Synthesis Applications of Cationic Aza-Cope Rearrangements.[1] Stereocontrolled Synthesis of Hexahydro-1*H*-pyrrolo[2,3-*d*]carbazoles

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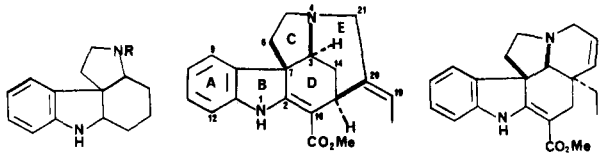
The synthesis of a series of 5-substituted octahydro-1*H*-pyrrolo[2,3-*d*]carbazoles **4**, potential intermediates for the synthesis of the *Strychnos* alkaloid akuammicine **2**, is described. The known β-keto ester **9** was converted to the (*E*)-epoxy alcohol **7** in 39% yield. In seven subsequent steps (19–38% yield), this intermediate was transformed to the octahydro-1*H*-pyrrolo[2,3-*d*]carbazoles **4**. The key step in this transformation was tandem cationic aza-Cope rearrangement–Mannich cyclization of **19** which gave **4** in 51–99% yield. Unfortunately, no method could be found for converting **4** to akuammicine.

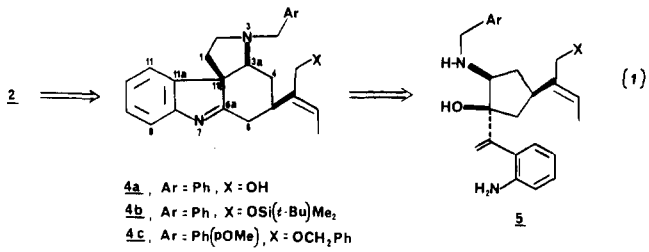
The hexahydro-1*H*-pyrrolo[2,3-*d*]carbazole ring system **1** is a common structural element of a wide variety of indole alkaloids.[2] Simple examples include the *Strychnos* alkaloid akummicine (**2**) and the *Aspidosperma* alkaloid[3]



1 **2**, AKUAMMICINE **3**, TABERSONINE

(−)-tabersonine (**3**). A number of excellent methods have been developed for preparing hydropyrrolocarbazoles of this type, which often serve as key intermediates for the synthesis of pentacyclic *Aspidosperma* alkaloids.[3,4] Not surprisingly, hexahydro-1*H*-pyrrolo[2,3-*d*]carbazoles have typically been assembled from indole precursors.

In this paper we report a new method for preparing hexahydro-1*H*-pyrrolo[2,3-*d*]carbazoles that, significantly, does not employ indole starting materials. Specifically, we detail the synthesis of tetracycles **4** having a cis relationship[5] between a C(5) methylpropenyl substituent and the pyrrolidine ring. These specific hexahydro-1*H*-pyrrolo[2,3-*d*]carbazoles were of interest as potential precursors (see eq 1) of the *Strychnos* alkaloid akuammicine.[6] Tetracycles **4** are formed with complete stereocontrol by tandem cationic aza-Cope rearrangement–Mannich cyclization[1,7–10] of cyclopentanols **5**. We also briefly relate our, to date, unsuccessful efforts to convert intermediates **4** to the pentacyclic strychnan ring system.

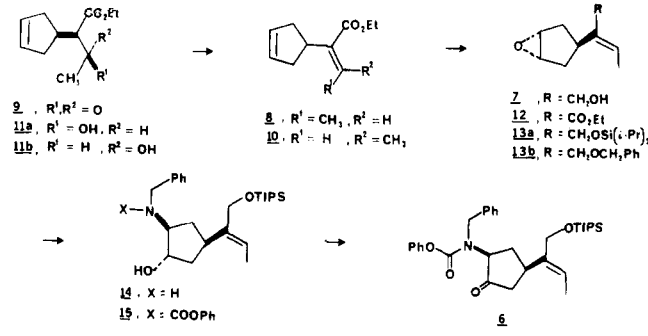


2 **4a**, Ar = Ph, X = OH
4b, Ar = Ph, X = OSi(*t*-Bu)Me₂
4c, Ar = Ph(*p*OMe), X = OCH₂Ph
5

Results and Discussion

Preparation of *cis*-2-Amino-1-(1-arylvinyl)cyclopentanols 5. The high stereoselectivity of the tandem aza-Cope–Mannich rearrangement of 2-amino-1-vinylcyclopentanols[1,7] simplifies the stereochemical problems involved in assembling **4**. In essence one need only establish the cis relationship between the amine and methylpropenyl substituents of **5**. Ketone **6** would serve as a logical precursor to amino alcohol **5**.

Ketone **6** was assembled in an efficient stereoselective fashion from the known[11] diene ester **8**. This ester had previously been prepared by van Tamelen[11] from β-keto ester **9** by a nonstereoselective sequence which gave the



difficult to separate (*E*)- and (*Z*)-alkenes **8** and **10** in a 3:2 ratio. An alternative stereoselective synthesis of the desired (*E*)-alkene was developed. An examination of the

(1) Part 15 in the series. For part 14, see: Overman, L. E.; Sugai, S. *Helv. Chem. Acta* **1985**, *68*, 745.
(2) Phillipson, J. D., Zenk, M. H., Eds. "Indole and Biogenetically Related Alkaloids"; Academic Press: New York, 1980.
(3) The total synthesis of pentacyclic *Aspidosperma* alkaloids has been reviewed recently: Overman, L. E.; Sworin, M. In "Alkaloids: Chemical and Biological Perspectives"; Pelletier, S. W., Ed.; Wiley: New York, 1984; Vol. 3, Chapter 7.
(4) For a review of earlier synthetic work, see: Cordell, G. A. "The Alkaloids", Manske, R. H. F., Rodrigo, R., Eds.; Academic Press: New York, 1979; Vol. XVII, Chapter 3.
(5) The strychnan numbering system[2] (see structure **2**) will be employed for all intermediates.
(6) Synthetic efforts in this area have been reviewed, see: (a) Husson, H. P. In "Indoles. The Monoterpenoid Indole Alkaloids"; Saxton, J. E., Ed.; Wiley: New York, 1983; Chapter 7. (b) Smith G. F. "The Alkaloids"; Manske, R. H. F., Ed.; Academic Press: New York, 1965; pp 591ff.
(7) Overman, L. E.; Mendelson, L.; Jacobsen, E. J. *J. Am. Chem. Soc.* **1983**, *105*, 6629.
(8) Overman, L. E.; Kakimoto, M.; Okazaki, M.; Meier, G. P. *J. Am. Chem. Soc.* **1983**, *105*, 6622.
(9) Overman, L. E.; Sworin, M.; Burk, R. *J. Org. Chem.* **1983**, *48*, 2685.
(10) Overman, L. E.; Sworin, M.; Bass, L. S.; Clardy, J. *Tetrahedron* **1981**, *37*, 4041.

0022-3263/85/1950-4021$01.50/0

reduction of readily available 9[11] with several reducing agents showed that zinc borohydride[12,13] was extremely selective and gave essentially pure *erythro* isomer **11a** as the only product. Large-scale reductions proceeded with slightly lower selectivity. For example, **11a** and **11b** were obtained in an 89:11 ratio from the reduction of **9** on a 17-g scale. The minor *threo* diastereomer **11b** was easily removed by flash chromatography. Dehydration of **11a** or **11b** under conditions known to give anti[14] [methanesulfonyl chloride (MsCl), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)] or syn[15] (dicyclohexylcarbodiimide, cuprous chloride) elimination was utilized to establish the stereostructures of isomers **11**. With these dehydration methods, either the (*E*)- or (*Z*)-alkene could be selectively prepared from both β-hydroxy ester diastereomers. In practice, it was most convenient to process only the pure *erythro* isomer **11a** which provided (*E*)-alkene **8** in 95% yield upon treatment with MsCl and DBU.

Epoxidation of **8** with *m*-chloroperbenzoic acid at 0 °C in CH_2Cl_2 proceeded with essentially complete stereoselectivity[16] to give the anti epoxide **12**. The stereochemistry of **12** was rigorously established by chemical transformations that are detailed elsewhere.[17] Reduction of **12** with 2 equiv of diisobutylaluminum hydride (DIBAL-H)[18] at −78 °C[18b] gave epoxy alcohol **7** in 78% yield or 39% overall yield from β-keto ester **9**.

Protection of **7** as the triisopropylsilyl ether[19] was followed by reaction with the dimethylaluminum amide of benzylamine[20] to give amino alcohol **14**. Subsequent acylation with phenyl chloroformate provided **15** in 60% overall yield from **7**. To isolate amino alcohol **14** in good yield, it was essential to use a NaF workup. This procedure had been previously described by Yamamoto and Maruoka[21] for workup of DIBAL-H reductions. Ketone **6** was

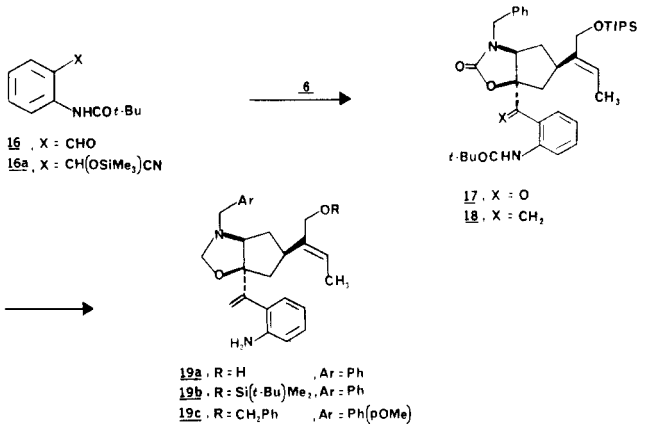
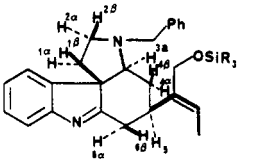


Table I. ^{1}H NMR Assignments for 4b



hydrogen	chemical shift, δ	multiplicity; *J*, Hz
3a	3.01	dd; 11.3 (3a,4β) 5.6 (3a,4α)
2α	2.95	not resolved
2β	3.36	dt
6	2.43	ddd
6	1.80	not resolved
4α	1.69	not resolved
4β	1.93	dt; 13 (4α,4β), 13 (4β,5)
5	2.55	dt; 12.8 (5,6β), 3.5 (5,6α)
6α	2.75	ddd; 12.9 (6α,6β), 1.5 (4α,6α)
6β	2.92	t

finally secured by Swern oxidation[22] of **15** which proceeded in 87% yield.

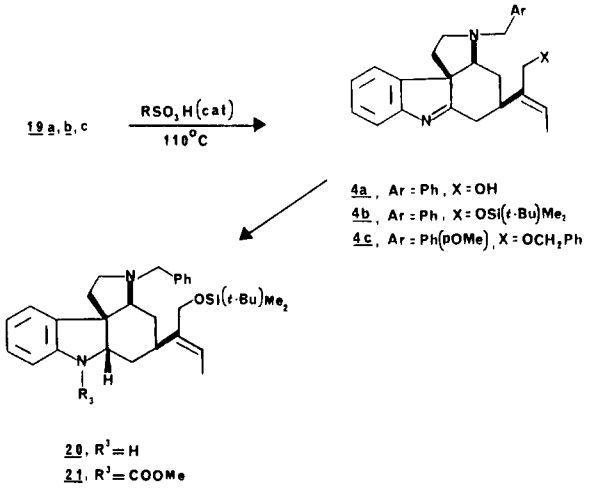
The required aromatic fragment was prepared from commercially available *o*-bromoaniline by acylation with 2,2-dimethylpropionyl chloride followed by formylation[23] (*t*-BuLi, dimethylformamide). Subsequent conversion of aldehyde **16** to silyl cyanohydrin **16a** was accomplished by treatment with trimethylsilyl cyanide in the presence of KCN and 18-crown-6.[24] The purity of cyanohydrin **16a** proved to be critical for the subsequent reaction of this intermediate. Chromatography of crude **16a** on silylated silica gel[25] provided a crystalline sample of cyanohydrin **16a**. With crystalline **16a** in hand, this intermediate was obtained in pure form in subsequent runs by direct crystallization of the crude reaction mixture. In this way, crystalline **16a** was obtained in 58% overall yield from *o*-bromoaniline.

Reaction[9] of the lithium dianion of **16a** with ketone **6** at −78 → 0 °C afforded a single adduct **17** in 70% yield. Cyclic carbamate **17** showed a diagnostic absorption in the IR spectrum at 1725 cm^{-1} for the carbonyl of the five-membered ring carbamate and a signal at δ 11.35 in the ^{1}H NMR spectrum for an intramolecularly hydrogen-bonded amide NH group. The stereochemistry assigned to **17** is consistent with existing precedent that 2-substituted cyclopentanones add nucleophiles from the less hindered side, opposite the 2-substituent.[26] Wittig olefination[27] of **17** gave **18**, which was hydrolyzed with hot 40% methanolic KOH to give amino alcohol **5** (Ar = Ph; X = OH; see eq 1) in 95% yield from **17**. Reaction of **5** with 1 equiv of paraformaldehyde at room temperature provided cyclopentoxazolidine **19a** in 97% yield. At this stage, the primary alcohol could be selectively protected, for example, as a *tert*-butyldimethylsilyl ether to give **19b**

(11) Yamada, K.; Aoki, K.; Kato, T.; Uemura, D.; van Tamelen, E. E. *J. Chem. Soc., Chem. Commun.* **1974**, 908.
(12) Gensler, W. J.; Johnson, F.; Sloan, D. B. *J. Am. Chem. Soc.* **1960**, *82*, 6074.
(13) Nakata, T.; Oishi, T. *Tetrahedron Lett.* **1980**, 1641.
(14) Kende, A. S.; Toder, B. H. *J. Org. Chem.* **1982**, *47*, 163.
(15) Alexandre, G.; Rauessac, F. *Bull Soc. Chim. Fr.* **1973**, 1837. Jerris, P. J.; Smith, A. B., III *J. Org. Chem.* **1981**, *46*, 577.
(16) Cf.: Whitesell, J. K.; Matthews, R. S.; Helbling, A. M. *J. Org. Chem.* **1978**, *43*, 784.
(17) Angle, S. R. Ph.D. Dissertation, University of California, Irvine, 1984.
(18) (a) Winterfeldt, E. *Synthesis* **1975**, 617. (b) Quenching the reduction of **12** above −78 °C led to the formation of side products, possibly resulting from epoxide opening.
(19) (a) Corey, E. J.; Cho, H.; Rucker, C.; Hua, D. *Tetrahedron Lett.* **1981**, 3455. (b) Ogilvie, K. K.; Sadana, K. L.; Thompson, E. A.; Quilliam, M. A.; Westmore, J. D. *Tetrahedron Lett.* **1974**, 2861, 2865.
(20) Overman, L. E.; Flippin, L. A. *Tetrahedron Lett.* **1981**, 195.
(21) Yamamoto, H.; Maruoka, K. *J. Am. Chem. Soc.* **1981**, *103*, 4186.
(22) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.
(23) Wender, P. A.; White, A. W. *Tetrahedron Lett.* **1981**, 1475.
(24) (a) Hunig, S.; Wehner, G. *Chem. Ber.* **1979**, *112*, 2062. (b) Evans, D. A.; Hoffman, A.; Truesdale, L. K. *J. Am. Chem. Soc.* **1973**, *95*, 5822.
(25) Silylated silica gel is now available commerically from Aldrich Chemical Co., Milwaukee, WI. In this case it was prepared by stirring silica gel with trimethylsilyl chloride and triethylamine in methylene chloride at room temperature, followed by filtration, washing with CH_2Cl_2, and vacuum-drying.
(26) (a) Sauleau, J. *Bull. Soc. Chim. Fr.* **1978**, 474. (b) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* 2199. (c) Cherest, M.; Felkin, H. *Tetrahedron Lett.* **1968**, 2205. (d) Mendelson, L. T. Ph.D. Dissertation, University of California, Irvine, 1981.
(27) (a) Vedejs, E.; Meier, G. P.; Snoble, K. A. J. *J. Am. Chem. Soc.* **1981**, *103*, 2823.

in 98% yield. In a similar fashion, epoxy alcohol **7** was O-benzylated to give **13b**, which was converted in seven subsequent steps to cyclopentoxazolidine **19c**.[17]

Rearrangement of Cyclopentoxazolidines 19. Treatment of **19b** with camphorsulfonic acid (0.4 equiv) and sodium sulfate (2.5 equiv) in refluxing toluene for 20 min provided tetracycle **4b** in essentially quantitative yield (eq 2). In a similar fashion, **19a** and **19b** were converted



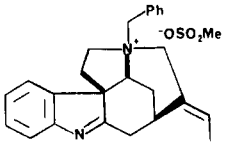
in 51% and 99% yields into hexahydro-1*H*-pyrrolo[2,3-*d*]carbazoles **4a** and **4c**. The structure of **4b** was established by a detailed analysis of its 250-MHz ^{1}H NMR spectrum, including extensive homonuclear decoupling experiments (see Table I). The ^{13}C NMR spectrum of **4b** showed a diagnostic signal for an imine carbon at δ 186.3. Assuming a cis C/D ring junction for **4b**, the ^{1}H NMR data uniquely define the stereostructure of **4b** to be as shown. In particular, the observed coupling constants require both H(3a) and H(5) to be axial. The alternate product with a trans C/D ring junction is unlikely for several reasons: (1) existing precedent that tandem aza-Cope–Mannich rearrangements of *trans*-2-amino-1-vinylcyclopentanols give cis-fused octahydroindoles,[7] (2) the considerable strain present in the trans-fused tetracyclic ring system,[28] and (3) the *W* coupling[29] observed between H(4α) and H(6α) would not be possible in the trans isomer, since Dreiding models show that this isomer would have a boat D ring. The structure of **4a** was established by chemical correlation with **4b**.

Reduction of imine **4b** with lithium aluminum hydride proceeded stereoselectively to provide **20** in 91% yield. The stereochemistry assigned to the newly introduced stereocenter C(6a) is consistent with the ^{1}H NMR coupling constants observed for the C(6a) methine hydrogen (triplet, J = 2 Hz) and previous results by Smith and Wrôbel[30] on the reduction of related imines with pentacyclic strychnan skeletons. Acylation of **20** with methyl chloroformate afforded carbamate **21** in 75% yield.

Tetracyclic carbamate **21** showed a characteristic downfield doublet at δ 7.73 in the ^{1}H NMR spectrum for the aromatic hydrogen adjacent to the N(7) carbamate group. The methine hydrogen at C(6a) was a clearly resolved triplet (J = 5.5 Hz), consistent only with the assigned β-stereochemistry for this hydrogen. Analysis of D-ring chair conformations of **21** and its C(6a) epimer show that in **21** this hydrogen is equatorial and should have the observed small coupling to each of the adjacent C(6) methylene hydrogens.[30b]

Octahydro-1*H*-pyrrolo[2,3-*d*]carbazoles **4** were thus available in 19–38% overall yield from epoxy alcohol **7** via a seven-step, stereoselective sequence. The tandem aza-Cope–Mannich rearrangement of unprotected oxazolidine **19a** to give imine **4a** well illustrates the mild reaction conditions of this complex transformation. In particular, a primary amine and a primary allylic alcohol survived the sequence in unprotected form.

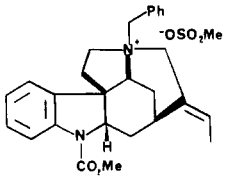
Attempts To Elaborate the Strychnan E Ring. Treatment of imine **4a** with methanesulfonic anhydride[31] in CH_2Cl_2 in the presence of a tertiary amine (pentamethylpiperidine, triethylamine, or diisopropylethylamine) gave a salt that we had hoped would be pentacycle **23**.



23

This salt could not be purified and, in light of our unsuccessful attempts to debenzylate it, was probably not **23**. Attempted debenzylation of this crude salt under dissolving metal conditions (Na or Li in NH_3), hydrogenolysis conditions[32] (H_2, $Pd/BaSO_4$, $Pd(OH)_2/C$, Pd/C), or nucleophilic conditions[33] (PhSNa) led only to intractable product mixtures.

Cleavage of silyl ether **21** with fluoride anion gave compound **21a**.[17] In a manner analogous to that described above, compound **21a** was treated with methanesulfonic anhydride in attempt to give salt **21b**. Again, this salt



21b

could not be purified. Attempted debenzylation of this crude salt using the methods listed above gave intractable product mixtures, leading us to conclude that we had probably not obtained the desired salt **21b**.

In the hope of removing the sensitive imine functionality before closure of the E ring, we examined acylation of imine **4b**. Attempts to acylate on either nitrogen or carbon with methyl chloroformate using conditions we had successfully employed in the *Aspidosperma* series[9] (or use of other bases [EtMgBr,[34] *t*-BuLi, $(i\text{-Pr})_2$EtN]) all gave indole-containing products.[34,35]

(28) Takano, S.; Shishido, K.; Matsuzaka, J.; Sato, M.; Ogasawara, K. *Heterocycles* **1979**, *13*, 307.

(29) (a) Sommer, H. Z.; Lipp, H. I.; Jackson, L. L. *J. Org. Chem.* **1971**, *36*, 824. (b) Jackman, L. M.; Sternhell, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd Ed.; Pergamon Press: New York, 1969; pp 280–304.

(30) (a) Smith, G. F.; Wrobel, J. T. *J. Chem. Soc.* **1960**, 792. (b) Tits, M.; Angenot, L.; Travernier, D. *Tetrahedron Lett.* **1980**, 2439.

(31) Linstead, R. P.; Owen, L. M.; Webb, R. F. *J. Chem. Soc.* **1953**, 1225.

(32) Wenkert, E.; Sklar, R. *J. Org. Chem.* **1966**, *31*, 2689.

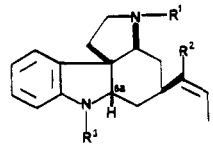
(33) (a) Ho, T.-L. *Synth. Commun.* **1973**, *3*, 99 and references cited therein. (b) Kametani, T.; Kigasawa, K.; Hiiragi, M.; Wagatsana, N.; Wakisaka, K. *Tetrahedron Lett.* **1969**, 635.

(34) Jackson, A. H.; Smith, P. *J. Chem. Soc. C* **1968**, 1667.

(35) An indole would result from fragmentation of the C/D ring fusion. Reactions of this type are well-known for C(1)–C(2) imines with the pentacyclic strychnan skeleton.[30a] Other workers have also recently reported[36] apparent limitations to the C-acylation procedure described in ref 9.

(36) Wenkert, E.; Porter, B.; Simmons, D. P.; Ardisson, J.; Kunesch, P.; Poisson, J. *J. Org. Chem.* **1984**, *49*, 3733.

Chart I



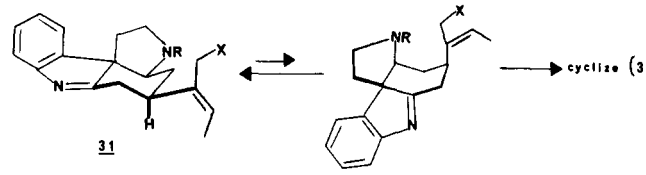
	R^1	R^2	R^3
20	CH_2Ph	$CH_2OSi(t\text{-}Bu)Me_2$	H
21	CH_2Ph	$CH_2OSi(t\text{-}Bu)Me_2$	CO_2Me
21a	CH_2Ph	CH_2OH	CO_2Me
22	$CO_2CH_2CCl_3$	$CH_2OSi(t\text{-}Bu)Me_2$	CO_2Me
24	$CO_2CH_2CCl_3$	CH_2OH	CO_2Me
25	$CO_2CH_2CCl_3$	$CH_2OSO_2CH_3$	CO_2Me
26	H	CH_2OH	CO_2Me
26b	H	$CH_2OSi(t\text{-}Bu)Me_2$	CO_2Me
27	SO_2CH_3	CH_2OH	CO_2Me
28	$SO_2Ph(pCH_3)$	CH_2OH	CO_2Me
29	$CO_2CH_2CCl_3$	$CH(OMe)_2$	CO_2Me
30	$CO_2CH_2CCl_3$	CO_2Me	CO_2Me

The benzyl group of **21** was removed by chloroformate debenzylation[37] to give carbamate **22** in 50% yield (Chart I). Reaction of **22** with tetrabutylammonium fluoride provided alcohol **24** (83% yield), which when treated with methanesulfonic anhydride,[31] gave mesylate **25**. All attempts to selectively remove the trichloroethyl carbamate group of **25** (Zn/KH_2PO_4,[38] Zn(Cu),[39] Rieke Zn,[40] 99.999% Zn[41]) resulted in intractable product mixtures.

Since all attempts to remove the trichloroethyl carbamate group in the presence of the allylic mesylate failed, we chose to first remove the carbamate then form the mesylate. Treatment of **22** with Zn/KH_2PO_4 in THF[38] followed by reaction of the product with tetrabutylammonium fluoride gave amino alcohol **26** (39% yield). Attempts to selectively activate the primary allylic alcohol [NaH/Ms_2O, NaH/TsCl, $LiN(SiMe_3)_2$/TsCl, Ms_2O/pyridine–pyridinium methanesulfonate (pH 5.6)] failed and gave complex reaction mixtures in which the sulfonamides **27** or **28** were the only recognizable products.

Similarly unsuccessful were attempts to close the strychnan E ring from acetal **29** or ester **30**.[17]

Although the Woodward strychnine synthesis does involve closure of the C(4)–C(21) bond of the strychnan skeleton,[6] this cyclization is obviously a difficult one. In our case, successful cyclization requires the butenyl group to assume an axial orientation, thus forcing the D ring, into a twist boat conformation (eq 3). The severe steric interactions in this conformation obviously adversely effect the cyclization reaction and are believed to be responsible for our failure to construct the pentacyclic strychnan ring system from intermediates such as **31**.



31

Conclusion

An efficient stereoselective route to epoxy alcohol **7**, a potential *Strychnos* alkaloid precursor, has been developed. The tandem aza-Cope–Mannich rearrangement of amino alcohols **5** has been shown to be a useful route for preparing hexahydro-1*H*-pyrrolo[2,3-*d*]carbazoles. In particular, this method allows a substituent to be introduced with complete stereocontrol at C(5) of this tetracyclic ring system. Further efforts to prepare the strychnan skeleton by aza-Cope–Mannich strategies will require elaboration of the E ring at an early stage. Investigations of this type are in progress.

Experimental Section[42]

(2*R,3*S**)-Ethyl 2-(3-Cyclopentenyl)-3-hydroxybutanoate (11a).** Zinc borohydride[12] (431 mL of a 0.2 M solution in ether, 86.1 mmol) was added dropwise over 1 h at 0 °C to a stirred solution of keto ester **9** (16.9 g, 86.1 mmol) and ether (800 mL). The resulting solution was stirred for 20 min at 0 °C, and then H_2O (50 mL) and acetic acid (5 mL) were added. After the mixture was stirred for 15 min, basic workup (ether, $MgSO_4$) afforded 15.9 g (91%) of a crude mixture of *erythro* (**11a**) and *threo* (**11b**) alcohols (89:11 ratio by capillary GC[43]) as a yellow oil. Chromatography on silica gel (230–400 mesh, 400 g; 95:5 hexane–ethyl acetate) gave 10.0 g (59%) of the *erythro* diastereomer **11a** (97.6% *erythro* by capillary GC):[43] ^1H NMR (250 MHz, $CDCl_3$) δ 5.7 (apparent s, 2 H, CHC=CHC), 4.20 (q, J = 7 Hz, 2 H, OCH_2CH_3), 4.15 (m, 1 H, OCH), 2.7–1.6 (m, 6 H), 1.30 (t, J = 7 Hz, 3 H, OCH_2CH_3), 1.24 (d, J = 6 Hz, 3 H, $OCHCH_3$). A sample of the minor *threo* diastereomer **11b** was also isolated: ^1H NMR (250 MHz, $CDCl_3$) δ 5.7 (apparent s, 2 H, CH=CH), 4.2 (q, J = 7 Hz, 2 H, OCH_2CH_3), 3.93 (m, 1 H, OCH), 2.9–1.9 (m, 6 H), 1.30 (t, J = 7 Hz, 3 H, OCH_2CH_3), 1.25 (d, J = 6 Hz, $OCHCH_3$).

Ethyl 2-(3-Cyclopentenyl)-2(*E*)-butenoate (8). Methanesulfonyl chloride (3.30 mL, 42.5 mmol) was added dropwise over 10 min to a stirred solution of alcohol **11a** (7.66 g, 38.6 mmol; 98% *erythro* diastereomer by capillary GC[43]), triethylamine (8.08 mL, 58.0 mmol), and CH_2Cl_2 (200 mL), at 0 °C. The mixture was stirred at 0 °C for 1 h, followed by basic workup (CH_2Cl_2, Na_2SO_4) to afford 10.3 g (97.0%) of crude mesylate as a yellow liquid. The crude mesylate was dissolved in toluene (80 mL) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 11.0 mL, 74.9 mmol) was added. The resulting solution was stirred at room temperature overnight. Acidic workup (ether, $MgSO_4$) afforded 7.58 g of a yellow oil. Chromatography (silica gel, 230–400 mesh, 85 g; 10:1 hexane–ethyl acetate) gave 6.61 g (95%) of known 8[11] as a clear oil: ^1H NMR (250 MHz, $CDCl_3$) δ 6.80 (q, J = 7 Hz, 1 H, $=CHCH_3$), 5.72

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(42) General experimental details were described recently.[11] In cases where synthetic intermediates or products were isolated by "aqueous workup (organic solvent, drying agent)", the procedure was to quench the reaction mixture with H_2O, dilute with the indicated organic solvent, separate the organic layer, extract the aqueous layer several times with the organic solvent, dry the combined organic layers with the indicated drying agent, and remove the solvent with a rotary evaporator at reduced pressure. When "basic workup (organic solvent, drying agent)" is indicated, the procedure was similar to aqueous workup except 1 N NaOH was used instead of H_2O. When "acidic workup (organic solvent, organic solvent, drying agent)" is indicated the procedure was to dilute the reaction mixture with the first indicated organic solvent, extract the organic solution several times with 1 N HCl, basify the combined acidic layers with solid KOH, extract the basic solution with the second indicated organic solvent several times, dry the organic layers with the indicated drying agent, and remove the solvent with a rotary evaporator under reduced pressure.

(43) This analysis was done with a 30-m Carbowax quartz capillary column.

(apparent s, 2 H, CHC=CHC), 4.17 (q, J = 7 Hz, 2 H, OCH_2CH_3), 3.47 (p, J = 9 Hz, 1 H, R_2CHR), 2.50 (d, J = 9 Hz, 4 H, RCH_2R), 1.81 (d, J = 7 Hz, 3 H, $=CHCH_3$), 1.27 (t, J = 7 Hz, 3 H, OCH_2CH_3); ^{13}C NMR (63 MHz, $CDCl_3$) δ 167.6, 136.8, 129.9, 129.6, 60.0, 38.6, 34.8, 14.2, 14.0.

The Z isomer of **8** showed a diagnostic signal in the 250-MHz ^1H NMR spectrum at δ 5.9 (q, J = 7 Hz, 1 H, $=CHCH_3$).

***trans*-3-(1-Carbethoxy-1(*E*)-propenyl)-6-oxabicyclo[3.1.0]hexane (12).** *m*-Chloroperbenzoic acid (5.17 g of 80% acid, 24.0 mmol) was added over 1 h to a stirred mixture of ester **8** (3.60 g, 20.0 mmol), $NaHCO_3$ (2.43 g, 29.0 mmol), and CH_2Cl_2 (40 mL) at 0 °C. After the mixture was stirred an additional 30 min at 0 °C, Na_2SO_3 (0.5 g) was added to destroy excess peracid. Basic workup (CH_2Cl_2, Na_2SO_4) afforded 3.92 g (92.5%) of **12** as a clear oil. This material was suitable for use in the following reduction. An analytical sample was prepared by chromatography of a sample of comparable material (silica gel, 230–400 mesh; 6:1 hexane–ethyl acetate) to give epoxide **12** as a clear oil: ^1H NMR (250 MHz, $CDCl_3$) δ 6.82 (q, J = 7 Hz, 1 H, $=CHCH_3$), 4.16 (q, J = 7 Hz, OCH_2CH_3), 3.56 (apparent s, 2 H, OCH), 2.96 (p, J = 8 Hz, 1 H, R_2CHR), 2.02 (br d, J = 8.8 Hz, 4 H, RCH_2R), 1.79 (d, J = 7 Hz, 3 H, CH_3), 1.28 (t, J = 7 Hz, 3 H, OCH_2CH_3); ^{13}C NMR (63 MHz, $CDCl_3$) δ 167.2, 138.4, 133.3, 60.3, 57.9, 32.2, 31.2, 14.4, 14.3; IR (film) 2979, 2930, 1740, 1713, 1131 cm^{-1}; MS (CI), m/z 197 (MH^+, 100%), 151 (23%), 133 (12%); high-resolution MS (EI), m/z 196.1087 (196.1099 calcd for $C_{11}H_{16}O_3$).

***trans*-3-[1-(Hydroxymethyl)-1(*E*)-propenyl]-6-oxabicyclo[3.1.0]hexane (7).** Neat diisobutylaluminum hydride (11.9 mL, 65.5 mmol) was added dropwise over 20 min to a stirred solution of ester **12** (6.12 g, 31.2 mmol) and toluene (200 mL) at −78 °C. After the mixture was stirred for 10 min at −78 °C, methanol (10.3 mL, 256 mmol) was added dropwise. The reaction mixture was stirred vigorously and allowed to warm to room temperature. The organic solution was separated, and the aluminum salts were washed with CH_2Cl_2 (500 mL). Concentration of the combined organic solutions gave 4.7 g of a yellow oil. Chromatography on silica gel (230–400 mesh, 100 g; 2:1 hexane–ethyl acetate) gave 3.75 g (78%) of **7** as a clear oil: ^1H NMR (250 MHz, $CDCl_3$) δ 5.58 (q, J = 6.9 Hz, 1 H, $=CHCH_3$), 4.04 (apparent s, 2 H, $HOCH_2$), 3.52 (apparent s, 2 H, OCH), 2.90 (m, 1 H, R_2CHR), 2.09 (dd, J = 7.6, 13.8 Hz, 2 H, RCH_2R), 1.68 (dd, J = 10.5, 13.9 Hz, 2 H, RCH_2R), 1.63 (d, J = 6.8 Hz, 3 H, $=CHCH_3$); ^{13}C NMR (63 MHz, $CDCl_3$) δ 138.8, 123.9, 65.4, 56.8, 31.7, 31.3, 13.0; IR (film) 3700–3150 (s, OH), 1445 (m), 1395 (m) cm^{-1}; MS (CI), m/z 155 (MH^+, 73%), 137 (100%); high-resolution MS (EI), m/z 154.0986 (154.0994 calcd for $C_9H_{14}O_2$).

1-Bromo-2-(trimethylacetamido)benzene. Trimethylacetyl chloride (19.0 mL, 0.154 mol) was added dropwise to a stirred solution of *o*-bromoaniline (26.5 g, 0.154 mol), triethylamine (32.3 mL, 0.231 mol), and CH_2Cl_2 (200 mL) at 0 °C. The resulting solution was concentrated and then diluted with ether (350 mL) and H_2O (50 mL). Acidic workup (CH_2Cl_2, $MgSO_4$) followed by recrystallization from pentane gave 34.2 g (87%) of the known[23] amide as white needles: mp 59–60 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 8.39 (dd, J = 1.5, 8.3 Hz, 1 H, Ar H), 7.53 (dd, J = 1.4, 8.0 Hz, 1 H, Ar H), 7.31 (m, 1 H, Ar H), 6.96 (dt, J = 1.6, 7.6 Hz, 1 H, Ar H), 1.35 (s, 9 H, *t*-Bu); IR (CCl_4) 3445 (m, NH), 2965 (m), 1700 (s, C=O), 1580 (m), 1520 (s), 1425 (s), 1295 (s), 1145 (m); MS (CI), m/z 258 (MH^+, 100%), 176 (7%).

2-(Trimethylacetamido)benzaldehyde (16). By use of a modification of a procedure reported by Wender and White,[23] MeLi (45.5 mL of a 1.30 M solution in ether, 59.2 mmol) was added dropwise to a stirred solution of the above bromide (14.4 g, 56.4 mmol) and THF (750 mL) at −78 °C. The resulting solution was stirred for 45 min, and then *t*-BuLi (59.3 mL of a 1.90 M solution in pentane, 112 mmol) was added over 15 min. The resulting solution was stirred at −78 °C for 1 h and then allowed to warm to −20 °C. Dimethylformamide (22.0 mL, 282 mmol) was added dropwise, and the resulting solution was stirred at −20 °C for 40 min. The mixture was diluted with NH_4Cl (saturated aqueous, 500 mL) and ether (100 mL), and the aqueous layer was extracted with ether (2 × 200 mL). The combined organic extracts were washed with H_2O (50 mL), brine (200 mL), dried ($MgSO_4$), and concentrated to a yellow oil. Distillation [112–115 °C (1 mm)] gave 10.7 g (92%) of aldehyde **16** as a pale yellow oil: ^1H NMR (250 MHz, $CDCl_3$) δ 12.4 (br s, 1 H, NH), 9.95 (s, 1 H, Ar CHO), 8.80 (d, J = 8.5 Hz, 1 H, Ar H), 7.68 (dd, J = 1.6, 7.6 Hz, 1 H, Ar H), 7.62 (dt, J = 1.5, 8.5 Hz, 1 H, Ar H), 7.22 (dt, J = 0.9, 7.6 Hz, 1 H, Ar H), 1.37 (s, 9 H, *t*-Bu); IR (film) 3300 (s, NH), 2968 (s), 2870 (m), 2750 (w), 1668 (s, C=O), 1587 (s), 1442, (s), 1287 (s), 1148 (s) cm^{-1}; MS (CI), m/z 206 (MH^+, 100%), 149 (4%); high-resolution MS (EI), m/z 205.1097 (205.1103 calcd for $C_{12}H_{15}O_2N$).

2-[2-(Trimethylacetamido)phenyl]-2-[(trimethylsilyl)oxy]acetonitrile (16a). In accordance with the general procedure of Evans and co-workers,[24b] potassium cyanide–18-crown-6 complex (3 mg) was added at room temperature to a stirred solution of aldehyde **16** (6.28 g, 30.6 mmol), chloroform (10 mL), and trimethylsilyl cyanide (16.0 mL, 122 mmol). The resulting solution was stirred at room temperature for 30 min and then concentrated to afford crude silyl cyanohydrin **16a** as a pale yellow oil. Crystallization from pentane gave 6.84 g (73%) of **16a** as a white solid: mp 65–66 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 8.75 (br s, 1 H, NH), 8.28 (d, J = 8.2 Hz, 1 H, Ar H), 7.43 (apparent dt, J = 1, 8 Hz, 1 H, Ar H), 7.20–7.06 (m, 2 H, Ar H), 5.42 (s, 1 H, CHCN), 1.36 (s, 9 H, *t*-Bu), 0.23 (s, 9 H, $SiMe_3$); IR (CCl_4) 3423 (s, NH), 2967 (s), 1690 (s, C=O), 1590 (m), 1476 (s), 1443 (s), 1399 (s), 1350 (s) cm^{-1}; MS (CI), m/z 305 (MH^+, 100%), 278 (46%), 215 (43%).

***(E)-trans*-3-[1-[(Triisopropylsilyl)oxy]methyl]-1(*E*)-propenyl]-6-oxabicyclo[3.1.0]hexane (13a).** Triisopropylsilyl chloride (1.5 mL, 7.1 mmol) was added dropwise to a stirred solution of epoxy alcohol **7** (0.99 g, 6.4 mmol), imidazole (0.87 g, 13 mmol), and dimethylformamide (6.0 mL) over 3 min. The mixture was stirred at room temperature for 4.3 h. Acidic workup (ether, $MgSO_4$) afforded 1.9 g (95%) of crude **13a** as a colorless oil. Material of this purity was suitable for use in the next reaction. An analytical sample was prepared by chromatography of a sample of comparable material on silica gel (230–400 mesh; 20:1 hexane–ethyl acetate) to give **13a** as a clear oil: ^1H NMR (250 MHz, $CDCl_3$) δ 5.53 (q, J = 6.9 Hz, 1 H, $=CHCH_3$), 4.13 (apparent s, 2 H, $=CCH_2O$), 3.51 (s, 2 H, OCH), 2.87 (m, 1 H, $RCHR_2$), 2.08 (dd, J = 7.7, 13.9 Hz, 2 H, RCHHR), 1.77 (dd, J = 10.3, 13.9 Hz, 2 H, RCHHR), 1.60 (d, J = 6.9 Hz, $=CHCH_3$), 1.06 (m, 21 H, i-Pr_3); IR (film) 3024 (m), 2934 (s), 2864 (s), 1463 (m), 1384 (m), 1093 (s), 1048 (s) cm^{-1}; MS (CI), 311 (MH^+, 9%), 267 (44%), 137 (73%), 119 (100%).

***(E,1R*,2R*,4S*)*-2-[*N*-(Phenylmethyl)-*N*-(phenoxycarbonyl)amino]-1-hydroxy-4-[1-[[(triisopropylsilyl)oxy]methyl]propenyl]cyclopentane (15).** In accordance with the general procedure of Overman and Flippin,[20] trimethylaluminum (3.9 mL of a 2.0 M solution in toluene, 7.8 mmol) was added dropwise over 10 min to a stirred solution of dry benzylamine (0.85 mL, 7.8 mmol) and CH_2Cl_2 (17 mL) at 0 °C. The resulting solution was stirred for 40 min, and then a solution of epoxide **13a** (2.3 g, 7.4 mmol) and CH_2Cl_2 (5.0 mL) was added. The resulting solution was stirred at 0 °C for 2 h, the ice bath was removed, and stirring was continued overnight. The reaction mixture was then diluted with CH_2Cl_2 (50 mL) and cooled to 0 °C, and NaF (1.3 g, 31 mmol) and H_2O (0.42 mL, 23 mmol) were added. The resulting mixture was stirred vigorously at room temperature for 1 h, and Celite (5 g) was added. The white aluminum salts were separated by filtration through a pad of Celite and then were washed with CH_2Cl_2 (200 mL). The combined organics were dried (K_2CO_3) and concentrated to give 4.2 g of crude amine **14** as a clear oil. Material of this purity was acceptable for use in the next reaction.

Phenyl chloroformate (freshly distilled, 1.1 mL, 8.6 mmol) was added to a stirred solution of crude amine **14** (4.2 g), triethylamine (2.2 mL, 16 mmol), and CH_2Cl_2 (23 mL) at 0 °C. The resulting solution was stirred at 0 °C for 1 h. Acidic workup (CH_2Cl_2, $MgSO_4$) gave 3.8 g of crude carbamate as a yellow oil. Chromatography on silica gel (230–400 mesh, 151 g; 5:1:0.2 hexane–ethyl acetate–triethylamine) gave 2.4 g (60% from epoxy alcohol **7**) of carbamate **15** as a colorless oil: ^1H NMR (250 MHz, $CDCl_3$) δ 7.40–7.06 (m, 10 H, Ar H), 5.56 (q, J = 7 Hz, 1 H, $=CHCH_3$), 4.66 (br s, 2 H, NCH_2Ph), 4.30 (br, 1 H, $NCHR_2$), 4.15 (m, 1 H, $HOCHR_2$), 4.27–4.12 (m, 1 H, R_2CHR), 4.07 (s, 2 H, $=CCH_2O$), 2.04–1.85 (m, 3 H, RCHHR), 1.76–1.60 (m, 1 H, RCHHR), 1.61 (d, J = 7 Hz, 3 H, $CHCH_3$), 1.02 (m, 21 H, i-Pr_3); IR (CCl_4) 3645–3220 (m, OH), 3033 (m), 2927 (s), 2861 (s), 1709 (s, C=O), 1595 (w), 1550 (m), 1369 (m), 1230 (s), 1188 (s), 1039 (m), 872 (m) cm^{-1}; MS (EI, 20 eV), m/z 537 (M, 0.9%), 495 (M − i-Pr, 100%);

high-resolution MS (EI), m/z 537.3230 (537.3276 calcd for $C_{32}H_{47}O_4NSi$).

(*E*,2*S,4*R**)-2-[*N*-(Phenylmethyl)-*N*-(phenoxycarbonyl)amino]-4-[1-[[(triisopropylsilyl)oxy]methyl]propenyl]cyclopentan-1-one (6).** In accordance with the general procedure of Swern and co-workers,[22] dimethyl sulfoxide (0.87 mL, 12 mmol) was added dropwise to a stirred solution of freshly distilled oxalyl chloride (0.54 mL, 6.1 mmol) and CH_2Cl_2 (37 mL) at −78 °C. The resulting solution was stirred for 10 min, and then a solution of alcohol **15** (3.0 g, 5.6 mmol) and CH_2Cl_2 (7.0 mL) was added. The mixture was stirred for 15 min, and then triethylamine (3.9 mL, 28 mmol) was added dropwise. After the reaction mixture was stirred an additional 10 min at −78 °C, it was allowed to warm to room temperature over 1 h. Aqueous workup (CH_2Cl_2, K_2CO_3) gave 3.25 g of crude ketone as a yellow oil. Chromatography on silica gel (230–400 mesh, 120 g; 8:1:0.2 hexane–ethyl acetate–triethylamine) gave 2.6 g (87%) of ketone **6** as a colorless oil: ^{1}H NMR (250 MHz, $CDCl_3$, mixture of carbamate isomers) δ 7.38–7.05 (m, 10 H, Ar H), 5.62 (q, J = 7 Hz, 1 H, =CC*H*CH_3), 4.71 and 4.68 (s, 2 H, =CCH_2O), 4.12 and 4.09 (s, 2 H, NCH_2Ph), 3.86 and 3.71 (dd, J = 12, 8 Hz, 1 H, NCHR_2), 3.05 (m, 1 H, RCHR_2), 2.57–2.23 (m, 3 H, =CHCH_3), 0.98 (m, 21 H, i-Pr_3); IR (CCl_4) 2947 (s), 2867 (s), 1760 (s, C=O), 1722 (s, C=O), 1597 (w), 1455 (m), 1418 (m), 1203 (s) cm^{-1}; MS (CI), m/z 536 (MH^+, 47%), 492 (27%), 362 (100%); high-resolution MS (CI), m/z 536.3200 (536.3198 calcd for $C_{32}H_{46}NO_4Si$).

(*E*,3a*R,5*S*,6a*S**)-3-(Phenylmethyl)-2-oxo-3,3a,4,5,6,6a-hexahydro-5-[1-[[(triisopropylsilyl)oxy]methyl]propenyl]-6a-[2-(trimethylacetamido)benzoyl]-2*H*-cyclopentoxazole (17).** *n*-BuLi (3.0 mL of a 1.5 M solution in hexane, 4.6 mmol) was added to a solution of trimethylsilyl cyanohydrin **16a** (698 mg, 2.29 mmol) and THF (48 mL) at −78 °C. After the mixture was stirred for 40 min, a solution of ketone **6** (1.16 g, 2.17 mmol) and THF (48 mL) was added dropwise. After the reaction mixture was stirred at −78 °C for an additional 30 min, it was allowed to warm to 0 °C and then was quenched with 1:1 THF–H_2O (5.0 mL). Aqueous workup (ether, K_2CO_3) gave a light brown oil. Crystallization from pentane gave 986 mg (70%) of carbamate **17** as a white solid: mp 128.5–130 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 11.35 (s, 1 H, NH), 8.76 (dd, J = 1.0, 8.6 Hz, 1 H, Ar H), 8.16 (dd, J = 8.1, 1.0 Hz, 1 H, Ar H), 7.57 (apparent t, J = 8.7 Hz, 1 H, Ar H), 7.27 (m, 5 H, Ph H), 7.12 (apparent t, J = 8.3 Hz, 1 H, Ar H), 5.55 (q, J = 6.8 Hz, 1 H, =C*H*CH_3), 4.58 (dd, J = 8.3, 7.2 Hz, 1 H, NCHR_2), 4.46 (AB q, J = 14.9 Hz, $\Delta\nu$ = 142.9 Hz, 2 H, NCH_2Ph), 4.13 (s, 2 H, =CCH_2O), 2.81 (m, 1 H, RCHR_2), 2.59 (m, 2 H, RCH*H*R), 2.16 (m, 1 H, RC*H*HR), 1.80 (m, 1 H, RC*H*HR), 1.54 (d, J = 6.8 Hz, 3 H, =CHCH_3), 1.32 (s, 9 H, t-Bu), 1.08 (m, 21 H, i-Pr_3); ^{13}C NMR (63 MHz, $CDCl_3$) δ 200.3, 178.3, 156.4, 155.6, 142.4, 136.1, 135.6, 135.4, 133.1, 129.5, 128.9, 128.3, 128.1, 124.1, 122.4, 121.4, 120.1, 118.5, 115.5, 91.8, 66.4, 60.6, 47.2, 43.4, 40.5, 36.5, 27.6, 18.2, 13.0, 12.0; IR (CCl_4) 3380–3240 (m, NH), 2947 (s), 2867 (s), 1771 (s, C=O), 1697 (s), 1645 (m), 1612 (m), 1448 (m) cm^{-1}; MS (CI), m/z 647 (MH^+, 78%), 493 (100%).

Anal. Calcd for $C_{38}H_{54}N_2O_5Si$: C, 70.55; H, 8.41; N, 4.33. Found: C, 70.58; H, 8.12; N, 4.45.

(*E*,3a*R,5*S**,6a*R**)-3-(Phenylmethyl)-2-oxo-3,3a,4,5,6,6a-hexahydro-5-[1-[[(triisopropylsilyl)oxy]methyl]propenyl]-6a-[1-[2-(trimethylacetamido)phenyl]ethenyl]-2*H*-cyclopentoxazole (18).** *n*-BuLi (36.9 mL of a 1.51 M solution in hexane, 55.3 mmol) was added dropwise to a stirred solution of methyltriphenylphosphonium bromide (21.2 g, 59.3 mmol) and THF (140 mL) at −78 °C. The resulting solution was allowed to warm to room temperature for 15 min and then cooled back to −78 °C. A solution of ketone **17** (1.94 g, 2.99 mmol) and THF (7 mL) was added, and the resulting solution was allowed to warm to room temperature and stirred for 64 h. The reaction mixture was cooled to 0 °C and then poured into a cold (0 °C) rapidly stirred solution of 1 N HCl (100 mL) and ether (200 mL). Aqueous workup (ether, $MgSO_4$) afforded crude **18** as a pale yellow oil, which was contaminated with triphenylphosphine oxide. Chromatography on silica gel (230–400 mesh, 200 g; 8:1:0.2 hexane–ethyl acetate–triethylamine) gave 1.90 g (99%) of carbamate **18** as a clear colorless oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.25 (d, J = 8.1 Hz, 1 H, Ar H), 8.01 (s, 1 H, NH), 7.99–7.26 (m, 5 H, Ph H), 7.02 (m, 2 H, Ar H), 6.97 (dd, J = 7.4, 1.1 Hz, 1 H, Ar H), 6.86 (dd, J = 7.6, 1.6 Hz, 1 H, Ar H), 5.77 (s, 1 H, =CH*H*), 5.50 (q, J = 6.7 Hz, 1 H, =C*H*CH_3), 5.25 (s, 1 H, =C*H*H), 4.35 (AB q, J = 15.0 Hz, $\Delta\nu$ = 183 Hz, 2 H, NCH_2Ph), 3.76 (t, J = 7.4 Hz, 1 H, NCHR_2), 2.49 (m, 1 H, RCHR_2), 2.36 (m, 1 H, RCH*H*R), 2.20 (apparent t, J = 13.5 Hz, 1 H, RC*H*HR), 2.01 (m, 1 H, RC*H*HR), 1.75 (ddd, J = 12.6, 12.6, 7.9 Hz, 1 H, RCH*H*R), 1.36 (d, J = 6.7 Hz, 3 H, =CHCH_3), 1.26 (s, 9 *H*, t-Bu), 1.05 (m, 21 H, i-Pr_3); ^{13}C NMR (63 MHz, $CDCl_3$) δ 176.7, 155.9, 146.4, 136.6, 136.2, 135.3, 129.7, 129.3, 128.9, 128.1, 127.9, 123.7, 123.6, 122.3, 118.6, 88.4, 66.1, 62.6, 46.8, 41.0, 40.0, 36.7, 27.6, 18.1, 12.7, 12.0; IR (CCl_4) 3430 (m, NH), 2940 (s), 2868 (s), 1750 (s), 1680 (s), 1578 (m), 1440 (s), 1295 (s) cm^{-1}; MS (CI), m/z 645 (MH^+, 100%), 601 (51%), 471 (44%); high-resolution MS (CI), m/z 645.4088 (645.4090 calcd for $C_{39}H_{56}O_4N_2Si$).

(*E*,3a*R,5*R**,6a*S**)-6a-[1-[2-Aminophenyl]ethenyl]-5-[1-(hydroxymethyl)propenyl]-3-(phenylmethyl)-3,3a,4,5,6,6a-hexahydro-2*H*-cyclopentoxazole (19a).** KOH (46.1 g, 0.822 mol) was added to a degassed solution of carbamate **18** (454 mg, 0.707 mmol), methanol (51 mL), and H_2O (4.0 mL). The resulting solution was heated at vigorous reflux for 18 h. After cooling to room temperature, the reaction mixture was diluted with H_2O (25 mL) and extracted with ether (4 × 40 mL). The combined organic extracts were washed with 1 N HCl (3 × 30 mL). The combined aqueous washings were cooled to 0 °C and saturated with KOH. Extraction (ether, K_2CO_3) afforded 256 mg (96%) of amino alcohol **5** as a white solid: mp 116–118 °C; IR (CCl_4) 3580–3100 (m, br), 2963 (s), 1617 (m), 1451 (s) cm^{-1}; MS (CI), m/z 379 (MH^+, 100%), 254 (67%).

A sample of a comparable material of amino alcohol **5** (308 mg, 0.814 mmol), finely ground paraformaldehyde (26.0 mg, 0.854 mmol), and THF (6.0 mL) was stirred at room temperature for 8 h. The mixture was concentrated and chromatographed on silica gel (230–400 mesh, 30.5 g; 3:1:0.2 hexane–ethyl acetate–triethylamine) to give 307 mg (97%) of oxazolidine **19a** as a clear oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.35–7.14 (m, 5 H, Ph H), 7.10 (dt, J = 1.5, 7.6 Hz, 1 H, Ar H), 6.99 (dd, J = 1, 7 Hz, 1 H, Ar H), 6.72 (m, 2 H, Ar H), 5.79 (d, J = 1.8 Hz, 1 H, =C*H*H), 5.46 (q, J = 6.8 Hz, 1 H, =C*H*CH_3), 5.11 (d, J = 1.8 Hz, 1 H, =CH*H*), 4.55 (s, 2 H, NCH_2O), 4.03 (s, 2 H, CH_2O), 3.69 (m, 3 H, NCH_2Ph, NCHR_2), 2.44 (m, 1 H, RCHR_2), 2.30 (ddd, J = 2, 6, 13 Hz, 1 H, RC*H*HR), 1.94 (m, 1 H, RCH*H*R), 1.84 (t, J = 12.9 Hz, 1 H, RC*H*HR), 1.63 (dt, J = 8.3, 12.5 Hz, 1 H, RCH*H*R), 1.37 (d, J = 6.8 Hz, 3 H, =CHCH_3); ^{13}C NMR (63 MHz, $CDCl_3$) δ 150.6, 144.8, 139.6, 139.4, 130.7, 128.8, 128.6, 128.5, 127.2, 127.0, 123.8, 117.9, 115.9, 115.2, 92.1, 84.2, 71.9, 65.4, 58.2, 40.9, 36.3, 35.4, 12.8; IR (CCl_4) 3630 (w), 3470 (s), 3489 (s), 3110 (s), 2930 (s), 2880 (s), 1605 (s), 1447 (s), 1290 (s) cm^{-1}; MS (CI), m/z 391 (MH^+, 100%), 373 (31%); high-resolution MS (CI), m/z 391.2369 (391.2387 calcd for $C_{25}H_{31}N_2O_2$).

(*E*,3a*R,5*R**,6a*S**)-6a-[(2-Aminophenyl)ethenyl]-3-(phenylmethyl)-5-[1-[[(*tert*-butyldimethylsilyl)oxy]methyl]propenyl]-3,3a,4,5,6,6a-hexahydro-2*H*-cyclopentoxazole (19b).** *tert*-Butyldimethylsilyl chloride (87.3 mg, 0.597 mmol) was added to a stirred solution of oxazolidine **19a** (107.4 mg, 0.276 mmol), triethylamine (0.11 mL, 0.83 mmol), 4-(dimethylamino)pyridine (2 mg), and dimethylformamide (1.9 mL). The resulting solution was stirred at room temperature for 2.5 h. Aqueous workup (ether, K_2CO_3) afforded 188 mg of crude **19b** as a yellow oil contaminated with DMF. Chromatography on silica gel (230–400 mesh, 11.8 g; 10:1:0.3 hexane–ethyl acetate–triethylamine, column packed with hexane) gave 137.2 mg (98%) of silyl ether **19b** as a slightly yellow oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.35–7.23 (m, 5 H, Ph H), 7.10 (m, 1 H, Ar H), 7.00 (dd, J = 1.6, 7.9 Hz, 1 H, Ar H), 6.72 (m, 2 H, Ar H), 5.79 (d, J = 1.8 Hz, 1 H, =CH*H*), 5.43 (q, J = 6.9 Hz, 1 H, =C*H*CH_3), 5.10 (d, J = 1.8 Hz, 1 H, =C*H*H), 4.56 (AB q, J = 6.9 Hz, $\Delta\nu$ = 12.7 Hz, 2 H, NCH_2O), 4.04 (m, 2 H, CH_2O), 3.82–3.61 (m, 3 H, NCH_2Ph, NCHR_2), 2.42–2.24 (m, 2 H, RCHR_2, RCH*H*R), 1.94 (m, 1 H, RCH*H*R), 1.82 (t, J = 12.9 Hz, 1 H, RCH*H*R) 1.69–1.50 (m, 1 H, RCH*H*R), 1.35 (d, J = 6.9 Hz, 3 H, =CHCH_3), 0.89 (s, 9 H, t-Bu), 0.03 (s, 6 H, $SiMe_2$); IR (CCl_4) 3485 (w), 3389 (w), 2940 (s), 2872 (s), 1610 (m), 1483 (m), 1449 (m), 1250 (s) cm^{-1}; MS (CI), m/z 505 (MH^+, 100%), 487 (84%).

(*E*,3a*R,5*S**,11b*S**)-5-[1-(Hydroxymethyl)propenyl]-2,3,3a,4,5,6-hexahydro-3-(phenylmethyl)-1*H*-pyrrolo[2,3-*d*]carbazole (4a).** A suspension of oxazolidine **19a** (46.6 mg, 0.124 mmol), 10-camphorsulfonic acid (11.5 mg, 0.0496 mmol), an-

hydrous sodium sulfate (45.0 mg, 0.314 mmol), and toluene (2.5 mL) was heated at reflux for 1.2 h. After cooling to room temperature, the reaction mixture was poured into a mixture of ether (25 mL) and NH_4OH (5% aqueous, 10 mL). Aqueous workup (ether, K_2CO_3) afforded 41.8 mg of crude **4a** as a brown oil. Chromatography on silica gel (230–400 mesh, 4 g; 1:1:0.1 hexane–ethyl acetate–triethylamine) gave 21.1 mg (51%) of labile imine **4a** as a yellow oil: ^1H NMR (250 MHz, $CDCl_3$) δ 7.74 (d, J = 7.0 Hz, 1 H, Ar H), 7.56 (d, J = 7.1 Hz, 1 H, Ar H), 7.54–7.15 (m, 7 H, Ar H, Ph H), 5.61 (q, J = 6.8 Hz, 1 H, =C*H*CH_3), 4.24 (s, 2 H, CH_2O), 3.91 (AB q, J = 13.3 Hz, $\Delta\nu$ = 31.9 Hz, 2 H, NC*H*$_2$Ph), 3.36 (dt, J = 6.1, 9.0 Hz, 1 H), 3.06–2.74 (m, 4 H), 2.63–2.42 (m, 2 H), 1.92–1.62 (m, 3 H), 1.58 (d, J = 6.8 Hz, 3 H, =CHC*H*$_3$); MS (CI), m/z 373 (100%), 355 (21%). This material deteriorates within days at room temperature, so analytical data were not obtained.

(*E*,3a*R,5*S**,11b*S**)-5-[1-[[(*tert*-Butyldimethylsilyl)oxy]methyl]propenyl]-2,3,3a,4,5,6-hexahydro-3-(phenylmethyl)-1*H*-pyrrolo[2,3-*d*]carbazole (4b). Method A.** A suspension of silyl ether oxazolidine **19b** (235.3 mg, 0.466 mmol), 10-camphorsulfonic acid (32.5 mg, 0.140 mmol), anhydrous sodium sulfate (166 mg, 1.16 mmol), and toluene (3.5 mL) was refluxed for 40 min. After cooling to room temperature, the mixture was poured into 1:1 ether–NH_4OH (5% aqueous, 15 mL). Aqueous workup (ether, K_2CO_3) afforded 227 mg (100%) of crude imine **4b**.

Method B. *tert*-Butyldimethylsilyl chloride (11.1 mg, 0.0739 mmol) was added to a stirring solution of imine **4a** (25.0 mg, 0.0672 mmol), triethylamine (0.019 mL, 0.134 mmol), 4-(dimethylamino)pyridine (2 mg), and dimethylformamide (1.0 mL) at room temperature. The resulting solution was stirred for 30 min at room temperature. Aqueous workup (ether, K_2CO_3) afforded crude **4b** as a yellow oil. Chromatography on silica gel (230–400 mesh, 3.1 g; 10:1 hexane–ethyl acetate) gave 15.1 mg (46%) of imine **4b** as a clear oil: ^1H NMR (250 MHz, $CDCl_3$, see Table I for detailed assignments) δ 7.74 (d, J = 7.0 Hz, 1 H, Ar H), 7.56 (d, J = 7.2 Hz, 1 H, Ar H), 7.43–7.16 (m, 7 H, Ar H, Ph H), 5.53 (q, J = 6.9 Hz, 1 H, =C*H*CH_3), 4.21 (s, 2 H, CH_2O), 3.90 (AB q, J = 13.3 Hz, $\Delta\nu$ = 35.9 Hz, 2 H, NCH_2Ph), 3.36 (dt, J = 5.9, 9.0 Hz, 1 H), 3.04–2.78 (m, 3 H), 2.75 (ddd, J = 1.4, 3.5, 12.8 Hz, 1 H), 2.58–2.39 (m, 2 H), 2.01–1.65 (m, 3 H), 1.55 (d, J = 6.9 Hz, 3 H, =CHC*H*$_3$), 0.96 (s, 9 H, *t*-Bu), 0.13 (s, 6 H, $SiMe_2$); ^{13}C NMR (63 MHz, $CDCl_3$) δ 186.4, 146.8, 139.8, 128.6, 127.7, 127.2, 125.4, 123.3, 123.0, 120.0, 69.6, 66.8, 64.6, 62.8, 55.1, 49.4, 38.6, 34.6, 31.5, 27.4, 26.3, 18.6, 13.1; IR (film) 2930 (s), 2852 (s), 1674 (w), 1447 (m), 1333 (m), 1241 (m), 1030 (m), 818 (s) cm^{-1}; MS (CI), m/z 487 (MH^+, 100%), 134 (6%); high-resolution MS (EI), m/z 486.3070 (486.3068 calcd for $C_{31}H_{42}N_2OSi$).

(*E*,3a*R,5*R**,11b*R**)-5-[1-[[(*tert*-Butyldimethylsilyl)oxy]methyl]propenyl]-3-(phenylmethyl)-2,3,3a,4,5,6,6a,7-octahydro-1*H*-pyrrolo[2,3-*d*]carbazole (20).** A solution of imine **4b** (420 mg, 0.864 mmol) and THF was added to a stirring suspension of lithium aluminum hydride (49.0 mg, 1.29 mmol) and THF (10 mL) at 0 °C. The resulting suspension was stirred at 0 °C for 2.5 h, diluted with 1:1 THF–ether (100 mL), and then quenched with $Na_2SO_4 \cdot 10H_2O$ (1.0 g). The resulting suspension was stirred for 1 h. The mixture was filtered, and the white salts were washed with ether (100 mL). Concentration gave 380 mg (90.5%) of crude **20** as a yellow oil. Material of this purity was suitable for use in the next reaction. Chromatography of a sample of comparable material (543 mg) on silica gel (230–400 mesh, 20 g; 10:1:0.1 hexane–ethyl acetate–triethylamine) gave 189 mg (45%) of amine **20** as a clear oil: ^1H NMR (250 MHz, $CDCl_3$) δ 7.38–7.16 (m, 6 H, Ar H, Ph H), 7.07 (dt, J = 1.3, 7.5 Hz, 1 H, Ar H), 6.81 (apparent dt, J = 1.0, 7.4 Hz, 1 H, Ar H), 6.64 (d, J = 7.5 Hz, 1 H, Ar H), 5.49 (q, J = 6.6 Hz, 1 H, =C*H*CH_3), 4.13 (br s, 2 H, CH_2O), 3.85 (t, J = 2 Hz, 1 H, ArNC*H*) 3.73 (AB q, J = 13.5 Hz, $\Delta\nu$ = 53.2 Hz, 2 H, NC*H*$_2$Ph), 3.10 (m, 1 H), 2.87 (m, 1 H), 2.76 (dd, J = 5.5, 11.6 Hz, 1 H), 2.64 (m, 1 H), 2.30–1.58 (m, 6 H), 1.61 (d, J = 6.8 Hz, 3 H, =CHC*H*$_3$), 0.96 (s, 9 H, *t*-Bu), 0.12 (s, 6 H, $SiMe_2$); IR (CCl_4) 3394 (w, NH), 3034 (w), 2932 (s), 2861 (s), 1611 (w), 1483 (m), 1462 (m), 1251 (m), 1094 (m) cm^{-1}; MS (EI, 18 eV), m/z 488 (M, 100%).

(*E*,3a*R,5*S**,6a*R**,11b*S**)-5-[1-[[(*tert*-Butyldimethylsilyl)oxy]methyl]propenyl]-7-(methoxycarbonyl)-3-(phenylmethyl)-2,3,3a,4,5,6,6a,7-octahydro-1*H*-pyrrolo[2,3-*d*]carbazole (21).** Methyl chloroformate (0.080 mL, 1.0 mmol) was added to a stirring solution of crude amine **20** (380 mg, 0.778 mmol), 1,2,2,6,6-pentamethylpiperidine (PMP, 0.35 mL, 0.78 mmol), and CH_2Cl_2 (8.0 mL) at 0 °C. The resulting solution was stirred at 0 °C for 3.5 h. Aqueous workup (CH_2Cl_2, K_2CO_3) afforded crude carbamate **21** contaminated with PMP. Chromatography on silica gel (230–400 mesh, 20 g; 10:1:0.1 hexane–ethyl acetate–triethylamine) gave 330 mg (73%) of carbamate **21** as a clear oil: ^1H NMR (250 MHz, $CDCl_3$) δ 7.73 (d, J = 7.7 Hz, 1 H, Ar H), 7.77–7.07 (m, 6 H, Ar H, Ph H), 7.02 (m, 2 H, Ar H), 5.46 (q, J = 7.0 Hz, 1 H, =C*H*CH_3), 4.33 (t, J = 5.5 Hz, 1 H, ArNC*H*R$_2$), 4.14 (AB q, J = 13.0 Hz, $\Delta\nu$ = 13.1 Hz, 2 H, CH_2O), 3.83 (s, 3 H, OMe), 3.81 (AB q, J = 13.3 Hz, $\Delta\nu$ = 93.2 Hz, 2 H, NC*H*$_2$Ph), 2.91 (m, 2 H), 2.74–2.58 (m, 2 H), 2.14–1.80 (m, 4 H), 1.59 (m, 2 H), 1.48 (d, J = 6.8 Hz, 3 H, =CHC*H*$_3$), 0.92 (s, 9 H, *t*-Bu), 0.07 (s, 6 H, $SiMe_2$); IR (CCl_4) 3130 (w), 2932 (s), 2855 (m), 1792 (s), 1439 (s), 1380 (m), 1247 (s) cm^{-1}; MS (CI), m/z 547 (MH^+, 100%), 415 (82%), 325 (17%); high-resolution MS (CI), m/z 547.3360 (547.3358 calcd for $C_{33}H_{47}N_2O_3Si$).

(*E*,3a*R,5*R**,6a*R**,11b*R**)-5-[1-[[(*tert*-Butyldimethylsilyl)oxy]methyl]propenyl]-7-(methoxycarbonyl)-2,3,3a,4,5,6,6a,7-octahydro-3-[(2,2,2-trichloroethoxy)carbonyl]-1*H*-pyrrolo[2,3-*d*]carbazole (22).** A suspension of amine **21** (179 mg, 0.328 mmol), 2,2,2-trichloroethyl chloroformate (0.23 mL, 1.6 mmol), $NaHCO_3$ (150 mg, 1.80 mmol), and chloroform (3.0 mL) was refluxed for 16 h. After cooling to room temperature, the mixture was filtered and excess chloroformate was removed by distillation [65–80 °C (0.15 mm)] to give a clear oil. Chromatography of the residue on silica gel (230–400 mesh, 20 g; 15:1 hexane–ethyl acetate) gave 103 mg (49.5%) of carbamate **22** as a clear oil: ^1H NMR (250 MHz, $CDCl_3$) δ 7.78 (dd, J = 2.9, 8.1 Hz, 1 H, Ar H), 7.27 (m, 1 H, Ar H), 6.99 (m, 1 H, Ar H), 5.50 (q, J = 6.8 Hz, 1 H, =C*H*CH_3), 4.95–4.65 (m, 2 H, CH_2CCl_3), 4.48 (m, 1 H, NCH), 4.34 (dd, J = 6.4, 12.4 Hz, 1 H, NCH), 4.13 (m, 1 H), 3.92 (dt, J = 12.6, 3.5 Hz, 1 H), 3.86 (s, 3 H, OMe), 3.68 (m, 2 H), 2.97 (br s, 1 H), 2.35–2.02 (m, 3 H), 1.58 (m, 3 H, =CHC*H*$_3$), 0.93 (s, 9 H, *t*-Bu), 0.10 (s, 6 H, $SiMe_2$); IR (CCl_4) 2946 (s), 2921 (s), 2848 (m), 1722 (s, C=O), 1596 (w), 1471 (s), 1433 (s), 1398 (s), 1380 (s), 1326 (s), 1102 (s), 1043 (s); MS (EI, 18 eV), m/z 632 (M, 2%), 574 (M – *t*-Bu, 100%).

(*E*,3a*R,5*R**,6a*R**,11b*R**)-5-[1-(Hydroxymethyl)propenyl]-7-(methoxycarbonyl)-2,3,3a,4,5,6,6a,7-octahydro-3-[(2,2,2-trichloroethoxy)carbonyl]-1*H*-pyrrolo[2,3-*d*]carbazole (24).** Tetrabutylammonium fluoride (0.24 mL of a 1.0 M solution in THF, 0.24 mmol) was added to a stirring solution of silyl ether **22** (137 mg, 0.216 mmol) and THF (2.0 mL) at room temperature. The resulting solution was stirred for 35 min. Aqueous workup (ether, $MgSO_4$) afforded crude **24** as a yellow oil. Chromatography on silica gel (230–400 mesh, 13 g; 3:1 hexane–ethyl acetate) gave 92.7 mg (83%) of alcohol **24** as a clear oil: ^1H NMR (250 MHz, $CDCl_3$, mixture of carbamate isomers) δ 7.72 (d, J = 8.2 Hz, 1 H, Ar H), 7.26 (m, 1 H, Ar H), 7.03 (m, 2 H, Ar H), 5.56 (q, J = 6.8 Hz, 1 H, =C*H*CH_3), 4.82 (d of AB q, J = 11.9 Hz, $\Delta\nu$ = 73.2 Hz, J = 12.0 Hz, $\Delta\nu$ = 19.8 Hz, 2 H, CH_2CCl_3), 4.56 (dd, J = 4.5, 11.0 Hz, 1 H), 4.25 (m, 2 H), 3.97 (m, 1 H), 3.88 and 3.87 (s, 3 H, OMe), 3.69 (m, 2 H), 3.05 (br m, 1 H), 2.39–2.17 (m, 2 H), 2.01 (m, 2 H), 1.85–1.66 (m, 2 H), 1.62 (m, 3 H, =CHC*H*$_3$); IR (CCl_4) 3580–3300 (br, OH), 2949 (s), 1713 (s, C=O), 1595 (w), 1477 (m), 1440 (s), 1382 (s), 1332 (s), 1119 (s) cm^{-1}; MS (CI), m/z 517 (MH^+, 8%), 501 (100%), 467 (36%), 465 (60%), 325 (23%); high-resolution MS (CI), m/z 517.1064 (517.1066 calcd for $C_{23}H_{28}Cl_3N_2O_5$).

(*E*,3a*R,5*R**,6a*R**,11b*R**)-5-[1-[(Methylsulfonyl)methyl]propenyl]-7-(methoxycarbonyl)-2,3,3a,4,5,6,6a,7-octahydro-3-[(2,2,2-trichloroethoxy)carbonyl]-1*H*-pyrrolo[2,3-*d*]carbazole (25).** Methanesulfonic anhydride (4.7 mg, 0.027 mmol) was added to a stirred solution of alcohol **24** (6.7 mg, 0.013 mmol), triethylamine (0.060 mL, 0.040 mmol), and THF (0.8 mL) at room temperature. The resulting solution was stirred for 40 min. Aqueous workup (ether, $MgSO_4$) afforded 9.0 mg (100%) of crude mesylate **25** as a yellow oil: ^1H NMR (250 MHz, $CDCl_3$, mixture of carbamate isomers) δ 7.71 (m, 1 H, Ar H), 7.26 (m, obscured by $CHCl_3$, 1 H, Ar H), 7.00 (m, 2 H, Ar H), 5.80 (q, J = 6.9 Hz, 1 H, =C*H*CH_3), 4.96–4.64 (m, 4 H, CH_2CCl_3, CH_2O), 4.75 (m, 1 H), 3.96 (m, 1 H), 3.88 and 3.86 (s, 3 H, OCH_3), 3.80–3.58 (m, 3 H), 3.09 and 3.08 (s, 3 H, SO_2CH_3), 3.00 (m, 1 H), 2.63–1.80

(m, 7 H), 1.68 and 1.61 (d, J = 6.9 Hz, 3 H, =CHCH_3).

(*E*,3a*R,5*R**,6a*R**,11b*S**)-5-[1-[[(*tert*-Butyldimethylsilyl)oxy]methyl]propenyl]-7-(methoxycarbonyl)-2,3,3a,4,5,6,6a,7-octahydro-1*H*-pyrrolo[2,3-*d*]carbazole (26b).** Activated zinc[38] (230 mg) was added to a stirred solution of carbamate **22** (141 mg, 0.223 mol), THF (3.5 mL), and KH_2PO_4 (1 M, 0.2 mL) in small portions over 6 h. The resulting suspension was stirred at room temperature overnight. Filtration, followed by basic workup (ether, K_2CO_3), afforded 53.2 mg of crude **26b** as a yellow oil. Chromatography on silica gel (230–400 mesh, 10 g; 1:1:0.2 hexane–ethyl acetate–triethylamine) gave 39.7 mg (39%) of amine **26b** as a clear oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.76 (d, J = 8.0 Hz, 1 H, Ar H), 7.23 (dt, J = 1.4, 8.1 Hz, 1 H, Ar H), 7.13 (dd, J = 1.2, 7.3 Hz, 1 H, Ar H), 7.01 (apparent dt, J = 1.0, 7.4 Hz, 1 H, Ar H), 5.48 (q, J = 7.0 Hz, 1 H, =C*H*CH$_3$), 4.37 (dd, J = 4.7, 6.1 Hz, 1 H, O_2CNCH), 4.16 (AB q, J = 12.8 Hz, $\Delta\nu$ = 12.1 Hz, 2 H, CH_2O), 3.85 (s, 3 H, OCH_3), 3.15 (m, 2 H), 2.76 (m, 1 H), 2.14–1.87 (m, 5 H), 1.70–1.52 (m, 2 H), 1.54 (d, J = 6.9 Hz, 3 H, =CHCH_3), 0.92 (s, 9 H, t-Bu), 0.08 (s, 6 H, $SiMe_2$); IR (CCl_4) 2937 (s), 2861 (m), 1716 (s), 1479 (s), 1466 (m), 1440 (s), 1383 (s), 1249 (m), 1093 (m), 826 (m) cm^{-1}; MS (EI, 18 eV), m/z 456 (M, 33%), 311 (100%), 283 (23%), 254 (42%).

(*E*,3a*R,5*S**,6a*R**,11b*S**)-5-[1-(Hydroxymethyl)propenyl]-7-(methoxycarbonyl)-2,3,3a,4,5,6,6a,7-octahydro-1*H*-pyrrolo[2,3-*d*]carbazole (26).** Tetrabutylammonium fluoride (0.015 mL of a 1.0 M solution in THF, 0.015 mmol) was added to a stirred solution of silyl ether **26b** (6.0 mg, 0.013 mmol) and THF (0.7 mL) at room temperature. The resulting solution was stirred for 15 min. Aqueous workup (ether, K_2CO_3) gave 4.2 mg (94%) of crude amino alcohol **26** as a light yellow oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.78 (d, J = 8.1 Hz, 1 H, Ar H), 7.22 (dd, J = 1.3, 8.0 Hz, 1 H, Ar H), 7.12 (dd, J = 1.2, 7.4 Hz, 1 H, Ar H), 7.03 (m, 1 H, Ar H), 5.53 (q, J = 6.8 Hz, 1 H, =C*H*CH$_3$), 4.41 (t, J = 5.2 Hz, 1 H, O_2CNCH), 4.15 (AB q, J = 12.4 Hz, $\Delta\nu$ = 10.0 Hz, 2 H, CH_2O), 3.86 (s, 3 H, OCH_3), 3.36 (m, 2 H), 3.16 (m, 1 H), 2.88 (m, 1 H), 2.03 (m, 2 H), 1.85–1.59 (m, 2 H), 1.57 (d, J = 6.8 Hz, 3 H, =CHCH_3), 1.44 (m, 2 H); IR (CCl_4) 3450–3150 (br w), 2831 (s), 2769 (s), 1712 (s), 1477 (s), 1440 (s), 1379 (s), 1255 (m) cm^{-1}; MS (EI, 18 eV), m/z 342 (M, 100%), 324 (47%), 311 (25%), 271 (31%).

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Registry No. (±)-**4a**, 97552-20-0; (±)-**4b**, 97552-21-1; (±)-**5**, 97552-34-6; (±)-**6**, 97570-05-3; **7**, 97552-22-2; **8**, 97552-23-3; (±)-**9**, 97552-42-6; **10**, 97552-44-8; (±)-**11a**, 97552-24-4; (±)-**11a** (mesylate), 97552-43-7; (±)-**11b**, 97552-25-5; **12**, 97552-26-6; **13a**, 97552-27-7; (±)-**14**, 97552-29-9; (±)-**15**, 97552-30-2; **16**, 6141-21-5; (±)-**16a**, 97552-28-8; (±)-**17**, 97552-31-3; (±)-**18**, 97552-32-4; (±)-**19a**, 97552-33-5; (±)-**19b**, 97570-06-4; (±)-**20**, 97552-35-7; (±)-**21**, 97552-36-8; (±)-**22**, 97552-37-9; (±)-**24**, 97552-38-0; (±)-**25**, 97552-39-1; (±)-**26**, 97552-41-5; (±)-**26b**, 97552-40-4; t-BuCOCl, 3282-30-2; o-$BrC_6H_4NH_2$, 615-36-1; o-$BrC_6H_4NHCOBu$-t, 65854-92-4; $ClCO_2CH_2CCl_3$, 17341-93-4.

Studies on Quinolizine Derivatives. 20.[1] Syntheses of Cycl[3.3.3]azine Derivatives

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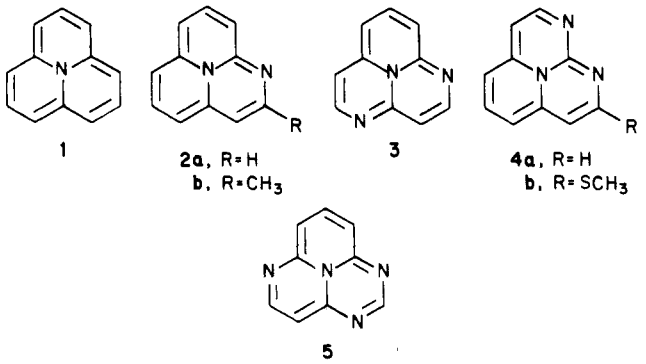
By the Diels-Alder reaction of azacyclazines (**6**, **11**) with dienophiles, methyl acetylenecarboxylate (MAC), dimethyl acetylenedicarboxylate (DMAD), and *N*-phenylmaleimide (PMI), the corresponding cyclazine derivatives (**7–10**, **12**, **13**) were obtained. 1,6-Diazacycl[3.3.3]azine (**15**), which was a very unstable free base, was prepared by the degradation of **13**. The ^{1}H nuclear magnetic resonance spectral data of **15** may be interpreted in terms of a paramagnetic ring current.

Since the first synthesis of cycl[3.3.3]azine[2] by Farquhar and Leaver, this molecule, which exhibits a paratropic ^{1}H NMR shift, has been examined by Dewar and Trinajstic[3], who have advanced a simple and convincing argument to show that **1** is aptly characterized as a nitrogen-bridged, "antiaromatic" [12]annulene. Previously, we reported the synthesis of various azacycl[3.3.3]azines, 1-aza-, 1,4-diaza-, 1,9-diaza–, and 1,3,6-triazacycl[3.3.3]azine derivatives (**2–5**)[4] (Scheme I).

In this paper, we have examined the chemical reactivity of 1-azacyclazine derivatives (**6**) and 4-cyano-1,3,6-triazacycl[3.3.3]azine (**11**) with some dienophiles. The reaction of **6** with methyl acetylenecarboxylate (MAC) readily gave

Scheme I



cycl[3.3.3]azine derivatives **7**. Furthermore, our attempts to extend this Diels-Alder reaction to **11** with dimethyl acetylenedicarboxylate (DMAD) led to the formation of a new ring system, as shown by the 1,6-diazacycl[3.3.3]-azine derivatives **12** and **13**. We now report the full details of this work, including a new preparation of 1,6-diazacycl[3.3.3]azine (**15**) as an unstable free base.[5]

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