Formal Total Synthesis of Deserpidine Demonstrating a Versatile Amino-Claisen Rearrangement/Wenkert Cyclization Strategy for the Preparation of Functionalized Yohimbane Ring Systems

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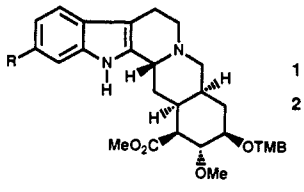
Abstract: A strategy for the synthesis of the functionally complex yohimbane, deserpidine, based upon a combination of zwitterionic amino-Claisen rearrangement and Wenkert cyclization methodologies is presented. Key elements in this plan include (1) the construction of the intermediate *N*-tryptophylisoquinuclidene 7-ketal **19** and its transformation with *tert*-butyl propiolate to the *N*-tryptophylhydroisoquinoline enone **22**, (2) stereocontrolled introduction of the E-ring C-16 ester, C-17 methoxyl, and C-18 benzoate functionality, and (3) Wenkert cyclization of the *N*-tryptophyltetrahydronicotinate containing intermediate **30** to produce the yohimbane **39**. A formal total synthesis of deserpidine is then accomplished by preparation of the isodeserpidine related C-18-alcohol **42**, an advanced intermediate in Szantay's previous total synthesis of this target.

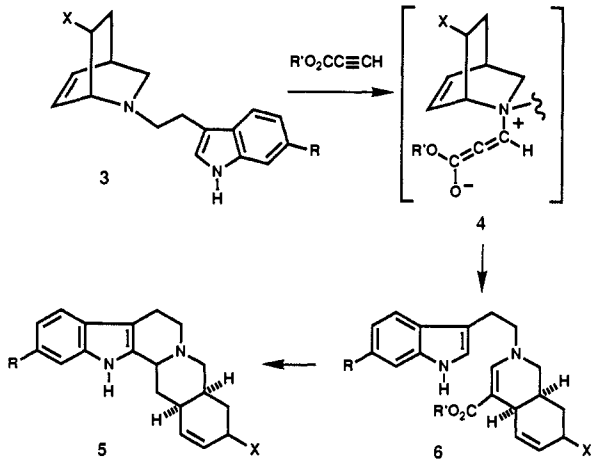
Introduction

The plant species in the Rauwolfia family have been the source of a number of interesting indole alkaloids which have the yohimbane pentacyclic skeleton.[1] Among these, reserpine (**1**) and its close relative deserpidine (**2**)[2] have attracted wide interest owing to their roles both as targets for natural product synthetic adventures[3] and as medicinal agents in the treatment of hypertension and other disorders.[4] In recent years, reserpine and deserpidine have been the focus of numerous studies aimed at the development and application of new strategies for preparation of functionalized yohimbanes. Key synthetic elements in these approaches have included photocycloaddition (Pearlman),[3b] oxy-Cope rearrangement (Wender),[3c] Diels–Alder cycloaddition (Martin),[3d] photocyclization (Ninomiya),[3e] and radical cyclization (Stork)[3f] processes.

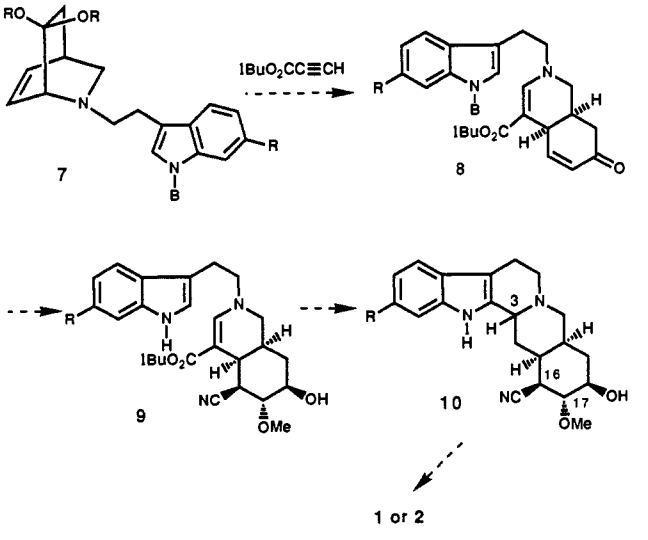


In investigations conducted during the past decade,[5] we have outlined and tested a potentially efficient strategy for construction of DE-ring cis-fused yohimbanes which is founded on a combination of zwitterionic amino-Claisen rearrangement and Wenkert cyclization[6] methodologies. The design (Scheme I) stems from

Scheme I



Scheme II



the observation that zwitterionic intermediates **4**, formed by conjugate addition of *N*-tryptophylisoquinuclidenes **3** to alkyl propiolates, undergo amino-Claisen rearrangements to form functionalized cis-fused hydroisoquinolines **6**. This process ad-

(1) Lucas, R. A. In *Progress in Medicinal Chemistry*; Ellis, G. P., West, G. P., West, G. B., Ed.; Butterworths: London, 1963; p 146.
(2) Mueller, J. M.; Schlittler, E.; Bein, H. J. *Experentia* **1952**, *8*, 338. Hesse, M. *Indolalkaloide in Tabellen*; Springer-Verlag: Berlin, 1964.
(3) (a) Woodward, R. B.; Bader, F. E.; Bickel, H.; Frey, A. J.; Kierstead, R. W. *J. Am. Chem. Soc.* **1956**, *78*, 2023, 2657; *Tetrahedron* **1958**, *2*, 1. (b) Pearlman, B. A. *J. Am. Chem. Soc.* **1979**, *101*, 6398, 6404. (c) Wender, P. A.; Schaus, J. M.; White, A. W. *J. Am. Chem. Soc.* **1980**, *102*, 6157; *Heterocycles* **1987**, *25*, 263. (d) Martin, S. F.; Grzejszczak, S.; Ruger, H.; Williamson, S. A. *J. Am. Chem. Soc.* **1985**, *107*, 4072; **1987**, *109*, 6124. (e) Miyata, O.; Hirata, Y.; Naifo, T.; Ninomiya, I. *Heterocycles* **1984**, *22*, 1041. (f) Stork, G.; Goodman, B. A. *Abstracts of Papers*; 192nd National Meeting of the American Chemical Society, Anaheim, CA; American Chemical Society: Washington, DC, 1986; ORGN 136. Stork, G. *Pure Appl. Chem.* **1989**, *51*, 439. (g) Szantay, C.; Blasko, G.; Honty, K.; Baitz-Gacs, E.; Tamas, J.; Toke, L. *Liebigs Ann. Chem.* **1983**, 1292. (h) Wenkert, E. *J. Serb. Chem. Soc.* **1987**, *52*, 679.
(4) Woodson, R. E.; Younken, H. W.; Schlittler, E.; Schneider, J. A. *Rauwolfia: Botany, Pharmacognosy, Chemistry and Pharmacology*; Little, Brown and Co.: Boston, 1957; see ref 1.
(5) (a) Kunng, F. A.; Gu, J. M.; Chao, S.; Chen, Y.; Mariano, P. S. *J. Org. Chem.* **1983**, *48*, 4262. (b) Chao, S.; Kunng, F. A.; Mariano, P. S. *J. Org. Chem.* **1984**, *49*, 2708. (c) Baxter, E. W.; Labaree, D.; Chao, S.; Mariano, P. S. *J. Org. Chem.* **1989**, *54*, 2893.
(6) (a) Wenkert, E.; Dave, K. G.; Haglid, F. *J. Am. Chem. Soc.* **1965**, *87*, 5461. (b) Wenkert, E.; Sprague, P. W.; Webb, R. L. *J. Org. Chem.* **1973**, *38*, 4305.

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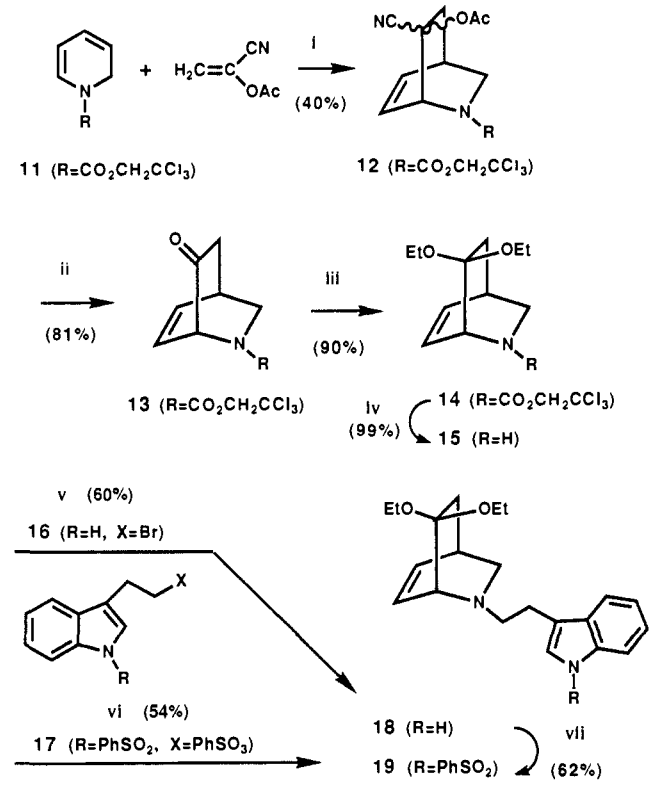
vantageously installs an *N*-tryptophyltetrahydronicotinate ester unit in the products of rearrangement. In accord with the results of Wenkert's earlier efforts,[6] base- (R′ = Me or Et) or acid- (R′ = tBu) induced decarboxylative cyclization of the hydroisoquinolines **6** furnishes the DE-ring cis-fused yohimbanes **5**. Because (1) the starting isoquinuclidenes can be prepared by Diels–Alder additions of dienophiles to N-blocked 1,2-dihydropyridines[7] or of imine derivatives to cyclohexadienes[8] and (2) the derived yohimbanes **5** or their precursor hydroisoquinolines **6** possess strategic E-ring functionality, the overall design represents a novel and potentially efficient synthetic entry to structurally complex yohimbanes such as reserpine and deserpidine.

In more recent studies[5c] with a model system, we have successfully tested one general protocol for stereocontrolled introduction of the E-ring functionality found in reserpine and deserpidine. These efforts have led to the plan for synthesis of these alkaloids outlined in Scheme II which utilizes the *N*-tryptophylhydroisoquinoline enones **8** as key intermediates. In routes based upon this plan, **8** would be furnished by reaction of the isoquinuclidene 7-ketals **7** with *tert*-butyl propiolate. Introduction of the requisite one-carbon ester equivalent group at C-16 in the targets would be accomplished by an axially controlled silylcyanation reaction of **8**. The differentially functionalized C-17, C-18 trans- diol functions in the target alkaloids would then be introduced by convex face hydroboration–oxidation of the resulting silyl enol ether. Importantly, this sequence avoids the C-18 ketone whose reduction stereochemistry has been shown to be problematic.[3c]

At the outset we envisaged that Wenkert cyclization of the *tert*-butyl tetrahydronicotinate intermediate **9** to produce yohimbane **10** could be performed under acidic (HOAc) conditions, thus avoiding problems associated with possible based-induced elimination or epimerization reactions associated with the sensitive E-ring functionality. Furthermore, we anticipated the tetrahydro-β-carboline ring in cyclization product **10** would be formed with the desired C-3 stereochemistry, i.e., 3H-β as found in reserpine and deserpidine. This proposal was based upon Wenkert's reasonable assumption that the decarboxylative cyclization process proceeds via an ultimate cyclic iminium cation intermediate. In accord with Wenkert's observation[6,9,10] and those made by others in studies of related processes[11] intramolecular addition of the indole to this iminium cation should occur preferentially from the axial direction thus providing the 3H-β stereochemistry. Lastly, employment of this method for β-carboline ring construction would avoid problems associated with cyclization regiochemistry (i.e., the inside–outside reserpine problem) encountered in some of the earlier[3c,d] reserpine syntheses.

Even though the Wenkert cyclization stereochemistry has proven to be an enigmatic feature of our approach, the overall strategy for yohimbane synthesis based upon this chemistry appears to be viable. Outlined below are the results of our recent efforts in this area in which we have reduced the strategy to practice in the context of a formal total synthesis of racemic deserpidine (**2**).

Scheme III[a]



[a] (i) neat, 110 °C, 5.5 days; (ii) 10% NaOH, H_2O–THF, 25 °C, 5 h; (iii) $HC(OEt)_3$, EtOH, pTSOH, 70 °C, 24 h; (iv) Zn, EtOH, reflux 1 h; (v) NaI, DIPEA, DMSO, 25 °C, 5 days; (vi) nBuLi, THF; 0 °C; (vii) nBuLi, THF; $PhSO_2Cl$.

Preparation of the *N*-Tryptophylisoquinuclidene Ketals 18 and 19. The sequence we have developed for synthesis of deserpidine begins with preparation of the *N*-tryptophylisoquinuclidene ketals, **18** and **19**. These substances, which are potential substrates for the key zwitterionic amino-Claisen rearrangement step, were obtained by use of a route (Scheme III) initiated by Diels–Alder cycloaddition of the ketene equivalent, 1-cyanovinyl acetate,[12] to the known[13] *N*-[(trichloroethoxy)carbonyl]-1,2-dihydropyridine **11**. This reaction, run on a neat mixture at 110 °C affords the 7-acetoxy-7-cyanoisoquinuclidene **12** as a mixture of C-7 epimers in a modest but acceptable 40% yield. Attempts to improve the efficiency of this reaction by use of solvents to dilute substrates, by varying reaction temperature, and by including catalytic quantities of copper salts[14] or radical scavengers were unsuccessful. In addition, reaction of **11** with an alternate ketene equivalent, nitroethylene,[15] met with failure.

Conversion of the desired isoquinuclidene **12** to the corresponding 7-ketone **13** was performed by use of a procedure (NaOMe, MeOH)[16] employed successfully in our model studies.[5c] However, under these conditions **13** was produced in low yields. In contrast, treatment of **12** with 10% NaOH in a H_2O–THF mixture at 25 °C[17] led to efficient (81%) formation of the isoquinuclidene ketone **13**. Ketalization followed by removal of the

(7) (a) Greuter, H.; Schmid, H. *Helv. Chem. Acta.* **1974**, *57*, 1204. Knaus, E. E.; Pasutto, F. M.; Giam, C. S. *J. Heterocycl. Chem.* **1974**, *11*, 843. Schenker, K.; Druey, J. *Helv. Chem. Acta* **1959**, *42*, 1960, 1961 and references cited therein. Sliwa, H.; LeBot, Y. *Tetrahedron Lett.* **1971**, 4129. A potentially enantioselective synthesis based upon cycloaddition to an N-chiral-substituted 1,2-dihydropyridine is suggested by the work of Marazano (ref 7b). (b) Marazano, C.; Yannic, S.; Genisson, Y.; Mehmandoust, M.; Das, B. C. *Tetrahedron Lett.* **1980**, *31*, 1995.

(8) See: Larsen, S. D.; Grieco, P. A. *J. Am. Chem. Soc.* **1985**, *107*, 1768 and references therein.

(9) The stereochemistry of this process (ref 6a) was confirmed by direct comparison of the product (±)-epialloyohimbane with an authentic sample as well as by transformation of the product to alloyohimbane by C-3 epimerization.

(10) Several observations have been made which suggest that the stereochemical course of this cyclization process is sometimes unpredictable (refs 29 and 5b).

(11) Ziegler, F. E.; Spitzner, E. B. *Tetrahedron Lett.* **1978**, 3609. Stevens, R. V. *Acc. Chem. Res.* **1984**, *17*, 289. Beaulieu, N.; Dickenson, R. A.; Deslongchamps, P. *Can. J. Chem.* **1980**, *58*, 2531 and references cited therein. van Tamelen, E. E.; Shamma, M.; Burgstahler, A. W.; Wolinsky, J.; Tamm, R.; Aldrich, P. E. *J. Am. Chem. Soc.* **1969**, *91*, 7315. Stevens, R. V.; Lee, A. W. M. *J. Am. Chem. Soc.* **1979**, *101*, 7032.

(12) Oku, A.; Arita, S. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 3337.

(13) Mariano, P. S.; Dunaway-Mariano, D.; Huesmann, P. L. *J. Org. Chem.* **1979**, *44*, 124.

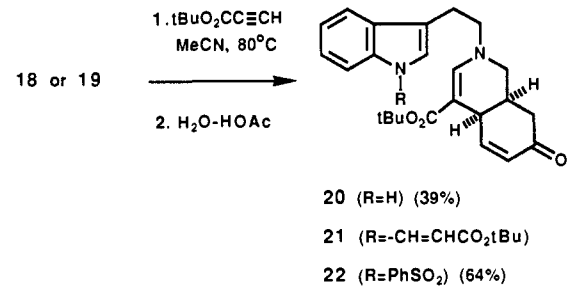
(14) (a) Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W. *J. Am. Chem. Soc.* **1969**, *91*, 5675. (b) Viera, E.; Vogel, P. *Helv. Chim. Acta* **1982**, *65*, 1700. (c) Moore, J. A.; Partain, E. M. *J.Org. Chem.* **1983**, *48*, 1105.

(15) Ranganathan, S.; Ranganathan, D.; Mehrotra, D. K. *J. Am. Chem. Soc.* **1974**, *96*, 5261.

(16) Ranganathan, S.; Ranganathan, D.; Mehrotra, A. K. *Synthesis* **1977**, 289.

(17) Oku, A.; Hasegawa, H.; Shimazu, H.; Nishimura, J.; Harada, T. *J. Org. Chem.* **1981**, *46*, 4152.

Scheme IV

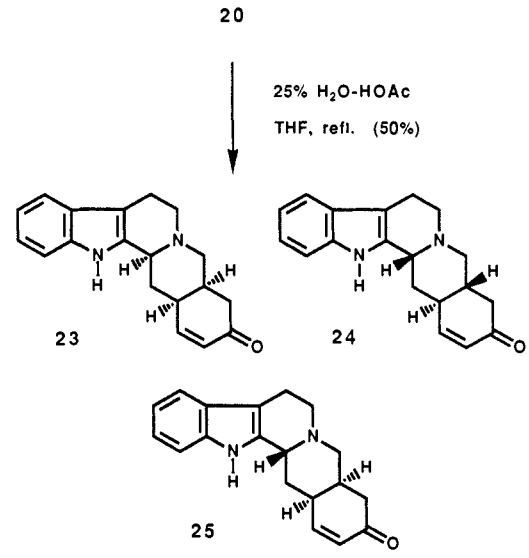


nitrogen protecting group under standard conditions furnished the secondary amine **15** properly structured for attachment of the *N*-tryptophyl moiety. Alkylation of **15** with tryptophyl bromide (**16**)[18] under conditions suggested by Rapoport[19] ($NaHCO_3$, MeCN, reflux) led to formation of the *N*-tryptophylisoquinuclidene **18** in a poor yield. The efficiency of this alkylation reaction is significantly improved (60%) by use of the Martin methodology involving[3d] reaction of **15** and **16** in DMSO containing diisopropylethylamine and sodium iodide at 25 °C. Owing to problems encountered later (see below) with the zwitterionic amino-Claisen rearrangement of **18** and associated with the presence of a free indole moiety, the *N*-benzenesulfonamide derivative **19** was prepared. This material was generated either by benzenesulfonylation of **18** ((1) nBuLi, (2) $PhSO_2Cl$) or more directly and in better overall yields by alkylation of isoquinuclidene **15** with the *N,O*-bis(phenylsulfonyl) derivative, **17**, of tryptophol.

N-Tryptophylhydroisoquinoline-Enone Preparation by the Zwitterionic Amino-Claisen Rearrangement Procedure. In earlier efforts we demonstrated that isoquinuclidenes are transformed to cis-fused hydroisoquinolines upon reaction with propiolate esters.[5] At that time we had noted that the efficiencies of these processes are dependent on the nature and degree of C-7 substitution within the isoquinuclidene skeleton. For example, while 7-keto isoquinuclidenes do not undergo this addition–rearrangement reaction and 7-unsubstituted analogues react only inefficiently, 7-substituted (alkyl or alkoxy) members react smoothly to furnish hydroisoquinolines in modestly high yields. In addition, preliminary model studies showed that the presence of non-indole blocked *N*-trytophyl moieties did not complicate these addition–rearrangement reactions. Thus, we were surprised by the results of our studies with isoquinuclidene **18**. Accordingly, the reaction of this substance with *tert*-butyl propiolate (MeCN, 80 °C), followed by mild acid hydrolysis to liberate the enone function and silica gel chromatography, afforded the desired hydroisoquinoline-enone **20** in only a 30% yield (Scheme IV). The source of this inefficiency became evident when the ^1H NMR spectrum of the crude product mixture was inspected. This revealed the presence of near equal amounts of **20** and the *N*-β-acrylate derivative **21**. The latter substance rapidly decomposes on silica gel so that its isolated yield is low. In any event, formation of this product by Michael addition of the indole nitrogen[21] to the propiolate ester either before or after rearrangement results in a reduced yield of the target **20**. This complication appears to be unique to isoquinuclidene **18**.

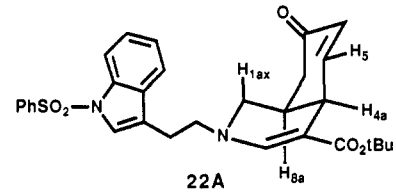
To avoid this problem, our efforts turned to zwitterionic amino-Claisen rearrangement of the *N*-benzenesulfonamide blocked tryptophyl derivative **19**. This decision was also influenced by subsequent observations (see below) which indicated that the conditions for Wenkert cyclization of the hydroisoquinoline-enone **20** causes epimerization at C-15 (see below). This result dictated

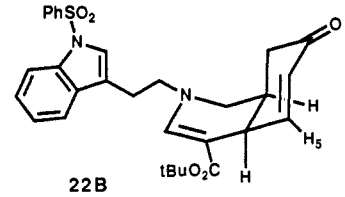
Scheme V



the use of a protocol for synthesis of deserpidine in which E-ring functional group introduction would occur prior to β-carboline ring formation. In addition the chemistry planned for E-ring manipulation required an electron withdrawing group blocked indole moiety as part of the *N*-tryptophylhydroisoquinoline-enone structure.

As a result of these restrictions, reaction of the *N*-benzenesulfonamide-protected isoquinuclidene **19** with *tert*-butyl propiolate was explored. This addition–rearrangement process led to formation of hydroisoquinoline **22** in an acceptable 60% yield. Characterization of this key intermediate as a cis-fused hydroisoquinoline was easily made based upon its ^1H NMR spectral parameters and comparisons of these data with those for a number of related compounds prepared in our earlier work.[5,13] X-ray crystallographic analysis on a later intermediate in this sequence (i.e., **39**) unambiguously establishes this stereochemistry assignment. Finally, the large (12 Hz) diaxial coupling constant between $H\text{-}1_{ax}$ and H-8a and the small (1.9 Hz) vicinal coupling constant between H-5 and H-4a indicate that this cis-fused hydroisoquinoline exists predominantly in the conformation **22A** in which a high-energy $A^{1,2}$-interaction between H-5 and CO_2tBu (in the alternate conformer **22B**) is avoided. The energetic and conformational consequences of this interaction in hydroisoquinolines related to **22** have been discussed earlier.[5c] Importantly the conformational preference in **22** represents a key element of our strategy for stereoselective introduction of the deserpidine E-ring functionality (see below).[5c]

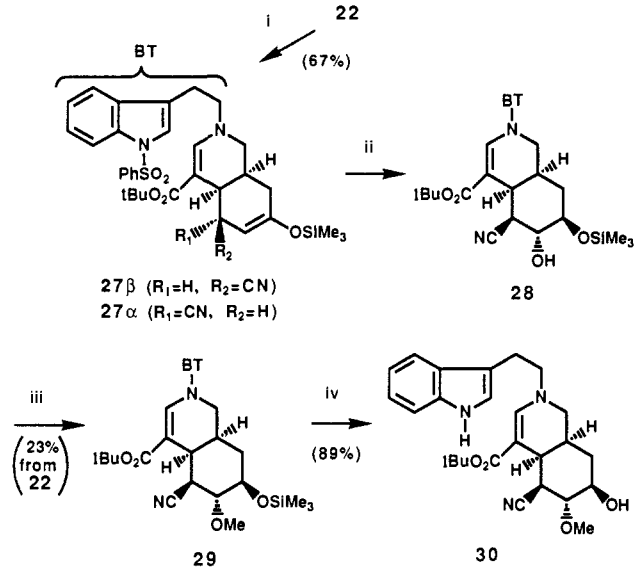




Wenkert Cyclization of the *N*-Tryptophylhydroisoquinoline-Enone 20. In the plan outlined above for deserpidine synthesis at least two general protocols are possible for introduction of the C-16 methoxycarbonyl and differentially functionalized C-17, C-18 vicinal glycol groupings. These differ in the relative timing of pentacyclic yohimbane ring construction by the Wenkert cy-

(18) Neumeyer, J. L.; Moyer, U. V.; Leonard, J. E. *J. Med. Chem.* **1969**, *12*, 450.
(19) Johansen, J. E.; Christie, B. D.; Rapoport, H. *J. Org. Chem.* **1981**, *46*, 4914.
(20) The bis-benzenesulfonate **17** was prepared from commercially available tryptophol (51%) (see Experimental Section).
(21) Indoles typically add to Michael acceptors at their 3-position (ref 22a). However 3-substituted indoles have been reported to undergo Michael additions at nitrogen under both acidic (ref 22b) and basic (ref 22c) conditions.

Scheme VI[a]



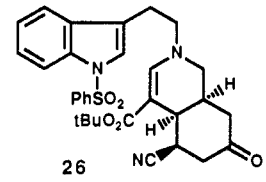
[a] (i) Et_3Al, TMSCN, C_6H_6, 25 °C; (ii) BH_3–THF, 0 °C; 3 N NaOH, 30% H_2O_2, −10 °C; (iii) nBuLi, THF, −78 °C; $CF_3SO_3CH_3$, −40 °C; (iv) 6% Na–Hg, Na_2HPO_4, MeOH, 25 °C.

clization process and E-ring functionality introduction. The results of studies of the Wenkert cyclization chemistry of the *N*-tryptophylhydroisoquinoline-enone **20** have guided our selection of what we judge to be the better protocol and, as a result, the more efficient plan for accomplishing the overall synthetic goal. We have found that when **20** reacts under the Wenkert conditions (25% H_2O–HOAc, THF, reflux) it produces a mixture of three separable and identifiable yohimbane enones, **23**, **24** and **25** (Scheme V). These substances are generated in a respective ratio of 1.6:1.0:1.9 and in an overall yield of 50–60%. A fourth substance is also formed under these conditions but only in trace quantities.

Spectroscopic analyses of these yohimbanes revealed that they are diastereomeric. The major isomers, **23** and **25**, both possess the same hydroisoquinoline cis ring fusion stereochemistry present in the starting material **20** and are epimeric at C-3. The minor isomer **24** has spectroscopic data consistent with its characterization as a D,E-trans-fused yohimbane with H-3 β stereochemistry. These results suggest that epimerization occurs at the enone γ-carbon on either the reactant and/or initially formed products under the acidic conditions used in the Wenkert cyclization process.

E-Ring Functionality Manipulation. Several factors in addition to the detrimental C-14 epimerization mentioned above have led us to the actual strategy used for execution of the final stages of our deserpidine synthesis. Clearly, the epimerization finding dictates that Wenkert cyclization to construct the β-carboline unit in the target must be conducted to an intermediate hydroisoquinoline in which the enone functionality is no longer present. In addition, the chemistry planned for installation of the C-16 ester group and C-17 and C-18 diol functionality (see below) requires that the indole group be blocked by an EWG substituent on nitrogen. We were aware of the potential difficulties associated with N-protection of an indole when it is incorporated in a fully elaborated yohimbane. From another perspective, we anticipated that the desired stereocontrol in introduction of a one-carbon equivalent of the C-16 ester would be optimized in a process which employs conjugate addition to an enone when it is present in an N-substituted hydroisoquinoline like **22**. This is due to the large preference for the conformer **22A** and a requirement for axial addition of a nucleophile to the enone β-carbon under kinetically controlled conditions.

As a result of the criteria outlined above, we have focused on a route for a deserpidine synthesis in which E-ring functionality is introduced prior to yohimbane ring construction. The methodology takes advantage of a cyano-silylation process to install simultaneously the C-16 cyano and $\Delta^{17,18}$-silyl enol ether functions in a highly stereo- and regiocontrolled fashion. In model studies[5c] we have demonstrated that a hydroisoquinoline-enone closely related to **22** is transformed in this fshion to a corresponding cyano silyl enol ether. In accord with this earlier observation, we have found that treatment of **22** with Et_3Al and TMSCN (C_6H_6, 25 °C)[23] furnishes the desired adduct **27** in a 67% yield and with a strong (9:1) preference for the β-cyano diastereomer (**27B**) (Scheme VI). Interestingly, when the cyanosilylation conditions (Et_2AlCN, TMSCl) found to be optimal in our model study[5c] are applied to **22**, the desired adduct **27** is obtained in very low yields and with an exceptionally poor (2:1) β:α ratio. The major product formed under these conditions is cyano-ketone **26**. The reasons



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for these differences are not completely clear, but they may be related to the sensitivity of **27** to desilylation induced by trace quantities of acidic impurities.

Hydroboration–oxidation of the silyl enol ether **27** (9:1 β:α mixture) under the conditions developed earlier[5c,24] provided the corresponding monosilylated *trans*-glycol **28**. The stereoselectivity of this process can be attributed to a preference for addition of borane from the convex face of the *cis*-hydroisoquinoline **27B** further reinforced by the β-cyano group at C-16. An important feature of this methodology is that the diol function in **28** is selectively protected at C-18, thus allowing for differentiation of the two alcohol functions. Accordingly, O-methylation of **28** can be performed, albeit under forcing conditions ((1) nBuLi, (2) $CF_3SO_3CH_3$), to generate the C-17 methoxyhydroisoquinoline **29**. The difficulty with this methylation is probably due to the existence of **28** in the conformation **28A** in which the C-17 hydroxyl along with C-16 CN and C-18 OTMS groups occupy axial positions. This preference has been observed in related model systems[5c] and can be attributed to a severe $A^{1,2}$-interaction in the alternative conformer **28B**. Indole deprotection is then performed on **29** by use of the sodium amalgam conditions suggested by Trost[25] and Sundberg.[26] This reaction produces the hydroisoquinoline **30** demonstrating that nondetrimental desilylation at C-18 also occurs under these deblocking conditions.

Yohimbane Ring Formation by the Wenkert Cyclization Process. With the *N*-tryptophylhydroisoquinoline **30** in hand, our attention turned to the final stages of our deserpidine synthesis. Our overall strategy embodied a plan for this purpose which is based upon acid-induced cyclization of **30** to form the tetrahydro-β-carboline unit of a fully elaborated yohimbane skeleton. A number of considerations suggested that employment of the Wenkert cyclization chemistry[6] would allow us to execute this plan successfully. Firstly, we felt that the tetrahydronicotinate ester moiety in **30** would serve as an excellent regiochemical control element for this cyclization process. Unlike several other related reserpine

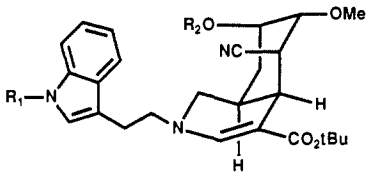
(22) (a) Sundberg, R. J. *The Chemistry of Indoles*; Academic Press: New York, 1970; pp 67–77. Remers, W. A. In Indoles, Part 1; Houlihan, W. J., Ed.; John Wiley and Sons, Inc.: New York, 1972; pp 100–105. Rush, K. In Indoles, Part 1; Houlihan, W. J., Ed.; John Wiley and Sons, Inc.: New York, 1972; p 562. Jones, R. A. In *Comprehensive Heterocyclic Chemistry*; Bird, C. W.; Cheeseman, G. W. H., Eds.; Pergamon Press, Ltd.; Oxford, 1984; pp 226–7. (b) Heuber, H.-J.; Cornelius, D.; Pfaff, H. *Chem. Ber.* **1963**, *96*, 2617. (c) Gray, A. P.; Kraus, H.; Heitmeier, D. E. *J. org. Chem.* **1960**, *25*, 1939. Noland, W.; Kuryla, W. C.; Lange, R. F. *J. Am. Chem. Soc.* **1959**, *81*, 6010.

(23) (a) Utimoto, K.; Obayashi, M.; Shishiyama, Y.; Inoue, M.; Nozaki, H. *Tetrahedron Lett.* **1980**, 3389. (b) Utimoto, K.; Wakabayashi, Y.; Inoue, M.; Horile, T.; Shishiyama, Y.; Obayashi, M.; Nozaki, M. *Tetrahedron* **1983**, *39*, 967.

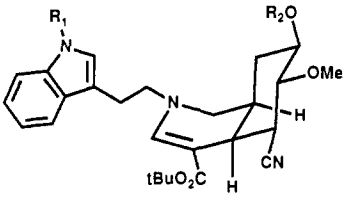
(24) Larsen, G. L.; Prieto, J. A. *Tetrahedron* **1983**, *39*, 855.

(25) Trost, B. M.; Arndt, H. C.; Stiege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, *39*, 3477.

(26) Sundberg, R. J.; Bloom, J. D. *J. Org. Chem.* **1981**, *46*, 4836.



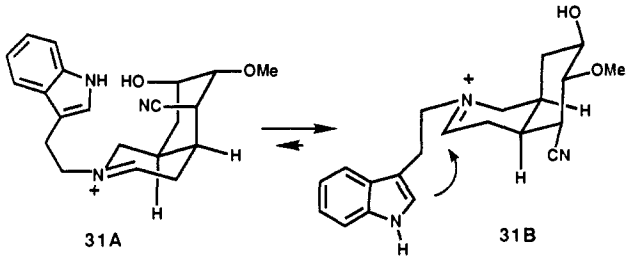
28A (R_1=$PhSO_2$, R_2=TMS)
30A (R_1=R_2=H)



28B (R_1=$PhSO_2$, R_2=TMS)
30B (R_1=R_2=H)

syntheses[3c,d] which depend upon oxidative methods for tetrahydro-β-carboline ring formation, Wenkert cyclization of **30** should occur to produce the deserpidine-like product **32** (Scheme VII) uncomplicated by formation of an inside-deserpidine-like regioisomer. This expectation is based on the probable mechanism for the acid-induced, decarboxylative reaction which involves regiocontrolled formation and cyclization of an ultimate cyclic iminium ion intermediate **31** (see below).

Secondly, we anticipated a high degree of stereochemical control in the Wenkert cyclization of **30**. Thus, even though **30** exists preferentially in the triaxial conformation **30A**,[5c] the cyclic iminium ion arising by acid-catalyzed decarboxylation of this substance should strongly favor a triequatorial conformation **31B** rather than its triaxial counterpart **31A**. Removal of the *tert*-butoxycarbonyl group and the C-14 sp^2-center in **30** should lead to relief of the severe $A^{1,2}$-strain interaction which is responsible for the equilibrium in **30** favoring **30A**.[27] Importantly, cationic cyclization of the iminium ion **31** should prefer a transition state having the



31A 31B

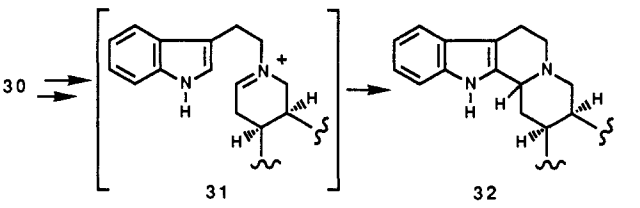
triequatorial conformation and in which the nucleophilic indole C-2 carbon approaches from an axial direction.[11] As a result, we expected that Wenkert cyclization of **30** would selectively produce the desired, deserpidine-type, H-3β stereoisomer of yohimbane **32**. This type of stereoelectronic preference for axial iminium ion cyclization has been observed and discussed by a number of other workers.[28,11] Moreover, Wenkert has provided several examples in which acid-induced cyclizations of *N*-tryptophyltetrahydronicotinates appear to adhere to these stereochemical controls. Particularly noteworthy is the high yielding generation of yohimbane **34** by treatment of the cis-fused hydroisoquinoline **33** with HOAc-MeOH.[6a] The H-3β stereoisomer is reported to be the exclusive product of this process. However, Wenkert,[29a] Lounasmma,[29b] and Mariano[5b] have detected exceptions to this general trend. For example, acid-induced cyclization of **35** is known[5b] to produce a nearly equal mixture of C-3 epimeric yohimbanes **36**, and the analogous reaction of nicotinate **37** has been reported to produce a mixture of products **38** in which the H-3

(27) Strain energy calculations (Macromodel, MM2 force field) on models related to **30** and **31** confirms these conclusions.

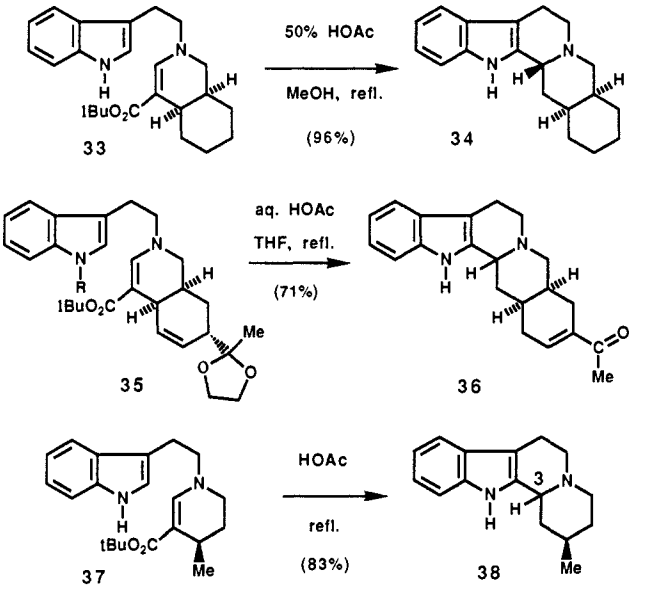
(28) For an excellent review of this subject, see: Overman, L. E. In *Comprehensive Organic Synthesis*; Trost, B. M. Ed.; Pergamon Press: Oxford, 1989.

(29) (a) Wenkert, E.; Han, A.-L.; Michelotti, E. L. *Croat. Chem. Acta* **1985**, *58*, 737. (b) Lounasmaa, M.; Koskinen, A. *Tetrahedron Lett.* **1982**, 1489.

Scheme VII



Scheme VIII[a]



[a](i) 2:1 25% HOAc-THF, 70 °C, 50 h; (ii) 1 N NaOH, 15% H_2O_2, MeOH, 90 °C, 2.5 h; (iii) 18% HCl, 100 °C, 5 h; (iv) CH_2N_2, Et_2O, 25 °C, 1 h.

Table I. Comparative ^1H NMR and ^{13}C NMR Spectroscopic Data for Yohimbane **32α**, Deserpidine, and Isodeserpidine

chemical shifts (ppm rel to Me_4Si)	yohimbane **32α**	isodeserpidine	deserpidine
	^1H NMR		
H-3	3.24	3.18	4.52
H-14ax	1.78	1.87	2.33
H-15	2.29	2.31	2.04
H-21ax	2.82	2.82	2.47
H-21eq	2.60	2.62	3.04
	^{13}C NMR		
C-5	60.8	60.7	52.2
C-6	22.8	22.8	17.5
C-19	28.9	28.8	24.9
C-21	54.0	54.0	50.1

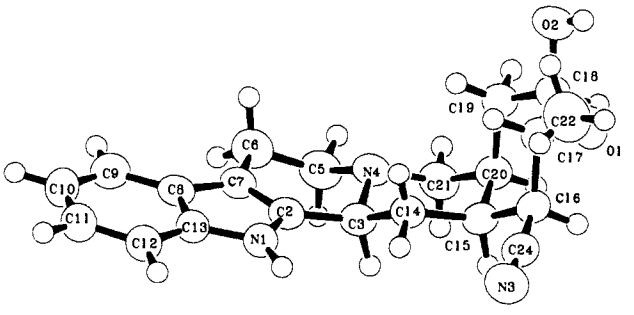
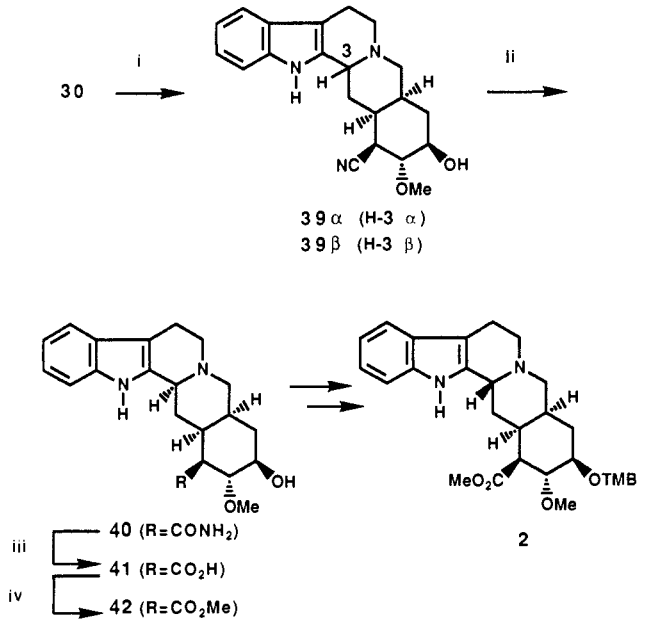


Figure 1. ORTEP drawing of the X-ray crystallographically determined structure of **39α**. See the Experimental Section for details. The C, N, and O atoms are drawn as 50% ellipses and the H atoms as B = 1.5 Å circles.

Scheme IX



α epimer predominates by 4:1. The combined observations appear to leave uncertain the question of stereochemistry for Wenkert cyclization of the *N*-tryptophylhydroisoquinoline **30**.

Despite our awareness of these considerations, we were still surprised to find that Wenkert cyclization of the *N*-tryptophylhydroisoquinoline **30**, promoted by treatment with 25% H_2O–HOAc at 70 °C for 50 h, leads to nearly exclusive formation (64%) of the yohimbane **39α**, having the H-3 α stereochemistry (Scheme IX). A trace amount (ca. 5%) of the H-3β epimer, **39β**, was also produced in this process. The spectroscopic properties of **39α** are in full accord with its assignment as a yohimbane possessing isodeserpidine-like C-3 stereochemistry (see Table I for comparative NMR data). The unusual stereochemical course of this reaction mandated that we obtain more unambiguous structural and stereochemical information. This was made possible by the crystalline nature of **32α**. X-ray crystallographic analysis of this substance (see Figure 1 and the Experimental Section) demonstrated conclusively that it has the H-3 α stereochemistry as well as the expected relative configurations at the five contiguous E-ring chiral centers.

To insure that the stereochemical course of the tetrahydro-β-carboline ring forming cyclization of **30** was not a result of thermodynamic control, the minor yohimbane H-3β product, **39β**, was subjected to the Wenkert cyclization conditions. As expected, **39β** was inert under these conditions which are much less acidic than those normally required for H-3 epimerization in related yohimbanes.[30] Clearly, the stereochemistry for cyclization of the intermediate iminium cation **31**, derived from **30**,[31] is a consequence of an unusual and difficult to understand kinetic control.[32]

Even though the final stage of our synthetic route to deserpidine would have been more direct had cyclization of **30** favored formation of **39β**, the observed result does not greatly detract from the success of the overall strategy. Accordingly, **39α** can be transformed to the E-ring C-16 methyl ester **42** by a sequence involving nitrile hydrolysis via the amide **40** to the acid **41** followed by esterification (Scheme IX). The spectroscopic and physical properties of synthetic **42** match those of the substance which was independently prepared by known methods (C-3 epimerization[33] and C-18 debenzoylation)[34] from deserpidine (**2**) and which previously served as a late stage intermediate in Szantay's[3g] synthesis of deserpidine. Thus, the preparation of yohimbane **42** in 15 steps from pyridine constitutes a formal total synthesis of deserpidine (**2**) by a strategy which could find utility in the synthesis of other DE-ring cis-fused yohimbane natural products.

Experimental Section

General Methods. ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions with an IBM WP-200, Bruker AF-200, or Bruker AM-400 NMR spectrometer. Chemical shifts are reported in parts per million relative to either tetramethylsilane or $CHCl_3$. ^{13}C NMR resonances are assigned on the basis of INEPT results. IR spectra were recorded in $CHCl_3$ solutions by using a Perkin-Elmer 238 spectrometer. Mass spectra were recorded by using either a low-resolution Hitachi RMU-6E or a Hewlett-Packard HP-5988A instrument and a VG-7700 high-resolution instrument. Melting points were recorded with a Griffin Mel-Temp apparatus and are reported uncorrected. Column chromatography was performed with Florisil (100–200 mesh), Alcoa type F-20 alumina (80–200 mesh), flash Woelm N 32–63 alumina (170–230 mesh); or flash silica gel 60 (230–400 mesh). Preparative thin-layer chromatography was performed on silica gel (Merck EM type 60, GF-254) plates. All reactions were carried out under a nitrogen atmosphere. Drying of organic solutions following workup of reaction mixtures was done with anhydrous sodium sulfate unless indicated otherwise. The purity of all substances described below were determined to be >90% by ^{13}C NMR and chromatographic methods unless otherwise noted.

1-[(2,2,2-Trichloroethoxy)carbonyl]-7-acetoxy-7-cyanoisoquinuclidene (12). A mixture of 1-[(2,2,2-trichloroethoxy)carbonyl]-1,2-dihydropyridine[13] (21.6 g, 0.084 mol) and 1-cyanovinylacetate (14.0 g, 0.126 mol) was heated at 110 °C for 5.5 days. After cooling, the crude reaction mixture was eluted through a short Florisil column (4:1 hexanes–ethyl acetate). Repurification using a second Florisil column (4:1 hexanes–ethyl acetate) afforded 8.91 g (40%) of the isoquinuclidene **12** as an oil (mixture of C-7 epimers). Pure samples of each epimer could be obtained by this chromatographic process. The less polar epimer (7-*exo*-acetoxy, 7-endo-cyano) was isolated as a pale yellow oil. ^1H and ^{13}C NMR analyses of these substances showed that they consist of slowly interconverting carbamate C–N rotamers: ^1H NMR 1.82 (dd, J = 6.9, 1.9 Hz, 0.45 H, H-8 exo), 1.90 (dd, J = 6.9, 1.9 Hz, 0.55 H, H-8 exo), 2.05 (s, 1.35 H, CH_3), 2.10 (s, 1.65 H, CH_3), 2.38 (dt, J = 11.1, 3.1 Hz, 0.55 H, H-8 endo), 2.43 (dt, J = 11.1, 3.1 Hz, 0.45 H, H-8 endo), 2.95 (br m, 1 H, H-4), 3.06 (dt, J = 10.2, 2.3 Hz, 0.45 H, H-3 endo), 3.12 (dt, J = 10.2, 2.3 Hz, 0.55 H, H-3 endo), 3.40 (dd, J = 10.2, 2.3 Hz, 0.45 H, H-3 exo), 3.51 (dd, J = 10.2, 2.3 Hz, 0.55 H, H-3 exo), 4.60 (t, J = 12.5 Hz, 0.9 H, CH_2CCl_3), 4.87 (t, J = 12.5 Hz, 1.1 H, CH_2CCl_3), 5.32 (d, J = 6.5 Hz, 0.45 H, H-1),5.36 (d, J = 6.5 Hz, 0.55 H, H-1) 6.53 (br t, J = 6.6 Hz, 1 H, H-5), 6.69 (br t, J = 6.6 Hz, 1 H, H-6); ^{13}C NMR 20.8/20.9 (CH_3), 29.9/30.0 (C-4), 37.0/37.1 (C-8), 46.8/47.2 (C-3), 50.8/51.5 (C-1), 72.2 (C-7), 75.1/75.2 (CH_2CCl_3), 95.4/95.8 (CCl_3), 117.8 (CN), 128.4/128.6 (C-6), 137.7 (C-5), 153.3/154.2 (C=O (carbamate)), 169.0 (C=O (ester)); IR 1745, 1715, 1425, 1405 cm^{-1}; mass spectrum (CI-NH_3), m/e (relative intensity) 367 (MH^+, 100), 335 (11), 333 (17), 309 (14), 307 (13.7), 297 (5), 193 (17), 191 (13); high-resolution mass spectrum, m/e 365.9936 ($C_{13}H_{14}Cl_3N_2O_4$ requires 365.9940).

The more polar epimer (7-*endo*-acetoxy, 7-*exo*-cyano) was isolated as a pale yellow oil: ^1H NMR 1.82 (dd, J = 6.1, 3.4 Hz, 0.45 H, H-8 exo), 1.89 (dd, J = 6.1, 3.1 Hz, 0.55 H, H-8 exo), 2.03 (s, 1.65 H, CH_3), 2.04 (s, 1.35 H, CH_3), 2.50 (dd, J = 5.1, 2.1 Hz, 0.55 H, H-8 endo), 2.57 (dd,

(30) (a) Epimerization at C-3 in yohimbanes normally requires strongly acidic reaction conditions (ref 30b). (b) MacPhillamy, H. B.; Dorfman, L.; Huebner, C. F.; Schlittler, E. *J. Am. Chem. Soc.* **1955**, *77*, 1071. Wenkert, E.; Liang, H. L. *Experentia* **1955**, *11*, 302. Zhang, L.-H.; Gupta, A. K.; Cook, J. M. *J. Org. Chem.* **1989**, *54*, 4708.

(31) An alternative mechanism for the Wenkert cyclization process involves acid-catalyzed cyclization to generate the tetrahydro-β-carboline ring system prior to decarboxylation. While a pathway can be envisaged for the required decarboxylation (via C–N bond cleavage to produce a macrocyclic 2-indolylmethyl cation) this is an unlikely alternative since the reaction conditions used do not favor C–N bond cleavage of an N-protonated intermediate. Indeed the lack of C-3 epimerization of **39b** under the Wenkert cyclization conditions evidences this conclusion.

(32) Another intriguing stereochemical observation for a related iminium ion cyclization reaction has been reported by Stork (ref 3f) in his paper outlining a reserpine synthetic approach.

(33) Gaskell, A. J.; Joule, J. A. *Tetrahedron* **1967**, *23*, 4053. Weichet, J.; Pelz, K.; Blaha, L. *Coll. Czech. Chem. Commun.* **1961**, *26*, 1529.

(34) MacPhillamy, M. B.; Huebner, C. F.; Schlittler, E.; St. Andre, A. F.; Ulshafer, P. R. *J. Am. Chem. Soc.* **1955**, *77*, 4335.

(35) Molecular Structure Corporation, TEXSAN, structure analysis package, Version 2.0, 3200A Research Forest Drive, The Woodlands, TX 77381, 1987.

(36) Gilmore, C. J. MITHRIL, a computer program for the automatic solution of crystal structures, University of Glasgow, Scotland, 1983.

(37) Zachariasen, W. H. *Acta Crystallogr.* **1981**, *A39*, 158–166.

(38) Johnson, C. K. ORTEP, Report ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, TN 37830.

(39) Luo, J.; Ammon, H.L.; Gilliland, G. *J. Appl. Cryst.* **1989**, *22*, 186.

J = 7.3, 2.3 Hz, 0.45 H, H-8 endo), 2.98 (br m, 1 H, H-4), 3.07 (ddd, J = 11.5 2.4, 2.3 Hz, 1 H, H-3 endo), 3.39 (dd, J = 10.5, 2.3 Hz, 0.55 H, H-3 exo), 3.49 (dd, J = 10.3, 2.2 Hz, 0.45 H, H-3 exo), 4.75 (s, 1.1 H, CH_2CCl_3), 4.77 (AB quartet, J = 11.8 Hz, 0.9 H, CH_2CCl_3), 5.38 (d, J = 4.7 Hz, 0.55 H, H-1), 5.40 (d, J = 4.7 Hz, 0.45 H, H-1), 6.30 (m, J = 11.1, 6.3, 3.0 Hz, 1H, H-6), 6.60 (m, J = 7.4, 1.9 Hz, 1 H, H-5); ^{13}C NMR 20.6 (CH_3), 30.2/30.5 (C-4), 39.1/39.3 (C-8), 45.4/45.9 (C-3), 50.0/50.3 (C-1), 71.8 (C-7), 75.2 (CH_2CCl_3), 95.3 (CCl_3), 118.0 (CN) 127.4/127.9 (C-6), 136.4/136.7 (C-5), 153.7 (C=O (carbamate)), 168.2 (C=O (ester)); IR 1750, 1705, 1400 cm^{-1}; mass spectrum (EI), m/e (relative intensity) 366 (M, 0.1), 325 (5), 323 (2), 259 (16), 258 (13), 159 (16), 133 (33), 131 (37); high-resolution mass spectrum, m/e 365.9941 ($C_{13}H_{13}Cl_3N_2O_4$ requires 365.9940).

1-[(2,2,2-Trichloroethoxy)carbonyl]-7-ketoisoquinuclidene (13). To a solution of the 7-acetoxy-7-cyanoisoquinuclidene **12** (12.0 g, 0.033 mol) in 415 mL of tetrahydrofuran was added 50 mL of 10% aqueous NaOH solution. The reaction mixture was stirred at 25 °C for 5 h and poured into ethyl acetate. The organic layer was separated, washed with brine, dried, and concentrated in vacuo to afford an oil which was subjected to Florisil chromatography (4:1 hexanes–ethyl acetate) to yield 7.92 g (81%) of ketone **13** as a pale green oil. ^{1}H NMR and ^{13}C NMR analyses of this substance showed that it consists of slowly interconverting carbamate C-N rotamers: ^{1}H NMR 2.21 (m, J = 2.0, 0.7 Hz, 2 H, H-8), 3.20 (br m, 1 H, H-4), 3.28 (br d, J = 10.5 Hz, 1 H, H-3 exo), 3.55 (ddd, J = 12.1, 11.4, 2.4 Hz, 1 H, H-3 endo), 4.73 (AB quartet, J = 11.9 Hz, 1 H, CH_2CCl_3), 4.76 (AB quartet, J = 11.9 Hz, 1 H, CH_2CCl_3), 4.96 (dd, J = 6.2, 2.3 Hz, 1 H, H-1), 6.23 (m, 1 H, H-6), 6.66 (m, 1 H, H-5); ^{13}C NMR 31.9/32.1 (C-4), 36.4 (C-8), 46.2/46.8 (C-3), 57.6/58.1 (C-1), 75.1 (CH_2CCl_3), 95.3 (CCl_3), 127.7/128.1 (C-6), 139.3/139.8 (C-5), 152.8/153.2 (C=O (carbamate)), 202.3 (C=O (ketone)); IR 1720, 1700, 1400 cm^{-1}; mass spectrum (CI) m/e (relative intensity) 298 (MH^+, 8), 273 (14), 272 (18), 271 (44), 270 (47), 269 (44), 268 (44), 259 (86), 258 (87), 257 (99), 256 (99), 255 (99), 243 (8), 242 (11), 241 (6), 220 (20), 205 (49), 151 (23), 150 (99); high-resolution mass spectrum (CI) 297.9849 ($C_{10}H_{11}NO_3Cl_3$ requires 297.9804).

2-[(2,2,2-Trichloroethoxy)carbonyl]-7,7-diethoxyisoquinuclidene (14). A mixture of 7-ketoisoquinuclidene **13** (6.10 g, 0.0220 mol), ethanol (10.4 g, 0.225 mol), triethyl orthoformate (31.5 g, 0.212 mol), and p-toluenesulfonic acid (0.389 g, 0.002 mol) was stirred at 70 °C for 24 h. After cooling, the reaction mixture was poured into saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution, dried over anhydrous K_2CO_3, and concentrated in vacuo to afford an orange oil. Purification by Florisil chromatography (4:1 hexanes–ethyl acetate) afforded 6.86 g (90%) of ketal **14** as a pale green oil. ^{1}H and ^{13}C NMR analyses of this substance showed that it consists of slowly interconverting carbamate C–N rotamers: ^{1}H NMR 1.09 (m, 6 H, CH_3), 1.59 (dt, J = 13.0, 3.2 Hz, 1 H, H-8 endo), 1.72 (m, J = 13.1, 2.3 Hz, 1 H, H-8 exo), 2.78 (br m, 1 H, H-4), 3.05 (m, J = 10.2, 2.4 Hz, 1 H, H-3 endo), 3.25–3.65 (m, 5 H, CH_2CH_3, H-3 exo), 4.70 (AB quartet, J = 11.9 Hz, 1 H, CH_2CCl_3), 4.71 (AB quartet, J = 12.0 Hz, 1 H, CH_2CCl_3), 4.80 (br m, 1 H, H-1), 6.38 (m, 2 H, H-5, H-6); ^{13}C NMR 14.1/15.2 (CH_2CH_3), 31.1/31.2 (C-4), 36.6 (C-8), 46.0/46.5 (C-3), 50.9/51.3 (C-1), 55.8 (CH_2CH_3), 56.6/56.8 (CH_2CH_3), 74.8/75.0 (CH_2CCl_3), 95.6/96.0 (CCl_3), 104.3/104.5 (C-7), 130.8/131.2 (C-5 or C-6), 133.9/134.3 (C-5 or C-6), 153.2/153.7 (C=O); IR 1705, 1415 cm^{-1}; mass spectrum (EI), m/e (relative intensity) 371 (M, 1), 330 (11), 329 (6), 328 (39), 327 (7), 326 (44), 259 (19), 258 (18), 257 (57), 256 (44), 255 (62), 254 (38), 150 (30), 124 (51), 123 (65), 117 (93), 116 (21), 80 (100); high-resolution mass spectrum, m/e 371.0459 ($C_{14}H_{20}NO_4Cl_3$ requires 371.0458).

7,7-Diethoxyisoquinuclidene (15). A solution of carbamate 14 (7.10 g, 0.019 mol) in 180 mL of absolute ethanol containing acid-washed zinc (25.4 g, 0.400 g-at) was stirred at reflux for 1 h. After cooling, the reaction mixture was filtered through Celite. The collected precipitate was washed with chloroform (420 mL). The combined filtrates were eluted through an F-20 alumina column which was subsequently washed with three bed volumes of 3:7 (v/v) ethanol–chloroform. Concentration of the eluant in vacuo gave the isoquinuclidene **15** (3.72 g, 99%) as an oil: ^{1}H NMR 1.08 (t, J = 7.1, Hz, 3 H, CH_2CH_3), 1.16 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 1.53 (dt, J = 12.8, 2.8 Hz, 1 H, H-8 endo), 1.64 (dd, J = 12.9, 2.6 Hz, 1 H, H-8 exo), 1.95 (br s, 1 H, NH), 2.42 (dt, J = 9.7, 2.1 Hz, 1 H, H-3 endo), 2.62 (br m, 1 H, H-4), 2.83 (dd, J = 9.7, 2.0 Hz, 1 H, H-3 exo), 3.30–3.65 (m, 4 H, OCH_2CH_3), 3.58 (m, J = 5.1, 2.3 Hz, 1 H, H-1), 6.32 (m, 2 H, H-5, H-6); ^{13}C NMR 15.2 (CH_3), 15.4 (CH_3), 31.0 (C-4), 36.7 (C-8), 44.0 (C-3), 51.7 (C-1), 55.7 (OCH_2CH_3), 56.6 (OCH_2CH_3), 104.1 (C-7), 130.6 (C-5 or C-6), 134.1 (C-5 or C-6); IR 3310, 1405 cm^{-1}; mass spectrum (EI), m/e (relative intensity) 197 (M, 1), 196 (2), 180 (1), 168 (3), 152 (2), 138 (1), 123 (22), 117 (59), 108 (44), 89 (11), 80 (100); high-resolution mass spectrum, m/e 197.1411 ($C_{11}H_{19}NO_2$ requires 197.1416).

2-Tryptophyl-7,7-diethoxyisoquinuclidene (18). A solution of isoquinuclidene **15** (3.00 g, 0.015 mol), tryptophyl bromide[18] **16** (4.09 g, 0.018 mol), and sodium iodide (0.616 g, 0.004 mol) in 35 mL of anhydrous dimethyl sulfoxide containing diisopropylethylamine (7.87 g, 0.061 mol) was stirred at 25 °C for 5 days, poured into saturated sodium bicarbonate, and extracted with ether. The ether extracts were washed with saturated aqueous bicarbonate and brine, dried, and concentrated in vacuo to afford a viscous red-orange oil. Purification by chromatography on Florisil (5% MeOH–$CHCl_3$) afforded 3.05 g (60%) of the 2-tryptophylisoquinuclidene **18** as an oil: ^{1}H NMR 1.15 (t, J = 7.0 Hz, 3 H, CH_3), 1.21 (t, J = 7.0 Hz, 3 H, CH_3), 1.65 (m, J = 2.2 Hz, 2 H, H-8), 2.07 (br d, J = 9.2 Hz, H-3 endo), 2.61 (br m, 1 H, H-4), 2.64 (m, 1 H, NCH_2CH_2), 2.81–3.00 (m, 3 H, NCH_2CH_2, NCH_2CH_2 (1)), 3.21 (dd, J = 9.3, 2.0 Hz, 1 H, H-3 exo), 3.41–3.71 (m, 5 H, OCH_2CH_3, H-1), 6.27 (td, J = 6.7, 1.2 Hz, 1 H, H-5 or H-6), 6.41 (td, J = 7.1, 1.0 Hz, H-5 or H-6), 7.03 (br s, 1 H, indole 2-H), 7.03–7.24 (m, 2 H, indole 5-H, 6-H), 7.34 (br d, J = 8.2 Hz, 1 H, indole H-4), 7.58 (br d, J = 7.4 Hz, 1 H, indole H-7), 8.36 (br s, 1 H, indole N-H); ^{13}C NMR 15.4 (CH_3), 24.3 (NCH_2CH_2), 32.0 (C-4), 36.3 (C-8), 53.8 (C-3, OCH_2CH_3, OCH_2CH_3, or NCH_2CH_2), 55.4 (C-3, OCH_2CH_3, OCH_2CH_3, or NCH_2CH_2), 56.4 (C-3, OCH_2CH_3, $OCHH_2CH_3$, or NCH_2CH_2), 58.1 (C-1), 58.2 (C-3, OCH_2CH_3, OCH_2CH_2), 105.7 (C-7), 111.0 (indole C-7), 114.7 (indole C-3), 118.8 (indole C-2, C-4, C-5, or C-6), 119.0 (indole C-2, C-4, C-5, or C-6), 121.7 (indole C-2, C-4, C-5, or C-6), 121.7 (indole C-2, C-4, C-5, or C-6), 127.7 (indole C-3a), 130.0 (C-5 or C-6), 133.0 (C-5 or C-6), 136.3 (indole C-7a); IR 3460, 3300, 1450, 1230 cm^{-1}; mass spectrum (EI), m/e (relative intensity) 340 (M, 0.1), 294 (6), 224 (10), 184 (35), 172 (21), 144 (21), 143 (55), 130 (100); high-resolution mass spectrum, m/e 340.2141 ($C_{21}H_{28}N_2O_2$ requires 340.2151).

2-Tryptophyl-4-(*tert*-butoxycarbonyl)-7-keto-1,2,7,8,9,10-hexahydroisoquinoline (20). A solution of the 2-tryptophylisoquinuclidene **18** (0.920 g, 0.003 mol) in 13.5 mL of anhydrous acetonitrile in base washed glassware containing *tert*-butyl propiolate (1.36 g, 0.011 mol) was stirred at 80 °C for 3 days. After cooling, the reaction mixture was concentrated in vacuo to afford a viscous dark brown oil which was dissolved in 13.5 mL of 1:1 (v/v) 25% aqueous acetic acid–tetrahydrofuran. The resulting solution was stirred at 25 °C for 6 h and was then poured into saturated aqueous bicarbonate solution. The ethyl acetate extracts of this solution were combined, washed with brine, dried, and concentrated in vacuo to afford a dark brown residue. Purification by flash silica gel chromatography (1:1 chloroform–hexanes to chloroform) afforded the hexahydroisoquinoline **20** (0.41 g, 39%) as a foam: ^{1}H NMR 1.42 (s, 9 H, $C(CH_3)_3$), 2.33 (dd, J = 16.7, 2.3 Hz, 1 H, H-8 eq), 2.50 (br m, 1 H, H-8a), 2.79 (dd, J = 16.7, 5.4 Hz, 1 H, H-8 ax), 2.82 (dd, J = 12.0, 4.2 Hz, 1 H, H-1 eq), 2.95 (ABCD system, J = 14.4, 7.4, 6.2 Hz, 2 H, CH_2CH_2N), 3.13 (t, J = 12.0 Hz, 1 H, H-1 ax), 3.41 (m, 2 H, CH_2CH_2N), 3.59 (br m, 1 H, H-4a), 5.81 (dd, J = 10.1, 2.7 Hz, 1 H, H-6), 6.84 (br d, J = 9.6 Hz, 1 H, H-5), 6.93 (d, J = 1.8 Hz, 1 H, indole H-2), 7.10 (td, J = 7.5 Hz, 1 H, indole H-5 or H-6), 7.13–7.24 (m, 2 H, H-3, indole H-5 or H-6), 7.34 (dd, J = 7.7, 0.6 Hz, 1 H, indole H-4), 7.51 (d, J = 7.8 Hz, 1 H, indole H-7), 8.07 (br s, 1 H, N–H); ^{13}C NMR 24.8 (CH_2CH_2N), 28.5 ($C(CH_3)_3$), 32.3 (C-4a or C-8a), 32.7 (C-4a or C-8a), 40.5 (C-8), 46.5 (C-1), 56.1 (CH_2CH_2N), 78.5 ($OC(CH_3)_3$), 95.7 (C-4), 111.3 (indole C-7), 111.8 (indole C-3), 118.3 (indole C-2, C-4, C-5, C-6), 119.3 (indole C-2, C-4, C-5, C-6), 122.0 (indole C-2, C-4, C-5, C-6), 122.1 (indole C-2, C-4, C-5, C-6), 125.5 (C-6), 126.9 (indole-3a), 136.3 (indole C-7a), 146.4 (C-3), 155.7 (C-6), 167.3 (CO (ester)), 197.6 (CO (ketone)); IR 3460, 3280, 1655, 1605, 1440, 1355 cm^{-1}; mass spectrum (EI), m/e (relative intensity) 392 (M, 17), 338 (15), 337 (65), 293 (9), 262 (13), 206 (65), 162 (21), 144 (65), 162 (21), 144 (65), 130 (100); high-resolution mass spectrum, m/e 392.2100 ($C_{24}H_{28}N_2O_3$ requires 392.2100).

The *N*-acrylate derivative **21** of tryptophylhexahydroisoquinoline was also isolated, albeit in low (ca. 5–10%) yield, as an oil: ^{1}H NMR 1.41 (s, 9 H, $C(CH_3)_3$), 1.52 (s, 9 H, $C(CH_3)_3$), 2.36 (dd, J = 16.7, 1.5 Hz, 1 H, H-8 eq), 2.51 (br m, 1 H, H-8a), 2.82 (dd, J = 16.6, 5.4 Hz, 1 H, H-8 ax), 2.82 (m, 1 H, H-1 eq), 2.94 (m, 2 H, CH_2CH_2N), 3.16 (t, J = 12.0 Hz, 1 H, H-1 ax), 3.42 (ABCD system, J = 13.8, 7.4, 5.9 Hz, 2 H, CH_2CH_2N), 3.61 (br m, 1 H, H-4a), 5.79 (d, J = 14.0 Hz, 1 H, indole NCH=$CHCO_2tBu$), 5.83 (ddd, J = 10.5, 2.4, 0.5 Hz, 1 H, H-6), 6.83 (dt, J = 10.1, 1.9 Hz, H-5), 7.10 (s, 1 H, indole H-2), 7.18–7.28 (m, 2 H, H-3, indole H-5 or indole H-6), 7.32 (td, J = 7.7, 1.0 Hz, indole H-5 or indole H-6), 7.49 (d, J = 7.7 Hz, 1 H, indole H-4 or H-7), 7.53 (d, J = 8.3 Hz, 1 H, indole H-4 or H-7), 8.12 (d, J = 14.0 Hz, 1 H, indole NCH=$CHCO_2tBu$); ^{13}C NMR 24.7 (CH_2CH_2N), 28.3 ($C(CH_3)_3$), 28.5 ($C(CH_3)_3$), 32.5 (C-4a or C-8a), 32.8 (C-4a or C-8a), 40.7 (C-8), 46.5 (C-1), 55.4 (CH_2CH_2N), 78.8 ($OC(CH_3)_3$), 80.5 ($OC(CH_3)_3$), 96.6 (C-4), 102.3 (indole NCH=$CHCO_2tBu$), 110.3 (indole C-7), 118.2 (indole C-3), 119.1 (indole C-2, C-4, C-5, or C-6), 121.4 (indole

C-2, C-4, C-5, or C-6), 122.3 (indole C-2, C-4, C-5, or C-6), 124.3 (indole C-2, C-4, C-5, or C-6), 124.3 (indole C-2, C-4, C-5, or C-6), 125.7 (C-6), 129.1 (indole C-3a), 135.9 (indole NCH=CHCO$_2$tBu), 136.5 (indole C-7a), 145.9 (C-3), 155.4 (C-5), 166.7 (C=O (ester)), 167.0 (C=O (ester)), 197.5 (C=O (ketone)); IR 1650, 1605, 1445, 1350 cm^{-1}; mass spectrum (EI), *m/e* (relative intensity) 518 (M, 45), 462 (9), 445 (28), 406 (12), 392 (17), 389 (24), 363 (15), 337 (12), 270 (56), 263 (13), 262 (77), 256 (35), 244 (34), 222 (12), 214 (89), 207 (48), 206 (99), 200 (100); high-resolution mass spectrum, $m/$e 518.2770 ($C_{31}H_{38}N_2O_5$ requires 518.2781).

Conversion of *N*-Tryptophylhexahydroisoquinoline 20 into the Epimeric Yohimbanes 23–25. A solution of the hydroisoquinoline **20** in 3.5 mL of tetrahydrofuran containing 7.0 mL of 25% aqueous acetic acid was stirred at reflux for 5 days, cooled to 25 °C, and poured into aqueous saturated bicarbonate solution. The extracts obtained by chloroform extraction were combined, washed with bicarbonate, dried, and concentrated in vacuo to afford a brown residue. Purification by flash silica gel chromatography (0.5% methanol–chloroform to 1% methanol–chloroform) afforded 0.068 g (48%) of a mixture of the epimeric yohimbanes **23**, **24**, and **25** in a ratio (by ^{1}H NMR) of 1.6:1.0:1.9, respectively. Pure samples of these substances could be obtained by this chromatographic procedure even though separation was not complete.

Yohimbane **23** (0.024 g, 17%) was isolated as a glass: ^{1}H NMR 2.16 (dt, *J* = 12.9, 3.4 Hz, 1 H, H-14 eq), 2.31 (dd, *J* = 16.4 4.3 Hz, 1 H, H-19 eq), 2.36 (m, 1 H, H-20), 2.57 (m, *J* = 5.7, 3.3 Hz, 1 H, H-15), 2.68 (dd, *J* = 15.2, 3.2 Hz, 1 H, H-21 eq), 2.61–2.75 (m, 3 H, H-14 ax, H-19 ax, H-6 ax), 2.83 (dd, *J* = 11.5, 1.2 Hz, 1 H, H-21 ax), 2.93 (ddd, *J* = 11.9, 5.6, 2.4 Hz, 1 H, H-5 eq), 2.93–3.03 (m, 2 H, H-5ax, H-l eq), 3.26 (br d, *J* = 11.6 Hz, 1 H, H-3), 6.00 (d, *J* = 10.0 Hz, 1 H, H-17), 6.97 (dd, *J* = 10.0, 5.7 Hz, 1 H, H-16), 7.05–7.15 (m, 2 H, H-10 and H-11), 7.28 (d, *J* = 7.8 Hz, H-9), 7.46 (d, *J* = 7.5 Hz, 1 H, H-12), 7.80 (br s, 1 H, indole NH); ^{13}C NMR 21.7 (C-6), 31.6 (C-14), 33.9 (C-15 or C-20), 35.8 (C-15 or C-20), 39.2 (C-19), 53.1 (C-21), 59.2 (C-3), 59.7 (C-5), 108.8 (C-7), 110.8 (C-12), 118.2 (C-9, C-10, C-11), 119.6 (C-9, C-10, or C-11), 121.6 (C-9, C-10, or C-11), 127.3 (C-8), 129.3 (C-17), 134.0 (C-2 or C-13), 136.1 (C-2 or C-13), 152.0 (C-16), 200.6 (C-18); IR 3450, 3320, 2910, 2780, 2730, 1660 cm^{-1}; mass spectrum (EI) *m/e* (relative intensity) 292 (M, 100), 291 (95), 184 (53), 169 (43), 156 (47); high-resolution mass spectrum *m/e* 292.1575 ($C_{19}H_{20}N_2O$ requires 292.1576).

Yohimbane **24** (0.0151 g, 11%) was isolated as a film: ^{1}H NMR 2.19–2.27 (m, 2 H, H-19 ax, H-20), 2.29–2.41 (m, 3 H, H-14 ax, H-14 eq, H-15), 2.38 (t, *J* = 10.5 Hz, 1 H, H-21 ax), 2.48 (d, *J* = 13.0 Hz, 1 H, H-19 eq), 2.65 (dd, *J* = 11.2, 4.3 Hz, 1 H, H-6 eq), 2.72 (m, 1 H, H-6 ax), 2.98 (m, 1 H, H-5 ax), 3.00 (dd, *J* = 10.7, 2.2 Hz, 1 H, H-21 eq), 3.10 (dd. *J* = 10.7, 5.6 Hz, 1 H, H-5 eq), 3.46 (dd, *J* = 11.2, 1.5 Hz, 1 H, H-3), 6.01 (dd, *J* = 9.9, 2.0 Hz, 1 H, H-17), 6.81 (dd, *J* = 10.0, 0.7 Hz, 1 H, H-16), 7.08 (td, *J* = 7.3, 1.0 Hz, 1 H, H-10 or H-11), 7.14 (dt, *J* = 7.5, 1.2 Hz, 1 H, H-10 or H-11), 7.30 (d, *J* = 7.9 Hz, 1 H, H-9 or H-12), 7.47 (d, *J* = 7.7 Hz, 1 H, H-9 or H-12), 7.80 (br s, 1 H, NH); ^{13}C NMR 21.8 (C-6), 34.5 (C-14), 40.5 (C-15 or C-20), 40.8 (C-15 or C-20), 42.2 (C-19), 52.8 (C-21), 60.1 (C-3), 60.5 (C-5), 108.7 (C-7), 110.8 (C-12), 118.3 (C-9, C-10, or C-11), 119.6 (C-9, C-10, or C-11), 121.7 (C-9, C-10, or C-11), 127.4 (C-8), 130.0 (C-17), 133.9 (C-2 or C-13), 136.1 (C-2 or C-13), 152.8 (C-16), 198.6 (C-18); IR 3435, 2870, 2760, 1660, cm^{-1}; mass spectrum (EI), *m/e* (relative intensity) 292 (M, 100), 291 (78), 184 (64), 169 (33), 156 (44); high-resolution mass spectrum, *m/e* 292.1567 ($C_{19}H_{20}N_2O$ requires 292.1576).

Yohimbane **25** (0.029 g, 20%) was isolated as a glass: ^{1}H NMR 2.00 (br dt, *J* = 10.3, 4.3 Hz, 1 H, H-14 ax), 2.22 (dt, *J* = 13.3, 2.4 Hz, 1 H, H-14 eq), 2.36 (br d, *J* = 13.6 Hz, 1 H, H-18 eq), 2.65 (m, *J* = 13.6 Hz, 1 H, H-18 ax), 2.51–2.79 (m, 5 H, H-5 eq, H-6 eq, H-6 ax, H-20, H-21 eq), 2.91–3.10 (m, 3 H, H-5 ax, H-15, H-21 ax), 3.36 (br d, *J* = 12.1 Hz, 1 H, H-3), 6.07 (dd, *J* = 10.2, 2.8 Hz, 1 H, H-6), 6.70 (d, *J* = 10.2 Hz, 1 H, H-5), 7.08 (dt, *J* = 7.4, 0.9 Hz, 1 H, H-10 or H-11), 7.13 (dt, *J* = 7.2, 1.2 Hz, 1 H, H-10 or H-11), 7.30 (d, *J* = 7.9 Hz, 1 H, H-9 or H-12), 7.45 (d, *J* = 7.6 Hz, 1 H, H-9 or H-12), 7.87 (br s, 1 H, N-H); ^{13}C NMR 21.4 (C-6), 34.7 (C-15 or C-20), 35.0 (C-14), 35.4 (C-15 or C-20), 41.6 (C-19), 53.0 (C-21), 54.8 (C-3), 55.4 (C-5), 109.0 (C-7), 110.8 (C-12), 118.2 (C-9, C-10, or C-11), 119.6 (C-9, C-10, or C-11), 121.6 (C-9, C-10, or C-11), 127.4 (C-8), 130.4 (C-17), 133.9 (C-2 or C-13), 136.2 (C-2 or C-13), 152.0 (C-16), 198.3 (C-18); IR 3450, 2885, 1660, 1449, 1410, 1388, 1255 cm^{-1}; mass spectrum (EI), *m/e* (relative intensity) 292 (M, 100), 291 (86), 221 (38), 184 (52), 156 (43); high resolution mass spectrum, *m/e* 292.1573 ($C_{19}H_{20}N_2O$ requires 292.1576).

2-[(1-Phenylsulfonyl)tryptophyl]-7,7-diethoxyisoquinuclidene (19). To a solution of the isoquinuclidene **18** (0.200 g, 0.059 mol) in 1.9 mL of anhydrous THF at −78 °C was added a solution of *n*-butyllithium in hexanes (1.40 M, 0.59 mL, 0.82 mmol) dropwise. The reaction mixture was stirred at −78 °C for 30 min and then at 0 °C for 4 h. The reaction mixture was cooled to −78 °C, and benzenesulfonyl chloride (0.156 g, 0.881 mol) was added dropwise. After the addition was complete, the reaction mixture was warmed to 25 °C, stirred for 24 h, poured into saturated aqueous sodium bicarbonate (0 °C), and extracted with dichloromethane. The dichloromethane extracts were combined, washed with aqueous sodium bicarbonate, dried, and concentrated in vacuo to afford a dark brown oil. Purification on F-20 alumina (1:2 dichloromethane–hexanes) afforded isoquinuclidene **19** (0.174 g, 62%) as a glass (spectroscopic data for **19** given below).

***N,O*-Bis(phenylsulfonyl)tryptophol 17.** To a solution of tryptophol (Aldrich) (3.35 g, 20.8 mmol) in 69 mL of anhydrous THF at −78 °C was added a solution of nBuLi (1.48 M, 30.8 mL, 45.6 mmol) in hexanes, and the mixture was stirred slowly for 2 h at 0 °C. The solution was cooled to −78 °C, benzenesulfonyl chloride (29.3 g, 16.6 mmol) was added, and the mixture obtained was warmed to 25 °C, stirred for 48 h, poured into 200 mL of brine, and extracted with chloroform. The chloroform extracts were washed with water, dried, and concentrated in vacuo to afford a tan solid which was purified on Florisil (4:1 hexanes–ethyl acetate) giving 4.63 g (51%) of **17** as a tan solid. Recrystallization from $CHCl_3$–hexanes gave **17** as white needles (mp 126–128 °C): ^{1}H NMR 3.03 (t, *J* = 6.6 Hz, 2 H, $-CH_2CH_2O-$), 4.27 (t, *J* = 6.6 Hz, 2 H, $-CH_2CH_2O-$), 7.14–7.59 (m, 10 H, indole and aromatic), 7.71 (d, *J* = 8.3 Hz, 2 H, aromatic), 7.86 (d, *J* = 8.1 Hz, 2 H, aromatic), 7.96 (dd, *J* = 8.6, 0.9 Hz, 1 H, aromatic); ^{13}C NMR 24.7 ($-CH_2CH_2O-$), 68.8 ($-CH_2CH_2O-$), 113.6, 117.3, 119.0, 123.2, 124.0, 124.8, 126.6, 127.5, 129.0, 129.2, 130.1, 133.6, 133.8, 134.9, 135.4, 137.0 (indole and aromatic); IR 1140, 1350, 1160, 1120 cm^{-1}; mass spectrum (EI), *m/e* (relative intensity) 441 (M, 11), 283 (45), 142 (72), 115 (31), 77 (100); high-resolution mass spectrum, *m/e* 441.0708 ($C_{22}H_{19}NO_5S$ requires 441.0705).

2-[(*N*-Phenylsulfonyl)tryptophyl]-7,7-diethoxyisoquinuclidene (19). A mixture of bis-phenylsulfonylated tryptophol **17** (4.3 g, 9.7 mmol) and isoquinuclidene **15** (2.4 g, 12 mmol) in 27 mL of DMSO containing diisopropylethylamine (6.2 g, 47 mmol) and sodium iodide (485 mg, 3.2 mmol) was stirred at 25 °C for 24 h, poured into 400 mL of saturated aqueous $NaHCO_3$, and extracted with ether. The ethereal extracts were washed with brine, dried, and concentrated in vacuo yielding 5.4 g of a tan solid. Purification using first F-20 alumina (4:1 hexanes–ethyl acetate followed by chloroform) and then Florisil (chloroform followed by 5% methanol–chloroform) afforded 2.5 g (54%) of **19** as a light tan solid (mp 152–154 °C, EtOAc–hexane): ^{1}H NMR 1.10 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 1.17 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 1.59 (d, *J* = 2.2 Hz, 2 H, H-8), 2.02 (br d, *J* = 9.1 Hz, H-3 endo), 2.58 (m, 2 H, indole CH_2CH_2N), 2.79 (m, 3 H, indole CH_2CH_2N, H-4), 3.11 (dd, *J* = 9.2, 2.0 Hz, 1 H, H-3 exo), 3.35–3.65 (m, 5 H, OCH_2CH_3, H-1), 6.23 (td, *J* = 6.8, 1.5 Hz, 1 H, H-5 or H-6), 6.38 (td, *J* =7.2, 1.2 Hz, 1 H, H-5 or H-6), 7.15–7.55 (m, 7 H, indole H-2, H-4, H-5, H-6, and H-7, $PhSO_2$-3,5-H), 7.83 (dt, *J* = 6.8, 1.8 Hz, 2 H, $PhSO_2$-2,6-H), 7.96 (dt, *J* = 8.1, 1.0 Hz, 1 H, $PhSO_2$-4-H); ^{13}C NMR 15.4 (CH_3), 24.3 (indole CH_2CH_2N), 32.0 (C-4), 36.4 (C-8), 53.7 (C-3, indole CH_2CH_2N, or OCH_2CH_3), 55.4 (C-3, indole CH_2CH_2N or OCH_2CH_3), 56.5 (C-3, indole CH_2CH_2N, or OCH_2CH_3), 57.0 (C-3, indole CH_2CH_2N, or OCH_2CH_3), 58.4 (C-1), 105.5 (C-7), 113.7, 119.5, 121.9, 123.0, 123.2, 124.5 (indole C), 126.6 ($PhSO_2$-C-3,5), 129.0 ($PhSO_2$-C-2,6), 130.2 (C-5 or C-6), 131.3 (indole C), 132.9 (C-5, C-6, or $PhSO_2$-C-4), 134.4 (C-5, C-6, or $PhSO_2$-C-4), 135.4 ($PhSO_2$-C-1 or indole C), 138.7 ($PhSO_2$-C-1 or indole C); IR 2900, 1430, 1355; mass spectrum (CI), *m/e* (relative intensity) 481 (MH^+, 7), 435 (14), 402 (6), 369 (9), 355 (5), 341 (17), 314 (29), 301 (19), 297 (15), 296 (10), 295 (41), 293 (12), 281 (13), 224 (14), 223 (20), 221 (10), 215 (12), 175 (60), 173 (55), 172 (24), 161 (46), 130 (100); high-resolution mass spectrum (CI), *m/e* 481.2166 ($C_{27}H_{33}N_2O_4S$ (MH^+) requires 481.2166).

2-[(1-Phenylsulfonyl)tryptophyl]-4-(*tert*-butoxycarbonyl)-7-keto-1,2,7,8,9,10-hexahydroisoquinoline (22). A solution of the *N*-[(phenylsulfonyl)tryptophyl]isoquinuclidene **19** (0.500 g, 1.04 mmol) in 5.3 mL of anhydrous acetonitrile in base washed glassware containing *tert*-butyl propiolate (0.787 g, 6.24 mmol) was stirred at reflux for 6.5 days. After cooling to 25 °C, the reaction mixture was concentrated in vacuo to afford a dark brown viscous oil which was dissolved in 5.3 mL of a 1:1 (v/v) 25% aqueous acetic acid–tetrahydrofuran solution. This solution was stirred at 24 °C for 3 h, poured into saturated aqueous sodium bicarbonate, and extracted with dichloromethane. The dichloromethane extracts were washed with saturated aqueous sodium bicarbonate, dried, and concentrated in vacuo to afford a viscous brown-black oil. Purification on Florisil afforded the isoquinoline enone **22** (0.34 g, 61%) as a

foam: ^{1}H NMR 1.43 (s, 9 H, C(CH_3)$_3$), 2.31 (br d, J = 16.4 Hz, 1 H, H-8 eq), 2.45 (br m, 1 H, H-8a), 2.72–2.95 (m, 4 H, indole CH_2CH$_2$N, H-1 eq, H-8a), 3.12 (t, J = 12.0 Hz, 1 H, H-1 ax), 3.38 (br t, J = 7.2 Hz, 2 H, indole CH$_2$CH_2N), 3.60 (br m, 1 H, H-4a), 5.83 (dd, J = 10.2, 2.8 Hz, 1 H, H-6), 6.86 (dt, J = 10.2, 1.9 Hz, 1 H, H-5), 7.15–7.55 (m, 8 H, H-3, indole H-2, 4, 5, 6, 7, PhSO$_2$-H-3,5), 7.85 (dt, J = 10.0, 1.6 Hz, 2 H, PhSO$_2$-2,6-H), 7.97 (dd, J = 7.3, 0.7 Hz, 1 H, PhSO$_2$-4-H); ^{13}C NMR 24.2 (indole CH_2CH$_2$N), 28.4 (C(CH_3)$_3$), 32.3 (C-4a or C-8a), 32.6 (C-4a or C-8a), 40.4 (C-8), 46.4 (C-1), 54.8 (indole CH$_2$CH_2N), 78.6 (OC(CH$_3$)$_3$, 96.8 (C-4), 113.7, 118.9, 119.0, 123.2, 123.5, 124.9 (indole C), 125.6 (C-6), 126.5 (PhSO$_2$-C-3,5), 129.1 (PhSO$_2$-C-2,6), 130.2 (indole C), 133.6 (PhSO$_2$-C-4), 135.2 (PhSO$_2$-C-1 or indole C), 138.3 (PhSO$_2$-C-1 or indole C), 145.7 (C-3), 155.1 (C-5), 166.8 (C=O) (ester)), 197.0 (C=O (ketone)); IR 1655, 1610, 1595, 1445, 1355 cm^{-1}; mass spectrum (EI), m/e (relative intensity) 532 (M, 6), 476 (3), 283 (9), 262 (6), 206 (18), 142 (16), 78 (100); high-resolution mass spectrum, m/e 532.2029 ($C_{30}H_{32}N_2O_5S$ requires 532.2032).

2-[(1-Phenylsulfonyl)tryptophyl]-4-(*tert*-butoxycarbonyl)-5-cyano-7-keto-1,2,5,6,7,8,9,10-octahydroisoquinoline (26). A solution of the hydroisoquinolinenone **22** (0.033 g, 0.062 mol) in 0.16 mL of anhydrous benzene was cooled to 0 °C, and a solution of diethyl aluminum cyanide in toluene (0.075 mL, 0.075 mmol, 1.0 M) was added dropwise. This solution was stirred at 0 °C for 1 h, and then pyridine (0.025 g, 0.31 mmol) and trimethylsilyl chloride (0.020 g, 0.19 mmol) were added. The reaction mixture was stirred at 0 °C for 1 h and was then diluted with 10 mL of cold benzene followed by the addition of 0.2 mL of ice water. The resulting suspension was filtered through Celite. The filtrate was washed with saturated aqueous sodium bicarbonate, dried, and concentrated in vacuo to afford a brown oil. Chromatography on F-20 alumina afforded the β-(β-cyano)ketone **26** (0.021 g, 60%) as a glass: ^{1}H NMR 1.44 (s, 9 H, C(CH_3)$_3$), 2.35 (br d, J = 15.1 Hz, 1 H, H-8 eq), 2.52 (br m, 1 H, H-8a), 2.63 (dt, J = 14.6, 2.0 Hz, 1 H, H-6 eq), 2.71 (dd, J = 14.6, 6.6 Hz, 1 H, H-6 ax), 2.77 (dd, J = 15.0, 7.5 Hz, 1 H, H-8 ax), 2.87 (dd, J = 14.2, 7.2 Hz, 1 H, indole CH_2CH$_2$N), 2.95 (m, 1 H, H-1 eq), 2.97 (m, 1 H, indole CH_2CH$_2$N), 3.11 (td, J = 5.2, 1.2 Hz, 1 H, H-4a), 3.45 (m, 2 H, indole CH$_2$CH_2N), 3.61 (t, J = 13.0 Hz, 1 H, H-1 ax), 3.80 (br t, J = 4.8 Hz, 1 H, H-5), 7.22–7.50 (m, 7 H, H-3, indole H-2, 4, 5, 6, PhSO$_2$-H-3,5), 7.50 (tt, J = 7.4, 1.2 Hz, 1 H, indole H-7), 7.83 (d, J = 7.4 Hz, PhSO$_2$-H-2,6), 7.97 (d, J = 8.2 Hz, 1 H, PhSO$_2$-H-4); ^{13}C NMR 24.2 (indole CH_2CH$_2$N), 28.5 (C(CH_3)$_3$), 32.4 (C-4a, C-5, or C-8a), 32.6 (C-4a, C-5, or C-8a), 33.9 (C-4a, C-5, or C-8a), 42.0 (C-6 or C-8), 43.0 (C-6 or C-8), 47.4 (C-1), 55.3 (indole CH$_2$CH_2N), 79.1 (OC(CH$_3$)$_3$), 95.0 (C-4), 113.9 (indole C), 119.0 (CN or indole C), 119.1 (indole C), 120.8 (CN or indole C), 123.3 (indole C), 125.0 (indole C), 126.7 (PhSO$_2$-C-3,5), 129.3 (PhSO$_2$-C-2,6), 129.4 (indole C0, 130.3 (indole C), 133.8 (PhSO$_2$-C-4), 135.3 (indole C or PhSO$_2$-C-1), 138.3 (indole C or PhSO$_2$-C-1), 146.2 (C-3), 167.0 (C=O (ester)), 205.2 (C=O (ketone)); IR 1712, 1650, 1608, 1438, 1355 cm^{-1}; mass spectrum (EI), m/e (relative intensity) 559 (M, 11), 503 (6), 419 (7), 362 (6), 289 (19), 270 (10), 233 (100), 206 (7), 189 (11), 130 (39); high-resolution mass spectrum, m/e 559.2136 ($C_{31}H_{33}N_3O_5S$ requires 559.2141).

In addition, the α-cyano epimer of **26** was also isolated in trace quantities as a glass: ^{1}H NMR 1.46 (s, 9 H, C(CH_3)$_3$), 2.25 (dd, J = 14.2, 4.9 Hz, 1 H, H-8 eq), 2.51 (br m, 1 H, H-8a), 2.53 (m, J = 15.2 Hz, 1 H, H-8 ax), 2.57 (m, J = 4.5 Hz, 2 H, H-6 eq, H-6 ax), 2.80 (dd, J = 13.1, 8.5 Hz, 1 H, H-1 eq), 2.91 (sextet, J = 14.7, 7.0 Hz, 2 H, indole CH_2CH$_2$N), 3.05 (ddd, J = 13.2, 3.4, 0.8 Hz, 1 H, H-1 ax), 3.21 (dd, J = 8.1, 4.0 Hz, 1 H, H-4a), 3.43 (m, 1 H, H-5), 3.45 (t, J = 7.3, 1 H, indole CH$_2$CH_2N), 7.20–7.56 (m, 8 H, H-3, indole H-2, 4, 5, 6, and 7, PhSO$_2$-H-3,5), 7.85 (d, J = 7.2 Hz, 2 H, PhSO$_2$-H-2,6), 7.99 (d, J = 8.3 Hz, 1 H, PhSO$_2$-H-4); IR 1715, 1650, 1600 cm^{-1}; mass spectrum (Cl), m/e (relative intensity) 560 (MH$^+$, 1), 521 (11), 504 (12), 422 (14), 420 (24), 365 (18), 364 (75), 238 (32), 175 (40), 160 (62), 144 (100); high-resolution mass spectrum, m/e 560.2185 ($C_{31}H_{34}N_3O_5S$ NMH$^+$) requires 560.2219).

2-[(1-Phenylsulfonyl)tryptophyl]-4-(*tert*-butoxycarbonyl)-5-cyano-7-(trimethylsiloxy)-1,2,5,8,9,10-hexahydroisoquinoline (27). A solution of triethylaluminum (0.976 mmol, 0.98 mL, 1.0 M) in hexanes was added to trimethylsilyl cyanide (0.107 g, 1.07 mmol). This solution was stirred for 5 min, and then a solution of the hydroisoquinoline-enone **22** (0.260 g, 0.488 mmol) in 2.0 mL of anhydrous benzene was added dropwise. The reaction mixture was stirred for 7 h at 25 °C and diluted with 15 mL of cold benzene and 1 mL of saturated aqueous ammonium chloride (0 °C). The resulting suspension was stirred vigorously for 5 min and filtered through Celite. The filtrate was washed with saturated aqueous ammonium chloride and saturated aqueous sodium bicarbonate, dried, and concentrated in vacuo to afford **27** (0.198 g, 64%) (8.9:1 mixture of β-CN/α-CN epimers by ^{1}H NMR analysis) as an oil. No attempt was made to purify or separate these isomers owing to their extreme lability. The major β-cyano epimer **27b**: ^{1}H NMR 0.10 (s, 9 H, Si(CH_3)$_3$), 1.35 (s, 9 H, C(CH_3)$_3$), 1.72 (d, J = 18.4 Hz, 1 H, H-8 eq), 2.09 (m, 1 H, H-8a), 2.38 (ddt, J = 18.3, 7.8, 2.0 Hz, 1 H, H-8 ax), 2.75 (ddd, J = 6.5, 4.5, 1.5 Hz, 1 H, H-4a), 2.81 (m, 2 H, H-1 eq, indole CH_2CH$_2$N-(1)), 2.91 (m, 1 H, indole CH_2CH$_2$N (1)), 3.35 (m, 2 H, indole CH$_2$CH_2N), 3.47 (t, J = 12.8 Hz, 1 H, H-1 ax), 3.65 (td, J = 6.0, 1.4 Hz, H-5), 4.62 (dd, J = 5.3, 1.6 Hz, 1 H, H-6), 7.14 (m, 1 H, indole H-2), 7.19–7.42 (br m, 7 H, H-3, indole H-4, 5, 6, 7, PhSO$_2$-H-3,5), 7.73 (d, J = 7.2 Hz, 2 H, PhSO$_2$-H-2,6), 7.87 (d, J = 8.3 Hz, 1 H, PhSO$_2$-H-4); ^{13}C NMR 0.18 (Si(CH_3)$_3$), 24.1 (indole CH_2CH$_2$N), 28.5 (C(CH_3)$_3$), 29.7 (C-4a, C-5, or C-8a), 29.9 (C-4a, C-5, or C-8a), 30.3 (C-4a, C-5, or C-8a), 31.6 (C-8), 47.7 (C-1), 55.3 (indole CH$_2$CH_2N), 78.6 (OC(CH$_3$)$_3$), 95.7 (C-17), 96.6 (C-14), 113.7 (indole C), 119.2 (indole C), 119.4 (CN or indole C), 121.0 (CN or indole C), 123.2 (indole C), 124.9 (indole C), 126.6 (PhSO$_2$-C-3,5), 128.2 (PhSO$_2$-C-2,6 or indole C), 129.2 (PhSO$_2$-C-2,6 or indole C), 130.6 (indole C), 133.7 (PhSO$_2$-C-4), 135.2 (indole C or PhSO$_2$-Ch1), 138.1 (indole C or PhSO$_2$-C-1), 145.9 (C-3), 151.7 (C-18), 167.2 (C=O (ester)); IR 1652, 1601, 1435, 1241 cm^{-1}.

2-[(1-Phenylsulfonyl)tryptophyl]-4-(*tert*-butoxycarbonyl)-5-cyano-6-hydroxy-7-(trimethylsiloxy)-1,2,5,6,7,8,9,10-octahydroisoquinoline (28). To an ice-cooled solution of silyl enol ethers **27** (0.19 g, 0.301 mol) in 0.95 mL of anhydrous tetrahydrofuran was added a solution of diborane in tetrahydrofuran (1.0 M, 0.45 mL, 0.451 mmol). The reaction mixture was warmed to 25 °C and stirred for 20 h. It was then cooled to −10 °C, and 0.95 mL of 3 N aqueous NaOH (0 °C) and 0.95 mL of 30% H_2O_2 (0 °C) were added. The resulting suspension was stirred at −10 °C for 20 min, diluted with dichloromethane and water, and separated. The aqueous layer was extracted with dichloromethane. The combined dichloromethane layers were dried and concentrated in vacuo to afford 0.20 g (ca. 99%) of **28** as a foam. No attempt was made to purify this substance owing to its lability: ^{1}H NMR 0.13 (s, 9 H, Si(CH_3)$_3$), 1.42 (s, 9 H, C(CH_3)$_3$), 1.58 (d, J = 14.4 Hz, 1 H, H-8 eq), 2.01 (br m, 1 H, H-8a), 2.23 (br m, J = 14.4 Hz, 1 H, H-8 ax), 2.86 (br m, 2 H, H-1 eq, NCH$_2$CH_2 indole (1)), 2.97 (m, 1 H, NCH$_2$CH_2 indole (1)), 3.04 (br t, J = 5.0 Hz, 1 H, H-4a), 3.31 (br d, J = 3.3 Hz, 1 H, H-5), 3.43 (br m, 2 H, NCH_2CH$_2$ indole), 3.92 (br d, J = 2.5 Hz, 1 H, H-7), 4.11 (br s, 1 H, H-6), 4.35 (t, J = 12.8 Hz, 1 H, H-1 ax), 7.22 (d, J = 7.5 Hz, indole H-2), 7.30–7.55 (br m, 7 H, H-3, indole H-4, 5, 6, and 7, PhSO$_2$-H-3, 5), 7.83 (d, J = 7.9 Hz, 2 H, PhSO$_2$-H-2, 6), 7.97 (d, J = 8.2 Hz, 1 H, PhSO$_2$-H-4).

2-[(1-Phenylsulfonyl)tryptophyl]-4-(*tert*-butoxycarbonyl)-5-cyano-6-methoxy-7-(trimethylsiloxy)-1,2,5,6,7,8,9,10-octahydroisoquinoline (29). To a solution of the alcohol **28** (0.227 g, 0.349 mmol) in 17.3 mL of anhydrous tetrahydrofuran at −78 °C was added n-butyllithium in hexanes (1.46 M, 0.29 mL, 0.419 mmol). After stirring for 1 h at −78 °C, methyl triflate (0.075 g, 0.46 mmol) was added, and stirring was continued at −78 °C for 1 h and then at −40 °C for 3 h. The mixture was quenched by the addition of 10% aqueous ammonium hydroxide (0 °C). After stirring at 0 °C for 5 min, the mixture was diluted with dichloromethane and poured into water. The layers were separated, and the aqueous layer was extracted with dichloromethane. The organic extracts were combined, dried, and concentrated in vacuo to afford an orange oil. Purification on flash neutral alumina (20% hexanes–dichloromethane) afforded 0.090 g (38%) of methyl ether **29** as a foam: ^{1}H NMR 0.15 (s, 9 H, Si(CH_3)$_3$), 1.45 (s, 9 H, C(CH_3)$_3$), 1.60 (d, J = 14.4 Hz, 1 H, H-8 eq), 2.03 (br m, 1 H, H-8a), 2.10 (ddd, J = 14.5, 6.4, 2.9 Hz, 1 H, H-8 ax), 2.81 (ddd, J = 12.7, 3.3, 1.0 Hz, 1 H, H-1 eq), 2.86–3.02 (br m, 3 H, H-4a, NCH$_2$CH_2 indole), 3.39 (br m, 2 H, NCH_2CH$_2$ indole), 3.40 (s, 3 H, OCH$_3$), 3.51 (dd, J = 5.3, 1.9 Hz, 1 H, -H-5), 3.56 (br t, J = 2.6 Hz, 1 H, H-6), 3.95 (br q, J = 3.0 Hz, 1 H, H-7), 4.32 (t, J = 12.6 Hz, 1 H, H-1 ax), 7.23 (td, J = 5.0 Hz, indole H), 7.30–7.55 (br m, 6 H, indole H(4), PhSO$_2$-H-3, 5), 7.36 (s, 1 H, H-3), 7.83 (br d, J = 8.4 Hz, 2 H, PhSO$_2$-H-2, 6), 7.97 (d, J = 8.4 Hz, 1 H, PhSO$_2$-H-4); ^{13}C NMR −0.1 (Si(CH_3)$_3$), 24.0 (-CH_2CH$_2$N-), 27.8 (C-4a, 5 or 20), 28.5 (C(CH_3)$_3$), 28.9 (C-4a, 5 or 20), 29.7 (C-4a, 5 or 20), 30.1 (C-8), 48.0 (C-1), 55.3 (-CH$_2$CH_2N-), 57.3 (OCH$_3$), 67.1 (C-7), 78.3 (C(CH$_3$)$_3$), 79.2 (C-6), 95.5 (C-4), 113.7, 119.1, 119.4, 123.2, 123.4, 124.8, 126.6, 129.2, 130.4, 133.7, 135.2, 138.1 (indole and aromatic), 120.5 (CN), 146.7 (C-3), 167.3 (O—C=O); IR 1660, 1612, 1450, 1365 cm^{-1}; mass spectrum, m/e (relative intensity) 664 (P, 4), 608 (10), 524 (6), 419 (24), 391 (46), 325 (71), 279 (38), 204 (57), 175 (68), 144 (100); high-resolution mass spectrum, m/e 664.2866 ($C_{35}H_{46}N_3SSi$ requires 664.2877).

4-(*tert*-Butoxycarbonyl)-5-cyano-6-methoxy-7-hydroxy-2-tryptophyl 1,2,4a,5,6,7,8,8a-octahydroisoquinoline (30). To a stirred solution of hydroisoquinoline **29** (87 mg, 0.13 mmol) in anhydrous methanol (23 mL) at 25 °C was added NaHPO$_4$ (576 mg, 4.00 mmol) and 6% sodium amalgum (228 mg) at 2-h intervals for a total of 5 h. After pouring into cold water the solution was decanted from Hg and extracted with CHCl$_3$.

Combined organic extracts were washed with water, dried, and concentrated in vacuo giving a residue which was subjected to flash neutral alumina chromatography ($CHCl_3$ followed by 5% EtOH/$CHCl_3$) to give **30** (53 mg, 89%) as an oil: ^{1}H NMR (400 MHz) 141 (s, 9 H, $C(CH_3)_3$), 1.68 (ddd, J = 14.7, 3.1, 3.1 Hz, 1 H, H-8 eq), 1.83 (br s, 1 H, OH), 2.04–2.09 (m, 1 H, H-8 ax), 2.16 (ddd, J = 14.6, 6.9, 3.5 Hz, 1 H, H-8 ax), 2.92 (dd, J = 11.8, 5.0 Hz, 1 H, H-1 eq), 2.96–3.09 (m, 2 H, $-NCH_2CH_2$ indole), 3.40–3.53 (m, 2 H, $-NCH_2CH_2$ indole), 3.42 (s, 3 H, OCH_3), 3.61 (d, J = 5.4 Hz, 1 H, H-5), 3.65 (br t, J = 2.8 Hz, 1 H, H-6), 4.06 (br q, J = 3.6 Hz, 1 H, H-7), 4.12 (t, J = 12.8 Hz, 1 H, H-1 ax), 7.04 (d, J = 2.2 Hz, 1 H, indole H-2), 7.09 (t, J = 7.4 Hz, 1 H, indole H-5 or 6), 7.17 (t, J = 7.5 Hz, 1 H, indole H-5 or 6), 7.32–7.36 (m, 2 H, H-3 and indole H-4), 7.55 (d, J = 7.9 Hz, 1 H, indole H-7), 8.08 (br s, 1 H, indole NH); ^{13}C NMR 24.8 ($-CH_2CH_2N-$), 28.1 (C-4a, 5 or 8a), 28.6 ($C(CH_3)_3$), 29.6 (C-8), 29.8 (C-4a, 5 or 8a), 29.9 (C-4a, 5 or 8a), 48.8 (C-1), 56.5 ($-CH_2CH_2N-$), 57.5 (OCH_3), 67.9 (C-7), 78.8 ($OC(CH_3)_3$), 80.6 (C-6), 94.7 (C-4), 111.3 (indole C-7), 112.7 (indole C-3), 118.6 (indole C-2, 4, 5 or 6), 119.5 (indole C-2, 4, 5 or 6), 121.1 (CN), 122.1 (indole C-2, 4, 5 or 6), 122.8 (indole C-2, 4, 5 or 6), 127.3 (indole C-3a), 136.6 (indole C-7a), 147.4 (C-3), 167.6 (O—C=O); IR ($CHCl_3$) 3480, 1650, 1600, 1140, 1090 cm^{-1}; mass spectrum (CI), m/e (relative intensity) 452 (MH^+, 14), 397 (23), 396 (100), 378 (19), 352 (47), 321 (21), 293 (5), 265 (47), 221 (21); high-resolution mass spectrum (CI), m/e 452.2549 ($C_{26}H_{34}O_4N_3$ (MH^+) requires 452.2549).

Wenkert Cyclization of 4-(*tert*-Butoxycarbonyl)-5-cyano-6-methoxy-7-hydroxy-1,2,4a,5,6,7,8,8a-octahydroisoquinoline (30) To Produce Yohimbanes 39α and 39β. A solution of **30** (35 mg, 0.077 mmol) in THF (0.54 mL) and 25% aqueous acetic acid (1 mL) was stirred at 70 °C for 50 h. The mixture was cooled to 25 °C, poured into saturated aqueous $NaHCO_3$, and extracted with $CHCl_3$. Combined organic extracts were washed with H_2O, dried, and concentrated in vacuo giving a tan solid. Purification by preparative TLC (4% EtOH/$CHCl_3$) gave 17 mg (64%) of **39α** and 2 mg (5%) of **39β**.

For **39α**: (mp 246 °C dec, benzene) ^{1}H NMR 1.73–1.84 (m, 1 H, H-14 ax), 1.79 (ddd, J = 12.7, 3.89, 3.89 Hz, 1 H, H-19 eq), 1.89 (m, 1 H, H-20), 2.17 (q, J = 12.7 Hz, 1 H, H-19 ax), 2.25–2.33 (m, 3 H, H-14 eq, 15, and OH), 2.51–2.57 (m, 1 H, H-6 ax or eq), 2.60 (dd, J = 11.6, 3.3 Hz, 1 H, H-21 eq), 2.66–2.71 (m, 1 H, H-6 ax or eq), 2.72 (dd, J = 10.9, 4.4 Hz, 1 H, H-16), 2.82 (dd, J = 11.6, 1.9 Hz, 1 H, H-21 ax), 2.90–2.98 (m, 2 H, H-5 ax and eq), 3.22 (dd, J = 10.9, 9.0, Hz 1 H, H-17), 3.24 (br d, J = 7.6 Hz, 1 H, H-3), 3.45–3.50 (m, 1 H, H-18), 3.67 (s, 3 H, OCH_3), 7.07 (ddd, J = 7.4, 7.4, 1.1 Hz, 1 H, H-10), 7.14 (ddd, J = 7.0, 7.0, 1.2 Hz, 1 H, H-11), 7.33 (dd, J = 7.0, 1.0 Hz, 1 H, H-12), 7.46 (d, J = 7.8 Hz, 1 H, H-9), 7.91 (br s, 1 H, indole NH); ^{13}C NMR (acetone-d_6) 22.8 (C-6), 28.9 (C-19), 34.7 (C-14), 35.3 (C-16, 15 or 20), 38.8 (C-16, 15 or 20), 39.1 (C-15, 16 or 20), 54.0 (C-21), 60.8 (C-5), 61.0 (OCH_3 or C-3), 61.4 (OCH_3 or C-3), 75.1 (C-18), 82.6 (C-17), 108.5 (C-7), 111.9 (C-12), 118.5 (C-11), 119.6 (C-9), 120.7 (CN) 121.6 (C-10), 128.4 (C-8), 136.1 (C-2), 137.9 (C-13); IR (KBr) 3560, 3400, 2940, 2900, 2840, 2760, 2220, 1450, 1120, 990 cm^{-1}; mass spectrum (EI), m/e (relative intensity 351 (M, 100), 350 (99), 336 (18), 320 (13), 293 (12), 237 (10), 224 (9), 223 (13), 222 (9), 221 (26), 211 (9), 209 (11), 207 (8), 184 (19), 170 (32), 169 (35), 168 (10), 157 (10), 156 (23), 144 (24), 143 (16), 142 (8), 130 (10); high-resolution mass spectrum (EI), m/e 351.1956 ($C_{21}H_{25}N_3O_2$ requires 351.1947).

For **39β**: ^{1}H NMR (400 MHz) 1.69–1.76 (m, 3 H, OH, H-14 eq, H-20), 1.80 (ddd, J = 13.0, 4.2, 4.2 Hz, 1 H, H-19 eq), 1.94–2.01 (m, 1 H, H-15), 2.22 (q, J = 13.0 Hz, 1 H, H-19 ax), 2.25–2.32 (m, 1 H, H-14 ax), 2.49 (dd, J = 11.7, 1.9 Hz, 1 H, H-21 ax), 2.52–2.55 (m, 1 H, H-6 eq), 2.62 (dd, J = 10.6, 4.7 Hz, 1 H, H-16), 2.92–3.00 (m, 1 H, H-6 eq), 2.99 (dd, J = 11.7, 3.8 Hz, 1 H, H-21 eq), 3.18–3.25 (m, 2 H, H-5 ax and H-5 eq), 3.36 (dd, J = 10.6, 9.0 Hz, 1 H, H-17), 3.42–3.48 (m, 1 H, H-18), 3.72 (s, 3 H, OCH_3), 4.55 (br s, 1 H, H-3), 7.08 (ddd, J = 7.8, 7.8, 1.0 Hz, 1 H, H-10), 7.15 (ddd, J = 7.1, 7.1, 1.1 Hz, 1 H, H-11), 7.37 (d, J = 8.0 Hz, 1 H, H-12), 7.44 (d, J = 8.0 Hz, 1 H, H-9), 7.96 (br s, 1 H, indole NH); mass spectrum (EI), m/e (relative intensity) 351 (P, 100), 350 (65), 336 (25), 320 (15), 293 (21), 237 (16), 224 (3), 223 (11), 221 (16), 209 (10), 184 (25), 170 (21), 169 (11), 130 (5); high-resolution mass spectrum (EI), m/e 351.1942 ($C_{21}H_{25}N_3O_2$ requires 351.1947).

Crystal structure determination of 39α: white crystal from benzene; 0.03 × 0.2 × 0.43 mm specimen for X-ray measurements; Enraf-Nonius CAD-4 diffractometer; Cu radiation with incident beam monochromator (Cu Kα λ = 1.5418 A); cell parameters from 25 reflections centered in the range 7.7 < Θ < 28.5°; monoclinic space group $P2_1/c$, a = 12.394 (4) Å, b = 9.697 (2) Å, c = 15.422 (5) Å, β = 101.96 (3)°; d_{calc} = 1.29 g cm^{-3} for Z = 4 (M_r = 351.45); intensity data measured with 2Θ–Θ scan at variable Θ scan speed of 8.24–0.66° min^{-1}; Θ scan range of 1.5 (0.6 + 0.14 tan Θ), scan recorded as 96 steps with two outermost 16 step blocks for background determination; six standard reflections measured every 1 h of X-ray exposure; 3090 data (includes 90 standards) measured from Θ = 2–60°; index range for h, k, l of −13–13, 0–10, 0–16; 2882 unique data; 2187 reflections with $I > 3\sigma(I)$; average change in standard intensities of −1.9% with range of −5.8–+2.3%; absorption ignored. All crystallographic calculations performed with the TEXSAN program system[35] on a Digital Equipment Corp. Microvax II computer; structure solved with the MITHRIL[36] direct methods link; refinement by full-matrix least-squares with anisotropic temperature factors for C, N, and O and isotropic terms for H; $\Sigma[1/\sigma(F_o)]^2(F_o - Fc)^2$ minimized; secondary extinction[37] refined; final R, R_w, and goodness-of-fit = 0.052, 0.082, 1.83; maximum Δ/σ = 0.28; maximum and minimum values in final difference map of 0.17 and −0.17 e A^{-3}. Tables of atomic coordinates, temperature factors, bond lengths and angles, and structure factors are included in the supplementary material. An ORTEP drawing[38] is shown in Figure 1. The drawing was labeled with the PLOTMD program and printed on a Hewlett-Packard Laserjet II printer.[39]

16-Carboxamido-18-hydroxy-17-methoxyalloyohimbane (40). A solution of **39α** (11 mg, 0.031 mmol) in MeOH (1.2 mL), 1 N NaOH (225 μL), and 15% H_2O_2 (75 μL) was stirred at 90 °C for 2.5 h. Excess H_2O_2 was quenched with $NaBH_4$ (28 mg) at 25 °C, the mixture was concentrated in vacuo, and the residue was suspended in H_2O and extracted with $CHCl_3$. Combined organic extracts were dried and concentrated in vacuo giving a tan solid which was subjected to preparative TLC (3.33:1 $CHCl_3$/EtOH (v/v)) to yield the carboxamide **40** (6 mg, 48%), as a tan solid (mp 266–270 °C days, $CHCl_3$–MeOH): ^{1}H NMR (400 MHz) 1.69–1.78 (m, 2 H, H-14 ax, H-19 eq), 1.86 (br d, J = 9.9 Hz, 1 H, H-20), 2.00–2.26 (m, 3 H, H-14 eq, H-15, OH), 2.18 (q, J = 12.8 Hz, 1 H, H-19 ax), 2.40 (dd, J = 10.8, 4.5 Hz, 1 H, H-16), 2.45–2.52 (m, 1 H, H-6 ax or eq), 2.55 (d, J = 11.4 Hz, 1 H, H-21 eq), 2.63–2.67 (m, 1 H, H-6 ax or eq), 2.80 (d, J = 11.4 Hz, 1 H, H-21 ax), 2.89–2.95 (m, 2 H, H-5 ax and eq), 3.11 (br d, J = 11.0 Hz, 1 H, H-3), 3.46 (dd, J = 10.6, 10.6, 1 H, H-17), 3.52 (s, 3 H, OCH_3), 3.58–3.66 (m, 1 H, H-18), 5.49 (br s, 1 H, NH), 5.89 (br s, 1 H, NH), 7.04 (dd, J = 7.2, 7.3, 1 H, H-10), 7.09 (dd, J = 7.5, 7.5 Hz, 1 H, H-11), 7.26 (d, J = 7.7 Hz, 1 H, H-12), 7.43 (d, J = 7.7 Hz, 1 H, H-9), 8.00 (br s, 1 H, indole NH); ^{13}C NMR (acetone-d_6) 22.9 (C-6), 28.7 (C-19), 35.2 (C-14), 36.8 (C-20 or C-15), 39.9 (C-20 or C-15), 53.3 (C-16), 5.43 (C-21), 60.7 (OCH_3 or C-3), 61.4 (C-5), 61.8 (OCH_3 or C-3), 76.1 (C-18), 82.5 (C-17), 108.2 (C-7), 112.0 (C-12), 118.4 (C-11), 119.5 (C-9), 121.4 (C-10), 128.4 (C-8), 136.8 (C-2), 138.1 (C-13), 174.5 (C=O); IR (KBr) 3422, 2924, 1654 cm^{-1}; mass spectrum (EI), m/e (relative intensity) 369 (M, 100), 368 (88), 354 (17), 337 (13), 293 (13), 239 (30), 221 (19), 184 (17), 169 (16), 144 (12); high-resolution mass spectrum, m/e 369.2055 ($C_{21}H_{27}N_3O_3$ requires 369.2052).

16-Carbomethoxy-18-hydroxy-17-methoxyalloyohimbane (42). A solution of the carbamide **40** (15 mg, 0.041 mmol) in 18% HCl (2.32 mL) was stirred at reflux (100 °C) for 5 h. The resulting brown solution was concentrated in vacuo to yield a black solid which was resuspended in MeOH (0.3 mL) and combined with an excess ethereal solution of diazomethane. After 1 h, unreacted diazomethane was quenched by the addition of glacial HOAc, and the mixture was concentrated in vacuo to yield a brown solid which was resuspended in saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. Combined organic extracts were dried and concentrated in vacuo yielding a yellow solid which was subjected to preparative TLC (5% MeOH/$CHCl_3$) giving the methyl ester **42** (5 mg, 30%) as a white solid (mp 144–148 °C dec, PhH–hexane): ^{1}H NMR (400 MHz) 1.65–1.83 (m, 3 H, H-19 eq, H-14 ax and OH), 1.91 (br d, J = 12.9 Hz, 1 H, H-20), 2.18 (q, J = 12.9 Hz, 1 H, H-19 ax), 2.21–2.25 (m, 2 H, H-15, H-14 eq), 2.46–2.53 (m, 1 H, H-6 ax or eq), 2.56 (dd, J = 11.5, 3.3 Hz, 1 H, H-21 eq), 2.62 (dd, J = 11.1, 4.6 Hz, 1 H, H-16), 2.66–2.69 (m, J = 11.5, 1.91 Hz, 1 H, H-6 ax or eq), 2.88–2.96 (m, 2 H, H-5 ax and eq), 3.12 (br d, J = 10.7 Hz, 1 H, H-3), 3.41 (dd, J = 11.1, 8.9 Hz, 1 H, H-17), 3.53 (s, 3 H, OCH_3), 3.53–3.60 (m, 1 H, H-18), 3.78 (s, 3 H, $COCH_3$), 7.05 (ddd, J = 7.5, 7.5, 0.9 Hz, 1 H, H-10), 7.11 (ddd, J = 7.5, 7.5, 1.2 Hz, 1 H, H-11), 7.29 (d, J = 7.5 Hz, 1 H, H-12), 7.44 (d, J = 7.5 Hz, 1 H, H-9), 7.78 (br s, 1 H, NH); ^{13}C NMR (acetone-d_6) 22.6 (C-6), 28.7 (C-19), 35.0 (C-14), 36.1 (C-15 or C-20), 38.9 (C-15 or C-20), 51.6 (C-16 or OCH_3), 52.9 (C-16 or OCH_3), 54.0 (C-21), 61.0 (C-3), 61.0 (OCH_3), 61.3 (C-5), 75.8 (C-18), 82.1 (C-17), 108.1 (C-7), 111.6 (C-12), 118.4 (C-11), 119.4 (C-9), 121.4 (C-10), 128.2 (C-8), 136.1 (C-2), 137.3 (C-13), 173.3 (C=O); IR (KBr) 3400, 2920, 2800, 2760, 1740, 1630, 1450 cm^{-1}; mass spectrum (EI), m/e (relative intensity) 384 (M, 20), 383 (17), 369 (4), 367 (2), 353 (3), 351 (3), 184 (3), 170 (2), 169 (3), 151 (4), 144 (2); high-resolution mass spectrum, m/e 384.2026 ($C_{22}H_{28}N_2O_4$ requires 384.2049).

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Supplementary Material Available: Tables of atomic coordinates, temperature factors, and bond lengths and angles (8 pages); table of observed and calculated structure factors (15 pages). Ordering information is given on any current masthead page.

Neighboring Group Participation in Carbene Chemistry. Effect of Neighboring Carboxylate Group on Carbene Reactivities[1]

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Abstract: Reactivities of (alkoxycarbonyl)carbenes are shown to be dramatically changed as one substitutes the ester group with carboxylate group. Thus, (methoxycarbonyl)- or carboxyl(4-nitrophenyl)carbene (**2a** and **2b**, respectively), generated by photolysis of the corresponding diazo compounds in a binary mixture of 2-methyl-2-butene and methanol, gives both cycloaddition products to the butene and OH inserts products into methanol, the relative reactivities (k_{OH}/k_{add}) being 0.3–0.5. In marked contrast, the "carboxylate" carbene (**2c**) generated from the sodium salt of the diazoacetate under the same conditions produces mostly the OH insertion product at the expense of the cyclopropanes, k_{OH}/k_{add} being > 100. The marked effect of the carboxylate group is nicely explained in terms of the participation by the neighboring carboxylate group, which interacts strongly with the vacant p orbital of the singlet carbene, resulting in the reduction of the electrophilicity. The competition experiments using two sets of alkenes with different electron density also support the above idea. Thus, **2c** is > 2000 times more reactive to α-chloroacrylonitrile relative to 1-hexene while **2a** is only 3–4 times more reactive. More intriguingly, a Hammett treatment of the addition of **2** to a series of substituted styrenes demonstrates that philicity of the carbene is converted from electrophilic to nucleophilic in going from **2a** to **2c**. The geometries of the singlet state of the parent carboxylate carbene optimized by the ab initio molecular orbital using the STO-3G basis set is very much like that of α-lactone anion, where strong interaction between carboxylate oxygen anion and the vacant p orbital is possible. ESR studies show, however, that both **2a** and **2c** have a triplet ground state with comparable thermal stability and that the geometry of the triplet state is not affected by the neighboring carboxylate group.

What is the most dramatic and therefore impressive effect of substituents in organic reactions is neighboring group participation[2-4] where the intramolecular association of one group in a molecule exerts a dramatic effect on the reaction course of the other. Thus, in the nucleophilic displacement (S_N) reaction, the reactions proceed particularly rapidly and/or with retained stereochemistry when the nucleophile and the leaving group are in the same molecule. In these molecules, internal nucleophiles become bonded (fully or partially) to the electron-deficient center for an interval of time during the reaction's progress. For example, *o*-(chloromethylsulfonyl)benzoate undergoes hydrolysis quite easily under the conditions where its para isomer is completely inert,[5] and the hydrolysis of α-bromoacetic acids proceeds with retention of configuration of the α-carbon.[6] These results are nicely explained in terms of intramolecular displacement leading to lactones which subsequently undergo attack by the solvent nucleophiles. Such intramolecular displacement, which has been termed anchimeric assistance or neighboring group participation, occurs not only in appropriate organic systems but also in many biological processes.

In carbene chemistry,[7,8] although substituent effects have sustained a high level of attention over the past 15 years, the effect of substituents which are directly bound to, or conjugated with the carbene center has been of primary interest, and no study of such magnitude has been made for the effect of substituents which are insulated from direct conjugation with the carbenic atom. Moreover, the effect of neighboring groups on the reactivity of carbene[9] has been much less dramatic than that in carbenium ion chemistry. This is apparently because carbenes are usually much less electrophilic than carbenium ions. Another reason which should be pointed out here may be that the internal nucleophiles which have been used in carbene reactions are heavily weighted with neutral heteroatom substituents, e.g., ether, carbonyl and halogens.[9]

It is rather surprising to note here that little is known about the effect of neighboring anionic groups such as carboxylate, phosphonate, or sulfonate anions, all of which have been known to act as the most effective participants in the nucleophilic dis-

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(1) Preliminary form of this work has appeared: Tomioka, H.; Tabayashi, K.; Izawa, Y. *Chem. Lett.* **1985**, 1103.
(2) Lambert, J. B.; Mark, H. W.; Holcomb, A. G.; Magyar, E. S. *Acc. Chem. Res.* **1979**, *12*, 317.
(3) Capon, B.; McManus, S. P. *Neighboring Group Participation*; Plenum: New York, 1976; Vol. 1.
(4) Brown, H. C. *The Nonclassical Ion Problem*; Plenum: New York, 1977.
(5) Bordwell, F. G.; Cooper, G. D. *J. Am. Chem. Soc.* **1957**, *79*, 916.
(6) Winstein, S.; Hanson, C.; Grunwald, E. *J. Am. Chem. Soc.* **1948**, *70*, 812.
(7) (a) Moss, R. A., Jones, M., Jr., Eds. *Carbenes*; Wiley: New York, 1973, 1975; Vols. 1 and 2. (b) Kirmse, W. *Carbene Chemistry*; Academic Press: New York, 1971. (c) Wentrup, C. *Reactive Molecules*; Wiley: New York, 1984; Chapter 4.
(8) *Recent Advances in Carbene Chemistry*; Platz, M. S., Ed.; Tetrahedron Symposium in Print 19 1985.
(9) For review, see: Taylor, K. G. *Tetrahedron* **1982**, *38*, 2751.

0002-7863/90/1512-7692$02.50/0