Studies on the Synthesis of *Strychnos* Alkaloids. A New Entry into the Azocino[4.3-*b*]indole Core Structure and Related Studies

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Treatment of cyclohexanone-3-acetic acid with phenylhydrazine hydrochloride gave the tetrahydrocarbazole **7** (73%). The derived methyl ester **8** (99.6%) was oxidized to the 4-oxo compound **9** in 85% yield by treatment with DDQ/90% aqueous THF at 0 °C. Treatment of **9** with NaH/DMF at 0 °C followed by (*p*-methoxyphenyl)sulfonyl chloride gave **10** (81%). Hydrolysis of **10** using lithium hydroxide in aqueous THF gave the acid **11** (86%). The acid **11** was converted into the amide **12** by treatment with ethylchloroformate/NEt_3/CH_2Cl_2 followed by aqueous NH_4OH. The ketoamide **12** was exposed to $NaBH_4$/MeOH/THF to give a single alcohol **13** (>95%). Exposure of **13** to trifluoroacetic acid (cat)/CH_2Cl_2/0–20 °C gave the azocino[4.3-*b*]indole core tetracyclic lactam **14** (90%). The amide **14** was reduced (BH_3·THF) to give **21**, which was directly acetylated ($PhSCH_2COCl$) to give exocyclic amide **22**. All attempts to close the C_{11}–C_{12} bond only resulted in decomposition. Treatment of the acid **11** with EtO_2CCl/Et_3N followed by [2-(phenylthio)ethyl]amine gave the amide **24** (90%). Reduction of **24** using $NaBH_4$ gave the alcohol **25** which upon exposure to CF_3CO_2H at room temperature cyclized to the tetracyclic amide **26** (96% overall). Oxidation of the sulfide **26** (*m*-CPBA) resulted in the diastereomeric sulfoxides **28**. When the sulfoxides **28** were exposed to Pummerer conditions the only products that could be isolated were the (*E*)- and (*Z*)-vinyl sulfides **29** (72% and 25%, respectively). Similarly the dimethylthio acetal **33** was converted into the aldehyde **34** (100%). Treatment of **26** with $POCl_3$/DMF gave **35** (90.8%) which was exposed to $PhNHNH_2$/AcOH/AcONa to give the pyrazole **36** (85%). Attempts to close the *E*-ring via sulfoxides derived from either the pyrazole **36** or the oxazole **37** were unsuccessful. Treatment of the chloride **40** with KH/$HN(SiMe_3)_2$ in toluene resulted in a slow conversion into the 3-oxindole **44**.

Introduction

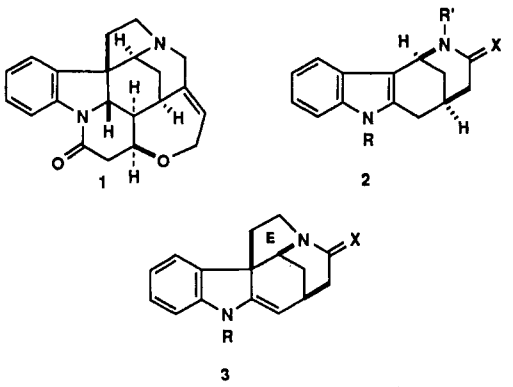
The *Strychnos* alkaloids have occupied a central position in the structural elucidation and synthesis of indole alkaloids for over a century.[1] Since the first and only synthesis of strychnine **1** by Woodward[2] in 1954, there have been a variety of different strategies developed for the construction of the basic skeletal framework.[3] As part of our studies on the synthesis of heptacyclic indole alkaloids[4] we report a new route to the azocino[4.3-*b*]indole core **2** of strychnine and attempts to close the *E* ring to give derivatives of **3**, Chart I.

Our initial entry into the azocino[4.3-*b*]indole structure **2** was based upon the indole-2,3-quinodimethane strategy,[5] followed by acid-catalyzed rearrangement of the so-called isogramine system **4** into **2**, Scheme I. We had speculated that **4** would undergo acid-catalyzed fragmentation, typical of an isogramine system, to give the iminium ion **4a**. This species has a number of reaction pathways. Proton loss from C-5 can lead to **4b**, which by C-2 protonation gives **4c**. These equilibria should favor **4c** since **4c** is more stable than **4a**. In principle, **4c** should cyclize to the azocino-[4.3-*b*]indole **2**, and thus the overall sequence provides, under thermodynamic control, a plausible route from **4** to **2**.[6]

In the event, treatment of **4** with aqueous acetic acid at 80 °C gave the carbazole derivatives **5**.[7] This suggests that **4a** was formed, but rapidly lost a proton from C-3 to give **4d** which is easily oxidized into **5**. Carrying out the above fragmentation in the presence of zinc dust gave the tetrahydrocarbazole **6**, confirming the intermediacy of either **4a** and/or **4d**. Consequently, we required a route to the iminium ion **4c** that does not proceed through the higher energy iminium ion **4a**.

In a regiospecific Fischer indole synthesis, treatment of cyclohexanone-3-acetic acid with phenylhydrazine hydrochloride gave the tetrahydrocarbazole **7** (73%).[8] The derived methyl ester **8** (99.6%) was oxidized to the 4-oxo compound **9** in 85% yield by treatment with DDQ/90%

Chart I



aqueous THF at 0 °C.[9] It was found that the subsequent transformations could only be achieved if the indole nitrogen atom was inductively deactivated. The *N*-(*p*-

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(1) Massiot, G.; Delaude, C. African Strychnos Alkaloids. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1988; Vol. 34, p 211. Bosch, J.; Bonjoch, J. Pentacyclic Strychnos Alkaloids. In *Studies in Natural Products Chemistry*; Rahman, A., Ed.; Elsevier: Amsterdam, 1988; Vol. 1, p 31.

(2) Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schenker, K. *J. Am. Chem. Soc.* **1954**, *76*, 4749. Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schenker, K. *Tetrahedron* **1963**, *19*, 247.

(3) Most recent published synthetic approaches: Fevig, J. M.; Marquis, R. W., Jr., Overman, L. E. *J. Am. Chem. Soc.* **1991**, *113*, 5085. Kuehne, M. E.; Frasier, D. A.; Spitzer, T. D. *J. Org. Chem.* **1991**, *56*, 2696. Grotjahn, D. B.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1990**, *112*, 5653. Kraus, G. A.; Thomas, P. J.; Bougie, D.; Chen, L. *J. Org. Chem.* **1990**, *55*, 1624. Legseir, B.; Henin, J.; Massiot, G.; Vercauteren, J. *Tetrahedron Lett.* **1987**, *28*, 3573. Bonjoch, J.; Casamitjana, N.; Quirante, J.; Rodriquez, M.; Bosch, J. *J. Org. Chem.* **1987**, *52*, 267. There are numerous other reports of synthetic endeavors and these are referred to in ref 1.

(4) Magnus, P.; Katoh, T.; Matthews, I.; Huffman, J. C. *J. Am. Chem. Soc.* **1989**, *111*, 6707. Magnus, P.; Gallagher, T.; Brown, P. *J. Am. Chem. Soc.* **1984**, *106*, 2105. Gallagher, T.; Huffman, J. C.; Magnus, P. *J. Am. Chem. Soc.* **1983**, *105*, 2086.

(5) Magnus, P.; Gallagher, T.; Brown, P.; Pappalardo, P. *Acc. Chem. Res.* **1984**, *17*, 35.

(6) Bosch, J.; Amat, M.; Domingo, A. *Heterocycles* **1984**, *22*, 561. Besseliévre, Husson, H.-P. *Tetrahedron* **1981**, *37*, Suppl 1, 241.

(7) Magnus, P.; Exon, C.; Sear, N. L. *Tetrahedron* **1983**, *39*, 3725.

(8) Berger, L.; Corraz, A. J. U. S. Patent 4,009,181, 1977.

(9) Oikama, Y.; Yonemitsu, O. *J. Org. Chem.* **1977**, *42*, 1213.

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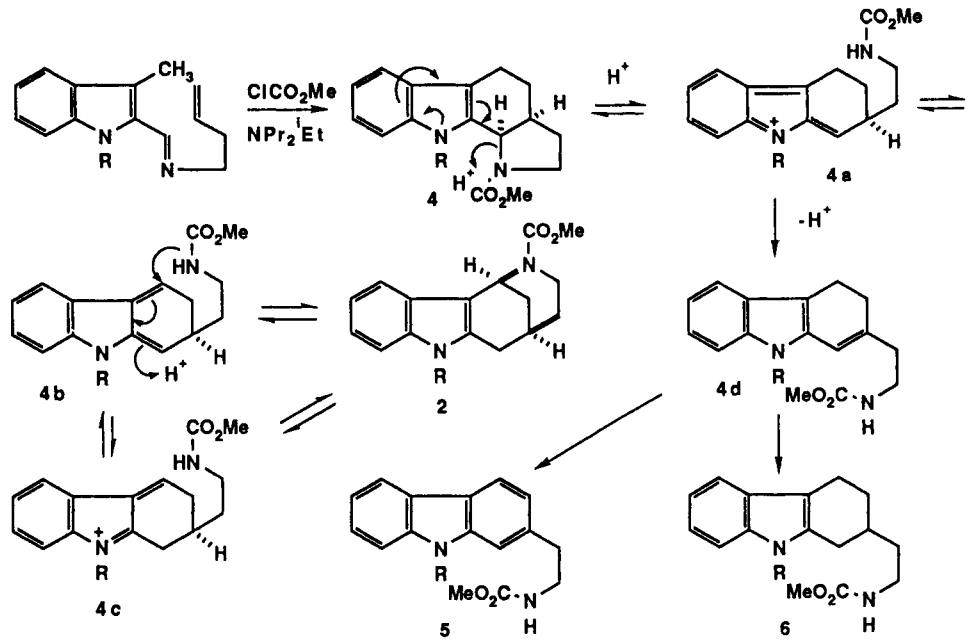
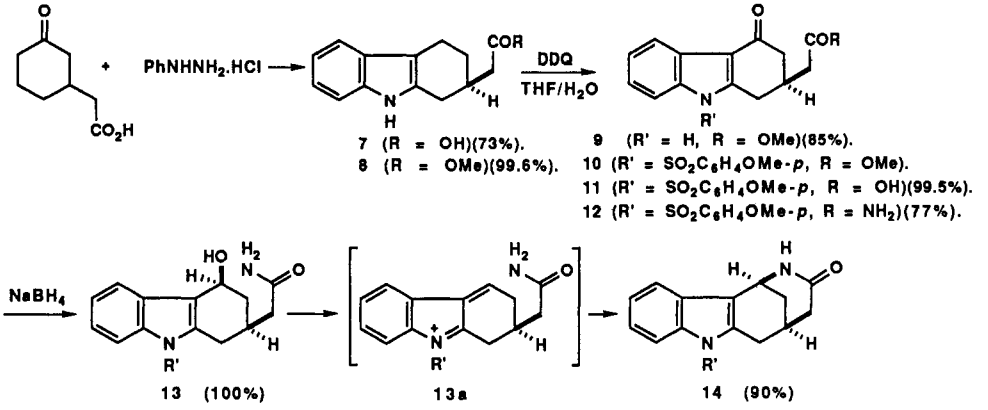
Scheme I (R = H)



Scheme II



methoxyphenyl)sulfonyl group was consistently successful in the *Aspidosperma* series, it survives a wide range of electrophilic and nucleophilic conditions, and it is removed by mild reductive cleavage.[10] Treatment of **9** with NaH/DMF at 0 °C followed by (*p*-methoxyphenyl)sulfonyl chloride gave **10** (81%). Hydrolysis of **10** using lithium hydroxide in aqueous THF gave the acid **11** (86%). The acid **11** was converted into the amide **12** by treatment with ethyl chloroformate/NEt_3/CH_2Cl_2 followed by aqueous NH_4OH. It should be noted that the *N*-(*p*-methoxyphenyl)sulfonyl electron-withdrawing group is necessary in order to be able to reduce the 4-carbonyl function with mild reducing agents. The ketoamide **12** was exposed to $NaBH_4$/MeOH/THF to give a single alcohol **13** (>95%). The assignment of relative stereochemistry is based upon the approach of the reducing agent to the face of the C-4 carbonyl group opposite to that of the 2-acetamido substituent. It is somewhat surprising that the reduction with $NaBH_4$ is stereospecific, although for the generation of the subsequent iminium ion **13a** it is not important. The alcohol **13** proved to be a rather labile compound. When it was treated with trifluoroacetic acid (cat)/CH_2Cl_2/0–20 °C the tetracyclic lactam **14** was produced in over 90% yield.[11] Its structure was unambiguously confirmed by single-crystal X-ray crystallography.[12] In principle, **14** is available in both enantiomeric forms since we have resolved cyclohexanone-3-acetic acid via its quinine salt.

During the course of our studies on the synthesis of *Aspidosperma* indole alkaloids we have used the intramolecular Pummerer reaction to close the crucial C_{11}–C_{12} bond to complete the construction of the pentacyclic skeleton, Scheme III.[13] In both the *exocyclic* amide series (**15** into **17**) and the *endocyclic* amide series (**18** into **20**) the overall features of the sequence are that treatment of the sulfoxides **15**/**18** with trifluoroacetic anhydride produces the sulfonium ions **16**/**19**, which are trapped by the nucleophilic indole 2,3-double bond to give after proton loss **17**/**20**, usually in excellent yields (>90%). The im-

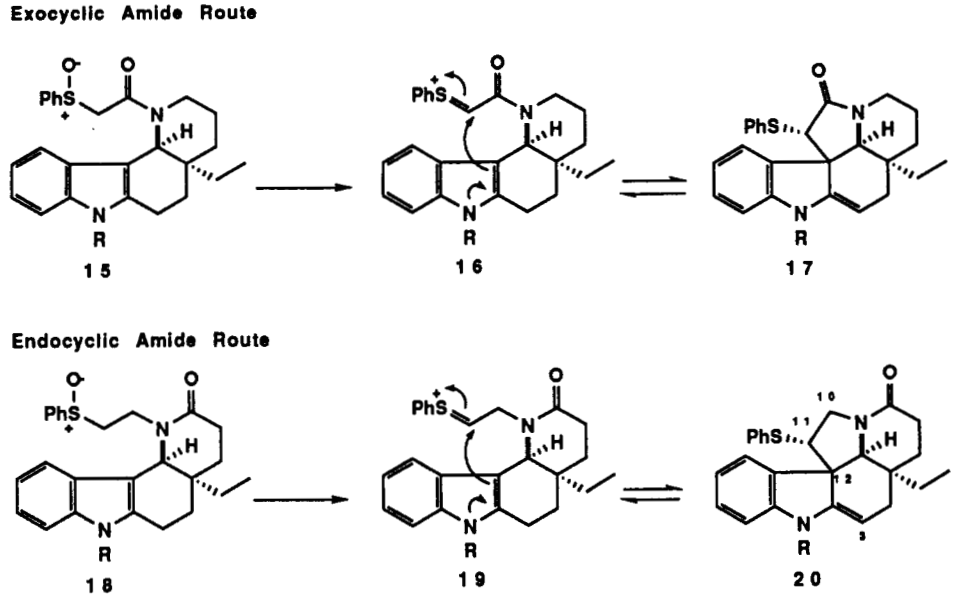
(10) Magnus, P.; Matthews, I. R.; Schultz, J.; Waditschatka, R.; Huffman, J. C. *J. Org. Chem.* **1988**, *53*, 5772.

(11) The structure **14** is the so-called dasycarpidone skeleton. Feliz, M.; Bosch, J.; Mauleón, D.; Amat, M.; Domingo, A. *J. Org. Chem.* **1982**, *47*, 2435. Dolby, L. J.; Biere, H.; *J. Org. Chem.* **1970**, *35*, 3843. Kametani, T.; Suzuki, J. *J. Chem. Soc. C* **1971**, 1053. Kametani, K.; Suzuki, *J. Org. Chem.* **1971**, *36*, 1291. Büchi, G.; Gould, S. J.; Näf, F. *J. Am. Chem. Soc.* **1971**, *93*, 2492. Natsume, M.; Sekine, Y.; Ogawa, M.; Soyagima, H.; Kitagawa, Y.; *Tetrahedron Lett.* **1979**, *20*, 3473. Susuki, T.; Sato, E.; Goto, K.; Unno, K. *Heterocycles* **1980**, *14*, 433. Jackson, A.; Wilson, N. D. V.; Gaskell, A. J.; Joule, J. A. *J. Chem. Soc. C* **1969**, 2738. Sundberg, R. J.; Russell, H. F.; Ligon, Jr. W. V.; Lin, L. *J. Org. Chem.* **1972**, *37*, 719.

(12) For details of the single-crystal X-ray structure determination of **14** request Report No. 85003 from Dr. John C. Huffman, Molecular Structure Center, Indiana University, Bloomington, IN 47405.

(13) Exon, C.; Gallagher, T.; Magnus, P. *J. Am. Chem. Soc.* **1983**, *105*, 4739. Gallagher, T.; Magnus, P. *J. Am. Chem. Soc.* **1983**, *105*, 4750.

Scheme III



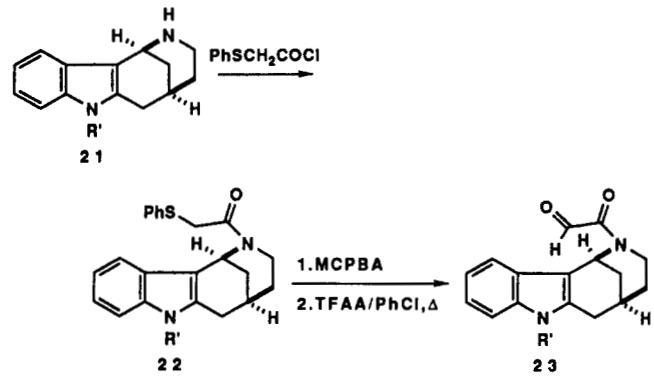
portant details are as follows: (i) The sulfonium ion must be aligned directly over the π-system of the indole 2,3-double bond and trans coplanar to it. This leads to the stereochemistry shown. (ii) The steps **16** into **17** and **19** into **20** are reversible; if **17** is treated with aqueous acid it is converted into the hydrolysis product of **16**, namely the derived aldehyde. (iii) The same equilibration of **17** except under anhydrous conditions leads to the 11-phenylthio epimer of **17**, thus demonstrating that **17** is the kinetic product and its 11-phenylthio epimer is the thermodynamic product. (iv) Inductive deactivation of indole nitrogen atom by the (*p*-methoxyphenyl)sulfonyl group does not prohibit cyclization of **16** into **17** and is crucial since the substrate **15** (R = H) is destroyed by the usual Pummerer reaction conditions. Given the above information we examined the following substrates with respect to their ability to undergo intramolecular Pummerer closure of the crucial C_{11}–C_{12} bond.

Exocyclic Amide Route. The amide **14** was reduced with diborane in tetrahydrofuran to give the *sec*-amine **21**, which was directly acetylated using (phenylthio)acetyl chloride to give the exocyclic amide **22**. All attempts to close the C_{11}–C_{12} bond using conditions that were successful in the *Aspidosperma* systems only resulted in decomposition. The ^1H NMR spectrum of the total crude product mixture indicated that a small amount of an aldehyde was present, possibly the glyoxamide **23** formed by hydrolysis of the intermediate sulfonium ion. In a series of analogues where R′ is hydrogen or $-CO_2Me$ the closure of the C_{11}–C_{12} bond proved equally unsuccessful.

Endocyclic Amide Route. The failure of the Pummerer reaction ring closure in the exocyclic amide series may be a consequence of having the intermediate sulfonium ion too far from the indole 2,3-double bond compared with the successful *Aspidosperma* series in Scheme III. This contention is supported by both molecular modeling and simple Dreiding models. The exocyclic amide imposes a severe constraint on the ability of the intermediate sulfonium ion to align, in an antiperiplanar fashion, over the indole 2,3-π bond. Positioning the amide carbonyl group in the piperidine ring imparts more flexibility in the C_{10}/C_{11} side chain, but the situation is still more strained than the *Aspidosperma* series.

Treatment of the acid **11** with ethyl chloroformate/triethylamine followed by [2-(phenylthio)ethyl]amine gave

Scheme IV

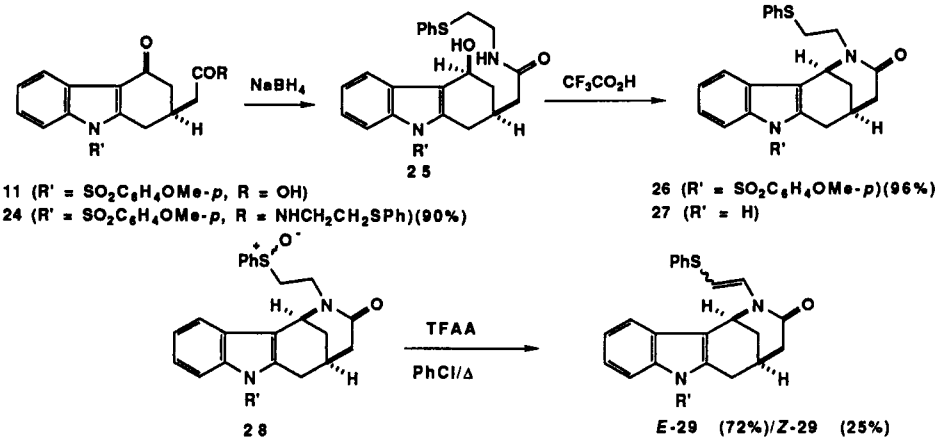


the amide **24** (90%). Reduction of **24** using sodium borohydride gave the alcohol **25** which upon exposure to trifluoroacetic acid at room temperature cyclized to the tetracyclic amide **26** (96% overall). Oxidation of the sulfide **26** with *m*-chloroperoxybenzoic acid resulted in a mixture of the diastereomeric sulfoxides **28**. When the sulfoxides **28** were treated with trifluoroacetic acid anhydride at 0 °C they were rapidly converted into the presumed intermediate α-trifluoroacetoxy sulfides which were immediately heated in chlorobenzene at 120 °C for 4 h. The only products that could be isolated from this reaction were the (*E*)- and (*Z*)-vinyl sulfides **29** (72% and 25% respectively).

The acid **11** was converted into the amide **30** (63%) by the mixed anhydride method. Sequential reduction followed by treatment of the alcohol **31** with trifluoroacetic acid in dichloromethane gave the tetracyclic amide **31** (98%). The dimethyl acetal was exchanged by treatment with $BF_3{\cdot}OEt_2$/MeSH in tetrahydrofuran to give the dimethylthio acetal **33** (80%). When **33** was exposed to a solution of (dimethylthio)sulfonium tetrafluoroborate in dichloromethane it was cleanly converted into the aldehyde **34** (100%). If R′ = CO_2Me or H we did not observe any ring closure to the 3-position of the indole ring but only slow hydrolysis to the corresponding aldehyde.

These results indicate that the planar amide nitrogen atom in **33** is not allowing sufficient flexibility in the appended side chain to align the intermediate sulfonium ion close to the indole 2,3-bond. Since it will eventually be

Scheme V



11 (R' = $SO_2C_6H_4OMe$-*p*, R = OH)
24 (R' = $SO_2C_6H_4OMe$-*p*, R = $NHCH_2CH_2SPh$)(90%)

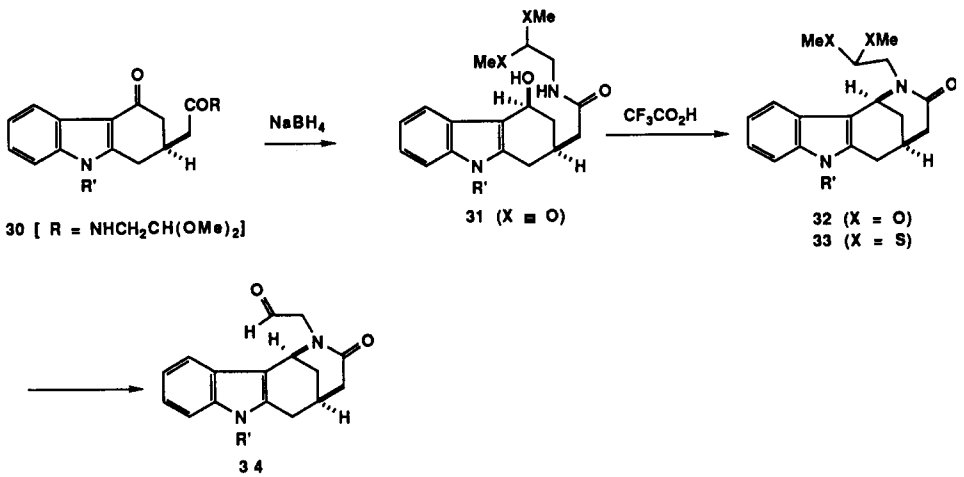
25

26 (R' = $SO_2C_6H_4OMe$-*p*)(96%)
27 (R' = H)

28

E-29 (72%)/*Z*-29 (25%)

Scheme VI (R' = $SO_2C_6H_4OMe$-*p*)



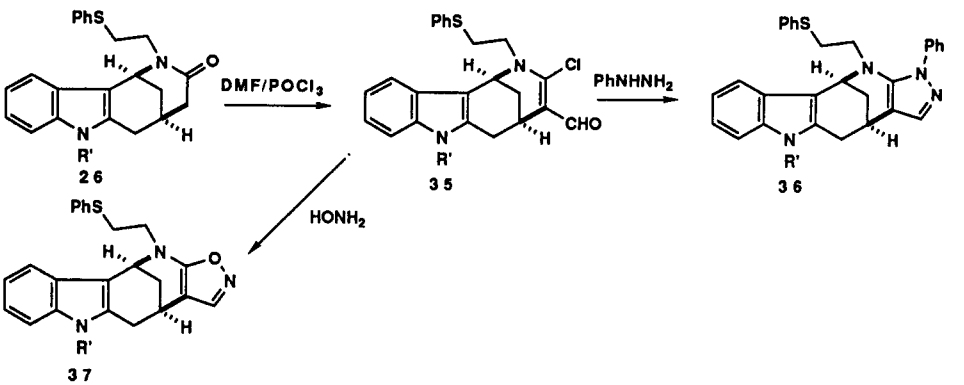
30 [R = $NHCH_2CH(OMe)_2$]

31 (X = O)

32 (X = O)
33 (X = S)

34

Scheme VII (R' = $SO_2C_6H_4OMe$-*p*)



26

35

36

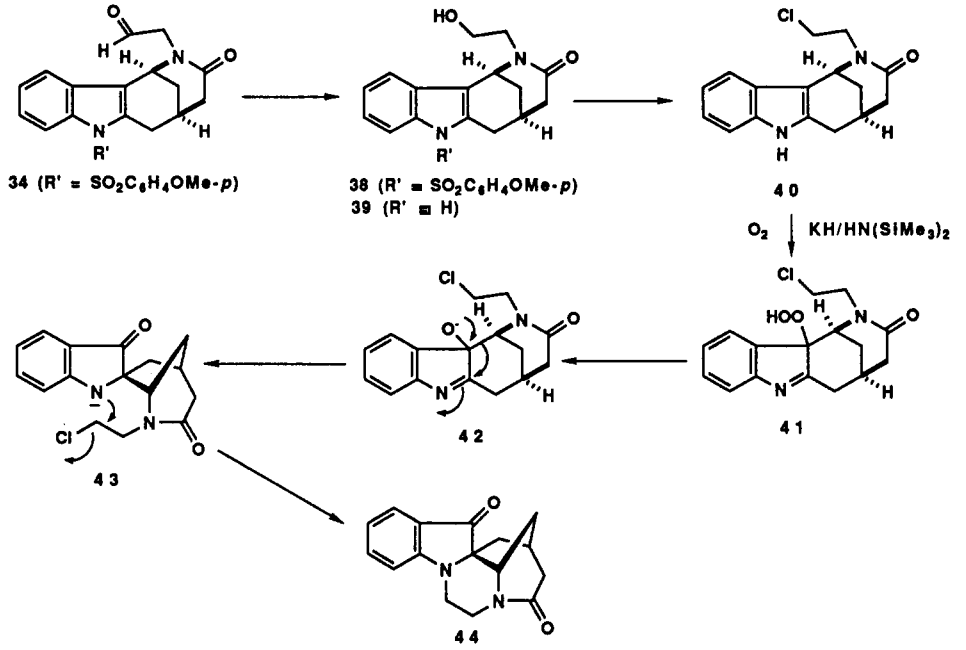
37

necessary to introduce a functionalized carbon side chain adjacent to the amide carbonyl group, we considered that an heteroaromatic ring annulated at the 3,4-position in, for example, **26**, would destroy amide resonance. This should have the effect of making the N-2 atom more pyramidal in character and therefore more flexible and able to reach the indole π-system. To test this notion we treated **26** with phosphorus oxychloride/dimethylformamide (Vilsmeier conditions) and isolated the β-chloro aldehyde **35** (90.8%).[14] Treatment of **35** with phenylhydrazine/AcOH/AcONa gave the pyrazole **36** (85%).[15] Interestingly, the ^{1}H NMR methoxy resonance in **26** and **35** appears at 3.78 and 3.76 ppm, respectively, whereas in the pyrazole **36** this signal is dramatically shifted to 3.38 ppm. Apparently the –OMe group sits over the π-system of the NPh group. The single-crystal X-ray analysis of **36** showed that (in the solid state) the methoxy group does indeed sit over the NPh group and more importantly the N-2 atom is now pyramidal.[16]

Unfortunately this short-lived success did not continue, for all attempts to close the *E* ring via sulfoxides derived from either the pyrazole **36** or the oxazole **37** were unsuccessful. The analogous compounds where R' = CO_2Me

(14) Klutchko, S.; Hansen, H. V.; Meltzer, R. I. *J. Org. Chem.* **1965**, *30*, 3454.
(15) *Pyrazoles, Pyrazolines and Condensed Rings*; Wiley, R. H., Ed.; Wiley-Interscience, New York, 1957.
(16) For details of the single-crystal X-ray structure determination of **36** request Report No. 86057 from Dr. John C. Huffman, Molecular Structure Center, Indiana University, Bloomington, IN 47405.

Scheme VIII (R' = $SO_2C_6H_4OMe$-*p*)

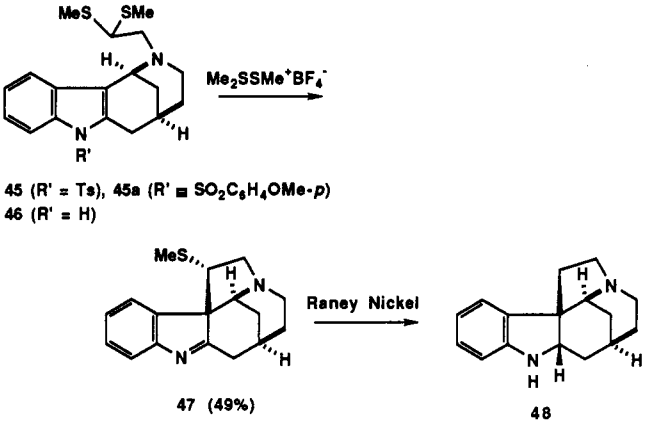


or H were also unsuccessful.

In an effort to form the *E* ring by an intramolecular nucleophilic displacement process the aldehyde **34** was reduced with sodium borohydride to give the alcohol **38**. The (*p*-methoxyphenyl)sulfonyl group was reductively cleaved by treatment of **38** with Na–Hg amalgam in THF/MeOH to give the deprotected indole **39**. Attempted mesylation of **39** with mesyl chloride in pyridine gave directly the unstable chloride **40**. Treatment of the chloride **40** with $KH/HN(SiMe_3)_2$ in toluene resulted in a slow conversion of **40** into a new highly fluorescent compound. The rate of formation of this new compound depended upon leakage of oxygen into the reaction mixture deliberately. Rigorous exclusion of oxygen gave no reaction, but deliverately opening the mixture to the atmosphere resulted in the rapid formation of the new compound. The ultraviolet spectrum exhibited a strong absorption at 410 nm, characteristic of the oxindole chromophore.[17] Therefore, the most probable structure for this compound is **44**. Its formation may be rationalized by oxygenation at the 3-position of the indole to give the hydroperoxide **41**. Such hydroperoxides are well-known from the classical work of Robertson and later Witkop to rearrange via the alkoxide **42** into the oxindole **43**.[18] The final step is simply alkylation of the nitrogen anion to form the hexahydropyrazine ring in **44**.[19]

Amine Route. It is clear from the experiments described in both the exo and endo cyclic amide series that the presence of the amide carbonyl functionality prohibits the formation of the *E* ring. Consequently, we decided to remove the amide carbonyl in **33** by reduction with diborane. While this study was in progress, Bosch reported virtually the same intended set of transformations in their approach to pentacyclic *Strychnos* alkaloids, Scheme IX.[20]

Scheme IX



Bosch described the treatment of **46** with dimethyl(methylthio)sulfonium tetrafluoroborate[21] to give **47** (49%) and subsequent Raney nickel desulfurization–hydrogenation to give **48**. They also noted that the NTs derivative **45** did not cyclize. In order to form the *E* ring via the Pummerer reaction (thionium ion) the indole nitrogen atom must be unprotected, and the N-2 nitrogen atom must be an amine rather than an amide. These constraints severely restrict the introduction of functionality for elaboration of the oxethylidene side chain. Consequently, for this reason, and overlap with the Bosch strategy, we have not pursued this route further.

Experimental Section

Melting points were taken on a Thomas-Hoover capillary tube apparatus and are uncorrected. Boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 881 grating spectrophotometer either neat or in $CHCl_3$ as indicated. Ultraviolet spectra were recorded on a Perkin-Elmer Lambda 3B UV/VIS spectrophotometer in the indicated solvents. Proton NMR spectra were recorded on a Varian 90-MHz spectrometer in the indicated solvent and are reported in ppm downfield from

(17) The brevianamides have the characteristic 3-oxindole chromophore, see: Birch, A. J.; Wright, J. J. *Chem. Commun.* **1967**, 644.

(18) Witkop, B.; Patrick, J. B. *J. Am. Chem. Soc.* **1951**, *73*, 2188. Witkop, B. *J. Am. Chem. Soc.* **1950**, *72*, 614. Beer, R. J. S.; McGrath, L.; Robertson, A. *J. Chem. Soc.* **1950**, 2118.

(19) O'Rell, D. D.; Lee, F. G. H.; Boekelheide, V. *J. Am. Chem. Soc.* **1972**, *94*, 3205.

(20) Pummerer approach: Bosch, J.; Amat, M. *Tetrahedron Lett.* **1985**, *26*, 4951. Amat, M.; Linares, A.; Bosch, J. *J. Org. Chem.* **1990**, *55*, 6299.

(21) Amat, M.; Alvarez, M.; Bonjoch, J.; Casamitjana, N.; Grâcia, J.; Lavilla, R.; Garcias, X.; Bosch, J. *Tetrahedron Lett.* **1990**, *31*, 3453. Smallcombe, S. H.; Caserio, M. C. *J. Am. Chem. Soc.* **1971**, *93*, 5826.

TMS. Elemental analyses were performed by Midwest Microlab in Indianapolis, IN. Routine monitoring of reactions was performed using Merck 60 F_{254} silica gel, aluminum-backed TLC plates. Preparative-layer chromatography was performed using Merck 60H F_{254} silica gel, glass supported plates. Flash column chromatography was performed with the indicated solvents on Merck 60H F_{254} silica gel.

Air- and moisture-sensitive reactions were performed under usual inert atmosphere techniques. Reactions requiring anhydrous conditions were performed in glassware dried by a Bunsen flame or in an oven at 140 °C, then cooled under argon, and performed under a blanket of argon. Solvents and commercial reagents were dried and purified before use: Et_2O and THF were distilled from sodium benzophenone ketyl; CH_2Cl_2 and benzene were distilled from calcium hydride under argon.

Resolution of Cyclohexanone-3-acetic Acid. Cyclohexanone-3-acetic acid (1.56 g, 10 mmol) and (+)-quinine (3.24 g, 10 mmol) were dissolved in warm absolute ethanol (10 mL) and cooled to −20 °C. After 48 h the precipitated salt was filtered, washed with ethanol/ether (1:3), and dried to give 1.83 g of a salt, mp 139.5–142 °C, $[\alpha]_D^{23}$ −127.2°. Two recrystallizations from absolute ethanol gave mp 143–144 °C, $[\alpha]_D^{23}$ − 130.2°. The mother liquors were concentrated and the residue recrystallized as above to give a diastereomeric salt, 123–124 °C, $[\alpha]_D^{23}$ −118°. Each salt was separately treated with aqueous ammonium hydroxide to give (−)-cyclohexanone-3-acetic acid, mp 58–59.5 °C, $[\alpha]_D^{23}$ −13.2° (1.01 abs EtOH), and (+)-cyclohexanone-3-acetic acid, mp 56–59 °C, $[\alpha]_D^{23}$ +11.4° (1.01 abs EtOH).

1,2,3,4-Tetrahydro-9*H*-carbazole-2-acetic Acid (7). A mixture of phenylhydrazine hydrochloride (11.95 g, 0.083 mol) and cyclohexanone-3-acetic acid (12.88 g, 0.083 mol) in 80% aqueous acetic acid (200 mL) was heated at reflux for 10 h. The mixture was evaporated in vacuo and the solid residue washed with water (100 mL × 3) and recrystallized from acetic acid to give 7 (14 g, 73%), mp 183–185 °C (lit.[8] mp 182–184 °C).

1,2,3,4-Tetrahydro-2-[(methoxycarbonyl)methyl]-9*H*-carbazole (8). A mixture of 7 (12.6 g, 0.055 mol) in methanol (50 mL), 2,2-dimethoxy propane (70 mL), and concd hydrochloric acid (7 mL) was stirred at 20 °C for 2 h. The mixture was concentrated in vacuo to give a crystalline residue which was dissolved in ethyl acetate (150 mL), washed with aqueous $NaHCO_3$ solution, dried ($MgSO_4$), and evaporated in vacuo to give 8 (13.31 g, 99.6%), mp 95–97 °C (lit.[8] mp 94–95 °C).

1,2,3,4-Tetrahydro-2-[(methoxycarbonyl)methyl]-4-oxocarbazole (9). To a mixture of 8 (5.94 g) in tetrahydrofuran (195 mL) and water (15 mL), under an atmosphere of nitrogen, at 0 °C, was added dichlorodicyanoquinone (11.22 g, in 75 mL of deoxygenated THF). After 2 h at 0 °C the mixture was evaporated in vacuo and the residue dissolved in ethyl acetate and washed with aqueous $NaHCO_3$ solution until no more DDQH was extracted. The ethyl acetate layer was dried ($MgSO_4$) and evaporated to give 9 (5.23 g, 85%): mp 221–222 °C; IR (Nujol) 3000, 1730, 1625, 1600, 1580 cm^{-1}; ^1H NMR (90 MHz, CD_3OD) δ 3.4–2.3 (7 H, m), 3.7 (3 H, s), 7.4–7.1 (4 H, m), 8.2 (1 H, m). Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.15; H, 6.21; N, 5.41.

1,2,3,4-Tetrahydro-4-oxo-9-[(*p*-methoxyphenyl)sulfonyl]carbazole-2-acetic Acid (11). The ester 9 (2.623 g, 10.2 mmol) in dichloromethane (90 mL) was cooled to 0 °C. To this solution was added ice-cold 30% NaOH (60 mL) followed by tetra-*N*-benzylammonium chloride (114 mg, 0.5 mol %) and (*p*-methoxyphenyl)sulfonyl chloride (2.4 g, 11.6 mmol). The mixture was stirred vigorously for 1 h and the organic layer separated, washed with 2 N HCl (20 mL), dried ($MgSO_4$), and evaporated in vacuo to give a brown oil 10. The oil was dissolved in tetrahydrofuran (40 mL) and lithium hydroxide (1.2 g, in 40 mL of water) added. The mixture was stirred for 1 h at 23 °C and evaporated. The residue was acidified with 3 N HCl and extracted with ethyl acetate (3 × 20 mL). The dried extracts were filtered through charcoal and evaporated to give 11 (4.9 g, 99.5%): mp 161–163 °C (MeOH); IR ($CHCl_3$) 3400–2800, 1710, 1665, 1600, 1580 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 2.60–2.30 (3 H, m), 3.20–2.70 (2 H, m), 3.60 (1 H, m), 3.80 (3 H, s), 6.85 (2 H, d, J = 9 Hz), 7.3 (2 H, m), 7.8 (2 H, d, J = 9 Hz), 8.15 (2 H, m). Anal. Calcd for $C_{21}H_{19}NO_6S$: C, 61.01; H, 4.63; N, 3.39. Found: C, 61.13; H, 4.79; N, 3.52.

1,2,3,4-Tetrahydro-4-oxo-9-[(*p*-methoxyphenyl)sulfonyl]carbazole-2-acetamide (12). To a solution of ethyl chloroformate (208 mg, 0.193 mmol) in dichloromethane (4 mL) at 0 °C was added dropwise a solution of the acid 11 (794 mg, 0.193 mmol) followed by triethylamine (390 mg, in 5 mL of CH_2Cl_2). The solution was stirred at 0 °C for 1 h and quenched with 58% aqueous ammonium hydroxide (4 mL). After 30 min of vigorous stirring the tan precipitate was filtered and the filtrate extracted with dichloromethane (20 mL). The organic material was washed with 2 N HCl (20 mL) and brine (20 mL) and dried ($MgSO_4$). Evaporation of the extract in vacuo gave 12 (673 mg, crude) as a tan solid which was crystallized from methanol to give 12 (615 mg, 77%): mp 214–214.5 °C (MeOH); IR ($CHCl_3$) 3420, 2940, 1670, 1650, 1600, 1580 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 2.45 (2 H, m), 2.71 (1 H, dd, J = 17, 4 Hz), 2.90 (1 H, m), 3.10 (1 H, dd, J = 18, 9 Hz), 3.69 (1 H, dd, J = 18, 5 Hz), 3.82 (3 H, s), 5.60 (2 H, m), 6.69 (2 H, d, J = 9 Hz), 7.35 (2 H, m), 7.86 (2 H, d, J = 9 Hz), 8.15 (1 H, d, J = 7 Hz), 8.22 (1 H, d, J = 7 Hz). Anal. Calcd for $C_{21}H_{20}N_2O_5S$: C, 61.15; H, 4.89; N, 6.79. Found: C, 61.35; H, 4.93; N, 6.53.

2,3,4,5,6,7-Hexahydro-1,5-methano-3-oxo-7-[(*p*-methoxyphenyl)sulfonyl]-1*H*-azocino[4,3-*b*]indole (14). The ketoamide 12 (415 mg, 1.00 mmol), in methanol (5 mL) and tetrahydrofuran (5 mL), was treated with sodium borohydride (190 mg, 5.02 mmol) and the mixture stirred at 21 °C for 2 h. The mixture was evaporated and the residue partitioned between chloroform (50 mL) and water (50 mL). The aqueous phase was extracted with an additional portion chloroform (50 mL), and the combined organic extracts dried (Na_2SO_4) and evaporated in vacuo to give the alcohol 13 (415 mg, 100%): IR ($CHCl_3$) 3500–2700, 1710, 1600, 1580 cm^{-1}: ^1H NMR (90 MHz, $CDCl_3$) δ 2.25 (2 H, m), 2.48–2.32 (3 H, m), 2.77 (1 H, dd, J = 9, 2 Hz), 3.24 (1 H, dd, J = 9, 4 Hz), 3.80 (3 H, s), 5.49 (1 H, bs), 5.74 (1 H, bs), 6.86 (2 H, d, J = 9 Hz), 7.31–7.21 (2 H, m), 7.69 (1 H, d, J = 8 Hz), 7.72 (2 H, d, J = 9 Hz), 8.14 (1 H, d, J = 8 Hz).

To a solution of the alcohol 13 (415 mg) in dichloromethane (10 mL) at 0 °C was added dropwise trifluoroacetic acid (171 mg, 1.5 mmol, 115 μL). The solution was warmed to 25 °C and allowed to stand for 12 h. The solvent was removed under reduced pressure to give a tan foam. The foam was crystallized from methanol to give 14 (358 mg, 90%): mp 241.5–242 °C (MeOH); IR ($CHCl_3$) 3400, 3000, 2955, 1660, 1600, 1590 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 2.08 (1 H, d, J = 14 Hz), 2.22 (2 H, d, J = 14 Hz), 2.71 (2 H, s), 3.18 (1 H, d, J = 18 Hz), 3.32 (1 H, dd, J = 18 and 5 Hz), 3.80 (3 H, s), 4.70 (1 H, bs), 6.88 (2 H, d, J = 9 Hz), 7.36–7.26 (2 H, m), 7.46 (1 H, d, J = 8 Hz), 7.73 (2 H, d, J = 9 Hz), 8.16 (1 H, d, J = 8 Hz). Anal. Calcd for $C_{21}H_{18}N_2O_4S$: C, 63.62; H, 5.08; N, 7.06. Found: C, 63.40; H, 4.97; N, 6.99.

2-[(Phenylthio)acetyl]-2,3,4,5,6,7-hexahydro-1,5-methano-7-[(*p*-methoxyphenyl)sulfonyl]-1*H*-azocino[4,3-*b*]indole (22). Diborane (1.2 mL of a 1.0 M solution in tetrahydrofuran) was added to a solution of the amide 14 (242 mg, 0.61 mmol) in tetrahydrofuran (5 mL). The mixture was heated at reflux for 2 h. The cooled solution was treated with 2 N sodium hydroxide (1 mL) and extracted with ethyl acetate (3 × 15 mL). Evaporation of the dried solution ($MgSO_4$) in vacuo gave a light yellow oil which was chromatographed over silica gel eluting with ethyl acetate/hexane (1:4) to give the amine 21 (131 mg, 56%). A solution of the amine 21 (110 mg, 0.29 mmol) in dichloromethane (1 mL) was treated with (phenylthio)acetyl chloride (54 mg, 0.29 mmol) and triethylamine (29 mg) and the mixture stirred at 21 °C for 12 h. The mixture was poured into dichloromethane (20 mL) and washed with 2 N HCl (1 mL). Evaporation of the dried ($MgSO_4$) extract gave a yellow oil which was chromatographed over silica gel eluting with ethyl acetate/hexane (1:3) to give 22 (132 mg, 96%): mp 172–173 °C (MeOH); IR ($CHCl_3$) 3050, 2940, 1633, 1600, 1580 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.65–1.55 (2 H, m), 2.12–1.78 (3 H, m), 2.51 (1 H, bs), 2.77 (1 H, dt, J = 13, 3 Hz), 3.11 (1 H, d, J = 19 Hz), 3.23 (1 H, dd, J = 19, 7 Hz), 3.44 (1 H, dd, J = 13, 5 Hz), 3.60 (2 H, s), 3.77 (3 H, s), 6.01 (1 H, bt), 6.84 (2 H, d, J = 9 Hz), 7.18–7.30 (4 H, m), 7.33–7.25 (3 H, m), 7.52 (1 H, d, J = 8 Hz), 7.71 (2 H, d, J = 9 Hz), 8.12 (1 H, d, J = 8 Hz). Anal. Calcd for $C_{29}H_{28}N_2O_4S_2$: C, 65.40; H, 5.30; N, 5.26. Found: C, 65.28; H, 5.15; N, 5.20.

***N*-[2′-(Phenylthio)ethyl]-1,2,3,4-tetrahydro-4-oxo-9-[(*p*-methoxyphenyl)sulfonyl]carbazole-2-acetamide (24).** To a

solution of ethyl chloroformate (263 mg, 2.42 mmol) in tetrahydrofuran (5.0 mL) at 0 °C was added a solution of the acid **11** (1.0 g, 2.42 mmol) in tetrahydrofuran (5.0 mL) and triethylamine (248 mg, 2.45 mmol). The mixture was stirred for 2 h at 0 °C and 2-[(phenylthio)ethyl]amine (370 mg, 2.42 mmol) added. After 12 h at 25 °C the mixture (now a slurry) was diluted with ethyl acetate (25 mL) and washed with water (10 mL) and saturated brine (10 mL). The organic extract was dried ($MgSO_4$) and evaporated in vacuo to give a residue which was purified by chromatography over silica gel eluting with EtOAc/hexane to yield **24** (1.21 g, 90%) as a clear glass: IR ($CHCl_3$) 3420, 2980, 2920, 1720, 1650, 1580 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 2.31 (2 H, t, J = 6 Hz), 2.37 (1 H, dd, J = 16, 11 Hz), 2.65 (1 H, dd, J = 16, 4 Hz), 2.85 (1 H, m), 3.05 (1 H, dd, J = 18, 9 Hz), 3.10 (2 H, t, J = 6 Hz), 3.52 (2 H, q, J = 6 Hz), 3.62 (1 H, dd, J = 18, 5 Hz), 3.80 (3 H, s), 5.95 (1 H, m), 6.95 (2 H, d, J = 9 Hz), 7.20 (1 H, t, J = 7 Hz), 7.41–7.26 (6 H, m), 7.83 (2 H, d, J = 9 Hz), 8.14 (1 H, d, J = 8 Hz), 8.21 (1 H, d, J = 8 Hz). Anal. Calcd for $C_{29}H_{28}N_2O_5S_2$: C, 63.48; H, 5.14; N, 5.11. Found: C, 63.30; H, 5.15; N, 5.20.

2-[2′-(Phenylthio)ethyl]-2,3,4,5,6,7-hexahydro-1,5-methano-3-oxo-7-[(*p*-methoxyphenyl)sulfonyl]-1*H*-azocino[4,3-*b*]indole (26). The ketoamide **24** (367 mg, 0.67 mmol) in methanol (2 mL) was treated with sodium borohydride (83 mg, 2.2 mmol) and stirred at 21 °C for 1 h. Workup as for **14** gave the alcohol **25** (372 mg, 100%) as a colorless foam: IR ($CHCl_3$) 3500–3200, 3000, 2940, 1660, 1600, 1580 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.40 (1 H, q, J = 8 Hz), 2.15 (1 H, d, J = 10 Hz), 2.21 (2 H, t, J = 5 Hz), 2.35 (1 H, m), 2.66 (1 H, dd, J = 18, 8 Hz), 3.03 (2 H, t, J = 7 Hz), 3.13 (1 H, dd, J = 18, 5 Hz), 3.42 (2 H, q, J = 7 Hz), 3.75 (3 H, s), 4.90 (1 H, t, J = 7 Hz), 6.47 (1 H, t, J = 6 Hz), 6.80 (2 H, d, J = 9 Hz), 7.15 (1 H, d, J = 3 Hz), 7.18 (1 H, d, J = 3 Hz), 7.25 (4 H, m), 7.68 (2 H, d, J = 9 Hz), 8.08 (1 H, d, J = 8 Hz). The hydroxamide **25** (362 mg, 0.66 mmol) in dichloromethane (3.3 mL) at 0 °C was treated with trifluoroacetic acid (75 mg, 0.66 mmol). After 2.5 h at 0 °C the mixture evaporated and the residue chromatographed over silica gel eluting with ethyl acetate/hexane (1:1) to give **26** (337 mg, 96%) as a colorless foam: IR ($CHCl_3$) 3000, 2940, 1632, 1600, 1580 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.93 (1 H, d, J = 13 Hz), 2.25–2.15 (2 H, m), 2.79 (1 H, bs), 2.86 (1 H, dd, J = 18, 9 Hz), 3.33–3.05 (5 H, m), 3.78 (3 H, s), 4.10–4.00 (1 H, m), 4.57 (1 H, bt), 6.86 (1 H, d, J = 9 Hz), 6.94 (1 H, d, J = 8 Hz), 7.12 (1 H, t, J = 7 Hz), 7.28–7.22 (2 H, m), 7.34 (2 H, t, J = 7 Hz), 7.42 (2 H, d, J = 7 Hz), 7.68 (2 H, d, J = 9 Hz), 8.12 (1 H, d, J = 8 Hz). Anal. Calcd for $C_{29}H_{28}N_2O_4S_2$: C, 65.39; H, 5.30; N, 5.26. Found: C, 65.03; H, 5.21; N, 4.98.

2-[2′-(Phenylthio)ethyl]-2,3,4,5,6,7-hexahydro-1,5-methano-3-oxo-1*H*-azocino[4,3-*b*]indole (27). The protected indole derivative **26** (222 mg, 0.42 mmol) in methanol/tetrahydrofuran (10 mL, 1:1) was treated with excess 4% sodium–mercury amalgam at 24 °C for 2 h. The mixture was filtered and evaporated in vacuo to give a solid. The solid was dissolved in ethyl acetate (10 mL) and washed with water (2 × 10 mL) and brine (2 × 10 mL). The dried (MgSO4) organic layer was evaporated in vacuo to give **27** (144 mg, 95%): mp 127–128 °C (MeOH); IR ($CHCl_3$) 3460, 3055, 2988, 2920, 1625, 1580 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 2.05 (1 H, d, J = 15 Hz), 2.32–2.24 (2 H, m), 2.71 (1 H, d, J = 17 Hz), 2.78 (1 H, bs), 2.89 (1 H, dd, J = 19, 8 Hz), 3.38–3.08 (4 H, m), 4.16–4.07 (1 H, t, J = 3 Hz), 7.01 (1 H, d, J = 7 Hz), 7.09 (2 H, d, J = 8 Hz), 7.28–7.24 (2 H, m), 7.36 (2 H, t, J = 8 Hz), 7.48 (2 H, d, J = 8 Hz), 7.92 (1 H, bs). Anal. Calcd for $C_{22}H_{22}N_2O_2S$: C, 72.90; H, 6.12; N, 7.73. Found: C, 72.79; H, 6.09; N, 7.42.

(*E*)- and (*Z*)-2-[2′-(Phenylthio)ethylene]-2,3,4,5,6,7-hexahydro-1,5-methano-3-oxo-7-[(*p*-methoxyphenyl)sulfonyl]-1*H*-azocino[4,3-*b*]indole (29). To a solution of the sulfide **26** (149 mg, 0.28 mmol) in dichloromethane (1 mL) and 10% aqueous $NaHCO_3$ (1 mL) at 0 °C was added *m*-chloroperoxybenzoic acid (53 mg, 0.28 mmol) in three portions over 15 min. The dichloromethane layer was separated, dried (Na_2SO_4), and evaporated in vacuo to give the diastereomeric sulfoxides (1:1), which were used directly in the next step.

A solution of the sulfoxides (40 mg, 0.074 mmol) in dichloromethane (500 μL) at 0 °C was treated with trifluoroacetic acid anhydride (78 mg, 0.37 mmol). After 30 min (disappearance of the sulfoxides by TLC), chlorobenzene (2 mL) was added and the mixture heated at 120 °C for 1 h then heated at reflux for 4 h. Evaporation of the solvent in vacuo and purification of the residue by chromatography over silica gel eluting with ethyl acetate/hexane (1:1) gave (*E*)-**29** (28 mg, 72%): IR ($CHCl_3$) 3050, 2940, 1645, 1600, 1590 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 2.15 (1 H, d, J = 13 Hz), 2.25 (1 H, d, J = 19 Hz), 2.30 (1 H, m), 2.88 (1 H, bs), 3.04 (1 H, dd, J = 19, 9 Hz), 3.21 (1 H, dd, J = 18, 2 Hz), 3.28 (1 H, dd, J = 18, 5 Hz), 3.82 (3 H, s), 5.16 (1 H, bs), 6.38 (1 H, d, J = 14 Hz), 6.92 (2 H, d, J = 9 Hz), 7.43–7.17 (7 H, m), 7.47 (1 H, d, J = 7 Hz), 7.58 (1 H, d, J = 14 Hz), 7.75 (2 H, d, J = 9 Hz), 8.18 (1 H, d, J = 8 Hz). Anal. Calcd for $C_{29}H_{26}N_2O_4S_2$: C, 65.64; H, 4.94; N, 5.28. Found: C, 65.86; H, 5.19; N, 5.40.

(*Z*)-**29** (11 mg, 25%): IR ($CHCl_3$) 3050, 2940, 1645, 1600, 1590 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 2.15 (1 H, d, J = 13 Hz), 2.25 (1 H, d, J = 19 Hz), 2.30 (1 H, m), 2.88 (1 H, bs), 3.04 (1 H, dd, J = 19, 9 Hz), 3.21 (1 H, dd, J = 18, 2 Hz), 3.28 (1 H, dd, J = 18, 5 Hz), 3.82 (3 H, s), 5.16 91 H, bs), 6.16 (1 H, d, J = 8 Hz), 6.62 (1 H, d, J = 8 Hz), 6.87 (2 H, d, J = 9 Hz), 7.35–7.22 (7 H, m), 7.51 (1 H, d, J = 8 Hz), 7.73 (2 H, d, J = 9 Hz), 8.14 (1 H, d, J = 8 Hz). Anal. Calcd for $C_{29}H_{26}N_2O_4S_2$: C, 65.64; H, 4.94; N, 5.28. Found: C, 65.72; H, 5.05; N, 5.24.

***N*-(2′,2′-Dimethoxyethyl)-1,2,3,4-tetrahydro-4-oxo-9-[(*p*-methoxyphenyl)sulfonyl]carbazole-2-acetamide (30).** To a solution of ethyl chloroformate (109 mg, 1.00 mmol) in dichloromethane (2.0 mL) at 0 °C was added a solution of the acid **11** (455 mg, 0.91 mmol) in dichloromethane (2.0 mL) and triethylamine (202 mg, 2.0 mmol). The mixture was stirred for 2 h at 0 °C and 2-aminoacetaldehyde dimethyl acetal (110 μL) added. After 12 h at 25 °C the mixture (now a slurry) was diluted with ethyl acetate (25 mL) and washed with water (10 mL) and saturated brine (10 mL). The organic extract was dried ($MgSO_4$) and evaporated in vacuo to give a residue which was purified by chromatography over silica gel eluting with EtOAc/hexane to yield **30** (287 mg, 63%) as a clear glass: IR ($CHCl_3$) 3440, 3000, 2942, 2820, 1663, 1598, 1580 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 2.45–2.35 (3 H, m), 2.71 (1 H, dd, J = 17, 4 Hz), 2.90 (1 H, m), 3.10 (1 H, dd, J = 18, 9 Hz), 3.41 (6 H, s), 3.44 (2 H, m), 3.69 (1 H, dd, J = 18, 5 Hz), 3.82 (3 H, s), 4.42 (1 H, m), 5.63 (1 H, m), 6.95 (2 H, d, J = 9 Hz), 7.35 (2 H, m), 7.86 (2 H, d, J = 9 Hz), 8.15 (1 H, d, J = 7 Hz), 8.22 (1 H, d, J = 7 Hz). Anal. Calcd for $C_{25}H_{28}N_2O_7S$: C, 59.99; H, 5.64; N, 5.60. Found: C, 59.70; H, 5.55; N, 5.36.

2-(2′,2′-Dimethoxyethyl)-2,3,4,5,6,7-hexahydro-1,5-methano-3-oxo-7-[(*p*-methoxyphenyl)sulfonyl]-1*H*-azocino[4,3-*b*]indole (32). The ketoamide **30** (287 mg, 0.57 mmol) in methanol (4 mL) was treated with sodium borohydride (105 mg, 2.8 mmol) and stirred at 21 °C for 1 h. Workup as for **14** gave the alcohol **31** (288 mg, 100%) as a colorless foam: IR ($CHCl_3$) 3440, 3000, 2940, 1665, 1600, 1580 cm^{-1}.

The hydroxyamide **31** (288 mg, 0.57 mmol) in dichloromethane (3.3 mL) at 0 °C was treated with trifluoroacetic acid (110 μL). After 12 h at 0 °C the mixture evaporated and the residue was chromatographed over silica gel eluting with ethyl acetate/hexane (1:1) to give **32** (271 mg, 98%) as a colorless foam which was crystallized from methanol: mp 167–169 °C (MeOH); IR ($CHCl_3$) 3000, 2940, 2820, 1625, 1600, 1580 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.98 (1 H, d, J = 13 Hz), 2.19 (1 H, d, J = 19 Hz), 2.24 (1 H, dt, J = 13, 3 Hz), 2.83 (1 H, bs), 2.90 (1 H, dd, J = 18, 9 Hz), 2.98 (1 H, dd, J = 14, 8 Hz), 3.14 (1 H, d, J = 19 Hz), 3.28 (1 H, dd, J = 19 and 6 Hz), 3.45 (3 H, s), 3.55 (3 H, s), 3.82 (3 H, s), 4.17 (1 H, dd, J = 14, 3 Hz), 4.51 (1 H, dd, J = 8, 3 Hz), 4.85 (1 H, bt), 6.85 (2 H, d, J = 9 Hz), 7.35–7.25 (2 H, m), 7.57 (1 H, d, J = 8 Hz), 7.73 (2 H, d, J = 9 Hz), 8.14 (1 H, d, J = 8 Hz). Anal. Calcd for $C_{25}H_{28}N_2O_6S$: C, 61.97; H, 5.82; N, 5.78. Found: C, 61.51; H, 5.75; N, 5.89.

2-[2′,2′-Bis(methylthio)ethyl]-2,3,4,5,6,7-hexahydro-1,5-methano-3-oxo-7-[(*p*-methoxyphenyl)sulfonyl]-1*H*-azocino[4,3-*b*]indole (33). To a solution of **32** (648 mg, 1.29 mmol) in tetrahydrofuran (10 mL) was added boron trifluoride etherate (0.25 mL). After stirring for 15 min at 21 °C methanethiol was bubbled through the mixture for 15 min. After a further 3 h at 21 °C the mixture was poured onto saturated aqueous sodium bicarbonate solution (10 mL) and extracted with ethyl acetate (3 × 40 mL). The dried ($MgSO_4$) extract was evaporated in vacuo and the residue purified by chromatography over silica gel eluting

with ethyl acetate/hexane (3:1) to give **33** (534 mg, 80%): mp 150–152 °C (MeOH); IR ($CHCl_3$) 3000, 2920, 1627, 1598, 1580 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 2.0 (1 H, d, J = 13 Hz), 2.17 (3 H, s), 2.23 (3 H, s), 2.44 (1 H, dt, J = 13, 3 Hz), 2.84 (1 H, bs), 2.92 (1 H, dd, J = 19, 9 Hz), 3.10 (1 H, dd, J = 19, 9 Hz), 3.14 (1 H, d, J = 19 Hz), 3.30 (1 H, dd, J = 19, 6 Hz), 3.80 (3 H, s), 4.11 (1 H, dd, J = 9, 7 Hz), 4.35 (1 H, dd, J = 14, 6 Hz), 4.68 (1 H, bt), 6.88 (2 H, d, J = 9 Hz), 7.35–7.25 (2 H, m), 7.45 (1 H, d, J = 8 Hz), 7.72 (2 H, d, J = 9 Hz), 8.16 (1 H, d, J = 8 Hz). Anal. Calcd for $C_{25}H_{28}N_2O_4S_3$: C, 58.11; H, 5.46; N, 5.42. Found: C, 58.14; H, 5.29; N, 5.60.

2-(Formylmethyl)-2,3,4,5,6,7-hexahydro-1,5-methano-3-oxo-7-[(*p*-methoxyphenyl)sulfonyl]-1*H*-azocino[4,3-*b*]indole (34). A solution of the dimethylthio compound **33** (25 mg) in dichloromethane 0.5 mL) was treated with (dimethylthio)-sulfonium tetrafluoroborate (10 mg). After stirring for 48 h at 21 °C, water was added to the mixture and it was extracted with dichloromethane (3 × 5 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue crystallized on standing and was recrystallized from ethyl acetate to give **34** (21 mg, 100%) as colorless crystals: mp 180–181 °C (MeOH); IR ($CHCl_3$) 2907, 2828, 1735, 1630, 1601, 1580 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 2.0 (1 H, d, J = 13 Hz), 2.24 (1 H, d, J = 18 Hz), 2.44 (1 H, d, J = 13 Hz), 2.96–2.82 (2 H, m), 3.15 (1 H, d, J = 19 Hz), 3.27 (1 H, dd, J = 19, 5 Hz), 3.76 (3 H, s), 3.89 (1 H, d, J = 19 Hz), 4.57–4.45 (2 H, m), 6.84 (2 H, d, J = 9 Hz), 7.33–7.17 (2 H, m), 7.67 (2 H, d, J = 9 Hz), 8.15 (1 H, d, J = 8 Hz), 9.32 (1 H, s). Anal. Calcd for $C_{23}H_{22}N_2O_5S$: C, 63.00; H, 5.06; N, 6.39. Found: C, 62.84; H, 5.18; N, 5.32.

2-[2′,2′-Bis(methylthio)ethyl]-2,3,4,5,6,7-hexahydro-1,5-methano-7-[(*p*-methoxyphenyl)sulfonyl]-1*H*-azocino[4,3-*b*]indole (45a). To a solution of the amide **33** (147 mg, 0.285 mmol) in tetrahydrofuran (0.5 mL) was added diborane (1 M in tetrahydrofuran, 0.75 mL). The mixture was stirred at 21 °C for 2 h and quenched with 2 N sodium hydroxide (1 mL). The mixture was extracted with ethyl acetate (3 × 5 mL), dried (Na_2SO_4), and evaporated in vacuo to give a residue which was purified by chromatography over silica gel eluting with ethyl acetate/hexane (1:1) to give **45a** (110 mg, 77%): IR ($CHCl_3$) 2913, 1600, 1580 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.52 (1 H, d, J = 8 Hz), 1.68 (1 H, d, J = 13 Hz), 1.75 (2 H, bs), 2.11 (3 H, s), 2.17 (3 H, s), 2.18 (1 H, dd, J = 10, 3 Hz), 2.37 (1 H, dd, J = 13, 6 Hz), 2.42 (1 H, m), 2.58 (1 H, m), 2.74 (1 H, dd, J = 13, 8 Hz), 3.02 (1 H, d, J = 19 Hz), 3.19 (1 H, dd, J = 19, 7 Hz), 3.81 (3 H, s), 3.85 (1 H, m), 4.08 (1 H, bt), 6.87 (2 H, d, J = 9 Hz), 7.25 (2 H, m), 7.43 (1 H, d, J = 8 Hz), 8.16 (1 H, d, J = 8 Hz). Anal. Calcd for $C_{25}H_{30}N_2O_3S_3$: C, 59.73; H, 6.02; N, 5.57. Found: C, 59.66; H, 5.80; N, 5.45.

2-[2′-(Phenylthio)ethyl]-2,5,6,7-tetrahydro-1,5-methano-3-chloro-4-formyl-7-[(*p*-methoxyphenyl)sulfonyl]-1*H*-azocino[4,3-*b*]indole (35). The ketoamide **26** (322 mg, 0.6 mmol) in dimethylformamide (1.5 mL) at 0 °C was treated with a solution of phosphorus oxychloride (0.6 mL) in dimethylformamide (2 mL). After 1.5 h at 25 °C the mixture was quenched with 2 N NaOH until the pH reached 9–10. The solution was extracted with dichloromethane (3 × 10 mL) and the extract washed with water until neutral. The dried (Na_2SO_4) extract was evaporated in vacuo to give **35** (318 mg, 90.8%) as a thick oil: IR (neat) 1630 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.9 (2 H, bs), 3.02 (1 H, dd, J = 18, 5 Hz), 3.15 (2 H, t, J = 7.2 Hz), 3.33 (1 H, d, J = 18 Hz), 3.48 (1 H, bs), 3.61 (1 H, m), 3.76 (3 H, s), 4.1 (1 H, m), 4.69 (1 H, s), 6.80 (2 H, d, J = 9 Hz), 6.99 (1 H, d, J = 7.6 Hz), 7.15 (1 H, t, J = 7.6 Hz), 7.29–7.30 (4 H, m), 7.36 (2 H, t, J = 7.2 Hz), 7.44 (2 H, d, J = 7.6 Hz), 7.62 (2 H, d, J = 8.6 Hz), 8.15 (1 H, d, J = 8.3 Hz), 9.8 (1 H, s). Anal. Calcd for $C_{30}H_{28}ClN_2O_4S_2$: C, 62.11; H, 4.86; N, 4.83. Found: C, 61.86; H, 4.70; N, 4.85.

Pyrazole 36. The chloroaldehyde **35** (100 mg, 0.17 mmol) in acetic acid (1.5 mL0 was treated with sodium acetate (100 mg) and phenylhydrazine hydrochloride (50 mg, 0.25 mmol). The mixture was heated at reflux for 1.5 h, cooled to room temperature, and extracted with dichloromethane (3 × 10 mL). The dried (Na_2SO_4) extract was evaporated in vacuo to give **36** (93 mg, 85%): mp 124–126 °C (ethyl acetate/petrol); IR ($CHCl_3$) 2900, 1600 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.80 (1 H, bd), 2.06 (1 H, bd), 3.0–3.2 (5 H, m), 3.38 (3 H, s), 3.40–3.44 (2 H, m), 4.49 (1 H, bs), 6.58 (2 H, d, J = 9.1 Hz), 6.91 (2 H, m), 7.1 (3 H, m), 7.2–7.4 (9 H, m), 7.44 (1 H, s), 7.52 (1 H, m), 8.11 (1 H, m). Anal. Calcd for $C_{36}H_{32}N_4O_3S_2$: C, 68.33; H, 5.10; N, 8.85. Found: C, 68.20; H, 5.01; N, 8.65.

Isoxazole 37. The chloroaldehyde **35** (188 mg) in dioxane (3 mL) was treated with hydroxylamine hydrochloride (75 mg) and pyridine (0.3 mL). The mixture was heated at 90 °C for 1.5 h and evaporated in vacuo to give a residue which was crystallized from ethyl acetate/petrol to give **37** (155 mg, 80%): mp 221–223 °C dec; IR ($CHCl_3$) 3590, 3300, 1600, 1580 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.96 (1 H, m), 3.10 (3 H, s), 3.45 (3 H, m), 3.80 (3 H, s), 4.0 (1 H, m), 4.65 (1 H, bs), 6.90 (2 H, d), 7.2–7.5 (8 H, m), 7.77 (2 H, m), 8.04 (1 H, s), 8.2 (1 H, d). Anal. Calcd for $C_{30}H_{27}N_3O_3S_2$: C, 64.61; H, 4.88; N, 7.53. Found: C, 64.53; H, 4.66; N, 7.40.

2-(2′-Hydroxyethyl)-2,3,4,5,6,7-hexahydro-1,5-methano-3-oxo-7-[(*p*-methoxyphenyl)sulfonyl]-1*H*-azocino[4,3-*b*]indole (38). To the aldehyde **34** (248 mg) in tetrahydrofuran/methanol (2 mL, 1:1) was added sodium borohydride (43 mg, 1.14 mmol). After stirring the mixture for 4 h at 21 °C, standard workup gave **38** (221 mg, 89%): mp 210–211 °C ($CHCl_3$/hexane); IR ($CHCl_3$) 3450–3160, 2930, 1613, 1601 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 2.01 (1 H, d, J = 13 Hz), 2.22 (1 H, d, J = 19 Hz), 2.29 (1 H, dt, J = 13, 3 Hz), 2.84 (1 H, bs), 2.91 (1 H, dd, J = 19, 9 Hz), 3.29 (1 H, dd, J = 19, 6 Hz), 3.47–3.37 (1 H, m), 3.60 (1 H, t, J = 5 Hz), 3.77–3.70 (2 H, m), 3.80 (3 H, s), 3.97–3.88 (1 H, m), 4.68 (1 H, bt), 6.88 (2 H, d, J = 9 Hz), 7.33–7.23 (2 H, m), 7.45 (1 H, d, J = 8 Hz), 7.72 (2 H, d, J = 9 Hz), 8.16 (1 H, d, J = 8 Hz). Anal. Calcd for $C_{23}H_{24}N_2O_5S$: C, 62.71; H, 5.49; N, 6.36. Found: C, 62.48; H, 5.65; N, 6.20.

2-(2′-Hydroxyethyl)-2,3,4,5,6,7-hexahydro-1,5-methano-3-oxo-1*H*-azocino[4,3-*b*]indole (39). The protected indole derivative **34** (2.86 g) in methanol/tetrahydrofuran (50 mL, 1:1) was treated with excess 4% sodium–mercury amalgam at 24 °C for 5 h. The mixture was filtered and evaporated in vacuo to give a solid. The solid was dissolved in ethyl acetate (50 mL) and washed with water (2 × 50 mL) and brine (2 × 50 mL). The dried ($MgSO_4$) organic layer was evaporated in vacuo to give **39** (1.713 g, 97.6%): mp 184–185.5 °C (MeOH); IR ($CHCl_3$) 3400, 3250, 2980, 2925, 1620, 1580 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 2.14–2.16 (1 H, m), 2.32–2.39 (2 H, m), 2.75 (1 H, d, J = 16.8 Hz), 2.84 (1 H, bs), 2.97 (1 H, dd, J = 18.8, 8.1 Hz), 3.18 (1 H, dd, J = 16.8, 5.8 Hz), 3.51–3.59 (1 H, m), 3.92–3.77 (1 H, m), 3.80–3.86 (1 H, m), 3.90–4.0 (1 H, m), 4.74 (1 H, bt), 7.1–7.2 (2 H, m), 7.30–7.34 (1 H, m), 7.49–7.52 (1 H, m), 8.29 (1 H, s). Anal. Calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 70.90; H, 6.55; N, 10.24.

Oxindole 44. To a solution of **39** (202 mg) in pyridine (6.0 mL) at 0 °C was added methanesulfonyl chloride (400 μL) and the mixture stirred at 0 °C for 50 min. The mixture was filtered, extracted with dichloromethane (10 mL), and washed with brine (10 mL). The dried ($MgSO_4$) extract was evaporated in vacuo to give the chloride **40** (187 mg, crude). The chloride **40** was sufficiently unstable towards chromatographic purification that it was used directly.

The chloride (37.5 mg) in dry tetrahydrofuran (6 mL) was treated with potassium hydride (26.8 mg) and hexamethyldisilazane (137 μL). After 16 h at 25 °C the mixture was quenched with aqueous NH_4Cl (10 mL) and extracted into ethyl acetate (15 mL). The dried ($MgSO_4$) extract was evaporated in vacuo to give a greenish yellow oil. The oil was purified by chromatography over silica gel eluting with ethyl acetate/petrol (2:3) to give **44** (29.7 mg, 84%) as yellow fluoresent plates: mp 214 °C dec (MeOH); IR ($CHCl_3$) 1690, 1660, 1650 cm^{-1}; UV (EtOH) λ_{max} 410, 257, 229 nm; ^1H NMR (90 MHz, $CDCl_3$) δ 1.71 (1 H, d, J = 14.6 Hz), 1.79 (1 H, d, J = 12.7 Hz), 2.37 (1 H, ddd, J = 14.5, 7.5, and 1.7 Hz), 2.53–2.62 (2 H, m), 2.67 (1 H, bs), 2.74–2.88 (1 H, m), 3.42 (1 H, d, J = 8.3 Hz), 3.50 (1 H, ddd, J = 13.1, 12.0, 3.5 Hz), 3.73 (1 H, dd, J = 14, 2.8 Hz), 4.51 (1 H, dd, J = 13, 3 Hz), 6.80 (1 H, t, J = 7.5 Hz), 6.89 (1 H, d, J = 8.4 Hz), 7.5 (1 H, t, J = 8.3 Hz), 7.62 (1 H, d, J = 7.8 Hz). Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.42; H, 6.11; N, 10.23.

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Registry No. (±)-7, 137333-36-9; (±)-8, 137333-37-0; (±)-9, 137333-38-1; (±)-10, 137333-39-2; (±)-11, 137333-40-5; (±)-12, 137333-41-6; (±)-13, 137333-42-7; (±)-14, 137333-43-8; (±)-21, 137333-44-9; (±)-22, 137362-83-5; (±)-24, 137333-45-0; (±)-25, 137333-46-1; (±)-26, 137333-47-2; (±)-27, 137333-48-3; (±)-28 (isomer 1), 137333-49-4; (±)-28 (isomer 2), 137333-50-7; (±)-(*E*)-**29**, 137333-51-8; (±)-(*Z*)-**29**, 137333-52-9; (±)-**30**, 137333-53-0; (±)-**31**, 137333-54-1; (±)-**32**, 137333-55-2; (±)-**33**, 137333-56-3; (±)-**33** (deoxo derivative), 137333-57-4; (±)-**34**, 137333-58-5; (±)-**35**, 137333-59-6; (±)-**36**, 137333-60-9; (±)-**37**, 137333-61-0; (±)-**38**, 137333-62-1; (±)-**39**, 137333-63-2; (±)-**40**, 137333-64-3; (±)-**44**, 137333-65-4; $PhNHNH_2$·HCl, 59-88-1; $PhSCH_2COCl$, 7031-27-8; $PhS(CH_2)_2NH_2$, 2014-75-7; $H_2NCH_2CH(OMe)_2$, 22483-09-6; (±)-cyclohexanone-3-acetic acid, 62646-12-2; (+)-cyclohexanone-3-acetic acid, 137333-34-7; (−)-cyclohexanone-3-acetic acid, 137333-35-8.

Efficient Syntheses of Vinyl Ethers of Spiroquinol Ketals and Their High-Yield Photochemical Oxygen-to-Carbon [1,3]-Shift to Spiro-Fused 2,5-Cyclohexadienones

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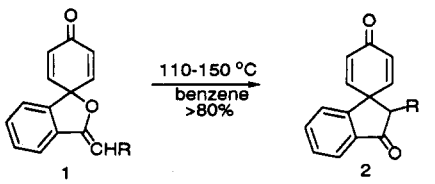
An efficient route to spiroquinol vinyl ethers involves addition of a 1-lithio-2-(trimethylsilyl)acetylene-substituted benzene to the monoethylene ketal of benzoquinone followed by desilylation/cyclization of the resulting product to give vinyl ethers of spiroquinol ketals. A high-yield photochemical conversion of these vinyl ethers of spiroquinol ketals to ketals of spiro-fused 2,5-cyclohexadienones has been developed. A complication in some of these photochemical reactions is formation of secondary products from light absorbed by the product, spiro dienone ketals. This has been solved by conducting the reaction in the presence of piperylene, which quenches the triplet-state chemistry of the product spiro dienone ketal without altering the singlet excited-state chemistry of the quinol ketal vinyl ether. The quantum yield for the photochemical [1,3]-shift reaction in a methyl-substituted vinyl ether is 0.4. Finally, irradiation of quinol spiro vinyl ethers was also observed to give spiro dienones in good yields. Although the spiro dienone is absorbing light in competition with starting quinol vinyl ether in this system, a high yield of product was obtained. The unexpected photochemical stability of these spiro dienones is discussed. The chemistry reported herein establishes an efficient high-yield route to spiro-fused 2,5-cyclohexadienones and their ketals under very mild conditions.

Introduction

Many methods for carbon–carbon bond formation are not applicable to the preparation of quaternary carbon–carbon centers.[1] Our interest in the functionalization chemistry of quinone monoketals[2] prompted investigation of the thermal [1,3] oxygen-to-carbon migration of quinol ethers such as **1**,[3] which are conveniently available from quinone monoketals. Indeed, heating **1** or its non-benzenoid derivatives to 110–150 °C gives the respective dienones **2**.[3-5] Not only is a quaternary carbon–carbon center constructed in high yield but also further reactions of **2** could lead to derivatives of the spiro ring system. Two features of this thermal chemistry could serve as limitations on its application to synthesis. First, the carbonyl groups in **2** are not differentiated chemically. Second, although many functional groups are stable at the temperature required for the thermal rearrangement, thermally sensitive linkages would lead to competing side reactions. Attempts to solve the first problem by thermolysis of the ketal of **1** led to low yields of the ketal of **2**.



1 2

Photochemical activation could be an alternative method of effecting the [1,3] oxygen-to-carbon migration;[6] however, the published work did not suggest that a synthetically useful process would be likely via this method. The photochemistry of vinyl ethers has not been studied extensively. Excitation of ethyl vinyl ether **3** in the gas phase leads to two primary processes:[7] (1) cleavage to an ethyl and a vinyloxy radical and (2) concerted rearrangement to acetaldehyde and ethylene. The example most relevant to the present work is the photorearrangement of α-(benzyloxy)styrenes **4**, which affords β-phenylpropiophenones **5** with quantum yields from 0.04 to 0.11.[8]

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