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General Strategies for the Synthesis of Indole Alkaloids. Total Syntheses of (±)-Reserpine and (±)-α-Yohimbine[1]

Stephen F. Martin,*[2] Heinrich Rüeger, Sidney A. Williamson, and Slawomir Grzejszczak

Contribution from the Department of Chemistry, The University of Texas, Austin, Texas 78712.
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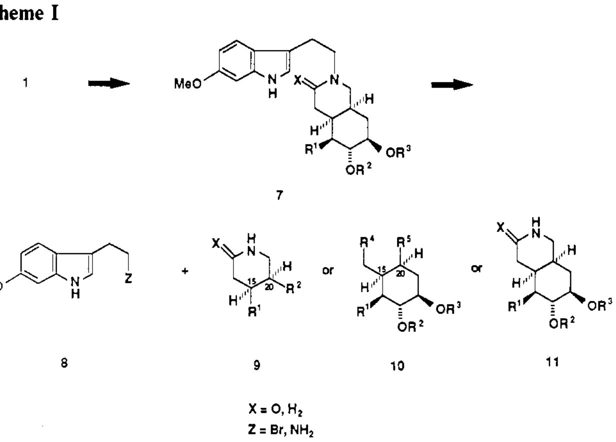
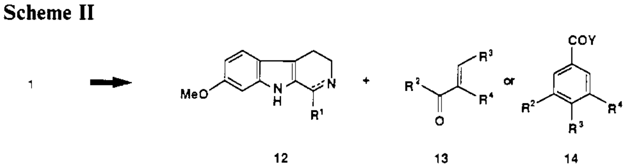
Abstract: The concise, total syntheses of the indole alkaloids (±)-reserpine (**1**) and (±)-α-yohimbine (**4**) have been completed by the application of a general strategy that features an intramolecular Diels–Alder reaction for the facile construction of the functionalized hydroisoquinoline ring system that comprises the essential D/E ring subunit of the target natural products. Thus, thermolysis of the trienic amide **23**, which was readily assembled in six steps from propargyl alcohol, delivered the cycloadduct **24**. Subsequent elaboration of **24** into the key intermediate **32**, which bears all five of the contiguous stereogenic centers present in the E ring of reserpine, required only four additional steps. Refunctionalization of the D/E ring subunit **32** provided the secondary amine **48**, which was converted into (±)-reserpine (**1**) by sequential alkylation with 6-methoxytryptophyl bromide followed by mercuric ion induced, oxidative cyclization. The unsaturated lactam **30**, which was an intermediate in the total synthesis of reserpine (**1**), also served as a precursor to the related indole alkaloid (±)-α-yohimbine (**4**). In the event, **30** was converted by a straightforward sequence of reactions into the bicyclic amine **60**, which was subjected to catalytic hydrogenation and hydrogenolysis to afford the secondary amine **61**. Coupling of **61** with tryptophyl bromide and subsequent oxidative cyclization under standard conditions afforded (±)-α-yohimbine (**4**). Efforts to employ the amine **60** as an intermediate in a synthesis of the novel alkaloid (±)-19,20-dehydro-α-yohimbine (**5**) were unsuccessful.

The monoterpenoid-derived indole alkaloids, which number in excess of 1000 natural bases, owe their common biosynthetic origin to the initial union of tryptophan and secologanin, an event that is then followed by a diversity of biogenetic refunctionalizations and several possible skeletal reorganizations.[3] Two important subgroups that possess an unrearranged secologanin skeleton are the yohimboid and the heteroyohimboid alkaloids, of which reserpine (**1**),[4–6] deserpidine (**2**),[7] yohimbine (**3**),[8] α-yohimbine (rauwolscine) (**4**),[9] 19,20-dehydro-α-yohimbine (**5**),[10–12] and ajmalicine (raubasine) (**6**)[13] are representative members. Over

Scheme I



Scheme II



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(2) Recipient of a National Institutes of Health (National Cancer Institute) Research Career Development Award, 1980–1985.

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(5) For some leading references to synthetic approaches to reserpine, see: (a) Wenkert, E.; Liu, L. H.; Johnston, D. B. R. *J. Org. Chem.* **1965**, *30*, 722. (b) Takano, S.; Ito, F.; Ogasawara, K. *Heterocycles* **1980**, *14*, 453. (c) Suzuki, T.; Tomino, A.; Unno, K.; Kametani, T. *Chem. Pharm. Bull. Jpn.* **1981**, *29*, 76; *Heterocycles* **1980**, *14*, 439. (d) Chao, S.; Kunng, F.-A.; Gu, J.-M.; Ammon, H. L.; Mariano, P. S. *J. Org. Chem.* **1984**, *49*, 2708. (e) Wenkert, E. *Heterocycles* **1984**, *21*, 325. (f) Jung, M. E.; Light, L. A. *J. Am. Chem. Soc.* **1984**, *106*, 7614. (g) Isobe, M.; Fukami, N.; Nishikawa, T.; Goto, T. *Heterocycles* **1987**, *25*, 521. (h) Polniaszek, R. P.; Stevens, R. V. *J. Org. Chem.* **1986**, *51*, 3023.

(6) For total syntheses of reserpine, see: (a) Woodward, R. B.; Bader, F. E.; Bickel, H.; Frey, A. J.; Kierstead, R. W. *J. Am. Chem. Soc.* **1956**, *78*, 2023, 2657; *Tetrahedron* **1958**, *2*, 1. (b) Pearlman, B. A. *J. Am. Chem. Soc.* **1979**, *101*, 6398, 6404. (c) Wender, P. A.; Schaus, J. M.; White, A. W. *Ibid.* **1980**, *102*, 6157. *Heterocycles* **1987**, *25*, 263. (d) Reference 1a. (e) Stork, G.; Goodman, B. A. *Abstracts of Papers*, 192nd National Meeting of the American Chemical Society, Anaheim, CA; American Chemical Society: Washington, DC, 1986; ORGN 136.

(7) For total syntheses of deserpidine, see: (a) Szántay, C.; Blaskõ, G.; Honty, K.; Baitz-Gacs, E.; Tamas, J.; Töke, L. *Liebigs Ann. Chem.* **1983**, 1292. (b) Miyata, O.; Hirata, Y.; Naito, T.; Ninomiya, I. *Heterocycles* **1984**, *22*, 1041. (c) Wenkert, E., personal communication. For the approach, see in ref 5e.

(8) For representative synthetic approaches and leading references to yohimbine, see: (a) van Tamelen, E. E.; Shamma, M.; Burgstahler, A. W.; Wolinsky, J.; Tamm, R.; Aldrich, P. E. *J. Am. Chem. Soc.* **1969**, *91*, 7315. (b) Töke, L.; Honty, K.; Szántay, C. *Chem. Ber.* **1969**, *102*, 3248. (c) Stork, G.; Guthikonda, R. N. *J. Am. Chem. Soc.* **1972**, *94*, 5109. (d) Kametani, T.; Hirai, Y.; Fukumoto, K. *Chem. Pharm. Bull. Jpn.* **1976**, *24*, 2500. (e) Szántay, C.; Honty, K.; Töke, L.; Szabo, L. *Chem. Ber.* **1976**, *109*, 1737. (f) Wenkert, E.; Chang, C.-J.; Chawla, H. P. S.; Cochran, D. W.; Hagaman, E. W.; King, J. C.; Orito, K. *J. Am. Chem. Soc.* **1976**, *98*, 3645. (g) Wenkert, E.; Halls, T. D. J.; Kunesch, G.; Orito, K.; Stephens, R. L.; Temple, W. A.; Yadav, J. S. *Ibid.* **1979**, *101*, 5370. (h) Kametani, T.; Suzuki, T.; Unno, K. *Tetrahedron* **1981**, *37*, 3819. (i) Burdick, D. C. Ph.D. Dissertation, University of Michigan, 1980. (j) Wenkert, E.; Pyrek, J. St.; Uesato, S.; Vankar, Y. D. *J. Am. Chem. Soc.* **1982**, *104*, 2244. (k) Miyata, O.; Hirata, Y.; Naito, T.; Ninomiya, I. *J. Chem. Soc., Chem. Commun.* **1983**, 1231. (l) Danishefsky, S.; Langer, M. E.; Vogel, C. *Tetrahedron Lett.* **1985**, *26*, 5983. (m) Blasko, G.; Knight, H.; Honty, K.; Szántay, C. *Liebigs Ann. Chem.* **1986**, 655.

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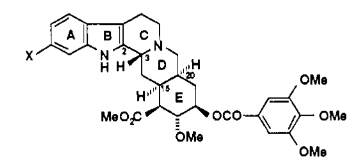
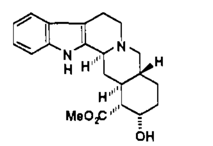
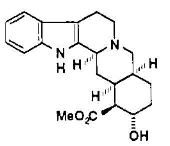
the years, these and related alkaloids have been the subjects of extensive pharmacological, chemical, and synthetic investigations. However, because of its structural complexity coupled with its clinical importance as a hypotensive agent exhibiting significant sedative and tranquilizing activity, reserpine (**1**), which was originally isolated from the Indian snake root *Rauwolfia serpentina* Benth., emerged as the preeminent member of the yohimboid class of indole alkaloids.



1: X = OMe
2: X = H



3



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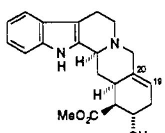

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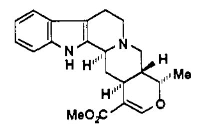
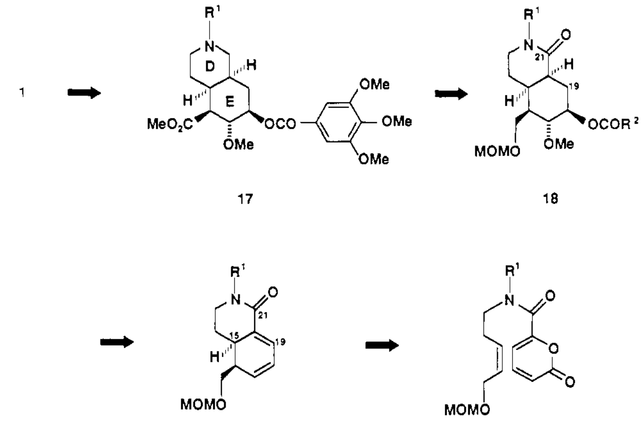


6

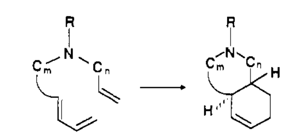
Historically, two fundamental strategies have provided access to the bases of the yohimboid class, and these entries are adumbrated in a retrosynthetic format in Schemes I and II using reserpine (**1**) for illustrative purposes. The more widely employed approach (Scheme I) features the cyclization of a seco derivative **7** by formation of the C(2)–C(3) bond as the final step in the construction of the pentacyclic skeleton. The preparation of synthetic subgoals such as **7** is typically achieved by coupling an appropriate tryptophyl synthon **8** with (1) a D-ring subunit **9** possessing substituents at C(15) and C(20) that are suitably functionalized for the eventual elaboration of the E ring, (2) an E-ring synthon **10** bearing alkyl appendages at C(15) and C(20) incorporated with functionality so the coupling step would occur concomitant with formation of the D ring, or (3) a fully substituted D/E-ring subunit **11**. An alternative strategy (Scheme II) involves the stepwise annelation of the D and E rings onto an intact ABC ring by the initial joining of a subunit as **12** with synthons of the general types **13** and **14**, followed by the requisite series of transformations to complete the pentacyclic nucleus.

Despite the myriad of efforts directed toward the preparation of the yohimboid alkaloids, the stereochemically and functionally most complex members of this class, reserpine (**1**) and its 6-demethoxy derivative deserpidine (**2**), have only occasionally yielded to total synthesis.[6,7] Nevertheless, the basic strategies that have been employed in achieving these successes nicely illustrate the general approaches outlined in Schemes I and II. For example, the elegant and historic synthesis of reserpine by Woodward[6a] entailed the condensation of a substituted E ring of the general type **10** with 6-methoxytryptamine to furnish a 2,3-seco derivative related to **7** (X = O). Different approaches to similar E-ring intermediates were employed by Pearlman[6b] and Stork,[6e] whereas Wender coupled an intact D/E-ring subunit of the type **11** (X = H_2) with 6-methoxytryptophyl bromide.[6c] The novel entry to deserpidine (**2**) recorded by Wenkert nicely exploited substituted pyridines as D-ring precursors related to **9**.[7c] Alternatively, the stepwise annelation of the D and E rings utilizing synthons related to **13** and **14**, respectively, onto an extant ABC framework played a key role in the synthesis of deserpidine by both Szántay[7a] and Ninomiya.[7b]

Scheme III



The design and development of general and efficient strategies for alkaloid synthesis have long been major focuses of research in our laboratories, and the considerable challenge of creating a new approach to the yohimboid alkaloids as well as other architecturally diverse alkaloids of the indole group emerged as a highly intriguing objective. The task of inventing an alternative entry to the yohimboid alkaloids might be formulated in one context as an exercise in the construction of substituted hydroisoquinolines, and in connection with a continuing interest in devising new applications of intramolecular Diels–Alder[14] reactions for the facile assemblage of fused heterocyclic ring systems,[15] it occurred to us that a process such as that depicted in eq 1 might



(1)

15 16

m = 1; n = 2
m = 2; n = 1

constitute an appealing solution to the problem at hand. Indeed, preliminary model studies quickly established that the thermal cyclizations of trienes **15** (m = 1, n = 2 and m = 2, n = 1) did provide convenient access to the corresponding hydroisoquinolines **16** (m = 1, n = 2 and m = 2, n = 1).[16]

With the aforementioned model studies as background, a strategy for the synthesis of reserpine (**1**) was conceived (Scheme III), and the principal challenge and the ultimate subgoal of this venture was the stereoselective elaboration of the fully intact D/E-ring subunit **17**, a *cis*-hydroisoquinoline richly endowed with stereochemistry and functionality. Access to **17** required the initial

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(14) For an excellent review of the intramolecular Diels–Alder reaction, see: Ciganek, E. *Org. React.* **1984**, *32*, 1.

(15) For other leading references for the use of intramolecular cycloadditions for the construction of nitrogen heterocycles, see: (a) Martin, S. F.; Tu, C.-Y; Kimura, M.; Simonsen, S. H. *J. Org. Chem.* **1982**, *47*, 3634. (b) Magnus, P.; Gallagher, T.; Brown, P.; Pappalardo, P. *Acc. Chem. Res.* **1984**, *17*, 35. (c) Weinreb, S. M. *Ibid.* **1985**, *18*, 16. (d) Reference 16.

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preparation of the hydroisoquinoline derivative **19** via the intramolecular [4 + 2] cycloaddition of the trienic amide **20**. Subsequent refunctionalization of **19** would then lead to **18**, which possesses the full complement of the five contiguous stereocenters adorning the E ring. If the reduction of the double bond in a 19,20-dehydro derivative of **18** did not proceed in a highly stereoselective fashion, the presence of the lactam carbonyl group at C(21) would allow the facile base-induced epimerization at C(20) to afford the thermodynamically more stable *cis*-hydroisoquinolone **18**. Manipulation of **18** to deliver the D/E subunit **17** and subsequent coupling of **17** (R^1 = H) with 6-methoxytryptophyl bromide would generate the 2,3-seco derivative of reserpine, which could then be converted to **1** via an oxidative cyclization according to established procedures.[17,18] Although it would be possible in principle to incorporate the 6-methoxyindole unit onto intermediates at an earlier stage of the synthesis, the susceptibility of this highly reactive ring system toward oxidation and electrophilic attack appeared to render such a tactic problematic in practice.

The alkaloid α-yohimbine (**4**) bears close structural resemblance to reserpine (**1**), suggesting that the general strategy outlined in Scheme III might be readily modified and then advantageously applied to its total synthesis as well. Indeed, during the course of the studies directed toward the synthesis of **1**, several crucial discoveries were made that supported this hypothesis. Although a minor alteration of the plan employed for the preparation of **4** was envisaged for the synthesis of 19,20-dehydro-α-yohimbine (**5**), access to this novel alkaloid was derailed by an unavoidable but not entirely unexpected side reaction. We now disclose the full details of these investigations.[1]

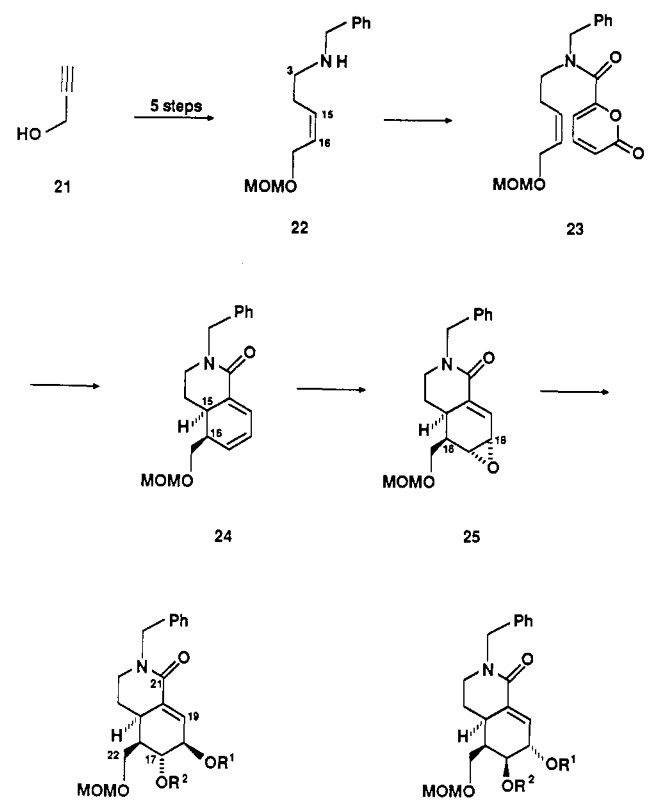
Results and Discussion

Total Synthesis of (±)-Reserpine (1). The amide **23** required for the pivotal intramolecular Diels–Alder reaction was conveniently prepared in 89% yield by coupling 2-oxopyran-6-carbonyl chloride[19] with the homoallylic secondary amine **22**, which we had previously prepared in five straightforward steps (60% overall yield) from propargyl alcohol (Scheme IV).[13k] Subsequent thermolysis of **23** in xylenes at reflux proceeded smoothly to afford the cycloadduct **24** in 93% yield. Although the feasibility of employing a furan ring as the dienic partner was evaluated in several preliminary experiments, the thermolysis of the furamide that was obtained from the reaction of **22** with 2-furoyl chloride provided an equilibrium mixture that favored the reactant over the cycloadduct by a ratio of greater than 9:1.

The ready accessibility of the lactam **24** set the stage for the stereoselective refunctionalization of the E ring, and the elaboration of the trans-vicinal glycol array at C(17) and C(18) was undertaken as the first objective. In the event, regioselective epoxidation of the more nucleophilic carbon–carbon double bond distal to the carbonyl group of **24** with *m*-chloroperoxybenzoic acid (MCPBA) proceeded with a high degree of stereoselectivity from the less encumbered α face to provide the epoxide **25** in 88% yield. Small quantities (<5%) of a diepoxide were occasionally isolated, and while the stereochemistry of this substance was not unambiguously determined, based upon steric considerations it was assumed to be derived from the epoxidation of the $\Delta^{19,20}$-double bond of **25** from the less hindered β face. None of the diastereoisomeric β-monoepoxide was detected.

We reasoned that epoxide **25** should undergo regioselective, nucleophilic opening at the allylic terminus at C(18), since such attack should be electronically activated by the $\Delta^{19,20}$-double bond.[20] Moreover, the protected hydroxymethylene substituent at C(16) was expected to provide a significant steric impediment along the trajectory that would be required for nucleophilic attack at C(17). Although attempts to open the epoxide moiety with several alcohols under either acidic or basic conditions did not proceed cleanly, treatment of **25** with AcOH/AcONa (1.1:1) in tetrahydrofuran (THF) at reflux provided a mixture (85:15) of the *trans*-hydroxy acetate **26** together with the undesired isomer **27**. Moreover, variable amounts of the isomeric acetates **28** and **29**, which presumably resulted from the intramolecular 1,2-acyl transfer of the acetyl group in **26** and **27**, respectively, were also isolated. While the acetates **26** and **27** could be easily separated by conventional reverse-phase chromatography, the facile 1,2-migration of the acetyl group precluded the efficacious utilization of **26** in subsequent steps of the synthesis. Several preliminary attempts to open the epoxide moiety of **25** using a similar combination of the sodium or lithium salts of either pivalic acid or benzoic acid in the presence of their respective acids were unsuccessful. However, when **25** was heated in dimethoxyethane (DME) at reflux with BuCH(Et)COOH and BuCH(Et)COOLi (2:1.5), scission of the epoxide occurred exclusively at C(18) to afford **30** in 90% yield. The trans-diaxial orientation of the two protons at C(16) and C(17) of **30** was evident from the observed coupling constant of 8.1 Hz, and other relevant coupling constants of $J_{17,18}$ = 5.5 Hz and $J_{18,19}$ = 2.5 Hz provided further support for the assigned structure.

Scheme IV



26: R^1 = Ac; R^2 = H
28: R^1 = H; R^2 = Ac
30: R^1 = COCH(Et)Bu; R^2 = H
31: R^1 = COCH(Et)Bu; R^2 = Me
35: R^1 = H; R^2 = Me

27: R^1 = H; R^2 = Ac
29: R^1 = Ac; R^2 = H

MOM = CH_2OCH_3

(17) Sakai, S.; Ogawa, M. *Heterocycles* **1978**, *10*, 67. We thank Professors S. Sakai and E. Yamanaka of Chiba University for supplying these experimental details.

(18) For related examples of oxidative cyclization, see: (a) Wenkert, E.; Wickberg, B. *J. Am. Chem. Soc.* **1962**, *84*, 4914. (b) Morrison, G. C.; Cetenko, W.; Shavel, J., Jr. *J. Org. Chem.* **1967**, *32*, 4089. (c) Husson, H.-P.; Chevolot, L.; Langlois, Y.; Thal, C.; Potier, P. *J. Chem. Soc., Chem. Commun.* **1972**, 930. (d) Aimi, N.; Yamanaka, E.; Endo, J.; Sakai, S.; Haginiwa, J. *Tetrahedron* **1973**, *29*, 2015. (e) Fujii, T.; Ohba, M.; Sasaki, N. *Heterocycles* **1984**, *22*, 1805. (f) See also ref 6c, 8c, 13e,g,i, and 17.

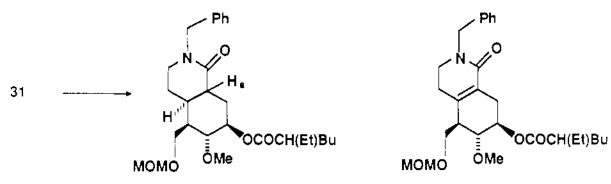
(19) Wiley, R. H.; Hart, A. J. *J. Am. Chem. Soc.* **1954**, *76*, 1942.

(20) For a related opening of an unsaturated epoxide, see: Baggiolini, E. G.; Iacobelli, J. A.; Hennessy, B. M.; Batcho, A. D.; Sereno, J. F.; Uskoković, M. R. *J. Org. Chem.* **1986**, *51*, 3098.

Owing to the hindered nature of the secondary hydroxyl function at C(17), methylation of **30** to deliver **31** proved to be somewhat sluggish and was best achieved (98% yield) under neutral conditions using methyl iodide as solvent in the presence of silver(I) oxide and $CaSO_4$. The use of the usual solvents such as dimethylformamide or acetone gave rise to the formation of small but significant quantities of unidentified impurities that rendered the purification of **31** more tedious.

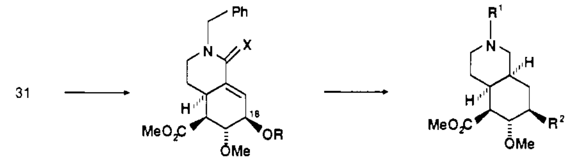
With four of the five requisite stereocenters in the E ring thus quickly secured, the ostensibly trivial task of reducing the $\Delta^{19,20}$-double bond of **31** to furnish **32** was all that remained to complete the critical stereochemical requirements of the synthesis. In the event that the delivery of hydrogen from the α face of **31** did not proceed with complete stereoselectivity, the lactam carbonyl group at C(21) was propitiously positioned so that mere base-catalyzed equilibration at C(20) would provide the thermodynamically more stable *cis*-hydroisoquinolone **32** in which all of the substituents on the E ring except the one at C(15) would be in the preferred equatorial orientation. In the energetically less favorable *trans*-hydroisoquinolone **33**, the E ring would be forced to reside in a twist boat or related conformation in order to avoid the simultaneous arrangement of each of the three substituents at C(16)–C(18) in an axial orientation.

Despite the deceptively straightforward nature of this reduction, considerable difficulty was encountered in its execution. Namely, subjection of **31** to hydrogenation in different solvents (e.g., alcohols, ethyl acetate, benzene) in the presence of a variety of catalysts (e.g., Pd/C, PtO_2, Pt/C, Rh/C, Rh/Al_2O_3, Ru/C, Os) at hydrogen pressures up to approximately 750 psi led either to the recovery of **31** or to the isolation of the isomeric, conjugated lactam **34** bearing a tetrasubstituted double bond. Several efforts to effect the 1,4-reduction of the unsaturated lactam arrays present in **31** and **35**, or the alkoxide derived therefrom, utilizing dissolving metals (Ca, Li, or Na in ammonia; lithium naphthalenide or sodium naphthalenide in THF or DME; and SmI_2 in THF) or cuprous hydride were also unavailing.



32: α-Ha
33: β-Ha
34

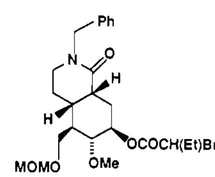
Since the acyl function present at C(21) in **31** was suspected of playing some role, perhaps electronic, in facilitating the isomerization of **31** to **34** prior to reduction, the possibility that its removal might lessen the proclivity toward this deleterious process was examined. Anticipating that some experimental difficulties might arise during the adjustment of the oxidation level at C(22) in the presence of a basic amino group, we elected to refunctionalize the protected primary hydroxyl group at C(22) prior to reduction of the lactam carbonyl at C(21). Hence, removal of the methoxymethyl protecting group from **31** by acid-catalyzed transketalization in methanol followed by sequential treatment of the intermediate primary alcohol with pyridinium dichromate (PDC)[21] in DMF and then diazomethane furnished the methyl ester **36** in 77% overall yield. Selective reduction of the lactam moiety with alane under carefully controlled conditions then delivered the tertiary, unsaturated amine **37**. Although reduction of the carbon–carbon double bond now proceeded smoothly without apparent isomerization, hydrogenolysis of the allylic ester function at C(18) intervened as a major and unavoidable side reaction, and depending upon the reaction conditions and the catalyst employed mixtures containing variable amounts of **39** and **40** were isolated. The fortuitous discovery that the allylic ester function at C(18) of **37** could be cleanly removed by hydrogenolysis would later be exploited as a key step in the total synthesis of (±)-α-yohimbine (**4**) (vide infra). Acid-catalyzed methanolysis of **37** gave the corresponding alcohol **38**, and although reductive cleavage of the allylic oxygen function no longer proved to be a nuisance, catalytic hydrogenation of **38** under a variety of conditions typically afforded several products, with the desired **41** being formed in only about 40% yield.



36: X = O; R = COCH(Et)Bu
37: X = H_2; R = COCH(Et)Bu
38: X = H_2; R = H

39: R^1 = Bn; R^2 = H
40: R^1 = R^2 = H
41: R^1 = Bn; R^2 = OH

Inasmuch as all previous efforts to exploit the tertiary amines **37** and **38** as intermediates en route to a viable D/E-ring subunit for the synthesis of reserpine were found wanting, the feasibility of directly reducing the lactam **31** by catalytic hydrogenation under more forcing conditions was examined. Ultimately, it was discovered that the reaction of **31** in methanol with hydrogen at 1800 psi in the presence of Pearlman's catalyst [20% $Pd(OH)_2/C$][22] provided **32** in 90% yield together with the isomeric *cis*-hydroisoquinolone **42** (6%) and even lesser amounts of two other stereoisomers that were not completely characterized. The coupling constant of 4.5 Hz measured for the protons at C(15) and C(20) of **32** was clearly indicative of a cis-ring fusion. In an independent experiment, it was determined that the tetrasubstituted double bond in **34** was also reduced under these conditions, albeit with significantly lower stereoselectivity, to give substantial amounts of **42** together with **32** and several other diastereomers. It therefore seems likely that **31** underwent preferential and highly stereoselective hydrogenation to deliver **32**, whereas the formation of **42** and the other diastereomeric products presumably arose from the reduction of the small quantity of **34** produced in situ by the competing isomerization of **31**.



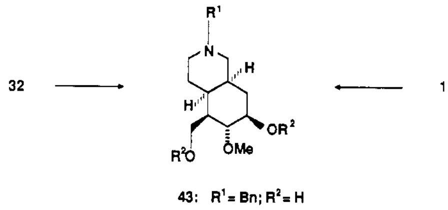
42

At this juncture, the relative stereochemistry at the five contiguous centers on the E ring of **32** was unambiguously established by chemical correlation with **44**, which was a key intermediate in Wender's elegant synthesis of (±)-reserpine (**1**).[6c] In the event, treatment of **32** with alane at room temperature effected the simultaneous reduction of the lactam moiety and cleavage of the ester protecting group at C(18), and subsequent removal of the methoxymethyl (MOM) group by acid-catalyzed hydrolysis delivered the diol **43**. Acetylation of **43** with excess acetic anhydride in the presence of 4-(dimethylamino)pyridine (DMAP) and subsequent N-debenzylation with methyl chloroformate furnished **44**, which was spectroscopically identical with an authentic sample that was available by the chemical degradation of reserpine.[6c] Although this preparation of **44** constituted in a formal sense a total synthesis of reserpine, an alternative and more direct sequence of reactions was devised to complete the task.

With the main stereochemical issues of the synthesis resolved, the next objective entailed the refunctionalization of the *cis*-hydroisoquinoline **32** to give **48**, which would then be linked to the 6-methoxytryptophyl moiety for the final elaboration to reserpine (Scheme V). Removal of the protecting group from the hydroxyl at C(22) was effected by heating (45 °C) a solution of **32** in methanol containing *p*-toluenesulfonic acid, and the

(21) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.

(22) Pearlman, W. M. *Tetrahedron Lett.* **1967**, 1663. We thank W. M. Pearlman (Warner Lambert-Parke Davis) for a generous gift of this catalyst.



43: R¹ = Bn; R² = H
44: R¹ = CO₂Me; R² = Ac

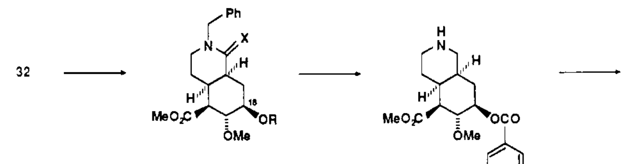
intermediate primary alcohol was then converted into the corresponding methyl ester **45** in 75% overall yield from **32** by sequential oxidation with PDC in DMF and reaction with excess diazomethane. The chemoselective hydride reduction of the lactam moiety in **45** with alane under carefully controlled conditions afforded the tertiary amine **46** in 80% yield. Whereas cleavage of the hindered ester function from the C(18) hydroxyl under basic conditions was plagued by side reactions involving, inter alia, β-elimination of the methoxy group from C(17) and subsequent aromatization, the acid-catalyzed transesterification of **46** to give **47** proceeded readily in 81% yield upon heating **46** at 85 °C in anhydrous methanol containing *p*-toluenesulfonic acid. The resulting tertiary amine **47** was smoothly transformed into **48** in 84% yield by O-acylation with 3,4,5-trimethoxybenzoyl chloride in pyridine in the presence of a catalytic amount of DMAP followed by removal of the *N*-benzyl group by hydrogenolysis over Pearlman's catalyst[22] in glacial acetic acid. The secondary amine **48**, which constitutes the fully intact D/E-ring subunit of reserpine (**1**), was thus available in only 18 steps and 17% overall yield from propargyl alcohol.

Completion of the total synthesis of reserpine required only two additional moves commencing with the N-alkylation of **48** with 6-methoxytryptophyl bromide[6c,23] in dimethyl sulfoxide (DMSO) to give racemic 2,3-secoreserpine (**49**) (69%), which was spectroscopically identical with an authentic sample prepared by the degradation of reserpine.[24] Employing a slight modification of the Sakai protocol,[17,18] **49** was oxidized with excess mercuric acetate in 5% aqueous acetic acid at 85–90 °C, and the resulting mixture was treated sequentially with hydrogen sulfide and then with zinc in 7% aqueous $HClO_4$/acetone/THF (1:1:1) at reflux to furnish (±)-reserpine (**1**) (35%) and (±)-isoreserpine (**50**) (8%) together with the two corresponding inside derivatives **51** (18%) and **52** (4%) and starting **49** (10%). The use of sodium borohydride instead of zinc metal as the reductant in the final step of this process led to the formation of slightly greater quantities of **50** together with correspondingly lesser amounts of **1**. The synthetic, racemic reserpine thus obtained was spectroscopically identical in all respects except optical rotation with an authentic sample of natural **1**.

Meritorious of some additional comment are the regio- and stereochemical aspects of the oxidative cyclization of **49**. Namely, a regiochemical issue arises during the initial oxidation of the tertiary amino function in **49**, a process that could proceed at C(3), C(21), or C(5) to give the corresponding iminium salts **53–55**, although no products arising from the oxidation at C(5) were detected. An analysis of the ratios of the final products revealed that the relative propensity toward oxidation at C(3) vs. C(20) typically varied within the range 1.7–2.2:1, with the modifications of a number of experimental conditions and parameters having only minor consequences. The modest level of regioselectivity observed in the present oxidation–cyclization sequence is wholly consistent with earlier reports of syntheses of yohimboid and heteroyohimboid alkaloids in which such a tactic was employed for the construction of the C ring.[17,18]

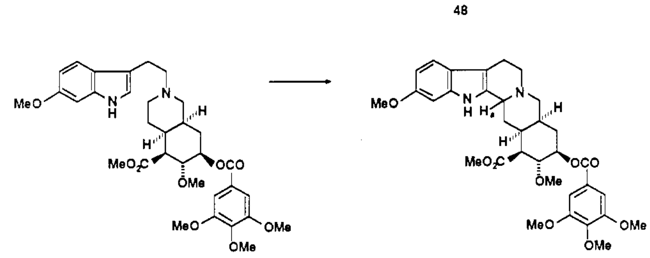
In essential control experiments, it was established that under the optimized conditions detailed above for the oxidation and cyclization of **49**, reserpine (**1**) underwent oxidation to afford 3,4-dehydroreserpine (**56**) at a slow but yet meaningful rate,[25]

Scheme V



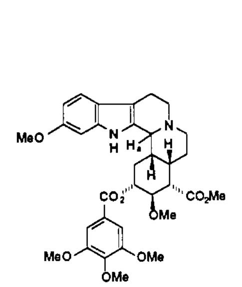
45: X = O; R = COCH(Et)Bu
46: X = H₂; R = COCH(Et)Bu
47: X = H₂; R = H

48



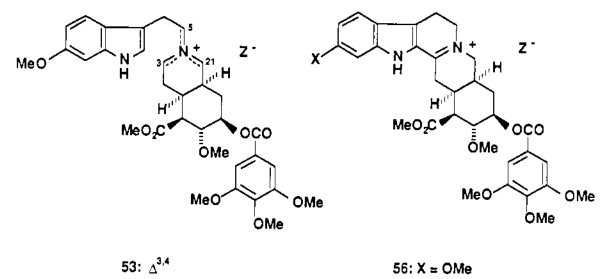
49

1: α-H,
50: β-H,



51: α-H,
52: β-H,

whereas isoreserpine (**50**) suffered rapid and essentially complete oxidation to **56** under these conditions. Consequently, since it seemed likely that a significant amount of **56** would be generated in situ during the mercuric ion induced oxidation and cyclization of **49**, it was necessary to utilize a procedure for the stereoselective reduction of **56** that would deliver the highest proportion of **1** relative to **50**.



53: $\Delta^{3,4}$
54: $\Delta^{4,21}$
55: $\Delta^{4,5}$

56: X = OMe
57: X = H

The stereochemistry of the reduction of different 3,4-dehydro yohimboid and heteroyohimboid derivatives under various conditions has been previously examined, and a brief overview of the area is warranted.[26-30] When these 3,4-dehydro derivatives are

(23) (a) Elderfield, R. C.; Fischer, B. A. *J. Org. Chem.* **1958**, *23*, 949. (b) We wish to thank Professor P. A. Wender (Stanford University) for supplying us with the details of a modification of this procedure.

(24) Sakai, S.; Ogawa, M. *Chem. Pharm. Bull.* **1978**, *26*, 678.

(25) This result may be compared to a previous account wherein it was reported that reserpine was inert to the action of mercuric acetate in aqueous acetic acid at 60 °C.[26] However, the oxidation of **1** by mercuric ion to provide **56** was markedly facilitated by the presence of EDTA·2Na.

(26) Weisenborn, F. L.; Diassi, P. A. *J. Am. Chem. Soc.* **1956**, *78*, 2022.

(27) For a leading discussion of relevant oxidation and reduction studies in the realm of the indole alkaloids, see: Wenkert, E.; Roychaudhuri, D. K. *J. Am. Chem. Soc.* **1958**, *80*, 1613. For other examples see, inter alia, ref 6a–c, 8c, 13f,g, and 18d.

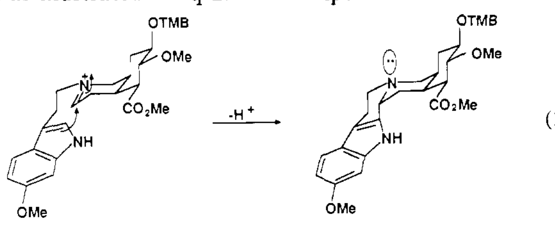
(28) (a) Blaha, L.; Weichet, J.; Zvacek, J.; Smolik, S.; Kakac, B. *Collect. Czech. Chem. Commun.* **1960**, *25*, 237. (b) Weichet, J.; Pelz, K.; Blaha, L. *Ibid.* **1961**, *26*, 1529.

(29) Jilek, J. O.; Ernest, I.; Novak, L.; Rajsner, M.; Protiva, M. *Collect. Czech. Chem. Commun.* **1961**, *26*, 687.

(30) Velluz, L.; Muller, G.; Joly, R.; Nomine, G.; Mathieu, J.; Allais, A.; Warnant, J.; Valls, J.; Bucourt, R.; Jolly, J. *Bull. Soc. Chim. Fr.* **1958**, 673.

subjected to reduction with hydride reagents or by catalytic hydrogenation, the normal or allo products rather than the C(3) epimeric pseudo or epiallo isomers are formed preferentially, and frequently this reaction occurs with a high degree of stereoselectivity[27] as illustrated by the reduction of **56** with sodium borohydride to produce **50** as the sole product.[6a,b,28b] On the other hand, the reduction of these salts with zinc and acid has been reported to lead primarily to the pseudo and epiallo products. For example, in studies that bear closely on the present investigation,[28-30] the reduction of 3,4-dehydrodeserpidine (**57**) with zinc and acid was found to afford mixtures (ca. 2.5–3:1) of deserpidine (**2**) and isodeserpidine,[28] and the reaction of 3,4-dehydroreserpine (**56**) with zinc in aqueous acetone containing perchloric acid was alleged to give reserpine (**1**) as the sole product.[26,30] However, in our hands, this dissolving-metal reduction of **56** invariably afforded mixtures (ca. 1:1.7–2.0, depending upon the source and nature of the zinc metal) of reserpine (**1**) and isoreserpine (**50**).

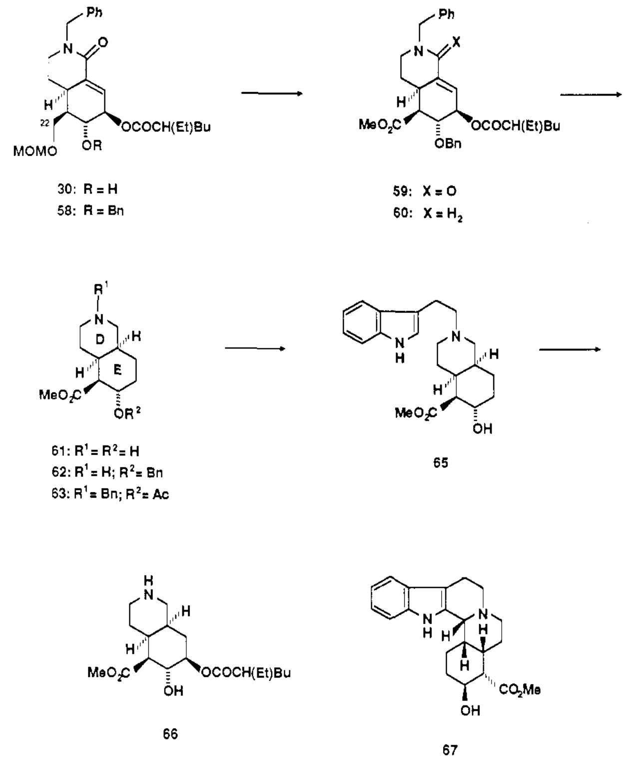
On the basis of our own observations coupled with those in the literature, it seems likely that the minor quantities (8%) of isoreserpine that were isolated from **49** by the oxidation–cyclization sequence detailed above arose exclusively from the nonstereoselective zinc reduction of the dehydroreserpine **56** generated in situ by oxidation of the **1** and **50** initially produced. In this context, reserpine (**1**) was evidently formed as the major, kinetic[31] product by the cyclization of **53** via a process involving the trans-diaxial addition of the indole ring to the double bond of the cyclic iminium salt moiety residing in its more stable half-chair/chair conformation as illustrated in eq 2. The importance of this stereochemical control element in nucleophilic additions to iminium ions has been previously recognized by a number of investigators,[33] and a closely related, kinetic cyclization was masterfully exploited by Stork in a recent synthesis of reserpine.[6e] The alternative mode of ring closure of **53** to produce isoreserpine (**50**) must proceed by a transition state involving an energetically more demanding boat-like or twist boat conformation. While cyclization via the latter topology is clearly less favorable, its occurrence cannot be rigorously excluded at present.



53   1   (2)

Total Synthesis of (±)-α-Yohimbine (4). The close structural relationship between reserpine (**1**) and α-yohimbine (**4**) suggested that one of the early intermediates in the synthesis of reserpine might also be utilized for the construction of the D/E-ring subunit of α-yohimbine. That the E ring of **25** might be elaborated in the requisite fashion by the reductive opening of the epoxide moiety stood as an obvious and intriguing possibility, but several preliminary attempts to effect the reductive scission of the epoxide at C(18) through the agency of various hydride reagents, catalytic hydrogenation, or dissolving-metal reduction led only to the production of complex mixtures. However, during our previous search for conditions necessary to reduce the $\Delta^{19,20}$-double bond in compounds related to and derived from **31**, it had been serendipitously discovered that the hydroxyl function at C(18) of

Scheme VI



the tertiary allylic amine **37** could be efficiently removed by catalytic hydrogenolysis. We than reasoned that the application of such a tactic to the problem at hand should allow facile access to the D/E ring of α-yohimbine.

In the event, O-benzylation of the secondary alcohol group in **30** with neat benzyl bromide in the presence of silver(I) oxide furnished **58** (76%; 93% based upon recovered **30**), which was converted to **59** in 64% overall yield by acid-catalyzed removal of the methoxymethyl protecting group at C(22) followed by oxidation of the resulting primary alcohol with PDC in DMF and esterification of the intermediate acid with diazomethane (Scheme VI). Chemoselective reduction of the lactam moiety of **59** with alane then delivered the unsaturated tertiary amine **60** in 89% yield.

A number of experimental procedures were then explored for effecting the reduction of **60** to the requisite secondary amino alcohol **61**. For example, hydrogenation (1 atm) of **60** over Pearlman's catalyst in glacial acetic acid provided the saturated amino benzyl ether **62** (81%) together with two other products, whereas when this reduction was conducted in the presence of concentrated H_2SO_4 (3–4%), the saturated *N*-benzylamino acetate **63** could be isolated as the sole product (82%). Removal of the *O*-benzyl protecting group from **60** or **62** by hydrogenolysis using Pearlman's catalyst in galcial acetic acid required the presence of an added mineral acid (H_2SO_4 or $HClO_4$) and invariably proceeded with concomitant O-acetylation. Although either **62** or **63** could be subsequently converted into **61** by hydrogenolysis and successive cleavage of the C(17) acetoxy group by acid-catalyzed methanolysis, the transformation of **60** into **61** via **63** proved both more expeditious and more efficient in practice and afforded **61** in 77% overall yield. During the course of these investigations, it was found that the reduction of **60** could be limited under controlled conditions largely to the hydrogenolysis of the allylic ester and the *O*-benzyl group to provide the unsaturated *N*-benzylamino acetate **64** as the major product (69%) together with lesser amounts (<15%) of **63**. This interesting discovery would be later exploited in the design of a potential entry to 19,20-dehydro-α-yohimbine (**5**) (vide infra).

The final stage of the synthesis of **4** commenced with the N-alkylation of **61** with tryptophyl bromide in DMF containing anhydrous K_2CO_3 to provide 2,3-seco-α-yohimbine (**65**) in 87% yield. A more direct, albeit somewhat less efficient, route to **65**

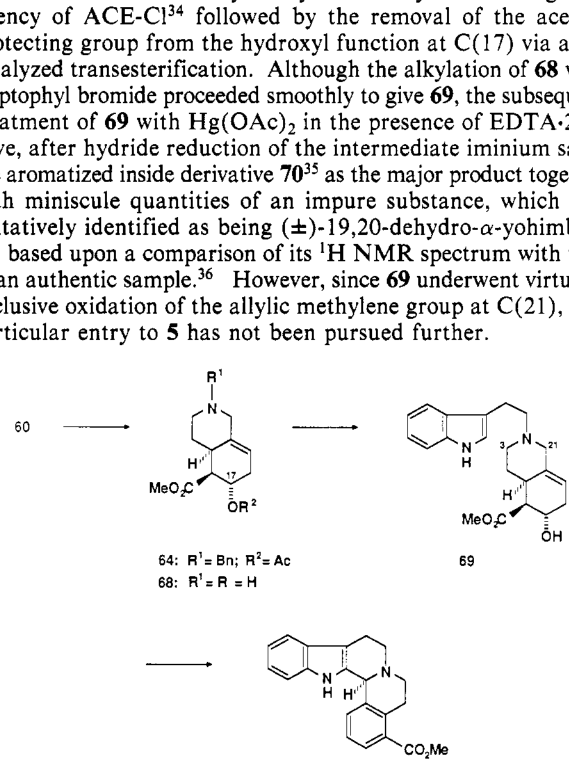
(31) Although reserpine was known to isomerize to the thermodynamically more stable isoreserpine upon refluxing in acetic acid,[32] it was established in independent control experiments that reserpine did not suffer acid-catalyzed isomerization under the acidic conditions of the oxidation–cyclization sequence or during the subsequent reduction with zinc dust in the presence of perchloric acid.

(32) Gaskell, A. J.; Joule, J. A. *Tetrahedron* **1967**, *23*, 4053.

(33) (a) Ziegler, F. E.; Spitzner, E. B. *J. Am. Chem. Soc.* **1973**, *95*, 7146. (b) Heathcock, C. H.; Kleinman, E. F.; Binkley, E. S. *Ibid.* **1982**, *104*, 1054. (c) Overman, L. E.; Lesuisse, D.; Hashimoto, M. *Ibid.* **1983**, *105*, 5373. (d) Stevens, R. V. *Acc. Chem. Res.* **1984**, *17*, 289 and references therein. (e) References 8a,c,f and 18b.

involved the catalytic hydrogenation of **60** in glacial acetic acid containing concentrated H_2SO_4 (0.08%) to afford a mixture (ca. 5:1), which proved difficult to separate on a preparative scale, of the desired amino alcohol **61** contaminated with **66**. Direct alkylation of this mixture with tryptophyl bromide and subsequent purification by HPLC provided **65** in 55% overall yield. After **65** was oxidized with $Hg(OAc)_2$ in the presence of the disodium salt of EDTA in aqueous ethanol at reflux, the mixture of intermediate iminium salts that was obtained was treated with sodium borohydride to deliver (±)-α-yohimbine (**4**) in 31% yield together with an equal amount of the corresponding inside isomer **67**. The synthetic **4** thus produced was spectroscopically identical in all respects except optical rotation with an authentic sample of naturally occurring material.

Attempted Synthesis of (±)-19,20-Dehydro-α-yohimbine (5). Despite a prior concern that the regioselective oxidation and subsequent cyclization of the 2,3-seco derivative **69** to give **5** might be problematic owing to the additional activation of the C(21) methylene group by the double bond at C(19), the prospect that such an undertaking could result in the remarkably facile access to this novel alkaloid encouraged a brief examination of the merits of such an approach. To this end **64** was converted into the amino alcohol **68** in 62% overall yield by N-debenzylation through the agency of ACE-Cl[34] followed by the removal of the acetate protecting group from the hydroxyl function at C(17) via acid-catalyzed transesterification. Although the alkylation of **68** with tryptophyl bromide proceeded smoothly to give **69**, the subsequent treatment of **69** with $Hg(OAc)_2$ in the presence of EDTA·2Na gave, after hydride reduction of the intermediate iminium salts, the aromatized inside derivative **70**[35] as the major product together with miniscule quantities of an impure substance, which was tentatively identified as being (±)-19,20-dehydro-α-yohimbine (**5**) based upon a comparison of its ^{1}H NMR spectrum with that of an authentic sample.[36] However, since **69** underwent virtually exclusive oxidation of the allylic methylene group at C(21), this particular entry to **5** has not been pursued further.



Conclusions

The concise and efficient total syntheses of the pentacyclic indole alkaloids (±)-reserpine (**1**) and (±)-α-yohimbine (**4**) have been completed by a novel strategy that features an intramolecular Diels–Alder cycloaddition as the key step for the facile assemblage of the highly functionalized hydroisoquinolines **48** and **61** that constitute the fully elaborated D/E-ring subunits of reserpine and α-yohimbine, respectively. Completion of the total syntheses of the title alkaloids merely required two successive operations involving N-alkylation followed by an oxidative cyclization of the resulting seco derivatives **49** and **65**. Although the construction of the $\Delta^{19,20}$-dehydro D/E-ring fragment **68** proceeded in a straightforward fashion, attempts to parlay this success into the total synthesis of (±)-19,20-dehydro-α-yohimbine (**5**) were derailed by the inability thus far to functionalize the seco derivative **69** selectively at C(3) via an oxidative process. Alternative approaches to **5** as well as even more concise entries to **1**, **4**, and related indole alkaloids are the subjects of current investigations, and the results of these studies will be communicated in due course.

Experimental Section

***N*-Benzyl-*N*-(5-(methoxymethoxy)pent-3(*Z*)-enyl)-2′-oxopyran-6′-carboxamide (23).** A solution of 2-oxopyran-6-carbonyl chloride[19] (19.1 g, 120 mmol) in CH_2Cl_2 (150 mL) and a solution of *N*-benzyl-*N*-(5-(methoxymethoxy)pent-3(*Z*)-enyl)amine (**22**)[13k] (25.8 g, 110 mmol) and triethylamine (14.1 g, 140 mmol) in CH_2Cl_2 (100 mL) were added simultaneously with stirring to CH_2Cl_2 (600 mL) at −30 °C within 1 h. After the addition the reaction mixture was warmed to 0 °C and stirred for 30 min at 0 °C. The reaction mixture was washed with cold 1 N HCl (250 mL), brine (250 mL), and saturated $NaHCO_3$ (250 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure, and the crude product was purified by flash chromatography on silica gel [hexanes/EtOAc (2:1)] to give pure **23** (34.8 g, 89%) as a yellow oil: IR ($CHCl_3$) ν 1760, 1670, 1625 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.31 (m, 6 H), 6.76 + 6.61 (rotameric d's, *J* = 6.5 Hz, 1 H), 6.5 (m, 1 H), 5.61 (m, 2 H), 4.68 (q, *J* = 8.5 Hz, 2 H), 4.60 (s, 2 H), 4.07 (d, *J* = 6.5 Hz, 2 H), 3.41 (m, 2 H), 3.35 (s, 3 H), 2.51 (m, 2 H); ^{13}C NMR δ 161.2, 158.8, 155.0, 142.4, 135.6, 128.1, 127.2, 116.7, 106.0, 94.8, 61.8, 54.4, 51.8 + 48.2, 46.7 + 45.0, 26.3 + 24.8; mass spectrum, *m/e* 357.1585 ($C_{20}H_{23}NO_5$ requires *m/e* 357.1576), 234, 91 (base), 45.

(4a*R,5*S**)-2-Benzyl-5-((methoxymethoxy)methyl)-3,4,4a,5-tetrahydro-1(2*H*)-isoquinolone (24).** A solution of **23** (28.5 g, 80 mmol) in xylene (2.5 L) was heated at reflux for 16 h. The reaction mixture was then concentrated under reduced pressure, and the residual yellow oil was purified by flash chromatography on silica gel [hexanes/EtOAc (4:1 → 1:2)] to yield **24** (23.3 g, 93%) as a pale yellow oil: IR ($CHCl_3$) ν 1660, 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.25–7.40 (m, 5 H), 7.17 (ddd, *J* = 4.0, 3.0, 2.0 Hz, 1 H), 6.10–6.25 (m, 2 H), 4.81 (d, *J* = 14.9 Hz, 1 H), 4.57 (d, *J* = 14.9 Hz, 1 H), 4.54 (s, 2 H), 3.56 (dd, *J* = 10.4, 6.3 Hz, 1 H), 3.39 (dd, *J* = 10.4, 7.0 Hz, 1 H), 3.25–3.40 (m, 2 H), 3.30 (s, 3 H), 2.95 (m, 1 H), 2.57 (dq, *J* = 6.3, 7.0 Hz, 1 H), 1.85–2.00 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 163.9, 137.1, 133.6, 128.8, 128.3, 128.0, 127.8, 127.1, 124.8, 96.4, 65.4, 55.0, 50.5, 46.2, 36.7, 36.5, 25.4; mass spectrum, *m/e* 313.1685 ($C_{19}H_{23}NO_3$ requires *m/e* 313.1678), 222, 177, 91 (base), 45.

(4a*R,5*S**,6*S**,7*R**)-2-Benzyl-3,4,4a,5,6,7-hexahydro-5-((methoxymethoxy)methyl)-6,7-oxy-1(2*H*)-isoquinolone (25).** To a solution of **24** (34.7 g, 111 mmol) in CH_2Cl_2 (1.0 L) was slowly added a solution of *m*-chloroperbenzoic acid (30.6 g, 133 mmol) in CH_2Cl_2 (500 mL) within 3 h at −10 °C. Subsequently the reaction mixture was stirred at 0 °C for 14 h and then concentrated in vacuo to about half of its volume. The resulting solution was washed with cold saturated $NaHCO_3$ (250 mL), water (250 mL), and brine (250 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by preparative HPLC [hexanes/EtOAc (1:1)] to give **25** (32.2 g, 88%) as a colorless oil: IR ($CHCl_3$) ν 1665, 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.20–7.60 (m, 5 H), 7.25 (dd, *J* = 3.0, 2.0 Hz, 1 H), 4.74 (d, *J* = 14.8 Hz, 1 H), 4.57 (s, 2 H), 4.56 (d, *J* = 14.8 Hz, 1 H), 3.69 (dd, *J* = 4.0, 2.0 Hz, 1 H), 3.58 (dd, *J* = 10.0, 4.0 Hz, 1 H), 3.47 (t, *J* = 4.0 Hz, 1 H), 3.40 (dd, *J* = 10.0, 7.0 Hz, 1 H), 3.34 (s, 3 H), 3.27 (m, 2 H), 2.80 (m, 1 H), 2.70 (ddt, *J* = 7.0, 6.0, 4.0 Hz, 1 H), 1.60–1.80 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 162.2, 136.7, 133.3, 129.5, 128.3, 127.7, 127.1, 96.3, 64.6, 57.2, 55.0, 50.6, 46.6, 45.9, 35.6, 32.9, 24.4; mass spectrum, *m/e* 329.1621 ($C_{19}H_{23}NO_4$ requires *m/e* 329.1627), 284, 238, 91 (base), 45.

(4a*R,5*S**,6*S**,7*S**)-2-Benzyl-7-((2′-ethylhexanoyl)oxy)-3,4,4a,5,6,7-hexahydro-6-hydroxy-5-((methoxymethoxy)methyl)-1-(2*H*)-isoquinolone (30).** A solution of lithium 2-ethylhexanoate (5.71 g, 38 mmol), 2-ethylhexanoic acid (7.20 g, 50 mmol), and **25** (6.90 g, 21 mmol) in DME (50 mL) was heated at reflux for 16 h. The solvent was then removed under reduced pressure at <30 °C (bath temperature), and the residual oil was purified by sequential flash chromatography on silica gel [hexanes/EtOAc (2:1 → 1:2)] and then by preparative HPLC [hexanes/EtOAc (1:1)] to yield **30** (8.92 g, 90%) as a homogeneous pale yellow oil: IR ($CHCl_3$) ν 3260, 1730, 1630 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.30 (m, 5 H), 6.68 (t, *J* = 2.5 Hz, 1 H), 5.38 (dt, *J* = 5.5, 2.5 Hz, 1 H), 4.73 (d, *J* = 14.5 Hz, 1 H), 4.59 (s, 2 H), 4.56 (d, *J* = 14.5 Hz, 1 H), 3.86 (dd, *J* = 8.1, 5.5 Hz, 1 H), 3.69 (m, 2 H), 3.34 (s, 3 H), 3.30 (m, 2 H), 2.86 (m, 2 H), 2.32 (m, 2 H), 2.01 (dq, *J* = 12.0, 3.0 Hz, 1 H), 1.79 (ddt, *J* = 12.0, 11.0, 5.0 Hz, 1 H), 1.40–1.70 (m, 4 H), 1.20–1.40 (m, 4 H), 0.92 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 176.1, 163.6,

(34) Olofson, R. A.; Martz, J. T.; Senet, J.-P.; Piteau, M.; Malfroot, T. *J. Org. Chem.* **1984**, *49*, 2081.

(35) The formation of **70** was previously observed as a side product from the oxidative cyclizations of 2,3-secoyohimbine[18d] and also 2,3-secotetrahydroalstonine.[13e]

(36) We thank Professor I. Ninomiya of Kobe University for an authentic spectrum of 19,20-dehydro-α-yohimbine (**5**).

136.8, 134.4, 129.3, 128.5, 128.0, 127.3, 96.7, 72.9, 69.0, 65.7, 55.3, 50.5, 47.2, 46.6, 40.6, 34.2, 31.5 + 31.2, 29.1, 25.0, 24.9, 22.2, 13.5, 11.4; mass spectrum, *m/e* 473.2764 ($C_{27}H_{39}NO_6$ requires *m/e* 473.2777), 91 (base), 45.

(4a*R,5*S**,6*S**,7*S**)-2-Benzyl-7-((2′-ethylhexanoyl)oxy)-3,4,4a,5,6,7-hexahydro-6-methoxy-5-((methoxymethoxy)methyl)-1-(2*H*)-isoquinolone (31).** To a solution of **30** (6.40 g, 13.5 mmol) in freshly distilled methyl iodide (25 mL) were added Ag_2O (4.07 g, 17.5 mmol) and pulverized $CaSO_4$ (10 g), and the resulting suspension was stirred for 4 days in the dark in a sealed flask at room temperature. The crude reaction mixture was then diluted with Et_2O (50 mL), filtered through Celite, and concentrated under reduced pressure to give **31** (6.45 g, 98%) as a colorless oil, which was homogeneous by TLC: IR ($CHCl_3$) ν 1735, 1630 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.28 (m, 5 H), 6.88 (m, 1 H), 5.44 (m, 1 H), 4.73 (d, J = 14.4 Hz, 1 H), 4.58 (d, J = 14.4 Hz, 1 H), 4.56 (s, 2 H), 3.62 (dd, J = 10.2, 7.0 Hz, 1 H), 3.54 (m, 1 H), 3.49 (s, 3 H), 3.44 (dd, J = 10.2, 7.0 Hz, 1 H), 3.33 (s, 3 H), 3.32 (m, 2 H), 2.86 (m, 1 H), 2.38 (m, 1 H), 2.25 (m, 1 H), 1.84 (m, 1 H), 1.40–1.80 (m, 4 H), 1.20–1.40 (m, 5 H), 0.92 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 175.0, 162.7, 136.8, 133.1, 128.7, 128.4, 127.9, 127.2, 96.5, 77.9, 67.3, 64.5, 57.4, 55.1, 50.7, 47.1, 46.4, 38.9, 32.6, 31.4 + 31.2, 29.4, 29.3, 25.6, 25.2 + 24.9, 22.4, 13.7, 11.6; mass spectrum, *m/e* 487.2923 ($C_{28}H_{41}NO_6$ requires *m/e* 487.2934), 364, 91 (base), 45.

(4a*R,5*S**,6*S**,7*S**,8a*S**)-2-Benzyl-7-((2′-ethylhexanoyl)oxy)-6-methoxy-5-((methoxymethoxy)methyl)-3,4,4a,5,6,7,8,8a-octahydro-1-(2*H*)-isoquinolone (32).** A solution of **31** (3.55 g, 7.28 mmol) in MeOH (75 mL) containing 20% $Pd(OH)_2/C$ (Pearlman's catalyst) (185 mg) was stirred under H_2 (1800 psi) for 24 h. The catalyst was removed by filtration, the solvent was evaporated under reduced pressure, and the resulting mixture of stereoisomers was separated by HPLC [hexanes/EtOAc (1.2:1)] to afford the *cis*-amide **42** (0.21 g, 6%) together with the desired amide **32** (3.21 g, 90%) as colorless oils. For **32**: IR ($CHCl_3$) ν 1730, 1630 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.20–7.40 (m, 5 H), 4.92 (ddd, J = 11.5, 9.6, 5.0 Hz, 1 H), 4.66 + 4.65 (d, J = 14.7 Hz, 1 H), 4.61 (d, J = 9.3 Hz, 1 H), 4.59 (d, J = 9.3 Hz, 1 H), 4.48 + 4.47 (d, J = 14.7 Hz, 1 H), 3.80 (dd, J = 9.6, 3.9 Hz, 1 H), 3.59 (t, J = 9.6 Hz, 1 H), 3.39 (s, 3 H), 3.33 (s, 3 H), 3.19 (comp, 3 H), 2.66 (dt, J = 13.0, 4.5 Hz, 1 H), 2.46 (ddd, J = 13.0, 5.0, 4.5 Hz, 1 H), 2.38 (dq, J = 13.5, 4.5 Hz, 1 H), 2.26 (m, 1 H), 1.99 (m, 1 H), 1.40–1.90 (m, 3 H), 1.20–1.40 (m, 6 H), 0.92 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 175.2, 171.0, 137.0, 128.5, 127.9, 127.3, 96.8, 78.7, 75.2, 65.9, 59.6, 55.3, 49.8, 47.5, 46.7, 43.3, 41.6, 34.2, 31.9 + 31.5, 31.1, 29.5 + 29.3, 25.6 + 25.2, 22.4, 18.6, 13.7, 11.6; mass spectrum, *m/e* 489.3083 ($C_{28}H_{43}NO_6$ requires *m/e* 489.3090), 444, 362, 347, 332, 318, 300, 269, 91 (base), 57, 45.

(4a*R,5*S**,6*S**,7*S**,8a*S**)-2-Benzyl-7-((2′-ethylhexanoyl)oxy)-5-(hydroxymethyl)-6-methoxy-3,4,4a,5,6,7,8,8a-octahydro-1(2*H*)-isoquinolone.** To a solution of **32** (2.74 g, 5.60 mmol) in methanol (25 mL) was added *p*-toluenesulfonic acid (1.60 g, 8.4 mmol), and the resulting solution was stirred at 45 °C for 18 h. The solvent was removed under reduced pressure, and the residue was partitioned between saturated $NaHCO_3$ (25 mL) and CH_2Cl_2 (25 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL), and the combined extracts were washed with brine (1 × 25 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel [hexanes/EtOAc (2:1)] to give the alcohol (2.17 g, 87%) as a colorless oil: IR ($CHCl_3$) ν 3440, 1725, 1630 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.20–7.40 (m, 5 H), 4.93 (ddd, J = 11.0, 9.5, 5.0 Hz, 1 H), 4.69 + 4.68 (d, J = 14.6 Hz, 1 H), 4.42 + 4.41 (d, J = 14.6 Hz, 1 H), 3.90 (dd, J = 11.0, 6.6 Hz, 1 H), 3.67 (m, 1 H), 3.49 (s, 3 H), 3.35 (dd, J = 11.0, 9.5 Hz, 1 H), 3.18 (m, 2 H), 2.68 (dt, J = 13.0, 4.7 Hz, 1 H), 2.48 (dt, J = 13.0, 4.7 Hz, 1 H), 2.20–2.40 (m, 3 H), 1.90 (m, 1 H), 1.50–1.80 (m, 7 H), 1.20–1.40 (m, 4 H), 0.93 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 175.1 170.9, 136.7, 128.4, 127.7, 127.2, 80.2, 75.3, 61.9, 59.6, 49.7, 47.4, 46.6, 45.1, 41.5, 34.4, 31.7 + 31.3, 30.9, 29.2, 25.4 + 25.1, 22.4, 18.6, 13.6, 11.6; mass spectrum, *m/e* 445.2821 ($C_{26}H_{39}NO_5$ requires *m/e* 445.2828), 319, 318 (base), 302, 301, 286, 270, 202, 188, 159, 91.

(4a*R,5*S**,6*S**,7*S**,8a*S**)-2-Benzyl-5-carboxyl-7-((2′-ethylhexanoyl)oxy)-6-methoxy-3,4,4a,5,6,7,8,8a-octahydro-1(2*H*)-isoquinolone.** To a solution of the above alcohol (1.94 g, 4.35 mmol) in DMF (35 mL) was added PDC (8.18 g, 21.75 mmol), and the resulting mixture was stirred for 20 h at room temperature. After addition of cold 0.2 N HCl (50 mL), the reaction mixture was extracted with Et_2O (3 × 50 mL). The combined Et_2O extracts were washed with H_2O (1 × 50 mL) and brine 1 × 50 mL), dried ($MgSO_4$), and then concentrated under reduced pressure. Recrystallization from EtOAc/hexanes yielded the pure acid (1.72 g, 86%) as white crystals: mp 238–239 °C; IR ($CHCl_3$) ν 2800–3300, 1730, 1635 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.15–7.35 (m, 5 H), 4.84 (ddd, J = 11.2, 9.5, 4.6 Hz, 1 H), 4.65 + 4.64 (dd, J = 14.6 Hz, 1 H), 4.45 + 4.44 (d, J = 14.6 Hz, 1 H), 3.62 (t, J = 9.5 Hz, 1 H), 3.47 (s, 3 H), 3.18 (m, 2 H), 2.80 (m, 1 H), 2.71 (dd, J = 11.2, 4.6 Hz, 1 H), 2.50 (m, 2 H), 2.26 (m, 1 H), 1.40–2.00 (m, 7 H), 1.20–1.40 (m, 4 H), 0.93 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 175.1, 173.9, 171.1, 136.3, 128.5, 127.8, 127.4, 77.4, 75.1, 60.5, 50.5, 50.1, 47.3, 46.5 + 46.4, 41.0, 34.7, 31.7 + 31.4, 30.8, 29.3, 25.4 + 25.1, 22.4, 19.8, 13.7, 11.6; mass spectrum, *m/e* 459.2611 ($C_{26}H_{37}NO_6$ requires *m/e* 459.2621), 333, 332 (base), 281, 256, 203, 91, 57, 43, 41. Anal. Calcd for $C_{26}H_{37}NO_6$: C, 67.95; H, 8.11; N, 3.05. Found: C, 67.30; H, 7.97; N, 3.05.

(4a*R,5*S**,6*S**,7*S**,8a*S**)-2-Benzyl-7-((2′-ethylhexanoyl)oxy)-6-methoxy-5-(methoxycarbonyl)-3,4,4a,5,6,7,8,8a-octahydro-1(2*H*)-isoquinolone (45).** To a solution of the acid prepared according to the preceding procedure (2.91 g, 6.33 mmol) in 1:2 $MeOH/Et_2O$ (200 mL) at 0 °C was slowly added a cold solution of diazomethane in Et_2O until the yellow color persisted. After 5 min of stirring at 0 °C, the excess diazomethane was destroyed by the addition of acetic acid, and the resulting solution was stirred over a mixture of Na_2SO_4 and Na_2CO_3, filtered, and then concentrated under reduced pressure. The residual oil, which was homogeneous by TLC, was dried at 25 °C (10^{-2} mmHg) to give **45** (3.00 g, 100%) as a colorless oil: IR ($CHCl_3$) ν 1730, 1635 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.20–7.35 (m, 5 H), 4.85 (ddd, J = 11.2, 9.6, 4.9 Hz, 1 H), 4.60 + 4.59 (d, J = 14.6 Hz, 1 H), 4.50 + 4.49 (d, J = 14.6 Hz, 1 H), 3.71 (s, 3 H), 3.65 (dd, J = 11.2, 9.6 Hz, 1 H), 3.47 (s, 3 H), 3.00–3.30 (m, 2 H), 2.74 (dt, J = 13.0, 4.5 Hz, 1 H), 2.69 (dd, J = 11.2, 4.9 Hz, 1 H), 2.48 (dt, J = 13.0, 4.6 Hz, 1 H), 2.42 (m, 1 H), 2.27 (m, 1 H), 1.89 (ddt, J = 11.4, 6.8, 13.0 Hz, 1 H), 1.65 (dt, J = 11.2, 13.0 Hz, 1 H), 1.63 (m, 1 H), 1.45–1.70 (m, 4 H), 1.20–1.40 (m, 4 H), 0.93 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 174.6, 171.3, 169.5, 136.5, 128.2, 127.5, 127.0, 77.3, 74.8, 60.2, 51.3, 50.5, 49.4, 47.1, 45.9, 41.1, 34.8, 31.5 + 31.2, 30.5, 29.1, 25.2 + 24.9, 22.1, 19.8, 13.5, 11.4; mass spectrum, *m/e* 473.2793 ($C_{27}H_{29}NO_6$ requires 473.2777), 347, 346 (base), 316, 302, 286, 131, 108, 107, 91.

(4a*R,5*S**,6*S**,7*S**,8a*S**)-2-Benzyl-7-((2′-ethylhexanoyl)oxy)-6-methoxy-5-(methoxycarbonyl)perhydroisoquinoline (46).** To a stirred solution of the amide **45** (2.08 g, 4.27 mmol) in THF (40 mL) at −70 °C was slowly added freshly prepared alane (38.5 mL of a ca. 0.2 N solution in THF). The reaction mixture was allowed to warm slowly to −20 °C over a period of 2 h, whereupon the excess alane was destroyed with 5% aqueous THF (20 mL) at −40 °C. The solvent was removed under reduced pressure, and the residue was partitioned between 0.05 N NaOH (10 mL) and CH_2Cl_2 (30 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic extracts were washed with H_2O (25 mL) and brine (25 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel [hexanes/EtOAc (4:1 → 3:1)] to yield **46** (1.575 g, 80%) as a colorless oil: IR ($CHCl_3$) ν 1730 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.20–7.35 (m, 5 H), 4.76 (ddd, J = 11.8, 9.5, 4.6 Hz, 1 H), 3.71 (dd, J = 11.0, 9.5 Hz, 1 H), 3.70 (s, 3 H), 3.49 (s, 3 H), 3.45 (d, J = 14.6 Hz, 1 H), 3.34 (d, J = 14.6 Hz, 1 H), 2.88 (m, 1 H), 2.64 (dd, J = 11.0, 4.5 Hz, 2 H), 2.29 (m, 1 H), 1.20–2.20 (m, 16 H), 0.93 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 175.6, 172.3, 138.7, 128.4, 128.0, 126.8, 77.5, 77.1, 62.7, 60.5, 57.7, 54.0, 52.1, 51.4, 47.7, 37.2, 34.8, 32.0 + 31.7, 29.9, 29.5, 25.7 + 25.4, 23.4, 22.5, 13.8, 11.7; mass spectrum, *m/e* 459.2991 ($C_{27}H_{41}NO_5$ requires *m/e* 459.2985), 458, 444, 428, 400, 368, 316 (base), 300, 91.

(4a*R,5*S**,6*S**,7*S**,8a*R**)-2-Benzyl-7-hydroxy-6-methoxy-5-(methoxycarbonyl)perhydroisoquinoline (47).** A solution of **46** (880 mg, 1.92 mmol) in MeOH (6 mL) containing *p*-toluenesulfonic acid (1.76 g, 4.26 mmol) in a resealable glass tube was heated at 85 °C for 72 h. The solvent was evaporated under reduced pressure, and the residue was partitioned between CH_2Cl_2 (25 mL) and saturated $NaHCO_3$ (25 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL), and the combined extracts were washed with water (25 mL) and brine (25 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification of the crude product by HPLC [hexanes/EtOAc (1:1)] gave **47** (520 mg, 81%) as white crystals: mp 147–148 °C; IR ($CHCl_3$) ν 3440, 1735 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.20–7.40 (m, 5 H), 3.70 (s, 3 H), 3.59 (s, 3 H), 3.55 (m, 2 H), 3.49 (d, J = 13.4 Hz, 1 H), 3.43 (d, J = 13.4 Hz, 1 H), 2.89 (br d, J = 9.3 Hz, 1 H), 2.67 (br d, J = 11.3 Hz, 1 H), 2.56 (dd, J = 10.5, 4.7 Hz, 1 H), 2.37 (br s, 1 H), 2.23 (q, J = 12.5 Hz, 1 H), 2.07 (dd, J = 11.3, 3.2 Hz, 1 H), 2.00 (m, 1 H), 1.75–1.95 (m, 3 H), 1.66 (dt, J = 13.0, 4.0 Hz, 1 H), 1.24 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 172.8, 139.0, 128.6, 128.1, 126.8, 81.6, 75.3, 62.8, 60.9, 58.1, 54.3, 51.8, 51.5, 37.9, 35.4, 32.6, 23.7; mass spectrum, *m/e* 333.1936 ($C_{19}H_{27}NO_4$ requires *m/e* 333.1940), 318, 315, 300, 268, 256, 242, 224, 210, 132, 91 (base). Anal. Calcd for $C_{19}H_{27}NO_4$: C, 68.44; H, 8.16; N, 4.20. Found: C, 68.09; H, 8.14; N, 4.06.

(4a*R,5*S**,6*S**,7*S**,8a*R**)-2-Benzyl-6-methoxy-5-(methoxycarbonyl)-7-((3,4,5-trimethoxybenzoyl)oxy)perhydroisoquinoline.** A mixture of the alcohol **47** (905 mg, 2.72 mmol), 4-(dimethylamino)-

pyridine (75 mg, 0.61 mmol), and 3,4,5-trimethoxybenzoyl chloride (760 mg, 3.30 mmol) in pyridine (25 mL) and CH_2Cl_2 (10 mL) was stirred at room temperature for 24 h. The reaction mixture was then cooled to 0 °C, acidified with cold dilute HCl, and extracted with CH_2Cl_2 (4 × 50 mL). The combined organic extracts were washed with saturated $NaHCO_3$ (1 × 50 mL), water (1 × 50 mL), and brine (1 × 50 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel [EtOAc/CH_2Cl_2 (3:1)] to afford the desired O-acylated tertiary amine (1.30 g, 91%) as white crystals: mp 149–150 °C; IR ($CHCl_3$) ν 1735, 1720 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.36 (s, 2 H), 7.26 (m, 5 H), 5.01 (ddd, *J* = 12.0, 9.5, 5.0 Hz, 1 H), 3.93 (s, 6 H), 3.92 (s, 3 H), 3.87 (dd, *J* = 11.0, 9.5 Hz, 1 H), 3.72 (s, 3 H), 3.53 (s, 3 H), 3.46 (d, *J* = 13.3 Hz, 1 H), 3.34 (d, *J* = 13.3 Hz, 1 H), 2.92 (m, 1 H), 2.72 (dd, *J* = 11.0, 6.0 Hz, 1 H), 2.69 (br d, 10.0 Hz, 1 H), 2.27 (q, *J* = 12.5 Hz, 1 H), 2.12 (dd, *J* = 11.5, 3.0 Hz, 1 H), 1.80–2.10 (m, 5 H), 1.28 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 172.4, 165.4, 153.0, 142.6, 138.6, 128.6, 128.1, 126.9, 125.5, 107.2, 78.3, 78.0, 62.9, 60.8, 60.7, 57.9, 56.3, 54.1, 52.2, 51.5, 37.3, 35.0, 30.1, 23.5; mass spectrum, *m/e* 528 (M^+ + 1), 527.2530 ($C_{29}H_{39}NO_8$ requires *m/e* 527.2519), 513, 497, 451, 437, 316 (base), 315, 300, 284, 224, 212, 195, 134, 91.

(4a*R,5*S**,6*S**,7*S**,8a*R**)-6-Methoxy-5-(methoxycarbonyl)-7-((3,4,5-trimethoxybenzoyl)oxy)perhydroisoquinoline (48).** A solution of the tertiary amine from the preceding procedure (510 mg, 0.97 mmol) in glacial acetic acid (10 mL) containing 20% $Pd(OH)_2/C$ (55 mg) was stirred under H_2 (1 atm) for 24 h. The catalyst was removed by filtration, the solvent was evaporated under reduced pressure, and the residue was made basic at 0 °C with saturated K_2CO_3 (15 mL). The aqueous mixture was then extracted with CH_2Cl_2 (3 × 25 mL), and the combined extracts were washed with brine (1 × 25 mL), dried (Na_2SO_4), and concentrated under reduced pressure to give the amine **48** (390 mg, 93%) as a colorless oil: IR ($CHCl_3$) ν 3330, 1730, 1715 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.26 (s, 2 H), 5.0 (m, 1 H), 3.85 (s, 9 H), 3.78 (dd, *J* = 11.0, 9.5 Hz, 1 H), 3.66 (s, 3 H), 3.45 (s, 3 H), 3.06 (m, 1 H), 2.81 (m, 2 H), 2.64 (dd, *J* = 11.0, 5.0 Hz, 1 H), 2.48 (dt, *J* = 2.0, 12.2 Hz, 1 H), 1.60–2.15 (m, 6 H), 1.22 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 172.1, 165.4, 153.0, 142.5, 125.3, 107.0, 78.1, 78.0, 60.8, 60.7, 56.2, 52.6, 51.5, 50.8, 46.8, 37.4, 34.3, 29.3, 23.7; mass spectrum, *m/e* 437.2043 ($C_{22}H_{31}NO_8$ requires *m/e* 437.2050), 406, 346, 242, 225, 212, 210, 195 (base), 178, 166, 154, 134, 57, 44.

2,3-Secoreserpine (49). To a solution of the amine **48** (376 mg, 0.88 mmol) in DMSO (2 mL) were added 6-methoxytryptophyl bromide (450 mg, 1.76 mmol), *N,N*-diisopropylethylamine (455 mg, 3.52 mmol) and a catalytic amount of NaI (36 mg), and the resulting mixture was stirred vigorously for 72 h at room temperature. The DMSO was removed in vacuo at 40 °C (bath temperature), and the residue was dissolved in CH_2Cl_2 (25 mL), which was then washed with saturated K_2CO_3 (1 × 10 mL) and brine (1 × 10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by HPLC [hexanes/EtOAc (1:1) containing 1% NEt_3] to afford **49** (370 mg, 69%), which was identical in all respects except optical rotation with a sample of authentic **49** obtained by degradation of reserpine,[24] as a light yellow foam: IR ($CHCl_3$) ν 3470, 1730, 1715, 1705, 1630 cm^{-1}; ^1H NMR (C_6D_6, 360 MHz) δ 7.63 (s, 2 H), 7.53 (d, *J* = 8.6 Hz, 1 H), 6.99 (dd, *J* = 8.6, 2.2 Hz, 1 H), 6.96 (br s, 1 H), 6.63 (d, *J* = 2.2 Hz, 1 H), 6.55 (m, 1 H), 5.43 (ddd, *J* = 12.5, 9.5, 5.2 Hz, 1 H), 4.11 (dd, *J* = 10.5, 9.5 Hz, 1 H), 3.81 (s, 3 H), 3.72 (s, 3 H), 3.52 (s, 3 H), 3.39 (s, 3 H), 3.38 (s, 6 H), 2.75–2.90 (m, 4 H), 2.50 (m, 3 H), 2.41 (q, *J* = 12.5 Hz, 1 H), 2.00 (dt, *J* = 12.5, 4.5 Hz, 1 H), 1.70–1.90 (m, 3 H), 1.62 (m, 1 H), 1.38 (m, 1 H), 1.24 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 172.4, 165.5, 156.5, 153.0, 142.5, 137.0, 125.5, 122.0, 120.1, 119.3, 114.6, 109.1, 107.1, 94.8, 78.2, 78.0, 60.9, 60.7, 59.3, 58.2, 56.3, 55.7, 54.4, 52.2, 51.6, 37.3, 34.8, 30.3, 23.6, 23.1; mass spectrum, *m/e* 610.2900 ($C_{33}H_{42}N_2O_9$ requires *m/e* 610.2890), 609, 608, 607, 579, 450 (base), 238, 225, 212, 197, 195, 173, 160, 58.

Oxidative Cyclization of 2,3-Secoreserpine (49). To a solution of 2,3-secoreserpine (**49**) (240 mg, 0.39 mmol) dissolved in degassed 5% acetic acid (20 mL) was added $Hg(OAc)_2$ (1.25 g, 3.9 mmol), and the resulting solution was stirred at 85–90 °C (oil bath temperature) for 1.25 h. A stream of H_2S gas was then passed through the mixture for 1 h during which time the mixture was allowed to cool to room temperature. A few drops of 70% $HClO_4$ were added, and the mixture was filtered through a Celite pad, which was washed thoroughly with acetone/THF (1:1). The filtrate was concentrated below 25 °C (bath temperature) under reduced pressure to approximately 20 mL, whereupon 70% aqueous $HClO_4$ (2 mL), THF (20 mL), and acetone (20 mL) were added. The resulting mixture was then treated with Zn dust (450 mg) at reflux for 15 min and filtered, and the organic solvents were removed under reduced pressure. The resulting aqueous solution was made basic at 0–5 °C with cold, concentrated NH_4OH and extracted with $CHCl_3$ (4 × 20 mL), and the combined extracts were washed with brine (1 × 25 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude mixture of products was separated by HPLC [hexanes/EtOAc (1:1) containing 1% NEt_3] to afford **50** (19 mg, 8%), starting **49** (24 mg, 10%), **52** (10 mg, 4%), **51** (43 mg, 18%), and **1** (84 mg, 35%).

For (±)-reserpine (1): mp (vac) 260.5–262.0 °C (dec) (from acetone/Et_2O), [lit.[6a] mp (vac) 260–262 °C (dec)]; IR ($CHCl_3$) ν 3480, 1720, 1660 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.56 (br s, 1 H), 7.33 (d, *J* = 8.6 Hz, 1 H), 7.32 (s, 2 H), 6.84 (d, *J* = 2.0 Hz, 1 H), 6.78 (dd, *J* = 8.6, 2.0 Hz, 1 H), 5.06 (ddd, *J* = 11.9, 9.5, 4.5 Hz, 1 H), 4.47 (br s, 1 H), 3.92 (s, 3 H), 3.91 (s, 6 H), 3.91 (dd, *J* = 11.5, 9.5 Hz, 1 H), 3.84 (s, 3 H), 3.83 (s, 3 H), 3.51 (s, 3 H), 3.18 (m, 2 H), 3.05 (dd, *J* = 11.5, 3.4 Hz, 1 H), 2.95 (m, 1 H), 2.70 (dd, *J* = 11.5, 4.5 Hz, 1 H), 2.49 (br d, *J* = 15.0 Hz, 1 H), 2.46 (br d, *J* = 11.5 Hz, 1 H), 2.35 (dt, *J* = 11.9, 12.5 Hz, 1 H), 2.31 (m, 1 H), 2.05 (m, 1 H), 1.99 (dt, *J* = 12.5, 4.5 Hz, 1 H), 1.90 (br d, *J* = 12.5 Hz, 1 H), 1.81 (br d, *J* = 13.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 172.8, 165.4, 156.4, 153.0, 142.5, 136.4, 130.5, 125.5, 122.3, 118.6, 109.1, 108.3, 107.0, 99.3, 78.1, 77.9, 60.9, 60.8, 56.3, 55.8, 53.8, 51.8, 51.3, 49.1, 34.1, 32.4, 29.8, 24.4, 16.9; mass spectrum, *m/e* 608.2718 ($C_{33}H_{40}N_2O_9$ requires *m/e* 608.2734), 607, 396, 395, 251, 212, 195, 57, 55, 44, 43.

For (±)-3-isoreserpine (50): mp 148–150 °C (from MeOH) [lit.[6b] mp 146–149 °C]; IR ($CHCl_3$) ν 3450, 2800, 2745, 1725, 1710, 1635 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.12 (br s, 1 H), 7.32 (d, *J* = 8.5 Hz, 1 H), 7.28 (s, 2 H), 6.84 (d, *J* = 2.1 Hz, 1 H), 6.76 (dd, *J* = 8.5, 2.1 Hz, 1 H), 5.09 (ddd, *J* = 12.0, 9.4, 5.0 Hz, 1 H), 3.89 (s, 3 H), 3.88 (s, 6 H), 3.84 (s, 3 H), 3.81 (s, 3 H), 3.79 (dd, *J* = 11.4, 9.4 Hz, 1 H), 3.46 (s, 3 H), 3.16 (br d, *J* = 10.2 Hz, 1 H), 2.75–3.00 (m, 3 H), 2.80 (dd, *J* = 11.4, 4.8 Hz, 1 H), 2.50–2.70 (m, 3 H), 2.32 (dt, *J* = 11.4, 12.5 Hz, 1 H), 2.31 (m, 1 H), 2.08 (m, 1 H), 1.99 (ddd, *J* = 12.5, 5.0, 4.0 Hz, 1 H), 1.87 (dt, *J* = 10.2, 12.5 Hz, 1 H), 1.75 (dt, *J* = 12.5, 4.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 172.3, 165.3, 156.0, 152.8, 142.2, 136.8, 133.1, 125.2, 121.7, 118.5, 108.7, 108.0, 106.8, 95.0, 78.0, 77.7, 60.7, 59.8, 59.6, 56.1, 55.6, 53.0, 52.0, 51.7, 37.2, 34.8, 30.4, 27.8, 21.8; mass spectrum, *m/e* 608.2744 ($C_{33}H_{40}N_2O_9$ requires *m/e* 608.2734), 607, 606, 605, 395 (base), 360, 359, 358, 321, 265, 251, 212, 197, 195, 141.

For (±)-inside reserpine (51): IR ($CHCl_3$) ν 3460, 3320, 1710–1740, 1630 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 8.11 (br s, 1 H), 7.35 (d, *J* = 8.5 Hz, 1 H), 7.33 (s, 2 H), 6.87 (d, *J* = 2.1 Hz, 1 H), 6.78 (dd, *J* = 8.5, 2.1 Hz, 1 H), 5.19 (ddd, *J* = 10.5, 9.5, 4.2 Hz, 1 H), 4.18 (br s, 1 H), 3.93 (s, 3 H), 3.92 (dd, *J* = 10.5, 9.5 Hz, 1 H), 3.91 (s, 6 H), 3.83 (s, 3 H), 3.63 (s, 3 H), 3.53 (s, 3 H), 3.26 (dd, *J* = 13.2, 5.5 Hz, 1 H), 3.12 (dt, *J* = 4.5, 11.5 Hz, 1 H), 2.96 (m, 1 H), 2.65–2.80 (m, 2 H), 2.72 (dd, *J* = 10.5, 9.4 Hz, 1 H), 2.49 (ddd, *J* = 10.5, 4.5, 2.0 Hz, 1 H), 2.35–2.50 (m, 2 H), 2.10–2.20 (m, 1 H), 1.85–2.05 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 172.2, 165.6, 156.1, 153.0, 142.4, 136.4, 130.7, 125.2, 122.0, 118.4, 108.9, 107.5, 106.9, 95.3, 78.1, 77.7, 60.8, 58.8, 56.2, 55.7, 51.9, 51.6, 51.2, 44.9, 35.9, 33.1, 30.6, 22.4, 16.7; mass spectrum, *m/e* 608.2749 ($C_{33}H_{40}N_2O_9$ requires *m/e* 608.2734), 607, 410, 396, 382, 378, 366, 226 (base), 216, 214, 200, 197, 195, 173, 155, 58.

For (±)-inside 3-isoreserpine (52): IR ($CHCl_3$) ν 3450, 2820, 2740, 1700–1740, 1630 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 8.29 (br s, 1 H), 7.29 (d, *J* = 8.6 Hz, 1 H), 7.22 (s, 2 H), 6.85 (d, *J* = 2.0 Hz, 1 H), 6.72 (dd, *J* = 8.6, 2.0 Hz, 1 H), 5.12 (dd, *J* = 11.0, 9.5 Hz, 1 H), 3.90 (m, 1 H), 3.87 (s, 3 H), 3.84 (s, 6 H), 3.79 (s, 3 H), 3.76 (s, 3 H), 3.47 (s, 3 H), 3.39 (br s, 1 H), 3.05 (br d, *J* = 10.0 Hz, 1 H), 2.99 (dd, *J* = 11.0, 5.0 Hz, 1 H), 2.83 (dd, *J* = 11.0, 4.4 Hz, 1 H), 2.8–2.95 (m, 1 H), 2.61 (br d, *J* = 13.0 Hz, 1 H), 2.50 (dt, *J* = 11.0, 4.0 Hz, 1 H), 2.25–2.45 (m, 3 H), 1.95–2.10 (m, 1 H), 1.97 (m, 1 H), 1.64 (dt, *J* = 13.0, 3.0 Hz, 1 H), 1.41 (br d, *J* = 11.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 172.2, 165.4, 156.1, 152.9, 142.4, 137.2, 131.4, 125.2, 121.6, 118.4, 109.5, 108.9, 107.0, 95.4, 78.4, 77.7, 62.9, 60.8, 58.8, 56.2, 55.8, 53.2, 52.2, 51.7, 45.8, 38.1, 37.6, 26.2, 23.5, 21.6; mass spectrum, *m/e* 609 (M^+ + 1), 608.2744 (base, $C_{33}H_{40}N_2O_9$ requires *m/e* 608.2734), 607, 397, 396, 395, 363, 227, 214, 212, 200, 199, 195, 186.

(4a*R,5*S**,6*S**,7*S**)-2-Benzyl-6-(benzyloxy)-7-((2′-ethylhexanoyl)oxy)-3,4,4a,5,6,7-hexahydro-5-((methoxymethoxy)methyl)-1(2*H*)-isoquinolone (58).** A solution of **30** (4.02 g, 8.5 mmol) in benzyl bromide (20 mL) containing Ag_2O (2.66 g, 11.5 mmol) and pulverized $CaSO_4$ (4.5 g) was stirred for 3.5 days at 50 °C. The reaction mixture was filtered through Celite, the precipitate was washed well with Et_2O, and then the filtrate was concentrated under reduced pressure (ca. 10^{-2} mmHg) to give crude **58**, which was purified by preparative HPLC [hexanes/EtOAc (5:1)] to afford some unreacted alcohol **30** (0.73 g, 15%) and **58** (3.66 g, 76%; 93% based on recovered starting material) as a light yellow oil: IR ($CHCl_3$) ν 1725, 1670, 1615 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.20–7.40 (m, 10 H), 6.93 (m, 1 H), 5.53 (m, 1 H), 4.82 (d, *J* = 11.8 Hz, 1 H), 4.78 (d, *J* = 15.0 Hz, 1 H), 4.65 (d, *J* = 11.8 Hz, 1 H), 4.54 (d, *J* = 15.0 Hz, 1 H), 4.51 (s, 2 H), 3.77 (m, 1 H), 3.59 (dd, *J* = 10.2, 7.0 Hz, 1 H), 3.42 (dd, *J* = 10.2, 7.0 Hz, 1 H), 3.28 (s, 3 H), 3.25–3.40 (m, 2 H), 2.96 (m, 1 H), 2.28 (m, 1 H), 2.25 (m, 1 H), 1.72 (dq, J = 5.0, 12.0 Hz, 1 H), 1.40–1.70 (m, 5 H), 1.15–1.35 (m, 4 H), 0.92 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 175.2, 162.8, 138.0, 136.8, 133.2, 128.8, 128.5, 128.2, 128.0, 127.8, 127.5, 127.3, 96.5, 75.7, 71.4, 67.5, 64.5, 55.2, 50.8, 47.2, 46.4, 39.8, 32.5, 31.5 + 31.3, 29.4, 25.7, 25.3, 25.0, 22.5, 13.8, 11.7; mass spectrum m/e 563.3235 ($C_{34}H_{45}NO_6$ requires m/e 563.3247), 518, 472, 419 (base), 355, 346, 314, 313, 258, 254, 238, 229, 105, 91.

(4a*R,5*S**,6*S**,7*S**)-2-Benzyl-6-(benzyloxy)-7-((2′-ethylhexanoyl)oxy)-3,4,4a,5,6,7-hexahydro-5-(hydroxymethyl)-1(2*H*)-isoquinolone.** A solution of **58** (4.90 g, 8.7 mmol) in MeOH (60 mL) containing p-toluenesulfonic acid (2.48 g, 13.05 mmol) was stirred for 30 h at 40 °C. The solvent was removed under reduced pressure, and the residue was partitioned between K_2CO_3 (50 mL) and CH_2Cl_2 (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL), and the combined extracts were dried (Na_2SO_4) and concentrated in vacuo to give a colorless oil, which was purified by flash chromatography on silica gel [hexanes/EtOAc (3:1 → 1:1)] to yield the primary alcohol (3.90 g, 86%): IR ($CHCl_3$) ν 3410, 1720, 1665, 1615 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.20–7.40 (m, 10 H), 6.89 (m, 1 H), 5.56 (m, 1 H), 4.81 (d, J = 11.8 Hz, 1 H), 4.78 + 4.74 (d, J = 14.5 Hz, 1 H), 4.64 (d, J = 11.8 Hz, 1 H), 5.56 + 5.52 (d, J = 14.5 Hz, 1 H), 3.78 (m, 1 H), 3.6–3.75 (m, 2 H), 3.25–3.40 (m, 2 H), 2.92 (m, 1 H), 2.20–2.35 (m, 2 H), 1.40–1.90 (m, 7 H), 1.20–1.35 (m, 4 H), 0.92 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 174.7, 162.7, 137.6, 136.3, 133.6, 128.1, 127.8, 127.5, 127.2, 127.0, 126.3, 75.4, 71.3, 68.0 + 67.9, 59.0, 50.4, 46.8, 46.3, 41.4, 32.6, 31.1 + 30.9, 29.0, 24.9 + 24.7, 22.1, 13.4, 11.3; mass spectrum, m/e 519.2997 ($C_{32}H_{41}NO_5$ requires m/e 519.2984), 428, 375 (base), 302, 284, 269, 268, 254, 241, 138, 229, 91.

(4a*R,5*S**,6*S**,7*S**)-2-Benzyl-6-(benzyloxy)-5-carboxy-7-((2′-ethylhexanoyl)oxy)-3,4,4a,5,6,7-hexahydro-1(2*H*)-isoquinolone.** To a solution of the primary alcohol obtained from the preceding experiment (2.65 g, 5.1 mmol) in DMF (40 mL) was added PDC (9.56 g, 25.5 mmol), and the resulting mixture was stirred for 20 h at 25 °C. The reaction mixture was then poured into ice water (50 mL) containing 5 mL of concentrated HCl, and the mixture was extracted with CH_2Cl_2 (4 × 50 mL). The combined extracts were washed with brine (3 × 50 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude oil thus obtained was filtered through a plug of silica gel with EtOAc/CH_2Cl_2 (3:1) and the combined filtrates were evaporated in vacuo. The crude acid was recrystallized from EtOAc/hexanes to give the acid (2.29 g, 84%) as white crystals: mp 187–189 °C; IR ($CHCl_3$) ν 1720, 1675, 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.20–7.35 (m, 10 H), 6.78 (m, 1 H), 5.55 (m, 1 H), 4.81 (d, J = 11.0 Hz, 1 H), 4.71 (d, J = 14.8 Hz, 1 H), 4.70 (d, J = 11.0 Hz, 1 H), 4.61 (d, J = 14.8 Hz, 1 H), 4.03 (m, 1 H), 3.20–3.40 (m, 2 H), 3.08 (t, J = 6.0 Hz, 1 H), 2.96 (m, 1 H), 2.10–2.25 (m, 2 H), 1.73 (m, 1 H), 1.35–1.65 (m, 4 H), 1.15–1.30 (m, 4 H), 0.92 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 175.1, 173.8, 163.0, 137.5, 136.3, 133.2, 129.3, 128.4, 128.1, 127.8, 127.3, 75.9, 72.7, 69.6 + 6.5, 50.7, 47.0, 46.0, 46.0, 32.5, 31.2 + 31.0, 29.5, 25.3, 25.0 + 24.7, 22.3, 13.6, 11.5; mass spectrum, m/e 533.2768 ($C_{32}H_{39}NO_6$ requires m/e 533.2777), 442, 389, 283, 254, 118, 91 (base).

(4a*R,5*S**,6*S**,7*S**)-2-Benzyl-6-(benzyloxy)-7-((2′-ethylhexanoyl)oxy)-3,4,4,5,6,7-hexahydro-5-(methoxycarbonyl)-1(2*H*)-isoquinolone (59).** To a suspension of the purified acid from the preceding experiment (2.67 g, 5 mmol) in 1:2 MeOH/Et_2O (50 mL) was slowly added a solution of diazomethane in Et_2O at 0 °C until the yellow color persisted. After 15 min of stirring at 0 °C, the excess diazomethane was destroyed with acetic acid, and the solvents were removed in vacuo. The remaining yellow oil, which crystallized on standing, was recrystallized from EtOAc/hexanes to yield **59** (2.62 g, 96%) as white crystals: mp 90–92 °C; IR ($CHCl_3$) ν 1730, 1670, 1625 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.20–7.40 (m, 10 H), 6.79 + 6.78 (t, J = 2.5 Hz,1 H), 5.56 + 5.55 (dd, J = 4.0, 2.5 Hz, 1 H), 4.81 (d, J = 11.4 Hz, 1 H), 4.75 + 4.71 (d, J = 14.6 Hz, 1 H), 4.69 (d, J = 11.4 Hz, 1 H), 4.62 + 4.58 (d, J = 14.6 Hz, 1 H), 4.01 (dd, J = 6.0, 4.0 Hz, 1 H), 3.64 (s, 3 H), 3.25–3.40 (m, 2 H), 3.10 (t, J = 6.0 Hz, 1 H), 2.94 (m, 1 H), 2.24 (m, 1 H), 2.13 (m, 1 H), 1.40–1.75 (m, 5 H), 1.20–1.35 (m, 4 H), 0.90 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 174.6, 169.7, 162.3, 137.3, 136.4, 133.2, 128.3, 128.0, 127.8, 127.5, 127.2, 127.0, 126.9, 75.8, 72.3, 69.3, 51.0, 50.1, 46.6, 45.7, 32.4, 31.0 + 30.8, 29.1 + 28.9, 25.1 + 24.9, 24.5, 22.0, 13.3, 11.2; mass spectrum, m/e 547.2952 ($C_{33}H_{41}NO_6$ requires m/e 547.2934), 456, 403, 297, 295, 172, 91 (base).

(4a*R,5*S**,6*S**,7*S**)-2-Benzyl-6-(benzyloxy)-7-((2′-ethylhexanoyl)oxy)-5-(methoxycarbonyl)-1,2,3,4,4a,5,6,7-octahydroisoquinoline (60).** To a solution of **59** (2.19 g, 4 mmol) in THF (60 mL) at −78 °C was slowly added freshly prepared alane (25.6 mL of a 0.25 M solution in THF, 6.4 mmol), and the reaction mixture was allowed to warm to −20 °C over 1.5 h. After 0.5 h of stirring at −20 to −30 °C, the reaction was quenched with 5% aqueous THF (20 mL) at −50 °C. The solvents were then removed under reduced pressure, and the residue was partitioned between 0.01 N NaOH (25 mL) and CH_2Cl_2 (25 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL), and the combined extracts were washed with brine (25 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel [hexanes/EtOAc (3:1 → 1:1)] to give pure **60** (1.91 g, 89%) as a colorless oil: IR ($CHCl_3$) ν 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.20–7.35 (m, 10 H), 5.41 (d, J = 8.0 Hz, 1 H), 5.28 (br s, 1 H), 4.77 (d, J = 10.7 Hz, 1 H), 4.73 (d, J = 10.7 Hz, 1 H), 4.04 (dd, J = 11.7, 8.0 Hz, 1 H), 3.67 (s, 3 H), 3.54 (s, 2 H), 3.20 (d, J = 11.4 Hz, 1 H), 3.09 (dd, J = 11.7, 8.0 Hz, 1 H), 3.01 (dt, J = 11.8, 3.0 Hz, 1 H), 2.58 (br d, J = 11.4 Hz, 1 H), 2.48 (ddd, J = 12.5, 7.2, 5.0 Hz, 1 H), 2.30 (m, 1 H), 2.17 (dt, J = 2.0, 11.8 Hz, 1 H), 1.72 (ddt, J = 4.0, 3.0, 12.5 Hz, 1 H), 1.40–1.80 (m, 5 H), 1.20–1.35 (m, 4 H), 0.91 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 175.6, 171.5, 138.3, 137.9, 137.4, 128.8, 127.9, 127.2, 126.9, 119.7, 75.1, 74.5, 61.9, 59.0, 53.1, 51.2, 48.3, 47.2, 38.8, 31.5 + 31.2, 29.3, 25.3 + 24.8, 22.4, 13.7, 11.7; mass spectrum, m/e 533.3126 ($C_{33}H_{43}NO_5$ requires m/e 533.3141), 444, 423, 389, 300, 284, 283 (base), 282, 281, 280, 190, 108.

(4a*R,5*S**,6*S**,8a*R**)-6-Acetoxy-2-benzyl-5-(methoxycarbonyl)perhydroisoquinoline (63).** A solution of **60** (96 mg, 0.18 mmol) in glacial acetic acid (4 mL) containing concentrated H_2SO_4 (0.16 mL) and 20% $Pd(OH)_2$/C (10 mg) was stirred under H_2 (1.05 atm) at 25 °C for 24 h. The catalyst was removed by filtration through Celite, and the filtrate was concentrated under reduced pressure. The remaining oil was partitioned between cold saturated K_2CO_3 (5 mL) and $CHCl_3$ (10 mL), and the aqueous layer was extracted with $CHCl_3$ (4 × 10 mL). The combined extracts were washed with water (5 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by HPLC [hexanes/EtOAc (4:1) containing 0.5% NEt_3] to afford **63** (51 mg, 82%) as a colorless oil: IR ($CHCl_3$) ν 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.20–7.40 (m, 5 H), 5.18 (dt, J = 4.5, 11.2 Hz, 1 H), 3.66 (s, 3 H), 3.52 (d, J = 13.4 Hz, 1 H), 3.38 (d, J = 13.4 Hz, 1 H), 2.91 (br d, J = 9.1 Hz, 1 H), 2.71 (br d, J = 11.2 Hz, 1 H), 2.69 (dd, J = 11.2, 5.0 Hz, 1 H), 2.10–2.30 (m, 3 H), 1.98 (s, 3 H), 1.75–1.95 (m, 2 H), 1.69 (m, 1 H), 1.43 (m, 1 H), 1.15–1.30 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 172.3, 169.9, 138.3, 128.7, 128.1, 126.9, 69.2, 62.7, 58.2, 54.1, 51.7, 51.4, 38.0, 36.5, 30.9, 23.9, 23.2, 21.0; mass spectrum, m/e 345.1948 ($C_{20}H_{27}NO_4$ requires m/e 345.1934), 344, 302, 286, 254, 226, 194, 134, 91 (base), 43.

(4a*R,5*S**,6*S**,8a*R**)-6-Hydroxy-5-(methoxycarbonyl)perhydroisoquinoline (61).** A solution of **63** (125 mg, 0.36 mmol) in glacial acetic acid (4 mL) containing 20% $Pd(OH)_2$/C (15 mg) was stirred under H_2 (1.05 atm) for 18 h. The catalyst was removed by filtration through Celite, and the filtrate was concentrated under reduced pressure. The residue was dissolved in 1 N methanolic HCl (5 mL) and heated at reflux for 1 h. The solvent was removed in vacuo, saturated Na_2CO_3 (5 mL) was added, and the solution was evaporated to dryness under reduced pressure. The remaining solid was triturated with MeOH/CH_2Cl_2 (1:1) (4 × 5 mL), and the combined organics were concentrated under reduced pressure. Recrystallization of the crude product from EtOAc/hexanes gave **61** (73 mg, 95%) as white crystals: mp 130–132 °C; IR ($CHCl_3$) ν 3540, 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.03 (ddd, J = 11.0, 10.4, 4.5 Hz, 1 H), 3.73 (s, 3 H), 3.07 (br d, J = 12.0 Hz, 1 H), 2.85 (m, 2 H), 2.52 (br t, J = 12.0 Hz, 1 H), 2.45 (dd, J = 10.4, 4.8 Hz, 1 H), 2.28 (dq, J = 13.0, 4.5 Hz, 1 H), 2.09 (ddt, J = 12.6, 4.8, 3.5 Hz, 1 H), 2.05 (br s, 2 H), 1.93 (dq, J = 3.7, 13.0 Hz, 1 H), 1.66 (m, 1 H), 1.53 (ddt, J = 4.0, 12.6, 13.0 Hz, 1 H), 1.46 (m, 1 H), 1.37 (ddt, J = 11.0, 4.5, 13.0 Hz, 1 H), 1.13 (br d, J = 13.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 174.5, 65.9, 55.2, 51.6, 51.5, 47.1, 38.0, 36.2, 33.1, 24.0, 23.3; mass spectrum, m/e 213.1373 ($C_{11}H_{19}NO_3$ requires m/e 213.1365), 196, 195, 182, 154 (base), 136, 96, 84, 57, 43.

2,3-Seco-α-yohimbine (65). Method A. To a solution of **61** (25 mg, 0.12 mmol) in DMF (3 mL) was added tryptophyl bromide (81 mg, 0.36 mmol) and anhydrous K_2CO_3 (50 mg, 0.36 mmol), and the resulting mixture was stirred at 55–60 °C for 5 h. The solvent was removed under reduced pressure, and the residue was partitioned between Na_2CO_3 (3 mL) and $CHCl_3$ (3 mL). The aqueous layer was extracted with $CHCl_3$ (3 × 3 mL), and the combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Purification of the crude product by HPLC [hexanes/EtOAc (1:3) containing 1% NEt_3] afforded **65** (37 mg, 87%): IR ($CHCl_3$) ν 3460, 3400, 2800, 2760, 1725, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 8.11 (br s, 1 H), 7.59 (d, J = 7.5 Hz, 1 H), 7.33 (d, J = 7.5 Hz, 1 H), 7.17 (t, J = 7.5 Hz, 1 H), 7.10 (t, J = 7.5 Hz, 1 H), 7.01 (br s, 1 H), 4.04 (ddd, J = 11.0, 10.5, 4.0 Hz, 1 H), 3.73 (s, 3 H), 2.97 (br d, J = 12.0 Hz, 1 H), 2.80–2.95 (m, 4 H), 2.52–2.70 (m, 2 H), 2.48 (dd, J = 10.5, 5.0 Hz, 1 H), 1.98–2.22 (m, 4 H), 1.92 (br t, J = 12.0 Hz, 1 H), 1.65–1.80 (m, 2 H), 1.51 (m, 1 H), 1.35 (dq, J = 3.0, 12.0 Hz, 1 H), 1.20 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 174.6, 136.2, 127.5, 121.7, 121.6, 119.0, 118.7, 111.4, 111.0, 66.0, 59.3, 58.7, 54.6, 54.5, 51.6, 37.8, 36.6, 33.2, 24.5, 23.3, 22.7; mass spectrum, *m/e* 356.2092 ($C_{21}H_{28}N_2O_3$ requires *m/e* 356.2100), 227, 226 (base), 208, 194, 166, 144, 130, 58, 44.

(±)-α-Yohimbine (4). To a solution of **65** (57 mg, 0.16 mmol) in EtOH (2.5 mL) was added $Hg(OAc)_2$/EDTA·2Na (1:1) (4.8 mL of a 0.1 M solution in H_2O, 0.48 mmol), and the resulting solution was heated at reflux for 3 h, whereupon the reaction mixture was cooled to 0–5 °C and 25% $HClO_4$ (5 mL) added. The aqueous mixture was extracted with $CHCl_3$ (4 × 10 mL), and the combined extracts were washed with brine (10 mL) and concentrated under reduced pressure. The residue of iminium salts was dissolved in MeOH/H_2O (9:1) (5 mL), the pH was adjusted to 6 with 5% $NaHCO_3$, $NaBH_4$ (50 mg) was added, and the reaction mixture was stirred for 1 h at 25 °C. The solvents were removed under reduced pressure, and the residue was partitioned between cold 10% NH_4OH (3 mL) and $CHCl_3$ (3 mL). The aqueous layer was extracted with $CHCl_3$ (3 × 5 mL), and the combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give a mixture of products, which was separated by HPLC [hexanes/EtOAc (1:2) containing 1% NEt_3] to afford **4** (17.5 mg, 31%) as a light yellow foam and **67** (17.5 mg, 31%) as a pale yellow solid.

For (±)-α-yohimbine (4): as white crystals from EtOAc/hexanes, mp 233–235 °C (dec); hydrochloride (from MeOH) mp 262–264 °C (dec); IR ($CHCl_3$) ν 3580, 3460, 3380, 2800, 2755, 1725 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.77 (br s, 1 H), 7.45 (d, *J* = 7.8 Hz, 1 H), 7.27 (br d, *J* = 7.8 Hz, 1 H), 7.12 (dt, *J* = 1.1, 7.8 Hz, 1 H), 7.07 (dt, *J* = 1.1, 7.8 Hz, 1 H), 3.99 (dt, *J* = 4.4, 11.0 Hz, 1 H), 3.83 (s, 3 H), 3.13 (dd, *J* = 11.2, 2.1 Hz, 1 H), 2.90–3.00 (m, 2 H), 2.83 (dd, *J* = 11.4, 1.9 Hz, 1 H), 2.77 (br s, 1 H), 2.67 (m, 1 H), 2.58 (dd, *J* = 11.4, 3.0 Hz, 1 H), 2.56 (dd, *J* = 11.0, 4.5 Hz, 1 H), 2.52 (m, 1 H), 2.42 (ddt, *J* = 12.5, 3.5, 4.5 Hz, 1 H), 2.09 (dq, *J* = 13.0, 3.5 Hz, 1 H), 2.04 (dq, *J* = 13.0, 3.5 Hz, 1 H), 1.81 (m, 1 H), 1.70 (dt, *J* = 11.2, 12.5 Hz, 1 H), 1.61 (dt, *J* = 12.5, 3.5 Hz, 1 H), 1.54 (dq, *J* = 13.0, 3.5 Hz, 1 H), 1.35 (ddt, *J* = 11.0, 3.5, 13.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 174.6, 136.1, 134.6, 127.4, 121.4, 119.5, 118.1, 110.8, 108.6, 66.1, 60.6, 60.3, 54.9, 53.3, 51.8, 38.1, 36.7, 33.3, 27.8, 24.7, 21.8; mass spectrum, *m/e* 354.1937 ($C_{21}H_{26}N_2O_3$ requires *m/e* 354.1943), 353 (base), 336, 335, 295, 223, 184, 170, 169, 156, 144, 86, 82, 57, 43, 41.

For (±)-inside α-yohimbine (67): mp 236–237 °C (dec) (from EtOAc/hexanes); hydrochloride (MeOH) mp 266–268 °C (dec); IR ($CDCl_3$) ν 3560, 3460, 3340, 2800, 2750, 1725, 1630 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.88 (br s, 1 H), 7.46 (dd, *J* = 6.5, 1.8 Hz, 1 H), 7.33 (dd, *J* = 6.5, 1.8 Hz, 1 H), 7.00–7.20 (m, 2 H), 4.10 (m, 1 H), 3.77 (s, 3 H), 3.38 (br s, 1 H), 2.25–3.10 (m, 9 H), 1.45–2.10 (m, 5 H), 1.2–1.40 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 174.5, 136.3, 133.3, 127.4, 121.4, 119.4, 118.1, 110.8, 109.9, 66.3, 63.4, 56.1, 54.9, 53.2, 51.8, 39.8, 38.8, 32.9, 23.5, 21.7, 20.0; mass spectrum, *m/e* 354.1947 ($C_{21}H_{26}N_2O_3$ requires *m/e* 354.1943), 353, 336, 335, 197, 185, 184 (base), 170, 169, 156, 143, 130, 115.

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Supplementary Material Available: General information for the Experimental Section and experimental details including infrared, proton magnetic resonance, carbon magnetic resonance, and mass spectra together with physical constants for other new compounds not described in the present Experimental Section (13 pages). Ordering information is given on any current masthead page.

A Novel Pentacyclic Aromatic Alkaloid from an Ascidian[1]

Stephen J. Bloor and Francis J. Schmitz*

Contribution from the Department of Chemistry, University of Oklahoma, Norman, Oklahoma 73019. *Received March 13, 1987*

Abstract: 2-Bromoleptoclinidinone, a pentacyclic aromatic alkaloid, $C_{18}H_8N_3OBr$, possessing a new skeleton, was isolated from an ascidian, and its structure was determined by making extensive use of long-range proton–carbon couplings. The new alkaloid is toxic in cell culture to lymphocytic leukemia cells (PS).

Fused tetra- and pentacyclic aromatic alkaloids are rare among the wide variety of alkaloids isolated from marine organisms.[2] The only examples are the sponge metabolite amphimedine (**1**, Chart I),[3] an anemone pigment, calliactine, and a hydrolysis product thereof, neocalliactine.[4] These highly fused structures have proven to be challenging structure elucidation problems as is indicated by the fact that calliactine and neocalliactine have been known for many years and their structures are still ambiguous in spite of analysis by modern spectrometric methods. Extensive long-range heterocorrelation and carbon–carbon correlations were needed to resolve the structure of amphimedine. We report here the isolation of a new fused pentacyclic alkaloid, designated 2-bromoleptoclinidinone, from an ascidian tentatively identified as a *Leptoclinides sp.* The structure elucidation required extensive utilization of long-range H/C coupling data.

The formula $C_{18}H_8N_3OBr$, implying 17 degrees of unsaturation, was established for the new alkaloid by high-resolution mass spectrometry. Only aromatic type protons were observed in the ^1H NMR spectrum, and these could be assigned to one benzene and two pyridine rings substituted as shown in partial structures A (see H-1, H-3, and H-4, Table I), B (see H-6 and H-7), and C (see H-9, H-10, and H-11) (see Chart II for A–C). The presence of two pyridine rings was inferred from the low-field position of two protons, 9.15 and 9.24 ppm, which showed no coupling to each other but did each show 5–6-Hz ortho couplings typical of the α-proton on a pyridine ring.[5] Definitive evidence for partial structures A–C was derived from one-bond and long-range proton–carbon correlations; see partial structures A–C and Table I. Two- and three-bond couplings determined by selective ^1H decoupling using low power are indicated by solid

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