Synthesis of Analogues of Iboga Alkaloids. Investigation of Electrophilic, Palladium-Catalyzed, and Radical Cyclizations for the Preparation of 5,6-Homoiboga Derivatives

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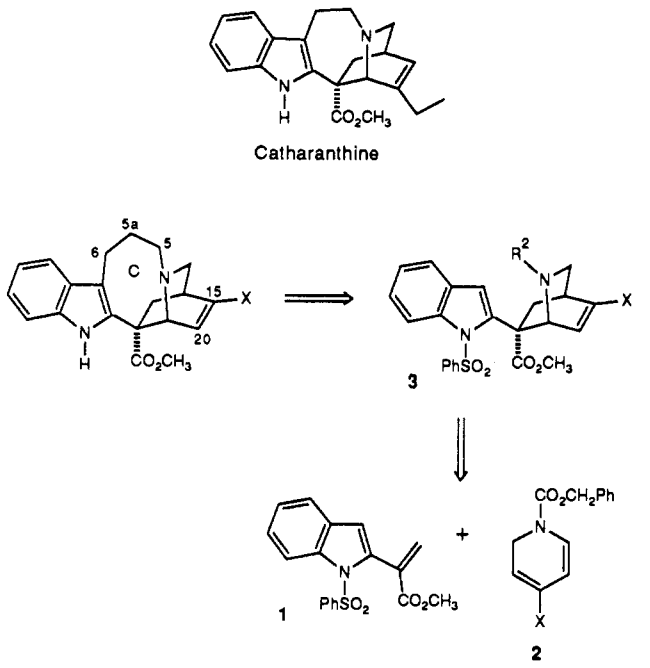
The Diels–Alder adducts formed from 1-(benzyloxycarbonyl)-1,2-dihydropyridine or 1-(benzyloxycarbonyl)-4-methoxy-1,2-dihydropyridine by reaction with methyl 2-[1-(phenylsulfonyl)-1*H*-indol-2-yl]-2-propenoate can serve as precursors of the 5,6-homologues of the iboga alkaloid skeleton. The eight-membered C-ring can be closed by introduction of a three-carbon bridge between the isoquinuclidine nitrogen and the 3-position of the indole ring. Electrophilic cyclization proceeds in modest yield. Intramolecular Heck reactions involving a 3-iodinated indole ring and *N*-acryloyl or *N*-allyl derivatives of the isoquinuclidine ring are efficient only when the indole ring is N-methylated. Intramolecular radical addition of a 3-iodinated indole occurs when a 2-ethoxycarbonyl, 2-phenylsulfonyl, or 2-phenylsulfinyl substituent is present on an *N*-allyl isoquinuclidine substituent. The cyclization products from the 2-phenylsulfonyl case can be converted to various homoiboga derivatives.

Analogues of the antineoplastic dimeric vinca alkaloids can be prepared by applying the Potier oxidative coupling method[1] to analogues of catharanthine and vindoline[2] or by several alternative approaches.[3] We are interested in preparing 5′,6′-homologues of vinblastine by the Potier method and have therefore undertaken the synthesis of 5,6-homologues of the iboga structure.[4] Utilization of 6-(2-indolyl)-2-azabicyclo[2.2.2]oct-7-ene-6-carboxylate esters (**3**), which are readily available from indole-2-acrylate (**1**) and dihydropyridine (**2**) and derivatives,[5] as intermediates requires a method for closure of the eight-membered C ring. In this paper we report the results of exploration of electrophilic, palladium-catalyzed, and radical reactions for the required cyclization.

A. Electrophilic Cyclization. In earlier work we had obtained moderate yields of iboga structures by BF_3-mediated cyclization of *N*-(2-oxoethyl) derivatives of the indolylisoquinuclidinone **6c**.[5c] Attention was therefore directed toward the homologous *N*-(3-oxopropyl) system, and a potential intermediate **3d** was sought by alkylation of **3c**[5b] with 2-(2-iodoethyl)-1,3-dioxolane.[6] The desired amine **3d** could be obtained only in low yield, however, and was accompanied by **4a**, which is stereoisomeric at C6 of the isoquinuclidine ring. Alkylation of **3c** with methyl acrylate also led to a mixture of C6 stereoisomers **3e** and **4b**. This is due to the epimerization of **3c** by reversible

Scheme I



Mannich fragmentation–recombination being competitive with alkylation. Support for the mechanistic interpretation comes from the isolation of **5** as a byproduct from alkylation of **3c** with 3-iodopropanol. This product can be formed by intramolecular trapping of the dihydropyridinium intermediate formed in the reverse Mannich step (Scheme II).

The epimerization problem shifted our attention to the 8-oxo and 8,8-dimethoxy amines **6c** and **6d**. Experience with these systems had indicated that they are much less prone to the reverse Mannich reaction. Alkylation of **6c** with 2-(2-iodoethyl)-1,3-dioxolane[6] introduced the 3-carbon chain to give **6e**. The dimethyl ketal **6d** was alkylated with 2-(2-iodoethyl)-1,3-dioxolane or 3,3-dimethoxy-1-iodopropane[7] to give **6f** and **6g**, respectively. In the alkylation of these systems, epimerization at C6 of the 2-azabicyclo[2.2.2]octane ring was not observed. Evidently the conjugation provided by the C7–C8 double bond in **3c** is important in facilitating the reverse Mannich reaction. Attempted cyclization of **6e** with either $TiCl_4$ or BF_3·OEt_2

(1) Langlois, N.; Guéritte, F.; Langlois, Y.; Potier, P. *J. Am. Chem. Soc.* **1976**, *98*, 7017.

(2) Raucher, S.; Bray, B. L.; Lawrence, R. F. *J. Am. Chem. Soc.* **1987**, *109*, 442. Guéritte, F.; Langlois, N.; Langlois, Y.; Sundberg, R. J.; Bloom, J. D. *J. Org. Chem.* **1981**, *46*, 5393. Honma, Y.; Ban, Y. *Tetrahedron Lett.* **1978**, 155. Kutney, J. P.; Joshua, A. V.; Liao, P.-H.; Worth, B. R. *Can. J. Chem.* **1977**, *55*, 3235.

(3) Vukovic, J.; Goodbody, A. E.; Kutney, J. P.; Misawa, M. *Tetrahedron* **1988**, *44*, 325. Misawa, M.; Endo, T.; Goodbody, A.; Vukovic, J.; Chapple, C.; Choi, L.; Kutney, J. P. *Photochemistry* **1988**, *27*, 1355. Kuehne, M. E.; Zebovitz, T. C.; Bornmann, W. G.; Marko, I. *J. Org. Chem.* **1987**, *52*, 4340. Schill, G.; Priester, C. U.; Windhövel, U. F.; Fritz, H. *Tetrahedron* **1987**, *43*, 3765. Kutney, J. P.; Beck, J.; Bylsma, F.; Cook, J.; Cretney, W. J.; Fuji, K.; Imhof, R.; Treasurywala, A. M. *Helv. Chim. Acta* **1975**, *58*, 1690. Harley-Mason, J.; Rahman, Atta-ur *Tetrahedron* **1980**, *36*, 1057. Kunesch, N.; Vaucamps, P.-L.; Cavé, A.; Poisson, J.; Wenkert, E. *Tetrahedron Lett.* **1979**, 5073.

(4) The alkaloid homologues are numbered according to the alkaloid scheme with the homologous carbon assigned as 5a; C15–C20 unsaturated systems are named as derivatives of catharanthine, while C15–C20 saturated analogues are named as derivatives of coronaridine. Intermediates are named and numbered as derivatives of 2-azabicyclo[2.2.2]octane-6-carboxylic acid.

(5) (a) Sundberg, R. J.; Bloom, J. D. *J. Org. Chem.* **1980**, *45*, 3382. (b) Sundberg, R. J.; Bloom, J. D. *J. Org. Chem.* **1981**, *46*, 4836. (c) Sundberg, R. J.; Amat, M.; Fernando, A. M. *J. Org. Chem.* **1987**, *52*, 3151.

(6) Larson, G. L.; Klesse, R. *J. Org. Chem.* **1985**, *50*, 3627.

(7) Feringa, B. L. *Synth. Commun.* **1985**, *15*, 87.

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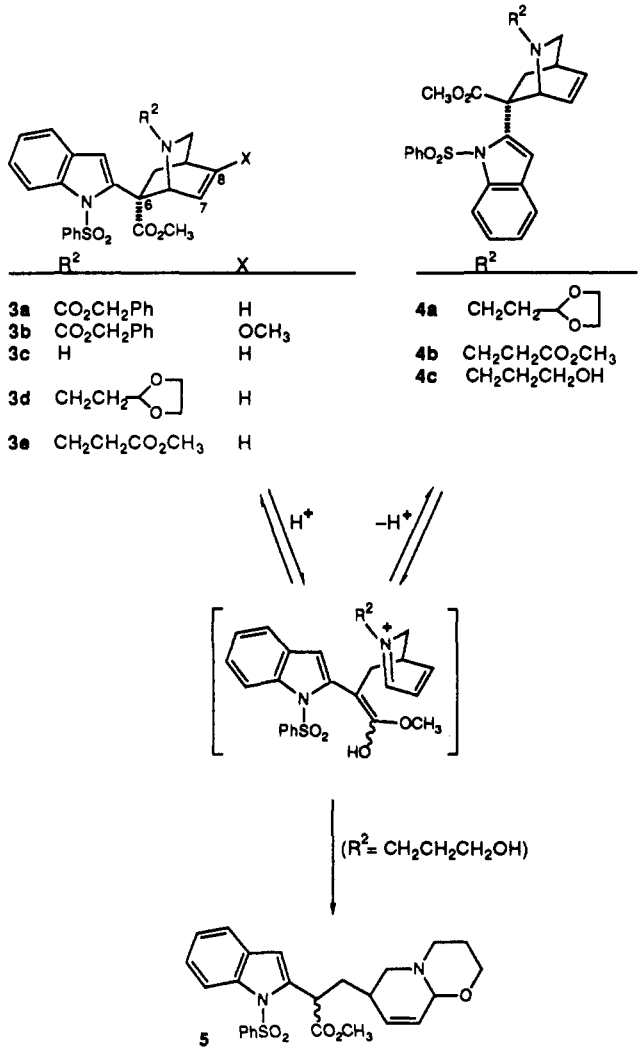
Scheme II

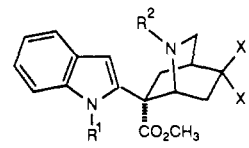


led to N-dealkylation with return of **6c** as the only recognizable product. The dealkylation can be attributed to a Grob-type fragmentation followed by hydrolysis of the resulting iminium ion.[8] Since it would be expected that N-desulfonylated indoles would be more reactive toward electrophilic cyclization, attention was turned to the N-desulfonylated indoles (Scheme III).

The N-alkylated derivatives **6e–g** could be desulfonylated by sodium amalgam, furnishing **7e**, **7f**, and **7g**. In the case of **6e**, reductive desulfonylation was accompanied by competing reduction of the C8 carbonyl to give alcohols **7c** and **7d**. The reactivity of **7e**, **7f**, and **7g** toward Lewis acids was then explored. A modest yield of the unsaturated ketone **8a** was obtained from reaction of **7e** with BF_3·OEt_2 at 40 °C. The same product was formed from **7f**, with the yields varying from 30 to 40%. The best results were obtained with **7g**, which provided 40–50% yields of **8a** on reaction with neat BF_3·OEt_3 at 40 °C. The "nor" ketone **9** was a byproduct, formed in up to 20% yield. The isolation of **9** provides evidence that Grob fragmentation occurs as a competing process, with **9** being formed by cyclization of the resulting iminium ion intermediate. The aldol condensation product **10** was also observed as a byproduct (Scheme IV). The yields from the BF_3·OEt_2 cyclizations were somewhat capricious. The most consistent results were obtained when 4–6 equiv of trifluoroacetic acid was included in the reaction mixture. This

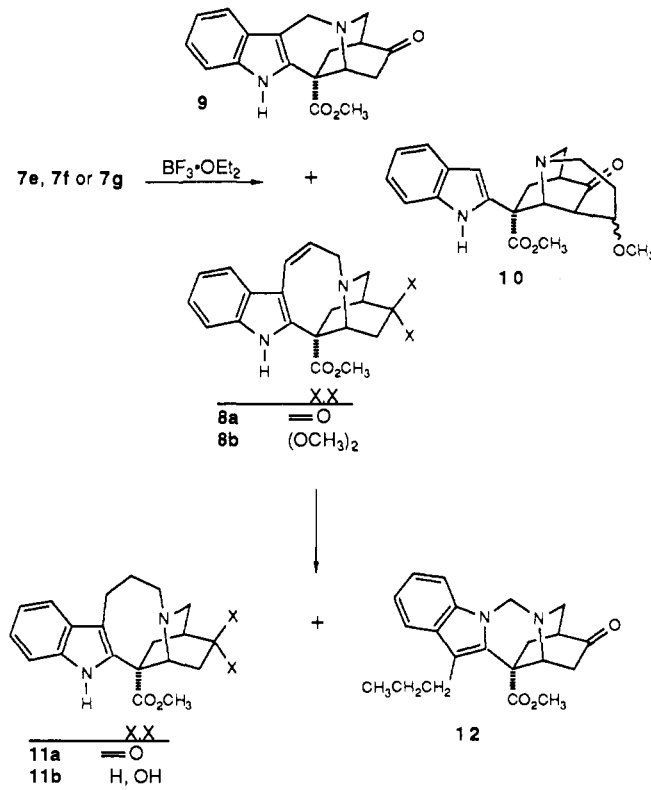
(8) Grob, C. A. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 535.

Scheme III



	R^1	R^2	X,X
6a	$PhSO_2$	CO_2CH_2Ph	$(OCH_3)_2$
6b	$PhSO_2$	CO_2CH_2Ph	=O
6c	$PhSO_2$	H	=O
6d	$PhSO_2$	H	$(OCH_3)_2$
6e	$PhSO_2$	CH_2CH_2 O O	=O
6f	$PhSO_2$	CH_2CH_2 O O	$(OCH_3)_2$
6g	$PhSO_2$	$CH_2CH_2CH(OCH_3)_2$	$(OCH_3)_2$
7a	H	CO_2CH_2Ph	$(OCH_3)_2$
7b	H	H	$(OCH_3)_2$
7c	H	CH_2CH_2 O O	OH, H
7d	H	CH_2CH_2 O O	H, OH
7e	H	CH_2CH_2 O O	=O
7f	H	CH_2CH_2 O O	$(OCH_3)_2$
7g	H	$CH_2CH_2CH(OCH_3)_2$	$(OCH_3)_2$
7h	H	$CH_2CH_2CH(SPh)_2$	$(OCH_3)_2$

Scheme IV

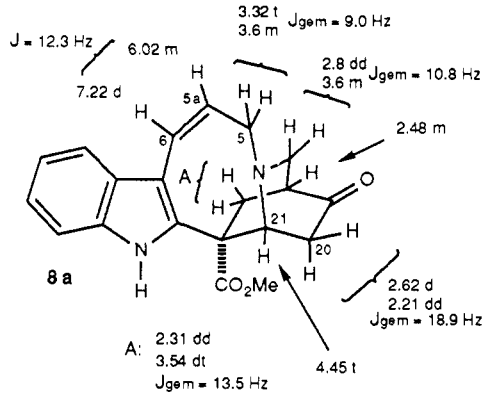


improvement may be due to suppression of the Grob fragmentation by N-protonation. Titanium tetrachloride was also examined as a Lewis acid but it was less effective.

The diphenyl thioacetal **7h** was also synthesized and its cyclization examined. It was prepared by alkylation of **7b** with 2,2-bis(phenylthio)ethyl benzenesulfonate.[9] Cyclization was carried out using silver trifluoroacetate in the presence of trifluoroacetic acid.[10] A mixture of **8a** and the

(9) Cohen, T.; Ritter, R. H.; Ouellette, D. *J. Am. Chem. Soc.* **1982**, *104*, 7142.

Scheme V



corresponding C15 ketal **8b** was obtained in a total yield of 53%. While the retention of the ketal group under these milder cyclization conditions is potentially useful, this procedure has not been studied extensively.

The structure of **8a** was confirmed by its NMR spectrum. The assignment of the nonaromatic protons are given in Scheme V. The following additional proton–proton couplings were proven by decoupling: 5/5a, 5a/6, and 20/21.

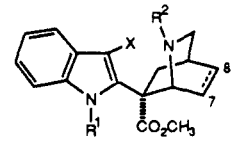
The reduction of **8a** to **11a** over Pd/C catalyst was accompanied by formation of the rearranged product **12** (Scheme IV). This compound is evidently formed by hydrogenolysis of the allylic C–N bond, followed by cyclization of the liberated secondary amine by formaldehyde (or an equivalent species) generated from the catalyst and the solvent methanol. Use of 5% rhodium on carbon also gave some **11a**. Raney nickel gave the corresponding C15 alcohol **11b**. The most reliably efficient procedure found for reduction of **8a** to **11a** used Wilkinson's catalyst in benzene–methanol and proceeded in 61% yield. The electrophilic route produced 15-oxo-20-deethyl-5,6-homocoronaridine (**11a**) in four steps and about 20% overall yield from **6d**.

B. Palladium-Catalyzed Reactions. The Heck reaction has become a valuable method for introducing vinyl substituents, including acrylate ester moieties, on aromatic and heteroaromatic systems.[11] Since an acrylate unit would provide the 3-carbon group necessary to construct the C ring of the homoiboga skeleton, we investigated both intermolecular and intramolecular Heck reactions.

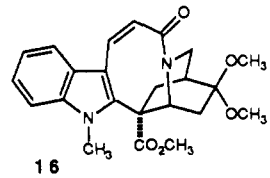
The desulfonylated Diels–Alder adduct **13a**[5b] was iodinated in good yield, using *N*-iodosuccinimide generated in situ from *N*-chlorosuccinimide and sodium iodide[12] to give 3-iodoindole **13b**. This compound was methylated on the indole nitrogen to give **13c**. Both **13b** and **13c** reacted with methyl acrylate in the presence of palladium acetate to give the corresponding 3-acrylate ester derivatives **14a** and **14b**. However, the reactions were sluggish and required quite high levels of $Pd(OAc)_2$ to achieve modest yields. The reaction was cleaner with the *N*-methylindole **13c**, which gave a 55% yield of **14b**, while the conversion of **13b** was only 33%. The 8,8-dimethoxy derivative **13e** also gave a modest conversion to **14c** (25% yield, with 50% recovery of starting material) (Scheme VI).

In view of the limited efficiency of these reactions, efforts were turned to intramolecular Heck reactions which have proved useful in forming five- through seven-membered

Scheme VI



	R^1	R^2	X	7,8
13a	H	CO_2CH_2Ph	H	dehydro
13b	H	CO_2CH_2Ph	I	dehydro
13c	CH_3	CO_2CH_2Ph	I	dehydro
13d	H	CO_2CH_2Ph	I	8,8-dimethoxy
13e	CH_3	CO_2CH_2Ph	I	8,8-dimethoxy
14a	H	CO_2CH_2Ph	$CH{=}CHCO_2CH_3$	dehydro
14b	CH_3	CO_2CH_2Ph	$CH{=}CHCO_2CH_3$	dehydro
14c	CH_3	CO_2CH_2Ph	$CH{=}CHCO_2CH_3$	8,8-dimethoxy
15a	H	$COCH{=}CH_2$	H	8,8-dimethoxy
15b	H	$COCH{=}CH_2$	I	8,8-dimethoxy
15c	CH_3	$COCH{=}CH_2$	I	8,8-dimethoxy



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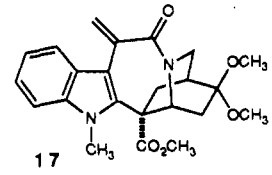


17

heterocyclic rings.[11,13] The reactant **15b** was readily prepared by treatment of **7b** with acryloyl chloride, followed by iodination with *N*-iodosuccinimide. Methylation of **15b** using sodium hydride–methyl iodide provided **15c**.

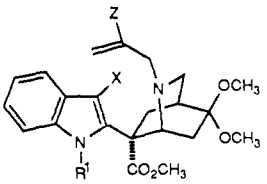
Application of standard conditions[11] for the Heck reaction to **15b** gave only dehalogenated material and starting material. Inclusion of tris(*o*-tolyl)phosphine did not significantly improve the results. Palladium mirrors were formed in the reaction vessel. The reaction of **15c** was more interesting. The cyclization products **16** and **17** were formed, but in a 2:1 ratio favoring the undesired regioisomer **17** (Scheme VI).

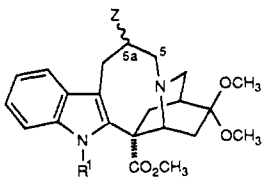
The conformationally more flexible reactant **18b** was then prepared by alkylation of **7b** with ethyl 2-(bromomethyl)acrylate[14] followed by iodination. N-Methylation of **18b** could also be accomplished in excellent yield to give **18c**. An analogous series of compound having a phenylsulfonyl substituent was prepared by using 3-bromo-2-(phenylsulfonyl)propene[15] (**1g**) as the alkylating agent.

Application of phase-transfer-catalyzed conditions[16] to the intramolecular Heck reaction of **18c** gave **19b** in an exceptionally clean reaction (89% yield). In contrast, the N-unsubstituted indole **18b** gave a poor yield of cyclization product **19a**. The product mixture also contains the 5a,6-double bond isomer (**19a***), but it was not completely purified. The vinyl sulfone **18e** was converted to **19c** in 14% yield under similar conditions. The assignment of the 5,5a-double bond position in **19a–c** is based on the position of the C-21 (bridgehead) proton, which is shifted downfield from its location in the precursors. The intramolecular Heck reaction therefore is capable of formation of the desired homoiboga skeleton, but appears to require an N-substituted 3-iodoindole for good yields to be obtained.

(10) Manas, A. R. B.; Smith, R. A. J. *Tetrahedron* **1987**, *43*, 1847.
(11) Heck, R. F. *Org. React.* **1982**, *27*, 345. Heck, R. F. *Palladium Reagents in Organic Syntheses*; Academic Press: London, 1985.
(12) Vankar, Y. D.; Kumaravel, G. *Tetrahedron Lett.* **1984**, *25*, 233.
(13) Abelman, M. M.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4130. Hegedus, L. S.; Sestrick, M. R.; Michaelson, E. T.; Harrington, P. J. *J. Org. Chem.* **1989**, *54*, 4141.
(14) Ferris, A. F. *J. Org. Cehm.* **1955**, *20*, 780.
(15) Knochel, P.; Normat, J. F. *Tetrahedron Lett.* **1985**, *26*, 425. 3-Bromo-2-(phenylsulfinyl)propene was prepared from 3-bromo-2-(phenylthio)propene using 1 equiv of *m*-chloroperoxybenzoic acid.
(16) Jeffery, T. *Synthesis* **1987**, 70. Larock, R. C.; Baker, B. E. *Tetrahedron Lettt.* **1988**, *29*, 905.

Scheme VII





	R^1	X	Z
18a	H	H	$CO_2C_2H_5$
18b	H	I	$CO_2C_2H_5$
18c	CH_3	I	$CO_2C_2H_5$
18d	H	H	SO_2Ph
18e	H	I	SO_2Ph
18f	H	H	SOPh
18g	H	I	SOPh
18h	H	H	H
18i	H	I	H
18j	CH_3	I	H
18k	CH_3	H	H
18l	H	H	a
18m	H	I	a
18n	CH_3	I	a
18o	CH_3	H	a

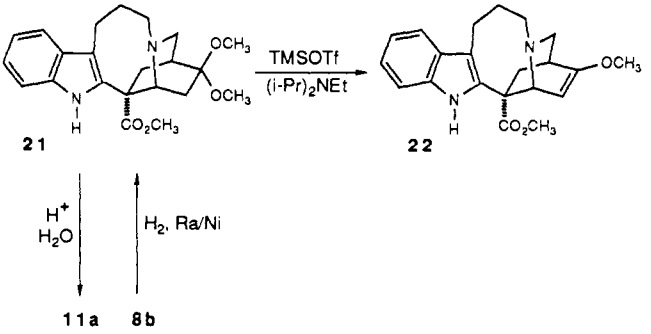
	R^1	Z	
19a	H	$CO_2C_2H_5$	5,5a-dehydro
19b	CH_3	$CO_2C_2H_5$	5,5a-dehydro
19c	H	SO_2Ph	5,5a-dehydro
20a	H	$CO_2C_2H_5$	
20b	CH_3	$CO_2C_2H_5$	
20c	H	SO_2Ph	
20d	H	SOPh	

a. isoquinuclidine substituent is N-propargyl

C. Radical Cyclizations. Compounds **18b,c,e,g** are potential starting materials for intramolecular radical cyclization. While relatively few of the many recent examples[17] of intramolecular radical additions have involved aryl halides,[18] compounds **18b,c,e,g** offer a favorable SOMO–LUMO interaction[19] between the electron-rich indol-3-yl radical and an electron-poor *N*-allyl moiety. Addition of a tri-*n*-butyltin hydride to **18b** in benzene containing AIBN at 80 °C led to two stereoisomeric cyclization products **20a** in overall 48% yield. Similarly, cyclization of the *N*-methyl analogue **18c** provided a mixture of the two diastereomers **20b** in overall 42% yield. One of these stereoisomers could be obtained from the Heck reaction product **19b** by hydrogenation using Wilkinson's catalyst. This isomer is tentatively assigned to be the α-stereoisomer by assuming that steric approach control operates in the hydrogenation.

The radical cyclization of the vinyl sulfone **18e** proceeded in 70% yield to give a mixture of two stereoisomers of **20c** in 20:1 ratio. The mixture could be reductively desulfonylated to **21** using sodium amalgam in liquid ammonia. The use of sodium amalgam avoids reduction of the ester group which occurred when sodium metal was used. Sodium amalgam in buffered methanol[20] was not satisfactory for this desulfonylation. Compound **21** was interrelated with **11a** obtained from the electrophilic cyclization route, by hydrolysis. The ketal **8b** gave **21** on

Scheme VIII



reduction over Raney nickel, providing a second correlation with the electrophilic cyclization series (Scheme VIII). The radical cyclization route provides **21** in five steps from **6d** in an overall 30% yield. The vinyl ether **22** can also be obtained from **21** using Gassman's conditions.[21]

We have not assigned stereochemistry to the **20c** stereoisomers. The major diastereomer is characterized by a large upfield shift of the indole ring protons. This implies that there may be a partial stacking of the indole and phenylsulfonyl rings in this isomer. The minor isomer is converted to the major isomer by sodium methoxide in methanol. The diasteresomers are designated **20c**(shift) and **20c**(normal) in the Experimental Section.

The vinyl sulfoxide **18g** was also subjected to radical cyclization conditions. A 28% yield of two stereoisomeric cyclization products **20d** was obtained. The cyclization product was interrelated with the sulfone **20b** by oxidation with *m*-chloroperoxybenzoic acid. The resulting product was the amine oxide of **20c**, as demonstrated by subsequent deoxygenation with phosphorus trichloride,[22] which gave the major stereoisomer of **20c**.

Neither the *N*-allyl nor *N*-propargyl derivatives **18j** or **18n** gave any cyclization product under the usual radical cyclization conditions. Only reductive dehalogenation was observed. The failure of these two reactants to cyclize indicates that an electron-accepting group on the unsaturated substituent is necessary for the radical addition reaction to occur.

Various methods were attempted, without success, to convert **11a** to the homoiboga analogue 20-deethyl-5,6-homocatharanthine **24f**. Our experience with this attempted transformation parallels that of Kuehne and coworkers.[23] This roadblock required us to investigate an alternate precursor of this analogue. The Diels–Alder adduct **3a** was dihydroxylated (OsO_4, *N*-methylmorpholine *N*-oxide), deprotected, alkylated with 3-bromo-2-(phenylsulfonyl)propene,[15] and iodinated to give the sulfone **23e**. Unexpectedly, this compound proved to be a poor reactant in the radical cyclization. However, the corresponding acetonide, **23j**, behaved normally. It was prepared by protection of the diol **23a**, using dimethoxypropane. Successive deprotection of the isoquinuclidine and indole nitrogens afforded **23h**. Alkylation with 3-bromo-2-(phenylsulfonyl)propene[15] and iodination gave the isopropylidene-protected reagent **23j**, which cyclized to **24a** in 63% yield as a 1:1 mixture of stereoisomers. After reductive desulfonylation and hydrolysis of the cyclized acetonide **24a**, we obtained **24c** as an alternative potential

(17) Reviews of radical cyclization reactions: Giese, B. *Radicals in Organic Synthesis; Formation of Carbon–Carbon Bonds*; Pergamon Press: New York, 1986. Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541. Curran, D. P. *Synthesis* **1988**, *417*, 489.

(18) Examples of cyclizations of aromatic radicals: Beckwith, A. L. J.; Gara, W. B. *J. Chem. Soc., Perkin Trans. 2* **1975**, 593, 795. Beckwith, A. L. J.; Meijs, G. *J. Chem. Soc., Chem. Commun.* **1981**, 136. Ueno, Y.; Chino, K.; Okawara, M. *Tetrahedron Lett.* **1982**, *25*, 2575. Parker, K. A.; Spero, D. M.; Inman, K. C. *Tetrahedron Lett.* **1988**, *27*, 2833. Parker, K. A.; Spero, D. M.; Van Epp, J. *J. Org. Chem.* **1988**, *53*, 4628. Meijs, G. F.; Bunnett, J. F.; Beckwith, A. L. J. *J. Am. Chem. Soc.* **1986**, *108*, 4899. Shankaran, K.; Sloan, C. P.; Snieckus, V. *Tetrahedron Lett.* **1985**, *26*, 6001. Jones, K.; Thompson, M.; Wright, C. *J. Chem. Soc., Chem. Commun.* **1986**, 115. Macleod, J. K.; Monahan, L. C. *Tetrahedron Lett.* **1988**, *29*, 391. Wright, C.; Schulkind, M.; Jones, K.; Thompson, M. *Tetrahedron Lett.* **1987**, *28*, 6389. Urabe, H.; Kuwajma, I. *Tetrahedron Lett.* **1986**, *27*, 1355. Dittami, J. P.; Ramanthan, H. *Tetrahedron Lett.* **1988**, *29*, 45. Bowman, W. R.; Heaney, H.; Jordan, B. M. *Tetrahedron Lett.* **1988**, *29*, 6657.

(19) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 753. Tedder, J. M. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 401.

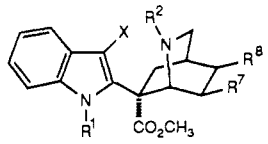
(20) Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, 3477.

(21) Gassman, P. G.; Burns, S. J. *J. Org. Chem.* **1988**, *53*, 5574.

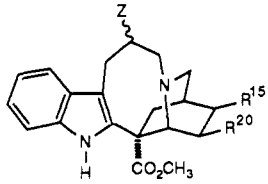
(22) Rowley, A. G. In *Organophosphorus Reagents in Organic Synthesis*; Cadogan, J. I. G., Ed.; Academic Press: New York, 1979; Chapter 7.

(23) Kuehne, M. E.; Bornmann, W. G.; Earley, W. G.; Marko, I. *J. Org. Chem.* **1986**, *51*, 2913.

Scheme IX



	R^1	X	R^2	R^7	R^8
23a	SO_2Ph	H	CO_2CH_2Ph	OH	OH
23b	SO_2Ph	H	H	OH	OH
23c	H	H	H	OH	OH
23d	H	H	$CH_2C(SO_2Ph)CH_2$	OH	OH
23e	H	I	$CH_2C(SO_2Ph)CH_2$	OH	OH
23f	SO_2Ph	H	CO_2CH_2Ph	$-OC(CH_3)_2O-$	
23g	SO_2Ph	H	H	$-OC(CH_3)_2O-$	
23h	H	H	H	$-OC(CH_3)_2O-$	
23i	H	H	$CH_2C(SO_2Ph)CH_2$	$-OC(CH_3)_2O-$	
23j	H	I	$CH_2C(SO_2Ph)CH_2$	$-OC(CH_3)_2O-$	



	Z	R^{15}	R^{20}
24a	SO_2Ph	$-OC(CH_3)_2O-$	
24b	H	$-OC(CH_3)_2O-$	
24c	H	OH	OH
24d	H	-OC(S)O-	
24e	H	$-OSO_2CH_3$	$-OSO_2CH_3$
24f	H	15,20-dehydro	

precursor of the target **24f** (Scheme IX).

Initial efforts at effecting the conversion of **24c** to **24f** were directed toward desulfurization of the thionocarbonate **24d**.[24] However, this reaction failed with either trimethyl phosphite or the more reactive reagent, 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine.[25] Successful deoxygenation was achieved by conversion of **24c** to the dimesylate **24e** which was smoothly converted to **24f** by sodium naphthalenide.[26] This sequence of reactions provides **24f** from **3a** in 10 steps with an overall 5% yield.

Summary. Electrophilic, palladium-catalyzed, and radical cyclization reactions have been demonstrated to be capable of forming the eight-membered ring required for conversion of 6-indol-2-yl-2-azabicyclo[2.2.2]octane-6-carboxylate esters to structures which are 5,6-homologues of the iboga alkaloids. The electrophilic cyclizations proceeded in modest yield and were quite sensitive to reaction conditions. Intramolecular Heck reactions can proceed in good yield but appear to be restricted to derivatives with substituents on the indole nitrogen. Intramolecular addition of the 3-indolyl radical, generated by deiodination with tri-*n*-butyltin hydride, to allylic substituents having electron-accepting groups appears to be a quite general reaction. The resulting cyclizations have provided intermediates which can be converted to 20-deethyl-5,6-homocatharanthine and to C15 oxygenated derivatives. To the best of our knowledge, these reactions represent the first synthetic application of intramolecular addition reactions of 3-indolyl radicals.

Experimental Section

General Methods. The following solvents were distilled from appropriate drying agents: acetonitrile (P_2O_5), dichloromethane (P_2O_5), benzene (CaH_2), toluene (CaH_2), dimethylformamide (CaH_2), methanol (magnesium methoxide), tetrahydrofuran (sodium/benzophenone). Amines used as reagents were distilled from calcium hydride. Tributylstannane was prepared by the method of Hayashi.[27] Most reactions were processed by a conventional extractive workup by treating the reaction mixture with water, extracting several times with CH_2Cl_2, and washing with brine and with dilute aqueous acid or base, if appropriate. Purification was normally done by flash chromatography using 230–400-mesh silica gel. Unless noted otherwise, elution was done with ethyl acetate–hexane mixtures. All new compounds reported were >95% pure to TLC and NMR except as noted for **19a***. NMR spectra were recorded on a GE QE-300 or a Nicolet 360 instrument at 300 and 360 MHz, respectively. Mass spectra were recorded on a Finnigan 4600 operated in electron impact [EIMS] or chemical ionization [CIMS] mode.

General Procedure for Desulfonylation of *N*-(Phenylsulfonyl)indole Derivatives. The reactant was dissolved in methanol (~0.01 M), and a large excess of Na_2HPO_4 (5–10× by weight) and 5% Na–Hg amalgam (10–15× weight) was added. The solution was stirred at room temperature for 6–8 h. The reaction mixture was then poured into water, extracted with methylene chloride, and dried. The product was isolated by flash chromatography.

General Procedure for Iodination of Indoles by *N*-Chlorosuccinimide–Sodium Iodide in Acetone. A solution of *N*-iodosuccinimide was prepared by dropwise addition of *N*-chlorosuccinimide to a solution of sodium iodide (1.2 equiv, ~0.1 M) in acetone.[12] This solution was stirred at room temperature for 15 min. The indole in acetone (~0.1 M) was then added dropwise. The reaction solution was then stirred for 15 min prior to pouring into aqueous sodium thiosulfate solution. The product was isolated by an extractive workup followed by flash chromatography.

General Procedure for N-Methylation of Indoles. The indole derivative (0.1 mmol) was dissolved in a small amount of DMF or THF (1 mL) and added to 60% NaH (1.8 equiv) suspended in DMF or THF (1.5 mL) at 0 °C. After 15 min, the mixture was warmed to room temperature, and methyl iodide (10 equiv) was added. The mixture was stirred at room temperature for 8 h, and then the solvent was evaporated in vacuo. Standard workup and flash chromatography was used for product isolation.

Methyl 2-(Benzyloxycarbonyl)-8,8-dimethoxy-6-*exo*-[1-(phenylsulfonyl)indol-2-yl]-2-azabicyclo[2.2.2]octane-6-*endo*-carboxylate (6a). The Diels–Alder adduct **3b**[5c] (200 mg, 0.34 mmol) was dissolved in trimethyl orthoformate (2.5 mL), and *p*-toluenesulfonic acid (84 mg, 0.44 mmol, 1.3 equiv) was added. After stirring for 8 h, the solution was concentrated to an oil and dissolved in CH_2Cl_2. The CH_2Cl_2 was washed with 20% aqueous Na_2CO_3, and the product was purified by flash chromatography. The ketal **6a** was obtained as a white foam (192 mg 0.31 mmol, 91%) ($CDCl_3$, δ ppm, 300 MHz) (rotamers) 7.7–7.6 (m, 1 H), 7.5 (d, 2 H), 7.4 (t, 2 H), 7.25–7.2 (m, 2 H), 7.15–7.05 (m, 2 H), 7.0 (s, 1 H), 5.26 (d, 1 H), 5.06 (d, 1 H), 4.9 (dd, 1 H), 3.65 (s, 3 H), 3.65–3.59 (m, 1 H), 3.4 (d, 1 H), 3.25 (s, 3 H), 3.18 (s, 3 H), 2.8 (dd, 1 H), 2.4–2.25 (m, 2 H), 2.12–1.98 (m, 2 H); EIMS *m/z* (rel intensity) 619 (M^+, 1), 586 (6), 401 (4), 341 (7), 245 (80), 91 (100).

Methyl 2-(Benzyloxycarbonyl)-8,8-dimethoxy-6-*exo*-indol-2-yl-2-azabicyclo[2.2.2]octane-6-*endo*-carboxylate (7a). The ketal **6a** (192 mg, 0.31 mmol) was dissolved in MeOH (20 mL) and desulfonylated following the standard procedure. Flash chromatography provided ketal carbamate **7a** (127 mg, 0.26 mmol, 86%) as a white foam: ^1H NMR ($CDCl_3$ δ ppm, 300 MHz) (rotamers) 9.1 (br s, 1 H), 7.53 (d, 1 H) 7.34 (d, 1 H), 7.2–7.04 (m, 8 H), 6.48 (s, 1 H), 5.11 (t, 1 H), 5.09 (d, 1 H), 4.97 (d, 1 H), 3.65 (s, 3 H), 3.55 (d, 1 H), 3.2 (s, 3 H), 3.19 (s, 3 H), 3.21 (dd, 1 H), 3.14 (dd, 1 H), 2.35 (t, 1 H), 2.2 (dt, 1 H), 2.08 (dd, 1 H), 1.98 (dd, 1 H).

Methyl 8,8-Dimethoxy-2-(3,3-dimethoxypropyl)-6-*exo*-[1-(phenylsulfonyl)indol-2-yl]-2-azabicyclo[2.2.2]octane-6-*endo*-carboxylate (6g). Dimethoxyamine **6d**[5c] (198 mg, 0.41 mmol) was dissolved in CH_3CN (8 mL) followed by addition of Na_2CO_3 (173 mg, 1.63 mmol, 4 equiv) and 1,1-dimethoxy-3-iodopropane[7] (469 mg, 2.04 mmol, 5 equiv). After 4 h at 60 °C,

(24) Block, E. *Org. React.* **1984**, *30*, 457.
(25) Corey, E. J.; Hopkins, P. B. *Tetrahedron Lett.* **1982**, *23*, 1979.
(26) Carnahan, J. C., Jr.; Closson, W. D. *Tetrahedron Lett.* **1972**, 3447.
(27) Hayashi, K.; Iyoda, J.; Shihara, I. *J. Organomet. Chem.* **1967**, *10*, 81.

the CH_3CN was removed and the product was isolated by extraction. Flash chromatography provided **6g** (194 mg, 0.33 mmol, 81%) as a white foam: ^1H NMR ($CDCl_3$, δ ppm, 300 MHz) 7.7 (dd, 1 H), 7.55 (d, 2 H), 7.48 (m, 1 H), 7.4 (t, 1 H), 7.3 (t, 2 H), 7.1 (m, 2 H), 7.04 (s, 1 H), 4.31 (dd, 1 H), 3.58 (s, 3 H), 3.5 (br s, 1 H), 3.26 (s, 3 H), 3.25 (s, 3 H), 3.17 (s, 3 H), 3.15 (s, 3 H), 3.14 (d, 1 H), 2.75–2.65 (m, 2 H), 2.6 (m, 3 H), 2.2 (d, 1 H), 2.1 (d, 2 H), 2.05 (m, 1 H), 1.7–1.55 (m, 2 H).

Methyl 8,8-Dimethoxy-2-(3,3-dimethoxypropyl)-6-*exo*-indol-2-yl-2-azabicyclo[2.2.2]octane-6-*endo*-carboxylate (7g). The acetal **6g** (174 mg, 0.30 mmol) was desulfonylated by the standard procedure to give **7g** (121 mg, 0.26 mmol, 89%) as a white foam: ^1H NMR ($CDCl_3$, δ ppm, 300 MHz) 10.58 (br s, 1 H), 7.5 (d, 1 H, J = 7.5 Hz), 7.38 (d, 1 H, J = 7.5 Hz), 7.1 (t, 1 H, J = 7.5 Hz), 7.05 (t, 1 H, J = 7.5 Hz), 6.14 (d, 1 H, J = 1.5 Hz), 4.5 (t, 1 H, J = 6.0 Hz), 3.8 (s, 3 H), 3.4 (t, 1 H, J = 3.0 Hz), 3.35 (s, 3 H), 3.28 (s, 3 H), 3.16 (s, 3 H), 3.10 (dd, 1 H, J = 9.3, 3.3 Hz), 2.95 (dq, 1 H, J = 13.5, 2.7 Hz), 2.7 (t, 2 H, J = 6.3 Hz), 2.6 (dt, 1 H, J = 9.3, 1.5 Hz), 2.15 (br s, 1 H), 2.12 (dd, 1 H, J = 15.0, 3.0 Hz), 1.92 (dd, 1 H, J = 5.7, 3.0 Hz), 1.88–1.8 (m, 3 H); IR (KBr) 3236, 2948, 1739, 1246, 1058 cm^{-1}; CIMS (CH_4) m/z (rel intensity) 447 (M^+ + 1, 100), 415 (60), 357 (15). Anal. Calcd for $C_{24}H_{34}N_2O_6$: C, 64.55; H, 7.67; N, 6.27. Found: C, 64.45; H, 7.71; N, 6.31.

20-Deethyl-5a,6-didehydro-5,6-homo-15-oxocoronaridine (8a). The acetal **7g** (39 mg, 0.09 mmol) was dissolved in CH_2Cl_2 (0.2 mL) and added dropwise to $BF_3{\cdot}OEt_2$ (1.5 mL) containing TFA (0.027 mL, 0.35 mmol, 4 equiv) at 40 °C. After the addition was complete, 20% aqueous Na_2CO_3 solution (10 mL) was added, and the product was isolated by extraction. Flash chromatography afforded the cyclized product **8a** (15.1 mg, 0.045 mmol, 51%) as a white solid along with byproducts **9**[5c] (4.0 mg, 0.013 mmol, 23%) and **10** (1.6 mg, 5%).

8a: mp 245–248 °C; ^1H NMR ($CDCl_3$, δ ppm, 300 MHz) 7.88 (br s, 1 H), 7.55 (dd, 1 H, J = 7.5 Hz), 7.29 (d, 1 H, J = 7.5 Hz), 7.23 (t, 1 H, J = 7.5 Hz), 7.22 (d, 1 H, J = 12.0 Hz), 7.15 (t, 1 H, J = 7.5 Hz), 6.02 (m, 1 H), 4.54 (br t, 1 H), 3.64 (br d, 2 H, J = 10.8 Hz), 3.56 (s, 3 H), 3.54 (dt, 1 H, J = 13.5, 3.0 Hz), 3.32 (t, 1 H, J = 9.0 Hz), 2.8 (dd, 1 H, J = 10.8, 3.0 Hz), 2.6 (br d, 1 H, J = 18.9 Hz), 2.48 (br s, 1 H), 2.3 (dd, 1 H, J = 13.5, 2.4 Hz), 2.21 (dd, 1 H, J = 18.9, 3.3 Hz); IR (KBr) 3362, 3024, 2955, 2887, 1732, 1710, 1442, 1238 cm^{-1}; EIMS m/z (rel intensity) 336 (M^+, 80), 335 (55), 208 (20), 180 (100). Anal. Calcd for $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33. Found: C, 71.39; H, 6.02; N, 8.27.

10: ^1H NMR ($CDCl_3$, δ ppm 300 MHz) 10.72 (br s, 1 H), 7.53 (d, 1 H, J = 7.5 Hz), 7.38 (d, 1 H, J = 7.5 Hz), 7.38 (d, 1 H, J = 7.5 Hz), 7.16 (t, 1 H, J = 7.5 Hz), 7.06 (t, 1 H, J = 7.5 Hz), 6.26 (s, 1 H), 4.31 (s, 1 H), 3.92 (m, 1 H), 3.77 (s, 3 H), 3.44–3.33 (m, 2 H), 3.36 (s, 3 H), 3.12 (dt, 1 H, J = 14.7, 3.0 Hz), 3.01 (dt, 1 H, J = 13.5, 3.0 Hz), 2.79 (dd, 1 H, J = 14.7, 5.1 Hz), 2.56 (br d, 1 H), 2.25 (dd, 1 H, J = 14.7, 3.2 Hz), 1.77 (m, 1 H), 1.54 (d, 1 H, J = 14.7 Hz); EIMS m/z (rel intensity) 368 (M^+, 100).

Methyl 8,8-Dimethoxy-2-[3,3-bis(phenylthio)propyl]-6-*exo*-indol-2-yl-2-azabicyclo[2.2.2]octane-6-*endo*-carboxylate (7h). A mixture containg dimethoxyamine **7b** (30 mg, 0.087 mmol), $(PhS)_2CHCH_2OSO_2Ph$[9] (220 mg, 0.53 mmol, 6 equiv), Na_2CO_3 (30 mg, 0.28 mmol, 3 equiv), and NaI (77 mg, 0.53 mmol, 6 equiv) in CH_3CN (4 mL) was stirred at room temperature for 18 h. The CH_3CN was evaporated, and the product was isolated by extraction. Flash chromatography provided thioacetal **7h** (36 mg, 0.06 mmol, 70%) as a white solid: ^1H NMR ($CDCl_3$, δ ppm, 300 MHz) 9.94 (br s, 1 H), 7.51 (d, 1 H, J = 7.5 Hz), 7.39–7.28 (m, 5 H), 7.27–7.23 (m, 5 H), 7.18 (d, 1 H, J = 7.5 Hz), 7.1 (t, 1 H, J = 7.5 Hz), 7.05 (t, 1 H, J = 7.5 Hz), 6.2 (s, 1 H), 4.38 (t, 1 H, J = 6.3 Hz), 3.76 (s, 3 H), 3.42 (t, 1 H, J = 3.3 Hz), 3.18 (s, 3 H), 3.14 (s, 3 H), 2.98–2.84 (m, 3 H), 2.78 (m, 1 H), 2.52 (br d, 1 H, J = 10.5 Hz), 2.12 (br s, 1 H), 2.08 (dd, 1 H, J = 14.7, 3.0 Hz), 2.0–1.84 (m, 4 H); EIMS m/z (rel intensity) 602 (M^+, 50), 571 (20), 382 (100), 368 (40), 123 (90), 101 (100).

Silver Ion Promoted Cyclization of Thioacetal (7h). Thioacetal **7h** (25 mg, 0.041 mmol) was dissolved in CH_2Cl_2 (2 mL) followed by addition of trifluoroacetic acid (0.013 mL, 0.16 mmol, 4 equiv) and silver trifluoroacetate (36 mg, 0.164 mmol, 4 equiv). After 5 h at 40 °C and 8 h at room temperature, the mixture was treated with 20% aqueous Na_2CO_3 solution and the product was isolated by extraction. Flash chromatography gave compound **8a** (4.3 mg, 0.013 mmol, 31%) and the corresponding ketal **8b** (3.5 mg, 0.01 mmol, 22%). The NMR (300 MHz) of **8a** prepared in this manner was in exact agreement with that of the material produced by way of cyclization of **7g**.

8b: ^1H NMR ($CDCl_3$ δ ppm, 300 MHz) 8.16 (br s, 1 H), 7.51 (d, 1 H, J = 7.5 Hz), 7.26 (d, 1 H, J = 7.5 Hz), 7.18 (t, 1 H, J = 7.5 Hz), 7.13–7.08 (m, 2 H), 5.93 (m, 1 H), 4.22 (t, 1 H, J = 3.3 Hz), 3.58 (s, 3 H), 3.58–3.48 (m, 2 H), 3.29 (dt, 1 H, J = 13.5, 3.3 Hz), 3.22 (s, 3 H), 3.18 (s, 3 H), 3.22–3.14 (m, 1 H), 2.5 (dd, 1 H, J = 10.5, 3.6 Hz), 2.12 (br s, 1 H), 2.0–1.91 (m, 3 H); EIMS m/z (rel intensity) 382 (M^+, 100) 381 (75), 356 (30), 336 (45), 102 (90), 180 (100).

20-Deethyl-15-oxo-5,6-homocoronaridine (11a). In a Parr bottle, the oxohomoene **8a** (10 mg, 0.031 mmol) and Wilkinson's catalyst (4 mg, 0.004 mmol, 0.14 equiv) was dissolved in a benzene–methanol mixture (2.5 mL, 80% in benzene, v/v). After 19 h under a 50 psi hydrogen atmosphere, the solution was concentrated to a reddish oil. Flash chromatography provided **11a** (6.4 mg, 0.019 mmol, 61%) as a white foam: ^1H NMR ($CDCl_3$, δ ppm, 300 MHz) 7.95 (br s, 1 H), 7.55 (d, 1 H, J = 7.5 Hz), 7.25 (d, 1 H, J = 7.5 Hz), 7.18 (t, 1 H), 7.12 (t, 1 H), 4.66 (br s, 1 H), 3.63 (s, 3 H), 3.3–3.23 (m, 2 H), 3.16 (dt, 1 H, J = 13.5, 3.0 Hz), 3.15–2.93 (m, 2 H), 2.88–2.8 (m, 1 H), 2.79 (dd, 1 H, J = 9.6, 2.4 Hz), 2.68 (dd, 1 H, J = 18.6, 4.5 Hz), 2.58 (br s, 1 H), 2.48 (dd, 1 H, J = 13.5, 9.3 Hz), 2.29 (dd, 1 H, J = 18.6, 1.0 Hz), 2.0–1.78 (m, 2 H); ^{13}C NMR ($CDCl_3$) 213.0, 174.1, 135.4, 134.0, 128.7, 122.3, 119.3, 118.2, 112.4, 110.5, 55.5, 53.9, 53.0, 52.3, 51.2, 45.3, 44.8, 33.7, 26.8, 21.5; EIMS m/z (rel intensity) 338 (M^+, 100), 310 (30), 214 (40), 135 (100).

Methyl 8,8-Dimethoxy-6-*exo*-indol-2-yl-2-(1-oxoprop-2-enyl)-2-azabicyclo[2.2.2]octane-6-*endo*-carboxylate (15a). Dimethoxyamine **7b** (30.5 mg, 0.088 mmol) was dissolved in CH_2Cl_2 (2 mL), and pyridine (0.011 mL, 0.13 mmol, 1.5 equiv) and acryloyl chloride (0.007 mL, 0.089 mmol, 1.1 equiv) were added at 0 °C. After 5 min, more acryloyl chloride (0.007 mL, 0.087 mmol, 1.1 equiv) was added at 0 °C. After the mixture was warmed to room temperature, the product was isolated by extraction. Flash chromatography provided amide **15a** (27 mg, 0.067 mmol, 75%) as a white foam: ^1H NMR ($CDCl_3$, δ ppm, 360 MHz) 9.5 (br s, 1 H), 7.5 (d, 1 H), 7.36 (d, 1 H), 7.12 (t, 1 H), 7.03 (t, 1 H), 6.44 (s, 1 H), 6.35 (dd, 1 H), 6.32 (dd, 1 H), 5.65 (dd, 1 H), 5.58 (t, 1 H), 3.75 (dt, 1 H), 3.65 (s, 3 H), 3.32 (dt, 1 H), 3.25 (dd, 1 H), 3.22 (s, 1 H), 3.18 (s, 3 H), 2.41 (t, 1 H), 2.18 (dd, 1 H), 2.10 (dd, 1 H), 1.97 (dd, 1 H); EIMS m/z (rel intensity) 398 (M^+, 32), 201 (100), 165 (45).

Methyl 8,8-Dimethoxy-2-(1-oxoprop-2-enyl)-6-*exo*-(3-iodoindol-2-yl)-2-azabicyclo[2.2.2]octane-6-*endo*-carboxylate (15b). The acrylamide **15a** was iodinated according to the standard procedure. Flash chromatography provided the 3-iodo derivative **15b** (58 mg, 0.11 mmol, 91%) as a white foam: ^1H NMR ($CDCl_3$, δ ppm, 360 MHz) 10.6 (br s, 1 H), 7.38 (t, 1 H), 6.5 (dd, 1 H, J = 16.5, 3.0 Hz), 6.4 (dd, 1 H, J = 16.5, 9.6 Hz), 5.75 (dd, 1 H, J = 9.6, 3.0 Hz), 5.58 (t, 1 H), 3.82 (dt, 1 H), 3.67 (dt, 1 H), 3.64 (s, 3 H), 3.25 (dd, 1 H), 3.25 (s, 3 H), 3.21 (s, 3 H), 2.48 (br s, 1 H), 2.2 (dd, 1 H), 2.07 (dd, 1 H), 1.94 (dd, 1 H); EIMS m/z (rel intensity) 524 (M^+, 28), 327 (50), 165 (100).

Methyl 8,8-Dimethoxy-2-(1-oxoprop-2-enyl)-6-*exo*-(3-iodo-1-methylindol-2-yl)-2-azabicyclo[2.2.2]octane-6-carboxylate (15c). The 3-iodoacrylamide **15b** (57 mg, 0.10 mmol) was methylated in THF according to the standard procedure. Flash chromatography provided **15c** (29 mg, 0.054 mmol, 54%) as a white foam: ^1H NMR ($CDCl_3$, δ ppm, 360 MHz) 7.5 (dd, 1 H), 7.24 (dd, 1 H), 7.15 (m, 2 H), 6.16 (dd, 1 H, J = 16.8, 10.5 Hz), 5.96 (dd, 1 H, J = 10.5, 3.0 Hz), 5.73 (br s, 1 H), 5.47 (dd, 1 H, J = 10.5, 3.0 Hz), 3.94 (s, 3 H), 3.92 (dd, 1 H), 3.67 (dd, 1 H), 3.65 (s, 3 H), 3.64 (dd, 1 H), 3.24 (s, 3 H), 3.2 (dd, 1 H), 3.18 (s, 3 H), 2.6 (m, 1 H), 2.47 (br s, 1 H), 2.15 (dd, 1 H); EIMS m/z (rel intensity) 538 (M^+, 3), 411 (100), 341 (50).

20-Deethyl-5a,6-didehydro-1-methyl-5-oxo-5,6-homocatharanthine (16). The 3-iodoacrylamide **15c** (25 mg, 0.046 mmol) was dissolved in CH_3CN (0.5 mL) and placed in a sealed tube along with Et_3N (0.013 mL, 0.09 mmol, 2 equiv) and $Pd(OAc)_2$ (2.0 mg, 0.009 mmol, 0.2 equiv). This mixture was heated at 100 °C for 13 h. After cooling, the mixture was concentrated and the product was isolated by extraction. Flash chromatography provided recovered **15c** (3.4 mg, 0.006 mmol, 12%), the 7-membered lactam **17** (8.4 mg, 0.02 mmol, 44%), and the desired lactam

16 (4.3 mg, 0.01 mmol, 23%). 16: ^{1}H NMR ($CDCl_3$, δ ppm, 360 MHz) 7.58 (d, 1 H, J = 7.5 Hz), 7.25 (m, 2 H), 7.16 (m, 2 H), 6.08 (d, 1 H, J = 12.3 Hz), 5.21 (t, 1 H, J = 3.0 Hz), 3.76 (s, 3 H), 3.61 (s, 3 H), 3.5 (dt, 1 H, J = 13.5, 3.0 Hz), 3.4 (dd, 1 H, J = 12.3, 3.3 Hz), 3.24 (s, 3 H), 3.25–3.15 (m, 1 H), 3.19 (s, 3 H), 2.46 (br s, 1 H), 2.06 (dd, 1 H, J = 15.0, 3.9 Hz), 1.94 (dd, 1 H, J = 13.5, 3.0 Hz), 1.85 (dd, 1 H, J = 15.0, 3.0 Hz); EIMS m/z (rel intensity) 410 (M^+, 85), 379 (31), 268 (100), 208 (50).

17: ^{1}H NMR ($CDCl_3$, δ ppm, 360 MHz) 7.81 (d, 1 H, J = 7.5 Hz), 7.25 (m, 1 H), 7.16 (m, 2 H), 5.91 (s, 1 H), 5.78 (s, 1 H), 4.75 (t, 1 H, J = 3.3 Hz), 3.66 (s, 3 H), 3.7–3.63 (m, 1 H), 3.62 (s, 3 H), 3.48 (dd, 1 H, J = 11.4, 3.6 Hz), 3.35 (dq, 1 H, J = 13.8, 3.0 Hz), 3.21 (s, 3 H), 3.22 (s, 3 H), 2.46 (br s, 1 H), 2.2 (dd, 1 H, J = 15.0, 3.3 Hz), 1.94 (dd, 1 H, J = 15.0, 3.6 Hz), 1.75 (dd, 1 H, J = 13.8, 3.0 Hz); EIMS m/z (rel intensity) 410 (M^+, 100), 379 (15), 204 (15), 110 (50), 101 (60).

Methyl 2-[2-(Ethoxycarbonyl)prop-2-enyl]-8,8-dimethoxy-6-*exo*-indol-2-yl-2-azabicyclo[2.2.2]octane-6-*endo*-carboxylate (18a). The dimethoxyamine **7b** (100 mg, 0.29 mmol) was dissolved in CH_3CN (6 mL) prior to the addition of Na_2CO_3 (92 mg, 0.87 mmol, 3 equiv) and $CH_2{=}C(CH_2Br)CO_2Et$[14] (280 mg, 1.45 mmol, 5 equiv). After the mixture had stirred at room temperature for 4 h, the solution was concentrated to an oil and taken up in CH_2Cl_2. This solution was washed with brine, dried, and concentrated. Flash chromatography provided the unsaturated ester **18a** (100 mg, 0.22 mmol, 76%) as a white foam: ^{1}H NMR ($CDCl_3$, δ ppm, 300 MHz) 11.0 (br s, 1 H), 7.58 (d, 1 H, J = 7.5 Hz), 7.47 (d, 1 H, J = 7.5 Hz), 7.12 (t, 1 H, J = 7.5 Hz), 7.02 (t, 1 H, J = 7.5 Hz), 6.28 (s, 1 H), 5.81 (s, 1 H), 4.38–4.22 (m, 2 H), 3.8 (s, 3 H), 3.65 (d, 1 H, J = 12.3 Hz), 3.52 (t, 1 H, J = 3.0 Hz), 3.32 (d, 1 H, J = 12.3 Hz), 3.21 (s, 3 H), 3.15 (s, 3 H), 2.96 (dq, 1 H, J = 15.0, 1.5 Hz), 2.92 (dd, 1 H, J = 10.5, 3.9 Hz), 2.56 (dt, 1 H, J = 10.5, 1.5 Hz), 2.14 (dd, 1 H, J = 15.0, 3.3 Hz), 2.1 (br s, 1 H), 1.93 (dd, 1 H, J = 15.0, 2.7 Hz), 1.83 (dd, 1 H, J = 14.7, 2.4 Hz), 1.13 (t, 3 H, J = 8.7 Hz); IR (KBr) 3292, 2947, 1740, 1706, 1117 cm^{-1}; CIMS (CH_4) m/z (rel intensity) 457 (M^+ + 1, 100), 425 (40), 131 (100).

Methyl 2-[2-(Ethoxycarbonyl)prop-2-enyl]-8,8-dimethoxy-6-*exo*-(3-iodoindol-2-yl)-2-azabicyclo[2.2.2]octane-6-*endo*-carboxylate (18b). The unsaturated ester **18a** was iodinated according to the standard procedure. Flash chromatography provided the 3-iodo derivative **18b** (50 mg, 0.087 mmol, 80%) as a white foam: ^{1}H NMR ($CDCl_3$, δ ppm, 300 MHz) 11.5 (br s, 1H), 7.63 (d, 1 H, J = 7.5 Hz), 7.38 (d, 1 H, J = 7.5 Hz), 7.18 (t, 1 H, J = 7.5 Hz), 6.27 (s, 1 H), 5.81 (s, 1 H), 4.41–4.23 (m, 2 H), 3.79 (br s, 1 H), 7.76 (d, 1 H, J = 12.2 Hz), 3.67 (s, 3 H), 3.43 (dt, 1 H, J = 14.4, 3.0 Hz), 3.37 (d, 1 H, J = 12.2 Hz), 3.24 (s, 3 H), 2.67 (dt, 1 H, J = 10.5, 2.4 Hz), 2.63 (dd, 1 H, J = 10.5, 2.7 Hz), 2.25 (dd, 1 H, J = 15.3, 4.5 Hz), 2.12 (br t, 1 H), 1.83 (dd, 1 H, J = 13.5, 3.3 Hz), 1.58 (dd, 1 H, J = 14.4, 1.8 Hz), 1.32 (t, 1 H, J = 7.5 Hz); IR (KBr) 3282, 2945, 1743, 1703, 1119 cm^{-1}; CIMS (CH_4) m/z (rel intensity) 583 (M^+ + 1, 80), 551 (30), 457 (100).

Methyl 2-[2-(Ethoxycarbonyl)prop-2-enyl]-8,8-dimethoxy-6-*exo*-(3-iodo-1-methylindol-2-yl)-2-azabicyclo[2.2.2]octane-6-*endo*-carboxylate (18c). The 3-iodoindole **18b** (53 mg, 0.091 mmol) was methylated in DMF according to the standard procedure. Flash chromatography provided *N*-methyl-3-iodoindole **18c** (40 mg, 0.067 mmol, 74%) as a white foam: ^{1}H NMR ($CDCl_3$, δ ppm, 300 MHz) 7.52 (d, 1 H, J = 7.5 Hz), 7.25 (d, 1 H, J = 7.5 Hz), 7.19 (d, 1 H, J = 7.5 Hz), 7.17 (t, 1 H, J = 7.5 Hz), 6.13 (br s, 1 H), 5.54 (br s, 1 H), 4.2–4.05 (m, 4 H), 3.88 (s, 3 H), 3.65 (s, 3 H), 3.45 (d, 1 H, J = 16.5 Hz), 3.32–3.15 (m, 2 H), 3.22 (s, 3 H), 3.18 (s, 3 H), 2.85 (m, 1 H), 2.4 (d, 1 H, J = 10.5 Hz), 2.25 (dd, 1 H, J = 14.4, 3.3 Hz), 2.16 (br s, 1 H), 1.3–1.2 (m, 4 H); CIMS (i-Bu) m/z (rel intensity) 597 (M^+ + 1, 60), 583 (100), 455 (100).

Methyl 8,8-Dimthoxy-6-*exo*-indol-2-yl-2-[2-(phenylsulfonyl)-2-propenyl]-2-azabicyclo[2.2.2]octane-6-*endo*-carboxylate (18d). The dimethoxyamine **7b** (26 mg, 0.73 mmol) was dissolved in CH_3CN (8 mL) followed by the addition of Na_2CO_3 (232 mg, 2.19 mmol, 3 equiv) and $CH_2{=}C(CH_2Br)SO_2Ph$[15] (762 mg, 2.92 mmol, 4 equiv). The mixture was kept at room temperature for 4 h. After isolation of the product by extraction, flash chromatography provided vinyl sulfone **18d** (309 mg, 0.59 mmol, 81%) as a white foam: mp 179–180 °C; ^{1}H NMR ($CDCl_3$, δ ppm, 300 MHz) 10.38 (br s, 1 H), 7.76 (d, 1 H, J = 7.5 Hz), 7.61–7.5 (m, 3 H), 7.43 (t, 2 H, J = 7.5 Hz), 7.13 (t, 1 H, J = 7.5 Hz), 6.33 (s, 1 H), 6.18 (s, 1 H), 5.81 (s, 1 H), 3.78 (s, 3 H), 3.38 (t, 1 H, J = 3.0 Hz), 3.36 (d, 1 H, J = 14.7 Hz), 3.27 (d, 1 H, J = 14.7 Hz), 3.16 (s, 3 H), 3.14 (s, 3 H), 3.0–2.88 (m, 2 H), 2.52 (br d, 1 H, J = 10.5 Hz), 2.14 (br s, 1 H), 2.02 (dd, 1 H, J = 14.4, 3.0 Hz), 1.97 (dd, 1 H, J = 13.5 Hz), 1.86 (dd, 1 H, J = 14.5, 3.0 Hz); IR (KBr) 3287, 3098, 2963, 1744, 1446, 1305, 1137 cm^{-1}; CIMS (CH_4) m/z (rel intensity) 525 (M^+ + 1, 100), 493 (40). Anal. Calcd for $C_{28}H_{32}N_2O_6S$: C, 64.13; H, 6.11; N, 5.34; S, 6.11. Found: C, 64.20; H, 6.18; N, 5.31; S, 6.05.

Methyl 8,8-Dimethoxy-6-*exo*-(3-iodoindol-2-yl)-2-[2-(phenylsulfonyl)prop-2-enyl]-2-azabicyclo[2.2.2]octane-6-*endo*-carboxylate (18e). The vinyl sulfone **18d** (48 mg, 0.091 mmol) in acetone (2 mL) was iodinated by the standard procedure. Flash chromatography provided the 3-iodo derivative **18e** (50 mg, 0.077 mmol, 85%) as a white foam: mp 170–171 °C; ^{1}H NMR ($CDCl_3$, δ ppm, 300 MHz) 11.43 (br s, 1 H), 7.82 (d, 2 H, J = 7.5 Hz), 7.62 (t, 2 H, J = 9.0 Hz), 7.5–7.38 (m, 3 H), 7.18 (t, 1 H, J = 7.5 Hz), 7.14 (t, 1 H, J = 7.5 Hz), 6.35 (s, 1 H), 5.96 (s, 1 H), 3.75 (m, 1 H), 3.68 (s, 3 H), 3.65 (d, 1 H, J = 13.8 Hz), 3.55 (d, 1 H, J = 13.8 Hz), 3.38 (br d, 1 H, J = 13.6 Hz), 3.2 (s, 3 H), 3.13 (s, 3 H), 2.6 (s, 2 H), 2.16 (dd, 1 H, J = 15.0, 3.3 Hz), 2.11 (t, 1 H, J = 3.3 Hz), 1.84 (dd, 1 H, J = 14.7, 3.3 Hz), 1.59 (dd, 1 H, J = 15.0, 0.9 Hz); IR (KBr) 3321, 3110, 2947, 1748, 1305, 1110 cm^{-1}; CIMS (i-Bu) m/z (rel intensity) 651 (M^+ + 1), 525 (100), 323 (70), 277 (100). Anal. Calcd for $C_{28}H_{31}IN_2O_6S$: C, 51.69; H, 4.80; N, 4.31. Found: C, 51.70; H, 4.85; N, 4.28.

Intramolecular Heck Reaction of 18b. The 3-iodoindole **18b** (20 mg, 0.034 mmol) was dissolved in DMF (1 mL) followed by the addition of Bu_4NCl (15.4 mg, 0.068 mmol, 2 equiv), KOAc (16.6 mg, 0.17 mmol, 5 equiv), and $Pd(OAc)_2$ (0.6 mg, 0.0027 mmol, 0.08 equiv). This mixture was heated at 40 °C for 1.75 h and then at 80 °C for 15 min. Once cooled, the solution was concentrated, and flash chromatography of the residue provided the cyclized vinylogous carbamate **19a** (2.8 mg, 0.006 mmol, 18%) and an impure sample of the double bond regioisomer **19a*** (1.8 mg, 0.004 mmol, 12%).

Major isomer **19a**: ^{1}H NMR ($CDCl_3$, δ ppm, 300 MHz) 7.96 (br s, 1 H), 7.75 (d, 1 H, J = 7.5 Hz), 7.28 (s, 1 H), 7.25 (d, 1 H, J = 7.5 Hz), 7.12 (quintet, 2 H, J = 7.5 Hz), 5.32 (t, 1 H, J = 3.0 Hz), 4.46 (d, 1 H, J = 16.5 Hz), 4.25–4.05 (m, 2 H), 3.76 (d, 1 H, J = 10.5 Hz), 3.68 (s, 3 H), 3.67 (d, 1 H, J = 16.5 Hz), 3.25 (s, 3 H), 3.18 (s, 3 H), 3.18–3.12 (m, 1 H), 3.04 (dd, 1 H, J = 10.5, 3.9 Hz), 2.38–2.29 (m, 2 H), 2.08 (dd, 1 H, J = 14.4, 3.3 Hz), 1.94 (dd, 1 H, J = 14.4, 3.0 Hz); CIMS (CH_4) m/z (rel intensity) 455 (M^+ + 1, 100).

Minor isomer **19a***: ^{1}H NMR ($CDCl_3$, δ ppm, 300 MHz) 7.99 (br s, 1 H), 7.55 (t, 1 H, J = 4.5 Hz), 7.35 (dd, 1 H, J = 4.5, 2.7 Hz), 7.14 (m, 3 H), 4.34 (t, 1 H, J = 2.7 Hz), 4.2–4.08 (m, 1 H), 3.84 (s, 3 H), 3.78–3.66 (m, 1 H), 3.49 (d, 1 H, J = 12.9 Hz), 3.25 (s, 3 H), 3.20 (s, 3 H), 3.18–3.14 (m, 2 H), 2.74 (dd, 1 H, J = 14.5, 3.6 Hz), 2.46–2.36 (m, 3 H), 2.14 (br s, 1 H), 1.93 (dd, 1 H, J = 13.5, 4.5 Hz); CIMS (CH_4) m/z (rel intensity) 455 (M^+ + 1, 10), 343 (100), 311 (60).

Intramolecular Heck Reaction of 18c. The *N*-methyl-3-iodoindole **18c** (120 mg, 0.202 mmol) was dissolved in DMF (3 mL) followed by the addition of Bu_4NCl (92 mg, 0.404 mmol, 2 equiv), KOAc (98 mg, 1.1 mmol, 5 equiv), and $Pd(OAc)_2$ (2.5 mg, 0.012 mmol, 0.06 equiv). This mixture was heated at 80 °C for 6 h. The reaction mixture was concentrated, and flash chromatography of the residue provided the cyclized vinylogous carbamate **19b** (84 mg, 0.179 mmol, 89%) as a white solid: mp 184–185 °C; ^{1}H NMR ($CDCl_3$, δ ppm, 300 MHz) 7.8 (d, 1 H, J = 8.7 Hz), 7.2 (d, 2 H, J = 3.3 Hz), 7.15–7.08 (m, 2 H), 5.48 (t, 1 H, J = 3.6 Hz), 4.54 (d, 1 H, J = 17.4 Hz), 4.28–4.06 (m, 2 H), 3.75 (s, 3 H), 3.73 (m, 2 H), 3.4 (dt, 1 H, J = 13.5, 3.0 Hz), 3.24 (s, 3 H), 3.18 (s, 3 H), 3.3 (dd, 1 H, J = 10.5, 3.3 Hz), 2.37 (br s, 1 H), 2.12 (dd, 1 H, J = 15.3, 3.3 Hz), 1.96 (dd, 1 H, J = 15.3, 3.3 Hz), 1.93 (dd, 1 H, J = 13.5, 3.3 Hz), 1.28 (t, 1 H, J = 7.5 Hz); IR (KBr) 2944, 1737, 1677, 1595, 1229, 1086 cm^{-1}; CIMS (CH_4) m/z (rel intensity) 469 (M^+ + 1, 100), 443 (40), 440 (40). Anal. Calcd for $C_{26}H_{32}N_2O_6$: C, 66.65; H, 6.88; N, 5.98. Found: C, 66.70; H, 6.89; N, 5.94.

Catalytic Reduction of 19b to 20bα. In a Parr bottle, the vinylogous carbamate **19b** (13.5 mg, 0.03 mmol) and Wilkinson's catalyst (5 mg, 0.004 mmol, 0.2 equiv) was dissolved in a benzene–methanol mixture (2.5 mL, 80% in benzene v/v). After 24

h under a 50 psi hydrogen atmosphere, the solution was concentrated to a reddish oil. Flash chromatography provided the diastereomer **20bα** (3.3 mg, 0.007 mmol, 25%) along with recovered **19b** (5.1 mg, 0.001, 39%).

Diastereomers of 5a-(Ethoxycarbonyl)-20-deethyl-15,15-dimethoxy-5,6-homocoronaridine (20aα and 20aβ). The 3-iodoindole **18b** (25 mg, 0.043 mmol) was dissolved in benzene (10 mL) along with AIBN (catalytic) and heated to reflux. Over 20 min Bu_3SnH (0.014 mL, 0.051 mmol, 1.3 equiv) in benzene (2 mL) was added dropwise into the refluxing solution. After the addition was complete, the solution was stirred an additional 20 min. After cooling, the solution was concentrated to a solid. Flash chromatography provided the two diastereomeric cyclized esters **20aα** (6.3 mg, 0.014 mmol, 32%) and **20aβ** (4.0 mg, 0.007 mmol, 16%) along with some of the dehalogenation product **18a** (4 mg, 0.008 mmol, 18%).

Major diastereomer 20aβ: mp 175–176 °C; ^1H NMR ($CDCl_3$, δ ppm, 300 MHz) 8.08 (br s, 1 H), 7.53 (d, 1 H, J = 7.5 Hz), 7.28 (d, 1 H, J = 7.5 Hz), 7.15 (t, 1 H, J = 7.5 Hz), 7.09 (t, 1 H, J = 7.5 Hz), 4.25–4.15 (m, 3 H), 3.65 (s, 3 H), 3.41 (dd, 1 H, J = 15.0, 3.0 Hz), 3.28–3.15 (m, 2 H), 3.22 (s, 3 H), 3.15 (s, 3 H), 3.10–3.00 (m, 3 H), 2.80–2.66 (m, 1 H), 2.63 (dd, 1 H, J = 8.7, 3.3 Hz), 2.19 (br s, 1 H), 2.06 (dd, 1 H, J = 13.5, 3.3 Hz), 1.91 (dt, 2 H, J = 13.5, 3.0 Hz); IR (KBr) 3378, 2950, 1714, 1120 cm^{-1}; EIMS m/z (rel intensity) 456 (M^+, 50), 425 (40), 101 (100). Anal. Calcd for $C_{25}H_{32}N_2O_6$: C, 65.77; H, 7.07; N, 6.14. Found: C, 65.64; H, 7.11; N, 6.07.

Minor diastereomer 20aα: mp 180–181 °C; ^1H NMR ($CDCl_3$, δ ppm, 300 MHz) 8.07 (br s, 1 H), 7.62 (d, 1 H, J = 7.5 Hz), 7.24 (d, 1 H, J = 7.5 Hz), 7.08 (quintet, 2 H, J = 7.5 Hz), 4.15 (br s, 1 H), 4.05–3.94 (m, 1 H), 3.88–3.79 (m, 1 H), 3.64 (s, 3 H), 3.62 (dd, 1 H, J = 15.0, 4.5 Hz), 3.35 (dd, 1 H, J = 15.0, 6.0 Hz), 3.25–3.20 (m, 1 H), 3.21 (s, 3 H), 3.16 (s, 3 H), 3.11 (dd, 1 H, J = 9.3, 2.7 Hz), 3.05 (dt, 1 H, J = 15.3, 2.7 Hz), 3.0–2.85 (m, 2 H), 2.67 (dd, 1 H, J = 10.5, 4.5 Hz), 2.18 (br s, 1 H), 2.08 (d, 1 H, J = 13.5 Hz), 2.04 (dd, 1 H, J = 13.5, 3.0 Hz), 1.95 (dd, 1 H, J = 13.5, 2.7 Hz); IR (KBr) 3379, 2985, 2933, 1736, 1712, 1183 cm^{-1}; EIMS m/z (rel intensity) 456 (M^+, 60), 425 (50), 101 (100). Anal. Calcd for $C_{25}H_{32}N_2O_6$: C, 65.77; H, 7.07. Found: C, 65.61; H, 7.14.

Diastereomers of 5a-(Ethoxycarbonyl)-20-deethyl-15,15-dimethoxy-1-methyl-15,16-homocoronaridine (20bα and 20bβ). The 3-iodoindole **18c** (26 mg, 0.043 mmol) was dissolved in benzene (20 mL) along with AIBN (0.8 mg, 0.0043 mmol, 0.1 equiv) and heated to reflux. Over 20 min Bu_3SnH (0.075 mL, 0.27 mmol, 1.5 equiv) in benzene (2 mL) was added dropwise into the refluxing solution. After the addition was complete, the solution was refluxed an additional 20 min. Flash chromatography provided the two cyclized ester epimers **20bβ** (4.8 mg, 0.01 mmol, 23%) and **20bα** (3.7 mg, 0.008 mmol, 19%) along with some of the dehalogenated starting material (2.9 mg, 0.006 mmol, 14%).

Major diastereomer 20bβ: ^1H NMR ($CDCl_3$, δ ppm, 300 MHz) 7.55 (d, 1 H, J = 7.5 Hz), 7.22 (m, 2 H), 7.12 (t, 1 H, J = 7.5 Hz), 4.34 (t, 1 H, J = 3.0 Hz), 4.21 (q, 2 H, J = 7.5 Hz), 3.69 (s, 3 H), 3.61 (s, 3 H), 3.45 (dd, 1 H, J = 15.3, 3.6 Hz), 3.35–3.25 (m, 2 H), 3.21–3.15 (m, 1 H), 3.19 (s, 3 H), 3.09 (dt, 1 H, J = 8.4, 2.7 Hz), 2.22 (br t, 1 H, J = 2.7 Hz), 2.03 (dd, 1 H, J = 14.4, 2.7 Hz), 1.30 (t, 3 H, J = 7.5 Hz); CIMS (CH_4) m/z (rel intensity) 471 (M^+ + 1, 100), 439 (50).

Minor diastereomer 20bα: ^1H NMR ($CDCl_3$, δ ppm, 300 MHz) 7.65 (d, 1 H, J = 7.5 Hz), 7.18 (m, 2 H, J = 7.5 Hz), 7.08 (t, 1 H, J = 7.5 Hz), 4.4 (br s, 1 H), 4.08–4.01 (m, 1 H), 3.99–3.90 (m, 1 H), 3.75–3.70 (m, 1 H), 3.71 (s, 3 H), 3.59 (s, 3 H), 3.6–3.45 (m, 2 H), 3.4–3.28 (m, 2 H), 3.23 (s, 3 H), 3.14 (m, 1 H), 2.81 (dd, 1 H, J = 11.1, 8.4 Hz), 2.5 (dd, 1 H, J = 9.0, 3.0 Hz), 2.22 (m, 1 H), 2.06 (dd, 1 H, J = 14.4, 3.6 Hz), 1.96 (dd, 1 H, J = 13.5, 3.3 Hz), 1.7 (dd, 1 H, J = 14.4, 2.7 Hz), 1.17 (t, 3 H, J = 7.5 Hz); CIMS (CH_4) m/z (rel intensity) 471 (M^+ + 1, 100), 439 (40).

Diastereomers of 20-Deethyl-15,15-dimethoxy-5a-(phenylsulfonyl)-5,6-homocoronaridine [20c(shift) and 20c(normal)]. The vinyl sulfone **18e** (284 mg, 0.437 mmol) was dissolved in benzene (170 mL) along with AIBN (7.1 mg, 0.044 mmol, 0.1 equiv) and heated to reflux. Over 2.5 h, Bu_3SnH (159 mg, 0.55 mmol, 1.3 equiv) in benzene (25 mL) was added dropwise (via syringe pump) into the refluxing solution. After the addition was complete, the solution was refluxed an additional 20 min. The cooled solution was concentrated to a crude solid. Recrystallization (benzene–hexane) of this crude solid and flash chromatography of the mother liquor afforded the major cyclized sulfone diastereomer **20c**(shift) (147 mg, 0.279 mmol, 64%) and the minor epimer **20c**(normal) (6.8 mg, 0.013 mmol, 3%) along with some of the dehalogenation product **18d** (11.4 mg, 0.022 mmol, 5%).

Major diastereomer 20c(shift): mp 274–275 °C; ^1H NMR ($CDCl_3$, δ ppm, 300 MHz) 8.8 (br s, 1H), 7.8 (d, 2 H, J = 7.5 Hz), 7.75 (t, 1 H, J = 7.5 Hz), 7.64 (t, 2 H, J = 7.5 Hz), 7.22 (d, 1 H, J = 7.5 Hz), 7.8 (t, 1 H, J = 7.5 Hz), 6.88 (t, 1 H, J = 7.5 Hz), 6.64 (d, 1 H, J = 7.5 Hz), 4.06 (t, 1 H, J = 3.0 Hz), 3.64 (s, 3 H), 3.56–3.32 (m, 2 H), 3.36 (dd, 1 H, J = 15.0, 4.5 Hz), 3.25–3.1 (m, 2 H), 3.2 (s, 3 H), 3.14 (s, 3 H), 3.04–2.94 (m, 2 H), 2.64 (dd, 1 H, J = 8.7, 3.3 Hz), 2.18 (br s, 1 H), 2.1 (dd, 1 H, J = 15.0, 3.3 Hz), 1.9 (dd, 1 H, J = 15.0, 3.0 Hz), 1.82 (dd, 1 H, J = 13.5, 3.3 Hz); IR (KBr) 3411, 2950, 1713, 1306, 1145 cm^{-1}; CIMS (CH_4) m/z (rel intensity) 525 (M^+ + 1, 100), 493 (25), 383 (30). Anal. Calcd for $C_{28}H_{32}N_2O_6S$: C, 64.13; H, 6.11; N, 5.34. Found: C, 63.95; H, 6.15; N, 5.29.

Minor diastereomer 20c(normal): mp 275–276 °C; ^1H NMR ($CDCl_3$, δ ppm, 300 MHz) 8.06 (br s, 1 H), 7.86 (d, 2 H), 7.68–7.48 (m, 5 H), 7.15 (t, 1 H), 7.12 (t, 1 H), 4.0 (t, 1 H), 3.87–3.7 (m, 2 H), 3.64 (s, 3 H), 3.55–3.48 (m, 1 H), 3.25–3.04 (m, 3 H), 2.88 (q, 1 H), 2.33 (dd, 1 H, J = 9.1, 3.0 Hz), 2.14 (br s, 1 H), 1.98–1.9 (br d, 3 H); IR (KBr) 3348, 2950, 1715, 1307, 1254, 1084 cm^{-1}; CIMS (CH_4) m/z (rel intensity) 525 (M^+ + 1, 100), 493 (25), 384 (40), 143 (80). Anal. Calcd for $C_{28}H_{32}N_2O_6S$: C, 64.13; H, 6.11; N, 5.34. Found: C, 63.91; H, 6.19; N, 5.30.

20-Deethyl-15,15-dimethoxy-5,6-homocoronaridine (21). The cyclized sulfone **20c** (72 mg, 0.14 mmol) was dissolved in DMF (0.8 mL) and added to ammonia (75 mL) at −33 °C. Over 5.5 h, 5% Na–Hg amalgam (600 mg) was added in three portions (200 mg each). After the addition was complete, the reaction was quenched with solid NH_4Cl. The residue which remained after evaporation of the ammonia was partitioned between basic brine and CH_2Cl_2. The CH_2Cl_2 was dried and concentrated to a crude foam. Flash chromatography provided the product **21** (40 mg, 0.10 mmol, 76%) as a white solid: mp 184–185 °C; ^1H NMR ($CDCl_3$, δ ppm, 300 MHz) 8.07 (br s, 1 H), (t, 1 H, J = 7.5 Hz), 7.28 (t, 1 H, J = 7.5 Hz), 7.15 (t, 1 H, J = 7.5 Hz), 7.08 (t, 1 H, J = 7.5 Hz), 4.47 (t, 1 H, J = 7.5 Hz), 3.63 (s, 3 H), 3.2–3.1 (m, 3 H), 3.15 (s, 3 H), 2.95 (ddd, 1 H, J = 12.9, 6.6, 2.7 Hz), 2.63 (ddd, 1 H, J = 13.3, 11.7, 3.0 Hz), 2.39 (dd, 1 H, J = 10.5, 3.0 Hz), 2.2 (br s, 1 H), 2.16 (dd, 1 H, J = 13.5, 3.3 Hz), 2.2–2.05 (m, 1 H), 2.03 (dd, 1 H, J = 12.9, 3.0 Hz), 1.98 (dd, 1 H, J = 13.5, 3.0 Hz), 1.9–1.75 (m, 1 H); IR (KBr) 3383, 2950, 2932, 1712, 1238, 1119, 1048 cm^{-1}; ^{13}C NMR ($CDCl_3$) 174.1, 135.2, 128.7, 121.8, 119.1, 118.0, 111.6, 110.4, 100.6, 53.2, 52.5, 51.9, 51.0, 50.9, 48.2, 37.9, 33.8, 32.7, 26.9, 21.4; CIMS (CH_4) m/z (rel intensity) 385 (M^+ + 1, 53), 384 (60), 353 (100). Anal. Calcd for $C_{22}H_{38}N_2O_4$: C, 68.73; H, 7.34. Found: C, 68.58; H, 7.40.

Hydrolysis of 21 to 11a. The ketal **21** (30.7 mg, 0.08 mmol) was dissolved in reagent grade THF (1 mL) prior to the addition of concentrated HCl (1 mL). After 5 min at room temperature, 20% aqueous Na_2CO_3 was added to the reaction mixture until basic. The resulting solution was extracted with CH_2Cl_2, dried, and concentrated. Flash chromatography provided the previously characterized ketone **11a** (19.2 mg, 0.06 mmol, 67%).

20-Deethyl-15,15-dimethoxy-5,6-homocoronaridine (21) by Reduction of 8b. The cyclized ketal **8b** (27 mg, 0.07 mmol) was dissolved in MeOH (10 mL) followed by the addition of Raney nickel (approximately 0.1 mL as a slurry in MeOH after H_2O and MeOH wash). After 15 h under a H_2 atmosphere, the mixture was filtered through Celite and concentrated. Flash chromatography gave **21** (10 mg, 0.026 mmol, 37%) as a white foam: mp 184–185 °C. The spectral properties of this material were identical with those of **21** prepared as above.

20-Deethyl-15-methoxy-5,6-homocatharanthine (22). The ketal **21** (13 mg, 0.03 mmol) was dissolved in CH_2Cl_2 (1 mL) followed by the addition of $(i\text{-}Pr)_2NEt$ (0.02 mL, 0.13 mmol, 4 equiv). In one portion, trimethylsilyl triflate (0.02 mL, 0.12 mmol, 3.5 equiv) was quickly added. The solution was stirred for 1 min before being poured into 20% aqueous Na_2CO_3 solution, extracted with CH_2Cl_2, dried, and concentrated. Flash chromatography provided enol ether **22** (6.0 mg, 0.017 mmol, 50%) and recovered **21** (5.0 mg, 0.013 mmol, 40%). **22**: ^1H NMR ($CDCl_3$, δ ppm, 300

MHz) 7.9 (br s, 1 H), 7.54 (d, 1 H, J = 7.5 Hz), 7.26 (d, 1 H, J = 7.5 Hz), 7.14 (t, 1 H, J = 7.5 Hz), 7.06 (t, 1 H, J = 7.5 Hz), 5.15 (dd, 1 H, J = 7.2, 2.7 Hz), 5.03 (d, 1 H, J = 7.2 Hz), 3.55 (s, 3 H), 3.53 (s, 3 H), 3.55–3.47 (m, 1 H), 3.25 (dt, 1 H, J = 8.7, 3.0 Hz), 3.07 (dd, 2 H, J = 10.5, 3.0 Hz), 2.92 (qd, 1 H, J = 6.3, 2.7 Hz), 2.65–2.55 (m, 2 H), 2.37 (dd, 1 H, J = 8.7, 3.0 Hz), 2.21–2.09 (m, 1 H), 1.99 (dd, 1 H, J = 13.5, 1.8 Hz), 1.95–1.84 (m, 1 H); IR (KBr) 3388, 3057, 2951, 2853, 1730, 1645, 1232 cm^{-1}; CIMS (CH_4) m/z (rel intensity) 355 (60), 353 (M^+ + 1, 100), 352 (30), 83 (50).

Methyl 2-(Benzyloxycarbonyl)-7,8-*exo*,*exo*-dihydroxy-6-*exo*-[1-(phenylsulfonyl)indol-2-yl]-2-azabicyclo[2.2.2]octane-6-*endo*-carboxylate (23a). The Diels–Alder adduct **3a** (50 mg, 0.089 mmol) was dissolved in reagent grade THF (10 mL) followed by the addition of H_2O (0.03 mL), 4-methylmorpholine N-oxide (12.4 mg, 0.011 mmol, 1.2 equiv), and 0.05 M OsO_4 solution (0.02 mL, 0.01 equiv). The reaction mixture was stirred for 12 h before being poured into a mixture of 10% HCl (6 mL) and 15% aqueous $NaHSO_3$ (6 mL). This solution was extracted with CH_2Cl_2, dried, and concentrated to give diol **23a** (45 mg, 0.077 mmol, 86%) as a white foam: ^1H NMR ($CDCl_3$, δ ppm, 300 MHz) 7.5 (d, 2 H, J = 7.5 Hz), 7.45–7.25 (m, 5 H), 7.24 (s, 4 H), 7.18 (s, 1 H), 7.15–7.05 (m, 2 H), 5.28 (d, 1 H, J = 12.9 Hz), 5.12 (d, 1 H, J = 12.9 Hz), 4.86 (d, 1 H, J = 3.3 Hz), 4.36 (dd, 1 H, J = 8.4, 2.1 Hz), 4.15 (dd, 1 H, J = 8.4, 3.3 Hz), 3.64 (s, 3 H), 3.24 (dt, 1 H, J = 14.42, 2.4 Hz), 2.94 (dd, 1 H, J = 10.8, 1.5 Hz), 2.85 (br d, 1 H, J = 5.4 Hz), 2.19 (dd, 1 H, J = 14.4, 3.3 Hz), 2.14 (dd, 1 H, J = 10.8, 3.0 Hz); CIMS (CH_4) m/z (rel intensity) 591 (M^+ + 1, 100), 450 (30), 102 (80), 91 (100).

Isopropylidene Derivative of Methyl 2-(Benzyloxycarbonyl)-7,8-*exo*,*exo*-dihydroxy-6-*exo*-[1-(phenylsulfonyl)indol-2-yl]-2-azabicyclo[2.2.2]octane-6-*endo*-carboxylate (23f). The carbamate diol **23a** (50 mg, 0.08 mmol) was dissolved in a mixture of CH_2Cl_2 (1 mL) and 2,2-dimethoxypropane (1 mL), and a catalytic amount of p-toluenesulfonic acid was added. The reaction mixture was stirred for 0.5 h before being concentrated. Flash chromatography provided acetonide **23f** (46 mg, 0.07 mmol, 87%) as a white foam: ^1H NMR ($CDCl_3$, δ ppm, 300 MHz) (rotamers) 7.62–7.52 (m, 2 H), 7.48 (t, 2 H), 7.41 (d, 2 H, J = 7.5 Hz), 7.32–7.24 (m, 5 H), 7.18 (6.89) (s, 1 H), 7.15–7.02 (m, 3 H), 5.25 (5.26) (d, 1 H, J = 13.5 Hz), 5.15 (d, 1 H, J = 13.5 Hz), 5.02 (4.89) (d, 1 H, J = 3.0 Hz), 4.49 (dd, 1 H, J = 7.5, 1.5 Hz), 4.28 (dd, 1 H, J = 7.5, 3.0 Hz), 3.71 (3.8) (d, 1 H, J = 10.8 Hz), 3.17 (d, 1 H, J = 12.6 Hz), 2.82 (2.71) (d, 1 H, J = 10.8 Hz), 2.33–2.2 (m, 2 H), 1.33–1.42 (s, 3 H), 1.27 (1.35) (s, 3 H); CIMS (CH_4) m/z (rel intensity) 631 (M^+ + 1, 40), 490 (30), 220 (100).

Isopropylidene Derivative of Methyl 7,8-*exo*,*exo*-Dihydroxy-6-*exo*-[1-(phenylsulfonyl)indol-2-yl]-2-azabicyclo[2.2.2]octane-6-*endo*-carboxylate (23g). The protected diol **23f** (604 mg, 0.96 mmol) was dissolved in MeOH (15 mL) followed by the addition of Pd/C (600 mg), cyclohexadiene (0.90 mL, 9.6 mmol, 10 equiv), and TFA (0.30 mL, 3.8 mmol, 4 equiv). The mixture was stirred for 12 h before it was filtered through Celite and concentrated. Extractive workup gave amine **23g** (409 mg, 0.824 mmol, 85%) as a white foam: ^1H NMR ($CDCl_3$, δ ppm, 300 MHz) 7.65 (d, 1 H, J = 7.5 Hz), 7.56 (d, 2 H, J = 7.5 Hz), 7.5 (d, 1 H, J = 7.5 Hz), 7.44 (d, 1 H, J = 7.5 Hz), (t, 2 H, J = 8.4 Hz), 7.2 (s, 1 H), 7.15 (m, 2 H), 4.5 (dd, 1 H, J = 8.4, 3.0 Hz), 4.24 (dd, 1 H, J = 8.4, 3.0 Hz), 3.62 (s, 3 H), 3.58 (d, 1 H, J = 3.0 Hz), 3.14 (dd, 1 H, J = 10.5, 3.0 Hz), 3.07 (dt, 1 H, J = 14.4, 3.0 Hz), 2.35 (d, 1 H, J = 10.5 Hz), 2.21 (dd, 1 H, J = 14.4, 3.3 Hz), 2.0 (br s, 1 H), 1.6 (s, 3 H), 1.4 (s, 3 H); CIMS (CH_4) m/z (rel intensity) 497 (M^+ + 1, 100), 355 (25).

Isopropylidene Derivative of Methyl 7,8-*exo*,*exo*-Dihydroxy-6-*exo*-indol-2-yl-2-azabicyclo[2.2.2]octane-6-*endo*-carboxylate (23h). The acetonide **23g** (497 mg, 1.00 mmol) was desulfonylated by the standard procedure to afford **23h** (280 mg, 0.79 mmol, 79%) as a white foam: ^1H NMR ($CDCl_3$, δ ppm, 300 MHz) 11.25 (br s, 1 H), 7.53 (d, 1 H, J = 7.5 Hz), 7.36 (d, 1 H, J = 7.5 Hz), 7.14 (t, 1 H, J = 7.5 Hz), 7.06 (t, 1 H, J = 7.5 Hz), 6.15 (s, 1 H), 4.23 (dd, 1 H, J = 11.4, 4.3 Hz), 3.96 (dd, 1 H, J = 11.4, 2.7 Hz), 3.76 (s, 3 H), 3.7 (d, 1 H, J = 2.7 Hz), 3.26 (dt, 1 H, J = 10.5, 1.5 Hz), 2.86 (dt, 1 H, J = 14.7, 2.4 Hz), 2.71 (d, 1 H, J = 10.5 Hz), 2.05 (br s, 1 H), 1.98 (dd, 1 H, J = 14.7, 3.6 Hz), 1.6 (s, 3 H), 1.4 (s, 1 H); CIMS (CH_4) m/z (rel intensity) 357 (M^+ + 1, 100), 356 (40).

Isopropylidene Derivative of Methyl 7,8-*exo*,*exo*-Dihydroxy-6-*exo*-indol-2-yl-2-[2-(phenylsulfonyl)prop-2-enyl]-2-azabicyclo[2.2.2]octane-6-*endo*-carboxylate (23i). The acetonide **23h** (515 mg, 1.45 mmol) was dissolved in CH_2CL_2 (8 mL) followed by the addition of Na_2CO_3 (107 mg, 10.1 mmol, 7 equiv) and $CH_2{=}C(CH_2Br)SO_2Ph$[15] (681 mg, 2.61 mmol, 1.8 equiv). After 30 min at room temperature a standard workup and flash chromatography gave **23i** (662 mg, 1.23 mmol, 85%) as a white foam: mp 181–183 °C; ^1H NMR ($CDCl_3$, δ ppm, 300 MHz) 10.5 (br s, 1 H), 7.75 (d, 1 H, J = 9.0 Hz), 7.56 (m, 1 H), 7.52 (d, 1 H, J = 9.0 Hz), 7.44 (t, 1 H, J = 9.0 Hz), 7.15 (t, 1 H, J = 8.4 Hz), 7.06 (t, 1 H, J = 8.4 Hz), 6.28 (s, 1 H), 6.18 (s, 1 H), 5.73 (s, 1 H), 4.18 (dd, 1 H, J = 8.4, 0.9 Hz), 4.12 (dd, 1 H, J = 8.4, 0.9 Hz), 3.84 (d, 1 H, J = 15.0 Hz), 3.78 (s, 3 H), 3.67 (d, 1 H, J = 2.7 Hz), 3.61 (d, 1 H, J = 15.0 Hz), 2.8 (d, 3 H, J = 12.3 Hz), 2.09 (br s, 1 H), 2.07 (dd, 1 H, J = 18.0, 2.7 Hz), 1.52 (s, 3 H), 1.3 (s, 3 H); IR (KBr) 3387, 2987, 2901, 1736, 1303 cm^{-1}; CIMS (CH_4) m/z (rel intensity) 537 (M^+ + 1, 100), 491 (10). Anal. Calcd for $C_{29}H_{32}N_2O_6S$: C, 64.94; H, 5.97; N, 5.22. Found: C, 64.85; H, 6.03; N, 5.19.

Isopropylidene Derivative of Methyl 7,8-*exo*,*exo*-Dihydroxy-6-*exo*-(3-iodoindol-2-yl)-2-[2-(phenylsulfonyl)-prop-2-enyl]-2-azabicyclo[2.2.2]octane-6-*endo*-carboxylate (23j). The vinyl sulfone **23i** (660 mg, 1.23 mmol) was iodinated following the standard procedure. Flash chromatography provided the 3-iodo derivative **23j** (655 mg, 0.98 mmol, 81%) as a white foam: ^1H NMR ($CDCL_3$, δ ppm, 300 MHz) 10.54 (br s, 1 H), 7.69 (d, 2 H, J = 9.0 Hz), 7.64 (d, 1 H, J = 7.5 Hz), 7.56 (t, 1 H, J = 9.0 Hz), 7.4 (br t, 1 H), 7.17 (quintet, 1 H, J = 7.5 Hz), 6.4 (s, 1 H), 5.96 (s, 1 H), 4.35 (dd, 1 H, J = 11.4, 2.1 Hz), 4.15 (d, 1 H, J = 15.5 Hz), 4.04 (dd, 1 H, J = 11.4, 3.0 Hz), 4.02 (d, 1 H, J = 15.0 Hz), 3.86 (d, 1 H, J = 3.0 Hz), 3.7 (s, 3 H), 3.18 (dt, 1 H, J = 14.7, 2.4 Hz), 2.76 (d, 1 H, J = 10.5 Hz), 2.43 (dd, 1 H, J = 10.5, 3.0 Hz), 2.05 (br s, 1 H), 1.75 (dd, 1 H, J = 14.7, 3.0 Hz), 1.54 (s, 3 H), 1.32 (s, 3 H); IR (KBr) 3427, 2905, 1724, 1304 cm^{-1}; CIMS (CH_4) m/z (rel intensity) 663 (M^+ + 1, 20), 537 (50), 355 (50), 309 (100). Anal. Calcd for $C_{29}H_{31}IN_2O_6S$: C, 52.57; H, 4.72; N, 4.23. Found: C, 52.63; H, 4.74; N, 4.19.

Diastereomers of 20-Deethyl-15,20-*exo*,*exo*-dihydroxy-5a-(phenylsulfonyl)-5,6-homocoronaridine [24a(shift) and 24a(normal)]. The vinyl sulfone **23j** (120 mg, 0.18 mmol) was dissolved in benzene (100 mL) along with AIBN (2.9 mg, 0.018 mmol, 0.1 equiv) and heated to a refluex. Over 2 h Bu_3SnH (0.075 mL, 0.27 mmol, 1.5 equiv) in benzene (20 mL) was added via syringe pump into the refluxing solution. After the addition was complete, the solution was refluxed an additional 20 min. The solution was concentrated to a solid. Flash chromatography provided the two cyclized sulfone diastereomers **24a**(shift) (29 mg, 0.054 mmol, 30%) and **24a**(normal) (32 mg, 0.061 mmol, 33%) along with some of the dehalogenation product **23i** (5 mg, 0.009 mmol, 5%). **24a**(shift): mp 254–255 °C; ^1H NMR ($CDCl_3$, δ ppm, 300 MHz) 8.0 (d, 2 H, J = 7.5 Hz), 7.88 (br s, 1 H), 7.77 (q, 1 H, J = 7.5 Hz), 7.66 (t, 2 H, J = 7.5 Hz), 7.2 (d, 1 H, J = 8.4 Hz), 7.09 (t, 1 H, J = 7.5 Hz), 6.84 (t, 1 H, J = 7.5 Hz), 6.37 (d, 1 H, J = 7.5 Hz), 4.16 (dd, 1 H, J = 7.5, 4.5 Hz), 4.15 (d, 1 H, J = 2.5 Hz), 3.96 (dd, 1 H, J = 7.5, 2.4 Hz), 3.7 (m, 2 H), 3.62 (s, 3 H), 3.44 (dd, 1 H, J = 15.0 Hz), 3.25–3.05 (m, 3 H), 2.62 (dt, 1 H, J = 13.5, 2.1 Hz), 2.58 (d, 1 H, J = 9.0 Hz), 2.2 (br s, 1 H), 2.1 (dd, 1 H, J = 13.5, 4.5 Hz), 1.53 (s, 3 H), 1.26 (s, 3 H); IR (KBr) 3340, 2890, 1720, 1130 cm^{-1}; CIMS (CH_4) m/z (rel intensity) 537 (M^+ + 1, 100), 394 (15). Anal. Calcd for $C_{29}H_{32}N_2O_6S$: C, 64.94; H, 5.97. Found: C, 64.75; H, 6.02.

24a(normal): ^1H NMR ($CDCl_3$, δ ppm, 300 MHz) 7.88 (d, 2 H, J = 8.4 Hz), 7.84 (br s, 1 H), 7.63 (t, 1 H, J = 8.4 Hz), 7.55 (t, 2 H, J = 7.5 Hz), 7.42 (d, 1 H, J = 7.5 Hz), 7.24 (d, 1 H, J = 7.5 Hz), 7.14 (t, 1 H, J = 7.5 Hz), 7.07 (t, 1 H, J = 7.5 Hz), 4.15 (dd, 1 H, J = 8.4, 3.0 Hz), 4.03 (dd, 1 H, J = 8.4, 3.0 Hz), 3.87 (d, 1 H, J = 3.0 Hz), 3.66 (s, 3 H), 3.61 (m, 1 H), 3.54–3.4 (m, 3 H), 3.3 (dt, 1 H, J = 8.4, 1.5 Hz), 3.04 (dd, 1 H, J = 13.5, 9.0 Hz), 2.76 (dt, 1 H, J = 14.4, 1.5 Hz), 2.52 (dd, 1 H, J = 8.4, 2.0 Hz), 2.1 (br s, 1 H), 2.02 (dd, 1 H, J = 14.4, 3.3 Hz), 1.49 (s, 3 H), 1.33 (s, 3 H); IR (KBr) 3316, 2951, 1742, 1208, 1142 cm^{-1}; CIMS (CH_4) m/z (rel intensity) 537 (M^+ + 1, 100), 395 (20), 258 (20).

Isopropylidene Derivative of 20-Deethyl-15,20-*exo*,*exo*-dihydroxy-5,6-homocoronaridine (24b). A mixture of sulfone diastereomers **24a**(shift) and **24a**(normal) (68 mg, 0.12 mmol) was

dissolved in DMF (0.2 mL) before being added to ammonia (75 mL) at −33 °C. Over 7 h, 5% Na–Hg amalgam (1 g) was added in five portions (200 mg each). After the reaction was complete, the solution was treated with solid NH_4Cl. The residue resulting from the evaporation of the ammonia was worked up by extraction. Flash chromatography provided acetonide **24b** (32 mg, 0.082 mmol, 65%) as a white foam: ^1H NMR ($CDCl_3$, δ ppm, 300 MHz) 7.84 (br s, 1 H), 7.54 (d, 1 H, J = 8.4 Hz), 7.6 (d, 1 H, J = 7.5 Hz), 7.15 (t, 1 H, J = 7.5 Hz), 7.08 (t, 1 H, J = 8.4 Hz), 4.18 (m, 2 H), 3.99 (dd, 1 H, J = 8.1, 2.1 Hz), 3.62 (s, 3 H), 3.25–3.09 (m, 3 H), 3.01 (dt, 1 H, J = 14.7, 3.3 Hz), 2.85–2.75 (m, 1 H), 2.68 (dd, 1 H, J = 10.8, 2.7 Hz), 2.64 (d, 1 H, J = 9.0 Hz), 2.18 (br s, 1 H), 2.68 (dd, 1 H, J = 10.8, 2.7 Hz), 2.64 (d, 1 H, J = 9.0 Hz), 2.18 (br s, 1 H), 2.17 (dd, 1 H, J = 14.7, 3.6 Hz), 1.75–1.65 (m, 2 H), 1.53 (s, 3 H), 1.35 (s, 3H); IR (KBr) 3387, 2927, 1725, 1208 cm^{-1}; CIMS (CH_4) m/z (rel intensity) 397 (M^+ + 1, 100), 396 (40).

20-Deethyl-15,20-*exo*,*exo*-dihydroxy-5,6-homocoronaridine (24c). The acetonide **24b** (44 mg, 0.11 mmol) was dissolved in MeOH (0.5 mL) followed by dropwise addition of concentrated HCl (1.0 mL). After 5 min, the solution was cooled to 0 °C and 20% aqueous Na_2CO_3 was added until basic. This solution was extracted with CH_2Cl_2, dried, and concentrated to yield **24c** (36 mg, 0.1 mmol, 92%) as a white foam: ^1H NMR ($CDCl_3$, δ ppm, 300 MHz) 7.95 (br s, 1 H), 7.53 (d, 1 H, J = 8.4 Hz), 7.29 (d, 1 H, J = 8.4 Hz), 7.17 (t, 1 H, J = 7.5 Hz), 7.11 (t, 1 H, J = 7.5 Hz), 4.41 (d, 1 H, J = 3.0 Hz), 3.81 (dd, 1 H, J = 7.5, 3.0 Hz), 3.74 (br d, 1 H, J = 7.5 Hz), 3.62 (s, 3 H), 3.31 (dt, 1 H, J = 10.5, 2.4 Hz), 3.28–3.2 (m, 1 H), 3.11 (q, 1 H, J = 7.5 Hz), 3.01 (dt, 1 H, J = 14.7, 2.7 Hz), 2.95 (dd, 1 H, J = 6.0, 3.0 Hz), 2.71 (qd, 1 H, J = 10.5, 3.0 Hz), 2.23 (br d, 1 H, J = 10.5 Hz), 2.1 (dd, 1 H, J = 14.7, 3.3 Hz), 2.01–1.9 (m, 2 H); IR (KBr) 3387, 3290, 2929, 1724, 1238 cm^{-1}; CIMS (CH_4) m/z (rel intensity) 357 (M^+ + 1, 100), 356 (20).

20-Deethyl-15,20-*exo*,*exo*-bis[(methylsulfonyl)oxy]-5,6-homocoronaridine (24e). The diol **24c** (35 mg, 0.1 mmol) was dissolved in CH_2Cl_2 (2 mL) followed by the addition of Et_3N (28 mg, 0.27 mmol, 2.8 equiv). After this mixture cooled to 0 °C, a catalytic amount of DMAP was added followed by methanesulfonyl chloride (28 mg, 0.24 mmol, 2.5 equiv). After 10 min at 0 °C, the solution was allowed to reach room temperature before being quenched with 20% aqueous Na_2CO_3. After workup, flash chromatography provided the dimesylate **24e** (26 mg, 0.05 mmol, 52%) as a white foam: ^1H NMR ($CDCl_3$, δ ppm, 300 MHz) 7.94 (br s, 1 H), 7.54 (d, 1 H, J = 7.5 Hz), 7.29 (d, 1 H, J = 7.5 Hz), 7.18 (t, 1 H, J = 7.5 Hz), 7.12 (t, 1 H, J = 7.5 Hz), 4.88 (dd, 1 H, J = 8.4, 3.9 Hz), 4.68 (d, 1 H, J = 8.4 Hz), 4.43 (br s, 1 H), 3.69 (s, 3 H), 3.3–3.19 (m, 3 H), 3.18 (s, 3 H), 3.13 (s, 3 H), 3.0 (dt, 1 H, J = 14.7, 4.5 Hz), 2.85–2.75 (m, 1 H), 2.68 (br d, 1 H, J = 13.5 Hz), 2.63 (br d, 1 H, J = 9.3 Hz), 2.44 (br s, 1 H), 2.37 (dd, 1 H, J = 14.7, 5.4 Hz), 1.89–1.75 (m, 2 H); IR (KBr) 3394, 2931, 1722, 1356, 1175 cm^{-1}; CIMS (CH_4) m/z (rel intensity) 513 (M^+ + 1, 100), 418 (20), 101 (60).

20-Deethyl-5,6-homocatharanthine (24f). The dimesylate **24e** (35 mg, 0.07 mmol) was dissolved in THF (8 mL) before being cooled to −42 °C. A stock solution of the naphthalene radical anion [prepared by stirring Na (23.4 mg, 1.02 mmol, 15 equiv) and naphthalene (131 mg, 1.02 mmol, 15 equiv) in THF (15 mL) at room temperature for 6 h] was cooled to −42 °C, and several aliquots were delivered (by canulla) to the THF solution of **24e**. The seventh aliquot caused the green color of the radical anion to persist. The solution was stirred for an additional 10 min, before being quenched with methanol. The reaction mixture was concentrated to a small volume and processed by the standard workup. Flash chromatography provided **24f** (14.3 mg, 0.05 mmol, 74%) as a white solid: ^1H NMR ($CDCl_3$, δ ppm, 300 MHz) 7.94 (br s, 1 H), 7.54 (d, 1 H, J = 7.5 Hz), 7.27 (d, 1 H, J = 7.5 Hz), 7.14 (t, 1 H, J = 7.5 Hz), 7.07 (t, 1 H, J = 7.5 Hz), 6.47 (t, 1 H, J = 6.3, 2.4 Hz), 6.44 (t, 1 H, J = 6.3 Hz), 4.96 (d, 1 H, J = 6.3 Hz), 3.57 (s, 3 H), 3.25 (q, 2 H, J = 5.5 Hz), 2.94 (qd, 1 H, J = 6.9, 3.0 Hz), 2.88–2.79 (m, 2 H), 2.72–2.64 (m, 2 H), 2.46 (dd, 1 H, J = 9.0, 2.4 Hz), 2.17–2.04 (m, 1 H), 1.98 (dd, 1 H, J = 12.6, 2.1 Hz), 1.95–1.81 (m, 1 H); IR ($CHCl_3$) 3332, 3008, 2827, 1713 cm^{-1}; ^{13}C NMR ($CDCl_3$) 173.8, 153.4, 134.4, 133.0, 128.7, 121.9, 119.2, 118.0, 110.9, 110.2, 55.3, 54.3, 52.9, 52.6, 52.2, 35.4, 31.0, 26.8, 21.5; CIMS (CH_4) m/z (rel intensity) 323 (M^+ + 1, 100), 322; HRMS exact mass calcd 322.1681, found 322.1665.

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Supplementary Material Available: Brief description of the preparation and summary of the proton NMR peak positions are given for the following new compounds: **3d,e**, **4a–c**, **5**, **6e,f**, **7b,e,f**, **11b**, **12**, **13a–e**, **14a–c**, **18f–o**, **19c**, **23b–e**, **24d**; 300-MHz NMR spectra for compounds **16** and **17** (24 pages). Ordering information is given on any current masthead page.

Tandem Photochemical Synthesis of *N*-Amino β-Lactams from Pyrazolidin-3-ones

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Substituted pyrazolidin-3-ones **8–13** were prepared by condensation of hydrazine hydrate with α,β-unsaturated carboxylic acids or esters and were converted to 1-(*o*-nitrobenzyl) derivatives **22–26**. Acylation of these heterocycles afforded 1-(*o*-nitrobenzyl)-2-acylpyrazolidin-3-ones **27–39** which, upon irradiation through Pyrex and then through Vycor, yielded 1-(acylamino)azetidin-2-ones **40–50**. Removal of the acyl residue from the extraannular nitrogen produced 1-aminoazetidin-2-ones **57–62**. Application of this route to *N*-amino β-lactams from pyrazolidin-3-one **67** resulted in **70** possessing the hydroxyethyl side chain characteristic of thienamycin. A mechanism is suggested for this tandem photochemical synthesis of β-lactams that involves initial removal of the N-1 *o*-nitrobenzyl substituent, followed by ring contraction via diazabicyclo[2.1.0]pentane intermediate **54**.

The presence of a β-lactam nucleus in the largest and most extensively used group of antibiotics has led to a broad effort directed toward synthesis of this ring system.[1] As the intense activity that had been focused on penicillins for over three decades began to wane in the 1970s, several new classes of β-lactam antibiotics emerged which were found to have valuable therapeutic properties.[2,3] These include the monocyclic β-lactams (monobactams),[4] a group

(1) Morin, R. B., Gorman, M., Eds. *Chemistry and Biology of β-Lactam Antibiotics*; Academic Press: New York, 1982; Vols. 1–3.

(2) Stapley, E. O. In *β-Lactam Antibiotics*; Salton, M., Shockman, G. D., Eds.; Academic Press: New York, 1981; p 327.

(3) Cooper, R. D. G. In *Topics in Antibiotic Chemistry*, Sammes, P. G., Ed.; Ellis Horwood; Chichester, 1979; Vol. 3, p 39.

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