Total Synthesis of *dl*-Tazettine and 6a-Epipretazettine: A Formal Synthesis of *dl*-Pretazettine. Some Observations on the Relationship of 6a-Epipretazettine and Tazettine

Samuel Danishefsky,*† Joel Morris, George Mullen, and Ronald Gammill

Contribution from the Departments of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, and Yale University, New Haven, Connecticut 06511.
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Abstract: Diels–Alder cycloaddition of dienophile **26** with diene **8** produces the protected 4-aryl-4-acylcyclohexadienone **37**. This is converted in two steps to the oxidized mesembrine derivative **11**. Through the novel use of trimethyl orthoformate as a C_1 interpolating agent at the formic acid level of oxidation, alcohol **46** is converted to 6a-epipretazettine *O*-methyl ether (**49**) and thence to 6a-epipretazettine (**5**). The latter is transformed in four steps to *dl*-tazettine (**4**).

Background and Synthetic Planning

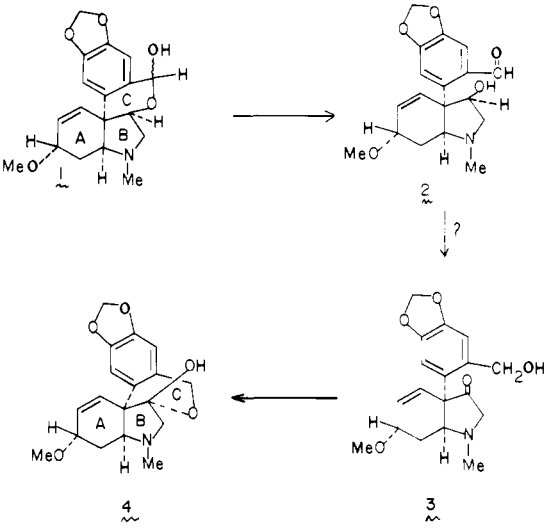
It was largely through the inspired research of William C. Wildman[1] and his associates that the structures of the amaryllidacae alkaloids were properly formulated.[2] The original target of the research to be described below was the chemically labile but biologically promising (vide infra) pretazettine (**1**).[3] The unearthing of the chemical relationship between pretazettine and (what was then the better known) tazettine (**4**) was one of the highpoints of Wildman's odyssey. Even under rather mildly basic conditions (pH ~10), pretazettine (**1**) suffers unidirectional conversion to tazettine (**4**). This conversion, which in net terms involves an otherwise baffling 1,3 interchange of a hydroxyl group and a hydrogem atom, was interpreted in terms of an undetectable ring → chain tautomer, **2**. The latter undergoes Cannizzaro equilibration to the hydroxy ketone **3**, which is the chain → ring tautomer of **4**. These relationships are summarized in Scheme I.

On inspection it is seen that the fusion of the B and C rings of pretazettine (**1**) is trans. The corresponding rings in tazettine (**4**) are fused in a cis fashion. The relief of the strain associated with such a trans fusion was perceived by Wildman to provide the major kinetic thrust for the pretazettine → tazettine rearrangement. However, it was also felt that this amelioration of strain energy was not obligatory for such a transformation. Thus, it was claimed that 6a-epipretazettine (**5**)[5] also suffers base-induced conversion to tazettine (**4**),[4] though at a much slower rate than the corresponding rearrangement of **1**.[3] The rearrangement of **5** was assumed to involve the intermediacy of the epimeric 6a-hydroxy compound, **6**. Crossed Cannizzaro equilibration of the hypothetical **6** would give rise to the previously encountered **3**, which, as noted above, is the hypothetical chain → ring tautomer of **4**. Of all of Wildman's reports, it is only with this one that we shall have experimentally based reasons for disagreement (vide infra).

It is also helpful to recall the relationship of haemanthidine to these alkaloids.[2-4] Structure **7**, which is the methiodide of haemanthidine, suffers transformation to pretazettine (**1**) on treatment with sodium bicarbonate and immediate extraction into chloroform.[4] Again, it is seen that deprotonation of **7** and ring → chain tautomerization afford the hypothetical hydroxyaldehyde **2**, which upon chain → ring tautomerization gives compound **1**. Under less moderate conditions, the pretazettine thus produced suffers its usual transformation to tazettine, presumably by way of **2** and **3**. These findings are summarized in Scheme II.

The attentions that we directed toward this series of alkaloids developed from a convergence of several considerations. The designation of pretazettine as a target was in keeping with our interest in the total synthesis of chemically labile natural products of promising biological activity. Furusawa and colleagues have reported on the potentialities of pretazettine as an antitumor drug.[6]

Scheme I



Indeed, pretazettine showed considerable efficacy in prolonging the life expectancy of leukemic mice infected with Raucher virus. In this capacity it has been claimed that pretazettine is superior to several drugs that have found clinical usage (cf. cyclophosphamide and vincristine).[6] *It should be emphasized that to our knowledge, neither the efficacy nor the safety of pretazettine has been certified at the clinical level.*

Our major, chemically based, interest accrued from the emergence of a plan of total synthesis that would allow us to gain further insights into the limits of practicality of our recently developed Diels–Alder strategies and methodologies.[7] It was hoped that enedione **11** might serve as a generally useful inter-

† To whom correspondence should be addressed at Yale University.

(1) We dedicate this paper to the memory of the late William C. Wildman.
(2) For a general review of this field, see: Sanisbury, M. In "Rodds Chemistry of Carbon Compounds, IV B"; Coffey, S., Ed.; Elsevier Scientific: Amsterdam, The Netherlands, 1977.
(3) Wildman, W. C.; Bailey, D. T. *J. Org. Chem.* **1968**, *33*, 3749.
(4) Wildman, W. C.; Bailey, D. T. *J. Am. Chem. Soc.* **1969**, *91*, 150.
(5) The numbering system we use here in the discussion section is that suggested by Wildman. The numbering system used for nomenclature in the Experimental Section conforms to Chemical Abstracts practice.
(6) Cf., inter alia: (a) Furusawa, E.; Suzuki, N.; Ramanathan, S.; Furusawa, S.; Cutting, W. *Proc. Soc. Expl. Biol. Med.* **1972**, *140*, 1034. (b) Furusawa, E.; Suzuki, N.; Furusawa, S.; Lee, J. Y. B. *Ibid.* **1975**, *149*, 771. (c) Papas, T. S.; Sandhaus, L.; Chirigos, M. A.; Furusawa, E. *Biochem. Biophys. Res. Commun.* **1972**, *52*, 88. (d) Suzuki, N.; Tani, S.; Furusawa, S.; Furusawa, E., *Proc. Soc. Expl. Biol. Med.*, **1974**, *145*, 771. (e) Furusawa, E.; Furusawa, S.; Lee, J. Y. B.; Patanovich, S. *Ibid.* **1976**, *152*, 186.
(7) (a) Danishefsky, S.; Harayama, T.; Singh, R. K. *J. Am. Chem. Soc.* **1979**, *101*, 7008. (b) Danishefsky, S.; Hirama, M.; Fritsch, N.; Clardy, J. *Ibid.* **1979**, *101*, 7013.

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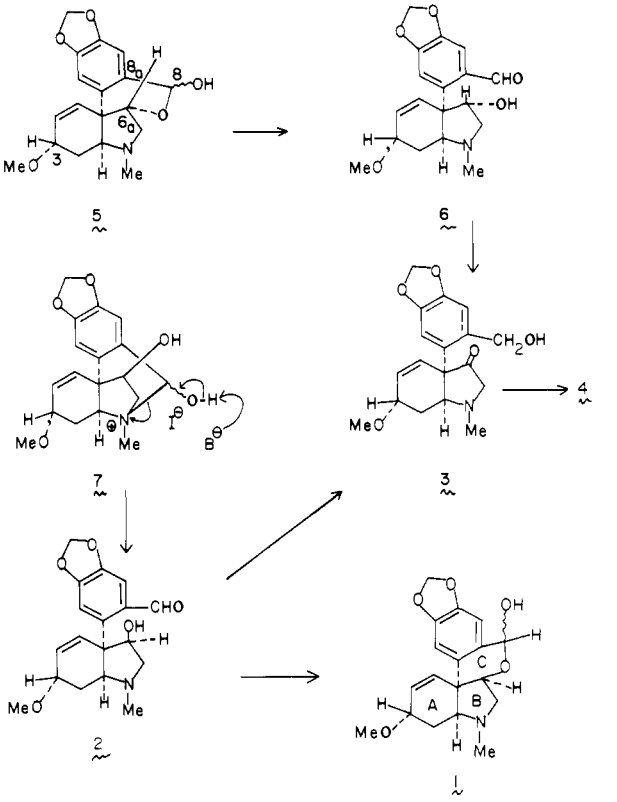
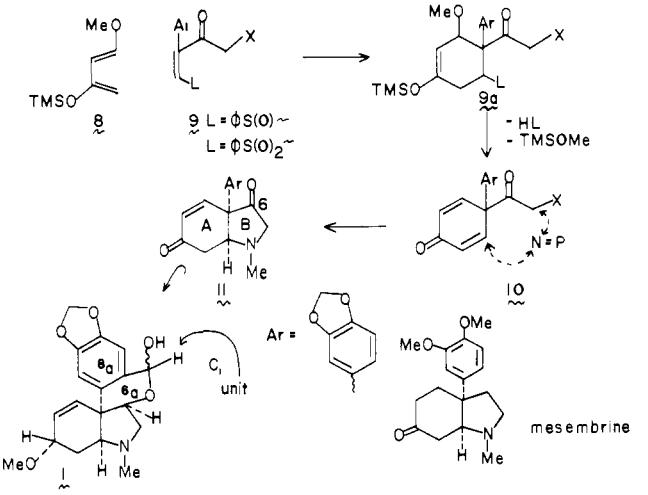
Scheme II



Scheme III



mediate to reach pretazettine (**1**) or tazettine (**4**). This hope rested on several expectations. Presumably, means could be uncovered wherein the necessary reductions and modifications at C_{6a} and C_3 could be conducted independently from one another. Were this managed, it was further supposed that a C_1 unit could be interpolated between a properly positioned alcohol at C_{6a} and the appropriate (C_{8a}) carbon of the angular methylenedioxyphenyl ring.[5] It will be shown that this supposition was vindicated in practice only in the synthesis of 6a-epipretazettine (**5**) in which the hydroxyl group and the angular aryl group are cis (α as drawn). With respect to our major goal, pretazettine, wherein these termini are disposed in a trans fashion with respect to the five-membered ring, we were unable to achieve this interpolation (vide infra).

Continuing in a retrosynthetic vein, it was expected that **11** might arise from a precursor of the type **10**. The designation "N = P" represents an actual or a latent methylamino function. One formulation of **10** → **11** that comes to mind is that of an intramolecular Michael reaction. This would cover the permutation wherein the methylamino function was first appended to the "enolonium equivalent", $C(O)CH_2X$. Alternatively, one could envision joining, in the first instance, the methylamino functionality in an intermolecular Michael reaction. Bond formation between the nitrogen and the enolonium center would then close the B ring. It was further recognized that the synthesis of system **10**, a 4,4-disubstituted cyclohexadienone, might, in principle, fall within the scope of our Diels–Alder methodology. Thus, cycloaddition of a highly functionalized diene of the type **8**[8] with a dienophile of the type **9** might afford an adduct such as **9a**. The latter might suffer the appropriate eliminations to give the required system **10**. It was through the implementation of this strategy that we hoped to gain a concise and effective entry to these complex alkaloids. The projected approach is summarized in Scheme III.

It must be emphasized that a considerable prior art of synthesis in this series had already existed. Thus, the total synthesis of *dl*-haemanthidine (**7**) recorded by Hendrickson and Fisch must be acknowledged as the major ground-breaking accomplishment in this field.[9] Given the connectivity between haemanthidine and the pretazettine → tazettine series,[2-4] the Hendrickson synthesis of haemanthidine also constitutes a total synthesis of these two alkaloids.

In addition, one was cognizant of the contributions of Tsuda et al.[10a-c] Again their efforts were directed at haemanthidine, and they did indeed describe the second total synthesis of this alkaloid.[11] Eventually, using apparently totally synthetic *dl*-haemanthidine, Tsuda repeated the Wildman experiments and recorded the total syntheses of racemic pretazettine (**1**) and racemic tazettine (**4**). It was hoped that the distinctive feature of our work would be that it might achieve a direct entry into the pretazettine → tazettine series, thus avoiding the tangent of passing through the haemanthidine system.

As noted above, a key intermediate in this regard was to be the enedione (**11**). It is well to take note of the relationship between **11** and a simpler amaryllidacae alkaloid, mesembrine.[2] Of course, a considerable prior art existed in connection with the total synthesis of mesembrine. It was our feeling at the time that however elegant those mesembrine syntheses certainly were,[12] they did not lend themselves to the inclusion of the additional keto group at C_6 in the target system (**11**). We note that the most recent success in the mesembrine area, achieved by Martin,[13] does have considerable potential for a more elaborate target such as **11**.

We describe with full experimental and spectral documentation the total synthesis of *dl*-tazettine (**4**) and *dl*-6a-epipretazettine (**5**). Through these studies,[14] in conjunction with the work of others,[15] a formal total synthesis of *dl*-pretazettine may also be claimed, through in unacceptably poor efficiency. Finally, these synthetic studies necessitate some revision in the relationship between **5** and **4** from that which was previously described.

Results

The Synthesis of Enedione 11. The known piperonyl ketone **12**[16] was the starting material for our investigation. To test the

(8) (a) Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807. (b) Danishefsky, S.; Kitahara, T. *J. Org. Chem.* **1975**, *40*, 538.

(9) (a) Hendrickson, J. B.; Bogard, T. L.; Fisch, M. E. *J. Am. Chem. Soc.* **1970**, *92*, 5538. (b) Hendrickson, J. B.; Bogard, T. L.; Fisch, M. E.; Grossert, S.; Yoshimura, N. *Ibid.* **1974**, *96*, 7781.

(10) (a) Tsuda, Y.; Ukai, A.; Isobe, K. *Tetrahedron Lett.* **1972**, 3153. (b) Tsuda, Y.; Isobe, K. *J. Chem. Soc. D* **1971**, 1555. (c) Isobe, K.; Taga, J.; Tsuda, Y. *Tetrahedron Lett.* **1976**, 2331.

(11) For a general review of this area of synthesis, see: Tsuda, Y. *Heterocycles* **1978**, *10*, 555.

(12) For an outstanding early synthesis of *dl*-mesembrine, see: Stevens, R. V.; Wentland, M. P. *J. Am. Chem. Soc.* **1968**, *90*, 5580.

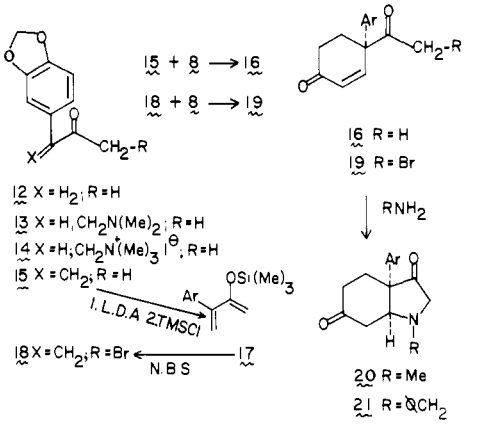
(13) Martin, S. F.; Puckette, T. A.; Colapret, J. *J. Org. Chem.* **1979**, *44*, 3391 and references therein.

(14) For a preliminary communication of these results, see: Danishefsky, S.; Morris, J.; Mullen, G.; Gammill, R. *J. Am. Chem. Soc.* **1980**, *102*, 2838.

(15) (a) Kobayashi, S.; Kihara, M. *Heterocycles* **1979**, *12*, 1547. (b) Kobayashi, S.; Kihara, M.; Shingu, T.; Shinagu, K. *Chem. Pharm. Bull.* **1980**, *28*, 2924.

(16) (a) Biniechi, S.; Muszynski, E.; Jagiellowicz, H.; Chojnache, Z. *Acta. Pol. Pharm.* **1962**, *19*, 31. (b) *Chem. Abstr.* **1962**, *58*, 3334g.

Scheme IV



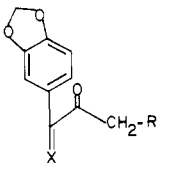
general feasibility of our approach, we subjected **12** to the action of *N,N*-dimethylmethyleneammonium chloride.[17] There was obtained a 69% yield of the amine **13**. The methiodide (**14**) obtained upon quaternization of **13** with methyl iodide gave upon reaction with potassium carbonate the unstable α-methylene ketone **15**. A Diels–Alder reaction between **15** and diene **8** (benzene, reflux, 48 h), followed by hydrolysis gave a 45% yield of cyclohexenone **16**.[8]

We next explored the possibility of using as our dienophile the bromomethyl ketone **18**. Dienophile **18** was obtained through the action of *N*-bromosuccinimide on (silyloxy)diene **17**.[18] The latter was in turn obtained from the action of lithium diisopropylamide on **15** followed by quenching of the presumed lithium dienolate with trimethylsilyl chloride. Bromomethyl enone was quite unstable and was accordingly subjected in crude form to the Diels–Alder reaction with diene **8**. A 33% yield of **19** (from **17**) was obtained.

We were encouraged to find that reaction of **19** with aqueous methylamine in tetrahydrofuran gave a 40% yield of the "mesembranedione" system **20**. Similarly, reaction of **19** with benzylamine gave the indolinone **21** in 68% yield. We were not, at this juncture, concerned with optimizing the yields of these model reactions. The assignment of the cis fusion to compounds **20** and **21** is in accord with expectation. If the B ring is formed by an intramolecular Michael reaction, a cis stereochemistry would be expected. If the sequence of events involves intermolecular addition of methylamine to the enone followed by ring closure by displacement of bromide, an a priori prediction of stereochemistry is less certain. However, in practice the cis stereochemistry follows from the NMR spectra of these compounds wherein the junction proton appears as a poorly resolved multiplet in the region 3.4 ppm, which is clearly symptomatic of its equatorial character, vis-à-vis, the A ring. These early results are summarized in Scheme IV.

Of course we were not unmindful of the possibility that compound **20**, prepared as a "model" system for the purpose of testing the rudimentary notions described above, might, in fact, serve as a precursor to the desired system **11** through some type of net dehydrogenation process. Aside from avoiding the need to seek an ad hoc solution to the obvious regiochemical issues raised by a transformation of **20** to **11**, a serious consideration in our planning was that of testing in a more discriminating fashion, the outer limits of our direct Diels–Alder route to cyclohexadienones. For this purpose we hoped that an examination of the behavior of more oxidized dienophiles (cf. generic systems **9**) might prove to be instructive. Thus, in concert with the experiments described above, we were studying the "cyclohexadienone" possibility.

Reaction of **12** with *N,N*-dimethylformamide dimethyl acetal[19] afforded a quantitative crude yield of **22**, mp 87–88 °C. Reaction of **22** with thiophenol in the presence of *p*-toluenesulfonic acid



22 X = $CHN(Me)_2$; R = H
23 X = CHS⬡; R = H
24 X = CHS⬡; R = Br
25 X = CHS(O)⬡; R = Br
26 X = $CHS(O)_2$⬡; R = Br
27 X = CHS(O)⬡; R = H
28 X = $CHS(O)_2$⬡; R = H

afforded the vinyl sulfides **23** as a 5:1 mixture of geometric isomers in 90% yield.[20] Our next goal became the bromomethyl sulfide **24**. Our first approach involved recourse to the same procedure followed in the case of **18**. Thus, **23** was converted to its silyl enol ether derivative, which reacted with *N*-bromosuccinimide as above to afford the desired **24**. A considerable simplification was achieved by the finding that compound **23** reacts directly with phenyltrimethylammonium perbromide.[21] Compound **24**, thus obtained, was not purified but subjected to the action of *m*-chloroperoxybenzoic acid. Depending on the reaction conditions (see Experimental Section), there could be obtained either the sulfoxide **25** or the sulfone **26** in quite acceptable yield.

As noted above, compound **23** was in fact a 5:1 mixture of geometric isomers. This mixture was carried together as the bromomethyl sulfides (**24**) and persisted at the level of the bromomethyl sulfones (**26**). Since it was subsequently found that only one of these isomers undergoes successful Diels–Alder reaction with diene **8** it was prudent to take advantage of their ready separability at the level of **26**. Fortunately, the major product, which was also the lower R_f (5% ethyl acetate–benzene) isomer (mp 105–107 °C), was the one that reacted with diene **8**. We tentatively assign to this reactive compound the *Z* configuration (i.e., bromoacetyl cis to phenylsulfonyl). In this compound, the chemical shift of the vinylic proton is at 7.26 ppm, whereas in the minor isomer the chemical shift of the corresponding proton is at 6.44 ppm.

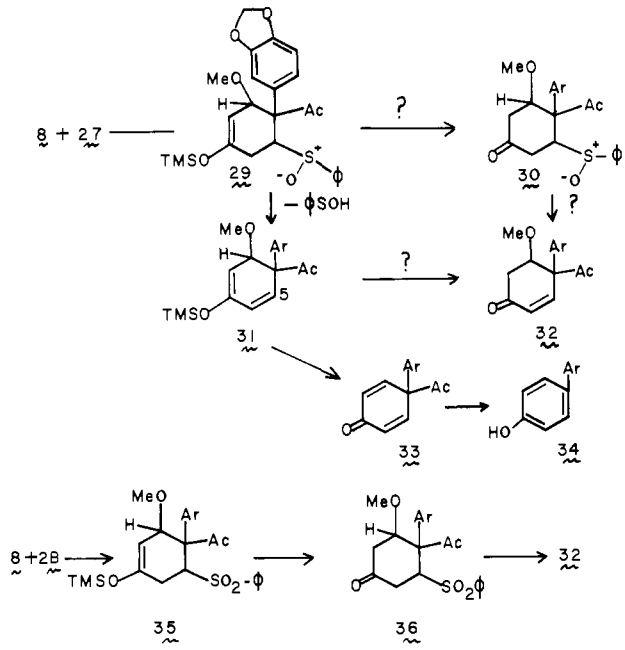
The first investigations into the feasibility of using our Diels–Alder methodology to produce the required cyclohexadienone were conducted with the model dienophiles **27** and **28**. Disappointingly, reactions of **27** with **8** under standard conditions (benzene, 100 °C, sealed tube)[7] followed by the usual workup afforded none of the expected **33**. Instead there could be obtained low yields of the phenol **34** and the methoxy ketone epimers **32**. It seemed likely that **34** was arising from the deacylation of **33**. Though we had previously succeeded in isolating a variety of 4-(alkoxycarbonyl)-4-alkylcyclohexadienones similar to **33**, the 4-aryl 4-keto combination in **33** proved, in our hands, to be too fragile for isolation and instead gave rise to phenol **34**.

The tendency toward aromatization experienced with the elusive **33** was much attenuated in the β-methoxy ketone epimers (**32**), which are quite stable. Happily, these compounds could be obtained in ca. 50% yield by use of the phenylsulfonyl dienophile (**28**). In this instance, we encountered no significant problem from the formation of phenol **34**. We reasoned that the difference arose in the post-Diels–Alder behavior of the respective adducts **29** and **35**. Adduct **29**, bearing as it does a homoallylic sulfoxide, suffers substantial elimination of phenylsulfenic acid to afford **31**. When **31** is subjected to the usual acid workup, it undergoes the typical concurrent desilylation and β elimination leading to **33**, and thence **34**. The stable system **32** is produced only to a small extent from either **30** or from the alternate mode of unraveling of **31**.

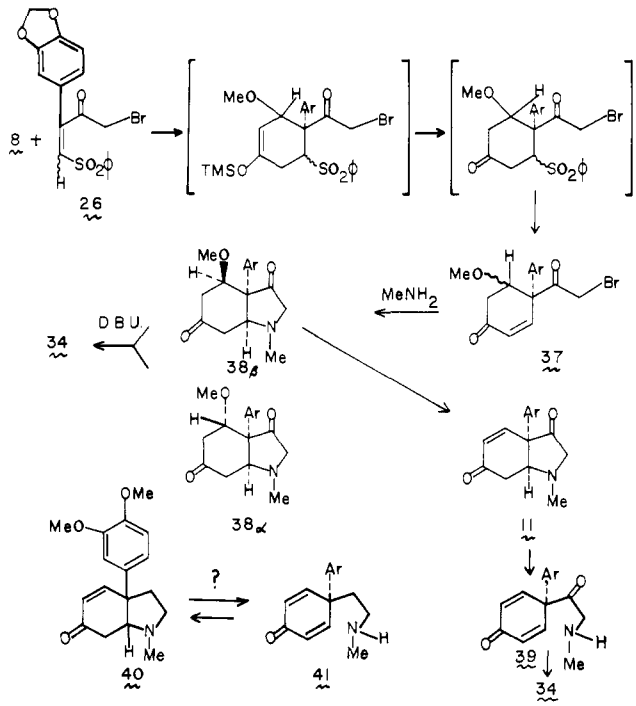
In contrast, the adduct **35** arising from **28** is substantially more stable to thermolytic elimination. Unraveling of **35** produces **36**. The phenylsulfonyl group is lost by β elimination only after the

(17) Kinast, G.; Tietze, L. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 239.
(18) Cf.: Reuss, R. H.; Hassner, A. *J. Org. Chem.* **1974**, *39*, 1785.
(19) Abdulla, R. F.; Brinkmeyer, R. S. *Tetrahedron* **1979**, *35*, 1674.
(20) Martin, S. F.; Moore, D. R. *Tetrahedron Lett.* **1976**, 4459.
(21) Johnson, W. S.; Bass, J. D.; Williamson, *Tetrahedron* **1963**, *19*, 861.

Scheme V



Scheme VI



keto group is unveiled. *The critical point is that compound* **35** *retains the methoxy function during the desilylation step.* We had previously noted the relationship in the mode of unraveling of Diels–Alder adducts of diene **8** with the presence or absence of substitution of C_5.[22] It had already been found that when C_5 was unsubstituted, concurrent elimination of methanol prevailed, whereas when it is substituted,[23] the methoxy group is retained. The findings here with the more oxidized dienophiles **27** and **28** were in keeping with this trend. These data are summarized in Scheme V.

Thus, on the basis of these studies, it seemed likely that in the series directed at tazettine, the dienophile **26** would prove to be more useful than **25**. Indeed, it was the case that attempted Diels–Alder of **25** with **8** followed by acidic hydrolysis afforded the same phenol **34** as substantially the only recognizable product. Fortunately, dienophile **26** proved to be more amenable to our designs.

Reaction of the major isomer of **26** with diene **8** was carried out in benzene at 70 °C. The mixture was subjected to chromatography on silica gel. Elution with 4:1 benzene:ethyl acetate afforded (55% yield) a 4:1 mixture of epimers **37**. This mixture could be separated (see Experimental Section for the full characterization of each component). However, the two component mixture could be conveniently carried into the next step. The mixture in tetrahydrofuran at room temperature was treated with aqueous methylamine to afford an 80% yield of the hexahydroindolinone **38**.

System **38** was obtained as a 9:1 mixture of epimers. Again, it was possible to separate this mixture and to fully characterize each of its components. However, in practice, this mixture could be carried forward into the next step.

The next objective to be overcome would appear at first glance to be the simplest in the synthesis. The methoxy group that had in effect protected the system against conversion to phenol **34** via a cyclohexadienone (cf., **37** and, similarly, **32**) was to be eliminated from compound **38** to provide the key intermediate, **11**. In practice, great difficulties were encountered in achieving this goal. For instance, the reaction of **38** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave as the principal product the phenol **34**.

It seemed not unlikely that **11** was in fact produced but that it had suffered β elimination of the methylamino function giving rise to cyclohexadienone **39**. The latter undergoes deacylation to give **34**. Such an interpretation would be in keeping with the previous finding of Jeffs and co-workers, wherein optically active **40** suffers base-induced racemization, presumably via cyclohexadienone **41**.[24] In our case, the corresponding dienone **39** is, of course, highly vulnerable to deacylation with the corresponding formation of phenol **34**.

Fortunately, absorption of **38** on a short column of alumina for 30 min afforded, after recycling, a 55% yield of **11**. It was noted that only the major component of the 9:1 epimer mixture of epimers **38** underwent this elimination reaction. This selective reactivity is no doubt due to the axial disposition of the methoxy function in this isomer. Thus, while mixtures were encountered at the stage of **37** and **38**, it developed that in each of the subsequent reactions the minor component was substantially (**37** → **38**) or totally (**38** → **11**) unreactive. In this way, compound **11** was obtained as a crystalline substance (mp 158–159 °C) in ca. 20% yield in three steps from dienophile **26** and the diene **8**. Even in this bicyclic form, the tendency of this system toward aromatization is always latent. For instance, under inappropriate handling (sodium methoxide–methanol or even sodium borohydride–ethanol), the phenol **34** is produced (see Scheme VI).

Synthesis of 6a-Epipretazettine. With compound **11** in hand, our efforts were directed toward the modification of the oxygen functionality at C_3 and C_{6a} and the interpolation of the C_1 fragment, i.e., C_8, between C_{6a} and C_{8a}. The first step in this objective involved differentiation of the two ketonic functions at C_3 and C_{6a}. Treatment of **11** with diisobutylaluminum hydride[25] in THF–hexane at −78 °C accomplished this differentiation and resulted in a 3:1 mixture of **42** and **43**. Chromatography on silica gel provided the homogeneous compounds in yields of 61% and 19%, respectively. We did not, at this stage, concern ourselves with improvement of the stereoselectivity, since each component could be processed efficiently to afford the required α-methoxy system **44**.

The major epimer **42** (mp 118–119 °C) was clearly the 3-β-hydroxy system arising from the attack of hydride on the exo (α)

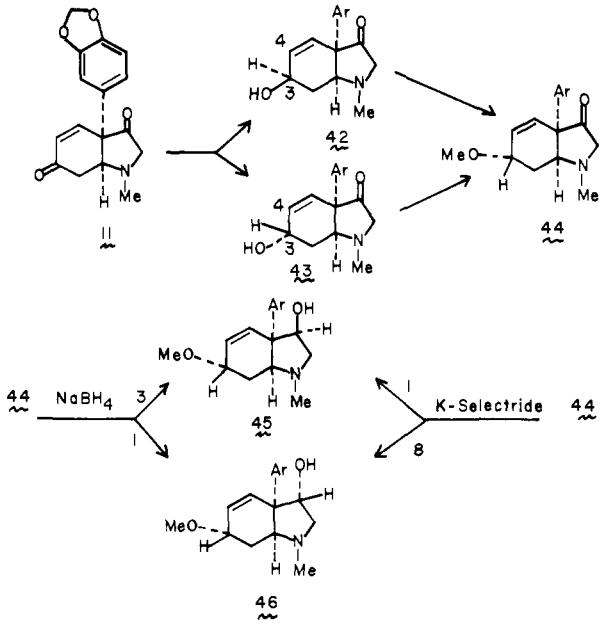
(22) Danishefsky, S.; Kitahara, T.; Yan, C. F.; Morris, J. *J. Am. Chem. Soc.* **1979**, *101*, 6996.

(23) Presumably the effect is most pronounced when the substitutent at C_5 is cis to the methoxyl function. In this way, the axial conformation of the methoxyl group that is most conducive to its elimination is energetically discouraged. However, the stereochemical dependence of the C_5 substitutent effect on the maintenance or elimination of the methoxyl function has not been rigorously demonstrated.

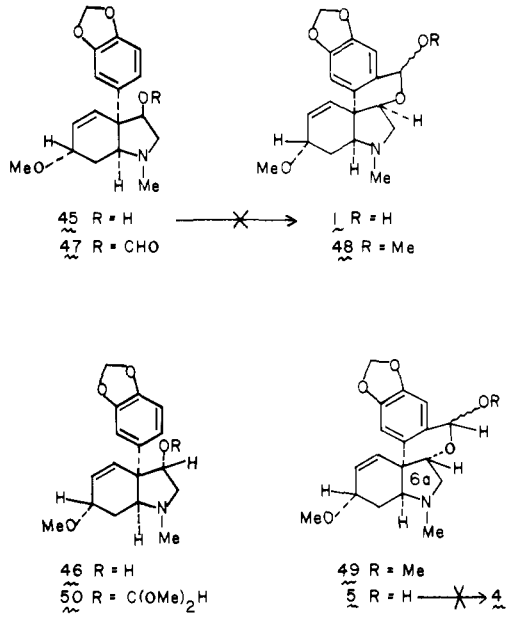
(24) Jeffs, P. W.; Ahmann, G.; Campbell, H. F.; Farrier, D. S.; Ganguli, G.; Hawks, R. L. *J. Org. Chem.* **1970**, *35*, 3512.

(25) Winterfeldt, E. *Synthesis* **1975**, 617.

Scheme VII



Scheme VIII



face of the hydroindoline system. This was evident by comparison of the NMR spectra of **42** and **43** (see Experimental Section) with those of the known epimesembrenol and mesembrenol previously prepared by Jeffs.[24] A particularly decisive feature of the spectrum in this connection is the multiplicity of the olefinic proton at C_4. In the case of **42**, this proton (δ $CDCl_3$ = 6.41 ppm) is coupled to the C_3 carbinyl proton (equatorial by the Jeffs rules) by 4.2 Hz. In contrast, the corresponding proton in **43** (6.05 ppm) is coupled to the C_3 carbinyl proton (axial) by the Jeffs rules by only 1.2 Hz. The correctness of these assignments will become clear shortly.

Using methodology similar to that developed earlier in a related series by Whitlock,[26] we could invert the β-hydroxyl group of **42** to obtain the required **44**. Thus, reaction of **42** with methanesulfonic anhydride in THF–triethylamine afforded a labile mesylate that was solvolyzed in excess methanol to give **44**; mp 134–136 °C. The same **44** was obtained in 95% yield by reaction of the minor allylic alcohol **43** with diazomethane in the presence of anhydrous aluminum chloride.[27]

The setting for the projected total synthesis of pretazettine was now completed by the reduction of **44**. When this reduction was carried out with sodium borohydride, the major product (3:1) by analogy with the previous work of Tsuda[10a-c] was the then desired β-alcohol **45**. Thus in this reaction, hydride delivery had occurred cis to the angular aryl function but from the exo face of the bicyclic system. Conversely, when reduction was carried out with K-Selectride in tetrahydrofuran at 0 °C, the major product (8:1) was the α-alcohol **46**. Although subsequently these alcohols were separated and characterized, the experiments to be described were performed on the mixutres (see Scheme VII).

We first turned to the system enriched in epimer **45** (i.e., the mixture derived from the sodium borohydride reduction of **44**). Of course, the hope was to achieve a one-carbon interpolation between the hydroxyl function and the aromatic ring. The presumption was that this might be accomplished through the use of an electrophile at the formic acid level of oxidation. A sample of pretazettine hydrochloride[28] was made available to us to help in the assessment of our experiments. We were able to obtain authentic pretazettine (**1**) from its hydrochloride and we were able to prepare the known *O*-methylpretazettine (**48**) following the procedures of Wildman.[3] With these authentic samples in hand, we were in a position to detect even small quantities of synthetic products were they to be produced from the reaction of **45**.

Unfortunately, all efforts to produce synthetic *dl*-pretazettine or its methyl ether in this way were unsuccessful. Four approaches were surveyed under a variety of conditions. First, a variety of Lewis acids were employed, unsuccessfully, in attempting to cyclize the formate ester **47** derived from the reaction of **45** with formic–acetic anhydride. These failed to produce any detectable **1**, leading instead to either deformylation and/or substantial changes in the system.

We also investigated a variety of Vilsmeir–Haack (DMF/$POCl_3$)[29] and dichloromethyl methyl ether formylations.[30] The scales on which these reactions are conducted were such that we can only attest to the absence of the formation of pretazettine by chromatographic comparison with authentic material. We cannot exclude the formation of the ring system in addition to some other transformation, though no positive indication in this connection was forthcoming.

Another C_1 interpolating agent that we used was trimethyl orthoformate.[31] The hope was to reach pretazettine methyl ether. Fortunately for our purposes (vide infra) the reaction was carried out on the 3:1 mixture of alcohols **45** and **46**. This mixture was heated with trimethyl orthoformate in 115% polyphosphoric acid at 100 °C for 20 min. Chromatography resulted in the isolation of pure **45**. There was also produced small amounts of a new compound that was, however, not chromatographically or spectrally identical with pretazettine methyl ether. *We reasoned that this must be coming from the minor alcohol* (**46**). With the alcohol cis to the aryl ring (as in **46**), the C_1 interpolation with trimethyl orthoformate was successful. With the alcohol trans to the aryl ring (as in **45**), no such interpolation could be achieved.

This hypothesis was tested in a preparatively useful context starting with an 8:1 mixture of **46**:**45** (prepared by reduction of **44** with K-Selectride). There was thus obtained 6a-epipretazettine *O*-methyl ether (**49**) in 65% yield. The soundness of this structural assignment was further supported by the obtainment, in quantitative yield, of 6a-epipretazettine (**5**) by the acid-catalyzed hydrolysis of **49**. The NMR spectrum of **5** thus obtained is identical with that reported by Wildman and Bailey for compound

(26) Cf.: Whitlock, H. W.; Smith, G. L. *J. Am. Chem. Soc.* **1967**, *39*, 3600.

(27) Cf.: Muller, E.; Heischkeil, R.; Bauer, M. *Liebigs Ann. Chem.* **1964**, *677*, 55.

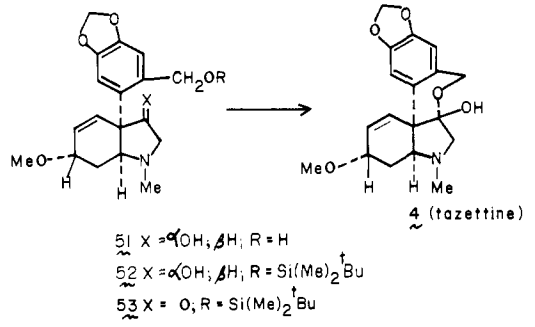
(28) We thank Professors P. Scheuer and E. Furusawa of the University of Hawaii for providing us with a generous sample of pretazettine hydrochloride.

(29) Cf.: Khimii, U. *Russ. Chem. Rev.* (*Engl. Transl.*) **1960**, *29*, 599.

(30) Cf.: Rieche, A.; Gross, H.; Hoft, E. *Org. Synth.* **1967**, *47*, 1.

(31) Cf.: inter alia: Gross, H.; Rieche, A.; Matthey, G. *Chem. Ber.* **1963**, *96*, 308. Li, T.; Lesko, P.; Ellison, R. H.; Subramanian, N.; Fried, J. H. *J. Org. Chem.* **1981**, *46*, 111.

Scheme IX



5 derived from the natural series.[32]

While we have not explored the mechanism of this cyclization in great detail, presumptive evidence is now available that a key intermediate in the conversion of **46** → **49** is the mixed orthoformate ester **50**. Thus compound **50** was, in fact, generated from the reaction of **46** with trimethyl orthoformate in the presence of aluminum chloride. The same compound could be detected by TLC analysis in the early stages of the conversion of **46** → **49** with polyphosphoric acid. As the reaction ensues, this intermediate disappears. The final steps in the total synthesis of 6a-epipretazettine are shown in Scheme VIII.

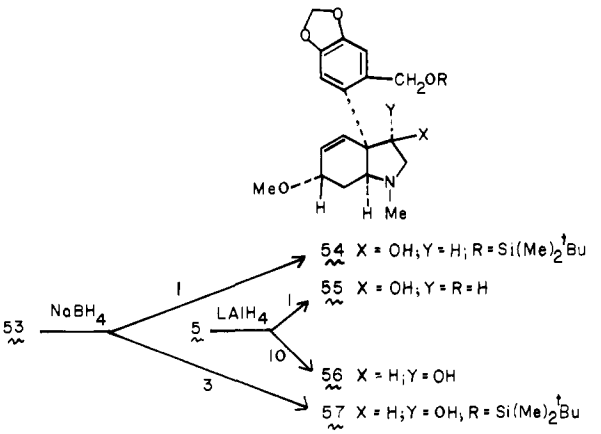
Synthesis of Tazettine. Though we were unsuccessful in reaching pretazettine, we had obtained 6a-epipretazettine in a total of 8 steps from diene **8** (12 steps from the readily available ketone **12**). At this point, on the basis of literature reports, we thought we stood within one step of tazettine **4**. This optimism was based on the report of Wildman and Bailey,[4,32] to the effect that compound **5** suffers base-induced conversion to **4**, though with the requirement of more severe conditions than is the case for pretazettine (**1**) itself.

Unfortunately, under all conditions we could devise, we could find no evidence for the formation of tazettine (**4**) from **5**. We used the conditions described in the Wildman–Bailey paper,[4,32] but in our hands the only material obtained was unreacted **5**. We also increased the severity of the reaction conditions but again could detect no tazettine. We continued this process, stepping up the harshness of the conditions to the point of destruction of **5** without any success in detecting **4**. This nondetection was particularly significant since we had in hand an authentic sample of tazettine. This "authentic" tazettine was prepared from our sample of pretazettine (**1**), alluded to above, following Wildman's excellent procedure.[3] *It appears to us that the claimed conversion of 6a-epipretazettine to tazettine may well be in error.*

Given our failure to achieve the C_1 interpolation in the trans series (i.e., alcohol **45**), our inability to achieve the Cannizzaro equilibration implied in the transformation of **5** → **4** (Scheme II) is perhaps not surprising. In any case, it was now necessary to develop a new route from synthetic **5** to **4**. Fortunately, this was accomplished.

Reaction of **5** with LAH afforded tazettine diol **51**. The primary alcohol function of **51** could be selectively silylated with *tert*-butyldimethylsilyl chloride in the presence of triethylamine and 4-pyrrolidinopyridine at room temperature. The monosilyl system **52** thus obtained was oxidized (Moffat–Pfitzner) to afford **53**. Treatment of **53** with $(Bu)_4N^+F^+$ afforded *dl*-tazettine **5** (mp 175–176 °C). The infrared and NMR (600 MHz) spectra of *dl*-tazettine were indistinguishable from those of an authentic sample. The chromatographic mobilities were identical.[33] The completion of the total synthesis of tazettine is summarized in Scheme IX.

Finally, we describe one last effort to reach pretazettine. The thought was that reduction of either **53** or indeed **4** might be used to reach the 6a-β-alcohol (cf. **54** or **55**). Given such a result,



it would seem possible to reach system **2**. The hope was that such reduction might parallel the reduction of **44** with sodium borohydride that gave primarily **45** (vide supra). Unfortunately, in the event, both reductions gave primarily the α-alcohol **56**, which is suitable for a synthesis of **5** but not for a synthesis of **1**. While these results were in progress, similar findings were reported from another laboratory.[15] Thus, with ortho substitution in the aryl ring, reduction of the ketone at position 6 occurs predominantly from the exo (β) face. Accordingly, we did not continue on to achieve the total synthesis of pretazettine. In principle, since tazettine has been converted to pretazettine, albeit in very poor yield,[15] our total synthesis of tazettine constitutes, in the narrowest technical sense, a total synthesis of pretazettine.

Experimental Section

4-(Dimethylamino)-3-[3,4-(methylenedioxy)phenyl]-3-buten-2-one (22). A solution of 1.04 g (5.84 mmol) of piperonal acetone (**12**)[16] in 5 mL of *N,N*-dimethylformamide dimethyl acetal was heated to 80 °C and stirred for 3 h. Upon cooling the solution to room temperature, the excess solvent was removed at reduced pressure leaving a yellow solid. Chromatography (neutral alumina, ether) gave the enaminone **22** (1.20 g, 88%) as a white solid: mp 87–88 °C (ether/pentane); IR λ_{max} ($CHCl_3$) 6.08 μm; ^1H NMR ($CDCl_3$) δ 1.95 (s, 3), 2.74 (s, 6), 5.97 (s, 2), 6.68 (m, 3), 7.53 (s, 1). Mass spectrum, *m/e* calcd for $C_{13}H_{15}NO_3$: 233.1052. Found: 233.1052.

3-[3,4-(Methylenedioxy)phenyl]-4-(phenylthio)-3-buten-2-one (23). A solution of *p*-toluenesulfonic acid monohydrate (8.9 g, 1.1 equiv) in 400 mL of benzene was refluxed with separation of water (Dean–Stark trap) for 4 h. Thiophenol (4.8 mL, 1.1 equiv) was then added, followed by a solution of enaminone **22** (9.94 g, 42.6 mmol) in 50 mL of dry benzene. The resulting solution was refluxed for 20 h, cooled to room temperature, and washed successively with water (3 × 250 mL) and saturated sodium chloride (1 × 250 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo. Chromatography (silica gel, 95:5 benzene/acetone) and bulb-to-bulb distillation (200 °C, 0.05

(32) The NMR spectrum of 6a-epipretazettine is provided in: Bailey, D. T. Ph.D. Dissertation, Iowa State University, 1968.

(33) We cannot account for a major discrepancy in the melting point of our racemic tazettine and that reported[10a] (237–238 °C). However, the identity (600 MHz) of the NMR spectrum of our synthetic material as compared with that of an authentic sample of tazettine and the identity of the infrared and mass spectra leave us with no doubt as to the correct formulation of our material. Picture of these spectra as well as those of all intermediates in the synthesis are given in: Morris, J. Ph.D. Dissertation, Yale University, 1981.

(34) Melting points were determined on a Thomas-Hoover Uni-Melt capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on sodium chloride plates on either a Perkin-Elmer 137, 247, or 710B infrared spectrometer. Absorptions are reported with the polystyrene absorption at 6.24 μm as a reference. Low-resolution mass spectra were measured on a LKB-9000A or HP5985 system by direct insertion. High-resolution mass spectra were obtained from a Varian Associates CH-5 system. The ^1H NMR spectra were measured at 60 MHz on a Varian T-60 spectrometer, at 100 MHz on a Jeol JNM-MH-100 spectrometer, or at 90 MHz on a Varian EM-390 spectrometer unless otherwise mentioned. The NMR spectra at 250 and 600 MHz were obtained from Carnegie–Mellon University, Pittsburgh, PA, while those at 270 MHz were obtained on a Bruker HX-270 from the Southern New England NMR facility at Yale University. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane.

TLC analyses were obtained on E. M. Merck Silica gel 60 F-254 plates and were developed by iodine or ammonium molybdate/cerric sulfate solution. Analyses were obtained from the Olin Corporation, New Haven, CT.

mmHg) afforded 11.52 g (90%) of **23** as a mixture of geometric isomers (higher R_f:lower R_f 1:5). Higher R_f isomer: R_f 0.30, benzene; IR λ_{max}($CHCl_3$) 6.05 μm; NMR ($CDCl_3$) δ 2.20 (s, 3), 5.91 (s, 2), 6.75 (m, 3), 7.17 (s, 1), 7.33 (m, 2), 7.48 (m, 3); mass spectrum, *m/e* 298 (P). Lower R_f isomer: R_f 0.19, benzene; mp 77–79 °C (acetone/hexane); IR λ_{max} ($CHCl_3$) 6.02 μm; ^1H NMR ($CDCl_3$) δ 2.17 (s, 3), 5.94 (s, 2), 6.80 (m, 3), 7.41 (m, 5), 7.87 (s, 1); mass spectrum, *m/e* 298 (P). Anal. Calcd for $C_{17}H_{14}O_3S$: C, 68.46; H, 4.70. Found: C, 68.23, H, 4.75.

1-Bromo-3-[3,4-(methylenedioxy)phenyl]-4-(phenylthio)-3-buten-2-one (24). Method A. A solution of lithium diisopropylamide was prepared from diisopropylamine (3.47 mL, 24.80 mmol), and a 1.53 M hexane solution of *n*-butyllithium (16.21 mL, 24.80 mmol) in 40 mL of dry tetrahydrofuran under argon at −78 °C. After 20 minutes of stirring, a solution of ketone **23** (6.72 g, 22.55 mmol) in 40 mL of dry tetrahydrofuran was added dropwise over a 90-min period. The mixture was allowed to stir at −78 °C for an additional 30 min. The orange enolate solution was quenched by the rapid addition of trimethylsilyl chloride (4.29 mL, 33.82 mmol) at −78 °C. The resulting mixture was allowed to stir for 30 s at −78 °C and then for an additional 20 min while warming to room temperature. The reaction was poured into 100 mL of 5% sodium bicarbonate and diluted with ether. The organic layer was washed with saturated sodium chloride and dried over anhydrous sodium sulfate. Filtration followed by evaporation of volatiles in vacuo afforded a crude silyl enol ether as a light yellow oil (83% pure by ^1H NMR: ($CDCl_3$) δ 0.24 (s, 9), 4.03 (s, 1), 4.28 (s, 1), 5.92 (s, 2), 6.72 (m, 3), 6.92 (s, 1), 7.08–7.44 (m, 5)).

The crude silyl enol ether was dissolved in 70 mL of dry tetrahydrofuran and cooled to 0 °C. *N*-bromosuccinimide (4.01 g, 22.55 mmol) was added at once, and the resulting mixture was allowed to stir at 0 °C for 2 h. The dark brown solution was poured into 100 mL of 5% sodium bicarbonate and diluted with ether. The organic layer was washed with saturated sodium bisulfite (100 mL) and saturated sodium chloride (100 mL). The solution was dried over anhydrous sodium sulfate and concentrated in vacuo to afford the crude bromo ketone **24**, which was used directly in the next step.

Method B. A solution of methyl ketone **23** (15.0 g, 50.3 mmol) in 150 mL of dry tetrahydrofuran was cooled to 0 °C and 20.5 g (52.8 mmol) of phenyltrimethylammonium perbromide was added all at once. The mixture was allowed to stir at 0 °C for 90 min. The reaction was poured into a separatory funnel and partitioned between ether and saturated sodium bicarbonate. The organic layer was washed successively with saturated sodium bisulfite and saturated sodium chloride. The solution was dried (Na_2SO_4), and the volatiles were evaporated in vacuo to afford the crude bromo ketone **24**, which was used immediately in the next step: IR λ_{max} ($CHCl_3$) 6.05 μm; ^1H NMR ($CDCl_3$), δ 3.98 (s, 2), 5.90 (s, 2), 6.72 (m, 3), 7.28 (m, 5), 8.0 (s, 1).

1-Bromo-3-[3,4-(methylenedioxy)phenyl]-4-(phenylsulfonyl)-3-buten-2-one (26). The crude bromo ketone **24** obtained from method A was dissolved in 140 mL of dry methylene chloride and cooled to 0 °C. *m*-Chloroperbenzoic acid (85%, 9.16 g, 45.10 mmol) was added at once, and the resulting suspension was allowed to stir at 0 °C for 2 h and at room temperature overnight. The reaction mixture was transferred to a separatory funnel and washed successively with saturated sodium bicarbonate (3 × 100 mL), water (1 × 100 mL), and saturated sodium chloride (1 × 100 mL). The organic solution was dried over anhydrous sodium sulfate and concentrated in vacuo to afford the crude product. Chromatography on 750 g of silica gel (95:5 benzene/ethyl acetate) afforded 5.08 g (55% from **23**) of the sulfone **26** as a mixture of isomers.

In another experiment, the crude bromo ketone **24**, obtained from method B, was submitted to the oxidation conditions reported above. Workup and chromatography in the same manner afforded 14.6 g (71% from **23**) of sulfone **26** as a mixture of isomers. (Higher R_f:lower R_f ca. 1:3, exact ratio was dependent on the isomer composition of methyl ketone **23**; the isomers were routinely separated utilizing the above chromatographic conditions.) Higher R_f isomer: R_f 0.33, 5% ethyl acetate in benzene; mp 126–127 °C; IR λ_{max} ($CHCl_3$) 5.69, 5.75 μm: ^1H NMR ($CDCl_3$) δ 4.44 (s, 2), 6.00 (s, 2), 6.44 (s, 1), 6.82 (s, 3), 7.40–7.73 (m, 3), 7.83–8.03 (m, 2); mass spectrum *m/e* 408, 410, (P). Lower R_f isomer: R_f 0.24, 5% ethyl acetate in benzene; mp 105–107 °C; IR λ_{max} ($CHCl_3$) 5.78, 5.85 μm; ^1H NMR ($CDCl_3$) δ 3.96 (s, 2), 6.01 (s, 2), 6.50–6.87 (m, 3), 7.26 (s, 1), 7.30–7.83 (m, 5); mass spectrum, *m/e* 408, 410 (P). Anal. Calcd for $C_{17}H_{13}O_5SBr$: C, 49.87; H, 3.18. Found: C, 49.75; H, 3.12.

4-(Bromoacetyl)-5-methoxy-4-[3,4-(methylenedioxy)phenyl]-cyclohex-2-en-1-one (37). A solution of compound **26** (lower R_f isomer, 1.5141 g, 3.70 mmol) and *trans*-1-methoxy-3((trimethylsilyl)oxy)-1,3-butadiene (**8**) in 4.5 mL of dry benzene was heated at 70 °C in a sealed tube for 3 h. After cooling the solution to room temperature, the reaction mixture was immediately chromatographed on 200 g of silica gel (Baker, 60–200 mesh, 1% ethyl acetate in benzene) to give 270.7 mg of pure **37** along with 870 mg of impure material. Rechromatography of the impure material on 80 g of silica gel (1% ethyl acetate in benzene) afforded an additional 470.9 mg of **37**. The pure adducts were combined to afford a total of 741.6 mg (54.5%) of **37** as a 5:1 mixture of epimers. The isomers could be separated by preperative thick-layer chromatography (Analtech, silica gel 6F, 1000 μm, 98:2 benzene/ethyl acetate). Higher R_f (minor) isomer: R_f 0.32, 5% ethyl acetate/benzene; IR λ_{max} ($CHCl_3$) 5.80, 5.94 μm; ^1H NMR ($CDCl_3$) δ 2.51 (dd, J_{AX} = 6 Hz, J_{AB} = 17 Hz, 1), 2.75 (dd, J_{BX} = 3.5 Hz, J_{BA} = 17 Hz, 1), 2.98 (s, 3), 3.85 (s, 2), 4.12 (m, 1), 5.82 (s, 2), 6.13 (d, J = 10.5 Hz, 1), 6.58 (m, 3), 6.89 (dd, J = 1.5, 10.5 Hz, 1). Lower R_f (major) isomer: R_f 0.26, 5% ethyl acetate/benzene; IR λ_{max}($CHCl_3$) 5.82, 5.93 μm; ^1H NMR ($CDCl_3$) δ 2.37 (dd, J_{AX} = 3 Hz, J_{AB} = 17 Hz, 1), 2.70 (dd, J_{BX} = 4.5 Hz, J_{BA} = 17 Hz, 1), 3.25 (s, 3), 3.95 (s, 2), 4.31 (m, 1), 5.81 (s, 2), 6.09 (d, J = 10.5 Hz, 1), 6.70 (m, 3), 7.17 (dd, J = 2, 10.5 Hz, 1). Mass spectrum, *m/e* (mixture) 366, 368 (P).

(3aα,7aα)-3a,4,5,6,7,7a-Hexahydro-4-methoxy-1-methyl-3a-[3,4-(methylenedioxy)phenyl]-6-oxo-3-indolinone (38α,β). Aqueous methylamine (40%, 0.730 mL, 9.42 mmol) was added rapidly dropwise to a solution of **37** (mixture of isomers, 1.1521 g, 3.14 mmol) in 39 mL of dry tetrahydrofuran at room temperature. The reaction was allowed to stir at room temperature for 30 min during which time a precipitate formed. The reaction was poured into 100 mL of 1 N aqueous hydrochloric acid and extracted with ether (2 × 60 mL) to remove neutral materials. The acid layer was basified at 0 °C with solid sodium bicarbonate and extracted with methylene chloride (5 × 60 mL). The combined organic layers were dried (Na_2SO_4) and evaporated in vacuo to give 798.8 mg (80.3%) of the crude bicyclic amine **38** as a 9:1 **38β**:**38α** mixture of isomers. The isomers could be separated by chromatography on silica gel (230–400 mesh, 55% ethyl acetate in hexane). Higher R_f isomer **38α**: R_f 0.58, ethyl acetate; mp 108–110 °C; IR λ_{max} ($CHCl_3$) 5.73, 5.83 μm; ^1H NMR ($CDCl_3$, 250 MHz) δ 2.41 (s, 3), 2.46 (dd, J_{AX} = 2.3 Hz, J_{AB} = 17.3 Hz, 1), 2.65 (dd, J_{BX} = 4.2 Hz, J_{BA} = 17.3 Hz, 1), 2.76 (dd, J_{AX} = 3.3 Hz, J_{BA} = 16.6 Hz, 1), 2.95 (dd, J_{BX} = 3.3 Hz, J_{BA} = 16.6 Hz, 1), 2.98 (s, 3), 3.01 (d, J = 15.4 Hz, 1), 3.37 (d, J = 15.4 Hz, 1), 3.63 (t, J = 3.3 Hz, 1), 3.92 (dd, J_{XA} = 2.3 Hz, J_{XB} = 4.2 Hz, 1), 5.97 (s, 2), 6.79 (d, J = 8.2 Hz, 1), 6.91 (dd, J = 1.9, 8.2 Hz, 1), 7.02 (d, J = 1.9 Hz, 1); mass spectrum, *m/e* 317 (P). Lower R_f isomer **38β**: R_f 0.26, ethyl acetate; mp 131–132 °C; IR λ_{max} ($CHCl_3$) 5.71, 5.81 μm; ^1H NMR ($CDCl_3$, 250 MHz) δ 2.26 (dd, J_{AX} = 3.3 Hz, J_{AB} = 16.8 Hz, 1) 2.48 (s, 3), 2.58 (dd, J_{BX} = 3.7 Hz, J_{BA} = 16.8 Hz, 1), 2.82 (dd, J_{AX} = 5.6 Hz, J_{AB} = 15.9 Hz, 1), 2.85 (d, J = 17.0 Hz, 1), 2.97 (dd, J_{BX} = 4.7 Hz, J_{BA} = 15.9 Hz, 1), 3.32 (s, 3), 3.61 (d, J = 17.0 Hz, 1), 3.66 (dd, J_{XA} = 4.7 Hz, J_{XB} = 5.6 Hz, 1), 4.09 (dd, J_{XA} = 3.3 Hz, J_{XB} = 3.7 Hz, 1), 5.97 (s, 2), 6.80 (d, J = 8.2 Hz, 1), 6.94 (dd, J = 1.9, 8.2 Hz, 1), 7.19 (d, J = 1.9 Hz, 1). Mass spectrum *m/e* calcd for $C_{17}H_{19}NO_5$: 317.1263 (P). Found: 317.1260.

(3aα,7aα)-3a,6,7,7a-Tetrahydro-1-methyl-3a-[3,4-(methylenedioxy)-phenyl]-6-oxo-3-indolinone (11). A solution of **38** (1.60 g, 5.0 mmol, 9:1 mixture of **38β**:**38α** in a minimum amount of methylene chloride was absorbed on a column of neutral alumina (50 g). The material was allowed to stand on the column for 30 min after which time it was removed by elution with ethyl acetate. Evaporation of the volatiles in vacuo produced an oil, which was chromatographed on silica gel (230–400 mesh, 55% ethyl acetate in hexane) to afford 400.1 mg (28%) of enedione **11** along with 158.7 mg (9.9%) of **38α**. Further elution with ethyl acetate afforded 645.8 mg (40.4%) of β-methoxy diketone **38β**. Resubmission of **38β** to the above conditions two additional times afforded a total of 775.5 mg (54.2%) of the desired enedione **11** along with 140.1 mg (8.7%) of recovered starting material **38β**. **11**: R_f 0.49, ethyl acetate; mp 158–159 °C; IR λ_{max} ($CHCl_3$) 5.69, 5.93 μm; ^1H NMR ($CDCl_3$) δ 2.37 (s, 3), 2.64 (m, 2), 2.95 (d, J = 18 Hz, 1), 3.14 (m, 1), 3.71 (d, J = 18 Hz, 1), 5.94 (s, 2), 6.26 (d, J = 10.5 Hz, 1), 6.5–6.9 (m, 4). Mass spectrum, *m/e* calcd for $C_{16}H_{15}NO_4$: 285.1001 (P). Found: 285.0988.

(3aα,7aα)-3a,6,7,7a-Tetrahydro-6-hydroxy-1-methyl-3a-[3,4(methylenedioxy)phenyl]-3-indolinone (42 and 43). A solution of enedione **11** (325.3 mg, 1.14 mmol) in 36.1 mL of dry tetrahydrofuran was cooled to −78 °C under an argon atmosphere, and a solution of diisobutylaluminum hydride (3.78 mL, 0.90 M, 3.42 mmol) in hexane was added slowly dropwise over a 10-min period. The reaction was allowed to stir at −78 °C for 20 min. The excess hydride was destroyed by careful addition of water (6 mL) at −78 °C after which the solution was allowed to warm to room temperature. The reaction mixture was transferred to a separatory funnel and partitioned between ethyl acetate and water. The aqueous layer was extracted three times with ethyl acetate, and the combined organic layers were dried ($NaSO_4$) and evaporated in vacuo to afford a mixture of the crude allylic alcohols. Chromatography on silica gel (230–400 mesh, 60% ethyl acetate in hexane) afforded 199.0 mg (61%) of **42**. Further elution with 70% ethyl acetate in hexane gave

63 mg (19%) of **43**. Compound **42**, β alcohol: R_f 0.37 ethyl acetate, mp 118–119 °C; IR λ_{max} ($CHCl_3$) 3.02, 5.72 μm; ^1H NMR ($CDCl_3$, 250 MHz) 1.66 (ddd, J = 2.4, 4.2, 15.3 Hz, 1), 2.37 (ddd, J = 1.6, 3.3, 15.3 Hz, 1), 2.54 (s, 3), 2.95 (d, J = 18 Hz, 1), 3.10 (m, 1), 3.79 (d, J = 18 Hz, 1), 4.08 (m, 1), 4.50 (m, 1, OH), 5.55 (dd, J = 1.3, 9.9 Hz, 1), 5.94 (s, 2), 6.41 (br dd, J = 5.2, 9.7 Hz, 1), 6.57 (dd, J = 1.7, 6.9 Hz, 1), 6.58 (br s, 1), 6.76 (dd, J = 1.7, 6.9 Hz, 1). Mass spectrum, m/e calcd for $C_{16}H_{17}NO_4$: 287.1158. Found: 287.1155.

Compound **43** α alcohol: R_f 0.26, ethyl acetate; IR λ_{max} ($CHCl_3$) 3.05, 5.73 μm; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.49 (ddd, J = 2.2, 10.6, 13.2 Hz, 1), 2.33 (m, 1), 2.46 (s, 3), 2.92 (d, J = 17.3 Hz, 1), 2.90 (m, 1), 3.68 (d, J = 17.3 Hz, 1), 4.46 (m, 1), 5.52 (dt, J = 1.6, 9.9 Hz, 1), 5.94 (s, 2), 6.05 (dt, J = 1.2, 9.9 Hz, 1), 6.68 (m, 3).

(3aα,6α,7aα)-3a,6,7,7a-Tetrahydro-6-methoxy-1-methyl-3a-[3,4-(methylenedioxy)phenyl]-3-indolinone (44). (A) From the β-Alcohol 42. A solution of methanesulfonic anhydride (705 mg, 4.05 mmol) in 2.5 mL of dry tetrahydrofuran was added to a solution of **42** (166.3 mg, 0.579 mmol) and triethylamine (0.56 mL, 4.05 mmol) in 14.2 mL of dry tetrahydrofuran at 0 °C. The reaction was allowed to stir at 0 °C for 20 min, after which thin-layer chromatographic analysis (R_f 0.51, ethyl acetate) indicated mesylate formation was complete. Anhydrous methanol (8.3 mL) was added, and the resulting mixture was stirred at 0 °C for 10 min and at room temperature for 48 h. The reaction mixture was poured into 1 N aqueous hydrochloric acid and diluted with ether. The ether layer was extracted one time with 1 N aqueous hydrochloric acid. The combined acid layers were neutralized with solid sodium bicarbonate and extracted three times with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo to afford the crude product. Chromatography on silica gel (230–400 mesh, 50% ethyl acetate in hexane) gave 90.5 mg (52%) of the pure allylic methyl ether **44**. **(B) From the α-Alcohol 43.** Anhydrous aluminum chloride (6 mg) was added to a solution of **43** (45.2 mg, 0.157 mmol) in 4 mL of dry methylene chloride. The mixture was cooled to 0 °C, and excess diazomethane in ether was added. More aluminum chloride and diazomethane in ether were added until TLC analysis showed the reaction to be complete. The reaction mixture was partitioned between 5% sodium bicarbonate and ethyl acetate. The aqueous layer was extracted two additional times with ethyl acetate, and the combined organic layers were dried over anhydrous sodium sulfate. Evaporation of the volatiles in vacuo afforded 44.5 mg (94%) of allylic methyl ether **44**: R_f 0.45, ethyl acetate; mp 134–136 °C; IR λ_{max} ($CHCl_3$) 5.72 μm; ^1H NMR ($CDCl_3$) δ 1.3–1.8 (m, 1), 2.1–2.5 (m, 1), 2.43 (s, 3), 2.87 (d, J = 17 Hz, 1), 2.87 (m, 1), 3.40 (s, 3), 3.65 (d, J = 17 Hz, 1), 4.01 (m, 1), 5.51 (br d, J = 10 Hz, 1), 5.91 (s, 2), 6.19 (br d, J = 10 Hz, 1), 6.52–6.92 (m, 3). Mass spectrum, m/e calcd for $C_{17}H_{19}NO_4$: 301.1315. Found: 301.1314.

(3α,3aα,6α,7aα)-3a,6,7,7a-Tetrahydro-6-methoxy-1-methyl-3a-[3,4-(methylenedioxy)phenyl]-3-indolinol (46). A solution of potassium tri-*sec*-butylborohydride (2.82 mL, 0.5 M, 1.41 mmols) in tetrahydrofuran was added slowly dropwise to a solution of ketone **44** (141.4 mg, 0.47 mmol) in 7.85 mL of dry tetrahydrofuran at 0 °C. The reaction was allowed to stir for 1 h at 0 °C followed by 2 h at 4 °C. The reaction mixture was quenched by the careful addition of 10% sodium hydroxide (6.3 mL), followed by 30% hydrogen peroxide (3.75 mL) at 0 °C. The resulting mixture was allowed to stir at room temperature for 4 h. The reaction mixture was poured into water and extracted three times with ethyl acetate. The combined organic layers were washed twice with saturated aqueous sodium thiosulfate and once with saturated sodium chloride. The solution was dried over anhydrous sodium sulfate and evaporated in vacuo to give 137.8 mg (97%) of an 8:1 mixture of **46**:**45**. These alcohols could be readily separated by flash chromatography on silica gel (230–400 mesh, 3% methanol in chloroform). **46**: R_f 0.37, 15% methanol/chloroform; IR λ_{max} ($CHCl_3$) 2.95 μm; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.48 (dd, J = 2.0, 10.5, 13.0 Hz, 1), 2.27 (m, 1), 2.35 (dd, J = 6, 10 Hz, 1), 2.44 (s, 3), 2.97 (m, 1), 3.36 (s, 3), 3.56 (dd, J = 6.2, 10.3 Hz, 1) 3.96 (m, 1), 4.12 (t, J = 5.9 Hz, 1), 5.86 (br d, J = 10.6 Hz, 1), 5.94 (d, J = 10.6 Hz, 1), 5.95 (s, 2), 6.80 (br s, 2), 6.88 (s, 1). **45**: R_f 0.42, 15% methanol/chloroform; ^1H NMR ($CDCl_3$, 270 MHz)δ 1.43 (ddd, J = 2.9, 11.0, 13.6 Hz, 1), 2.17 (dddd, J = 1.5, 3.7, 5.1, 13.6 Hz, 1), 2.32 (s, 3), 2.35 (m, 1), 2.60 (dd, J = 5.5, 10.5 Hz, 1), 3.09 (d, J = 10.5 Hz, 1), 3.41 (s, 3), 3.94 (ddt, J = 1.5, 5.2, 11.0 Hz, 1), 4.40 (m, 1), 5.78 (dt, J = 1.5, 10.6 Hz, 1), 5.93 (s, 2), 6.16 (dt, J = 1.5, 10.6 Hz, 1), 6.74 (br s, 2), 6.79 (br s, 1). Mass spectrum, m/e (mixture) calcd for $C_{17}H_{21}NO_4$: 303.1471. Found: 303.1475.

(3β,3aα,6α,7aα)-3a,6,7,7a-Tetrahydro-6-methoxy-1-methyl-3a-[3,4-(methylenedioxy)phenyl-3-indolinol (45). A solution of ketone **44** (90.5 mg, 0.30 mmol) in 20 mL of tetrahydrofuran/ethanol (1:1) was cooled to 0 °C, and excess sodium borohydride was added. The reaction was allowed to stir for 1 h at 0 °C over which time more sodium borohydride was added to drive the reaction to completion. The volatiles were removed in vacuo, and the residue was taken up in water/ethyl acetate. The aqueous phase was extracted twice with ethyl acetate. The combined organic layers were dried (Na_2SO_4) and evaporated in vacuo to afford 84.9 mg (93%) of a 3:1 mixture of **45**:**46**. These alcohols could be separated by chromatography on silica gel (230–400 mesh, 3% methanol/chloroform) as above.

***O*-Methyl-6a-epipretazettine (49).** Alcohol **46** (34.3 mg, 0.113 mmol, contaminated with 11% **45**) was dissolved in 2 mL of trimethyl orthoformate. The solution was heated to 100 °C, and a "drop" of 115% polyphosphoric acid was added. The reaction was heated at 100 °C for 15 min until the mixture appeared uniform. (If the reaction mixture was not uniform after 15 min, more polyphosphoric acid was added and heating was continued.) The reaction was allowed to cool to room temperature and 5% sodium bicarbonate was added. The mixture was transferred to a separatory funnel and extracted three times with ethyl acetate. The combined organic layers were washed twice with 5% sodium bicarbonate and once with saturated sodium chloride, dried over anhydrous sodium sulfate, and concentrated in vacuo. The crude residue was chromatographed on silica gel (230–400 mesh, 90% ethyl acetate in hexane) to give 25.4 mg (65%) of **49**: ^1H NMR ($CDCl_3$) δ 1.53–1.90 (m, 1), 2.2 (m, 1), 2.47 (s, 3), 2.53 (m, 1), 2.83 (m, 1), 3.47 (m, 1), 3.43 (s, 3), 3.52 (s, 3), 4.13 (m, 1), 4.23 (br d, J = 4.5 Hz, 1), 5.33 (s, 1), 5.37 (br d, J = 10 Hz, 1), 5.92 (s, 2), 6.08 (br d, J = 10 Hz, 1), 6.68 (s, 1), 6.90 (s, 1). Mass spectrum, m/e calcd for $C_{19}H_{23}NO_5$: 345.1576 (P). Found: 345.1572.

6a-Epipretazettine (5). *O*-Methyl-6a-epipretazettine (**49**) (25.6 mg, 0.074 mmol) was dissolved in 1 mL of 0.1 N aqueous hydrochloric acid. The solution was allowed to stir at room temperature for 90 min, neutralized with 5% sodium bicarbonate, and extracted three times with chloroform. The combined organic layers were dried (Na_2SO_4) and evaporated in vacuo to afford 24.6 mg (100%) of **5**: IR λ_{max} ($CHCl_3$) 2.79, 2.97 μm; ^1H NMR ($CDCl_3$) δ 1.47–1.90 (m, 1), 2.03–2.66 (m, 2), 2.48 (s, 3), 2.80 (m, 1), 3.49 (s, 3), 3.50 (m, 1), 4.13 (m, 1), 4.41 (br d, J = 4.5 Hz, 1), 5.40 (br d, J = 10 Hz, 1), 5.79 and 5.90 (s, 2 parts of benzylic H, 1), 5.96 (s, 2), 6.11 (br d, J = 10 Hz, 1), 6.78 (s, 1), 6.93 (s, 1). Mass spectrum, m/e calcd for $C_{18}H_{21}NO_5$: 331.1418. Found: 331.1420.

(3α,3aα,6α,7aα)-3a,6,7,7a-Tetrahydro-3a-[2-(hydroxymethyl)-4,5-(methylenedioxy)phenyl]-6-methoxy-1-methyl-3-indolinol (51). 6a-Epipretazetttine (**49**) (25.4 mg, 0.077 mmol) was dissolved in 1.5 mL of dry tetrahydrofuran under an argon atmosphere. A solution of lithium aluminum hydride in ether (0.46 mL, 1.0 M, 0.46 mmol) was added dropwise at room temperature. The mixture was allowed to stir at room temperature for 4 h. The excess hydride was quenched by the careful successive addition of water (17.4 μL), 15% sodium hydroxide (17.4 μL), and water (52.4 μL) after which the mixture was stirred vigorously for 1 h. The suspension was filtered, and the aluminum salts were washed several times with ethyl acetate. The organic solution was dried (Na_2SO_4) and evaporated in vacuo to afford 23.8 mg (93%) of diol **51**: IR λ_{max} ($CHCl_3$) 3.00 μm; ^1H NMR ($CDCl_3$) δ 1.48–1.93 (m, 1), 2.20 (dd, J_{AX} = 5 Hz, J_{AB} = 10.5 Hz, 1), 2.42 (s, 3), 2.43 (m, 1), 3.23 (m, 1) 3.35 (s, 3), 3.60 (dd, J_{BX} = 7.5 Hz, J_{BA} = 10.5 Hz, 1), 3.92 (dd, J = 6, 10.5 Hz, 1), 4.32 (dd, J_{XA} = 5 Hz, J_{XB} = 7.5 Hz, 1), 4.47 (d, J = 11.5 Hz, 1), 4.72 (d, J = 11.5 Hz, 1), 5.78 (m, 2), 5.93 (s, 2), 6.78 (s, 1), 6.85 (s, 1).

(3α,3aα,6α,7α)-3a,6,7,7a-Tetrahydro-3a-[2-(((*tert*-butyldimethylsilyl)oxy)methyl)-4,5-(methylenedioxy)phenyl]-6-methoxy-1-methyl-3-indolinol (52). Diol **51** (23.8 mg, 0.0714 mmol) was combined with triethylamine (49.7 μL, 0.357 mmol) and *tert*-butyldimethylsilyl chloride (53.8 mg, 0.357 mmol) in 2 mL of dry methylene chloride. A catalytic amount of 4-pyrrolidinopyridine was added, and the mixture was allowed to stir at room temperature for 14 h. The solution was diluted with methylene chloride and washed with 5% sodium bicarbonate and saturated sodium chloride. The organic layer was dried over anhydrous sodium sulfate and evaporated in vacuo. The residue was chromatographed on silica gel (230–400 mesh, 65% ethyl acetate in hexane) to afford 23.6 mg (74%) of **52**: IR λ_{max} ($CHCl_3$) 2.95 μm; ^1H NMR ($CDCl_3$) δ 0.17 (s, 3), 0.18 (s, 3), 0.91 (s, 9), 1.57–2.00 (m, 1), 2.23 (dd, J_{AX} = 5 Hz, J_{AB} = 10.5 Hz, 1), 2.42 (s, 3), 2.47 (m, 1), 3.11 (m, 1), 3.34 (s, 3), 3.59 (dd, J_{BX} = 7 Hz, J_{BA} = 10.5 Hz, 1), 3.90 (dd, J = 6, 10 Hz, 1), 4.32 (dd, J_{XA} = 5 Hz, J_{XB} = 7 Hz, 1), 4.46 (d, J = 11.5 Hz, 1), 4.90 (d, J = 11.5 Hz, 1), 5.79 (m, 2), 5.91 (s, 2), 6.75 (s, 1), 6.77 (s, 1). Mass spectrum, m/e calcd for $C_{24}H_{37}NO_5Si$: 447.2441. Found: 447.2443.

(3aα,6α,7aα)-3a,6,7,7a-Tetrahydro-3a-[2-(((*tert*-butyldimethylsilyl)oxy)methyl)-4,5-(methylenedioxy)phenyl]-6-methoxy-1-methyl-3-indolinone (53). Alcohol **52** (25.9 mg, 0.0579 mmol) was dissolved in 300 μL of dimethyl sulfoxide and 200 μL of acetic anhydride. The mixture was allowed to stir at room temperature for 24 h. The solvents were evaporated in vacuo (0.1 mmHg, overnight). The residue was dissolved in chloroform and washed twice with saturated sodium chloride.

The solution was dried over anhydrous sodium sulfate and concentrated in vacuo. Chromatography of the crude residue on silica gel (230–400 mesh, 10% ethyl acetate in hexane) afforded 14.7 mg (57%) of the desired ketone **53** as a white solid: mp 131–133 °C; IR λ_{max} ($CHCl_3$) 5.75 μm; ^1H NMR ($CDCl_3$) δ 0.11 (s, 6), 0.93 (s, 9), 1.17–1.73 (m, 1), 2.07–2.43 (m, 1), 2.51 (s, 3), 3.14 (d, J= 18 Hz, 1), 3.17 (m, 1), 3.43 (s, 3), 3.66 (d, J = 18 Hz, 1), 4.03 (m, 1), 4.33 (s, 2), 5.34 (br d, J = 10.5 Hz, 1), 5.91 (s, 2), 6.26 (br d, J = 10.5 Hz, 1), 6.91 (s, 1), 7.09 (s, 1). Mass spectrum, m/e calcd for $C_{24}H_{35}NO_5Si$: 445.2285 (P). Found: 445.2256.

Further elution with 30% ethyl acetate in hexane gave 9.5 mg (33%) of the acetate of **52** as a side product: IR λ_{max} ($CHCl_3$) 5.72 μm; ^1H NMR ($CDCl_3$) δ 0.14 (s, 6), 0.94 (s, 9), 1.4–1.7 (m, 1), 1.71 (s, 3), 2.0–2.6 (m, 2), 2.43 (s, 3), 3.11 (m, 1), 3.35 (s, 3), 3.60 (m, 1), 3.88 (m, 1), 4.65 (s, 2), 5.14 (t, J = 7 Hz, 1), 5.75–6.05 (m, 2), 5.91 (s, 2), 6.86 (s, 1), 7.00 (s, 1); mass spectrum, m/e 489 (P).

***dl*-Tazettine (4).** The ketone **53** (14.0 mg, 0.0314 mmol) was dissolved in 2 mL of dry tetrahydrofuran. A solution of tetra-*n*-butylammonium fluoride (85 μL, 0.5 M, 0.0425 mmol) was added, and the mixture was allowed to stir at room temperature for 20 min. The solvent was evaporated in vacuo, and the residue that remained was chromatographed on silica gel (230–400 mesh, 3% methanol in chloroform) to afford 10.1 mg (97%) of *dl*-tazettine (**4**): mp 175–176 °C (acetone); IR λ_{max} ($CHCl_3$) 2.97, 3.00 μm; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.63 (ddd, J = 2.2, 10.1, 13.1 Hz, 1), 2.23 (ddd, J = 4.8, 5.2, 13.5 Hz, 1), 2.40 (s, 3), 2.68 (d, J = 10.5 Hz, 1), 2.87 (m, 1), 3.31 (d, J = 10.5 Hz, 1), 3.47 (s, 3), 4.13 (br dd, J = 5.2, 10.1 Hz, 1), 4.64 (d, J = 14.4 Hz, 1), 4.96 (d, J = 14.4 Hz, 1), 5.61 (br d, J = 10.1 Hz, 1), 5.90 (s, 2), 6.14 (br dd, J = 10.1 Hz, 1), 6.50 (s, 1), 6.85 (s, 1). Mass spectrum, m/e calcd for $C_{18}H_{21}NO_5$: 331.1420. Found: 331.1408.

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Registry No. (±)-**1**, 83379-58-2; (±)-**4**, 28405-99-4; (±)-**5**, 74120-60-8; (*E*)-**8**, 54125-02-9; (±)-**11**, 74120-50-6; **12**, 4676-39-5; (±)-**13**, 83379-59-3; (±)-**14**, 83379-60-6; **15**, 77627-83-9; (±)-**16**, 83379-61-7; **17**, 83379-64-0; **18**, 83379-62-8; (±)-**19**, 83379-63-9; **22**, 74120-41-5; **23**, 83379-54-8; **23** silyl enol ether, 83379-56-0; **24**, 83379-55-9; (*E*)-**26**, 74120-46-0; (*Z*)-**26**, 74120-47-1; (±)-**37** (isomer 1), 74120-48-2; (±)-**37** (isomer 2), 74120-49-3; (±)-**38**α, 74120-59-5; (±)-**38**β, 74120-51-7; (±)-**42**, 74120-57-3; (±)-**43**, 74120-58-4; (±)-**44**, 74120-52-8; (±)-**45**, 74120-54-0; (±)-**46**, 74120-53-9; (±)-**49**, 74165-12-1; (±)-**51**, 74165-11-0; (±)-**52**, 74120-55-1; (±)-**52** acetate, 83379-57-1; (±)-**53**, 74120-56-2; thiophenol, 108-98-5; *N*,*N*-dimethylformamide dimethyl acetal, 4637-24-5; methylamine, 74-89-5; trimethyl orthoformate, 149-73-5.

Supplementary Material Available: Experimental procedures for the preparation of model compounds **13**, **15**, **16**, **17**, **18**, **19**, and **20** and infrared and NMR (600 MHz) spectra of authentic and synthetic tazettine (7 pages). Ordering information is given on any current masthead page.

Transition-State Barrier for Electrophilic Reactions. Solvation of Charge-Transfer Ion Pairs as the Unifying Factor in Alkene Addition and Aromatic Substitution with Bromine

S. Fukuzumi and J. K. Kochi*

Contribution from the Department of Chemistry, Indiana University, Bloomington, Indiana 47405. *Received March 11, 1982*

Abstract: Alkenes and arenes are known to form 1:1 electron donor–acceptor complexes with molecular bromine. The disappearance of the charge-transfer (CT) absorption bands for these alkene and aromatic complexes coincides with the kinetics of electrophilic addition and electrophilic aromatic substitution, respectively. The rate constants (log k_{Br}) for both classes of electrophilic brominations follow linear but separate correlations with the CT transition energies ($h\nu_{CT}$). However, a *single* free energy relationship in eq 29 obtains for both alkene addition and aromatic substitution when the solvation energies of alkene and aromatic cations are specifically included. Solvation energies (ΔG^s) for these transient cations are evaluated from the gas-phase ionization potentials of the alkene and aromatic donors together with their rates of oxidation in solution by a prescribed series of outer-sphere iron(III) oxidants. The theoretical basis of eq 29 is shown to derive directly from Mulliken theory, in which the CT transition $h\nu_{CT}$ relates to the vertical excitation of the donor–acceptor complex to the ion-pair state, i.e., $[D\,Br_2] \rightarrow [D^+Br_2^-]^*$, where D represents the alkene and aromatic donors. Inclusion of the solvation term ΔG^s with $h\nu_{CT}$ corresponds to the formation of the solvated ion pair $[D^+Br_2^-]_s$. The single, remarkable correlation in Figure 8 indicates that the activation process is equivalent to the formation of solvated ion pairs in both classes of electrophilic brominations. The CT formulation thus unifies the activation processes for electrophilic additions to alkenes and electrophilic aromatic substitution into a single concept readily amenable to physical interpretation. Its significance to the more conventional linear free energy relationships based on the Taft σ^* and Brown σ^+ correlations for alkenes and arenes, respectively, is delineated.

The definition of an *electrophilic reaction* forms an important mechanistic basis of organic chemistry, especially as it refers to olefin additions and aromatic substitutions.[1,2] In particular, molecular bromine has served as an ideal electrophile for mechanistic studies owing to its facile reactions with both olefins and aromatic compounds.[3,4] Since these reactions occur at measurable

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