, *49*, 1671.

(7) (a) Danishefsky, S.; Regan, J.; Doehner, R. J. Org. Chem. 1981, 46, 5255. (b) Danishefsky, S.; Regan, J. Tetrahedron Lett. 1981, 22, 3919.

(8) (a) Nakatsubo, F.; Cocuzza, A. J.; Keeley, D. E.; Kishi, Y. J. Am. Chem. Soc. 1977, 99, 4835. (b) Nakatsubo, F.; Fukuyama, T.; Cocuzza, A. J.; Kishi, Y. Ibid. 1977, 99, 8115. (c) Fukuyama, T.; Nakatsubo, F.; Cocuzza, A. J.; Kishi, Y. Tetrahedron Lett. 1977, 18, 4295.

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

(10) For the recently re-formulated absolute configuration of mitomycin

C, see: Shirahata, K.; Hirayama, N. J. Am. Chem. Soc. 1983, 105, 7199. (11) (a) Yahashi, R.; Matsubara, I. J. Antibiot. 1976, 29, 104. (b) Yahashi, R.; Matsubara, I. Ibid. 1978, 31, 6. The absolute configuration of mitomycin B presented in this paper has recently been questioned by Shirahata<sup>10</sup> and disproven by Hornemann and Heins (Hornemann, U.; Heins, M. J. J. Org. Chem. 1985, 50, 1301).

(12) Morton, G. O.; van Lear, G. E.; Fulmor, W. J. Am. Chem. Soc. 1970, 92, 2588.

(13) Urakawa, C.; Tsuchiya, H.; Nakano, K.-I. J. Antibiot. 1981, 34, 243.



Such systems might lend themselves to introduction of the aziridine linkage in a stereospecific fashion. A riskier venture would involve an attempt to introduce the required 9a hetero functionality through a position-specific oxidation of these or related compounds. The chemical issues to be explored were: (i) the feasibility of the Claisen rearrangement<sup>14</sup> with such an extensively functionalized phenyl allyl ether; (ii) the feasibility of, and stereoselectivity of, pyrroline ring construction via the format suggested in the transformation of  $\mathbf{b} \rightarrow \mathbf{c}$ ; and (iii) the feasibility and stereospecificity of introduction of the aziridine ring. An account of our findings is provided herein.

#### **Discussion of Results**

Partial reduction of the benzylidene acetal  $1^{15}$  provided the monobenzyl ether 2. This compound has also served as a valuable

(14) An account of earlier work in this area is provided in: Regan, J. Dissertation, University of Pittsburgh, 1980.

<sup>(1)</sup> Kametani, T.; Takahashi, K. Heterocycles 1978, 9, 293.

<sup>(2)</sup> Franck, R. W. Fortschs. Chem. Org. Naturst. 1979, 38, 1.

<sup>(15)</sup> Eliel, E. L.; Badding, V. G.; Rerick, M. N. J. Am. Chem. Soc. 1962, 84, 237.



differentiated functionalized intermediate for other activities.<sup>16</sup> Oxidation of 2 with pyridinium chlorochromate<sup>17</sup> afforded the useful enal 3. In the course of the oxidation, the Z double bond had undergone isomerization. By a simple Reformatsky-like transformation,<sup>18</sup> compound 4 is available from 3 in quantitative (crude) yield. Compound 4 is reduced with lithium aluminum hydride. The diol 5 is thus available in 80% yield from 3. Reaction of 5 with tert-butyldimethylchlorosilane<sup>19</sup> in the presence of di-

methylaminopyridine provided the monosilyl ether 6 (80%). Little need be said about the synthesis of the required phenol

 $7.^{8,9,20,21}$  Initial attempts to attach the phenol to the allylic carbinyl center by a derived allylic mesylate or bromide met with failure. Some years ago, Manhas<sup>22</sup> et al. described the application of the Mitsunobu condensation<sup>23</sup> reaction to the synthesis of cholesteryl phenyl ether. Several other instances<sup>24</sup> of the use of the azodicarboxylate-phosphine mediated "dehydrations" in the synthesis of phenolic ethers had also appeared during the course of our investigations.

The extendability of this reaction to the allylic alcohol system present in 6 was investigated. In the event, coupling was achieved in ca. 80% yield through the use of tri-n-butylphosphine and ethyl azodicarboxylate in ether. Examination of the crude coupling product indicated a ca. 10:1 ratio of two closely related compounds. These products were separated by preparative scale HPLC, though not without considerable loss of tempo. The NMR spectra of compounds 8 and 9 are quite similar and do not rigorously reveal the structures of the allylic isomers.

It was presumed that the major isomer is 8 while the minor product is the  $S_N2'$ -derived system 9. This surmise was shown

(24) (a) Cooper, R. D. G.; Jose, F.; McShane, L.; Koppel, G. A. Tetra-hedron Lett. 1978, 19, 2243. (b) Bittner, S. B.; Assaf, Y. Chem. Ind. (London) 1975, 6, 281. (c) Nakano, J.; Mimura, M.; Hayashida, M.; Kimura, K.; Nakanishi, T. Heterocycles 1983, 20, 1975.

to be correct. Compound 8 was converted to its Claisen rearrangement product, presumed to be 10, and thence, via its benzyl ether, 12a, through a series of steps which served to corroborate the structural assignments (vide infra). The minor product 9 also suffers Claisen rearrangement. However, when the resultant compound 11 is carried through the same steps, it produces products which are no longer related to those obtained starting with 10. Accordingly, in practice it was not necessary to effect the separation between 8 and 9.

Compound 10 was converted to the bisbenzyl ether 12a, and to the ether acetate 12b. The bisbenzyl ether 12a was converted by nitration (90% fuming nitric acid-acetic anhydride-mercuric acetate)<sup>25</sup> to 13a, which was accompanied by some of its free alcohol arising from cleavage of the silyl group. Reaction of this material with zinc dust and aqueous HCl afforded compound 14a. The primary hydroxyl function underwent smooth displacement upon reaction with carbon tetrabromide-triphenylphosphine.<sup>26</sup> The amino group did not seem to complicate the transformation. In this sequence, compounds 12a, 14a, and 15a were fully characterized.

The corresponding transformations were conducted on large scale in the acetate series (12b-15b) without chromatography and without full characterization of intermediates between the coupling product mixture (10 + 11) to the tricyclic olefin 22. As in the benzyl ether series, nitration was carried out with nitric acid and mercuric acetate in acetic anhydride, and reduction was conducted with zinc dust in aqueous HCl. Once again, the primary hydroxyl group thus generated (see structure 14b) underwent clean conversion to the anilino bromide 15b.<sup>26</sup>

The stage was now set for the critical biscyclization of the properly functionalized, properly positioned hexenylaniline system. As expected, the trans double bond in 15a and 15b mitigated against intramolecular alkylation of the amino group by the primary carbon bearing the bromide. It was hoped that attack of a suitable electrophile  $E^+$ , upon the double bond, leading to establishment of the indoline ring, would also set the stage for a second alkylation to generate the complete pyrroloindoline system required. In fact, we have reduced this concept to practice with several electrophiles.<sup>27</sup> However, here we describe the outcome when the electrophile is the very interesting Nicolaou

<sup>(16)</sup> Ko, S. Y.; Lee, A. W. M.; Masamune, S.; Reed, L. A., III; Sharpless,

<sup>(16)</sup> NO, S. F.; Lee, A. W. M.; Masamune, S.; Reed, L. A., III; Snarpiess,
K. B.; Walker, F. J. Science 1983, 220, 949.
(17) Corey, E. J.; Suggs, J. W. Tetrahedron Lett. 1975, 16, 2647.
(18) (a) Rathke, M. W. Org. React. 1975, 22, 423. (b) Rathke, M. W.;
Lindert, A. J. Org. Chem. 1970, 35, 3966.
(19) Corey, E. J.; Venkateswarlu, A. J. Am. Chem. Soc. 1972, 94, 6190.
(20) Roger, R.; Demerseman, P.; Laval-Heantet, A.-M.; Rossignol, J.-F.;
Cheutin, A. Bull. Soc. Chim. Fr. 1968, 1026. See also ref 8 and 9.

<sup>(21)</sup> Our somewhat modified route to phenol 7 is provided in the supplementary material.

<sup>(22)</sup> Manhas, M. S.; Hoffmann, W. H.; Lal, B.; Bose, A. K. J. Chem. Soc., Perkin Trans. 1 1975, 461.

<sup>(23)</sup> Mitsunobu, O. Synthesis 1981, 1.

<sup>(25)</sup> Stock, L. M.; Wright, T. L. J. Org. Chem. 1977, 42, 2875.

<sup>(26)</sup> Hooz, J.; Gilani, S. S. H. Can. J. Chem. 1968, 46, 86.

<sup>(27)</sup> For an account of these efforts, see: Berman, E. M. Dissertation, Yale University, 1983.

reagent, N-phenylselenophthalimide (N-PSP).<sup>28</sup>

Contrary to earlier precedents,<sup>29</sup> reaction of 15a with N-PSP in methylene chloride followed by basic extraction afforded a high yield of a diastereomeric mixture of selenides formulated as 16 and 17. At this stage, the stereochemistry of these products was



not known. The relationship of the phenylseleno function of the junction hydrogen was assumed to be trans by the mechanism of the process (i.e., trans addition of "amino" and "phenylseleno" to the E double bond). It was therefore assumed that the two substances were "facial isomers" differing in the configurations of the chiral centers at  $C_1$  and  $C_{9a}$ , relative to that at  $C_9$ . Indeed, oxidative deselenylation produced a 1:4 mixture of olefins 18-19. Again, at this stage, the stereochemistry of these compounds could not be assigned with certainty.<sup>30</sup> However, subsequent work with compound 19 also produced via a stereospecific route (vide infra), established it to be the compound which bears the exo-oriented benzyloxymethyl group, as shown.

The practicalities of synthetic processing would be well served if the cyclization were more specific. When the N-PSP reaction was carried out with the acetate 15b, a single tricyclic product was obtained. When this product, formulated as 21, was subjected to the action of *m*-chloroperoxybenzoic acid, a single tricyclic olefin, 22,<sup>31</sup> was produced. The overall yield of compound 22 from the 10:1 mixture of coupled isomers (8-9), without chromatography of any intermediates, was 31%. The Experimental Section provides the details of this "flask-to-flask" conversion.

Since a benzyl ether at the phenolic center would provide more suitable protection in the installation of the aziridine, the acetate was cleaved with potassium carbonate-methanol. The phenol 23, upon benzylation with benzyl bromide, afforded compound 19. The relative configurations at carbons 9a and 10 in these compounds was not known at this stage,<sup>30</sup> but became rigorously defined at the stage of the aziridine derivative, 32.

The reasons for the stereospecificity in the case of the acetate 15b and, indeed, the reasons for the direction of stereoselectivity in the case of the benzyl ether 15a are not clear. It can be argued



that the formation of a cyclic selenonium ion through the action of N-PSP on the double bond is highly reversible and that the process critically depends on anchimeric displacement by the nitrogen. It can further be postulated that such displacement is more ready in the diastereomer leading to 20 since the two large groups emerge trans relative to the indoline ring. The corresponding pyrroline ring which would lead to 18 had its large groups disposed in a syn fashion. The reasons for the much greater specificity in the case of the acetate 15b relative to the benzyl ether 15a must lie in subtle conformational differences which are not readily understood in detail. In any case, a stereospecific and highly processable route to compound 19 was now available.

With a practical route to 19 and 22 having been achieved, the remaining issues in unspecified order involve (i) quinone formation, (ii) installation of the aziridine, and (iii) introduction of  $C_{9a}$ heterofunctionality. The optimal stage, a priori, for attempting the most difficult of these challenges, i.e., oxidation of the 9a position, can be debated. We chose to demonstrate that the aziridine can, in fact, be fashioned from the double bond of compound 19 and to learn the stereochemical course of such a process. Of the various early attempts to functionalize the double bond of 19 (without effecting aromatization),<sup>32</sup> the reaction with osmium tetroxide<sup>33</sup> seemed to be the most promising. At this stage, it was not possible to deduce the stereochemistry of the diol. Indeed, even the configurational relationship between  $C_{10}$  and  $C_{9a}$ was not known with certainty although it was assumed<sup>30</sup> to be as shown. The stereochemistry of the eventual aziridine which was obtained, 32 (vide infra), shows the diol to be structure 24, wherein hydroxylation has actually occurred from the concave face anti to the exo-disposed benzyloxymethyl group. Monomesylation<sup>34</sup> was achieved through reaction of 24 with mesyl chloride and triethylamine in methylene chloride. The monomesylate 25 was not well characterized. Rather, in crude form, it was subjected to the action of tetra-N-butylammonium azide35 in benzene under reflux. Examination of the infrared and mass spectra of the product indicated that an azidohydrin, presumably compound 26, had been produced. This product, upon treatment with excess methanesulfonyl chloride and triethylamine in methylene chloride gave rise to a crude product whose infrared and NMR spectra are consistent with its being an azidomesylate. Reaction of this product, formulated as 27, with trimethyl phosphite in tetrahydrofuran,<sup>8,9</sup> led to a crude product, presumed to be 28, which was treated with sodium hydride in tetrahydro-

<sup>(28) (</sup>a) Nicolaou, K. C.; Clarmon, D. A.; Narnette, W. E.; Sietz, S. P. Am. Chem. Soc. 1979, 101, 3704. (b) Nicolaou, K. C. Tetrahedron 1981, 37, 4097.

<sup>(29) (</sup>a) Clive, D. L. J.; Wong, C. K.; Kiel, W. A.; Menchen, S. M. J. Chem. Soc., Chem. Commun. 1978, 379. (b) Clive, D. L. J.; Farina, V.; Singh, A.; Wong, C. K.; Kiel, W. A.; Menchen, S. M. J. Org. Chem. 1980, 45, 2120.

<sup>(30)</sup> The NMR spectrum of the major olefin isomer is very similar to that of an analogous compound previously<sup>7,14</sup> obtained by Regan in a very lengthy route using activated cyclopropane chemistry. In that work, the stereochemistry at C<sub>9</sub> was formulated as exo on mechanistic considerations. Therefore, the stereochemistry of the major olefin was formulated as shown above. That this assignment is rigorously proven via compound 32 also supports the previous proposal.

<sup>(31)</sup> A portion of crude acetoxy olefin 22 was hydrolyzed and O-benzylated as described in the Experimental Section. HPLC analysis of the crude dibenzyl olefin thus obtained revealed no contamination by the isomer 18.

<sup>(32)</sup> An extensive discussion of these attempts is provided in: Berman, E. M. Disseration, Yale University, 1983, and unpublished results.
 (33) Van Rheenen, V.; Kelly, R. C.; Cha, D. Y. Tetrahedron Lett. 1976,

<sup>1973.</sup> 

<sup>(34)</sup> Considerable difficulty was experienced in various attempts to produce the bis mesylate of diol 24, reflecting the unreactive nature of the C-1 hydroxyl, and allowing a ready and clean entry into the monoactivated species.

<sup>(35)</sup> Brandstrom, A.; Lamm, B.; Palmertz, I. Acta Chem. Scand., Ser. B 1974, 28, 699.



furan. The presumed resultant, N-phosphorylaziridine, was subjected to reduction with lithium aluminum hydride. There was thus obtained, after silica gel chromatography, the homogeneous secondary aziridine, now known to be **30**. Unfortunately, the yields of pure **30** from diol **24** were in the range of 30-40%.

We sought to relate our synthetic intermediates to the 9adeoxymitomycin series<sup>36</sup> by methylation of the aziridino "N-H" group. Methylation was accomplished albeit only in 60-65% yield through the agency of methyllithium and methyl iodide in ether. The resultant compound 31 underwent debenzylation via reaction with sodium and liquid ammonia-THF. A highly crystalline intermediate, mp 155.5-156.5 °C, was produced in essentially quantitative yield. There need be no uncertainty about either the gross structure of stereochemistry of this aziridino diol since an X-ray crystallographic determination revealed its structure to be that shown in 32.<sup>37</sup> Barring some most improbable happenings in going from the diol to the aziridine, the stereochemical assignments of the various intermediates must be those shown in formulas 24-31. Thus, the relationship  $C_1$ - $C_2$  imino linkage relative to the C<sub>9</sub> hydroxymethyl group of this stereospecifically generated aziridine is one of the mitomycin A,C-porfiromycin family (vide supra).

The oxidation of *p*-methoxyphenol derivatives with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in methanol to afford *p*quinone monoketals is well known.<sup>38</sup> Indeed, this reaction was used in our work to prepare quinoketal **37** (vide infra). For the purpose at hand, it was of interest to develop a direct oxidation of compound **32** to its corresponding quinone. It was reasoned that this might be accomplished if aqueous rather than methanolic solvent were used. In the event, reaction of diol **32** with DDQ in aqueous THF furnished a 61% yield of a purple powder, mp 146-152 °C. The spectral properties of this compound in conjunction with the rigorously defined structure of its precursor, **32**, define it to be the hydroxymethylquinone **33**, related in stereochemistry to the major classes of mitomycins.

Future synthetic work in this area will require a more concise and higher yielding route for installation of the aziridine. Furthermore, to reach the actual mitomycins, a workable solution to the  $C_{9a}$  functionalization problem, at an appropriate stage of the synthesis, must be devised. Preliminary forays toward this most challenging goal have only resently been initiated. Some possible future directions which these pursuits might follow a foreshadowed by the following three experiments. It was found that oxidation of the now readily available compound 19 with *m*-chloroperoxybenzoic acid affords, very cleanly, the *N*-oxide 34.<sup>39,40</sup>

Also of interest with the finding that the N-methylaziridine 31 reacts with the same reagent to afford the anilino N-oxide 35, without any apparent interference from the tertiary aziridino nitrogen.



Finally, we note that partial catalytic debenzylation of compound 30 occurs specifically, such as to liberate the phenolic ether. Reaction of compound 36 with DDQ in methanol affords the quinone ketal 37 in high yield. It is possible that quinone ketals might prove to be more stable than quinones themselves toward some of the operations which might be useful for introduction of the  $C_{9a}$  hetero function.

The results of ongoing investigations which seek to develop these findings more fully will be disclosed is due course.

## Experimental Section<sup>41</sup>

(Z)-2-Butene-1,4-diol Benzylidene Acetal (1). A solution of benzaldehyde (106 g, 102 mL, 1 mol), benzene (500 mL), (Z)-2-butene-1,4-diol (97 g of 91% pure eis compound, equivalent to 88 g of eis diol, 1 mol), and camphorsulfonic acid (1 g) was heated under reflux for 18 h with continuous azeotropic removal of water. The dark reaction mixture was cooled and washed with water (3 × 150 mL) and with brine (1 × 200 mL). Removal of the solvent under reduced pressure left a residue which was vacuum-distilled to give 139 g of pure acetal (79%), bp 99–100 °C (0.25 mmHg). A forerun was also obtained (18 g) as a 1:1 mixture of benzaldehyde and derived acetal. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 90 MHz) 7.55–7.20 (m, 5 H), 5.81 (s, 1 H), 5.72 (m, 2 H), 4.30 (m, 4 H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 2.2.5 MHz) 138.7, 129.7, 128.1, 127.9, 126.2, 101.9, 64.2. IR (CDCl<sub>3</sub>, Cm<sup>-1</sup>) 3000, 2940, 2850. *m/e* 176 (P<sup>+</sup>). Calcd for C<sub>11</sub>H<sub>12</sub>O<sub>4</sub>: *m/e* 176.0837. Found: *m/e* 176.0820.

(Z)-4-Benzyloxy-2-buten-1-ol (2). A solution of  $LiAlH_4$  (8.5 g, 0.22 mol) in ether (200 mL) was carefully added (cannula) to a solution of AlCl<sub>3</sub> (90 g, 0.67 mol) in ether (500 mL). The temperature of the resultant mixture was maintained at 0 °C by cooling with an ice bath. A solution of the acetal 1 (60 g, 0.34 mol) in ether (400 mL) was added dropwise to the mixture of LiAlH<sub>4</sub>/AlCl<sub>3</sub>, with good stirring and cooling. The addition required 30 min, after which time the reaction was stirred (0° to room temperature) for an additional 2 h. The reaction was quenched by addition of 500 mL of 10% aqueous H<sub>2</sub>SO<sub>4</sub> (0 °C). The mixture was transferred to a separatory funnel and diluted with more water to dissolve the aluminum salts. The organic phase was removed, and the aqueous solution was extracted with more ether. The combined ether extracts were dried (MgSO<sub>4</sub>) and concentrated to give 58 g of product (96%). The compound was used without further purification. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 90 MHz) 7.33 (s, 5 H), 5.80 (m, 2 H), 4.43 (s, 2 H), 4.05 (m, 4 H), 2.70 (br s, 1 H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 22.5 MHz) 137.6, 132.2, 218.1, 127.5 (two overlapping resonances), 127.3, 71.9, 65.3, 57.8).

<sup>(36)</sup> Kinoshita, S.; Uzu, K.; Nakano, M.; Shimizu, M.; Takahasi, T.; Matsui, M. J. Med. Chem. 1971, 14, 103.

<sup>(37)</sup> Crystallographic data for this compound are provided as supplementary material.

<sup>(38)</sup> Buchi, G.; Chu, P.-S.; Hoppmann, A.; Mak, C.-P.; Pearce, A. J. Org. Chem. 1978, 43, 3983.

<sup>(39)</sup> The olefinic linkage of N-oxide 34 proved to be entirely resistant to peracid epoxidation even under forcing conditions.

<sup>(40)</sup> N-Oxide 34 was produced by Dr. William H. Pearson of our laboratories. The same experimental procedure may be applied to the synthesis of the N-oxide corresponding to compound 19 (95% yield after chromatography).

<sup>(41)</sup> Protocols are provided as supplementary material.

IR (CHCl<sub>3</sub>, cm<sup>-1</sup>) 3400, 3000, 2350. m/e 160 (P<sup>+</sup> - 18). Calcd for C<sub>11</sub>H<sub>12</sub>O: m/e 160.0888. Found: 160.0898 m/e.

(E)-4-Benzyloxy-2-butenal (3). Alcohol 2 (150 g, 0.84 mol) was added in one portion to a cool, rapidly stirring suspension of pyridinium chlorochromate<sup>17</sup> (279 g, 1.29 mol) and Celite (300 g) in dichloromethane (2.5 L). After stirring for 3 h, the resulting dark mixture was diluted with 1.5 L of ether. Filtration through a pad of Florisil (suction) left a dark solid residue which was washed with more ether. The combined filtrates were concentrated to give crude aldehyde 3 (95 g, 64%) as an oil, which was used without further purification. <sup>1</sup>H NMR, (CDCl<sub>3</sub>, 90 MHz) 9.59 (d, 1 H, J = 8 Hz), 7.33 (s, 5 H), 6.81 (dt, 1 H,  $J_1 = 4$ ,  $J_2 = 15$  Hz), 6.42 (dd, 1 H,  $J_1 = 8$ ,  $J_2 = 15$  Hz), 4.57 (s, 2 H), 4.23 (m, 2 H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 22.5 MHz) 192.7, 152.8, 137.2, 131.2, 128.1, 127.5, 127.2, 72.5, 68.2. IR (CHCl<sub>3</sub>, cm<sup>-1</sup>) 1684. *m/e* 176 (P<sup>+</sup>).

(E)-6-Benzyloxy-3-hydroxy-4-hexenoate (4). Methyl bromoacetate (103.6 g, 0.68 mol) was added in a single portion to a mixture of aldehyde 3 (92 g, 0.52 mol), trimethyl borate (160 mL), and zinc dust (53 g, 0.81 mol) in THF (160 mL). A rapid exothermic reaction was observed. After the mixture was stirred for 6 h, the reaction was quenched by the sequential addition of glycerol (200 mL), saturated aqueous NH<sub>4</sub>Cl (200 mL), ether (500 mL), and water (300 mL), with continuous stirring. Separation of the organic layer and extraction of the aqueous phase with ether  $(2 \times 300 \text{ mL})$ , followed by concentration of the combined ether extracts, afforded a residue of crude  $\beta$ -hydroxy ester. Dilution with 300 mL of CH<sub>2</sub>Cl<sub>2</sub> and filtration through a pad of anhydrous Na<sub>2</sub>SO<sub>4</sub> gave a solution of  $\beta$ -hydroxy ester which was concentrated in vacuo. The product thus obtained (131 g, 100%) was used without further purification. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 90 MHz) 7.32 (s, 5 H), 5.75-5.90 (m, 2 H), 4.45-4.70 (broad 1 H multiplet containing a 2 H singlet at 4.50, 3 H), 4.00 (m, 2 H), 3.67 (s, 3 H), 3.07 (br s, 1 H), 2.53 (d, 2 H, J = 6 Hz). IR (CHCl<sub>3</sub>, cm<sup>-1</sup>) 3480, 1720. m/e 250 (P<sup>+</sup>).

(E)-1-Benzyloxy-2-hexene-4,6-diol (5). A solution of  $\beta$ -hydroxy ester 4 (66.5 g, 0.27 mol) in ether (500 mL) was added dropwise to a solution of lithium aluminum hydride (15.2 g, 0.40 mol) in ether (500 mL), with vigorous mechanical stirring. The temperature of the reaction was kept below 10 °C. Addition of the ester required 1.5 h, after which time stirring was continued for another 15 min. The reaction was quenched by the sequential addition of water (15 mL), 20% aqueous NaOH (15 mL), and water (45 mL). The granular precipitate of aluminum salts was separated by suction-filtration and concentration of the filtrate gave the crude diol (52 g, 88%). The crude compound was suction-filtered through a pad of Merck 230-400 mesh silica gel, which was further washed with ethyl acetate. Concentration gave 47 g of clear, colorless diol (80%) which was submitted directly to silvlation. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 90 MHz) 7.34 (s, 5 H), 5.72-5.87 (m, 2 H), 4.52 (s, 2 H), 4.40 (m, 1 H), 4.30 (m, 2 H), 3.80 (br t, 2 H, J = 6 Hz), 2.50-2.88 (br, 2 H), 1.60–1.83 (m, 2 H). IR (CHCl<sub>3</sub>, cm<sup>-1</sup>) 3380. m/e 131 (P<sup>+</sup> – C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>).

(E)-1-Benzyloxy-6-tert-butyldimethylsilyloxy-2-hexen-4-ol (6). To a solution of crude diol 5 (20.0 g, 90.1 mol) in 590 mL of dry methylene chloride was added 4-dimethylaminopyridine (440 mg, 3.6 mmol) and triethylamine (13.8 mL, 99.2 mmol). To this system was added, dropwise over 1.5 h, a solution of tert-butyldimethylsilyl chloride (11.56 g, 76.6 mmol) in 140 mL of methylene chloride. The reaction was stirred at room temperature under nitrogen for 16 h. The solution was washed with 3% aqueous sulfuric acid ( $1 \times 300 \text{ mL}$ ), saturated sodium bicarbonate  $(1 \times 300 \text{ mL})$ , and then brine. The organic layer was dried over sodium sulfate, filtered, and concentrated in vacuo to afford a yellow oil. Chromatography on silica gel with 15% ethyl acetate in hexanes afforded 24.39 g (80%) of allylic alcohol. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 90 MHz) 7.33 (s, 5 H), 5.84 (m, 2 H), 4.50 (br s, 2 H), 4.45 (br m, 1 H), 4.05 (d, 2 H, J = 4 Hz), 3.82 (dt, 2 H,  $J_1 = 3$ ,  $J_2 = 6$  Hz), 3.27 (d, 1 H, J = 3 Hz), 1.74 (m, 2 H), 0.89 (s, 9 H), 0.10 (s, 6 H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 22.5 MHz) 138.5, 135.9, 128.5, 127.8, 127.7, 126.5, 72.2, 70.9, 70.3, 61.5, 39.1, 26.1, 18.3, 5.3. IR (CHCl<sub>3</sub>, cm<sup>-1</sup>) 3470, 3000, 2940, 1470, 1360, 1260. m/e 279 (p<sup>+</sup> - t-Bu). Anal. Calcd for C<sub>19</sub>H<sub>32</sub>SiO<sub>3</sub>: C, 67.81; H, 9.58. Found: C, 67.59; H, 9.45.

(E)-1-Benzyloxy-6-tert-butyldimethylsilyloxy-4-[(2,4-dimethoxy-3methylphenyl)oxy]-2-hexene (8) Plus Allylic Isomer 9. A 500-mL, three-neck flask fitted with overhead stirrer was charged with alcohol 6 (12.3 g, 36.6 mmol) and ether (70 mL). Freshly distilled tri-*n*-butylphosphine was added (12.2 g, 60 mmol) and the mixture was cooled in a dry ice/CCl<sub>4</sub> bath (-25 °C). Neat diethyl azodicarboxylate (DEAD) was injected (2.1 g, 12.0 mmol), 1.9 mL), whereupon the orange color of the diester faded rapidly. Stirring at -25 °C was continued for 10 min, after which time exactly one-fifth of a solution of phenol 7 (5.1 g, 30.5 mmol) in 30 mL of ether was added dropwise. The resulting mixture was stirred for 1 h at -25 °C. The same sequential additions of DEAD [1.9 mL)/10 min at -25°/one-fifth of phenol solution/1 h at -25°] was repeated four more times until a total of 10.5 g (60 mmol) of DEAD had been used and all of the phenol solution had been added. The reaction mixture was stirred for 2 h following the last addition of phenol solution. The reaction mixture was warmed to room-temperature and the white precipitate of diethyl hydrazodicarboxylate was removed by suction filtration through a pad of Celite supported by a bed of Merck 70–230 mesh silica gel. The solid was washed well with ether and the filtrate was concentrated to a syrupy residue. Scrutiny of the crude reaction mixture by HPLC ( $\mu$ -Porasil, 5% EtOAc/hexane) established the presence of compound 8 contaminated by 10–11% of compound 9. Chromatography of the crude aryl ether (150 g of Merck 230–400 mesh silica gel, 2–5% EtOAc/Hex) provided 11.8 g of purified product (80%), still contaminated with 10–11% of the S<sub>N</sub>'-derived ether. Separation of the two isomers, while readily achieved by HPLC, proved impractical for preparative purposes. Therefore, the mixture of regioisomeric ethers 8 and 9, as prepared above, was used for further reaction.

**Compound 8.** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) 7.31–7.37 (m, 5 H), 6.75 (d, 1 H, J = 8 Hz), 6.49 (d, 1 H,  $J_{BA} = 8$  Hz), 5.80 (m, 2 H), 4.80 (m, 1 H), 4.42 (s, 2 H), 4.04 (dd, 1 H,  $J_1 = 5$ ,  $J_2 = 13$  Hz), 3.99 (dd, 1 H,  $J_1 = 5$ ,  $J_2 = 13$  Hz), 3.75–3.88 (a broad 2 H multiplet containing two 3 H singlets at 3.82 and 3.77, 8 H), 2.15 (s, 3 H), 2.10 (m, 1 H), 1.90 (m, 1 H), 0.90 (s, 9 H), 0.06 (s, 3 H), 0.04 (s, 3 H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 22.5 MHz) 152.6, 149.3, 145.1, 138.1, 133.0, 128.8, 129.1, 127.5, 127.3, 120.7, 113.9, 105.0, 76.4, 71.5, 69.7, 60.1, 59.2, 55.5, 38.8, 25.8, 18.1, 8.9, 55.5 IR (CHCl<sub>3</sub>, cm<sup>-1</sup>) 3000, 2950, 1590, 1480, 1250. m/e 486 (P<sup>+</sup>), 471, 378, 321, 291, 207, 168. Anal. Calcd for C<sub>28</sub>H<sub>42</sub>SiO<sub>5</sub>: C, 69.16; H, 8.70. Found: C, 68.90; H, 8.51.

**Compound 9.** <sup>1</sup>H NMR (CDCl<sub>3</sub> 500 MHz) 7.33–7.36 (m, 5 H), 6.75 (d, 1 H,  $J_{AB} = 9$  Hz), 6.49 (d, 1 H,  $J_{BA} = 9$  Hz), 5.75 (dt, 1 H, J = 6, J = 14 Hz), 5.61 (br dd, 1 H,  $J_1 = 14$   $J_2 = 7$  Hz), 4.73 (m, 1 H), 4.63 (s, 2 H), 3.88 (s, 3 H), 3.79 (s, 3 H), 3.75 (m, 1 H), 3.65 (dd, 1 H,  $J_1 = 6$ ,  $J_2 = 10$  Hz), 3.60 (t, 2 H, J = 6 Hz), 2.22–2.29 (m, 2 H), 2.15 (s, 3 H), 1.56 (s, 9 H), 0.06 (s, 6 H). IR (CHCl<sub>3</sub>, cm<sup>-1</sup>) 3000, 2950, 1590, 1480, 1250. m/e 486 (P<sup>+</sup>) 471, 378, 321, 291, 276, 261, 233, 207, 168.

(±)-(9R\*,9aS\*)-8-Acetoxy-9-[(benzyloxy)methyl]-9,9-dihydro-5,7dimethoxy-6-methyl-3H-pyrrolo[1,2-a]indole (22) without Purification of Intermediates.<sup>42</sup> A mixture of isomeric aryl ethers 8 and 9 (34.9 g, 72 mmol) was dissolved in 105 mL of N,N-dimethylaniline and the resulting solution was thoroughly purged with N2. The mixture was heated under reflux for 2 h. After cooling, the solution was poured into a separatory funnel containing ice (600 g) and concentrated HCl (116 mL). Extraction with ether produced an organic phase which was washed with H<sub>2</sub>O (1 × 300 mL) and brine (1 × 300 mL). The ether phase was further dried (MgSO<sub>4</sub>) and concentrated to afford crude phenol 10 in quantitative yield. Dissolution of phenol 10 in pyridine (100 mL) and treatment with neat Ac<sub>2</sub>O (23 g, 225 mmol) at 25 °C for 8 h produced acetate 12b (36.1 g, 95%) after an extractive workup (2.4 N HCl, ether, Na<sub>2</sub>SO<sub>4</sub>) followed by filtration of the combined extracts through a pad of Merck 230-400 mesh silica gel (suction). Nitration was effected by dissolving a portion of acetate 12b (24.5 g, 46.4 mmol) in Ac<sub>2</sub>O (250 mL). To that mixture column added a solution of Hg(OAc)<sub>2</sub> (1.42 g, 4.4 mmol) in glacial AcOH (125 mL). The mixture was stirred at 0 °C during addition of fuming 90% HNO3 (12.4 mL, 16.5 g of HNO<sub>3</sub>) over 5 min. Stirring at 0 °C was continued for another 10 min. The mixture was poured over 1.5 kg of ice and extracted with ether. The ether extracts were thoroughly washed with aq 5% K<sub>2</sub>CO<sub>3</sub> (removal of AcOH and Ac<sub>2</sub>O), then with brine. Drying over Na<sub>2</sub>SO<sub>4</sub>, filtration, and concentration furnished crude nitro compound 13b (25 g) which was directly submitted to reduction. The compound was thus diluted with 116 mL of methanol and 116 mL of concentrated HCl. Stirring at 25 °C was continued for 15 min. Zinc dust (60 g, 0.91 mol) was added in portions, and with good stirring (overhead), in such a way as to maintain a vigorous, but not violent, reaction. The mixture was allowed to reflux (without external application of heat) whereby the orange-red color of the nitro compound slowly disappeared. After 20 min, following addition of the last portion of Zn, the solution was filtered through a plug of glass wool. The zinc was washed well with methanol, then with CH<sub>2</sub>Cl<sub>2</sub> to ensure complete removal of adsorbed product. The clear, nearly colorless filtrates were diluted with 2 L of EtOAc. The mixture was washed well with saturated aqueous NaHCO3, whereby a pink color developed. The organic layer was also washed with brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration and concentration afforded crude amino alcohol 14b (20 g) which was used as such for the following bromination reaction. The compound was dissolved in 460 mL of  $CH_2Cl_2$  and diluted with 920 mL of ether. Solid  $CBr_4$  was added (30.4 g, 91.8 mmol) followed by triphenyl-phosphine (14.4 g, 55 mmol). Stirring at 25 °C was continued for 30 min, during which time a precipitate of triphenylphosphine oxide formed. The solution was concentrated to one-third of the original volume.

<sup>(42)</sup> The preparation of bromide 15a via the fully characterized intermediates 12a, 13a, and 14a is provided as supplementary material.

Filtration through a column of 500 g of Florisil (gradient hexane  $\rightarrow 15\%$ , EtOAc/hexane) removed phosphine-derived materials and afforded 16 g of bromide **15b** as a golden oil.

This unstable compound was immediately cyclized using the following procedure. To a solution of 16 g of bromide 15b in 2 L of CH<sub>2</sub>Cl<sub>2</sub> was added in one portion at room temperature and under  $N_2$  12 g of NPSP.<sup>28</sup> After 40 min the mixture was concentrated and taken up with ether. Treatment with 0.5 N aqueous NaOH  $(3 \times 200 \text{ mL})$  was necessary to remove phthalimide from the desired material. The organic layer was further washed with distilled water  $(2 \times 300 \text{ mL})$  and brine  $(1 \times 300 \text{ mL})$ mL), then dried over Na<sub>2</sub>SO<sub>4</sub>. Concentration furnished 18.2 g of crude tricyclic selenide 21. The compound was immediately submitted to oxidative deselenation. To this end, the material was dissolved in  $\text{CH}_2\text{Cl}_2$ (500 mL) and cooled to -25 °C (dry ice/CCl<sub>4</sub> bath). Portions of a solution of MCPBA (commercial 85% pure reagent, 6.6 g) in CH<sub>2</sub>Cl<sub>2</sub> (60 mL) were added until TLC analysis of the reaction mixture failed to indicate the presence of selenide 21. Diispropylamine was added (10 mL) and the cold solution of selenoxide was rapidly poured into 1 L of refluxing CCl<sub>4</sub>. Heating under reflux was continued for 10 min, after which time the solution was cooled and washed well with 1 N NaOH. The solution was also washed with brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration and concentration afforded a dark residue which was chromatographed over 700 g of Merck 230-400 mesh silica (gradient hexane -15% EtOAc/hexane). The pure acetoxy olefin 22 thus obtained amounted to 6.4 g (31% overall yield from the Mitsunobu product). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) 7.40-7.32 (m, 5), 5.80 (br s, 2 H), 4.77 (br d, 1 H, J = 4.6 Hz), 4.56 (br d, 2 H), 4.19 (dd, 1 H,  $J_1 = 4.3$ ,  $J_2 = 15.6$ Hz), 4.04 (br dd, 1 H,  $J_1 = 4.7$ ,  $J_2 = 15.6$  Hz), 3.82 (s, 3 H), 3.74 (dd, 1 H, J = 4.6,  $J_2 = 8.9$  Hz), 3.66 (s, 3 H), 3.61 (ddd, 1 H,  $J_1 = J_2 = 4.6$ , s = 8.9 Hz), 3.46 (dd,  $J_1 = J_2 = 8.9$  Hz), 2.18 (s, 3 H), 2.17 (s, 3 H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 22.5 MHz) 168.3, 144.1, 143.4, 143.2, 138.8, 136.8, 130.6, 128.1, 127.4, 125.0, 121.8, 76.6, 72.8, 72.0, 60.3, 60.0, 58.9, 57.5, 46.9, 20.1, 14.0, 9.3. IR (neat, cm<sup>-1</sup>) 2925, 2350, 1760, 1600, 1450, 1400, 1195, 725, 680. m/e 409 (P<sup>+</sup>), 366, 352, 300, 286, 258, 244, 214, 91.

(±)-(9R\*,9aS\*)-8-Benzyloxy-9-[(benzyloxy)methyl]-9,9-dihydro-5,7dimethoxy-6-methyl-3H-pyrrolo[1,2-a]indole (19). Acetate 22 (1.04 g, 2.54 mmol) was dissolved in 25 mL of dry methanol and treated with solid K<sub>2</sub>CO<sub>3</sub> (439 mg, 3.18 mmol). The suspension was stirred at room temperature for 2 h, after which time the reaction was quenched by addition of 5 mL of water which had been saturated with <sup>1</sup>H (dry ice). The solvent was removed under vacuum and the residue was passed through a short plug of silica gel (EtOAc). Concentration of the eluate left 896 mg of product (96%). This material was dissolved in 7 mL of DME and 7 mL of DMF. Solid KH (300 mg; thoroughly washed with pentane) was added to the solution and the resulting suspension was allowed to stir at 25 °C for 10 min. Neat benzyl bromide was added (500 mg, 2.9 mmol) and the resulting mixture was stirred at 25 °C for 3 h. The reaction was quenched by addition of 5 mL of water which had been saturated with CO<sub>2</sub> (dry ice). Dilution with 20 mL of water and 20 mL of saturated aqueous NaCl and extractive workup (ether) gave a crude product which was chromatographed (30 g of Merck 70-230 mesh silica gel, 50% EtOAc/hexane) to afford 1.06 g of dibenzyl olefin (91%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) 7.28-7.40 (m, 10 H), 5.78 (m, 1 H), 5.75 (m, 1 H), 5.04 (d, 1 H,  $J_{AB}$  = 11 Hz), 4.96 (d, 1 H,  $J_{BA}$  = 11 Hz), 4.78 (br m, 1 H), 4.54 (d, 1 H,  $J_{A'B'} = 12$  Hz), 4.48 (d, 1 H,  $J_{B'A'} = 12$  Hz), 4.18  $(dddd, 1 H, J_1 = 16, J_2 = 4.5, J_3 = 2 Hz), 4.04 (br d, 1 H, J = 16 Hz),$ 3.98 (dd, 1 H,  $J_1 = 9$ ,  $J_2 = 4$  Hz), 3.81 (s, 3 H), 3.79 (s, 3 H), 3.55 (ddd, 1 H,  $J_1 = 10$ ,  $J_2 = 4$ ,  $J_3 = 4$  Hz), 3.45 (dd, 1 H,  $J_1 = 10$ ,  $J_2 = 8.6$  Hz), 2.17 (s, 3 H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 22.5 MHz) 145.0, 144.6, 143.0, 141.4, 138.2, 137.6, 130.9, 128.0, 127.6, 127.4, 127.1, 126.7, 124.8, 121.3, 76.2, 74.2, 72.6, 72.2, 67.4, 60.0, 58.8, 57.6, 46.8, 25.2, 9.0. IR (CHCl<sub>3</sub>, cm<sup>-1</sup>) 2985, 2900, 1597, 1460, 1450, 1408, 1050. m/e 459 (P + 2), 458 (P + 1), 457 (P), 442, 336, 348, 258. Anal. Calcd for C<sub>29</sub>H<sub>31</sub>NO<sub>4</sub>: C, 76.12; H, 6.85; N, 3.06. Found: C, 76.02; H, 6.85; N, 2.95.

(±)-(1S\*,9R\*,9aS\*)-1-Phenylseleno-8-benzyloxy-9-[(benzyloxy)methyl]-2,3,9,9a-tetrahydro-5,7-dimethoxy-6-methyl-1H-pyrrolo[1,2-a]indole (16) Plus Stereoisomer 17. The bromide 15a<sup>2</sup> (3.67 g, 4.74 mmol) was dissolved in 56 mL of dry methylene chloride and a solution of N-phenylselenophthalimide (N-PSP) (1.43 g, 4.74 mmol) in 45 mL of methylene chloride was added dropwise over 1 h. After stirring for 30 min, the reaction was diluted with 350 mL of methylene chloride and washed with 0.5 M sodium hydroxide (1 × 200 mL) and then brine (1 × 200 mL). The organic phase was dried over sodium sulfate, filtered, and concentrated in vacuo to 3.90 g of a reddish oil. Rapid chromatography on 47 g of silica gel first with 5%, then 15% ethyl acetate in hexanes yielded 1.56 g (57%) of a mixture of stereoisomeric selenides (estimated HPLC ratio ca. 4:1).

**Major Selenide 16.** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) 7.20–7.60 (m, 15 H), 5.03 (d, 1 H,  $J_{AB} = 10$  Hz), 4.92 (d, 1 H,  $J_{BA} = 10$  Hz), 4.62 (d,

i H,  $J_{A'B'} = 12.5$  Hz), 4.45 (d,  $J_{B'A'} = 12.5$  Hz, 1 H), 3.78 (s, 3 H), 3.77-3.75 (m, 2 H), 3.70 (s, 3 H), 3.30-3.50 (m, 4 H), 2.83 (m, 1 H), 2.17 (s, 3 H), 2.17 (multiplet under methyl, 1 H), 1.90 (m, 1 h). IR (CHCl<sub>3</sub>, cm<sup>-1</sup>) 2960, 1587, 1470, 1450, 1410, 1047. m/e 615 (P<sup>+</sup>). Calcd for C<sub>35</sub>H<sub>37</sub>NO<sub>4</sub><sup>80</sup>Se: m/e 615.1888. Found: m/e 615.1887.

**Minor Selenide 17.** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) 7.60–7.20 (m, 15 H), 5.06 (d, 1 H,  $J_{AB} = 10$  Hz), 4.97 (d, 1 H,  $J_{AB} = 10$  Hz), 4.39 (br s, 2 H), 4.19 (dd, 1 H,  $J_1 = 8$ ,  $J_2 = 10$  Hz), 4.55 (m, 2 H,  $J_1 = 2$ ,  $J_2 = 10$  Hz), 3.77 (s, 3 H), 3.75 (m, 1 H,  $J_1 = 8$  Hz), 3.71 (s, 1 H), 3.55 (br t, 1 H, J = 8 Hz), 3.49 (m, 1 H), 3.23 (m, 1 H), 2.18 (s, 3 H, overlapping with a m, 1 H), 2.04 (m, 1 H). m/e 615 (P<sup>+</sup>), 337, 261, 246, 218.

(±)-(9R\*,9aS\*)-3-Benzyloxy-9-[(benzyloxy)methyl]-9,9-dihydro-5,7dimethoxy-6-methyl-3H-pyrrolo[1,2-a ]indole (19) Plus Stereoisomer 18. The mixture of isomeric selenides (1.56 g, 2.54 mmol) was dissolved in 32 mL of dry methylene chloride and cooled to  $-23 \,^{\circ}C \,(CO_2/CCl_4)$ . A solution of m-chloroperbenzoic acid (85%, 0.570 g, 2.80 mmol) in 32 mL of dry methylene chloride was added via a dropping funnel over about 10 min. The reaction mixture stirred at -23 °C for 30 min before 540  $\mu L$  of diisopropylamine was added. The faintly yellow solution was transferred to boiling carbon tetrachloride (ca. 100 mL) and the solution refluxed for 5 min. The reaction was cooled to room temperature with the aid of a cool water bath. After further diluting with 300 mL of methylene chloride, the solution was washed with 1.0 N sodium hydroxide  $(1 \times 100 \text{ mL})$  and then with brine  $(1 \times 100 \text{ mL})$ . The organic portion was dried over sodium sulfate and concentrated in vacuo at room temperature; the residue (1.65 g) was chromatographed on silica gel (10% ethyl acetate in hexanes). Scrutiny of the olefin so obtained (0.938 g, 82%) using analytical HPLC (Waters  $\mu$ -Porasil, 8% ethyl acetate in hexanes) revealed a mixture of isomeric olefins in a ratio of 3.8 to 1. Analytical samples at both olefins were obtained by HPLC separation of the mixture. However, the minor isomeric olefin was most easily removed after the mixture had been subjected to the action of OsO4. Apparently, osmylation of the minor olefin is less facile.

**Major Olefin 19.** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) 7.28–7.40 (m, 10 H), 5.78 (m, 1 H), 5.75 (m, 1 H), 5.04 (d, 1 H,  $J_{AB} = 11$  Hz), 4.96 (d, 1 H,  $J_{BA} = 11$  Hz), 4.78 (br m, 1 H), 4.54 (d, 1 H,  $J_{A'B'} = 12$  Hz), 4.48 (d, 1 H,  $J_{F'A'} = 12$  Hz), 4.18 (dddd, 1 H,  $J_1 = 16$ ,  $J_2 = 4.5$ ,  $J_3 = 2$  Hz), 4.04 (br d, 1 H, J = 16 Hz), 3.98 (dd, 1 H, J = 9, J = 4 Hz), 3.81 (s, 3 H), 3.79 (s, 3 H), 3.55 (ddd, 1 H,  $J_1 = 10$ ,  $J_2 = 4$ ,  $J_3 = 4$  Hz), 3.45 (dd, 1 H,  $J_1 = 10$ ,  $J_2 = 8$ , 6 Hz), 2.17 (s, 3 H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 22.5 MHz) 145.1, 144.6, 143.0, 141.4, 138.2, 137.6, 130.9, 128.0, 127.6, 127.4, 127.1, 126.7, 124.8, 121.4, 76.2, 74.2, 72.6, 72.3, 67.4, 60.0, 58.8, 57.6, 46.8, 25.2, 9.0. IR (CHCl<sub>3</sub>, cm<sup>-1</sup>) 2985, 2857, 1597, 1460, 1450, 1408, 1052. m/e 459 (P<sup>+</sup> + 2), 458 (P<sup>+</sup> + 1), 457 (P<sup>+</sup>), 442, 336, 348, 258. Anal. Calcd for C<sub>29</sub>H<sub>31</sub>NO<sub>4</sub>: C, 76.12; H, 6.85; N, 3.06. Found: C, 76.02; H, 6.85; N, 2.95.

**Minor Olefin 18.** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) 7.30–7.45 (m, 10 H), 6.03 (ddd, 1 H,  $J_1 = 5.5$ ,  $J_2 = 4$ ,  $J_3 = 2$  Hz), 5.85 (ddd, 1 H,  $J_1 = 5.5$ ,  $J_2 = 4$ ,  $J_3 = 2$  Hz), 5.06 (d, 1 H,  $J_{AB} = 11$  Hz), 5.00 (d, 1 H,  $J_{BA} = 11$ Hz), 5.03 (m, 1 H), 4.47 (d, 1 H,  $J_{A'B'} = 12$  Hz), 4.41 (d, 1 H,  $J_{B'A'} =$ 12 Hz), 4.14 (br dddd, 1 H,  $J_1 = 16$ ,  $J_2 = 4$ ,  $J_3 = 2$ ,  $J_4 = 1$  Hz), 4.07 (dddd, 1 H,  $J_1 = 16$ ,  $J_2 = 5.5$ ,  $J_3 = 2$ ,  $J_4 = 2$  Hz), 4.05 (dd,  $J_1 = 10$ ,  $J_2 = 4$  Hz), 3.80 (s, 3 H), 3.77 (s, 3 H), 3.66 (dddd, 1 H,  $J_1 = 13$ ,  $J_2 =$ 11.4,  $J_3 = 4$ ,  $J_4 = 1$  Hz), 3.34 (dd, 1 H,  $J_1 = 11.4$ ,  $J_2 = 10$  Hz), 2.19 (s, 3 H). m/e 459 (P<sup>+</sup> + 2), 458 (P<sup>+</sup> + 1), 457 (P<sup>+</sup>).

 $(\pm)$ - $(1S^*, 2R^*, 9R^*, 9aR^*)$ -8-Benzyloxy-9-[(benzyloxy)methyl]-2,3,9,9a-tetrahydro-5,7-dimethoxy-6-methyl-1H-pyrrolo[1,2-a]indole-1,2-diol (24). To a solution of N-methylmorpholine N-oxide (238 mg, 1.56 mmol) in 2.7 mL of tert-butyl alcohol, 950 µL of tetrahydrofuran, and 300  $\mu$ L of water was added 85  $\mu$ L of a solution of OsO<sub>4</sub> in tetrahydrofuran (1 g in 10 mL). The olefinic substrate (630 mg, 1.38 mmol), contaminated by ca. 15% of the stereoisomeric olefin, was added as a soltuion in 3.4 mL of tetrahydrofuran. The reaction mixture was stirred at room temperature for 8 h. The solution was diluted with ethyl acetate and washed with water and with brine. The organic portion was filtered through a short column of Florisil and the filtrate was concentrated to 593 mg of a white, foamy solid. Chromatography on 15 g of silica gel with 50% ethyl acetate in hexanes gave 413 mg (61%) of diol 24 as a single isomer. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) 7.30-7.40 (m, 10 H), 5.04 (d, 1 H,  $J_{AB} = 12$  Hz), 4.96 (d, 1 H,  $J_{BA} = 12$  Hz), 4.53 (d, 1 H,  $J_{A'B'} = 11$  Hz), 4.51 (d, 1 H,  $J_{B'A'} = 11$  Hz), 4.35 (m, 1 H), 4.12–4.60 (m, 2 H), 4.0 (m, 1 H), 3.90 (m, 1 H), 3.78 (s, 3 H), 3.73 (s, 3 H), 3.63 (m, 1 H), 3.39 (dd, 1 H,  $J_1 = 11$ ,  $J_2 = 8$  Hz), 3.17 (dd, 1 H,  $J_1 = 11$ ,  $J_2 = 6$  Hz), 2.16 (s, 3 H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 22.5 MHz) 145.3, 144.6, 143.2, 140.9, 138.1, 137.9, 128.4 (three overlapping resonances), 128.2, 127.9, 127.7, 125.3, 122.3, 74.7, 73.7, 73.1, 72.7, 72.3, 60.5, 58.6, 55.8, 42.5, 9.4. IR (CHCl<sub>3</sub>, cm<sup>-1</sup>) 3380, 1574, 1430. m/e 492 (P<sup>+</sup> + 1), 491 (P<sup>+</sup>), 400. 372. 309

(±)-(1aR\*,8R\*,8aR\*,8bS\*)-7-Benzyloxy-8-[(benzyloxy)methyl]-1,1a,2,8,8a,8b-hexahydro-4,6-dimethoxy-5-methylazirino[2',3':3,4]- **pyrrolo**[1,2-*a*]indole (30). To a solution of the diol 24 (390 mg, 0.79 mmol) in 4.4 mL of dry dichloromethane at 0 °C under argon was added methanesulfonyl chloride (68  $\mu$ L, 0.88 mmol, freshly distilled from P<sub>2</sub>O<sub>3</sub>) followed by triethylamine (170  $\mu$ L, 1.22 mmol). After stirring at 0 °C for 1 h 30 min, the reaction mixture was diluted with ether and washed with cold saturated sodium bicarbonate (2 × 10 mL) and then with brine (1 × 20 mL). The ethereal portion was dried over sodium sulfate, filtered, and concentrated to 471 mg (100%) of a faintly tan foamy solid: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 90 MHz) 2.95 (s, 3 H), *m/e* 569 (P<sup>+</sup>).

A solution of tetrabutylammonium azide (4.047 g, 14 mmol, previously dried by azeotropic distillation of a benzene solution in vacuo) in 22 mL of dry benzene was added to the crude monomesylate. The solution was gently refluxed for 2.5 h under an argon atmosphere. After cooling to room temperature, the reaction was diluted with ether and washed thoroughly with water ( $6 \times 50$  mL) and then brine ( $1 \times 50$  mL). The organic layer was dried over sodium sulfate and concentrated to 412 mg of crude azido alcohol **26** as a tan foamy solid: IR (CHCl<sub>3</sub>, cm<sup>-1</sup>) 2095; m/e 516 (P<sup>+</sup>), 488 (P<sup>+</sup> - N<sub>2</sub>), 474 (P<sup>+</sup> - N<sub>3</sub>).

To a solution of the crude azido alcohol in 4.3 mL of dry methylene chloride at 0 °C under argon were added freshly distilled methanesulfonyl chloride (87 µL, 1.1 mmol) and then triethylamine (180 µL, 1.3 mmol). After stirring for 2 h at 0 °C, the mixture was diluted with ether, washed with saturated sodium bicarbonate and then brine, and dried over sodium sulfate; the solvent was removed in vacuo to leave 447 mg of crude azido mesylate: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 90 MHz) 2.75 (s, 3 H), IR (CHCl<sub>3</sub>, cm<sup>-1</sup>) 2095. The crude azide was dissolved in 130 mL of tetrahydrofuran and heated at reflux with trimethyl phosphite (340  $\mu L,\,2.9$  mmol) for 4 h. After the solution had cooled to room temperature, the solvent was removed in vacuo and the residue was dissolved in 5 mL of anhydrous tetrahydrofuran. The solution was then transferred (via syringe) to a suspension of sodium hydride (250 mg, 60% dispersion in oil, previously washed with dry pentane) in 10 mL of tetrahydrofuran. After stirring at room temperature under argon for 4 h, the reaction was quenched by the addition of saturated sodium sulfate solution. The mixture was layered with methylene chloride and washed with saturated sodium bicarbonate. The organic portion was dried over sodium sulfate, filtered, and concentrated to 575 mg of crude phosphoryl aziridine 29. The aziridine was dissolved in 17 mL of anhydrous ether and subjected to the action of lithium aluminum hydride (0.90 mL, 1 M solution in ether, Aldrich) at 0 °C under an argon atmosphere. After 1 h, an additional portion of LiAlH<sub>4</sub> solution (0.90 mL) was added and the reaction continued at 0 °C for 45 min. The cooling bath was removed and the mixture warmed to room temperature over 15 min. The reaction was finally quenched at 0 °C with 3.6 mL of 20% aqueous sodium hydroxide solution. After stirring at room temperature for 30 min, the mixture was diluted with 0.1 N sodium hydroxide and extracted into methylene chloride. The combined extracts were washed once with brine and then dried over anhydrous potassium carbonate. Concentration in vacuo afforded 347 mg of crude aziridine 30. Chromatography of the residue on silica gel (10 g) with ethyl acetate-hexane-triethylamine 8:1:0.5) afforded 145 mg of pure aziridine (39% overall from diol 24). <sup>1</sup>H NMR  $(CDCl_3, 500 \text{ MHz})$  7.31–7.26 (m, 10 H) 4.93 (d, 1 H,  $J_{AB} = 11 \text{ Hz})$ , 4.85 (d, 1 H,  $J_{AB} = 11$  Hz), 4.48 (d, 1 H,  $J_{AB} = 12$  Hz), 4.43 (d, 1 H,  $J_{AB} = 12 \text{ Hz}$ ), 4.18 (m, 1 H,  $J_1 = 7 \text{ Hz}$ ), 3.95 (d, 1 H, J = 7 Hz), 3.71 (s, 3 H), 3.70 (s, 3 H), 3.57 (d, 1 H, J = 11 Hz), 3.44-3.41 (m, 2 H),2.97 (dd, 1 H,  $J_1 = 3$ ,  $J_2 = 11$  Hz), 2.82 (br s, 1 H), 2.72 (br d, 1 H, J = 3 Hz), 2.10 (s, 3 H). IR (CHCl<sub>3</sub>, cm<sup>-1</sup>) 2975, 1600, 1460, 1438, 1398, 1350, 1250. m/e 473 (P<sup>+</sup> + 1), 472 (P<sup>+</sup>), 458, 457, 381.

(±)-(1aR\*,8R\*,8aR\*,8bS\*)-7-(Benzyloxy)-8-[(benzyloxy)methyl]-1,1a,2,8,8a,8b-hexahydro-4,6-dimethoxy-1,5-dimethylazirino[2',3':3,4]pyrrolo[1,2-a]indole (31). To a solution of aziridine 30 (30 mg, 0.064 mmol) in 380  $\mu$ L of anhydrous ether at room temperature under argon was added MeLi (74  $\mu$ L, 0.115 mmol, 1.55 M solution in ether; Aldrich) via syringe in a single portion. After the reaction had stirred for 20 min at room temperature (turning slightly cloudy), methyl iodide (7.1  $\mu$ L, 0.114 mmol) was added. After 60 min, the mixture was diluted with methylene chloride and layered with a small amount of water. The mixture was washed once with 0.1 N aqueous sodium hydroxide and then with brine. The organic portion was then dried over anhydrous potassium carbonate. Evaporation of the volatiles left 28.1 mg of crude Nmethylaziridine. Chromatography on silica gel (ethyl acetate-hexanetriethylamine 8:1:0.5) afforded 20 mg (64%) of pure aziridine 31 and 4 mg of recovered starting material. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) 7.25–7.40 (m, 10 H), 5.01 (d, 1 H,  $J_{AB} = 11.5$  Hz), 4.93 (d, 1 H,  $J_{BA} = 11.5$  Hz), 4.56 (d, 1 H,  $J_{A'B'} = 11.7$  Hz), 4.54 (d, 1 H,  $J_{B'A'} = 11.7$  Hz), 4.12 (brd, 1 H, J = 4.8 Hz), 3.91 (d, 1 H, J = 6.9 Hz), 3.77 (s) 3 H), 3.75 (s, 3 H), 3.50 (d, 1 H, J = 11.1 Hz), 3.37 (m, 2 H), 2.94 (dd, 1 H,  $J_1 = 11.1$ ,  $J_2 = 3.6$  Hz), 2.35 (s, 3 H), 2.30 (dd, 1 H,  $J_1 = 3.6$ ,  $J_2 = 5.1$  Hz), 2.16 (s, 3 H), 2.12 (d, 1 H, J = 5.1 Hz). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 22.5 MHz) 146.0, 144.4, 143.9, 143.3, 142.0, 138.6, 137.7, 128.3 (three

overlapping resonances), 127.9, 127.4, 125.1, 123.4, 74.7, 73.6, 73.1, 72.3, 60.5, 58.1, 55.2, 50.1, 48.4, 46.9, 45.4, 9.3. IR (CHCl<sub>3</sub>, cm<sup>-1</sup>) 2906, 1590, 1440, 1398. m/e 486 (P<sup>+</sup>). Calcd for C<sub>30</sub>H<sub>34</sub>N<sub>2</sub>O<sub>4</sub> m/e 486.2519 (P<sup>+</sup>). Found: m/e 486.2509.

(±)-(1aR \*,8R \*,8aR \*,8bS \*)-7-Hydroxy-8-hydroxymethyl-1,1a,2,8,8a,8b-hexahydro-4,6-dimethoxy-1,5-dimethylazirino[2',3':3,4]pyrrolo[1,2-a]indole (32). To a solution of the dibenzyloxy aziridine 31 (35 mg, 0.072 mmol) in 250 µL of dry tetrahydrofuran was added liquid ammonia (ca. 1 mL). Sodium metal (ca. 60 mg) was added to the cold solution. The blue color was permitted to persist for about 10 min, before the reaction was quenched with the addition of solid ammonium chloride. The mixture was evaporated at room temperature under a flow of nitrogen. The residue was layered with ethyl acetate and water, then transferred to a separatory funnel. The mixture was diluted with ethyl acetate and the organic layer was separated. The aqueous portion was extracted twice with ethyl acetate. The combined extracts were dried over sodium sulfate and then concentrated in vacuo. Chromatography of the residue on silica gel (8% methanol/ethyl acetate) afforded white crystalline diol 32 (22 mg, 100%) mp 155.5-156.6 °C. <sup>1</sup>H NMR  $(CDCl_3, 500 \text{ MHz}) 4.02 \text{ (dd, 1 H, } J_1 = 10, J_2 = 4.2 \text{ Hz}), 3.88 \text{ (dd, 1)}$ H,  $J_1 = 10$ ,  $J_2 = 10$  Hz), 3.75 (s, 3 H), 3.75 (m, 1 H, under methoxy), 3.69 (s, 3 H), 3.65 (m, 1 H, under H<sub>3</sub>), 3.64 (d, 1 H, J = 11.2 Hz), 3.04 $(dd, 1 H, J_1 = 11.2, J_2 = 3.5 Hz), 2.41 (dd, 1 H, J_1 = 5.2, J_2 = 3.5 Hz),$ 2.35 (s, 3 H), 2.19 (d, 1 H, J = 5.2 Hz), 2.16 (s, 3 H). IR (CHCl<sub>3</sub>, cm<sup>-1</sup>) 3174, 2898, 1250. m/e 306 (P<sup>+</sup>). Anal. Calcd for C<sub>16</sub>H<sub>22</sub>N<sub>2</sub>O<sub>4</sub>: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.56; H, 7.33; N, 8.91.

(±)-(1a*R*\*,8*R*\*,8a*R*\*,8b*S*\*)-1,1a,2,8,8a,8b-Hexahydro-8-(hydroxymethyl)-6-methoxy-1,5-dimethylazirino[2',3':3,4]pyrrolo[1,2-a]indole-4,7-dione (33). Phenol 32 (9 mg, 0.029 mmol) was dissolved in 1 mL of 10% aqueous tetrahydrofuran and ca. one crystal of *p*-nitrophenol was added. To this colorless solution was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (7.3 mg, 0.032 mmol, added as a solution in 225  $\mu$ L of THF). Immediately on addition, the solution became deep purple. After the mixture was stirred at room temperature for 40 min, the volatiles were removed in vacuo to leave a black, purple powder. The powder was dissolved in chloroform and washed thoroughly with cold 10% aqueous potassium carbonate. The organic portion was washed once with brine and dried over sodium sulfate. Concentration in vacuo afforded 5.2 mg (61%) of quinone as purple needles, mp 146-152 °C dec. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) 5.15 (br, s, 1 H), 3.95 (dd, 1 H,  $J_1 = 13$ ,  $J_2 = 5$  Hz), 3.89 (br m, 1 H), 3.86 (s, 3 H), 3.81 (d, 1 H, J = 10 Hz), 3.75 (dd, J = 11,  $J_2 = 9$  Hz), 3.53 (m, 2 H, containing a d, 1 H, J =13 Hz), 2.62 (t, 1 H, J = 5 Hz), 2.41 (s, 3 H), 2.30 (d, 1 H, J = 5 Hz), 1.99 (s, 3 H). IR (CHCl<sub>3</sub>, cm<sup>-1</sup>) 3290, 2960, 1660, 1590, 1503, 1457, 1440, 1260. m/e 292 (P<sup>+</sup> + 2), 290 (P<sup>+</sup>), 262, 261, 232, 231, 190, 100.

*N*-Oxides 34 and 35. A solution of olefin 22 (165 mg, 0.403 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (4 mL) was cooled to 0 °C. Solid MCPBA was added in small portions (82 mg total, 0.403 mmol assuming 85% pure reagent). The reaction mixture was warmed to room temperature and stirred for 30 min. The solution was diluted with more CH<sub>2</sub>Cl<sub>2</sub> and washed with saturated aqueous NaHCO<sub>3</sub>, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated in vacuo to afford 171 mg of product (99.7%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 250 MHz) 7.47–7.24 (m, 5 H), 5.79 (br m, 2 H), 5.64 (br s, 1 H), 5.38 (br d, 1 H,  $J_{AB} = 16$  Hz), 5.12 (br d, 1 H,  $J_{AB} = 16$  Hz), 4.60 (d, 1 H,  $J_{AB} = 12$  Hz), 4.50 (d, 1 H,  $J_{AB} = 12$  Hz), 4.10 (s, 3 H), 3.90–3.76 (m, 2 H), 3.74 (s, 3 H), 3.43 (br t,  $J_1 = 7$ ,  $J_2 = 2$  Hz), 2.24 (s, 3 H), 2.17 (s, 3 H). IR (film, cm<sup>-1</sup>) 2900, 1760, 1660, 1465, 1185. *m/e* 425 (P<sup>+</sup>), 409, 407, 300, 244.

In a similar manner, 9 mg of N-oxide **35** was obtained from 9 mg of aziridine **31**. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 270 MHz) 7.43–7.26 (m, 10 H), 4.99 (d, 1 H,  $J_{AB} = 11$  Hz), 4.91 (d, 1 H,  $J_{AB} = 11$  Hz), 4.55 (d, 1 H,  $J_{AB} = 12$  Hz), 4.53 (d, 1 H,  $J_{AB} = 12$  Hz), 4.21 (d, 1 H, J = 5 Hz), 4.05 (d, 1 H, J = 7 Hz), 3.77–3.75 (m, 1 H), 3.76 (s, 3 H), 3.73 (s, 3 H), 3.63 (d, 1 H, J = 11 Hz), 3.46 (m, 1 H,  $J_1 = 6$  Hz), 3.06 (dd, 1 H,  $J_1 = 11$ ,  $J_2 = 4$  Hz), 2.41 (dd, 1 H,  $J_1 = 5$ ,  $J_2 = 4$  Hz), 2.39 (s, 3 H), 2.29 (d, 1 H, J = 5 Hz), 2.15 (s, 3 H). m/e 486 (P<sup>+</sup> – 16), 395, 367, 274, 259.

Quinone Ketal 37. A solution of aziridine 30 (25 mg, 0.053 mmol) in dry MeOH (1 mL) was added to a suspension of 10% Pd/C (20 mg) in 1 mL of MeOH. The mixture was saturated with H<sub>2</sub> (bubbling), and after 20 min at 25 °C the solution was filtered through Celite. Concentration of the filtrate left 20 mg (99%) of phenol 36. The compound was dissolved in 0.5 mL of MeOH and treated with 0.6 mL of a stock solution of DDQ (340 mg) and *p*-nitrophenol (13 mg) in 15 mL of MeOH. Stirring at 25 °C was continued for 45 min, then the solvent was removed in vacuo. The solid residue was taken up with CH<sub>2</sub>Cl<sub>2</sub> and washed with 1 N NaOH and brine. The organic phase was dried over K<sub>2</sub>CO<sub>3</sub> and evaporated, leaving 22 mg of crude product. Chromatography over 0.5 g of Merck 230-400 mesh silica gel (95:10:5 EtOAc/ hexane/Et<sub>3</sub>N) afforded 9 mg of ketal 37 as a yellow oil (40%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) 7.37-7.34 (m, 5 H), 4.63 (d, 1 H,  $J_{AB} = 12$  Hz), 4.3 (d, 1 H,  $J_{AB} = 12$  Hz), 4.21 (dd, 1 H,  $J_1 = 9$ ,  $J_2 = 4$  Hz), 4.03 (d, 1 H, J = 8 Hz), 3.87 (dd, 1 H,  $J_1 = 12$ ,  $J_2 = 4$  Hz), 3.65 (s, 3 H), 3.59 (m, 1 H), 3.49 (m, 1 H), 3.42 (m, 1 H), 3.23 (s, 3 H), 3.22 (s, 3 H), 3.08 (br s, 1 H), 2.87 (br s, 1 H), 1.87 (s, 3 H).

Acknowledgment. This work was supported by PHS Grant CA 28824. NMR spectra were obtained through the auspices of the Northeast Regional NSF/NMR Facility at Yale University, which was supported by NSF Chemistry Division Grant CHE 7916210.

Supplementary Material Available: An ORTEP drawing of

compound 32 as well as the procedures related to the solution of the crystal structure, thermal parameters (Table I), bond distances (Table II), and bond angles (Table III). Experimental protocols for the preparative work, as well as modifications in the synthesis of phenol 7, are also provided. In addition, experimental procedures for the conversion of purified ether 8 to 15a through fully characterized intermediates 12a, 13a, and 14a are included, as well as the spectral properties of the crude intermediates 12b, 13b, 14b, 15b, and selenide 21. Also included are the preliminary results of transformations of tricyclic amine oxides (17 pages). Ordering information given on any current masthead page.

## Comparative Tests of Theoretical Procedures for Studying Chemical Reactions<sup>1</sup>

## Michael J. S. Dewar\* and Donn M. Storch<sup>2</sup>

Contribution from the Department of Chemistry, The University of Texas at Austin, Austin, Texas 78712. Received October 29, 1984

Abstract: A simple procedure is described for estimating the effective errors in molecular energies calculated by ab initio methods with respect to use of the latter in studies of chemical reactions. The procedure is illustrated by application to the STO-3G, 3-21G, and 6-31G\* models. Parallel results from semiempirical models (MINDO/3, MNDO, AM1) are included for comparison.

### Introduction

The most basic problem in chemistry is to find out how chemical reactions take place. It is also, unfortunately, a problem that cannot be solved by experiment, because the time a chemical reaction takes is too short ( $<10^{-13} \sim s$ ) for its course to be observed.<sup>3</sup> Current "experimental" approaches rely on theory to delineate possible mechanisms for a reaction. Experiments are then devised to distinguish between the various possibilities. Such an approach is naturally limited by the efficacy of the theory on which it is based, and until recently only qualitative theories were used in this connection. Studies of reaction mechanisms would clearly be much more effective if they were based on a theoretical approach able to reproduce the properties of molecules, in particular their energies, quantitatively. Reaction mechanisms could indeed be predicted unambiguously if the corresponding potential energy surfaces could be calculated accurately.

To be chemically useful, such a calculation must be carried out properly, i.e., with full geometry optimization, etc., and without making any assumptions, and the method used must also be sufficiently accurate. Unfortunately, no current ab initio procedure comes anywhere near to achieving the needed accuracy, in an a priori sense. The errors in molecular energies, calculated by standard Hartree-Fock-type ab initio models, are indeed comparable with the corresponding heats of atomization.<sup>4</sup> Since this point is still not generally appreciated, some additional examples are shown in Table I. Indeed, since the calculated values refer to molecules at equilibrium geometries, without zero point or thermal energy, the real errors are greater than indicated, by ca. 5%. Some improvement is possible in "beyond HF (Hartree-Fock)" methods, but these are confined to small molecules and the residual errors are still enormous, by chemical standards.

Table I.	Errors <sup>a</sup> in	Total En	ergies $(E)$	and Heat	ts of Ato	mization
(HA), C	alculated h	ov the RH	Method	Using the	6-31G*	Basis Set <sup>a</sup>

molecule	error in E	error in HA	HA (obsd)
acetylene	324	106	392
propane	578	189	955
cyclopropane	494	176	814
cyclopropene	554	166	656
diacetylene	738	190	676
1,3-butadiene	682	221	972
hydrazine	444	162	412
hydrazoic acid	699	205	320
acetonitrile	523	51	478
cyanogen	799	207	478
methanol	515	130	487
dimethyl ether	704	94	671
ozone	631	68	145
acetone	896	225	938
dimethylamine	554	203	825
benzene	1301	649	1320

<sup>a</sup> All values in kcal/mol. The ab initio energies were taken from ref 14. These refer to calculations carried out with full geometry optimization, using the 6-31G\* basis set. Experimental total energies of atoms, relative to nuclei and electrons, were estimated from ionization energies (Weast, R. C. "CRC Handbook of Chemistry and Physics", 65th Ed.; CRC Press: Boca Raton, FL, 1984-5; pp E-63,64. Energies (eV): H, 13.598; C, 1030.080; N, 1486.029; O, 2043.794. For conversion factors, see Table II (footnote). Experimental heats of atomi-zation (standard state, gas phase, 25 °C) were estimated from thermochemical data listed by Cox and Pilcher. [Cox, J. D.; Pilcher, G. "Thermochemistry of Organic and Organometallic Compounds"; Academic Press: New York, 1970]. The experimental total energy of a molecule refers to the sum of its heat of formation and the total energies of the component atoms. It therefore includes kinetic energy terms. Since the calculated values for the molecular energies refer to equilibrium geometries, without corrections for zero point or thermal energy, the errors listed above are correspondingly too small; see text.

The errors are due primarily to neglect of electron correlation. If the correlation energy of a set of atoms did not change significantly when they combine to form a molecule, the errors might then cancel in calculating the differences in energy (heats of

Part 75 of a series of papers reporting the development and use of quantum molecular models. For part 74, see; Dewar, M. J. S.; Grady, G. L.; Merz, K. M., Jr.; Stewart, J. J. P. J. Am. Chem. Soc., in press.
 Present address: USAFA/DFC, Colorado Springs, Colo. 80840.

<sup>(3)</sup> Our inability to observe reactions is due not merely to lack of techniques but to the limits set by the Uncertainty Principle.

<sup>(4)</sup> Dewar, M. J. S.; Ford, G. P. J. Am. Chem. Soc. 1979, 101, 5558.