quirement that **13** be converted to an enol, which is also a methylenecyclobutane totally shuts down turnover. That **13** is not a better inhibitor reveals the subtlety of the recognition of this enzyme for its substrate. The isoleucine precursor α,β-dihydroxy-β-methylvaleric acid differs from **13** only by the addition of two hydrogens.

The activity of vinyl fluoride **15**, possibly acting as a stable enol surrogate, implicates an enol intermediate[42] in the reaction mechanism of spinach DHAD. Empirical force field calculations on **15** and the putative enol **2** show a very close correspondence in structure. The extremely poor activity of oxamide **17** is disappointing, since in principle this should be an excellent enol mimic. These examples serve to illustrate the need for a larger data base to aid in inhibitor design.

(42) Rose, I. A. *Methods Enzymol.* **1982**, *87*, 84-97.

Given the ultimate goal of this work, the screening of all of the inhibitors prepared in this study against whole plants was conducted. At an application rate (spray, greenhouse) of 4 kg/h, only **12** showed activity, with complete kills against quack grass, bindweed, and wild mustard and some activity against other species. That some postemergent herbicidal activity is detected is encouraging, but it should be emphasized that there is no evidence as yet which indicates that inhibition of DHAD is the mode of action. There is also little correlation between activity in vivo and in vitro.

Acknowledgment. D. Pompliano, L. Reimer, and D. Conley of this department provided many helpful suggestions. Hewlett-Packard is thanked for the gift of the HPLC. Screening of the compounds by American Cyanamid Co. is also appreciated. D. Horowitz provided invaluable aid in optimizing the enzyme purification.

Total Synthesis of (±)-Fawcettimine

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(±)-Fawcettimine (**7**) has been prepared in 13 steps from cyano enone **14** along the line: **14** → **16** → **17** → **19** → **22** → **23** → **24** → **25** → **35** → **42** → **43** → **45** → **54** → **7**. The overall yield is 16.6%, and no protecting groups are required in the synthesis. The tautomeric ring–chain equilibria of keto carbinolamines **7**, **57**, and **60** and diketo amines **56** and **59** have been investigated by NMR spectroscopy and molecular mechanics calculations. In the 4*R* ("epi") series, diketo amine **56** seems to predominate over keto carbinolamine form **57**. Isomer **60** cannot be observed spectrally, and the molecular mechanics calculations suggest that it should be 5 kJ/mol less stable than **57**. These experiments and calculations are in agreement with the observation that compound **54** exists wholly in the keto amine form, with none of the carbinolamine tautomer being observable spectrally. In the 4*S* ("natural") series, the keto carbinolamine form **7** greatly predominates over the diketo amine form **59**.

Background

In 1959, from extracts of alkaloids of *Lycopodium fawcetti* collected in the Blue Mountain Range of Jamaica in the Spring, R. H. Burnell isolated a compound of intermediate basicity, which he designated as base A.[1] Subsequent investigation gave the formula $C_{16}H_{25}NO_2$ and revealed that, whereas the infrared spectrum of the free amine in CCl_4 shows one carbonyl stretch (1730 cm^{-1}) and a hydroxyl absorption (3585 cm^{-1}), the acetyl and methiodide derivatives show two carbonyl absorptions (1690, 1730 cm^{-1} and 1710, 1730 cm^{-1}, respectively) and no hydroxyl absorption.[2-4] These early investigations led to the proposal of structure **1** for fawcettimine and structure **2** for the acetyl derivative (Scheme I).[4]

The gross structural assignment was confirmed by the chemical correlation of fawcettime with serratinine (**3**), the structure of which was proven by X-ray analysis.[5] As shown in Scheme I, the reduction of *N*-acetylfawcettimine with either sodium borohydride in methanol or sodium/isobutyl alcohol in toluene furnishes dihydro-*N*-acetylfawcettimine (**4**).[3,4] The latter compound was also obtained from 13-acetyl-8-deoxyserratinine (**5**)[6] by reduction with zinc in the presence of acetic anhydride, followed by alkaline saponification of the acetate group. This correlation did not permit assignment of relative configuration at C-4 in fawcettimine.

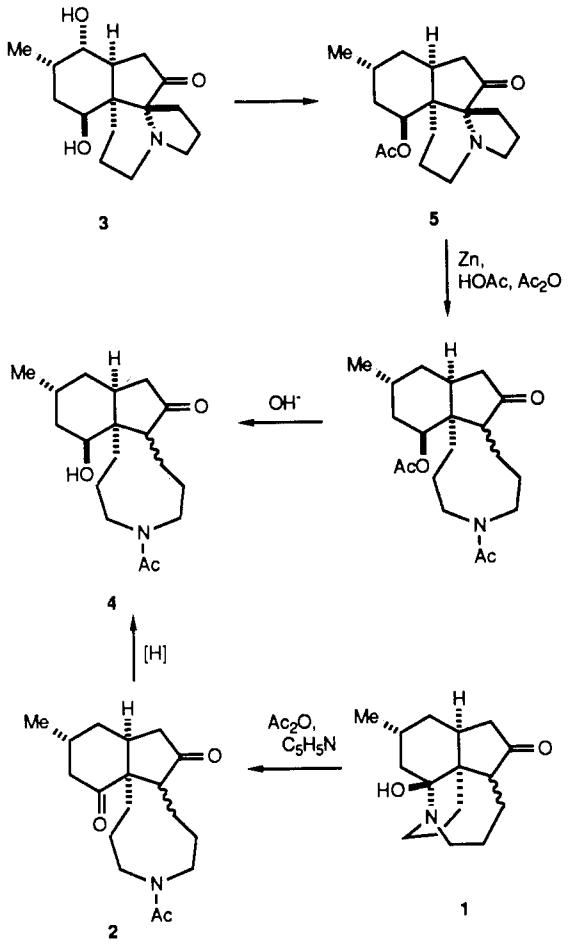
In 1974, Ayer and co-workers reported an X-ray analysis of allopecuridine, which revealed it to be **6**, the 4*R*-hydroxy derivative or fawcettimine.[7] Reduction of **6** with calcium in ammonia gives fawcettimine, confirming the previous structural assignment of the latter alkaloid. It was noted that allopecuridine and fawcettimine behave similarly with acetic anhydride, giving *N*-acetyl derivatives, and that *N*-acetylfawcettimine and *N*-acetylallopecuridine have similar positive Cotton effects at 300 nm in their circular dichroism spectra. From this optical similarity, Ayer assigned fawcettimine and *N*-acetylfawcettimine the 4*S* stereochemistry, as shown in Scheme II (**7** and **9**).

In 1981, Inubushi and Harayama elucidated the absolute stereostructure of lycothunine (**10**) by X-ray analysis of its acetyl derivative, **11**.[8] This investigation revealed lycothunine to be 10,11-dehydrofawcettimine. Unlike

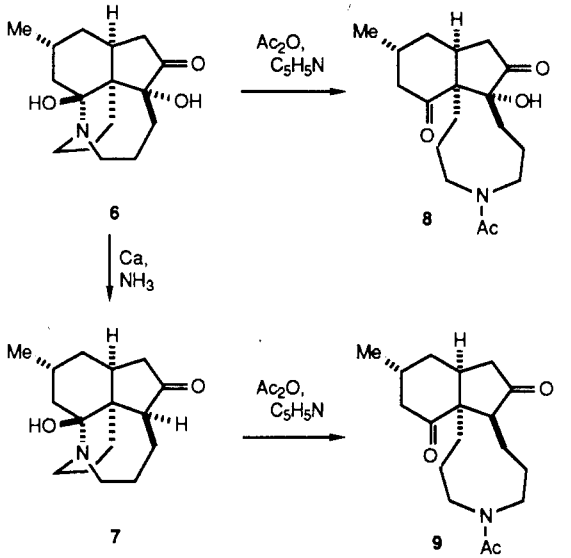
(1) Burnell, R. H. *J. Chem. Soc.* **1959**, 3091.
(2) Burnell, R. H.; Mootoo, B. C. *Can. J. Chem.* **1961**, *39*, 1090.
(3) Burnell, R. H.; Chin, C. G.; Mootoo, B. S.; Taylor, D. R. *Can. J. Chem.* **1963**, *41*, 3091.
(4) Inubushi, Y.; Ishii, H.; Harayama, T.; Burnell, R. H.; Ayer, W. A.; Altenkirk, B. *Tetrahedron Lett.* **1967**, 1069.
(5) Nishio, K.; Fujiwara, T.; Tomita, K.; Ishii, H.; Inubushi, Y.; Harayama, T. *Tetrahedron Lett.* **1969**, 861.
(6) Ishii, H.; Yasui, B.; Harayama, T.; Inubushi, Y. *Tetrahedron Lett.* **1966**, 6215.
(7) Ayer, W. A.; Altenkirk, B.; Fukazawa, Y. *Tetrahedron* **1974**, *30*, 4213.
(8) Inubushi, Y.; Harayama, T.; Yamaguchi, K.; Ishii, H. *Chem. Pharm. Bull.* **1981**, *29*, 3418.

0022-3263/89/1954-1548$01.50/0

Scheme I



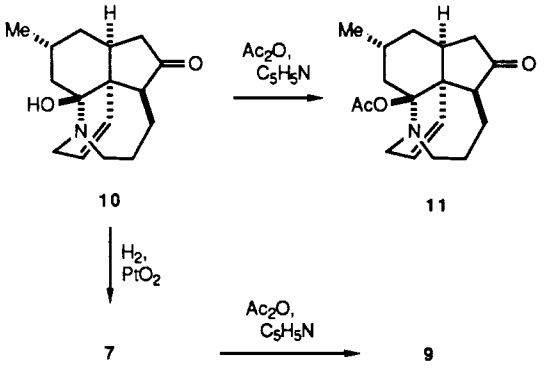
Scheme II



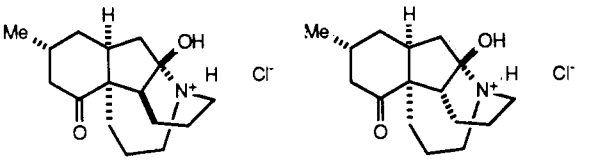
fawcettimine, lytothunine undergoes acetylation on oxygen in the carbinolamine tautomer, rather than on nitrogen in the amino ketone tautomer (Scheme III). Catalytic hydrogenation of lycothunine on Adams' catalyst gives fawcettimine, thus providing a seemingly unambiguous stereochemical proof of the stereostructure of fawcettimine.

One bewildering problem remained. In the early work on fawcettimine, Burnell reported that the hydrochloride and perchlorate salts of fawcettimine both have carbonyl absorptions at 1690 cm^{-1},[3] suggesting that these salts exist in a tautomeric form involving the cyclopentanone car-

Scheme III



bonyl in a carbinolamine function (e.g., **12**). However, a molecular model of **12** (4*S*) with reasonable bond lengths and angles cannot be constructed, although such a model can be easily constructed for the C-4 epimer **13** (4*R*). This information leaves open the possibility of isomerization, in the isolation of fawcettimine, in the formation of derivatives, and perhaps during the catalytic hydrogenation of lycothunine.



Prior to the current work, Inubushi and co-workers reported a 26-step total synthesis of fawcettimine, proceeding in 0.1% overall yield from dihydroorcinol.[9] The Inubushi synthesis does not further illuminate the question of stereochemistry at C-4, since this center is established by catalytic hydrogenation of an α,β-unsaturated ketone.

Following our interest in developing general synthetic routes to the *Lycopodium* alkaloids,[10] we have carried out a total synthesis of fawcettimine. Our studies fully clarify the situation with regard to the stereostructure of the alkaloid, particularly at C-4. In this paper, we report the full details of these investigations.[11]

Total Synthesis of (±)-Fawcettimine

Our synthesis begins with cyano enone **14**,[12] the starting material for our earlier synthesis of lycopodine, lycodine, and lycodoline.[10e] Reaction of this material with bis-silane **15**[13] provides adduct **16** in quantitative yield (Scheme IV). Although **16** is a mixture of C-2 diastereomers, the relative stereochemistry at C-3 and C-5 appears to be solely trans. The high facial selectivity shown in this reaction exceeds that seen in other conjugate additions to 5-alkylcyclo-

(9) Harayama, T.; Takatani, M.; Inubushi, Y. *Tetrahedron Lett.* **1979**, 4307; *Chem. Pharm. Bull.* **1980**, *28*, 2394.

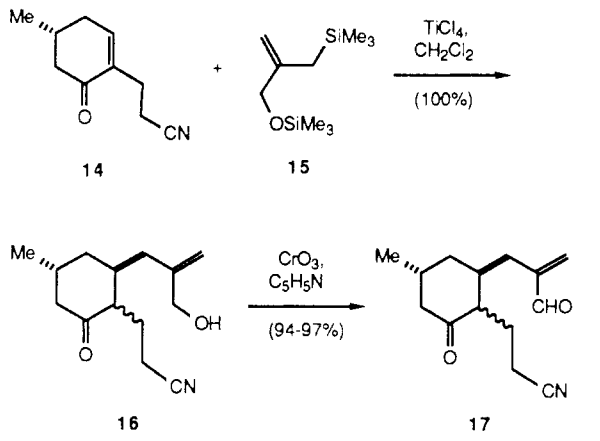
(10) (a) Heathcock, C. H.; Kleinman, E.; Binkley, E. S. *J. Am. Chem. Soc.* **1978**, *100*, 8036. (b) Heathcock, C. H.; Kleinman, E.; Binkley, E. S. *Stereoselective Synthesis of Natural Products: Proceedings of the Seventh Workshop Conference Hoechst, Schloss Reisenburg*, September 24–27, 1978, Bartmann, W., Winterfeldt, E., Eds.; Exercpta Medica: Amsterdam-Oxford. (c) Kleinman, E.; Heathcock, C. H. *Tetrahedron Lett.* **1979**, 4125. (d) Heathcock, C. H.; Kleinman, E. F. *J. Am. Chem. Soc.* **1981**, *103*, 222. (e) Heathcock, C. H.; Kleinman, E. F.; Binkley, E. S. *J. Am. Chem. Soc.* **1982**, *104*, 1054.

(11) This work has been reported in preliminary form: Heathcock, C. H.; Smith, K. M.; Blumenkopf, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 5022.

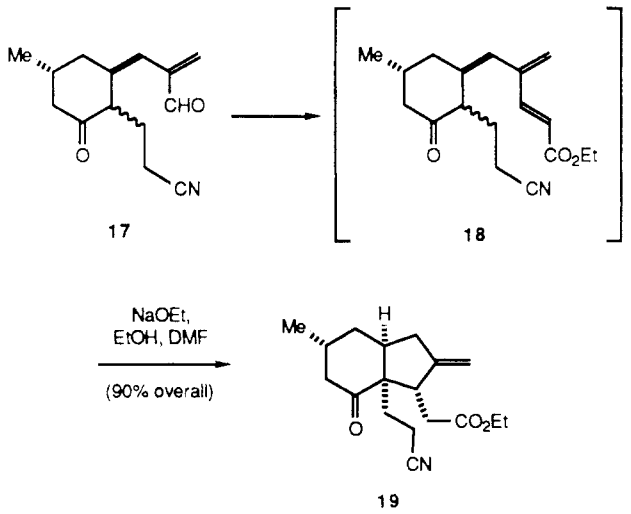
(12) Clark, R. D.; Heathcock, C. H. *J. Org. Chem.* **1973**, *38*, 3658.

(13) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1979**, *101*, 6429; **1983**, *105*, 2315, 2326. Trost, B. M.; Chan, D. M. T.; Nanninga, T. N. *Org. Synth.* **1984**, *62*, 58.

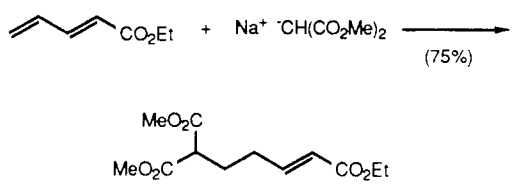
Scheme IV



Scheme V



Scheme VI

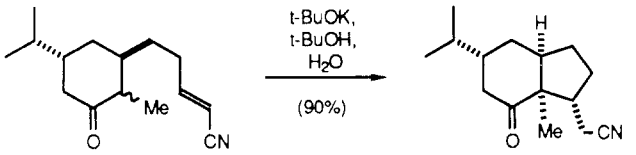


hexenones; an ancillary study has shown that the Hosomi–Sakurai reaction is a process that shows generally high facial selectivity in additions to cyclic enones.[14] Oxidation of **16** by a modified Sarratt procedure[15] provides α,β-unsaturated aldehyde **17** in 97% yield.

To prepare intermediate **17** for formation of the five-membered ring, we carried out a Wittig condensation with [(ethoxycarbonyl)methylene]triphenylphosphorane; dienoate **18** was obtained, as a mixture of C-2 epimers, in 96% yield (Scheme V). The two epimers are conveniently separable by chromatography; their ^{1}H NMR spectra clearly show that the new double bond has the *E* configuration. Compound **18** is obtained as a viscous oil or glass, which is insoluble in most organic solvents. On a small scale, **18** reacted with sodium ethoxide in a mixture of ethanol and dimethylformamide to give the bicyclic Michael adduct **19** in quantitative yield. On a larger scale, the foregoing two-step conversion of **17** to **19** was difficult, because of the low solubility of **18**. Therefore, an alternative one-pot procedure was developed. Treatment of **17** with [(ethoxycarbonyl)methylene]triphenylphosphorane in ethanol, followed by addition of ethanolic sodium ethoxide, provides **19** in 90% yield.

In principal, the enolate of **18** could undergo intramolecular 1,6- or 1,4-addition. Indeed, in a related intermolecular Michael reaction (Scheme VI), only 1,6-addition is seen.[16] However, the behavior of **18** conforms perfectly with Baldwin's rules for ring-closure reactions, since the observed cyclization is *5-Exo-Trig*.[17] These often-misunderstood generalizations are based on the stereoelectronic principles that govern nucleophilic displacement and nucleophilic addition reactions and provide guidance in predicting and understanding cyclization reactions. They are *not* absolute edicts on "allowed" and "disallowed" processes. The current reaction is an ideal example of the rules, since the two competing reactions (a) are both Michael reactions and (b) both form five-membered carbocycles and (c) the observed process is the unexpected process based on steric effects and intermolecular precedent (Scheme VI).

The intramolecular Michael reaction leading to **19** is also highly stereoselective; compound **19** is formed as a single diastereomer. The observed stereochemistry (vide infra) is precedented by the intramolecular Michael reaction of **20**, which yields solely keto nitrile **21**.[18]



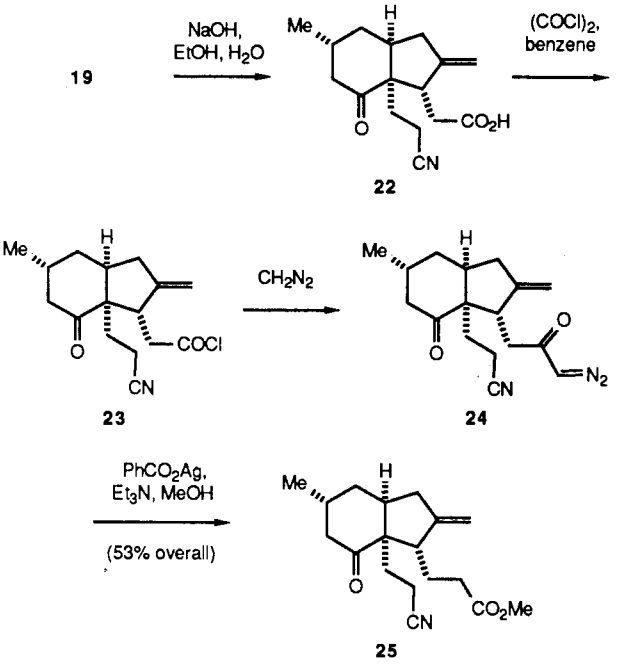
Intermediate **19** contains all but one carbon necessary for completion of the fawcettimine skeleton. This additional carbon was added by Arndt–Eistert homologation[19] of the acetic acid side chain of acid **22**, obtained by saponification of **19** (Scheme VII). Acyl chloride **23** reacts with diazomethane to give the crystalline α-diazo ketone **24**, which undergoes Wolff rearrangement to provide methyl ester **25** in 53% overall yield from **19**. It is noteworthy that the intermediate carbene in this rearrangement does not undergo intramolecular addition to the proximal double bond.

The Arndt–Eistert homologation provides a bicyclic intermediate (**25**) having the full complement of skeletal atoms for completion of the fawcettimine synthesis. However, after the exceedingly efficient elaboration of **19** (three steps from cyano enone **14**), it is disappointing that four more steps are required to add the final skeletal carbon. In an attempt to streamline this aspect of the synthesis, we spent some effort exploring alternative annulation strategies that might provide a version of **25** in a more direct manner. Two interesting, albeit unsuccessful, ventures in this direction will be recounted here.[20]

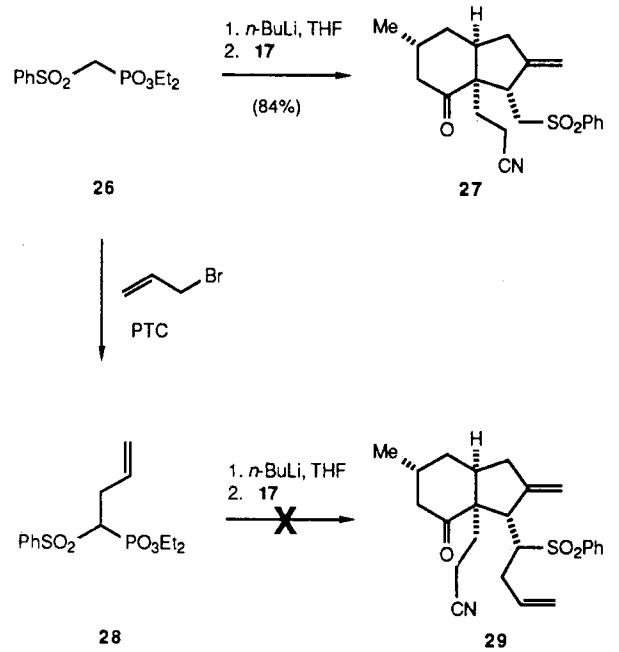
Diethyl [(phenylsulfonyl)methyl]phosphonate[21] (**26**) reacts smoothly with aldehyde **17** to provide the crystalline hydrindanone **27** in 84% yield (Scheme VIII). Analysis

(14) Blumenkopf, T. A.; Heathcock, C. H. *J. Am. Chem. Soc.* **1983**, *105*, 2354.
(15) Ratcliffe, R.; Rodehorst, R. *J. Org. Chem.* **1970**, *35*, 4000.
(16) Kohler, E. P.; Butler, F. R. *J. Am. Chem. Soc.* **1926**, *48*, 1036.
(17) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.
(18) Brattesani, D. N.; Heathcock, C. H. *J. Org. Chem.* **1975**, *40*, 2165.
(19) (a) Bachman, W. E.; Struve, W. S. *Org. React.* **1942**, *1*, 38. For a recent application, see: (b) Branca, S. J.; Lock, R. L.; Smith, A. B., III. *J. Org. Chem.* **1977**, *42*, 3165.
(20) For a full discussion, see: Blumenkopf, T. A. Dissertation, University of California, Berkeley; **1983**, pp 154–168; *Chem. Abstr.* **1984**, *23*, 211512k.
(21) Blumenkopf, T. A. *Synth. Commun.* **1986**, *16*, 139.

Scheme VII



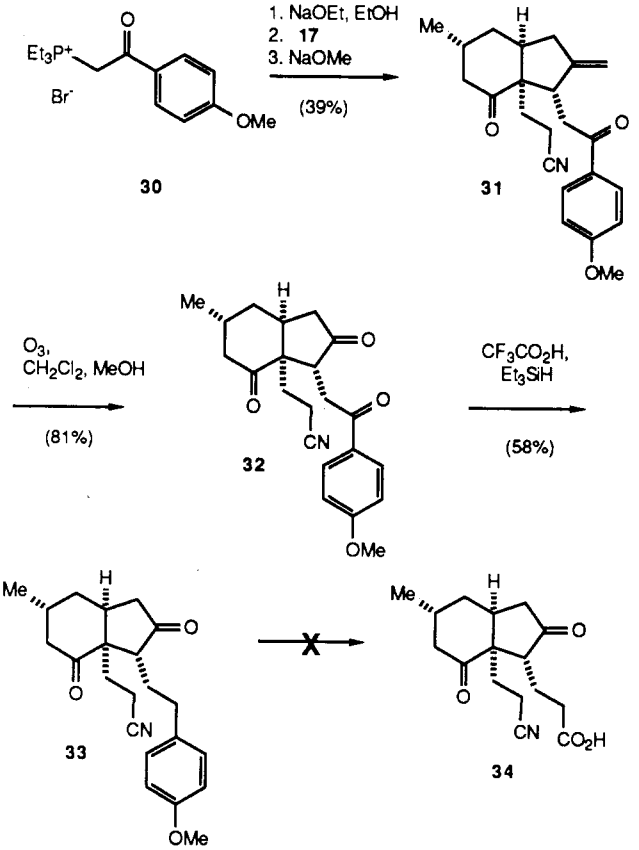
Scheme VIII



of **27** by ^{1}H NMR spectroscopy reveals that is is a 4:1 mixture of diastereomers; we assume that the major isomer has the sulfonylmethyl and cyanoethyl groups cis, as shown. Allylation of **26** occurs smoothly under phase-transfer conditions to give **28**.[22] However, we were unable to find conditions under which sulfonyl phosphonate **28** will react with aldehyde **17**.[23]

Aldehyde **17** does not react with (benzoylmethylene)-triphenylphosphorane[24] or its *p*-methoxy analogue.[25] Johnson has found that stabilized trialkylphosphonium ylides are considerably more reactive than their triaryl analogues.[26] Consequently, we prepared the triethyl-

Scheme IX



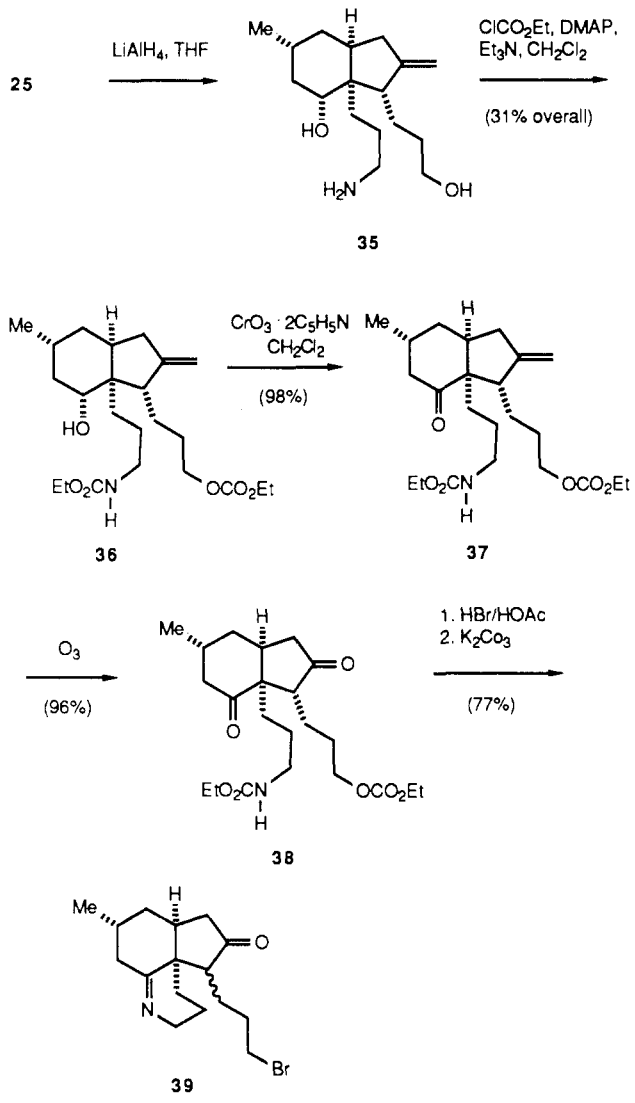
phosphonium salt **30** in 92% yield by the method of Issleib and Lindner.[27] The ylide of **30** is generated in situ by the action of sodium ethoxide on an ethanol slurry of the phosphonium salt. Successive additions of aldehyde **17** and base provide hydrindanone **31**, albeit as a 3:2 diastereomer mixture and in only 39% yield (Scheme IX). Our intention in this approach was to hydrogenolize the benzylic carbonyl group and oxidatively degrade the aromatic ring to a carboxy group, thus obtaining the desired propionic acid side chain. The *p*-methoxy group was included to facilitate both the hydrogenolytic and oxidative steps. However, the exocyclic double bond proved to be incompatible with the reaction conditions necessary to accomplish hydrogenolysis of the benzylic carbonyl group. Ozonolysis provides triketone **32**, which undergoes selective reduction upon treatment with triethylsilane in trifluoroacetic acid[28] to give diketone **33** in 58% yield. Unfortunately, this approach foundered when we were unable to oxidatively degrade the *p*-methoxyphenyl group.[29,30]

Because the foregoing approaches were not successful in providing a superior route to ester **25** or its equivalent, we returned to the Arndt–Eistert method and worked out a practical procedure whereby aldehyde **17** is converted into homologated ester **25** without purification of intermediates. In this manner, 8.00 g of **17** provides 4.90 g of **25** (47% overall yield).

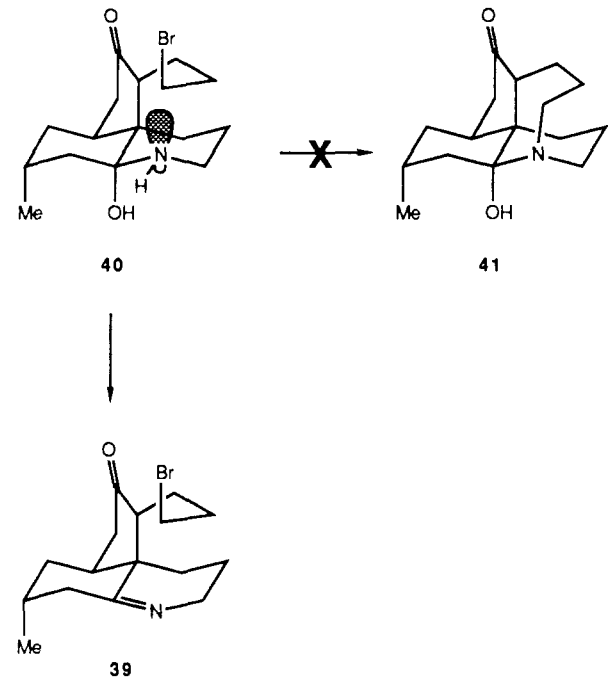
The most straightforward approach for completion of the synthesis from intermediate **25** would be (1) reduction

(22) Ellingsen, P. O.; Undheim, K. *Acta Chem. Scand.* **1979**, *B33*, 528.
(23) Phosphonate **28** also does not give characterizable products with benzaldehyde or cyclohexanone.
(24) Denny, D. B.; Ross, S. T. *J. Org. Chem.* **1962**, *27*, 998.
(25) Bianchini, J.-P.; Gaydou, E. M. *C. R. Seances Acad. Sci., Ser. C* **1975**, *280*, 1521.
(26) Johnson, A. W.; LaCount, R. B. *Tetrahedron* **1960**, *9*, 130.
(27) Issleib, K.; Lindner, R. *Ann. Chem.* **1967**, *707*, 120.
(28) (a) West, C. T.; Donnelly, S. J.; Kooistra, D. A.; Doyle, M. P. *J. Org. Chem.* **1973**, *38*, 2675. (b) Swenton, J. S.; Raynolds, P. W. *J. Am. Chem. Soc.* **1978**, *100*, 6188.
(29) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.
(30) Criegee, R.; Höver, H. *Chem. Ber.* **1960**, *93*, 2521.

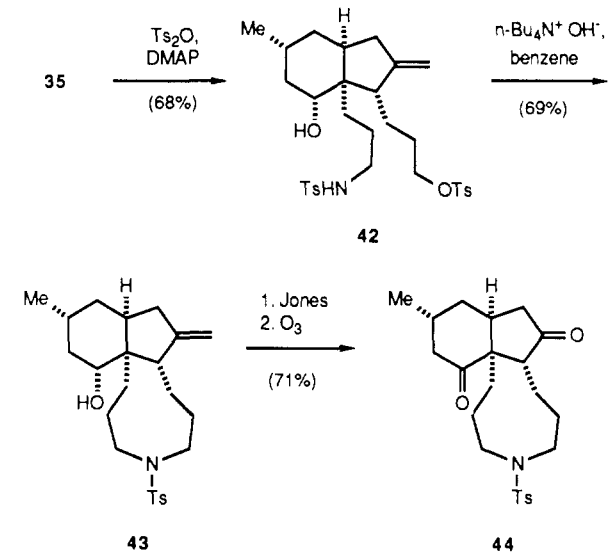
Scheme X



Scheme XI



Scheme XII



of the nitrile to a primary amine and (2) direct closure of a nine-membered ring. A related closure was, in fact, utilized in the Inubushi synthesis of fawcettimine.[9] Nevertheless, the formation of medium rings (8–11) is known to be difficult even under conditions of high dilution.[31] Therefore, our early attempts to form the heterocyclic rings of fawcettimine were designed to avoid direct formation of a nine-membered ring by using the cyclohexanone carbonyl group as a "template"; as will be seen in the sequel, this plan was overly complicated and did not succeed.

Reduction of **25** with lithium aluminum hydride in THF provides an amino diol (Scheme X). The stereochemistry of the reduction is highly dependent on reaction temperature; at 25 °C, −78 °C, and −110 °C, the diastereomer ratios are 1:1, 5:1, and 10:1, respectively. The major isomer was shown to have the stereostructure **35** by X-ray analysis of a conversion product (vide infra). Amino diol **35** reacts with ethyl chloroformate in a stepwise fashion, with the three functions reacting in the order: amine, primary hydroxy, secondary hydroxy. Under suitable conditions, derivative **36** may be obtained in 31% yield. Oxidation of the secondary hydroxy group and ozonolysis of the double bond gives diketone **38**. Treatment of this material with 48% HBr in glacial acetic acid, followed by mild basic workup, gives tetrahydropyridine **39** as a mixture of diastereomers in 77% yield.

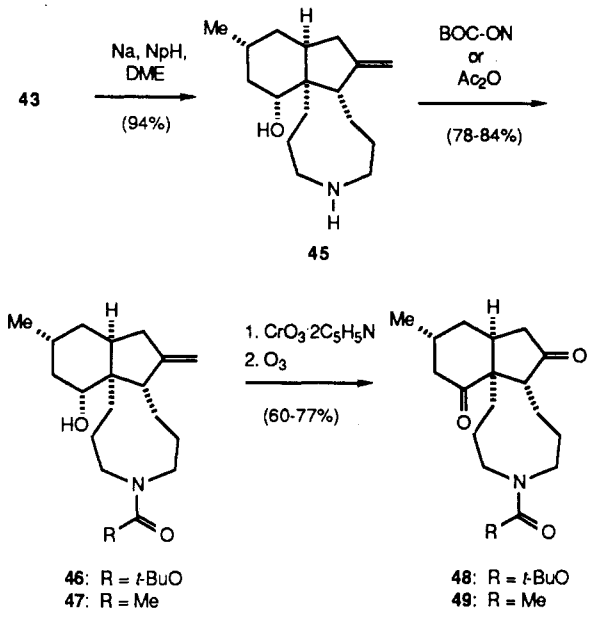
Reaction of **38** with HBr/HOAc presumably gives the hydrobromide of a keto amino alcohol. We had hoped that neutralization of this salt would give carbinolamine **40**, which might then undergo cyclization to fawcettimine (Scheme XI). This coveted transformation appears to be slower than dehydration of **40** to imine **39**, which is constituted in such a way that intramolecular nucleophilic displacement is impossible. Attempts to circumvent this problem by addition of HCN to the imine double bond and by preparation of an *N*-benzyl derivative of **38** were unfruitful.[32]

Having failed in the foregoing attempts to gain the nine-membered ring of the fawcettimine tautomer by indirection, we returned to examine the simplest possible solution—direct closure of the nine-membered heterocyclic ring. As shown in Scheme XII, treatment of amino diol

(31) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95.

(32) For a discussion of this chemistry, see: Smith, K. M. Dissertation, University of California, Berkeley; 1988; pp 24–34.

Scheme XIII

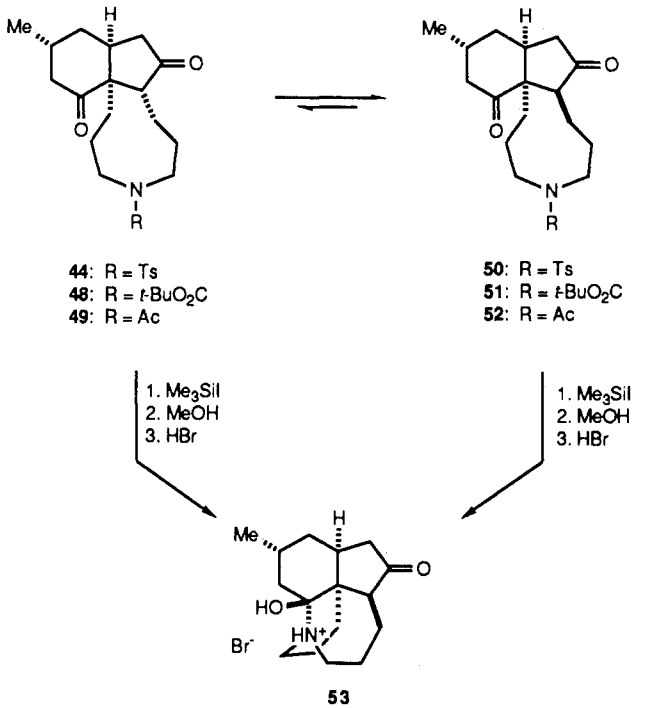


35 with *p*-toluenesulfonic anhydride in the presence of 4-(dimethylamino)pyridine in methylene chloride at −20 °C provides the *N,O*-bis(tosyl) derivative **42**. Other conditions for this transformation are less successful. Use of *p*-toluenesulfonyl chloride and pyridine in methylene chloride at 0 °C gives reasonable selectivity for the primary hydroxy group, but displacement of the primary tosyl group by chloride is a significant side reaction. Use of *p*-toluenesulfonic anhydride and pyridine in the same solvent at 0 °C eliminates the latter problem, but the primary/secondary chemoselectivity is lost. Treatment of compound **42** with tetra-*n*-butylammonium hydroxide in benzene leads smoothly to **43** in a respectable 69% yield. Jones oxidation and ozonolysis affords diketone **44**.

Removal of the *p*-toluenesulfonyl group from nitrogen in **44** should yield fawcettimine. However, attempts to accomplish this transformation by using HBr in acetic acid gave a complex mixture of products. A system reported as successful in removing the tosyl group from amines, photolysis with citric acid and dimethoxybenzene,[33] only returned starting material. The standard method for removing a tosyl group from nitrogen employs dissolving-metal reduction conditions.[34] Because this procedure would reduce the two carbonyl groups of **44**, it was necessary to perform the detosylation prior to the oxidation steps.

Removal of the tosyl group with lithium/ammonia/*tert*-butyl alcohol is accompanied by significant reduction of the exocyclic methylene group. This side reaction is almost completely eliminated by the use of sodium naphthalenide as reducing agent (Scheme XIII).[35] In this procedure, a solution of the tosylamide in dimethoxyethane is titrated with the dark-green sodium naphthalenide solution at −78 °C, with the end point occurring after the addition of approximately 1 equiv of reducing agent. Treatment of amino alcohol **45** with 2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile (BOC-ON)[36] or acetic anhydride affords carbamate **46** or amide **47**.

Scheme XIV



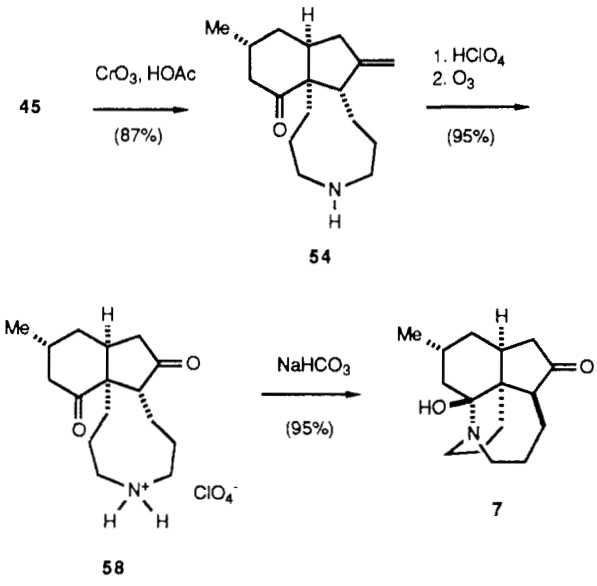
Two-stage oxidation of these two derivatives provides the diketo derivatives **48** and **49**.

In order to gain some information about the relative stabilities of the C-4 diastereomers, we studied the base-catalyzed equilibration of derivatives **44**, **48**, and **49** (Scheme XIV). In all three systems the trans-fused isomers predominate, with K_{eq} being [**50**]/[**44**] = 3, [**51**]/[**48**] = 7, and [**52**]/[**49**] = 2. The diastereomeric tosylamides **50**/**44** and acetamides **52**/**49** are separable by chromatography; unfortunately, the carbamates **51**/**48** are not. However, pure **48** is readily obtained as shown in Scheme XIII and a sample consisting of 87% **51** and 13% **48** may be obtained as shown in Scheme XIV.

Our next experiments were aimed at the careful deprotection of **51** and **48**, with a view to producing fawcettimine and 4-epifawcettimine. In our first attempt, carbamate **48** was treated with trifluoroacetic acid, and the resulting ammonium trifluoroacetate was treated with 1 N NaOH. These conditions gave a product that was obviously a mixture of several different components, as judged by the ^{1}H NMR and IR spectra. Both **51** and **48** react smoothly with trimethylsilyl iodide, followed by methanolysis,[37] to give clean products. The ^{1}H NMR spectra of the two products were almost identical and the IR spectra were identical. The IR spectra indicate that both reactions give products having a cyclopentanone carbonyl. The HBr salts of the two products were made with aqueous 1 N HBr and recrystallized from ethanol–acetone. The ^{1}H NMR and IR spectra of these two salts and of natural fawcettimine hydrobromide (**53**) were all identical (Scheme XIV). Our conclusion is that the two forms equilibrate, either during the deprotection step or in the course of formation of the hydrobromide. Apparently, the natural 4*S* configuration greatly predominates in the tetracyclic tautomer, as we could detect no other isomers other than **53**. This result taught us that the stereochemistry at the C-4 position need not be controlled for the synthesis, since fawcettimine is the sole thermo-

(33) Hamada, T.; Nishida, A.; Yonemitsu, O. *J. Am. Chem. Soc.* **1986**, *108*, 140.
(34) (a) Kovacs, J.; Ghatak, U. R. *J. Org. Chem.* **1966**, *31*, 119. (b) Closson, W. D.; Ji, S.; Schulenberg, S. *J. Am. Chem. Soc.* **1970**, *92*, 650.
(35) Ji, S.; Gortler, L. B.; Waring, A.; Battisti, A.; Bank, S.; Closson, W. D.; Wriede, P. *J. Am. Chem. Soc.* **1967**, *89*, 5311.
(36) Itoh, M.; Hagiwara, D.; Kamiya, T. *Tetrahedron Lett.* **1975**, 4393.
(37) Jung, M. E.; Lyster, M. A. *J. Chem. Soc., Chem. Commun.* **1978**, 315.

Scheme XV



dynamic product, but failed to fully clarify the situation regarding the stereochemistry the C-4.

To streamline the synthesis and eliminate the need for the carbamate protection step, we developed conditions whereby the two-stage oxidation of **45** could be performed on the unprotected amine (Scheme XV). Jones oxidation of the bisulfate salt of amino alcohol **45** provides the desired ketone **54**, but the yield is variable. Chromic acid oxidation of the amino alcohol in 80% aqueous acetic acid, however, consistently affords **54** in excellent yield. An interesting feature of this compound is that it exists completely in the amino ketone form; not a trace of a carbinolamine tautomer can be seen by ^1H or ^{13}C NMR spectroscopy. This behavior provides support for the 4*S* configuration of fawcettimine; since if this center were 4*R*, as in **54**, it would be difficult to explain why **54** does not also exist in the carbinolamine form.

The perchlorate salt of amine **54** was prepared and recrystallized from water. A solution of the salt in methanol–CH_2Cl_2 was treated at −78 °C with ozone and reduced with dimethyl sulfide to give the perchlorate salt of the diketo amine **58**. Neutralization of this salt with $NaHCO_3$ and treatment of the resulting amine with aqueous HBr gave fawcettimine hydrobromide in excellent yield. The ^1H NMR and IR spectra of this salt were identical with those of the hydrobromide of natural fawcettimine. Again, C-4 epimerization occurs, either during the neutralization or upon standing in $CHCl_3$ solution for several days. Crystals of the synthetic fawcettimine salt were grown from wet acetonitrile, and the structure was solved by X-ray crystallography. The structure, including stereochemistry, is exactly as had been proposed by earlier researchers. An ORTEP representation of (±)-fawcettimine hydrobromide is presented in Figure 1.

The full synthesis of (±)-fawcettimine requires 13 steps from cyano enone **14** and follows the line: **14** → **16** → **17** → **19** → **22** → **23** → **24** → **25** → **35** → **42** → **43** → **45** → **54** → **7**; the overall yield is 16.6%. It is notable that no protecting groups are required in the synthesis.

NMR Investigations of Tautomeric Equilibria

The synthesis provided conclusive evidence that the stereochemistry of the 4-position was correctly assigned. However, no light had been shed on the equilibrium of the diketo amine–carbinolamine forms and their possible role in forming the salts with the anomalous infrared carbonyl

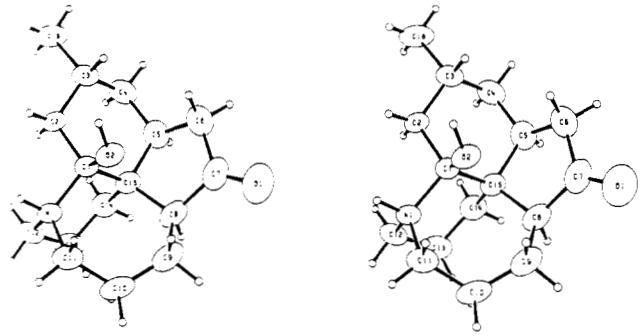


Figure 1. ORTEP representation of the single-crystal X-ray structure of (±)-fawcettimine hydrobromide.

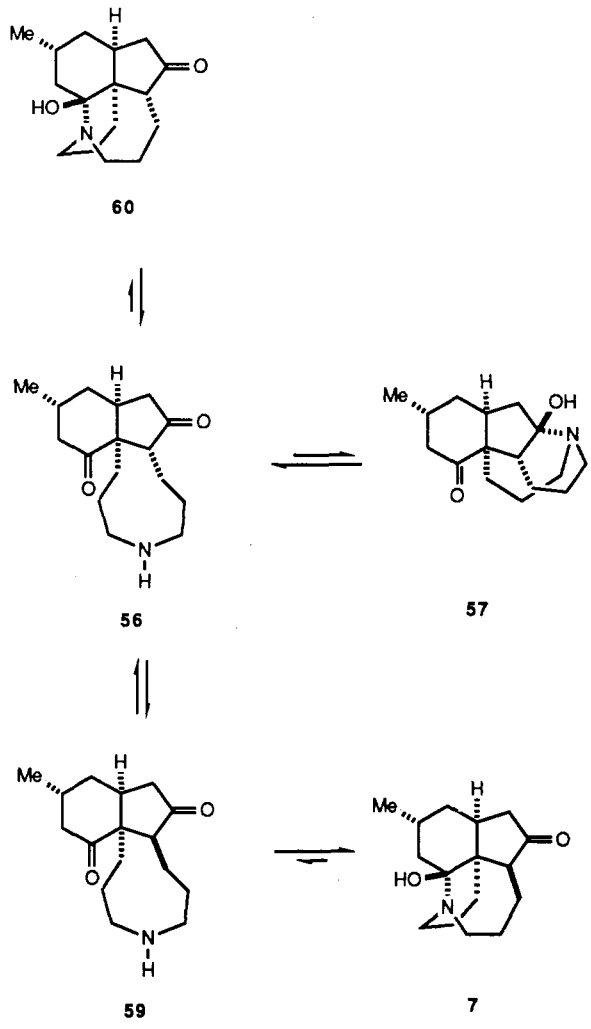
stretches. Since the ozonization must initially lead to 4-epifawcettimine, efforts were made to directly observe this intermediate, or its tautomeric forms, by IR, ^1H NMR, and ^{13}C NMR spectroscopy.

The ozonolysis product, as the perchlorate salt, gave two carbonyl stretches of about equal intensities in the infrared spectra. A $CDCl_3$ solution of this material was neutralized by multiple washings with sodium bicarbonate solution. Examination of the reaction product by IR spectroscopy within 10 min of neutralization still showed two carbonyl absorptions, with the cyclohexanone stretch being slightly weaker than the cyclopentanone stretch. After 1 h, the cyclohexanone stretch was significantly weaker than the cyclopentanone stretch, and after 5 h, the cyclohexanone stretch appeared as a shoulder on the other carbonyl band, barely forming a distinct peak. After standing overnight, the cyclohexanone stretch had disappeared completely into the cyclopentanone band.

The ^1H NMR spectrum taken shortly after neutralization showed a number of methyl doublets, suggesting that a number of isomeric intermediates were present. After 15 min, there were only three methyl doublets, two with rather similar chemical shifts and one further upfield at the position corresponding to that in fawcettimine. There were two sets of distinctive peaks attributable to the methylene protons α to nitrogen: one set corresponding to the pattern seen in fawcettimine, and an accompanying set that was similar in shape and chemical shift, probably arising from an isomeric carbinolamine. The chemical shifts of these multiplets, however, were different enough that they might arise from a carbinolamine involving the cyclopentanone carbonyl (e.g., **57**, Scheme XVI). Integration of the spectrum at this point showed a significant absorption in the region from δ 2.4 to 3.0, suggesting that the third product was in the diketo amine form (probably **56**), since the signals for the methylene protons α to the nitrogen in **54** fall in this same region. We saw no spectral evidence for the presence of a C-4 epimer of fawcettimine (**60**).

The proposed assignments for the three equilibrium forms (**56**, **57**, and **7**) is supported by the chemical shifts of the methyl doublets. One would expect the chemical shifts for the **56** and **57** methyl doublets to be similar, but different from the chemical shift of the upfield methyl doublet of **7**. After 6 h in $CDCl_3$, the two downfield doublets were both present, but integrated for significantly less than the fawcettimine carbinolamine doublet. After 30 h in $CDCl_3$ solution, only one of the downfield doublets, which integrated for less than one-fifth of that of the fawcettimine carbinolamine doublet, was present. After 60 h, the spectrum was that of pure fawcettimine (**7**). These observations are consistent with the view (Scheme XVI) that the initially formed free base exists largely as the diketo amine **56**, in equilibrium with a small amount

Scheme XVI



of keto carbinolamine **57**. With time, **56** epimerizes to **59**, which exists solely in the keto carbinolamine form **7**.

The ^{13}C NMR spectrum of the ozonolysis product showed the expected carbonyl peaks at δ 219 (cyclopentanone) and δ 214 (cyclohexanone). A weaker third carbonyl peak was also observed at δ 217. When the starting material was prepared for this experiment, the perchlorate salt of the methylene compound was not recrystallized, so there might have been a trace amount of perchloric acid present. This trace of acid, after the ozonolysis, might have catalyzed partial epimerization of the C-4 center and carbinolamine formation while the material was left overnight under high vacuum. The proton spectra of this material showed a smaller methyl doublet upfield from the methyl doublet corresponding to the ozonolysis product.

A 10-min ^{13}C NMR aquisition was begun 10 min after neutralization of the amine. No carbonyl peaks could be distinguished from the noise, and there were a large number of higher field peaks. A mixture of isomers in which the carbonyls were in rapid equilibrium with carbinolamines could explain these results, since the signal-to-noise ratio was poor enough to hide any relatively small peaks. Even after 6.5 h, there were a large number of peaks between δ 10 and 100, and there were peaks at δ 219 and 218, the latter being quite a bit weaker than the former. After 30 h, the ^{13}C NMR spectrum was that of pure fawcettimine, with a single carbonyl peak at δ 219. The carbonyl peak at δ 218 could have been the signal from the cyclopentanone of **59**, with the cyclohexanone signal hidden in the noise. Interestingly, a resonance for the carbinolamine carbon of fawcettimine was not observed, perhaps because of rapid equilibration between **7** and **59**.

Since we had ample quantities of fawcettimine and its hydrobromide salt in hand, all the proton and carbon resonances in the corresponding spectra were assigned except for the relative positions of the methylene hydrogens. This was accomplished by using the DEPT carbon spectrum and the two-dimensional COSY and proton-decoupled C–H correlation spectra of the compound. Details of these assignments may be found in the supplementary material.

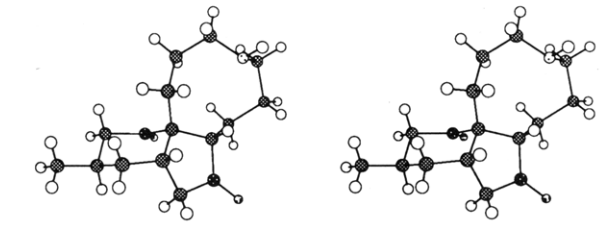
Molecular Mechanics Investigation

A theoretical study was undertaken to help clarify the behavior of fawcettimine with respect to epimerization and carbinolamine formation. The investigation was divided into two parts. The first was to calculate the strain energy of the low-energy conformations of the diketo amine forms (**56** and **59**, see Scheme XVI). Since the diketo amine forms are assuredly intermediates between the various carbinolamine forms, these calculations would indicate the likelihood of 4-epifawcettimine forms existing. Furthermore, the equilibrium ratio of *N*-acetylfawcettimine (**52**) and *N*-acetyl-4-epifawcettimine (**49**) is known, so the accuracy of the program could be tested by examining the difference in strain energy of these two compounds.

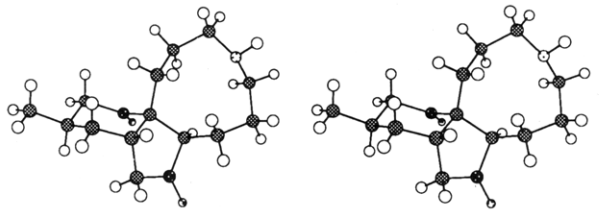
The second part of the study was to calculate the difference in strain energy of the low-energy conformations of the carbinolamine forms **7**, **60**, and **57**. This would suggest whether a carbinolamine involving the cyclopentanone carbonyl is low enough in energy that it might have been trapped in making the salts. If this is the case, then one could rationalize the amine salt data as a chance occurrence and that in the early Burnell work, crystallization of the less favored carbinolamine may have occurred.

A full explanation of the method used to find the low-energy conformations of **7**, **49**, **52**, **56–57**, and **59–60** is presented in the supplemental information. The computational results showed that the lowest energy diketo amine configurations of fawcettimine and 4-epifawcettimine (Figure 2a) have nearly the same strain energy. This is somewhat unexpected since N-substituted derivatives of fawcettimine favor the 4*S* ("natural") over the 4*R* ("epi") form. This fact was the main motivation for performing the calculations of the *N*-acetyl derivatives. Indeed, the calculations showed the expected trend for the *N*-acetyl compounds; the lowest energy conformation of *N*-acetylfawcettimine was about 5.7 kJ/mol lower in energy than that of *N*-acetyl-4-epifawcettimine (Figure 2b). This difference may be rationalized by taking into account the fact that the nitrogen of an amine is planarized when one forms an amide. This change in geometry partially relieves a bad transannular interaction that is worse in fawcettimine than in 4-epifawcettimine. Therefore, amide formation caused a greater drop in strain energy in fawcettimine than in 4-epifawcettimine. Admittedly, the energy difference between the epimeric acetates was larger than one would expect, since the equilibrium ratio of these two compounds, 2:1, would predict a difference in free energy of only 1.7 kJ/mol.

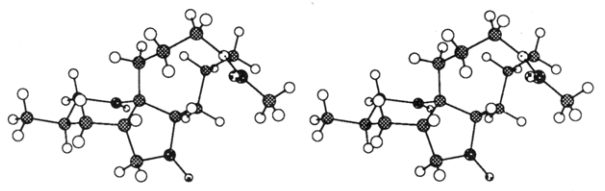
The results of the carbinolamine calculations also agreed with experimental data. The calculations predicted a strong preference (by more than 22 kJ/mol) for the fawcettimine cyclohexanone carbinolamine (**7**) over either carbinolamine of 4-epifawcettimine (Figure 3). Furthermore, the calculations indicated that for 4-epifawcettimine the cyclopentanone carbinolamine **57** is preferred by about



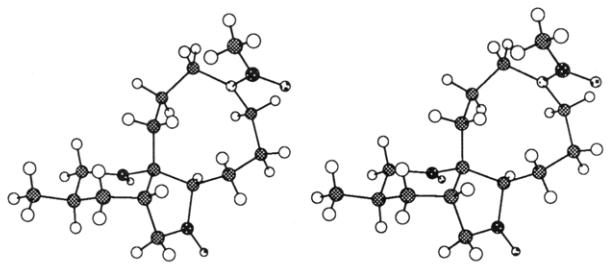
diketo amine **56**



diketo amine **59**



diketo amine **52**



diketo amine **49**

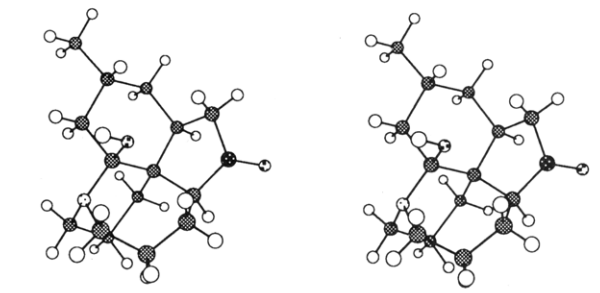
Figure 2. Three-dimensional representations of the lowest energy conformations of compounds **56**, **59**, **52**, and **49**.

5 kJ/mol over the cyclohexanone carbinolamine **60**. This provides good support for the presence of the 4-epi-fawcettimine cyclopentanone carbinolamine suggested by the ^{1}H NMR study and Burnell's anomalous IR data.

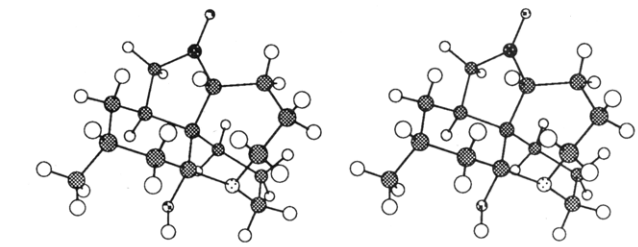
As a final note, it is interesting that the calculated lowest energy tautomer of fawcettimine has almost exactly the structure found by X-ray analysis for fawcettimine hydrobromide (compare Figures 1 and 3). The only difference in these two structures is that the hydrogen of the alcohol is found to be in an eclipsed position instead of the staggered position predicted. This was obviously due to the facts that the crystal structure is of a salt instead of the basic amine and that the calculations did not take into account intermolecular interactions present in the crystal structure. Nevertheless, the excellent agreement between the crystal structure conformation and the predicted conformation provides support to the accuracy of the calculations.

Experimental Section

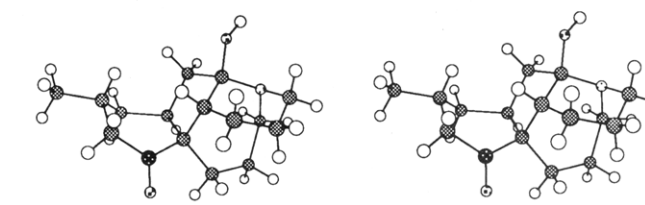
General. Unless otherwise noted, reagents were obtained from commercial suppliers and were used without further purification.



fawcettimine, **7**



carbinolamine **60**



carbinolamine **57**

Figure 3. Three-dimensional representations of the lowest energy conformations of fawcettimine (**7**) and isomeric carbinolamines **60** and **57**.

Solvents not described as reagents grade were purified in the following manner: ether, tetrahydrofuran (THF), and 1,2-dimethoxyethane (DME) were distilled from sodium/benzophenone ketyl immediately prior to use; diisopropylamine, *N,N,N′,N′*-tetramethylethylenediamine (TMEDA), pyridine, benzene, toluene, methylene chloride (CH_2Cl_2), acetonitrile (CH_3CN), and triethylamine were distilled from calcium hydride; methanol and ethanol were distilled from magnesium methoxide and ethoxide, respectively, immediately prior to use. Reagent grade solvents were used for chromatography without further purification. Chlorotrimethylsilane (TMSCl) was distilled from calcium hydride/diethylaniline immediately prior to use. Titanium tetrachloride was distilled from copper wire under dry nitrogen immediately prior to use. Alcohol-free ethereal solutions of diazomethane were prepared from the reaction of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (Diazald) with potassium hydroxide in the presence of 2-(2-ethoxyethoxy)ethanol and were stored at −20 °C over KOH pellets for at least 24 h before use. All reactions involving organometallic reagents were conducted under an atmosphere of dry nitrogen and in oven-dried glassware. Ozone was generated in oxygen by a Wellsbach ozonator. Boiling points and melting points (Pyrex capillary) are uncorrected. Complex ^{1}H NMR multiplets are indicated by comp (complex). If determined, the type of carbon in ^{13}C NMR spectra is indicated in parentheses after the chemical shift: 0, quaternary; 1, methine; 2, methylene; and 3, methyl. Analytical capillary gas chromatography was performed on a 25-m cross-linked, 5% phenyl methyl silicone, 0.20-m i.d. (Ultra #2) column. All compounds are racemates although they are indicated as a single enantiomer.

4-Methyl-6-oxo-1-cyclohexenepropanenitrile (14). Following the procedure of Clark and Heathcock,[38] 2-chloro-4-

methyl-6-oxo-1-cyclohexene-1-propanenitrile (22.8 g, 0.115 mmol) was reduced in methanol (100 mL) with the zinc–silver couple derived from zinc dust (52.5 g) and silver acetate (1.575 g) (Aldrich "Gold Label"). After 2 h, the reaction was complete as evidenced by TLC; workup gave a yellow oil from which 15.7 g (84%) of pure product was obtained by distillation through a 10-cm Vigreux column, mp 5–8 °C, bp 75–80 °C at 0.03 mm (lit.[38] bp 92 °C at 0.3 mm): IR (neat) 2240, 1675 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (d, 3, J = 7), 1.95–2.20 (comp, 3), 2.35–2.50 (comp, 6), 6.90–6.95 (m, 1); ^{13}C NMR ($CDCl_3$) δ 16.53, 20.75, 26.03, 30.16, 33.92, 45.97, 119.03, 135.27, 147.63, 198.68.

(2*SR*,4*RS*)-2-[2-(Hydroxymethyl)-2-propenyl]-4-methyl-6-oxocyclohexanepropanenitrile (16). An oven-dried, nitrogen-flushed 2-L three-necked flask, equipped with a 250-mL addition funnel, a mechanical stirrer, and a thermometer well with a nitrogen inlet, was charged with CH_2Cl_2 (700 mL) and cyano enone **14** (24.0 g, 147.4 mmol). The solution was cooled to −78 °C, and titanium tetrachloride (24.0 mL, 41.4 g, 218 mmol) was added in one portion by syringe. The yellow mixture was stirred at −78 °C for 30 min, and [2-[(trimethylsiloxy)methyl]-2-propenyl]trimethylsilane (**15**)[13] (48.0 g, 222 mmol) in CH_2Cl_2 (100 mL) was added dropwise so that the temperature remained below −70 °C. The burgundy solution was stirred at −78 °C for 4 h, and water (360 mL) was added dropwise so that the temperature remained below −65 °C. The purple solution was allowed to slowly warm to −10 °C overnight and added to ether (1 L) and saturated brine (1 L) in a separatory funnel. After thorough shaking, the layers were separated, and the organic layer was dried (Na_2SO_4). Removal of solvents under reduced pressure gave 34.7 g (>99%) of a yellow oil, which by TLC was homogeneous and by NMR was a 3:2 mixture of diastereomers: IR (neat) 3440, 2250, 1710, 900 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (major) and 0.99 (minor) (2 d, 3, J = 7.0 and 7.0), 1.40–1.78 (comp, 3), 1.80–2.50 (comp, 10.6), 2.70 (m, 0.4), 4.01 and 4.03 (2 bs, 2), 4.81 (minor) and 4.87 (major) (2 bs, 1), 5.10 (minor) and 5.13 (major) (2 bs, 1); ^{13}C NMR ($CDCl_3$) δ (major) 15.18, 20.14, 24.29, 29.29, 29.55, 36.57, 37.60, 51.70, 53.43, 65.15, 112.26, 119.58, 145.76; (minor) 15.35, 22.13, 22.59, 30.51, 35.00, 36.21, 38.26, 47.35, 50.01, 64.80, 112.16, 119.58, 145.71. Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.46; H, 8.99; N, 5.95. Found: C, 71.57; H, 9.00; N, 5.77.

(2*SR*,4*RS*)-2-(2-Formyl-2-propenyl)-4-methyl-6-oxocyclohexanepropanenitrile (17). An oven-dried, 1-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, a nitrogen inlet, and a septum was flushed with dry nitrogen while still hot and charged with pyridine (0.48 mmol, 38.0 g, 38.8 mL) and CH_2Cl_2 (460 mL). Chromic anhydride (0.23 mmol, 22.8 g) was added in one portion, and the reaction mixture was warmed briefly to a mild reflux. The burgundy solution was stirred for 30 min, and a solution of alcohol **16** (8.15 g, 34.6 mmol) in CH_2Cl_2 (30 mL) was added in one portion. A CH_2Cl_2 rinse (40 mL) was added in one portion. The mixture was stirred for 30 min. The solution was decanted from the tar, and the tar was rinsed with ether (2 × 250 mL). The combined organic extracts were washed with 1 N NaOH (3 × 500 mL), 1 N HCl (500 mL) (100 mL saturated brine added to aid in separation of layers), saturated $NaHCO_3$ (500 mL), and saturated brine (500 mL), dried ($MgSO_4$), and decolorized with a small amount of activated charcoal. Solvents were removed under reduced pressure, including turning under high vacuum for 2 h, to give 7.60 (94%) of product as a yellow-tinted thick oil. By TLC the oil was homogeneous and by ^1H NMR it was a 3:2 mixture of diastereomers: IR (neat) 2855, 2245, 1710, 1690, 1255 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (major) and 0.98 (minor) (2 d, 3, J = 7.0 and 7.0), 1.45–2.60 (comp, 12.6), 2.77 (m, 0.4), 6.10 (minor) and 6.14 (major) (2 s, 1), 6.23 (minor) and 6.34 (major) (2 s, 1), 9.55 (minor) and 9.57 (major) (2 s, 1); ^{13}C NMR ($CDCl_3$) δ (major isomer) 14.9, 19.8, 23.8, 29.1, 32.6, 34.8, 36.7, 47.2, 53.0, 119.3, 136.4, 147.0, 194.1 (minor isomer) 14.9, 22.0, 22.2, 25.8, 29.3, 35.7, 38.4, 49.8, 51.4, 122, 136.1, 147.2, 194.0. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.88; H, 8.19; N, 5.89.

(*E*,2*SR*,4*RS*)-2-(2-Methylene-4-(ethoxycarbonyl)-3-butenyl)-4-methyl-6-oxocyclohexanepropanenitrile (18). A solution of [(ethoxycarbonyl)methylene]triphenylphosphorane (751 mg, 2.16 mmol) in ethanol (15 mL) was added dropwise over a 10-min period to a solution of aldehyde **17** in ethanol (5 mL). The pale blue mixture was stirred for 4 h and concentrated under reduced pressure. The residue was filtered through silica (20 g) with 3:2 ether–hexane as eluant to afford 571 mg (96%) of a clear, colorless oil: IR (film) 2245, 1710, 1690, 1270, 1175 cm^{-1}; mass spectrum (70 eV), m/z 304 (0.32), 303 (1.42), 258 (0.68), 233 (0.38), 1.64 (2.10), 139 (3.69), 111 (0.90), 95 (2.93), 69 (3.83), 55 (3.71). Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62. Found: C, 71.20; H, 8.46; N, 4.56. The two diastereomers were separated by analytical HPLC with 7:13 ether–hexane as eluant. Less polar diastereomer: ^1H NMR ($CDCl_3$) δ 1.02 (d, 2, J = 7), 1.31 (t, 3, J = 7), 1.53 (m, 1), 1.66 (m, 1), 1.87 (dd, 2, J = 7), 1.31 (t, 3, J = 7), 1.53 (m, 1), 1.66 (m, 1), 1.87 (dd, 2, J = 10, 16), 2.12 (m, 2), 2.30 (m, 2), 2.46 (m, 4), 2.78 (m, 1), 4.23 (q, 2, J = 7), 5.28 (s, 1), 5.48 (s, 1), 5.83 (d, 1, J = 16), 7.36 (d, 1, J = 16). More polar diastereomer: ^1H NMR ($CDCl_3$) δ 0.95 (d, 3, J = 7), 1.31 (t, 3, J = 7), 1.53 (m, 1), 1.66 (m, 1), 1.87 (dd, 2, J = 10), 2.12 (m, 1), 2.30 (m, 2), 2.46 (m, 4), 2.78 (m, 1), 4.23 (q, 2, J = 7), 5.34 (s, 1), 5.49 (s, 1), 5.86 (d, 1, J = 16), 7.27 (d, 1, J = 16).

Ethyl (1*SR*,3a*SR*,5*RS*,7a*SR*)-7a-(2-Cyanoethyl)octahydro-5-methyl-2-methylene-7-oxo-1*H*-indene-1-acetate (19). [(Ethoxycarbonyl)methylene]triphenylphosphorane (2.34 g, 6.72 mmol) in ethanol (17 mL) was added to aldehyde **17** (1.30 g, 5.57 mmol) in ethanol (4 mL). The solution was stirred overnight, and a solution of sodium ethoxide in ethanol, prepared by allowing sodium (94 mg, 4.1 mmol) to react completely with ethanol (5 mL), was added over a 30-min period. The solution was stirred overnight and concentrated under reduced pressure. The residue was chromatographed on silica (60 g) with 3:7 ether–hexane as eluant to afford 1.52 g (90%) of product as a pale-yellow oil: IR (film) 2250, 1730, 1700, 890 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (d, 3, J = 7), 1.19 (t, 3, J = 7), 1.60 (m, 2), 1.82 (ddd, 1, J = 3, 10, 14), 2.05 (d, 1, J = 7), 2.11 (m, 2), 2.19 (d, 1, J = 7), 2.25 (m, 4), 2.43 m, 1), 2.60 (ddd, 1, J = 1, 16, 16), 2.73 (dd, 1, J = 7, 16), 3.45 (m, 1), 4.06 (q, 2, J = 7), 4.79 (d, 1, J = 2), 4.95 (d, 1, J = 2); ^{13}C NMR ($CDCl_3$) δ 12.5, 14.0, 19.5, 24.9, 29.6, 32.6, 34.3, 36.2, 37.8, 44.5, 45.7, 59.4, 60.7, 108.3, 119.7, 149.4, 171.9, 212.5; mass spectrum (70 eV), m/z 304 (0.11), 303 (0.52), 285 (0.34), 259 (3.65), 232 (1.38, 203 (1.39), 185 (2.80), 1.58 (3.52), 145 (2.08), 105 (4.21), 91 (3.86), 69 (3.54). Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62. Found: C, 71.10; H, 8.16; N, 4.42.

(1*SR*,3a*SR*,5*RS*,7a*SR*)-7a-(2-Cyanoethyl)octahydro-5-methyl-2-methylene-7-oxo-1*H*-indene-1-acetic Acid (22). To a solution of ester **19** (123 mg, 0.404 mmol) in 95% ethanol (4 mL) was added a solution of NaOH (18 mg, 0.45 mmol) in water (1 mL). After stirring for 24 h, additional NaOH (5.0 mg, 0.12 mmol) was added. After being stirred an additional 48 h, the mixture was poured into saturated $NaHCO_3$ and washed two times with ether. The combined ether washes were extracted with saturated $NaHCO_3$. The combined $NaHCO_3$ solutions were cooled in an ice bath, acidified to pH 1 with 6 N HCl, and extracted three times with ether. The combined ether extracts were dried ($MgSO_4$), and solvents were evaporated under reduced pressure to give 113 mg (100%) of product as a white powder, mp 98.5–101 °C: IR ($CHCl_3$) 3200, 2250, 1710, 1700, 890 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (d, 3, J = 7), 1.43 (m, 1), 1.67 (m, 1), 1.89 (ddd, 1, J = 3, 10, 14), 2.08 (d, 1, J = 7), 2.18 (m, 2), 2.24 (m, 1), 2.35 (m, 5), 2.53 (m, 1), 2.67 (ddd, 1, J = 1, 8, 8), 2.80 (dd, 1, J = 6, 14), 3.50 (m, 1), 4.92 (d, 1, J = 2), 5.03 (d, 1, J = 3). Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.74; H, 7.74; N, 4.85. When the reaction was performed on a larger scale (27.72 g of ester **19**), 24.65 g (98%) of carboxylic acid **22** was obtained.

Methyl (1*SR*,3a*SR*,5*RS*,7a*SR*)-7a-(2-Cyanoethyl)octahydro-5-methyl-2-methylene-7-oxo-1*H*-indene-1-propanoate (25). Directly from Aldehyde 17. To a solution of (carbethoxymethylene)triphenylphosphorane (14.4 g, 41.2 mmol) in ethanol (50 mL) was added, in one portion, a solution of aldehyde **17** (8.00 g, 4.3 mmol) in ethanol (25 mL). This solution was allowed to stand at room temperature under a nitrogen atmosphere for 48 h. A solution of sodium ethoxide, made by allowing sodium (0.25 g, 10.9 mmol) to react completely with ethanol (20 mL), was added to the reaction mixture. The resulting solution was allowed to stand at room temperature overnight and 1 N NaOH (40 mL) was added. The solution was allowed to stand at room temperature for 24 h and concentrated under reduced pressure. The

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residue was diluted with saturated $NaHCO_3$ (250 mL) and washed with benzene (3 × 150 mL) and ether (2 × 150 mL). The aqueous solution was acidified with 6 N HCl and extracted with ether (3 × 250 mL). The combined organic layers were washed with saturated brine (200 mL) and dried ($MgSO_4$). Solvents were removed under reduced pressure to give the carboxylic acid **22** as a yellow solid. This solid was added to an oven-dried, nitrogen-flushed 1-L three-necked flask equipped with a reflux condenser, a 125-mL addition funnel, and a mechanical stirrer. Benzene (350 mL) was added, and the mixture was heated slightly to dissolve all the carboxylic acid. Oxalyl chloride (14.8 mL, 21.5 g, 0.170 mol) was added, with stirring, in one portion, and the solution was quickly heated to reflux. The solution was heated at reflux and stirred vigorously for 2 h, and solvents were removed under reduced pressure. Benzene (75 mL) was added and removed under reduced pressure three times to give the acid chloride as a red-brown oil. A solution of this oil in THF (100 mL) was added to a alcohol-free solution (about 250 mL) of diazomethane made from Diazald (6.0 g). The solution was swirled to mix and allowed to warm slowly to room temperature overnight. Solvents were removed under a stream of dry nitrogen, and ether (100 mL) was added. The solution was filtered and solvents were removed under reduced pressure to give a brown oil. To a solution of this oil in methanol (100 mL) was added half of a solution of silver benzoate (2.0 g, 8.7 mmol) in triethylamine (20 mL). Once nitrogen evolution ceased, the rest of the silver benzoate solution was added, and the resulting mixture was stirred overnight. Solvents were removed under reduced pressure, and ether (200 mL) and 1 N HCl (200 mL) were added. The mixture was filtered with suction through a Celite pad, which was rinsed with ether (3 × 50 mL). The organic layer was washed with 1 N HCl (200 mL), saturated $NaHCO_3$ (2 × 200 mL), and saturated brine (100 mL) and dried ($MgSO_4$). Solvents were removed under reduced pressure to give 6.0 g of a crude red oil. This oil was purified by liquid chromatography (1:5 ethyl acetate/hexanes) to give 4.90 g (47% from **17**) of the product as a yellow-tinted, thick oil: IR (neat) 2240, 1740, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (d, 3, J = 6.4), 1.46 (m, 1), 1.62–1.65 (comp, 2), 1.76–1.87 (comp, 2), 2.00–2.22 (comp, 5), 2.34–2.63 (comp, 6), 2.95 (dd, 1, J = 2.4, 10.5), 3.68 (s, 3), 4.88 (d, 1, J = 1.5), 4.90 (d, 1, J = 1.7); ^{13}C NMR ($CDCl_3$) δ 12.45, 20.79, 21.83, 26.51, 29.05, 31.03, 33.32, 34.81, 40.74, 45.76, 47.00, 51.40, 59.79, 108.62, 119.29, 149.48, 173.42, 212.64. Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62. Found: C, 71.42; H, 8.27; N, 4.62.

From Acid 22. Carboxylic Acid **22** (672 mg, 2.44 mmol) was dissolved in 25 mL of dry benzene by heating the mixture at reflux for 5 min. The solution was cooled to room temperature and 5.0 mL (7.3 g, 57 mmol) of distilled oxalyl chloride was added. The reaction mixture was immediately placed into an 80 °C oil bath and vigorous gas evolution commenced 30 s thereafter. The reaction mixture was heated at reflux for 2 h and cooled to room temperature, and the volatile components were evaporated. Portions of dry benzene (15 mL) were added and evaporated five times to remove excess oxalyl chloride, leaving 897 mg of acid chloride **23**: IR (film) 2250, 1800, 1700, 975 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (d, 3, J = 7), 2.87 (d, 2, J = 6), 3.52 (m, 1), 4.91 (s, 1), 5.05 (s, 1). A solution of acid chloride **23** in 3 mL of dry THF was added dropwise over a 15-min period to 40 mL (11 mmol) of a 0.28 M ethereal solution of diazomethane at 0 °C. Gas evolution was evident and a tan precipitate formed. The temperature of the reaction mixture was maintained at 0 °C for 8 h and the solution was then allowed to gradually warm to room temperature over an 8-h period. Excess diazomethane was purged by bubbling a stream of nitrogen through the reaction mixture for a 15-min period; portions of dry ether were added periodically to maintain the solution volume at approximately 40 mL. The precipitate was removed by filtration and the solvent was evaporated under reduced pressure at room temperature to leave 718 mg of diazo ketone **24**: IR (film) 2240, 2100, 1690, 1640, 990 cm^{-1}. A solution of 110 mg (0.48 mmol) of silver benzoate in 1 mL of dry triethylamine was added in four portions, 15 min apart, to a solution of diazo ketone **24** in 5 mL of dry methanol. The reaction mixture turned black and was stirred for 3 h at room temperature. The reaction mixture was filtered, diluted with ether, and washed twice with 2 N aqueous hydrochloric acid. The combined aqueous layers were extracted once with ether. The combined ethereal layers were washed with saturated aqueous $NaHCO_3$ solution and dried over Na_2SO_4. The solvent was evaporated. The residue (980 mg) was purified by chromatography on 40 g of silica gel with 1:2 ether–hexane as eluant to afford 398 mg (54%) of a colorless oil: IR (film) 2250, 1735, 1700, 1440 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.99 (d, 2, J = 6), 2.95 (dd, 1, J = 3, 9), 3.67 (s, 3), 4.88 (s, 2); mass spectrum (70 eV), m/z 305 (0.04), 304 (0.27), 303 (1.34), 285 (0.57), 272 (0.73), 259 (2.56), 200 (2.33), 189 (1.16), 172 (1.45), 158 (2.01), 145 (1.49), 131 (1.12), 119 (1.68), 105 (3.04), 91 (3.31). Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62. Found: C, 71.42; H, 8.27; N, 4.62. When the procedure was carried out on a larger scale (7.02 g of carboxylic acid **22**), 4.24 g (55%) of ester **25** was obtained.

Diethyl [(Phenylsulfonyl)methyl]phosphonate (26). A solution of 91.5 g (300 mmol) of 49.5% potassium peroxymonosulfate (Oxone, $KHSO_5$) in 400 mL of water was added dropwise over 1 h to a solution of 26.06 g (100.1 mmol) of diethyl [(phenylthio)methyl]phosphonate[21] in 400 mL of methanol stirring in an ice bath. A white precipitate formed and the resulting slurry was stirred overnight. The mixture was concentrated at reduced pressure to remove most of the methanol. The concentrate was diluted with water until all the white powder dissolved, and the resulting mixture was extracted three times with CH_2Cl_2. The combined organic layers were washed with water and brine and dried (Na_2SO_4), and the solvent was evaporated. Distillation of the residue (38.5 g) afforded 27.44 g (94%) of a clear, colorless, hygroscopic liquid, bp 182–184 °C (0.25 Torr): IR (film) 1450, 1315, 1270, 1165, 1025, 990, 810 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (dt, 6, J = 2, 7), 3.63 (d, 2, J = 16), 4.02 (m, 4), 7.48 (m, 3), 7.90 (m, 2); mass spectrum (70 eV), m/z 293 (M + 1), 77 (base). Anal. Calcd for $C_{11}H_{17}O_5PS$: C, 45.20; H, 5.86; P, 10.60; S, 10.97. Found: C, 44.86; H, 5.87; P, 10.32; S, 10.73.

(1*SR*,3a*SR*,5*RS*,7a*SR*)-7a-(2-Cyanoethyl)octahydro-5-methyl-2-methylene-7-oxo-1-[(phenylsulfonyl)methyl]-1*H*-indene (27). To 1.48 g (5.06 mmol) of phosphonate **26** in 28 mL of dry THF at −78 °C was added 2.62 mL (5.00 mmol) of a 1.91 M solution of *n*-butyllithium in hexane over a 30-min period. The resulting solution was stirred for 2 h and then added over a 20-min period to a solution of 1.151 g (4.93 mmol) of aldehyde **17** in 7 mL of dry THF at −78 °C. The cooling bath was removed, and the mixture was allowed to warm to room temperature and was then stirred overnight. The mixture was then poured into cold, saturated aqueous ammonium chloride solution and extracted three times with ether. The ethereal extracts were washed once with water, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4 and the solvent was evaporated. The residue (1.96 g) was purified by chromatography on 60 g of silica gel with 3:2 ether–hexane as eluant to afford 1.53 g (84%) of a white powder, mp 157.5–159 °C. It was not possible to recrystallize the material, although IR, ^1H NMR, and TLC analysis showed it to be pure: IR ($CHCl_3$) 2448, 1695, 1445, 1310, 1150 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.08 (2 d, 3, J = 7), 1.32 (m, 1), 1.70 (m, 1), 1.85 (m, 1), 3.04 (m, 2), 3.54 (m, 1), 4.93 and 5.11 (m, 1), 5.03 and 5.16 (m, 1), 7.63 (m, 3), 7.90 (m, 2); ^{13}C NMR ($CDCl_3$) δ 12.4, 19.4, 24.8, 29.3, 34.5, 36.1, 36.9, 43.4, 44.0, 54.4, 59.9, 110.6, 119.4, 128.0, 129.4, 134.0, 139.0, 147.3, 211.9; mass spectrum (70 eV), m/z 371 (0.01), 327 (0.02), 318 (0.04), 230 (5.45), 212 (1.99), 186 (6.87), 159 (2.55), 145 (1.79), 119 (1.92), 105 (4.81), 91 (3.95), 77 (3.34), 69 (2.89). Anal. Calcd for $C_{21}H_{25}NO_3S$: C, 67.90; H, 6.78; N, 3.77; S, 8.63. Found: C, 67.77; H, 6.81; N, 3.70; S, 8.51.

Diethyl [1-(Phenylsulfonyl)-3-butenyl]phosphonate (28). To a rapidly stirring solution of 8.14 g (27.85 mmol) of phosphonate **26** and 9.70 mL (13.6 g, 112 mmol) of allyl bromide in 135 mL of CH_2Cl_2 was added 9.03 g (28.0 mmol) of tetra-*n*-butylammonium bromide in 56 mL of 0.5 N aqueous NaOH. The two-phase system was stirred vigorously for 20 h. The organic layer was separated and the aqueous layer was extracted two times with CH_2Cl_2. The organic layers were combined and concentrated under reduced pressure. The residual yellow oil was shaken vigorously with ether for several minutes until white crystals of tetra-*n*-butylammonium bromide precipitated. The ethereal layer was decanted and the precipitate was washed two times with ether. The combined ethereal layers were dried over $MgSO_4$ and the solvent was evaporated. Bulb-to-bulb distillation of the residue (7.96 g) using a Kugelrohr apparatus afforded 7.61 g of a clear, colorless, hygroscopic oil, bp 155–158 °C (0.002 Torr): IR (film)

1450, 1325, 1310, 1255, 1150, 1050, 1030, 970 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (t, 6, J = 7), 2.80 (m, 2), 3.59 (dt, 1, J = 6, 18), 4.18 (dq, 4, J = 7, 7) 5.08 (m, 2), 5.90 (m, 1), 7.65 (m, 3), 8.03 (dd, 2, J = 2, 7); mass spectrum (70 eV), m/z 332 (0.11), 308 (0.41), 268 (1.22), 163 (1.53), 135 (2.14), 93 (3.18). Anal. Calcd for $C_{14}H_{21}O_5PS$: C, 50.60; H, 6.37; P, 9.32; S, 9.65. Found: C, 50.24; H, 6.14; P, 9.37; S, 9.76.

[2-(4-Methoxyphenyl)-2-oxoethyl]triethylphosphonium Bromide (30). α-Bromo-*p*-methoxyacetophenone (1.83 g, 8.00 mmol) was added in several portions to a solution of 1.17 mL (948 mg, 8.00 mmol) of triethylphosphine in 36 mL of dry ether. The reaction mixture was stirred under nitrogen for 1 h, during which time a white precipitate formed. The precipitate was removed by filtration, washed with 100 mL of ether, and dried under vacuum to provide 2.55 g (92%) of a white powder, mp 186–188 °C: IR ($CHCl_3$) 1660, 1595, 1565, 1450, 1320, 1260, 1170 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (dt, 9, J = 7, 18), 2.60 (dq, 6, J = 7, 13), 3.76 (s, 3), 4.83 (d, 2, J = 13), 6.87 (d, 2, J = 9), 8.18 (d, 2, J = 9). Anal. Calcd for $C_{15}H_{24}BrO_2P$: C, 51.89; H, 6.97; Br, 23.01; P, 8.92. Found: C, 51.71; H, 6.94; Br, 23.20; P, 8.76.

(1*SR*,3a*SR*,5*RS*,7a*SR*)-7a-(2-Cyanoethyl)octahydro-5-methyl-2-methylene-7-oxo-1-[2-(4-methoxyphenyl)-2-oxoethyl]-1*H*-indene (31). A sodium ethoxide solution was prepared from 116 mg (5.04 mmol) of sodium metal and 2 mL of dry ethanol and was added to a suspension of 1.75 g (5.04 mmol) of phosphonium salt **30** and 2 mL of dry ethanol. The mixture was heated at reflux for 30 min and cooled to room temperature and a mixture of 787 mg (3.37 mmol) of aldehyde **17** and 10 mg (0.09 mmol) of hydroquinone in 1 mL of dry ethanol was added. The reaction mixture was stirred at room temperature. After 3 days, 54 mg (1.0 mmol) of sodium methoxide was added, and stirring was continued overnight. The reaction mixture was concentrated under reduced pressure, diluted with ether, and washed once each with 5% aqueous NaOH, 2 N aqueous hydrochloric acid, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4 and the solvent was evaporated. The residue (1.15 g) was purified by chromatography on 25 g of silica gel with 3:7 ether–hexane as eluant to afford 480 mg (39%) of a yellow solid, mp 65–69 °C: IR ($CHCl_3$) 3060, 2250, 1700, 1680, 1600, 1510, 1420, 1260, 1170, 1025, 990 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 and 1.05 (2 d, 2, J = 7), 3.89 (s, 3), 4.55–5.00 (m, 2), 6.94 and 6.95 (two overlapping d, 2, J = 9), 7.95 and 8.05 (2 d, 2, J = 9); mass spectrum (70 eV), m/z 366 (0.44), 365 (1.80), 136 (7.90), 135 (30.19). Anal. Calcd for $C_{23}H_{27}NO_3$: C, 75.59; H, 7.45; N, 3.83. Found: C, 75.74; H, 7.49; N, 3.80.

(1*RS*,3a*SR*,5*RS*,7a*SR*)-7a-(2-Cyanoethyl)octahydro-5-methyl-2,7-dioxo-1-[2-(4-methoxyphenyl)-2-oxoethyl]-1*H*-indene (32). A stream of ozone was bubbled through a solution of 77 mg (0.21 mmol) of compound **31** in 20 mL of a CH_2Cl_2–methanol (1:1) mixture at −78 °C until TLC analysis (6:4 ether–hexane) showed no remaining starting material. The remaining ozone was purged by allowing a stream of oxygen to bubble through the solution, 1 mL of dimethyl sulfide was added, and the reaction mixture was allowed to warm to room temperature. The solvent was evaporated and the residue (156 mg) was purified by chromatography on 5 g of silica gel with 3:1 ether–hexane as eluant to afford 62.3 mg (81%) of a yellow semisolid material: IR ($CHCl_3$) 3060, 2250, 1730, 1700, 1680, 1510, 1450, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03 and 1.12 (2 d, 3, J = 7), 3.15 and 3.28 (2 dd, 1, J = 5, 14), 3.90 and 3.92 (2 s, 3), 6.93 and 6.96 (2 d, 2, J = 9), 7.92 and 8.02 (2 d, 2, J = 9); mass spectrum (70 eV), m/z 368 (0.48), 367 (1.92), 339 (1.81), 150 (4.10), 136 (4.80), 135 (7.82), 107 (4.84), 92 (4.46). Anal. Calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 72.04; H, 6.94; N, 3.82.

(1*RS*,3a*SR*,5*RS*,7a*SR*)-7a-(2-Cyanoethyl)octahydro-5-methyl-2,7-dioxo-1-[2-(4-methoxyphenyl)ethyl]-1*H*-indene (33). To a solution of 48 mg (0.13 mmol) of hydrindanetrione **32** in 0.30 mL of trifluoroacetic acid was added 0.050 mL (0.31 mmol) of triethylsilane. After 45 min, the reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ and extracted two times with ether. The combined ethereal layers were dried over Na_2SO_4 and the solvent was evaporated. The residue (40 mg) was purified by chromatography on 2 g of silica gel with 2:3 ether–hexane as eluant to afford 26 mg (58%) of a yellow oil: IR (film) 3060, 1735, 1700, 1510, 1450, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 and 0.95 (2 d, 3, J = 7), 3.80 (s, 3), 6.83 (d, 2, J = 8), 7.07 (d, 2, J = 8); mass spectrum (70 eV), m/z 353 (0.46), 134 (10.40), 121 (4.48). Satisfactory values for combustion analysis could not be obtained. High resolution mass spectrum: required for $C_{22}H_{27}NO_3$, 353.1991; observed, 353.1996.

(1*SR*,3a*SR*,5*RS*,7*RS*,7a*SR*)-7a-(3-Aminopropyl)octahydro-7-hydroxy-5-methyl-2-methylene-1*H*-indene-1-propanol (35). A solution of 1.9 M $LiAlH_4$ in THF (6.3 mL, 12.0 mmol) was diluted with THF (8.0 mL) and ether (20.0 mL) and cooled to −120 °C in an ether–liquid nitrogen bath. A solution of ketone **25** (1.18 g, 3.89 mmol) in THF (5 mL) was added at such a rate so as to keep the temperature of the reaction mixture below −110 °C. The mixture was stirred at −120 °C for 2 h, copious amounts of dry ice cooled with liquid nitrogen were added to the cooling bath, and the reaction mixture was stirred and allowed to slowly warm to room temperature overnight. THF (60 mL) was added to the mixture, followed by a solution of water (0.455 mL) in THF (2 mL), 6 N NaOH (0.455 mL), and more water (1.364 mL). The resulting mixture was stirred for 15 min, and anhydrous K_2CO_3 was added to dry the mixture. The mixture was stirred for 3 h and filtered through a glass fritted funnel, and the solids were washed with THF (3 × 15 mL). Solvents were removed under reduced pressure, and the resulting white powder was allowed to stand under high vacuum (0.2 mm) at 70 °C overnight to give 1.04 g (95%) of a clear, colorless glass. This product was determined by ^1H NMR and ^{13}C NMR to be a 9–10:1 mixture of the desired isomer and the 7-epimer. It was also noted that when the reaction was performed at −78 °C or room temperature, instead of −120 °C, a 5:1 or 1:1 diastereomeric mixture, respectively, of these products was obtained, mp 95–100 °C: IR ($CHCl_3$) 3600–3050, 1650, 1590, 1455, 1435 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (d, 3, J = 6.2), 1.00–1.95 (comp, 13), 2.00–2.57 (comp, 6), 2.58 (bd, 1, J = 4.8), 2.67 (t, 1, J = 6.6), 3.54 (dd, 1, J = 8.3, 3.7), 3.60–3.78 (comp, 4), 4.87 (bs, 2); ^{13}C NMR ($CDCl_3$) δ 22.13, 24.00, 26.55, 27.00, 29.48, 30.21, 30.63, 32.84, 33.86, 39.19, 41.46, 43.03, 52.08, 61.77, 72.69, 108.22, 153.40. Anal. Calcd for $C_{17}H_{31}NO_2$: C, 72.55; H, 11.10; N, 4.98. Found: C, 72.72; H, 11.03; N, 4.64.

(1*SR*,3a*SR*,5*RS*,7*RS*,7a*SR*)-7a-[3-[(Ethoxycarbonyl)amino]propyl]octahydro-1-[3-[(ethoxycarbonyl)oxy]propyl]-7-hydroxy-5-methyl-2-methylene-1*H*-indene (36). A suspension of 3.20 g (84.3 mmol) of $LiAlH_4$ in 50 mL of dry ether was heated at reflux for 1 h. The mixture was cooled to −78 °C and 1.048 g (3.46 mmol) of compound **25** was added dropwise over a 30-min period. The reaction mixture was stirred for 4 h at −78 °C and was then allowed to warm to room temperature over a 2-h period. The mixture was stirred at room temperature for 2 h and heated at reflux for a 40-h period. The mixture was cooled to room temperature and quenched by the dropwise addition of 3.2 mL of water, 3.2 mL of 15% aqueous NaOH, and 9.6 mL of water. The resulting mixture was heated at reflux for 4 h, cooled to room temperature, and filtered. The solvent was evaporated to leave 940 mg of a yellow oil: IR (film) 3350, 1060, 910, 880 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (d, 3, J = 7), 3.65 (m, 5), 4.87 (bs, 2). The crude amino diol **35** was dissolved in 6 mL of CH_2Cl_2 and the mixture was cooled to 0 °C. To the mixture were added 3 mL (4.14 g, 40.8 mmol) of dry triethylamine, 210 mg (1.72 mmol) of 4-(dimethylamino)pyridine, and 0.85 mL (965 mg, 8.90 mmol) of ethyl chloroformate. The mixture was allowed to warm to room temperature and stirred for 16 h. The mixture was diluted with CH_2Cl_2 and washed twice with 2 N hydrochloric acid. The combined aqueous layers were extracted with CH_2Cl_2. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine and dried over Na_2SO_4. The solvent was evaporated. The residue (1.45 g) was purified by chromatography on 70 g of silica gel with 1:1 ether–hexane as eluant to give 456 mg (31%) of a clear, colorless oil shown to be a 6:1 mixture of diastereomers: IR (film) 3440, 3340, 1700 (br), 1650, 1520, 1260, 910 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (d, 3, J = 6), 1.23 (t, 3, J = 7), 1.31 (t, 3, J = 7), 2.50 (m, 2), 3.12 (m, 2), 3.57 (major-dd, 1, J = 4, 12), 3.94 (minor-dd, 1, J = 3, 7), 4.12 (q, 2, J = 7), 4.19 (q, 2, J = 7), 7.28 (bs, 2); mass spectrum (70 eV), m/z 426 (0.07), 425 (0.46), 407 (0.08), 379 (0.12), 362 (0.09), 335 (0.08), 317 (0.29), 276 (0.58), 240 (0.94), 187 (2.82), 151 (2.11), 102 (2.23), 55 (1.95). Anal. Calcd for $C_{23}H_{39}NO_6$: C, 64.91; H, 9.24; N, 3.29. Found: C, 64.80; H, 9.11; N, 3.30.

(1*SR*,3a*SR*,5*RS*,7a*SR*)-7a-[3-[(Ethoxycarbonyl)amino]propyl]octahydro-1-[3-[(ethoxycarbonyl)oxy]propyl]-5-methyl-2-methylene-7-oxo-1*H*-indene (37). To a solution of

0.4 mL of dry pyridine in 6 mL of CH_2Cl_2 was added 240 mg (2.40 mmol) of chromium trioxide in small portions. The resulting mixture was stirred for 20 min and 157 mg (0.369 mmol) of alcohol **36** in 1 mL of CH_2Cl_2 was added in one portion. After 2 h, the solvent was decanted and the residual material was washed three times with ether. The combined ether layers were washed three times with 5% aqueous NaOH. The combined aqueous layers were extracted with ether. The combined organic layers were washed twice with 2 N hydrochloric acid and once each with saturated aqueous $NaHCO_3$ and brine. The ethereal layer was dried over Na_2SO_4 and the solvent was evaporated to provide 152 mg (98%) of a pale yellow oil: IR (film) 3360, 1745, 1725, 1705, 1660, 1530, 1260, 980 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.99 (d, 3, J = 6), 1.23 (t, 3, J = 7), 1.31 (t, 3, J = 7), 2.96 (dd, 1, J = 3, 10), 3.12 (d, 2, J = 6), 4.09 (q, 2, J = 7), 4.19 (q, 2, J = 7), 4.85 (br s, 1), 4.94 (br s, 1); mass spectrum (70 eV), m/z 423 (0.43), 405 (0.13), 379 (0.15), 359 (0.29), 333 (0.08), 287 (1.65), 216 (1.33), 203 (6.10), 175 (2.45), 105 (1.83), 91 (2.34), 69 (3.08), 55 (2.38). An analytical sample was prepared by chromatography on 5 g of silica gel with 7:3 ether–hexane as eluant. Anal. Calcd for $C_{23}H_{37}NO_6$: C, 65.22; H, 8.81; N, 3.31. Found: C, 65.15; H, 8.67; N, 3.29.

(1*RS*,3a*SR*,5*RS*,7a*SR*)-7a-[3-[(Ethoxycarbonyl)amino]propyl]octahydro-1-[3-[(ethoxycarbonyl)oxy]propyl]-5-methyl-2,7-dioxo-1*H*-indene (38). Olefin **37** (91.2 mg, 0.215 mmol) was dissolved in 20 mL of a CH_2Cl_2–methanol (1:1) mixture. The mixture was cooled to −78 °C and a stream of ozone was passed through the solution until the medium turned blue. The remaining ozone was purged by allowing a stream of oxygen to bubble through the solution, 0.5 mL of dimethyl sulfide was added, and the mixture was allowed to warm to room temperature. The mixture was concentrated under reduced pressure, diluted with CH_2Cl_2, washed with brine, and dried over Na_2SO_4. The solvent was evaporated and the residue (99.1 mg) was purified by chromatography on 5 g of silica gel with 7:3 ether–hexane as eluant to give 87 mg (96%) of a clear, colorless oil: IR (film) 3370, 1740, 1720, 1700, 1550, 1265 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (d, 3, J = 6), 1.16 (t, 3, J = 7), 1.23 (t, 3, J = 7), 2.65 (t, 1, J = 8), 2.73 (dd, 1, J = 6, 9), 3.08 (dd, 2, J = 6, 12), 4.04 (q, 2, J = 7), 4.11 (q, 2, J = 7), 5.26 (bs, 1); mass spectrum (70 eV), m/z 426 (0.14), 425 (0.94), 407 (0.17), 335 (0.67), 233 (2.63), 205 (2.00), 177 (2.87), 69 (2.06), 55 (2.21). Anal. Calcd for $C_{22}H_{35}NO_7$: C, 62.10; H, 8.29; N, 3.29 Found: C, 61.87; H, 8.28; N, 3.22.

(3a*SR*,5*RS*,10a*SR*)-1-(3-Bromopropyl)-3a,4,5,6,8,9,10,10a-octahydro-5-methyl-2-cyclopenta[*e*]quinolone (39). To a solution of 20.5 mg (0.048 mmol) of diketone **38** in 1 mL of glacial acetic acid was added 1 mL of 48% hydrobromic acid. The mixture was stirred at 55 °C for 48 h and cooled to room temperature. The mixture was diluted with 1 M phosphoric acid and washed three times with ether. The aqueous layer was basified to pH 10 by addition of K_2CO_3 to the stirring mixture at 50 °C. The resulting mixture was extracted three times with CH_2Cl_2. The combined organic extracts were washed with brine and dried over K_2CO_3. The solvent was evaporated to leave 12 mg (77%) of a yellow oil, which showed one spot by TLC (R_f = 0.39; 95:4.5:0.5 CH_2Cl_2–methanol–ammonium hydroxide as eluant): IR (film) 1745, 1650, 1460 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (d, 3, J = 7), 2.46 (dd, 1, J = 7, 19), 2.83 (m, 2), 3.40 (m, 2), 3.62 (m, 3); mass spectrum (70 eV), m/z 328 (0.17), 327 (0.95), 326 (0.23), 325 (0.98), 312 (0.24), 310 (0.26), 246 (1.12), 232 (1.02), 230 (1.11), 218 (4.52), 204 (1.46), 162 (1.53), 149 (1.38), 119 (1.44), 117 (1.46), 91 (1.59), 55 (2.13). Satisfactory values for combustion analysis could not be obtained. High resolution mass spectrum: required for $C_{16}H_{24}BrNO$: 325.1041, 327.1021; observed, 325.1022, 327.1033.

(3*RS*,3a*SR*,4*RS*,6*RS*,7a*SR*)-4-Methyl-*N*-[3-[octahydro-4-hydroxy-6-methyl-2-methylene-3-[3-[[(4-methylphenyl)-sulfonyl]oxy]propyl]-3a*H*-inden-3a-yl]propyl]benzenesulfonamide (42). To a solution of tosic anhydride (1.28 g, 3.9 mmol) in CH_2Cl_2 (15 mL) at 0 °C under a dry nitrogen atmosphere was added 4-(dimethylamino)pyridine (0.95 g, 7.8 mmol). The solution was warmed to room temperature and stirred for 30 min, during which time a large amount of solid formed. The mixture was cooled to −25 °C, and amino diol **35** (0.54 g, 1.9 mmol) was added. The mixture was stirred at −25 °C for 4 h and allowed to stand in a freezer (−20 °C) for 48 h. The mixture was warmed to room temperature and concentrated under a stream of dry nitrogen. The residue was purified by liquid chromatography using 15 g of silica gel and eluting with 5:2 ether/hexanes to give 0.77 g (68%) of pure product as a white powder: mp 50.5–52.0 °C; IR ($CHCl_3$) 3530, 3380, 1650, 1595, 1450, 1355, 1325, 1175, 1155, 1090, 810 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (d, 3, J = 6.2), 0.99–1.14 (comp, 2), 1.17–1.30 (comp, 3), 1.31–1.78 (comp, 8), 1.80–1.87 (comp, 3), 2.02–2.10 (comp, 2), 2.42 (s, 3), 2.45 (s, 3), 2.87 (m, 2), 3.53 (dd, 1, J = 3.9, 12.0), 4.02 (m, 1), 4.15 (m, 1), 4.77 (s, 1), 4.83 (s, 1), 7.32 (d, 2, J = 8.2), 7.37 (d, 2, J = 8.2), 7.78 (d, 2, J = 8.2), 7.83 (d, 1, J = 8.2); ^{13}C NMR ($CDCl_3$) δ 21.45, 21.59, 22.00, 23.51, 26.17, 26.53, 26.84, 26.94, 32.51, 33.59, 39.20, 41.83, 44.41, 49.76, 51.33, 70.93, 73.24, 108.98, 127.08, 127.81, 129.57, 129.84, 133.00, 137.03, 143.02, 144.75, 152.42. Anal. Calcd for $C_{31}H_{43}NO_6S_2$: C, 63.13; H, 7.35; N, 2.37; S, 10.87. Found: C, 6.40; H, 7.52; N, 2.34; S, 10.69.

(4*SR*,13*RS*)-5-Methylene-17-[(4-methylphenyl)sulfonyl]-4,17-secoserratinan-13-ol (43). To a solution of tosylamide **42** (0.70 g, 1.19 mmol) in reagent grade toluene (250 mL) was added 40% aqueous tetrabutylammonium hydroxide (0.86 mL, 1.3 mmol). The solution was stirred vigorously and heated at reflux for 1 h. Solvent was removed under reduced pressure, and the residue was chromatographed using 20 g of silica and eluting with 2:3 ether–hexanes to give 0.34 g (69%) of pure product as a white foam, mp 158–160 °C: IR ($CHCl_3$) 3610, 1652, 1598, 1460, 1345, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (d, 3, J = 5.3), 1.00–2.35 (comp, H), 2.4–2.6 (comp, 2), 2.42 (s, 3), 2.87 (m, 1), 3.19 (ddd, 1, J = 3.6, 6.1, 14.7), 3.38 (td, 1, J = 3.8, 12.3), 3.57 (dd, 1, J = 3.7, 11.8), 4.69 (s, 1), 4.93 (s, 1), 7.30 (d, 2, J = 8.2), 7.67 (d, 2, J = 8.2); ^{13}C NMR ($CDCl_3$) δ 21.48 (3), 22.11 (3), 23.46 (2), 23.78 (2), 26.37 (2), 26.89 (1), 29.22 (2), 32.14 (2), 33.45 (2), 39.98 (2), 42.78 (1), 44.94 (2), 50.25 (2), 50.83 (0), 51.39 (1), 73.58 (1), 104.94 (2), 127.36 (1), 129.50 (1), 134.82 (0), 143.02 (0), 157.91 (0). Anal. Calcd for $C_{24}H_{35}NO_3S$: C, 69.03; H, 8.45; N, 3.35; S, 7.68. Found: C, 69.21; H, 8.56; N, 3.23; S, 7.57.

(4*SR*)-5-Methylene-17-[(4-methylphenyl)sulfonyl]-4,17-secoserratinan-13-one. To a solution of alcohol **43** (0.47 g, 1.1 mmol) in acetone (11 mL) was added, dropwise and with occasional swirling, a solution of Jones reagent until a red color persisted in the solution. Excess Jones reagent was quenched by addition of isopropyl alcohol (1 mL). After being allowed to stand for 30 min, the mixture was poured into ether (150 mL), and the resulting mixture was washed with 2 N NaOH (2 × 100 mL), 1 N HCl (100 mL), and saturated brine (100 mL) and dried ($MgSO_4$). Removal of solvents under reduced pressure gave 0.41 g (86%) of product as a white powder: mp 135–140 °C; IR ($CHCl_3$) 1700, 1345, 1170 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02 (d, 3, J = 5.9), 1.20–1.38 (comp, 3), 1.40–1.87 (comp, 6), 1.95–2.38 (comp, 7), 2.43 (s, 3), 2.50 (m, 1), 2.76 (ddd, 1, J = 4.7, 12.3, 15.0), 2.90 (bs, 1), 3.17 (ddd, 1, J = 1.6, 6.0, 15.0), 3.45 (ddd, 1, J = 4.7, 12.3, 11.3), 4.62 (s, 1), 4.89 (s, 1), 7.31 (d, 2, J = 8.1), 7.66 (d, 2, J = 8.2); ^{13}C NMR ($CDCl_3$) δ 21.15, 21.46, 22.36, 25.37, 26.13, 29.31, 29.44, 32.13, 33.86, 43.82, 44.28, 45.78, 47.03, 49.03, 61.69, 104.62, 127.42, 127.52, 129.55, 143.27, 155.86, 214.67. Anal. Calcd for $C_{24}H_{33}NO_3S$: C, 69.36; H, 8.00; N, 3.37; S, 7.71. Found: C, 69.55; H, 8.14; N, 3.17; S, 7.49.

(4*RS*)-17-[(4-Methylphenyl)sulfonyl]-4,17-secoserratinane-5,13-dione (44). Ozone was bubbled through a −78 °C solution of (4*SR*)-5-methylene-17-[(4-methylphenyl)sulfonyl]-4,17-secoserratinan-13-one (0.35 g, 0.84 mmol) in methanol (5 mL) and CH_2Cl_2 (5 mL) until a blue color developed. The solution was allowed to stand at −78 °C for 2 min, and dimethyl sulfide (2 mL) was added. The solution was allowed to stand overnight at room temperature. Solvents were removed under reduced pressure, and the residue was chromatographed on 10 g of silica and eluted with 3:2 ether–hexanes to give 0.29 (83%) pure product as a white solid: mp 133–137 °C; IR ($CHCl_3$) 1740, 1700, 1340, 1165 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.08 (d, 3, J = 6.2), 1.45 (m, 1), 1.56–1.70 (comp, 3), 1.75–1.87 (comp, 2), 1.93–2.04 (comp, 3), 2.12 (m, 1), 2.18–2.48 (comp, 6), 2.43 (s, 3), 2.60–2.68 (comp, 2), 2.82 (bs, 1), 3.18 (ddd, 1, J = 2.6, 6.0, 15.1), 3.48 (ddd, 1, J = 4.8, 12.5, 12.6), 7.31 (d, 2, J = 8.1), 7.65 (d, 2, J = 8.2); ^{13}C NMR ($CDCl_3$) δ 20.822 (2), 21.355 (2), 21.510 (3), 22.303 (3), 24.595 (2), 29.746 (2), 30.046 (1), 30.956 (2), 39.226 (2), 42.069 (1), 44.339 (2), 46.535 (2), 48.819 (2), 49.624 (1), 60.158 (0), 127.452 (1), 129.705 (1), 133.939 (0), 143.550 (0), 213.835 (0), 218.649 (0). Anal. Calcd for $C_{23}H_{31}NO_4S$: C, 66.16; H, 7.48; N, 3.35; S, 7.68. Found: C, 66.15; H, 7.70; N, 3.14; S, 7.45.

(4*SR*)-5-Methylene-4,17-secoserratinan-13-ol (45). A solution of sodium naphthalenide in DME was prepared by adding DME (10 mL) to a mixture of sodium (0.30 g, 13 mmol) and naphthalene (2.1 g, 16 mmol) and stirring the resulting mixture at room temperature for 2 h. A solution of tosylamide **43** (0.47 g, 1.13 mmol) in DME (20 mL) was cooled in a dry ice–isopropyl alcohol bath. The sodium naphthalenide solution was added, dropwise, to the well-stirring tosylamide solution until a light green color persisted. The reaction was quenched by addition of saturated $NaHCO_3$ (1 mL). Anhydrous K_2CO_3 (6 g) was added, and the mixture was stirred for 24 h. The mixture was filtered and the precipitates were rinsed with ether (3 × 20 mL). The combined filtrates were concentrated under reduced pressure, and the residue was chromatographed on 10 g of silica gel and eluted with 1:19 methanol–CH_2Cl_2 saturated with anhydrous ammonia to give 0.28 g (94%) of pure product as a light-yellow gum: IR ($CHCl_3$) 3180, 1650, 1460, 1115, 1105, 885 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (d, 3, J = 6.3), 1.15–1.30 (comp, 3), 1.42–1.78 (comp, 7), 1.81 (m, 1), 1.98–2.10 (comp, 3), 2.27 (m, 1), 2.35–2.42 (comp, 2), 2.57 (m, 2), 2.84 (m, 1), 2.96–3.03 (comp, 2), 3.12 (bd, 1, J = 12.1), 3.50 (dd, 1, J = 3.3, 12.2), 4.82 (s, 1), 4.91 (s, 1); ^{13}C NMR (C_6D_6) δ 23.19, 27.12, 27.36, 27.44, 27.71, 31.63, 33.49, 35.09, 40.55, 44.81, 46.43, 47.19, 52.06, 52.92, 74.03, 107.27, 159.64. Anal. Calcd for $C_{17}H_{29}NO$: C, 77.51; H, 11.10; N, 5.32. Found: C, 77.33; H, 11.18; N, 5.33.

(4*SR*,13*RS*)-17-(*tert*-Butoxycarbonyl)-5-methylene-4,17-secoserratinan-13-ol (46). A solution of amine **45** (158 mg, 0.60 mmol), triethylamine (0.5 mL), and BOC-ON (159 mg, 0.60 mmol) in CH_2Cl_2 (1.0 mL) was allowed to stand at room temperature for 24 h. Solvents were removed under reduced pressure and the residue was chromatographed on 6 g of silica gel and eluted with 1:2 ether–hexanes to give 170 mg (78%) of product as a white powder: mp 49–52 °C (shrinks to a gum); IR ($CHCl_3$) 3620, 3460, 1685, 1420, 1370, 1175 cm^{-1}; ^1H NMR ($CDCl_3$, 70 °C) δ 0.92 (d, 3, J = 6.3), 1.00–2.20 (comp, 16), 1.46 (s, 9), 2.42 (m, 1), 2.58 (b, 1), 2.96–3.20 (comp, 2), 3.30–3.70 (b comp, 3), 4.70 (s, 1), 4.93 (s, 1); ^{13}C NMR ($CDCl_3$, 60 °C) δ 22.14, 24.13, 26.99, 27.02, 28.69, 32.43, 33.64, 40.06, 42.88, 50.76, 51.99, 73.72, 79.10, 105.22, 158.04. Anal. Calcd for $C_{22}H_{37}NO_3$: C, 72.69; H, 10.26; N, 3.85. Found: C, 72.50; H, 10.35; N, 3.77.

(4*SR*)-17-(*tert*-Butoxycarbonyl)-5-methylene-4,17-secoserratinan-13-one. An oven-dried 50-mL round-bottomed flask equipped with a magnetic stirring bar was flushed with dry nitrogen and charged with pyridine (0.63 mL, 0.62 g, 7.8 mmol) and CH_2Cl_2 (17.5 mL). Chromic anhydride (0.37 g, 3.7 mmol) was added in one portion. The burgundy solution was stirred for 30 min, and a solution of alcohol **46** (150 mg, 0.41 mmol) in CH_2Cl_2 (10 mL) was added in one portion. A CH_2Cl_2 rinse (10 mL) was added. The mixture was stirred for 30 min. The solution was decanted from the tar, and the tar was rinsed with ether (3 × 25 mL). The combined organic extracts were washed with 1 N NaOH (3 × 75 mL), water (75 mL), saturated $CuSO_4$ (75 mL), water (75 mL), and brine (60 mL) and dried ($MgSO_4$). Solvents were removed under reduced pressure to give 122 mg (82%) of product as an oil: IR ($CHCl_3$) 1690 (br), 1420, 1370, 1175 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.01 (d, 3, J = 5.8), 1.15–1.38 (comp, 2), 1.47 (s, 9), 1.52–1.85 (comp, 6), 1.95–2.22 (comp, 6), 2.22–2.52 (comp, 2), 2.78–3.13 (comp, 3), 3.44 (m, 1), 3.67 (m, 1), 4.62 (s, 1), 4.91 (s, 1); ^{13}C NMR ($CDCl_3$, 60 °C) δ 22.40, 26.66, 28.63, 29.43, 32.39, 33.81, 44.40, 46.16, 61.69, 79.23, 104.71, 156.09, 213.47. Anal. Calcd for $C_{22}H_{35}NO_3$: C, 73.09; H, 9.76; N, 3.87. Found: C, 72.98; H, 9.73; N, 3.76.

(4*RS*)-17-(*tert*-Butoxycarbonyl)-4,17-secoserratinane-5,13-dione (48). Ozone was bubbled through a −78 °C solution of (4*SR*)-17-(*tert*-butoxycarbonyl)-5-methylene-4,17-secoserratinan-13-one (112 mg, 0.31 mmol) in methanol (5 mL) and CH_2Cl_2 (5 mL) until a blue color developed. The solution was allowed to stand at −78 °C for 5 min, and dimethyl sulfide (2 mL) was added. The colorless solution was warmed to room temperature and allowed to stand for 2 h. The solution was concentrated under reduced pressure and dissolved in CH_2Cl_2 (15 mL) and ether (15 mL). The solution was washed with saturated brine (3 × 25 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give 106 mg (94%) of pure product as a colorless gum: IR ($CHCl_3$) 1745, 1685 (br), 1420, 1375, 1170 cm^{-1}; ^1H NMR ($CDCl_3$, 60 °C) δ 1.06 (d, 3, J = 6.2), 1.10–2.60 (comp, 14), 1.47 (s, 9), 2.70–3.10 (comp, 4), 3.35–3.70 (b comp, 3); ^{13}C NMR ($CDCl_3$, 60 °C) δ 22.28 (3), 25.88 (2), 28.59 (3), 30.13 (3), 31.20 (2), 38.98 (2), 42.41 (1), 46.84 (2), 47.82 (2), 49.87 (1), 59.95 (0), 79.57 (0), 213.01 (0), 218.11 (0). Anal. Calcd for $C_{21}H_{33}NO_4$: C, 69.39; H, 9.15; N, 3.85. Found: C, 69.08; H, 9.27; N, 3.66.

(4*SR*,13*RS*)-17-Acetyl-5-methylene-4,17-secoserratinan-13-ol (47). A solution of amine **45** (350 mg, 1.33 mmol) in pyridine (5 mL) and acetic anhydride (5 mL) was allowed to stand at room temperature overnight. Solvents were removed under reduced pressure, and the residue was chromatographed on 10 g of silica gel and eluted with 1:24 MeOH–CH_2Cl_2 to give 341 mg (84%) of pure product as a colorless glass: mp 62–65 °C; IR ($CHCl_3$) 3620, 3430, 1635 cm^{-1}; ^1H NMR ($CDCl_3$, 100 °C) δ 0.95 (d, 3, J = 6.3), 1.00–2.50 (b comp, 16), 2.09 (s, 3), 2.67 (b, 1), 3.10–4.00 (b comp, 6), 4.77 (bs, 1), 4.96 (bs, 1); ^{13}C NMR ($CDCl_3$, 100 °C) δ 21.93, 24.13, 24.4 (b), 26.78, 27.9 (b), 32.50, 33.85, 40.03, 42.49, 45.3 (b), 47.7 (b), 50.4 (b), 50.78, 52.52, 73.48, 105.64 (b), 157.63, 171.37. Anal. Calcd for $C_{19}H_{31}NO_2$: C, 74.71; H, 10.23; N, 4.59. Found: C, 74.44; H, 10.31; N, 4.39.

(4*SR*)-17-Acetyl-5-methylene-4,17-secoserratinan-13-one. An oven-dried, 25-mL round-bottomed flask equipped with a magnetic stirring bar was flushed with dry nitrogen and charged with pyridine (0.57 mL, 0.56 g, 7.1 mmol) and CH_2Cl_2 (15 mL). Chromic anhydride (0.34 g, 3.4 mmol) was added in one portion. The burgundy solution was stirred for 30 min, and a solution of alcohol **47** (86 mg, 0.28 mmol) in CH_2Cl_2 (3 mL) was added in one portion. A CH_2Cl_2 rinse (2 mL) was added. The mixture was stirred for 30 min. The solution was decanted from the tar, and the tar was rinsed with ether (3 × 15 mL). The combined organic extracts were washed with 1 N NaOH (3 × 60 mL), 1 N HCl (2 × 60 mL), and saturated brine (60 mL) and dried ($MgSO_4$). Solvents were removed under reduced pressure to give 65 mg (76%) of product as a clear, colorless gum: IR ($CHCl_3$) 1695, 1630 cm^{-1}; ^1H NMR ($CDCl_3$, 120 °C) δ 1.00 (d, 3, J = 5.8), 1.10–2.50 (b comp, 14), 2.06 (s, 3), 2.83 (b, 1), 3.00–3.70 (b comp, 5), 3.93 (b, 1), 4.62 (bs, 1), 4.89 (bs, 1); ^{13}C NMR ($CDCl_3$, 120 °C) δ 21.87, 22.17, 23.43, 27.17, 27.8 (b), 29.29, 32.65, 34.28, 44.75, 46.88, 47.38, 61.78, 105.07, 155.79, 171.47, 212.38. Anal. Calcd for $C_{19}H_{29}NO_2$: C, 75.21; H, 9.63; N, 4.62. Found: C, 75.20; H, 9.67; N, 4.49.

(4*RS*)-17-Acetyl-4,17-secoserratinane-5,13-dione (49). Ozone was bubbled through a −78 °C solution of (4*SR*)-17-acetyl-5-methylene-4,17-secosarratinan-13-one (60 mg, 0.2 mmol) in methanol (5 mL) and CH_2Cl_2 (5 mL) until a blue color developed. The solution was allowed to stand at −78 °C for 5 min, and dimethyl sulfide (1 mL) was added. The colorless solution was warmed to room temperature and allowed to stand for 2 h. The solution was concentrated under reduced pressure and dissolved in CH_2Cl_2 (10 mL) and ether (10 mL). The solution was washed with saturated brine (3 × 15 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give 48 mg (79%) of pure product as a white powder: mp 52–55 °C (shrinks to a gum); IR ($CHCl_3$) 1740, 1705, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80–2.60 (comp, 13), 1.09 and 1.10 (2 d, 3, J = 6.1 and 6.2), 2.11 and 2.14 (2 s, 3), 2.65–3.50 (comp, 5), 3.52–3.78 (comp, 2), 3.90 (m, 1); ^{13}C NMR ($CDCl_3$) δ 21.40, 21.70, 22.29, 22.46, 22.61, 23.07, 25.18, 26.34, 27.04, 27.81, 29.67, 30.02, 30.99, 39.11, 42.05, 42.58, 44.05, 46.71, 47.17, 47.80, 48.56, 49.78, 49.90, 59.65, 59.86, 77.26, 171.96, 172.14, 212.52, 213.21, 218.18, 218.61. Anal. Calcd for $C_{18}H_{27}NO_3$: C, 70.79; H, 8.91; N, 4.59. Found: C, 70.56; H, 9.07; N, 4.30.

(4*SR*)-5-Methylene-4,17-secoserratinan-13-one (54). To a solution of alcohol **45** (146 mg, 0.55 mmol) in 80% aqueous acetic acid (6 mL) was added 1 M CrO_3 in 80% aqueous acetic acid (1.0 mL, 1.0 mmol). The resulting solution was allowed to stand at room temperature for 3 h, and isopropyl alcohol (1 mL) was added to quench the excess oxidant. This solution was allowed to stand for 3 h, added to 1:1 2 N NaOH–brine (50 mL), and extracted with 2:1 CH_2Cl_2–ether (5 × 50 mL). The combined organic extracts were dried (K_2CO_3), and solvents were removed under reduced pressure. The residue was chromatographed on 6 g of silica gel and eluted with 1:1:0.05 ethyl acetate–hexanes–triethylamine to give 126 mg (87%) of pure product as a white powder: mp 83.5–85 °C, $HClO_4$ salt (recrystallized from water) mp 209.5–210 °C; IR ($CHCl_3$) 1695, 1650, 1455, 1435, 1135, 885 cm^{-1}; ^1H NMR (C_6D_6) δ 0.79 (d, 3, J = 6.4), 1.13 (b, 1), 1.38–1.67 (comp, 8), 1.81 (b, 1), 1.96–2.00 (comp, 2), 2.05–2.22 (comp, 4), 2.27–2.39 (comp, 2), 2.46 (m, 1), 2.55–2.61 (comp, 2), 3.45 (bd, 1,

J = 4.7), 4.92 (s, 1), 5.21 (s, 1); ^{13}C NMR (C_6D_6) δ 23.01, 23.12, 26.30, 28.03, 29.97, 31.60, 33.16, 35.44, 42.58, 45.44, 47.07, 47.27, 47.79, 63.09, 105.37, 158.01, 212.56. Anal. Calcd for $C_{17}H_{27}NO$: C, 78.11; H, 10.41; N, 5.36. Found: C, 77.99; H, 10.36; N, 5.40.

(±)-Fawcettimine (7). Ozone was bubbled through a −78 °C solution of the perchlorate salt of aminoalkene **54** (58 mg, 0.16 mmol) in methanol (1.6 mL) and CH_2Cl_2 (1.6 mL) until a blue color developed. The solution was allowed to stand at −78 °C for 5 min, and dimethyl sulfide (1 mL) was added. The colorless solution was warmed to room temperature, allowed to stand for 4 h, and concentrated under reduced pressure. The resulting semicrystalline material was dissolved in chloroform (or deuteriochloroform) (5 mL), washed with saturated $NaHCO_3$ (5 × 3 mL), and dried ($MgSO_4$). After standing for 3 days, ^1H NMR shows the product to be completely converted into fawcettimine. Concentration under reduced pressure gave 41 mg (95%) of fawcettimine as a white solid: mp 87–90 °C. The IR spectra obtained for this sample was identical with that of an authentic sample of fawcettimine: IR ($CHCl_3$) 1735, 1465, 1415, 1385, 1360, 1340, 1325, 1290, 1255, 1150, 1105, 1060, 1030, 980, 915, 890, 875 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (d, 3, J = 6.3), 1.36–1.43 (comp, 2), 1.46–1.55 (comp, 2), 1.63 (dm, 1, J = 14.1), 1.84 (m, 1), 1.90–1.99 (comp, 3), 2.00–2.28 (comp, 7), 2.62 (dd, 1, J = 13.8, 17.7), 2.73 (ddd, 1, J = 4.0, 6.1, 14.3), 2.90 (dd, 1, J = 5.5, 14.7), 3.25 (td, 1, J = 4.2, 14.2), 3.53 (ddd, 1, J = 3.9, 9.4, 14.3), 3.90 (b, 1); ^{13}C NMR ($CDCl_3$) δ 21.792 (3), 22.120 (2), 23.693 (1), 28.004 (2), 28.214 (2), 31.844 (2), 35.569 (2), 41.823 (2), 43.229 (1), 43.741 (2), 48.201 (0), 50.114 (2), 53.604 (2), 60.071 (1), 219.833 (0). The hydrobromide salt, recrystallized from EtOH–acetone, mp 210–212 °C, had spectra identical with an authentic sample of fawcettimine hydrobromide: IR ($CHCl_3$) 3350, 3170, 2630, 1745, 1610, 1465, 1415, 1360, 1310, 1295, 1275, 1175, 1160, 1145, 1105, 1050, 980, 935, 915, 900, 890, 875, 860 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03 (d, 3, J = 6.5), 1.46 (ddd, 1, J = 5.6, 13.8, 14.3), 1.63 (ddd, 1, J = 2.3, 2.5, 14.6), 1.74 (ddd, 1, J = 1.7, 1.8, 14.3), 1.78–1.95 (comp, 5), 2.05–2.24 (comp, 5), 2.31–2.42 (comp, 2), 2.58 (dd, 1, J = 13.1, 17.6), 2.76 (bd, 1, J = 13.3), 3.00 (ddd, 1, J = 3.7, 7.8, 13.6), 3.18 (dd, 1, J = 5.1, 14.2), 3.56 (td, 1, J = 4.3, 14.2), 4.14 (ddd, 1, J = 4.0, 8.7, 13.6), 6.0 (b, 1), 10.1 (b, 1); ^{13}C NMR ($CDCl_3$) δ 18.916 (2), 21.335 (3), 23.759 (1), 23.864 (2), 26.576 (2), 31.132 (2), 33.291 (2), 39.779 (2), 41.040 (2), 43.088 (1), 47.574 (0), 51.075 (2), 55.263 (2), 58.972 (1), 95.947 (0), 216.382 (0).

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Registry No. (±)-**7**, 118892-07-2; (±)-**7**·HBr, 103498-99-3; (±)-**9**, 103616-04-2; (±)-**14**, 69060-78-2; (±)-**14** (2-chloro deriv), 71523-91-6; **15**, 83378-96-5; (±)-**16** (isomer 1), 118892-12-9; (±)-**16** (isomer 2), 118892-29-8; (±)-**17** (isomer 1), 118892-13-0; (±)-**17** (isomer 2), 118892-30-1; (±)-**18** (isomer 1), 118892-14-1; (±)-**18** (isomer 2), 118892-31-2; (±)-**19**, 118892-15-2; (±)-**22**, 103498-91-5; (±)-**23**, 118892-16-3; (±)-**24**, 118892-17-4; (±)-**25**, 103498-92-6; **26**, 56069-39-7; (±)-**27**, 118892-18-5; (±)-**28**, 118892-19-6; **30**, 118892-20-9; (±)-**31**, 118892-21-0; (±)-**32**, 118892-22-1; (±)-**33**, 118892-23-2; (±)-**35**, 103498-93-7; (±)-7β-**35**, 103498-94-8; (±)-**36**, 118892-24-3; (±)-7β-**36**, 118892-32-3; (±)-**37**, 118892-25-4; (±)-**38**, 118892-26-5; (±)-1α-**39**, 119006-96-1; (±)-1β-**39**, 118892-27-6; (±)-**42**, 103498-95-9; (±)-**43**, 103498-96-0; (±)-**43** (ketone), 118949-23-8; (±)-**44**, 118892-08-3; (±)-**45**, 103498-97-1; (±)-**46**, 118892-09-4; (±)-**46** (ketone), 118892-10-7; (±)-**47**, 103499-00-9; (±)-**47** (ketone), 103499-01-0; (±)-**48**, 118892-11-8; (±)-**49**, 103616-03-1; (±)-**54**, 103498-98-2; (±)-**56**, 119064-90-3; (±)-**57**, 118892-28-7; (±)-**59**, 74111-25-4; (±)-**60**, 118949-24-9; CH_2=CH-CH_2Br, 106-95-6; $BrCH_2COC_6H_4$-4-OMe, 2632-13-5.

Supplementary Material Available: Experimental procedures for the preparation of three compounds used in the proof of stereochemistry of amino diol **35**, single-crystal X-ray data for one of these compounds and for fawcettimine hydrobromide, detailed peak assignments for fawcettimine and fawcettimine hydrobromide, and details of the molecular mechanics investigation (35 pages). Ordering information is given on any current masthead page.

Total Synthesis Establishing the Correct Structures of Robustadials A and B. Reinterpretation of NMR Data

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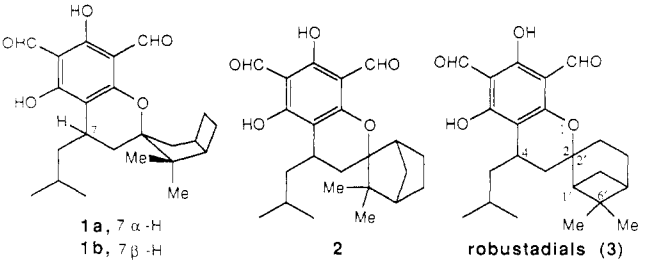
A total synthesis from (+)-nopinone establishes as **10f** and **11f** respectively the structures, including absolute stereochemistry, for robustadials A and B, natural products isolated from the antimalarial Chinese herbal medicinal extract of *Eucalyptus robusta* leaves. The ^1H and ^{13}C NMR spectral assignments for robustadial B dimethyl ether (**11e**) are examined in detail. It is then shown that the nuclear Overhauser enhancement data interpreted originally to support **1b** as the structure for this ether are actually consistent with both structures **1b** and **11e**.

An urgent need for the identification and total synthesis of new antimalarials inspired a persistent quest to unravel the elusive structures of robustadials A and B, natural products isolated from the antimalarial Chinese herbal medicinal extract of *Eucalyptus robusta* leaves.[1] The original presumption of bicyclo[3.2.0]heptyl structures **1a** and **1b** robustadials A and B, respectively,[2] was refuted by total synthesis.[3] A prenylphenol–terpenoid biogenesis



seemed likely since the aromatic acetogenin–isopentyl portion proposed for the robustadials is identical with that found in the euglobals, a family of biologically active compounds isolated from the buds and leaves of *Eucalyptus globulus*.[4] Generally the remaining terpenoid

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