A General Synthetic Entry to *Strychnos* Alkaloids of the Curan Type via a Common 3a-(2-Nitrophenyl)hexahydroindol-4-one Intermediate. Total Syntheses of (±)- and (−)-Tubifolidine, (±)-Akuammicine, (±)-19,20-Dihydroakuammicine, (±)-Norfluorocurarine, (±)-Echitamidine, and (±)-20-Epilochneridine[1]

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Abstract: A general strategy for the synthesis of pentacyclic *Strychnos* alkaloids with the curan skeleton has been developed. It utilizes 3a-(2-nitrophenyl)hexahydroindol-4-one (**23**), which was prepared from 2-allyl-2-(2-nitrophenyl)-1,3-cyclohexanedione (**15**), as the common, pivotal intermediate. Three different procedures have been employed for the closure of the bridged piperidine D ring from **23**: (i) an intramolecular Michael-type conjugate addition; (ii) a $Ni(COD)_2$-promoted biscyclization that assembles B and D rings in a single synthetic step, and (iii) an intramolecular cyclization of an enone−propargylic silane system. When necessary, depending on the procedure used, introduction of the oxidized one-carbon substituent at C-16, closure of the indole ring, and/or adjustment of the functionality of the C-20 two-carbon chain constitute the last stages of the synthetic route to the title alkaloids. The procedure involving the cyclization of a propargylic silane has been successfully extended to the enantiospecific synthesis of (−)-tubifolidine starting from the enantiopure 3a-(2-nitrophenyl)hexahydroindolone (−)-**51**, which was prepared taking advantage of the prochiral character of cyclohexanedione **15**.

Introduction

The *Strychnos* alkaloids constitute an important group of architecturally complex and widely distributed monoterpenoid indole alkaloids.[2] According to their biogenesis,[3] they can be arranged in two classes, Strychnan and Aspidospermatan, with a topographical relationship. The majority of Strychnan alkaloids belong to the curan type,[5] which are structurally characterized by the presence of a pentacyclic 3,5-ethanopyrrolo[2,3-*d*]carbazole framework (see Chart 1) bearing a two-carbon appendage at C-20 (alkyl, alkylidene or oxygenated) and an oxidized one-carbon substituent (C-17) at C-16 (hydroxymethyl, formyl, or methoxycarbonyl).

In the last decade, the Strychnan alkaloids have been the subject of intensive synthetic investigation. Much of this continuing interest has been focused on the synthesis of the heptacyclic alkaloid strychnine,[6−8] while the pentacyclic curan alkaloids have received less attention. The synthetic efforts made in this field, using the strategies outlined in Scheme 1, have culminated in the total syntheses of the curan alkaloids depicted in Chart 1 (which includes the alkaloids whose synthesis is reported in this paper). The several different strategies can be classified into those that form the crucial quaternary center at C-7 in the last synthetic steps[9−12] and those in which the strategic bonds around C-7 are preformed at the initial stages of the synthesis.[13−14]

Synthetic Plan. In this paper, we describe a new, general and flexible synthetic entry to the *Strychnos* alkaloids with the curan skeleton via 3a-(2-nitrophenyl)hexahydroindol-4-ones and

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(1) For preliminary accounts of parts of this work, see: (a) Bonjoch, J.; Solé, D.; Bosch, J. *J. Am. Chem. Soc.* **1993**, 115, 2064−2065. (b) Solé, D.; Bonjoch, J.; Bosch, J. *J. Am. Chem. Soc.* **1995**, *117*, 11017−11018. (c) Solé, D.; Bonjoch, J.; Bosch, J. *J. Org. Chem.* **1996**, *61*, 4194−4195. (d) Solé, D.; Bonjoch, J.; García-Rubio, S.; Suriol, R.; Bosch, J. *Tetrahedron Lett.* **1996**, *37*, 5213−5216.

(2) Reviews: (a) Sapi, J.; Massiot, G. In *Monoterpenoid Indole Alkaloids*; Saxton, J. E., Ed. In *The Chemistry of Heterocyclic Compounds*; Taylor, E. C., Ed.; Wiley: New York, 1994; Supplement to Vol. 25, Part 4, pp 279−355. (b) Bosch, J.; Bonjoch, J.; Amat, M. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1996; Vol. 48, pp 75−189.

(3) For a general classification of indole alkaloids, see: Kisakürek, M. V.; Leeuwenberg, A. J. M.; Hesse, M. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1983; Vol. 1, pp 211−376. The Strychnan class includes the alkaloids in which the unrearranged monoterpenoid unit is attached to the indole nucleus by C-2/C-16 and C-7/C-3 bonds.[4]

(4) The numbering system and ring labeling (ABCDE) based on the biogenetic interrelationship of indole alkaloids is used throughout this paper: Le Men, J.; Taylor, W. I. *Experientia* **1965**, *21*, 508−510.

(5) The curan alkaloids include the pentacyclic alkaloids of the akuammicine-group as well as the hexacyclic alkaloids of the diaboline and spermostrychnine groups, in which there is an additional oxygenated ring linking C-17 with the two-carbon chain at C-20. More than 125 alkaloids with the curan skeleton have been isolated so far (nearly half of all the *Strychnos* alkaloids).

(6) Since the classical pioneering work by Woodward,[7a] five different syntheses of strychnine have been completed, all of them in recent years, either via isostrychnine[7] or via Wieland−Gumlich aldehyde.[8]

(7) (a) Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schenker, K. *J. Am. Chem. Soc.* **1954**, *76*, 4749−4751. Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schenker, K. *Tetrahedron* **1963**, *19*, 247−288. (b) Kuehne, M. E.; Xu, F. *J. Org. Chem.* **1993**, *58*, 7490−7497. (c) Rawal, V. H.; Iwasa, S.; Michoud, C. *J. Org. Chem.* **1994**, *59*, 2685−2686.

(8) (a) Magnus, P.; Giles, M.; Bonnert, R.; Kim, C. S.; McQuire, L.; Merritt, A.; Vicker, N. *J. Am. Chem. Soc.* **1992**, *114*, 4403−4405. Magnus, P.; Giles, M.; Bonnert, R.; Johnson, G.; McQuire, L.; Deluca, M.; Merritt, A.; Kim, C. S.; Vicker, N. *J. Am. Chem. Soc.* **1993**, *115*, 8116−8129. (b) Stork, G. Reported at the Ischia Advanced School of Organic Chemistry, Ischia Porto, Italy, September 21, 1992. (c) Knight, S. D.; Overman, L. E.; Pairaudeau, *J. Am. Chem. Soc.* **1993**, *115*, 9293−9294. Knight, S. D.; Overman, L. E.; Pairaudeau, G. *J. Am. Chem. Soc.* **1995**, *117*, 5776−5788.

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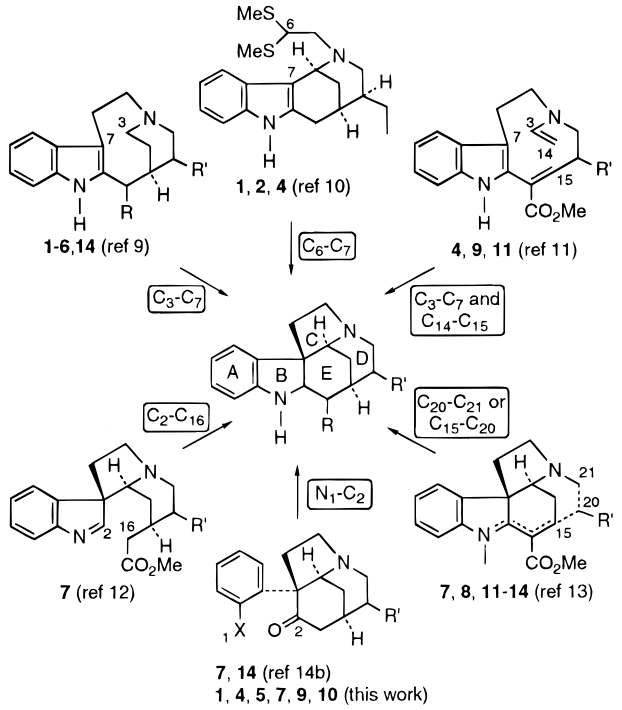
Scheme 1. Synthetic Strategies for the Synthesis of Curan Alkaloids[a]

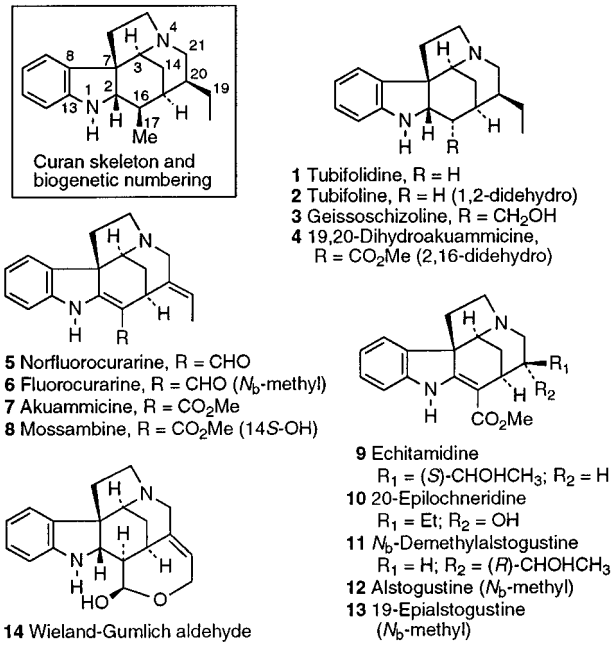


[a] The numbers in boldface indicate the alkaloids (see Chart 1) synthesized following each particular strategy.

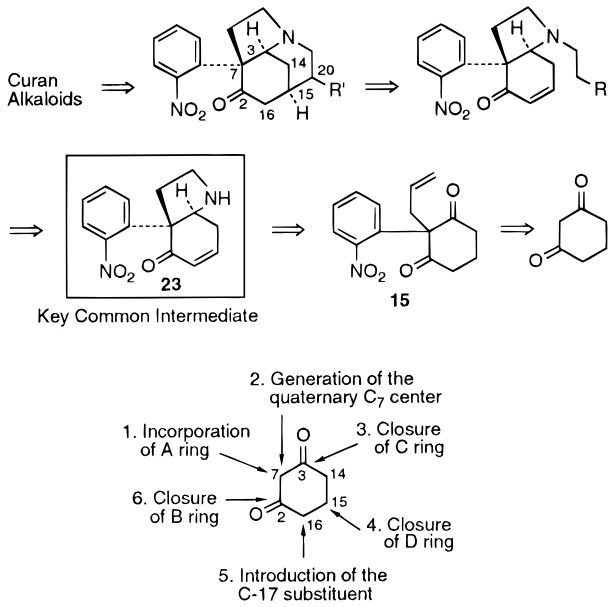
report the total syntheses of (±)- and (−)-tubifolidine (**1**), (±)-19,20-dihydroakuammicine (**4**), (±)-norfluorocurarine (**5**), (±)-akuammicine (**7**), (±)-echitamidine (**9**), and (±)-20-epilochneridine (**10**).

In planning our approach to curan alkaloids our aim was to develop a unified strategy for the synthesis of these compounds. As the main differences among the curan alkaloids are in the nature of the appendages at C-16 and C-20, we adopted a strategy in which these substituents are incorporated at advanced stages of the synthesis from a common intermediate. The cornerstone of our synthetic plan is the use of a non-indolic starting material, such as **23**, in which the crucial quaternary center has already been formed, the A, C, and E rings of *Strychnos* alkaloids have been incorporated, and the B ring is present in a latent form (Scheme 2). The approach involves a series of stepwise annelations from 1,3-cyclohexanedione, which preforms the core carbocyclic E ring of the target alkaloids. Once the nitrophenyl group (A ring) has been incorporated and

Chart 1. Structures of Curan Alkaloids Prepared by Total Synthesis



Scheme 2. Synthetic Strategy



the quaternary C-7 center has been formed, the crucial steps of the synthesis are as follows: (i) the closure of the pyrrolidine C ring from the symmetric 1,3-cyclohexanedione **15** through a one-pot procedure that involves the ozonolysis of the allyl group and a double (inter- and intramolecular) reductive amination;[15] (ii) the closure of the piperidine D ring by formation of C-15/C-20 bond from an appropriately substituted 3a-arylhexahydroindol-4-one (in Scheme 2, R and R′ represent, respectively, the requisite cyclization promoter and the two-carbon C-20 substituent); and (iii) the formation of the indoline ring in the last synthetic steps by reductive cyclization of the α-(2-nitrophenyl) ketone moiety. In addition, the introduction of the C-17 one-carbon appendage characteristic of curan alkaloids can be achieved prior to the closure of B ring, taking advantage of the activation exerted by the C-2 carbonyl group at C-16. The versatility of our strategy lies in the fact that closure of D ring can be brought about by different methodologies, leading to azatricyclic compounds bearing different piperidine substit-

(9) (a) Dadson, B. A.; Harley-Mason, J.; Foster, G. H. *J. Chem. Soc., Chem. Commun.* **1968**, 1233. (b) Dadson, B. A.; Harley-Mason, J. *J. Chem. Soc., Chem. Commun.* **1970**, 665. (c) Harley-Mason, J.; Taylor, C. G. *J. Chem. Soc., Chem. Commun.* **1970**, 812. (d) Crawley, G. C.; Harley-Mason, J. *J. Chem. Soc., Chem. Commun.* **1971**, 685−686. (e) Ban, Y.; Yoshida, K.; Goto, J.; Oishi, T.; Takeda, E. *Tetrahedron* **1983**, *39*, 3657−3668. (f) Amat, M.; Coll, M.-D.; Passarella, D.; Bosch, J. *Tetrahedron: Asymmetry* **1996**, *7*, 2775−2778. See also ref 8a.

(10) Amat, A.; Linares, A.; Bosch, J. *J. Org. Chem.* **1990**, *55*, 6299−6312.

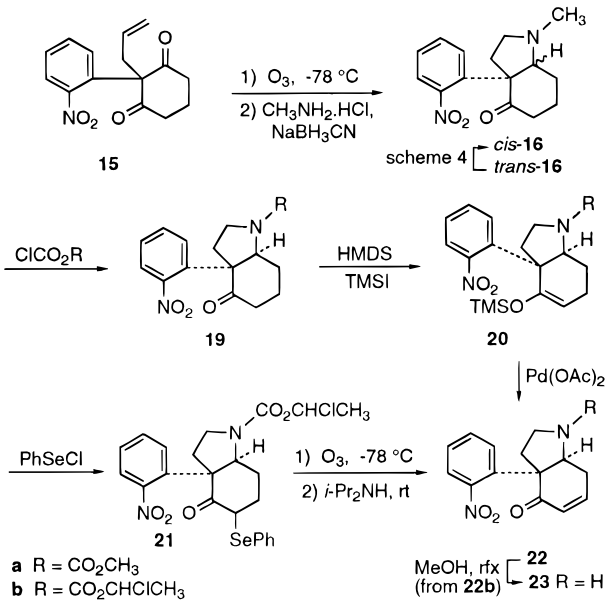
(11) (a) Kuehne, M. E.; Frasier, D. A.; Spitzer, T, D. *J. Org. Chem.* **1991**, *56*, 2696−2700. (b) Kuehne, M. E.; Brook, C. S.; Frasier, D. A.; Xu, F. *J. Org. Chem.* **1994**, *59*, 5977−5982.

(12) Martin, S. F.; Clark, C. W.; Ito, M.; Mortimore, M. *J. Am. Chem. Soc.* **1996**, *118*, 9804−9805.

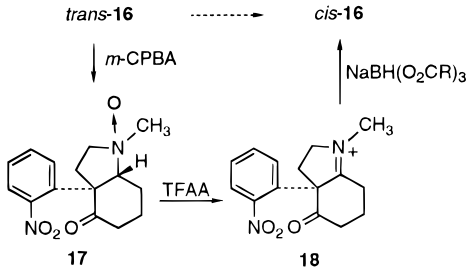
(13) (a) Formation of C-20/C-21 bond: Kuehne, M. E.; Xu, F.; Brook, C. S. *J. Org. Chem.* **1994**, *59*, 7803−7806. (b) Formation of C-15/C-20 bond: Kuehne, M. E.; Wang, T.; Seraphin, D. *J. Org. Chem.* **1996**, 61, 7873−7881. See also ref 8b.

(14) (a) Closure of the indole ring either from protected anilines[14b] or from nitro derivatives as reported in this work.[1] (b) Angle, S. R.; Fevig, J. M.; Knight, S. D.; Marquis, R. W., Jr.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 3966−3977. See also ref 8c.

Scheme 3. Preparation of the Key 3a-(2-Nitrophenyl)hexahydroindol-4-one



Scheme 4. Conversion of *trans*-**16** to *cis*-**16**



uents, which can be further elaborated into the variety of two-carbon substituents present at C-20 in *Strychnos* alkaloids.

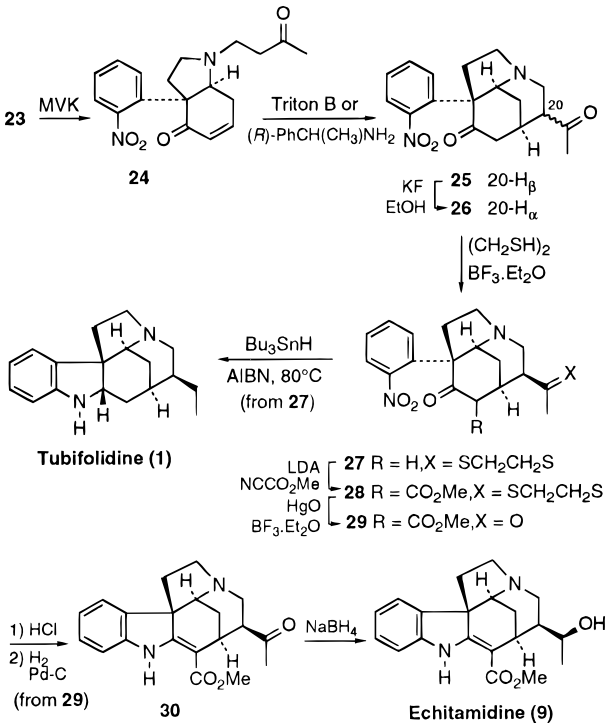
It is noteworthy that the above synthetic strategy is also applicable to the enantiospecific synthesis of curan alkaloids, because the key building block **23** can be prepared in both enantiopure forms starting from the prochiral dione **15**.

Results and Discussion

Synthesis of the Key Intermediate 23. The synthesis of the key intermediate **23** starts from the multigram available octahydroindolone **16**, which was prepared in 62% yield from dione **15** as a 1.5:1 mixture of cis and trans isomers (Scheme 3).[15] Conversion of *trans*-**16** to the cis isomer, which possesses the required C/E ring junction, was accomplished in 87% yield by the three-step sequence depicted in Scheme 4: oxidation of *trans*-**16** with *m*-CPBA afforded *N*-oxide **17**, which, on treatment with TFAA[16] followed by reduction of the resulting iminium salt **18** with tri-2-ethylhexanoyloxyborohydride,[17] stereoselectively gave *cis*-**16**. This efficient transformation of *trans*-**16** to *cis*-**16** allows the *cis*-3a-(2-nitrophenyl)octahydroindol-4-one system to be assembled in 24% overall yield from 1,3-cyclohexanedione.

For the closure of the piperidine ring it was necessary to activate the octahydroindole 6-position (C-15 biogenetic). This was accomplished by generating an enone moiety. Initially, ketone *cis*-**16** was converted via carbamate **19a** to silyl enol ether **20a**, which, upon palladium diacetate-mediated dehydrosilylation,[18] gave rise to the α,β-unsaturated ketone **22a**. However, attempts to remove the carbamate group led to complex unidentifiable mixtures. So, we then decided to use the carbamate **19b**, bearing a more easily removable protecting group.[19] In this series, as direct oxidation of silyl enol ether **20b** failed, the generation of the double bond was achieved through the phenylseleno derivative **21**. Oxidation of **21** gave the corresponding selenoxide, which underwent a β-elimination to give enone **22b** in 50% overall yield from *cis*-**16**. Finally, deprotection (MeOH, reflux) of the pyrrolidine nitrogen satisfactorily gave the secondary amine **23**.

Scheme 5. Closure of the Piperidine Ring by Michael Cyclization



The Intramolecular Michael Reaction Approach to Curan Alkaloids. Synthesis of (±)-Tubifolidine and (±)-Echitamidine. The first methodology we explored for the closure of the piperidine ring took advantage of an intramolecular Michael addition.[20] Conjugate addition of the secondary amine **23** to methyl vinyl ketone provided the alkylated hexahydroindolone **24** in 74% yield (Scheme 5). Initially, the base-catalyzed cyclization of **24** was effected by treatment with benzyltrimethylammonium hydroxide (Triton B) to give a 1:3 mixture of epimeric ketones **25** and **26** in 58% yield. This yield was improved using α-methylbenzylamine[21] as the cyclization promoter: hydrolysis of the initially formed imine afforded the azatricyclic derivatives **25** and **26**, with the same stereoselectivity as above, in 67% overall yield. The minor epimer **25**[22] was converted to **26** by treatment with KF-EtOH.

Conversion of **26** into tubifolidine (**1**) required the reductive cyclization of the α-(2-nitrophenyl) ketone moiety and the reduction of the acetyl group. For this purpose, tricyclic

(15) Solé, D.; Bosch, J.; Bonjoch, J. *Tetrahedron* **1996**, *52*, 4013−4028.
(16) Grierson, D. *Org. React.* **1990**, *39*, 85−295.
(17) Before the recent report about this reagent (McGill, J. M.; LaBell, E. S.; Williams, M. *Tetrahedron Lett.* **1996**, *37*, 3977−3980) we had used $NaBH_3CN$, although with a lower stereoselectivity (2:1 cis/trans ratio).
(18) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011−1013.
(19) Olofson, R. A.; Martz, J. T.; Senet, J.-P.; Piteau, M.; Malfroot, T. *J. Org. Chem.* **1984**, *49*, 2081−2082.
(20) Little, R. D.; Masjedizadeh, M. R.; Wallquist, O.; McLoughlin, J. I. *Org. React.* **1995**, *47*, 315−552.
(21) Pfau, M.; Revial, G.; Guingant, A.; d'Angelo, J. *J. Am. Chem. Soc.* **1985**, *107*, 173−179.
(22) This epimer could give access to the alstogustine alkaloid series, although this possibility was not explored.

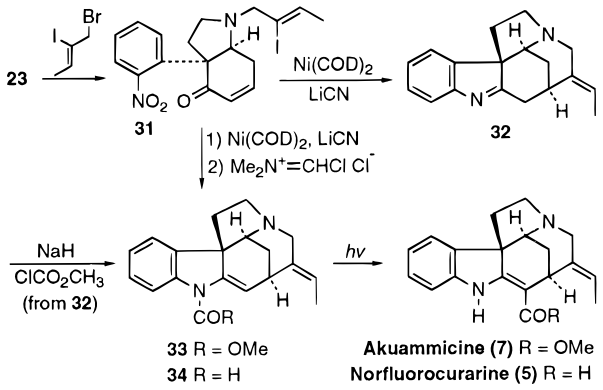
diketone **26** was chemoselectively converted into dithioacetal **27**. Reduction of **27** with Bu_3SnH in the presence of catalytic amounts of AIBN directly afforded (±)-tubifolidine (**1**)[23] in 50% yield, in a one-pot process involving desulfurization[24] and simultaneous closure of the indoline ring by reductive cyclization of the γ-nitro ketone unit.[25]

Next, we focused our attention on the alkaloid echitamidine (**9**). Methoxycarbonylation of azatricyclic ketone **27** rendered β-keto ester **28**. This reaction was troublesome, and the best results were obtained when the lithium enolate was generated at −78 °C in the presence of HMPA, and methyl cyanoformate was added to the mixture at room temperature. In this way, β-keto ester **28** was obtained in 50% yield, with recovering of the unreacted starting material.[26] Deprotection of the dithioacetal group of **28** with red HgO afforded ketone **29** in 85% yield. For the B ring closure, the best results were obtained when hydrogenation was done from the hydrochloride[27] derived from **29** using Pd−C as the catalyst: the pentacyclic compound **30** was obtained in 80% yield. Finally, $NaBH_4$ reduction of the acetyl side chain of **30** stereoselectively afforded (±)-echitamidine (**9**) in 75% yield.[28]

Synthesis of (±)-Akuammicine and (±)-Norfluorocurarine by Nickel(0)-Promoted Double Cyclization. Although the pentacyclic derivative **30** contains all the carbon atoms and the functionality necessary to undertake the synthesis of curan alkaloids bearing a C-20 ethylidene chain, we decided to explore an alternative procedure for the closure of the piperidine ring with simultaneous introduction of the aforementioned substituent. We focused our attention on the intramolecular nickel(0)-promoted cyclizations of vinyl halides with alkenes.[29] It was our original hope that this methodology might allow for both the closure of the ethylidene-bearing piperidine ring and the introduction of the one-carbon substituent present at C-16.

The required *N*-substituted 3a-arylhexahydroindol-4-one **31** was prepared by alkylation of **25** with (*Z*)-1-bromo-2-iodo-2-butene[30] (Scheme 6). Initial attempts to promote the tandem cyclization-capture process from **31** under the usual conditions ($Ni(COD)_2$, 2 equiv, then TMSCN) failed, affording complex unidentifiable mixtures. Initially, we attributed the failure of the reaction to the lack of a suitable stabilization of the transient σ-alkylnickel intermediate presumably formed in the process. Consequently, we decided to trap this intermediate while it was being generated. To our surprise, when **31** was treated with $Ni(COD)_2$ (6.6 equiv) in the presence of LiCN, 19,20-dehydrotubifoline (**32**)[31] was obtained in 40% yield. This one-pot transformation involves the Ni(0)-promoted cyclization of the vinyl iodide upon the carbon−carbon double bond[32] and the controlled reductive cyclization of the α-(2-nitrophenyl) ketone moiety to the imine functionality.

Scheme 6. $Ni(COD)_2$-Promoted Double Cyclization



With dehydrotubifoline (**32**) in hand, the synthesis of curan alkaloids simply required the introduction of the one-carbon substituent at C-16. For this purpose we took advantage of the known photochemical rearrangement of *N*-(methoxycarbonyl)-enamines to vinylogous carbamates.[33] Thus, treatment of **32** with methyl chloroformate in the presence of NaH gave (36%) the *N*-methoxycarbonyl enamine **33**, which was then photoisomerized (30%) to (±)-akuammicine (pseudoakuammicine).[34]

A more straightforward method for the introduction of the oxidized C-17 atom was the treatment of vinyl iodide **31** with $Ni(COD)_2$/LiCN, followed by trapping of the resulting intermediate with (chloromethylene)dimethyliminium chloride in a one-pot reaction. Under these conditions, the pentacyclic *N*-formyl enamine **34** was directly obtained from **31** in 15% yield. Probably, formylation occurs from a metalloenamine intermediate because dehydrotubifoline (**32**) was recovered unchanged after treatment with the above formylating agent (DMF, 80 °C, 15 h).[35] Photoisomerization[36] of **34** gave (±)-norfluorocurarine (vinervidine)[37] in 15% yield, the major product (69%) formed in this process being the deformylated indolenine **32**.

When the above one-pot treatment [$Ni(COD)_2$/LiCN/Me_2N^+=CHCl Cl^-] was applied to the (*E*)-vinyl iodide **35** (Scheme

(23) (a) Isolation and structural elucidation: Kump, W. G.; Patel, M. B.; Rowson, J. M.; Schmid, H. *Helv. Chim. Acta* **1964**, *47*, 1497−1503. (b) NMR data: ref 10. (c) Previous syntheses: refs 9a,e and 10.

(24) Gutierrez, C. G.; Stringham, R. A.; Nitasaka, T.; Glasscock, K. G. *J. Org. Chem.* **1980**, *45*, 3393−3395.

(25) We do not know examples of the generation of indolines by reduction of α-(2-nitrophenyl) ketones with Bu_3SnH. For the use of 2-nitrophenyl derivatives as precursors of the indoline nucleus in alkaloid synthesis, see *inter alia*: Takano, S.; Goto, E.; Hirama, M.; Ogasawara, K. *Chem. Pharm. Bull.* **1982**, *30*, 2641−2643. Heathcock, C. H.; Norman, M. H.; Dickman, D. A.; *J. Org. Chem.* **1990**, *55*, 798−811. Mittendorf, J.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1990**, *46*, 4049−4062.

(26) This result contrasts with those reported by Overman[14b] for the methoxycarbonylation of azatricyclic derivatives that differ from **27** in the substituent on the aromatic ring and makes evident that the nitro group is the cause of the different behavior. For an unusual reaction of nitro ketone **27** under basic conditions, see: Solé, D.; Parés, A.; Bonjoch, J. *Tetrahedron* **1994**, *50*, 9769−9774.

(27) Catalytic hydrogenation of **29** under either basic (Li_2CO_3) or neutral conditions afforded appreciable amounts of the corresponding carbinolamine.

(28) (a) Isolation and structural elucidation: Goodson, J. A. *J. Chem. Soc.* **1932**, 2626. Djerassi, C.; Nakagawa, Y.; Budzikiewicz, H.; Wilson, J. M.; LeMen, J.; Poisson, J.; Janot. M.-M. *Tetrahedron Lett.* **1962**, 653−659. Zèches, M.; Ravao, T.; Richard, B.; Massiot, G.; LeMen-Olivier, L.; Guilhem, J.; Pascard, C.; *Tetrahedron Lett.* **1984**, *25*, 659−662. (b) NMR data: Keawpradub, N.; Takayama, H.; Aimi, N.; Sakai, S. *Phytochemistry* **1994**, *37*, 1745−1749. (c) Since our preliminary communication,[1a] a second synthesis of (±)-echitamidine has been reported.[11b]

(29) (a) Solé, D.; Cancho, Y.; Llebaria, A.; Moretó, J. M.; Delgado, A. *J. Am. Chem. Soc.* **1994**, *116*, 12133−12134. (b) Solé, D.; Cancho, Y.; Llebaria, A.; Moretó, J. M.; Delgado, A. *J. Org. Chem.* **1996**, *61*, 5895−5904.

(30) Rawal, V. H.; Michoud, C.; Monestel, R. F. *J. Am. Chem. Soc.* **1993**, *115*, 3030−3031.

(31) Previous syntheses: (a) Takano, S.; Hirama, M.; Ogasawara, K. *Tetrahedron Lett.* **1982**, *23*, 881−884. (b) Hugel, G.; Lévy, J. *Tetrahedron Lett.* **1993**, *34*, 633−634. See also refs 9d, 14b, and 30.

(32) Formation of **32** requires the protolysis of the transient alkylnickel intermediate generated in the $Ni(COD)_2$-promoted cyclization. For a related example where an alkylnickel intermediate generated in such a process is protonated during the workup, see: Mori, M.; Ban, Y. *Tetrahedron Lett.* **1976**, 1807−1810.

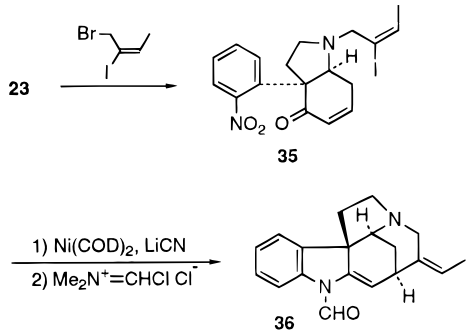
(33) For the use of this photoisomerization in the synthesis of *Strychnos* alkaloids, see: Gràcia, J.; Casamitjana, N.; Bonjoch, J.; Bosch, J. *J. Org. Chem.* **1994**, *59*, 3939−3951. See also ref 10.

(34) (a) Isolation of (±)-akuammicine (ψ-akuammicine): Edwards, P. N.; Smith, G. F. *Proc. Chem. Soc. (London)* **1960**, 215. (b) Isolation and structural elucidation of (−)-akuammicine: Aghoramurthy, K.; Robinson, R. *Tetrahedron* **1957**, *1*, 172−173. Edwards, P. N.; Smith, G. F. *J. Chem. Soc.* **1961**, 152−156 (c) NMR data: Hu, W.-L.; Zhu, J.-P.; Hesse, M. *Planta Med.* **1989**, *55*, 463−466. See also refs 13a. (d) Synthesis: ref 12, 13a, and 14b.

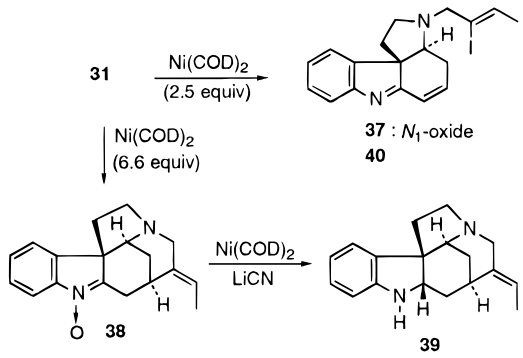
(35) Formylation ($POCl_3$, DMF, 50−60 °C) of dehydrotubifoline **32** to the *N*-formyl derivative **34** has been previously reported (no yield indicated): see ref 14b.

(36) Lenz, G. R. *Synthesis* **1978**, 489−518.

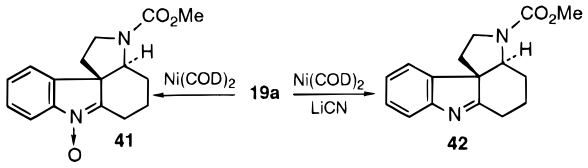
Scheme 7



Scheme 8



Scheme 9



7), the pentacyclic *N*-formyl enamine **36** was isolated in 20% yield. The constitution and relative configuration of **36** was unambiguously established from its ^{1}H and ^{13}C NMR data, with the aid of 2D-NMR experiments and ROESY. These data are clearly different from those reported for bharhingine, an alkaloid isolated from *Rhazya stricta*[38] for which the structure **36** had been proposed. Therefore, the structure of this natural product awaits further investigation.

Interestingly, the outcome of the Ni(0)-promoted double cyclization from vinyl iodide **31** was slightly different when the process was carried out [6.6 equiv of $Ni(COD)_2$] in the absence of LiCN/DMF. Under these conditions nitrone **38** was obtained in a single step in 40% yield. A further treatment of nitrone **38** with $Ni(COD)_2$, now in the presence of LiCN, afforded the pentacyclic indoline **39** (19,20-didehydrotubifolidine)[39] in 40% yield. The different course of the reduction when lithium cyanide is present in the medium could be attributed to a decrease in the redox potential of the original Ni(0) complex.[40,41]

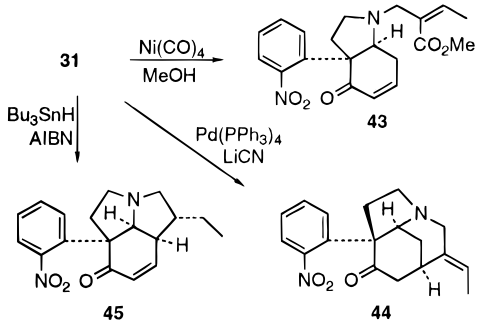
On the other hand, when the amount of $Ni(COD)_2$ was reduced to 2.5 equiv, the tetracyclic nitrone **37** was obtained in

(37) (a) Isolation of (±)-norfluorocurarine: Rakhimov, D. A.; Malikov, V. M.; Yusunov, C. Y. *Khim. Prir. Soedin* **1969**, *5*, 461−462; *Chem. Abstr.* **1970**, *72*, 67165n. (b) Isolation and structural elucidation of (−)-norfluorocurarine: Stauffacher, D. *Helv. Chim. Acta* **1961**, *44*, 2006−2015. (c) NMR data: Clivio, P.; Richard, B.; Deverre, J.-R.; Sevenet, T.; Zeches, M.; Le Men-Oliver, L. *Phytochemistry* **1991**, *30*, 3785−3792. (d) For the only previous synthesis of racemic norfluorocurarine, see ref 9d.

(38) Atta-ur-Rahman; Habib-ur-Rehman; Ahmad, Y.; Fatima, K.; Badar, Y. *Planta Med.* **1987**, *53*, 256−259.

(39) For a previous synthesis, see: Smith, G. F.; Wróbel, J. T. *J. Chem. Soc.* **1960**, 792−795.

Scheme 10



50% yield. This result seems to indicate that reduction of the nitro group occurs prior to the nickel-induced C−C bond formation.[42]

The controlled reductive cyclization of α-(2-nitrophenyl) ketones using $Ni(COD)_2$ is unprecedented and seems to be quite general. It can be exploited to assemble the partially reduced pyrrolo[2,3-*d*]carbazole unit, which is present in several groups of indole alkaloids.[43] Thus, treatment of octahydroindol-4-one **19a** with $Ni(COD)_2$ under the above conditions led either to nitrone **41** (50% yield) or indolenine **42** (51% yield) depending on the absence or presence of LiCN/DMF in the reaction mixture.

Other methodologies were explored for the closure of the piperidine ring from vinyl iodide **31** (Scheme 10). The use of $Ni(CO)_4$ to produce the tandem cyclization−carbonylation process failed. Thus, treatment of vinyl iodide **31** under the usual conditions[44] afforded the uncyclized−carbonylated compound **43** (27%). In this context, the Heck reaction[45] was also studied under a variety of conditions (catalytic or stoichiometric on palladium). Cyclization was only observed on treatment of vinyl iodide **31** with $Pd(PPh_3)_4$ (0.2 equiv) in the presence of LiCN:[46] the azatricyclic compound **44** was isolated in 26% yield, the starting material being recovered in part.[47] Although this reaction was not improved, it could also receive further application for the synthesis of curan alkaloids. On the other hand, treatment of **31** with Bu_3SnH and AIBN led to the D-nor derivative **45** (45%) instead of the desired bridged azatricycle **44**.[48]

(40) Cyanide species such as $K_4Ni(CN)_4$ and $K_2[Ni(CN)_2(CO)_2]$ have been well-characterized: del Rosario, R.; Sthul, L. S. *Organometallics* **1986**, *5*, 1260−1262. del Rosario, R.; Sthul, L. S. *J. Am. Chem. Soc.* **1984**, *106*, 1160−1161. Moreover, cyanonickelate(0) species have been postulated as intermediates in some reductions with cyanonickel complexes: Bingham, D.; Burnett, M. G. *J. Chem. Soc. (A)* **1971**, 1782.

(41) As a consequence of the great stability of the complex $[Ni(CN)_4]^{2-}$, the redox potential of Ni decreases in the presence of cyanide ions.

(42) The isolation of indolenine **40** when using decreasing amounts of $Ni(COD)_2$ in the presence of LiCN/DMF is in agreement with this interpretation.

(43) Octahydropyrrolo[2,3-*d*]carbazoles are valuable intermediates in the synthesis of *Aspidosperma* and ibophyllidine alkaloids: (a) Benchekroun-Mounir, N.; Dugat, D.; Gramain, J.-C.; Husson, H.-P. *J. Org. Chem.* **1993**, *58*, 6457−6465. (b) Kuehne, M. E.; Pitner, J. B. *J. Org. Chem.* **1989**, *54*, 4553−4569.

(44) Delgado, A.; Llebaria, A.; Camps, F.; Moretó, J. M. *Tetrahedron Lett.* **1994**, *35*, 4011−4014.

(45) Heck, R. F. Vinyl Substitution with Organopalladium Intermediates. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: New York, 1991; Vol. 4, pp 833−863.

(46) Grigg, R.; Santhakumar, S.; Sridharan, V. *Tetrahedron Lett.* **1993**, *34*, 3163−3164.

(47) Formation of **44** requires the protolysis of the transient alkylpalladium intermediate: Benhaddou, R.; Czernecki, S.; Ville, G. *J. Org. Chem.* **1992**, *57*, 4612−4616.

(48) The pyrrolidine ring is formed by a 1,5-hydrogen shift from the initially formed vinylic radical, followed by a 5-exo-trig cyclization of the resulting allylic radical: Lathbury, D. C.; Parsons, P. J.; Pinto, I. *J. Chem. Soc., Chem. Commun.* **1988**, 81−82.

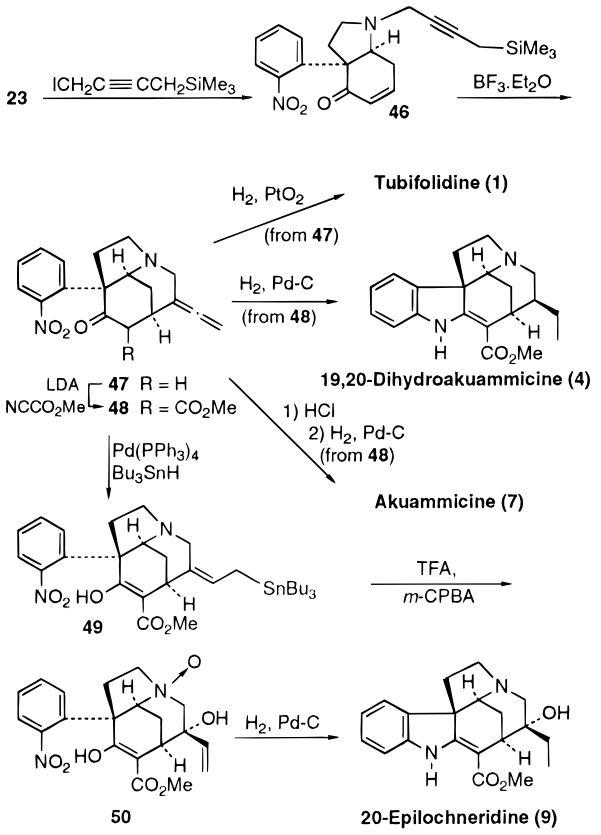
Synthesis of (±)-19,20-Dihydroakuammicine and (±)-20-Epilochneridine via Intramolecular Cyclization of an Enone-Propargylic Silane System. The third approach we have explored for the formation of the crucial $C_{15}-C_{20}$ bond of curan alkaloids from the key intermediate **23** is based on the intramolecular conjugate addition of a propargylic silane to an α,β-unsaturated ketone moiety[49] (Scheme 11). Alkylation of **23** with 1-iodo-4-(trimethylsilyl)-2-butyne[50,51] led to the propargylic silane **46**, which, upon treatment with $BF_3{\cdot}Et_2O$, underwent a smooth cyclization to give the bridged azatricyclic compound **47** in 55% overall yield. The ketone **47** bears a vinylidene side chain that can be further elaborated into the variety of two-carbon substituents present at C-20 in the *Strychnos* family.[52]

Catalytic hydrogenation of a methanolic solution of **47** using Pd on charcoal as the catalyst in the presence of Na_2CO_3 brought about both the reductive cyclization of the α-(2-nitrophenyl) ketone unit and the hydrogenation of the vinylidene side chain, which took place stereoselectively from the less hindered α-face of the ethylidene intermediate, to give (±)-tubifolidine[1d,23] in 60% yield.[53]

The introduction of the oxidized one-carbon substituent at the α-position of the carbonyl group in **47** entailed the same problems as the methoxycarbonylation of the above related azatricyclic ketone **27**. Thus, treatment of **47** with LDA and then with methyl cyanoformate gave β-ketoester **48** in 39% yield. Palladium-catalyzed hydrogenation of **48** in the presence of Na_2CO_3 afforded (±)-19,20-dihydroakuammicine[54] in 57% yield. Interestingly, when the above hydrogenation was carried out from **48**·hydrochloride at 100 psi for a short time, the alkaloid (±)-akuammicine (pseudoakuammicine)[1d,34] was isolated as the main product in 38% yield. The stereoselectivity of the process is worth noting because only the natural (*E*)-ethylidene isomer was isolated. The survival of the ethylidene double bond under these reaction conditions can be accounted for by the conjunction of several factors: (i) in the Pd-catalyzed hydrogenation of terminal allenes, after the initial regioselective reduction of the less substituted double bond, the resulting alkene reacts slower,[55] (ii) the protonation of the piperidine nitrogen introduces an axial interaction on the less hindered α-face that slows down the hydrogenation upon the remaining C-19/C-20 double bond, and (iii) under acidic conditions and a slight pressure, the rate of the reductive cyclization (closure of B ring) increases, thus allowing the reaction to be stopped after a shorter reaction time.

Our next goal was the synthesis of the alkaloid 20-epilochneridine. Palladium-catalyzed hydrostannation[56,57] of allene **48** afforded regio- and stereoselectively allylstannane **49** in 68% yield. All attempts to chemoselectively oxidize the allylstannane moiety after protection of the nitrogen atom as a BF_3 adduct[51] failed, and only traces of the desired allylic alcohol were obtained. The problem was circumvented by treating stannane **49** with an excess of *m*-CPBA[58] in the presence of an equimolecular amount of TFA. The allylic alcohol **50**, in which the piperidine nitrogen is in the *N*-oxide oxidation level, was stereoselectively formed in 76% yield. Catalytic hydrogenation of **50** with Pd on charcoal in the presence of Na_2CO_3 simultaneously accomplished the reduction of the vinyl double bond and the *N*-oxide functionality and the reductive cyclization of the α-(2-nitrophenyl) ketone moiety to give (±)-20-epilochneridine[59] in 48% yield.

Scheme 11. Closure of the Piperidine Ring by Cyclization of a Propargylic Silane



Synthesis of (−)-Tubifolidine (1). Apart from the enantioselective syntheses of (−)-Wieland-Gumlich aldehyde[8c] and tubifoline,[9f] the asymmetric synthesis of curan alkaloids has been little explored and remains a challenge for synthetic organic chemists.[60]

Following the schemes previously developed in the above total syntheses in the racemic series, the enantioselective synthesis of curan alkaloids simply requires the preparation of appropriate enantiopure *cis*-3a-(2-nitrophenyl)octahydroindol-

(49) Langkopf, E.; Schinzer, D. *Chem. Rev.* **1995**, *95*, 1375−1408.

(50) Klaver, W. J.; Moolenaar, M. J.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1988**, *44*, 3805−3818.

(51) Solé, D.; García-Rubio, S.; Bosch, J.; Bonjoch, J. *Heterocycles* **1996**, *43*, 2415−2424.

(52) For model studies from 3-vinylidenepiperidines, see ref 51. Although allenes have received extensive application in the synthesis of natural products, they have mainly been used as precursors of carbonyl groups: (a) Hiemstra, H.; Klaver, W. J.; Speckamp, W. N. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 299−306. (b) Klaver, W. J.; Hiemstra, H.; Speckamp, W. N. *J. Am. Chem. Soc.* **1989**, *111*, 2588−2595.

(53) The use of PtO_2 as the catalyst was less efficient from the synthetic standpoint, and the best result (48% yield of isolated tubifolidine) was obtained operating from **47**·hydrochloride using ethyl acetate as the solvent. The complete reduction (PtO_2) of the α-(2-nitrophenyl) ketone moiety of **47** was slower in ethanolic solution and, under these conditions, after longer reaction times (≈40 h) N_a-ethyltubifolidine was isolated as the major product (20%).

(54) (a) Isolation and structural elucidation: ref 23a. (b) NMR data and previous synthesis: ref 10. See also ref 11a.

(55) Schuster, H. E.; Coppola, G. M. *Allenes in Organic Synthesis*; Wiley: New York, 1984; Chapter 3.

(56) Mitchell. T. N.; Schneider, U. *J. Organomet. Chem.* **1991**, *405*, 195−199.

(57) Hydroboration of allene **47** with 9-borabicyclo[3.3.1]nonane (Brown, H. C.; Liotta, R.; Kramer, G. W. *J. Am. Chem. Soc.* **1979**, *101*, 2966−2979) did not give satisfactory results because the initially formed allylborane reacted with the ketone group.

(58) Ueno, Y.; Sano, H.; Okawara, M. *Synthesis* **1980**, 1011−1013.

(59) (a) Isolation and structural elucidation: Lathuillière, P.; Olivier, L.; Lévy, J.; Le Men, J. *Ann. Pharm. Fr.* **1966**, *24*, 547−549. (b) ^{13}C NMR data and hemisynthesis from akuammicine: Mirand, C.; Masiot, G.; Le Men-Olivier, L.; Lévy, J. *Tetrahedron Lett.* **1982**, *23*, 1257−1258.

(60) For a recent synthesis of (−)-tubifolidine and (−)-19,20-dihydroakuammicine following the methodology reported in ref 9f, see: Amat, M.; Coll, M.-D.; Bosch, J.; Espinosa, E.; Molins, E. *Tetrahedron: Asymmetry* **1997**, *8*, 935−948.

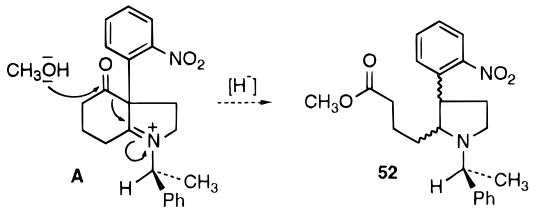
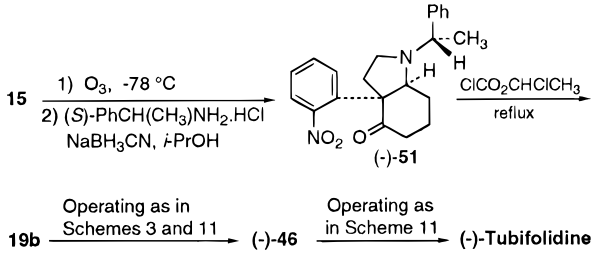


Figure 1.

Scheme 12. Synthesis of *Strychnos* Alkaloids in Enantiomerically Pure form: (−)-Tubifolidine



4-ones. As the double reductive amination leading to the 3a-(2-nitrophenyl)octahydroindole system takes place from a symmetric dione (**15**), the use of a chiral nonracemic amine as the aminocyclization agent in this step should afford the above-mentioned crucial building blocks in enantiomerically pure form.

Thus, the use of α-(*S*)-methylbenzylamine in the sequence of ozonolysis-double reductive amination from dione **15** afforded (−)-**51** in 37% yield and 78% of diastereoselectivity.[61] Positive diagnostic evidence for the (3a*R*, 7a*S*) configuration came from a NOESY experiment on (−)-**51**. The resulting 2D spectrum showed off-diagonal cross-peaks connecting H-7a and H-7_{eq} with a methyl proton, thus indicating their spacial proximity. The distance between these protons would increase in the alternative possible conformation[62] or in the derivative with the opposite configuration at the ring junction. The NOESY spectrum also showed interactions between the benzylic proton and the C-7 methylene and C-2 endo protons, thus corroborating the absolute configuration of (−)-**51**.

Removal of the α-methylbenzyl substituent required more drastic conditions than in the *N*-methyl series, presumably because of the steric hindrance. Successful debenzylation was achieved by refluxing a solution of (−)-**51** in 1-chloroethyl chloroformate for 48 h. From the resulting carbamate **19b** (mixture of epimers at the methine carbon of the carbamate group), the alkaloid (−)-tubifolidine was synthesized as in the above racemic series, following the sequence outlined in Scheme 12, by cyclization of the propragylic silane (−)-**46** to allene (−)-**47**, followed by hydrogenation. The resulting (−)-tubifolidine ([α_D]−56.6) had an ee of 84% determined by chiral HPLC.

Conclusion

cis-3a-(2-Nitrophenyl)octahydroindol-4-ones have proved to be particularly useful building blocks for assembling the pentacyclic ABCDE ring system of *Strychnos* alkaloids. After generation of an enone functionality, closure of the bridged piperidine D ring (bond formed $C_{15}-C_{20}$) has been accomplished either by intramolecular Michael addition or by nickel(0)-promoted cyclization of a vinyl halide or by intramolecular addition of a propargylic silane to an enone. Subsequent or concomitant reductive cyclization of the α-(2-nitrophenyl) ketone moiety completes the pentacyclic *Strychnos* system. The procedures reported here provide new solutions for the formation of the crucial $C_{15}-C_{20}$ bond of *Strychnos* alkaloids that can be applied to the synthesis of the most complex alkaloids of this group. The strategy we have developed not only allows the stereocontrolled synthesis of a variety of curan alkaloids in the racemic series from a common advanced intermediate but also can be extended to the enantiospecific synthesis of these alkaloids.

Experimental Section

General Methods. All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions. Unless otherwise noted, ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution, using Me_4Si as internal standard. Chemical shifts are reported in ppm downfield from Me_4Si. NMR peak assignments are given only when they are derived from definitive two-dimensional NMR experiments. The ^{13}C NMR spectra, when an unambiguous assignment is not available, are reported as follows: chemical shift (multiplicity determined from DEPT spectra). Only noteworthy IR absorptions are listed. Melting points were determined in a capillary tube and are uncorrected. TLC was carried out on SiO_2 (silica gel 60 F_{254}, Merck), and the spots were located with iodoplatinate reagent. Chromatography refers to flash chromatography and was carried out on SiO_2 (silica gel 60, SDS, 230−400 mesh ASTM) unless otherwise noted. Drying of organic extracts during workup of reactions was performed over anhydrous Na_2SO_4. Evaporation of solvents was accomplished with a rotatory evaporator. Microanalyses and HRMS were performed by Centro de Investigación y Desarrollo (CSIC), Barcelona.

***cis*-1-Methyl-3a-(2-nitrophenyl)octahydroindol-4-one (*cis*-16).** This compound was prepared from 1,3-cyclohexanedione by the published procedure.[15] For the conversion of *trans*-**16** to *cis*-**16**, see Supporting Information.

***cis*-1-[(1-Chloroethoxy)carbonyl]-3a-(2-nitrophenyl)octahydroindol-4-one (19b).** To a cooled (0 °C) solution of octahydroindole *cis*-**16** (8.46 g, 30.8 mmol) and 1,8-bis(dimethylamino)naphthalene (6.6 g, 30.8 mmol) in 1,2-dichloroethane (250 mL) was added dropwise α-chloroethyl chloroformate (13.3 mL, 123 mmol). After 15 min at 0 °C, the mixture was heated at reflux for 3 h. The solvent was evaporated, and the residue was partitioned between CH_2Cl_2 and 1 N aqueous HCl. The organic layer was washed with 10% aqueous $NaHCO_3$, dried, and concentrated to give carbamate **19b** (11.4 g, quantitative):[63] IR ($CHCl_3$) 1709, 1530, 1350 cm^{-1}; ^{1}H NMR (200 MHz) δ 1.60−1.85 (m, 3H), 1.86−2.05 (m, 1H), 2.15−2.65 (m, 7H), 3.60−4.05 (m, 2H), 4.27−4.55 (m, 1H), 6.35−6.50 (m, 1H), 7.25−7.70 (m, 3H), 8.05 (d, J = 8 Hz, 1H); ^{13}C NMR (50.3 MHz) δ 19.2 (t), 24.7−24.9 (q), 26.6−27.7 (t), 31.1−32.3 (t), 36.0−36.2 (t), 43.2−43.7 (t), 60.3−61.3 (s), 65.0−65.5 (d), 82.5−82.8 (d), 126.2−126.9 (d), 128.5−129.1 (d), 133.8−134.2 (d), 136.4−136.7 (s), 147.1−147.3 (s), 150.9−151.5 (s), 206.7 (s). Anal. Calcd for $C_{17}H_{19}ClN_2O_5$: C, 55.67; H, 5.22; N, 7.64. Found: C, 55.75; H, 5.34; N, 7.53.

***cis*-1-[(1-Chloroethoxy)carbonyl]-3a-(2-nitrophenyl)-5-(phenylselanyl)octahydroindol-4-one (21).** To a cooled (−20 °C) solution of ketone **19b** (11.4 g, 30.8 mmol) in 1:1 pentane-CH_2Cl_2 (700 mL) were added hexamethyldisilazane (17.5 mL, 83.3 mmol) and Me_3SiI (8.4 mL, 61.7 mmol). The resulting solution was stirred at −20 °C for 6 h and quenched by the addition of saturated aqueous $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were sequentially washed

(61) *i*-PrOH was the solvent of choise for the reductive amination. The use of MeOH[15] led to considerable amounts of **52** (four diastereomers). Its formation can be rationalized as outlined in the following scheme, taking into account that the hydride reduction of the iminium intermediate **A** is slower than in the *N*-methyl series as a consequence of the larger size of the *N*-substituent.

(62) Octahydroindolone (−)-**51** is in a preferred conformation that locates the 3a-aryl group in equatorial disposition with respect to the carbocyclic ring. A related 3a-aryloctahydroindolone (aryl = 3,4-methylenedioxyphenyl) possessing the same relative stereochemistry as (−)-**51** exists in a preferred conformation in which the aryl group is axial: Overman, L. E.; Sugai, S. *Helv. Chim. Acta* **1985**, *68*, 745−749. For the conformational behavior of 3a-aryloctahydroindoles, see: Bonjoch, J.; Solé, D.; Cuesta, X. *Heterocycles* **1997**, *45*, 315−322. See also ref 15.

(63) In the description of the ^{13}C NMR data of *N*-(α-chloroethoxycarbonyl) octahydroindoles a hyphen is used to indicate that the spectra are complex due to the existence of diastereoisomers and rotamers.

with 10% aqueous sodium thiosulfate and saturated aqueous $NaHCO_3$, dried, and concentrated to give silyl enol ether **20b** (13.6 g, quantitative): [63] ^{1}H NMR (200 MHz) δ 0.03−0.16 (m, 9H), 1.60−2.70 (m, 9H), 3.40−3.95 (m, 2H), 4.50−4.75 (m, 1H), 4.80−5.05 (m, 1H), 6.45−6.75 (m, 1H), 7.25−7.75 (m, 4H); ^{13}C NMR (50.3 MHz) δ 0.26 (q), 20.8 (t), 23.1 and 23.8 (2 t), 25.2 (q), 32.3−34.6 (t), 44.5−45.1 (t), 53.0−54.0 (s), 62.7−63.4 (d), 82.7−83.1 (d), 102.9−104.4 (d), 124.6 (d), 127.9 (d), 129.9−130.6 (d), 130.9−131.2 (d), 134.4 (s), 149.4−149.9 (s), 151.2−152.2 (s).

To a cooled (−35 °C) solution of **20b** (5.56 g, 12.7 mmol) and diphenyl diselenide (3.95 g, 12.7 mmol) in freshly distilled THF[64] (325 mL) was added dropwise over a 90 min period a solution of benzeneselenenyl chloride (2.42 g, 12.7 mmol) in THF (250 mL). The resulting solution was slowly warmed to rt (3 h) and then concentrated. Chromatography (Florisil, hexane−EtOAc from 7:3 to 1:1) yielded ketone **21**[65] (4.63 g, 70% from *cis*-**16**):[63] IR ($CHCl_3$) 1714, 1694, 1530, 1350 cm^{-1}; ^{1}H NMR (200 MHz) δ 1.60−1.85 (m, 3H), 1.87−2.42 (m, 3H), 2.55−2.84 (m, 2H), 3.04−3.34 (m, 1H), 3.60−3.98 (m, 2H), 4.14 (br s, 1H), 4.18−4.55 (m, 1H), 6.40−6.55 (m, 1H), 7.20−7.74 (m, 8H), 8.06 (m, 1H); ^{13}C NMR (50.3 MHz) δ 24.1−24.3 (t), 24.7−25.2 (q), 26.0 (t), 33.8−35.0 (t), 43.8−44.2 (t), 45.1−45.4 (d), 60.5−61.0 (s), 64.9−65.4 (d), 82.7−82.9 (d), 126.5−126.8 (d), 128.8 (d), 129.1 (d), 129.3 (d), 134.0−134.3 (d), 135.3 (d), 137.0 (s), 147.0 (s), 151.2−151.5 (s), 204.2−204.4 (s). Anal. Calcd for $C_{23}H_{23}ClN_2O_5Se\cdot{}^1/_4H_2O$: C, 52.48; H, 4.50; N, 5.32. Found: C, 52.50; H, 5.03; N, 5.36.

***cis*-1-[(1-Chloroethoxy)carbonyl]-3a-(2-nitrophenyl)-1,2,3,3a,7,-7a-hexahydroindol-4-one (22b).** A stream of ozone gas was bubbled through a cooled (−78 °C) solution of ketone **21** (4.63 g, 8.87 mmol) in CH_2Cl_2 (350 mL) until it turned to the characteristic pale blue color. The solution was purged with O_2, and diisopropylamine (1.3 mL, 8.9 mmol) was added. The resulting mixture was stirred at rt for 15 min and sequentially washed with 1 N aqueous HCl and 10% aqueous $NaHCO_3$. The organic extracts were dried and concentrated, and the residue was chromatographed (Florisil, 1:1 hexane−EtOAc) to give ketone **22b** (2.33 g, 72%):[63] IR (KBr) 1721, 1673, 1521, 1348 cm^{-1}; ^{1}H NMR (200 MHz) δ 1.60−1.85 (m, 3H), 2.30−2.60 (m, 2H), 2.65−2.80 (m, 1H), 3.00−3.45 (m, 1H), 3.65−4.00 (m, 2H), 4,58−4.90 (m, 1H), 6.19 (d, J = 10.5 Hz, 1H), 6.35−6.55 (m, 1H), 6.80−6.92 (m, 1H), 7.30−7.75 (m, 3H), 8.09 (m, 1H); ^{13}C NMR (50.3 MHz) δ 24.9−25.1 (q), 29.6−30.4 (t), 31.5−33.0 (t), 43.9−44.2 (t), 58.0−58.8 (s), 62.1-62.7 (d), 82.8−82.9 (d), 126.7−127.2 (d), 128.9−129.8 (d), 133.8−134.1 (d), 135.9−137.0 (s), 144.1−145.0 (d), 147.7 (s), 151.5 (s), 195.6−195.9 (s). Anal. Calcd for $C_{17}H_{17}ClN_2O_5$: C, 55.98; H, 4.70; N, 7.68. Found: C, 56.01; H, 5.10; N, 7.50.

***cis*-3a-(2-Nitrophenyl)-1,2,3,3a,7,7a-hexahydroindol-4-one (23).** A solution of carbamate **22b** (2.33g, 6.39 mmol) in MeOH (200 mL) was heated at reflux for 3 h. The solvent was removed *in vacuo* giving crude hexahydroindole **23**·hydrochloride (1.65 g, quantitative), which was used in the next step without purification: mp 171 °C (Et_2O); ^{1}H NMR (200 MHz, DMSO-d_6) δ 2.65−2.80 (m, 2H), 2.95−3.15 (m, 1H), 3.20−3.45 (m, 1H), 3.50−3.70 (m, 2H), 4.42 (t, J = 7.5 Hz, 1H), 6.11 (d, J = 10.5 Hz, 1H), 7.01 (ddd, J = 10.5, 5, 3 Hz, 1H), 7.55−7.91 (m, 3H), 8.12 (d, J = 7.5 Hz, 1H), 9.14 (br, 1H), 9.83 (br, 1H); ^{13}C NMR (50.3 MHz, DMSO-d_6) δ 26.8 (t), 32.3 (t), 42.4 (t), 59.0 (s), 62.8 (d), 126.5 (d), 126.9 (d), 130.1 (d), 131.2 (d), 134.0 (s), 135.1 (d), 145.9 (d), 148.2 (s), 194.6 (s). Amine **23** could never be isolated as the free base, probably due to its tendency to polymerization, and had to be used as the hydrochloride salt.

***cis*-3a-(2-Nitrophenyl)-1-(3-oxobutyl)-1,2,3,3a,7,7a-hexahydroindol-4-one (24).** To a solution of crude amine **23**·hydrochloride (1.09 g, 4.23 mmol) and triethylamine (0.65 mL, 4.66 mmol) in MeOH (100 mL) was added dropwise methyl vinyl ketone (0.4 mL, 4.7 mmol). The mixture was stirred at rt for 1 h 45 min. The solvent was removed *in vacuo*, and the residue was purified by chromatography (from EtOAc to 98:2 EtOAc−diethylamine) to give amine **24** (1.02 g, 74%):[66] IR ($CHCl_3$) 1708, 1669, 1524, 1354 cm^{-1}; ^{1}H NMR (200 MHz) δ 1.94 (s, 3H), 2.25−3.10 (m, 10H), 3.64 (t, J = 6 Hz, 1H), 6.12 (dt, J = 10, 2 Hz, 1H), 6.85 (dt, J = 10, 4 Hz, 1H), 7.35−7.48 (m, 2H), 7.57 (ddd, J = 8, 7, 1.5 Hz, 1H), 7.83 (dd, J = 8, 1.5 Hz, 1H); ^{13}C NMR (50.3 MHz) δ 24.8 (t), 29.4 (q), 34.4 (t), 42.3 (t), 46.2 (t), 49.7 (t), 59.1 (s), 67.0 (d), 125.2 (d), 127.9 (2 d), 130.8 (d), 132.5 (d), 137.5 (s), 145.7 (d), 148.2 (s), 197.7 (s), 208.2 (s). Anal. Calcd for $C_{18}H_{20}N_2O_4$: C, 65.84; H, 6.14; N, 8.53. Found: C, 65.66; H, 6.12; N, 8.29.

Cyclization of 24. Method A. To a solution of ketone **24** (0.98 g, 3 mmol) in THF (40 mL) were added dropwise (*R*)-α-methylbenzylamine (0.8 mL, 6 mmol) and 3Å molecular sieves. The mixture was stirred at rt for 4 days. After filtering through Celite, the solvent was removed *in vacuo*, the residue was dissolved in 20% aqueous AcOH (100 mL), and the solution was stirred at rt for 4 h. The mixture was basified with saturated aqueous Na_2CO_3 and extracted with CH_2Cl_2. The organic extracts were dried and concentrated, and the resulting residue was chromatographed. Elution with 98:2 CH_2Cl_2−MeOH gave azatricycle **25** (167 mg, 17%), whereas elution with 97:3 CH_2Cl_2−MeOH gave the C-2 epimer, **(1*RS*,2*SR*,7*RS*,8*SR*)-2-acetyl-7-(2-nitrophenyl)-4-azatricyclo[5.2.2.0^{4,8}]undecan-11-one** (**26**, 490 mg, 50%): IR (KBr) 1704−1698, 1530, 1366 cm^{-1}; ^{1}H NMR (200 MHz) δ 2.17 (s, 3H), 2.10−2.58 (m, 6H), 2.79 (br s, 1H), 2.75−3.25 (m, 5H), 3.78 (br s, 1H), 7.24 (dd, J = 7.8, 1.7 Hz, 1H), 7.37 (m, 1H), 7.45−7.55 (m, 2H); ^{13}C NMR (50.3 MHz) δ 26.5 (t), 28.2 (q), 29.1 (d), 39.5 (t), 41.9 (t), 45.7 (t), 52.1 (d), 54.8 (t), 61.8 (s), 65.0 (d), 125.5 (d), 128.1 (d), 129.9 (d), 132.0 (d), 134.2 (s), 151.2 (s), 208.0 (s), 212.3 (s). Anal. Calcd for $C_{18}H_{20}N_2O_4\cdot{}^1/_4H_2O$: C, 64.95; H, 6.20; N, 8.41. Found: C, 65.21; H, 6.21; N, 8.21.

Method B. To a cooled (−20 °C) solution of ketone **24** (0.42 g, 1.3 mmol) in DME (30 mL) was added dropwise Triton B (40% in MeOH, 0.55 mL, 1.3 mmol). The mixture was stirred at −20 °C for 2.5 h and partitioned between Et_2O and brine. The organic layer was washed several times with brine, dried, and concentrated. Chromatography of the residue yielded ketones **25** (59 mg, 14%) and **26** (186 mg, 44%).

(1*RS*,2*SR*,7*RS*,8*SR*)-2-[2-(2-Methyl-1,3-dithiolanyl)]-7-(2-nitrophenyl)-4-azatricyclo[5.2.2.0^{4,8}]undecan-11-one (27). $BF_3\cdot Et_2O$ (0.9 mL, 6.9 mmol) was added dropwise to a solution of ketone **26** (452 mg, 1.38 mmol) and 1,2-ethanedithiol (0.9 mL, 11 mmol) in glacial AcOH (9 mL). After stirring at rt for 24 h, the mixture was diluted with CH_2Cl_2 and basified with 2 N aqueous NaOH. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried, and concentrated to give a residue. Chromatography (98:2 CH_2Cl_2−MeOH) yielded dithioacetal **27** (435 mg, 80%): IR ($CHCl_3$) 1696, 1529, 1350 cm^{-1}; ^{1}H NMR (200 MHz) δ 1.80 (s, 3H), 2.05−2.55 (m, 6H), 2.75 (br s, 1H), 2.82−3.44 (m, 9H), 3.81 (br s, 1H), 7.27 (d, J = 7.8 Hz, 1H), 7.38 (m, 1H), 7.40−7.55 (m, 2H); ^{13}C NMR (50.3 MHz) δ 28.8 (t), 31.0 (d), 33.7 (q), 38.3 (t), 38.7 (t), 40.9 (t), 42.2 (t), 48.8 (t), 49.6 (d), 54.5 (t), 61.9 (s), 64.6 (d), 68.3 (s), 125.6 (d), 128.1 (d), 129.6 (d), 131.7 (d), 133.2 (s), 151.4 (s), 212.4 (s). Anal. Calcd for $C_{20}H_{24}N_2O_3S_2$: C, 59.38; H, 5.98; N, 6.92; 15.85. Found: C, 59.63; H, 5.89; N, 6.71; S, 15.73.

Methyl (1*RS*,2*RS*,7*SR*,8*RS*)-2-[2-(2-Methyl-1,3-dithiolanyl)]-7-(2-nitrophenyl)-11-oxo-4-azatricyclo[5.2.2.0^{4,8}]undecane-10-carboxylate (28). To a cooled (−78 °C) solution of diisopropylamine (0.33 mL, 2.39 mmol) in THF (10 mL) was added dropwise BuLi (1.6 M in hexane, 1.43 mL). After 10 min at −78 °C, were added HMPA (1 mL, 5.7 mmol) and a solution of ketone **27** (460 mg, 1.14 mmol) in THF (10 mL). After 30 min at −78 °C, the bath was removed, methyl cyanoformate (0.27 mL, 3.42 mmol) was added dropwise, and the mixture was stirred at rt for 3 h. The reaction was quenched by addition of saturated aqueous NH_4Cl (10 mL) and extracted with Et_2O. The organic layer was washed with brine, dried, and concentrated to give a residue, which was chromatographed. On elution with EtOAc, ester **28** (260 mg, 50%)[67] was obtained. IR ($CHCl_3$) 1649, 1599, 1531, 1355

(64) When the THF used had been kept with Na, appreciable amounts of the corresponding α-chloro ketone were formed: see Supporting Information.

(65) When ketone **19b** was treated with diphenyl diselenide (0.5 equiv)/SeO_2 (0.5 equiv)/H_2SO_4 (cat) the phenylseleno ketone **21** was obtained in 50% yield, with recovering of all the unreacted starting material. Increasing the amount of diphenyl diselenide and SeO_2 gave the same result.

(66) In some runs, tricycles **25** and **26** (3:1 ratio) were obtained together with the alkylated product. These compounds were formed during purification by column chromatography. All attempts to take advantage of this spontaneous cyclization resulted in failure.

(67) In some runs, the corresponding carbonate was formed as a minor byproduct: see Supporting Information.

cm^{-1}; ^{1}H NMR (200 MHz) δ 1.89 (s, 3H), 1.92 (dt, J = 12.5, 3.5 Hz, 1H), 2.07 (ddd, J = 12.5, 3.8, 2.5 Hz, 1H), 2.19 (dm, J = 11.5 Hz, 1H), 2.37 (dd, J = 15.3, 7 Hz, 1H), 2.54 (t, J = 11.4 Hz, 1H), 2.84 (m, 1H), 3.00 (m, 1H), 3.10−3.33 (masked, 1H), 3.22 (m, 4H), 3.44 (br s, 1H), 3.47 (dd, J = 11.5, 3 Hz, 1H), 3.76 (t, J = 2.5 Hz, 1H), 3.84 (s, 3H), 7.20−7.50 (m, 4H), 12.92 (br s, 1H); ^{13}C NMR (50.3 MHz) δ 27.4 (t), 27.5 (d), 31.9 (q), 36.4 (t), 38.9 (t), 41.4 (t), 49.2 (t), 51.0 (d), 51.5 (q), 55.0 (s), 56.0 (t), 65.6 (d), 68.4 (s), 101.2 (s), 124.8 (d), 127.7 (d), 131.1 (d), 132.0 (d), 134.5 (s), 150.9 (s), 172.5 (s), 174.9 (s). Anal. Calcd for $C_{22}H_{26}N_2O_5S_2$: C, 57.12; H, 5.66; N, 6.06; S, 13.86. Found: C, 57.50; H, 5.68; N, 5.97; S, 13.53. On elution with 97:3 EtOAc-MeOH, unreacted ketone **27** (230 mg, 50%) was recovered.

Methyl (1*RS*,2*RS*,7*SR*,8*RS*)-2-Acetyl-7-(2-nitrophenyl)-11-oxo-4-azatricyclo[5.2.2.0^{4,8}]undecane-10-carboxylate (29). A solution of red HgO (0.28 g, 1.3 mmol) and BF_3·Et_2O (0.3 mL, 2.6 mmol) in 85:15 THF−H_2O (23 mL) was stirred at rt for 5 min. A solution of dithioacetal **28** (300 mg, 0.65 mmol) in THF (7.5 mL) was added dropwise. After stirring at rt for 30 min, the mixture was partitioned between Et_2O and brine. The aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried, and concentrated. Chromatography (97:3 CH_2Cl_2−MeOH) of the residue yielded ketone **29** (215 mg, 86%): IR ($CHCl_3$) 1708, 1656, 1604, 1532, 1357 cm^{-1}; ^{1}H NMR (200 MHz) δ 1.99 (dt, J = 13.4, 3 Hz, 1H), 2.11 (dt, J = 13.4, 3 Hz, 1H), 2.25 (s, 3H), 2.35 (dd, J = 15.2, 6.5 Hz, 1H), 2.60−2.91 (m, 4H), 2.99 (m, 1H), 3.14 (dd, J = 11, 7 Hz, 1H), 3.40 (br s, 1H), 3.70 (s, 3H), 3.71 (br s, 1H), 7.25−7.52 (m, 4H); ^{13}C NMR (50.3 MHz) δ 25.7 (t), 28.5 (d), 29.1 (q), 37.0 (t), 45.9 (t), 50.8 (d), 51.3 (q), 54.9 (s), 55.8 (t), 65.4 (d), 98.3 (s), 124.5 (d), 127.5 (d), 130.9 (d), 131.7 (d), 134.1 (s), 150.5 (s), 171.4 (s), 175.5 (s), 208.2 (s). Anal. Calcd for $C_{20}H_{22}N_2O_6$·$^3/_4H_2O$: C, 60.06; H, 5.92; N, 7.00. Found: C, 60.17; H, 5.67; N, 6.91. HRMS calcd for $C_{20}H_{22}N_2O_6$ 386.1478, found 386.1488.

Methyl (±)-19-Oxo-2,16-didehydro-17-curanoate (30). To a solution of the nitro derivative **29** (100 mg, 0.26 mmol) in MeOH (25 mL) was added dropwise an excess of Et_2O solution of dry HCl. The solvent and the excess of acid were removed *in vacuo*, and the resulting residue was dissolved in MeOH (25 mL). The mixture was hydrogenated at rt and atmospheric pressure in the presence of 10% Pd−C (50 mg) for 2 h. After filtration through Celite and removal of the solvent, the residue was partitioned between CH_2Cl_2 and 10% aqueous Na_2CO_3. The dried extracts were concentrated and chromatographed (95:5 CH_2Cl_2−MeOH) to give pentacyclic ketone **30** (70 mg, 80%): IR ($CHCl_3$) 3380, 1708, 1675 cm^{-1}; ^{1}H NMR (200 MHz) δ 1.49 (dt, J = 13, 3 Hz, 1H), 1.80−2.15 (m, 3H), 2.16 (dt, J = 13, 3.5 Hz, 1H), 2.30 (s, 3H), 2.60−2.90 (m, 2H), 2.98 (dd, J = 15.5, 6 Hz, 1H), 3.05−3.15 (m, 1H), 3.49 (br s, 1H), 3.69 (s, 3H), 3.93 (br s, 1H), 6.81 (d, J = 7.5 Hz, 1H), 6.91 (t, J = 7.5 Hz, 1H), 7.08−7.20 (m, 2H), 8.94 (br s, 1H); ^{13}C NMR (50.3 MHz) δ 29.2 (q), 30.4 (d), 31.2 (t), 42.8 (t), 45.5 (t), 49.4 (d), 51.0 (q), 53.5 (t), 56.1 (s), 60.5 (d), 96.5 (s), 109.9 (d), 119.7 (d), 121.3 (d), 127.9 (d), 134.6 (s), 144.1 (s), 167.5 (s), 171.4 (s), 208.0 (s). Anal. Calcd for $C_{20}H_{22}N_2O_3$·$^1/_2H_2O$: C, 69.14; H, 6.67; N, 8.06. Found: C, 68.98; H, 6.53; N, 7.77. HRMS calcd for $C_{20}H_{22}N_2O_3$ 338.1630, found 338.1623.

(±)-Echitamidine (9). To a cooled (0 °C) solution of ketone **30** (20 mg, 0.059 mmol) in MeOH (3 mL) was added $NaBH_4$ (5 mg, 0.13 mmol). After 15 min at 0 °C and 2.5 h at room temperature, the reaction was quenched by the addition of water (3 mL). The mixture was partitioned between Et_2O and H_2O, and the organic extracts were dried and concentrated to give a residue. Chromatography (92:8 CH_2Cl_2−MeOH) yielded (±)-echitamidine (**9**, 15 mg, 75%). The ^{1}H and ^{13}C NMR spectral data were identical with those reported for the natural product:[28b] ^{1}H NMR (200 MHz) δ 1.16 (d, J = 6.2 Hz, 3H), 1.41 (ddd, J = 13.1, 3.9, 1.9 Hz, 1H), 1.70−2.10 (m, 3H), 2.03 (ddd, J = 13, 3, 2 Hz, 1H), 2.70−3.30 (m, 4H), 3.30 (br s, 1H), 3.87 (br s, 1H), 3.88 (s, 3H), 4.50 (br s, 1H), 6.84 (d, J = 7.5 Hz, 1H), 6.93 (td, J = 7.6, 1 Hz, 1H), 7.15 (td J = 7.6, 1.3 Hz, 1H,), 7.19 (d, J = 7.3 Hz, 1H), 8.65 (br s, 1H); ^{13}C NMR (50.3 MHz) δ 19.8 (q), 28.8 (d), 31.1 (t), 43.6 (t), 45.9 (d), 48.2 (t), 51.9 (t), 54.1 (t), 57.2 (s), 60.9 (d), 68.4 (d), 96.9 (s), 109.6 (s), 119.8 (d), 121.4 (d), 127.6 (d), 135.6 (s), 143.7 (s), 168.8 (s), 172.5 (s).

***cis*-1-[(*Z*)-2-Iodo-2-butenyl]-3a-(2-nitrophenyl)-1,2,3,3a,7,7a-hexahydroindol-4-one (31).** To a solution of crude amine **23** (1 g, 4 mmol) in CH_3CN (25 mL) were added anhydrous K_2CO_3 (1.1 g, 8 mmol) and (*Z*)-1-bromo-2-iodo-2-butene[30] (2.1 g, 8 mmol). The mixture was stirred at rt for 3 h. The solvent was removed *in vacuo*, and the residue was partitioned between H_2O and CH_2Cl_2. The dried organic extracts were concentrated and chromatographed (8:2 hexane−EtOAc) to give compound **31** (1.22 g, 70%): IR (film) 1670, 1525, 1360 cm^{-1}; ^{1}H NMR (200 MHz) δ 1.73 (d, J = 6.4 Hz, 3H), 2.30−2.70 (m, 4H), 2.90 (td, J = 9.5, 3.5 Hz, 1H), 3.08 (m, 1H), 3.34 (s, 2H), 3.75 (t, J = 6 Hz, 1H), 5.77 (q, J = 6.4 Hz, 1H), 6.15 (dt, J = 9.6, 1.9 Hz, 1H), 6.89 (dt, J = 9.6, 4.7 Hz, 1H), 7.42 (m, 1H), 7.60 (m, 2H), 7.90 (d, J = 7.5 Hz, 1H); ^{13}C NMR (50.3 MHz) δ 21.4 (q), 25.0 (t), 34.2 (t), 48.8 (t), 59.1 (s), 62.2 (t), 65.6 (d), 108.7 (s), 124.8 (d), 127.4 (d), 127.5 (d), 131.1 (d), 131.2 (d), 132.4 (d), 137.5 (s), 145.5 (d), 147.9 (s), 197.3 (s). Anal. Calcd for $C_{18}H_{19}IN_2O_3$: C, 49.33; H, 4.37; N, 6.39. Found: C, 49.81; H, 4.36; N, 5.99.

(±)-19,20-Didehydrotubifoline (32). A solution of vinyl iodide **31** (47 mg, 0.11 mmol), LiCN in DMF (2.15 mL, 0.5 M, 1.1 mmol), and Et_3N (45 μl, 0.32 mmol) in CH_3CN (5 mL) was added at rt to Ni(COD)$_2$ (195 mg, 0.71 mmol). The resulting mixture was stirred at rt for 2.5 h and filtered through Celite, washing carefully with Et_2O. The filtrate was sequentially washed with saturated aqueous Na_2CO_3 and brine. The dried organic phase was concentrated and chromatographed (Florisil, 95:5 CH_2Cl_2−MeOH) to give dehydrotubifoline (**32**,11 mg, 40%). The ^{1}H and ^{13}C NMR spectra of dehydrotubifoline were identical with those reported in the literature.[14b,30]

Methyl (±)-(19*E*)-2,16,19,20-Tetradehydro-17-norcuran-1-carboxylate (33). To a suspension of NaH (27 mg, 60% oil dispersion, 0.65 mmol), previously washed with hexane, in DME (20 mL) were added a solution of dehydrotubifoline (**32**, 87 mg, 0.33 mmol) in DME (5 mL) and methyl chloroformate (0.13 mL, 1.7 mmol). The mixture was warmed at 60 °C for 4 h. After cooling, the mixture was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic extracts were washed with brine, dried, and concentrated. Chromatography (95:5 Et_2O-diethylamine) of the residue yielded compound **33** (38 mg, 36%): IR (film) 1717, 1469, 1441, 1378, 1317, 1208 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.37 (dt, J = 13.2, 2.3 Hz, 1H), 1.70 (d, J = 6.6 Hz, 3H), 1.80 (ddd, J = 12.6, 9.3, 6.9 Hz, 1H), 2.09 (ddd, J = 12.9, 6.0, 4.4 Hz, 1H), 2.15 (dt, J = 10.1, 3.2 Hz, 1H), 2.77 (td, J = 9.7, 6.2 Hz, 1H), 2.92 (d, J = 14.9 Hz, 1H), 2.98 (ddd, J = 10.3, 6.6, 3.8 Hz, 1H), 3.31 (dm, J = 8.3 Hz, 1H), 3.70 (d, J = 15.6 Hz, 1H), 3.92 (s, 3H), 4.10 (t, J = 1.7 Hz, 1H), 5.34 (q, J = 6.8 Hz, 1H), 6.50 (d, J = 8.8 Hz, 1H), 7.05 (td, J = 7.4, 1 Hz, 1H), 7.18 (d, J = 6.9 Hz, 1H), 7.21 (td, J = 7.6, 1.3 Hz, 1H), 7.77 (d, J = 8.2 Hz, 1H); ^{13}C NMR (75 MHz) δ 13.0 (q), 27.0 (t), 30.2 (d), 41.6 (t), 51.6 (t), 52.7(q), 52.8 (t), 53.8 (s), 58.5 (d), 115.1 (d), 115.4 (d), 120.3 (d), 120.7 (d), 123.5 (d), 127.5 (d), 135.0 (s), 136.0 (s), 141.2 (s), 144.2 (s), 153.1 (s); HRMS calcd for $C_{20}H_{22}N_2O_2$ 322.1685, found 322.1681.

(±)-(19*E*)-2,16,19,20-Tetradehydro-17-norcuran-1-carboxaldehyde (34). A solution of vinyl iodide **31** (200 mg, 0.46 mmol), LiCN in DMF (9.1 mL, 0.5 M, 4.55 mmol), and Et_3N (190 μL, 1.37 mmol) in CH_3CN (20 mL) was added at rt to Ni(COD)$_2$ (830 mg, 3 mmol). After 2.5 h at room temperature, *N*,*N*-dimethyl(chloromethylene)-iminium chloride (1.17 g, 9.1 mmol) was added, and the mixture was stirred at rt for 2 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with Et_2O. The organic extracts were washed with brine, dried, and concentrated to give a residue that was purified by chromatography. On elution with 96:4 CH_2Cl_2−MeOH, pentacycle **34** (20 mg, 15%) was obtained: ^{1}H NMR (acetone-d_6, 300 MHz) δ 1.38 (dm, J = 12.3 Hz, 1H), 1.71 (d, J = 6.8 Hz, 3H), 1.76 (ddd, J = 12.4, 8.9, 7.1 Hz, 1H), 2.11 (m, 1H), 2.22 (dt, J = 13.3, 3.3 Hz, 1H), 2.75 (m, 1H), 2.88 (d, J = 15 Hz, 1H), 2.94 (m, 1H), 3.40 (m, 1H), 3.71 (d, J = 14.9 Hz, 1H), 4.10 (s, 1H), 5.35 (q, J = 6.7 Hz, 1H), 6.32 (d, J = 6.2 Hz, 2/3H), 6.95 (br, 1/3H), 7.19 (t, J = 7.5 Hz, 1H), 7.29 (t, J = 7.6 Hz, 1H), 7.38 (d, J = 7.4 Hz, 1H), 7.50 and 8.06 (2 br, 1H), 8.96 and 9.30 (2 br, 1H); ^{13}C NMR (acetone-d_6, 75 MHz, major rotamer) δ 13.2 (q), 28.0 (t), 30.8 (d), 41.9 (t), 52.3 (t), 53.4 (t), 54.3 (s), 58.8 (d), 114.0 (d), 116.2 (d), 120.7 (d), 121.7 (d), 125.6 (d), 128.3 (d), 137.6 (s), 141.2 (s), 145.4 (s), 157.9 (d); HRMS Calcd for $C_{19}H_{20}NO$ 292.1580, found 292.1576.

(±)-Norfluorocurarine (5). A solution of **34** (16 mg, 0.055 mmol) in MeOH (75 mL) was photolyzed under argon with a 125-W medium-pressure mercury lamp for 10 min. Evaporation of the solvent gave a

residue, which was chromatographed (95:5 Et_2O-diethylamine) yielding (±)-norfluorocurarine (**5**, 2.5 mg, 15%) and 19,20-didehydrotubifoline (**32**, 10 mg, 69%). The ^1H NMR spectral data of synthetic (±)-norfluorocurarine were identical with those reported for the natural product.[37c]

(±)-(19*Z*)-2,16,19,20-Tetradehydro-17-norcuran-1-carboxaldehyde (36). Operating as in the preparation of **34**, from vinyl iodide **35** (47 mg, 0.11 mmol) was obtained pentacycle **36** (6.5 mg, 20%) after chromatography (96:4 CH_2Cl_2−MeOH): IR (film) 1685, 1656, 1462, 1385 cm^{-1}; ^1H NMR (acetone-d_6, 300 MHz) δ 1.43 (dm, J = 11.8 Hz, 1H, H-14), 1.64 (d, J = 7.7 Hz, 3H, H-18), 1.72 (ddd, J = 12.8, 6.9, 5.9 Hz, 1H, H-6), 2.12 (m, 1H, H-14), 2.75 (dt, J = 10.7, 6.6 Hz, 1H, H-6), 2.84−3.04 (m, 1H, H-5), 3.02 (dt, J = 11.2, 7 Hz, 1H, H-5), 3.13 (m, 1H, H-15), 3.18 (d, J = 14.6 Hz, 1H, H-21), 3.63 (d, J = 14.6 Hz, 1H, H-21), 4.03 (m, 1H, H-3), 5.49 (qd, J = 6.8, 1.2 Hz, 1H, H-19), 6.07 (dm, J = 6 Hz, 2/3H, H-16), 6.73 (br, 1/3H, H-16), 7.18 (td, J = 7.5, 1.1 Hz, 1H, H-10), 7.28 (td, J = 7.7, 1.4 Hz, 1H, H-11), 7.39 (d, J = 7.7 Hz, 1H, H-9), 7.50 and 8.06 (2 br, 1H, H-12), 8.92 and 9.26 (2 br, 1H, CHO); ^{13}C NMR (acetone-d_6, 75 MHz, major rotamer) δ 13.0 (C-18), 29.1 (C-14), 36.2 (C-15), 41.8 (C-6), 46.7 (C-21), 53.4 (C-5), 54.2 (C-7), 59.7 (C-3), 114.4 (C-16), 116.3 (C-12), 120.3 (C-9), 121.4 (C-19), 125.7 (C-10), 128.2 (C-11), 137.0 (C-20), 141.3 (C-13), 146.2 (C-2), 157.8 (C-17); HRMS calcd for $C_{19}H_{20}N_2O$ 292.1582, found 292.1577.

***cis*-3a-(2-Nitrophenyl)-1-[4-(trimethylsilyl)-2-butynyl]-1,2,3,3a,7,7a-hexahydroindol-4-one (46).** To a solution of crude amine **23** (167 mg, 0.69 mmol) in 2-butanone (10 mL) were added 4-iodo-1-(trimethylsilyl)-2-butyne[51] (260 mg, 1.03 mmol) and anhydrous K_2CO_3 (140 mg, 1.03 mmol). The mixture was heated at reflux for 5 h. The solvent was removed *in vacuo*, and the residue was partitioned between H_2O and CH_2Cl_2. The organic extracts were dried and concentrated, and the resulting residue was purified by chromatography. On elution with 1:1 hexane−EtOAc, hexahydroindole **46** (340 mg, 65%) was obtained: IR (KBr) 1673, 1529, 1358, 1250, 850 cm^{-1}; ^1H NMR (200 MHz) δ 0.02 (s, 9H), 1.38 (t, J = 2.4 Hz, 2H), 2.44−2.56 (m, 3H), 2.80 (dq, J = 19, 3 Hz, 1H), 2.99−3.18 (m, 2H), 3.48 (t, J = 2.4 Hz, 2H), 3.63 (ddd, J = 5, 2.5, 1Hz, 1H), 6.18 (ddd, J = 10, 1.5, 1 Hz, 1H), 6.85 (m, 1H), 7.39 (t, J = 8 Hz, 1H), 7.51 (m, 2H), 7.78 (dd, J = 8, 1 Hz, 1H); ^{13}C NMR (50.3 MHz) δ −2.3 (q), 6.6 (t), 26.4 (t), 36.4 (t), 40.0 (t), 49.8 (t), 58.5 (s), 65.1 (d), 72.3 (s), 83.0 (s), 124.8 (d), 127.5 (d), 127.9 (d), 130.0 (d), 132.4 (d), 136.8 (s), 146.3 (d), 148.8 (s), 196.9 (s). Anal. Calcd for $C_{21}H_{26}N_2O_3Si$: C, 65.93; H, 6.85; N, 7.32. Found: C, 65.67; H, 6.87; N, 7.04.

(1*RS*,7*RS*,8*SR*)-7-(2-Nitrophenyl)-2-vinylidene-4-azatricyclo-[5.2.2.0^{4,8}]undecan-11-one (47). To a cooled solution (0 °C) of propargylic silane **46** (340 mg, 0.89 mmol) in CH_2Cl_2 (34 mL) was added dropwise $BF_3{\cdot}Et_2O$ (0.45 mL, 3.55 mmol). The mixture was stirred at 0 °C for 10 min and at rt for 6 h. After cooling to 0 °C, $BF_3{\cdot}Et_2O$ (0.23 mL, 1.78 mmol) was added dropwise, and the mixture was stirred at rt overnight. The reaction was quenched by addition of H_2O, basified with 10% aqueous Na_2CO_3, and extracted with CH_2Cl_2. The dried extracts were concentrated and chromatographed (Al_2O_3, 1:1 hexane−EtOAc) to give allene **47** (234 mg, 85%): IR (film) 1950, 1699, 1532, 1366 cm^{-1}; ^1H NMR (500 MHz) δ 2.21 (dm, J = 14.5 Hz, 1H, H-9), 2.20−2.30 (masked, 1H, H-6), 2.30 (dt, J = 14.5, 2.8 Hz, 1H, H-9), 2.61 (d, J = 4.5 Hz, 2H, H-10), 2.85−2.92 (m, 2H, H-5 and H-6), 2.95−3.12 (masked, 1H, H-1), 2.97 (dt, J = 14.5, 2.5 Hz, 1H, H-3), 3.14−3.22 (m, 1H, H-5), 3.58 (dt, J = 14.5, 2.5 Hz, 1H, H-3), 3.89 (br s, 1H, H-8), 4.67 (dd, J = 5, 2.5 Hz, 2H, =CH_2), 7.28−7.33 (m, 2H, H-4′ and H-6′), 7.42−7.47 (m, 2H, H-3′ and H-5′); ^{13}C NMR (50.3 MHz) δ 25.4 (C-9), 31.8 (C-1), 38.9 (C-6), 46.5 (C-10), 49.7 (C-3), 54.9 (C-5), 62.2 (C-7), 65.0 (C-8), 76.1 (=CH_2), 99.8 (C-2), 125.1 (C-3′), 127.9 (C-4′), 129.1 (C-6′), 132.0 (C-5′), 133.8 (C-1′), 150.9 (C-2′), 203.5 (=C=), 210.1 (C-11); HRMS calcd for $C_{18}H_{18}N_2O_3$ 310.1325, found 310.1317.

(±)-Tubifolidine (1). (a) From Dithioacetal 27. To a solution of dithioacetal **27** (50 mg, 0.12 mmol) in C_6H_6 (3 mL) were added Bu_3SnH (0.5 mL, 1.8 mmol) and AIBN (7.5 mg). After stirring at 80 °C for 16 h, the mixture was partitioned between C_6H_6 and 2 N aqueous NaOH. The organic extracts were dried and concentrated, and the residue was chromatographed (98:2 Et_2O−diethylamine) to give (±)-tubifolidine (**1**, 19 mg, 60%), which exhibited spectral data identical to those previously reported.[10]

(b) From Allene 47. To a solution of allene **47** (26 mg, 0.084 mmol) and anhydrous Na_2CO_3 (27 mg, 0.26 mmol) in MeOH (5 mL) was added 10% Pd−C (10 mg). The mixture was hydrogenated at rt and atmospheric pressure for 18 h. After filtration through Celite and removal of the solvent, the residue was partitioned between CH_2Cl_2 and H_2O. The organic extracts were dried and concentrated. Chromatography of the residue yielded (±)-tubifolidine (**1**, 14 mg, 60%).

Methyl (1*RS*,7*SR*,8*RS*)-7-(2-Nitrophenyl)-11-oxo-2-vinylidene-4-azatricyclo[5.2.2.0^{4,8}]undecane-10-carboxylate (48). Operating as in the preparation of **28**, from allene **47** (152 mg, 0.49 mmol) were obtained ester **48** (78 mg, 39%, 53% based on the consumed **47**) and starting allene **47** (43 mg, 28%) after chromatography (from hexane to 9:1 hexane−EtOAc).[67] **48**: IR (film) 1650, 1611, 1530, 1363, 1246 cm^{-1}; ^1H NMR (500 MHz) δ 2.00 (dt, J = 13.5, 3.5 Hz, 1H, H-9), 2.04 (dt, J = 13.5, 3.5 Hz, 2H, H-9), 2.37 (ddd, J = 15, 7.5, 3.5 Hz, 1H, H-6), 2.67 (ddd, J = 15, 8.75, 7.75 Hz, 1H, H-6), 2.91 (ddd, J = 11.75, 7.75, 3.5 Hz, 1H, H-5), 3.11 (dt, J = 13, 4 Hz, 1H, H-3), 3.13 (ddd, J = 12, 8.5, 7.75 Hz, 1H, H-5), 3.48 (d, J = 13 Hz, 1H, H-3), 3.58 (t, J = 2.75 Hz, 1H, H-1), 3.79 (s, 3H, OCH_3), 3.83 (t, J = 3 Hz, 1H, H-8), 4.64 (dd, J = 10, 3.25 Hz, 1H, =CH), 4.71 (dd, J = 10, 3 Hz, 1H, =CH), 7.31−7.35 (m, 2H, H-4′ and H-5′), 7.43−7.47 (m, 2H, H-3′ and H-6′), 12.51 (s, 1H, OH); ^{13}C NMR (75 MHz) δ 24.1 (C-9), 30.5 (C-1), 36.4 (C-6), 48.3 (C-3), 52.0 (OCH_3), 54.8 (C-5), 55.3 (C-7), 65.2 (C-8), 75.2 (=CH_2), 97.1 (C-2), 102.5 (C-10), 124.8 (C-3′), 127.8 (C-4′), 131.1 (C-6′), 132.0 (C-5′), 133.6 (C-1′), 150.9 (C-2′), 172.2 (C-11), 172.8 (COO), 203.2 (=C=). Anal. Calcd for $C_{20}H_{20}N_2O_5{\cdot}^1/_3H_2O$: C, 64.06; H, 5.57; N, 7.47. Found: C, 64.06; H, 5.75; N, 7.45.

(±)-19,20-Dihydroakuammicine (4). Operating as in the conversion of allene **47** to (±)-tubifolidine, from ester **48** (10 mg, 0.03 mmol) was obtained (±)-19,20-dihydroakuammicine (**4**, 5 mg, 57%) after chromatography (97:3 Et_2O−diethylamine). The NMR spectra were identical in all respects with those previously reported.[10]

(±)-Akuammicine (7). (a) From Carbamate 33. A solution of **33** (15 mg, 0.047 mmol) in MeOH (75 mL) was photolyzed under argon with a 125-W medium-pressure mercury lamp for 30 min. Evaporation of the solvent gave a residue which was chromatographed (95:5 Et_2O−diethylamine) yielding (±)-akuammicine (**7**, 4.5 mg, 30%), which was identical with an authentic sample by ^1H NMR and TLC comparison.[34c]

(b) From Allene 48. To a solution of ester **48** (10 mg, 0.03 mmol) in MeOH (10 mL) was added dropwise an excess of Et_2O solution of dry HCl. The solvent and the excess of acid were removed *in vacuo*, and the resulting residue was dissolved in MeOH (50 mL). The mixture was hydrogenated in the presence of 10% Pd-C (6 mg) at rt and 100 psi for 1 h 15 min. After filtration through Celite and removal of the solvent, the residue was partitioned between CH_2Cl_2 and 10% aqueous Na_2CO_3. The organic extracts were dried and concentrated, and the residue was chromatographed (from Et_2O to 96:4 Et_2O-diethylamine) to give (±)-19,20-dihydroakuammicine (**4**, 1 mg, 12%) and (±)-akuammicine (**7**, 3.5 mg, 38%).

Methyl (1*RS*,7*SR*,8*RS*)-7-(2-Nitrophenyl)-11-oxo-2-[(*Z*)-2-(tributylstannyl)ethylidene]-4-azatricyclo[5.2.2.0^{4,8}]undecane-10-carboxylate (49). To a solution of allene **48** (300 mg, 0.81 mmol) and $Pd(PPh_3)_4$ (47 mg) in THF (20 mL) was added dropwise Bu_3SnH (0.26 mL, 0.98 mmol). After 24 h at room temperature, the mixture was concentrated, and the residue was chromatographed (from hexane to 2:8 hexane−EtOAc) to give stannane **49** (363 mg, 68%): IR (film) 2920−2960, 1649, 1609, 1531, 1363 cm^{-1}; ^1H NMR (500 MHz) δ 0.75−0.95 (m, 14H), 1.20−1.65 (m, 14H), 1.84 (ddd, J = 13, 3.7, 3 Hz, 1H, H-9), 2.03 (dt, J = 13, 3 Hz, 1H, H-9), 2.12 (t, J = 11.5 Hz, 1H, CH_2Sn), 2.33 (dd, J = 15, 7 Hz, 1H, H-6), 2.78 (ddd, J = 15.5, 11, 8 Hz, 1H, H-6), 2.91 (dd, J = 12, 8 Hz, 1H, H-5), 3.11 (td, J = 11, 7.5 Hz, 1H, H-5), 3.15−3.20 (m, 2H, H-3), 3.78 (s, 3H, OCH_3), 3.76−3.82 (m, 2H, H-1 and H-8), 5.47 (m, 1H, =CH), 7.29−7.36 (m, 2H, H-4′ and H-5′), 7.42−7.48 (m, 2H, H-3′ and H-6′), 12.45 (s, 1H, OH); ^{13}C NMR (75 MHz) δ 9.2 ($C_3H_7CH_2Sn$), 9.4 (CH_2Sn), 13.7 (CH_3), 25.4 (C-9), 27.3 (CH_2), 27.6 (C-1), 29.1 (CH_2), 37.3 (C-6), 51.8 (OCH_3), 54.6 (C-3), 55.2 (C-7), 55.9 (C-5), 66.7 (C-8), 102.1 (C-10), 122.8 (=CH), 124.6 (C-3′), 127.4 (C-4′), 129.1 (C-2), 130.9 (C-6′), 132.0

(C-5′), 134.7 (C-1′), 151.0 (C-2′), 172.2 (C-11), 173.8 (CO); HRMS calcd for $C_{32}H_{48}N_2O_5Sn$ 660.2585, found 660.2552.

(1*RS*,2*RS*,7*RS*,8*SR*)-2-Hydroxy-11-(methoxycarbonyl)-7-(2-nitrophenyl)-11-oxo-2-vinyl-4-azatricyclo[5.2.2.0^{4,8}]undecane 4-Oxide (50). To a solution of stannane **49** (130 mg, 0.2 mmol) in CH_2Cl_2 (15 mL) was added TFA (15 μL, 0.2 mmol). After 2 min at room temperature, *m*-CPBA (94 mg, 0.46 mmol) was added, and the stirring was maintained for 2 h. The mixture was poured into H_2O, the pH of the solution was adjusted to 7 by addition of 10% aqueous Na_2CO_3, and the mixture was extracted with CH_2Cl_2. The dried extracts were concentrated and chromatographed (95:5 CH_2Cl_2−MeOH) to give *N*-oxide **50** (61 mg, 76%): IR (film) 3000−3200, 1648, 1605, 1530, 1365 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.86 (ddd, J = 14.6, 3.4, 2 Hz, 1H), 2.52−2.74 (m, 2H), 3.05 (ddd, J = 14.6, 4.2, 2.8 Hz, 1H), 3.13 (br s, 1H), 3.24 (d, J = 12.8 Hz, 1H), 3.60 (d, J = 12.8 Hz, 1H), 3.64−3.78 (m, 2H), 3.83 (s, 3H), 4.46 (br s, 1H), 5.14 (dd, J = 10.8, 1.1 Hz, 1H), 5.24 (dd, J = 17.4, 1.1 Hz, 1H), 5.65 (dd, J = 17.4, 10.8 Hz, 1H), 7.33 (dd, J = 7.9, 1.4 Hz, 1H), 7.48 (td, J = 7.6, 1.4 Hz, 1H), 7.57 (td, J = 7.8, 1.8 Hz, 1H), 7.61 (dd, J = 7.7, 1.6 Hz, 1H); ^{13}C NMR (75 MHz) δ 17.1 (t), 32.4 (t), 34.6 (d), 51.1 (s), 52.1 (q), 63.9 (t), 70.3 (t), 71.9 (s), 77.4 (d), 103.3 (s), 114.0 (t), 125.5 (d), 129.2 (d), 131.5 (s), 131.8 (d), 131.9 (d), 139.0 (d), 150.6 (s), 171.3 (s), 171.9 (s). Anal. Calcd for $C_{20}H_{22}N_2O_7 \cdot H_2O$: C, 57.14; H, 5.75; N, 6.66. Found: C, 56.76; H, 5.78; N, 6.47.

(−)-20-Epilochneridine (9). To a solution of alcohol **50** (26 mg, 0.065 mmol) and anhydrous Na_2CO_3 (21 mg, 0.19 mmol) in MeOH (8 mL) was added 10% Pd-C (10 mg). The mixture was hydrogenated at rt and atmospheric pressure for 24 h. After filtration through Celite and removal of the solvent, the residue was partitioned between CH_2Cl_2 and H_2O. The organic extracts were dried and concentrated, and the residue was chromatographed. Elution with 94:6 CH_2Cl_2−MeOH gave 20-epilochneridine (**9**, 10 mg, 48%): IR (film) 3000−3400, 1671, 1595, 1462, 1240 cm^{-1}; UV, (EtOH) λ_{max} 326, 296, 231, 203 nm; ^{1}H NMR (500 MHz) δ 0.96 (t, J = 7.2 Hz, 3H, H-18), 1.18 (dt, J = 14, 3 Hz, 1H, H-14), 1.37 (dq, J = 14.5, 7 Hz, 1H, H-19), 1.60 (dq, J = 14.5, 7 Hz, 1H, H-19), 1.89 (dd, J = 13, 7 Hz, 1H, H-6), 2.38 (d, J = 12.5 Hz, 1H, H-21), 2.69 (dt, J = 13.5, 3.2 Hz, 1H, H-14), 2.80−2.90 (m, 3H, H-5, H-6 and H-21), 3.03 (s, 1H, H-15), 3.10−3.20 (m, 1H, H-5), 3.73 (s, 3H, OCH_3), 3.95 (s, 1H, H-3), 6.79 (d, J = 7.5 Hz, 1H, H-12), 6.88 (td, J = 7.5, 1 Hz, 1H, H-10), 7.11 (td, J = 7.5, 1 Hz, 1H, H-11), 7.15 (dd, J = 7.5, 1 Hz, 1H, H-9), 9.03 (s, 1H, NH); ^{13}C NMR (75 MHz) δ 6.7 (C-18), 25.7 (C-14), 32.3 (C-19), 36.4 (C-15), 42.4 (C-6), 51.2 (OCH_3), 53.7 (C-5), 54.5 (C-21), 56.2 (C-7), 60.6 (C-3), 71.0 (C-20), 101.4 (C-16), 109.8 (C-12), 119.7 (C-9), 121.2 (C-10), 127.8 (C-11), 135.1 (C-8), 144.2 (C-13), 168.5 (C-2), 170.9 (C-17). HRMS Calcd for $C_{20}H_{24}N_2O_3$ 340.1787, found 340.1787. IR, UV and ^{13}C NMR data were identical with those reported for the natural product.[59]

(3a*R*,7a*S*)-*N*-[(*S*)-α-Methylbenzyl]-3a-(2-nitrophenyl)octahydroindol-4-one [(−)-51]. A stirred solution of **15** (5 g, 18.3 mmol) in CH_2Cl_2 (400 mL) at −78 °C was charged with a constant stream of ozone. After 3 h, the solution turned pale blue and was purged with oxygen. The solvent was removed with a rotatory evaporator without warming, and the residue was dissolved in *i*-PrOH (750 mL). To this solution were added first *L*-(−)-α-methylbenzylamine hydrochloride (11.5 g, 73.2 mmol) and then $NaBH_3CN$ (0.58 g, 9.15 mmol, 0.5 equiv). After 30 min of stirring, an additional portion of $NaBH_3CN$ (0.58 g, 9.15 mmol, 0.5 equiv) was added, and the stirring was continued for 1 h. At this time, an additional portion of $NaBH_3CN$ (1.74 g, 27.4 mmol, 1.5 equiv) was added, and the stirring was continued for 48 h. The solvent was removed under reduced pressure, and the residue was partitioned between CH_2Cl_2 and 10% aqueous $NaHCO_3$. The organic extracts were dried and concentrated, and the resulting oil was chromatographed (from hexane to 7:3 hexane−EtOAc) to give *cis*-octahydroindole **(−)-51** (2.47 g, 37%) and a mixture (1:3 ratio) of the two *trans*-octahydroindoles (0.53 g, 8%). **(−)-51:** IR ($CHCl_3$) 1697, 1527, 1356 cm^{-1}; ^{1}H NMR (500 MHz) δ 1.16 (d, J = 6.5 Hz, 3H, CH_3), 1.64 (dddd, J = 16.5, 13.5, 10.5, 3.5 Hz, 1H, H-7), 2.01 (dm, J = 13.5 Hz, 1H, H-6), 2.09 (dm, J = 13.5 Hz, 1H, H-7), 2.13−2.30 (m, 3H, H-3 and H-6), 2.42−2.54 (m, 2H, H-5), 2.63 (td, J = 10, 5 Hz, 1H, H-2), 2.83 (td, J = 9, 6.5 Hz, 1H, H-2), 3.64 (q, J = 6.5 Hz, 1H, NCH), 3.75 (dd, J = 10.5, 5 Hz, 1H, H-7a), 7.15 (d, J = 7 Hz, 2H, H-*o*), 7.21 (tm, J = 7 Hz, 1H, H-4′), 7.26 (tm, J = 7.5 Hz, 2H, H-*m*), 7.41−7.46 (m, 2H, and H-*p* and H-6′), 7.63 (td, J = 8, 1.5 Hz, 1H, H-5′), 7.97 (dd, J = 8.5, 1.5 Hz, 1H, H-3′); ^{13}C NMR (50 MHz) δ 19.5 (C-6), 20.7 (C-7), 22.2 (CH_3), 33.5 (C-3), 36.7 (C-5), 47.4 (C-2), 59.0 (NCH), 62.0 (C-3a), 66.1 (C-7a), 125.0 (C-3′), 126.8 (*o*-C), 127.0 (C-4′), 127.7 (*p*-C), 128.4 (*m*-C), 131.6 (C-6′), 132.5 (C-5′), 139.3 (C-1′), 145.9 (*ipso*-C), 148.0 (C-2′), 209.4 (C-4); $[\alpha]_D^{25}$ = −30.2 (*c* 0.01, MeOH). Anal. Calcd for $C_{22}H_{24}N_2O_3$: C, 72.17; H, 6.65; N, 7.68. Found: C, 72.01; H, 6.58; N, 7.63.

(3a*R*,7a*S*)-3a-(2-Nitrophenyl)-1-[4-(trimethylsilyl)-2-butinyl]-1,2,3,-3a,7,7a-hexahydroindol-4-one [(−)-46]. A solution of octahydroindole **(−)-51** (5 g, 13.72 mmol) in α-chloroethyl chloroformate (20 mL, 185 mmol) was heated at 135 °C for 2 days. The mixture was diluted with CH_2Cl_2 and sequentially washed with 4 N aqueous HCl and 10% aqueous $NaHCO_3$. The organic extract was dried and concentrated to give the nonracemic carbamate **19b** (3.62 g, 72%). Operating as in the racemic series, this carbamate was converted to propargylic silane **(−)-46**: $[\alpha]_D^{25}$ = −74.7 (*c* 0.01, $CHCl_3$).

(−)-Tubifolidine [(−)-1]. Operating as in the racemic series, cyclization of **(−)-46** afforded allene **(−)-47**: $[\alpha]_D^{25}$ = −111.9 (*c* 0.01, $CHCl_3$). Reduction of **(−)-47**, following the procedure above described for the racemic series, yielded (−)-tubifolidine [**(−)-1**]: $[\alpha]_D^{25}$ = −56.6 (*c* 0.01, $CHCl_3$); lit.[23a] $[\alpha]_D^{23}$ = −67 (*c* 0.61, $CHCl_3$). The ee (89%) was determined by HPLC using a chiral column (Chiralcel OD, 75:25:0.1 hexane−*i*-PrOH-diethylamine, 0.5 cm^3 min^{-1}, 254 nm) and racemic tubifolidine as reference.

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Supporting Information Available: Experimental details for the conversion of *trans*-**16** to *cis*-**16** and **25** to **26**, preparation and characterization data for **17**, **19a**, **20a**, **22a**, **35**, **37**−**39**, and **41**−**45**, NMR data for **25**, **34**, **36**, **40**, and **53**−**55**, and copies of NMR spectra and a plot of the NOESY experiment for (−)-**51** (14 pages). See any current masthead page for ordering information and Internet access instructions.

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