between C51/C55, C56/C60, and C68/C72 was established by the MS/MS experiments, in which the related molecular ion (M − Na)$^-$ at m/z 2306 (m/z 2305 in nominal mass) was selected as the precursor. Ion peaks at m/z 851/835 (821), 573/557 (543), and 469/453 (423) due to cleaved bonds at either side of the ether oxygens allowed us to sequence four blocks (C37–C53, C54–C57, C58–C69, and C70–C135, Figure 1). Characteristic fragmentations at specific sites of the rings[9] provided invaluable information about ring size (Figure 1). Particularly, they were of great help in assigning rings S and Y because ^{1}H NMR signals of C87/C88 and C108/C109 heavily overlapped and could not be interpreted with confidence.

Two-dimensional NMR data of **1** enabled us to connect **2** with the rest of the molecule, fragments A and C. DQF-COSY and TOCSY[8] revealed spin connections due to H35/H36/H37/H38 and H134/H135/H136/H137. Three vicinal diols in rings K, L, and N cleaved by periodate were reconstructed on the basis of $^3J_{\mathrm{H,H}}$ and NOESY data[8] of **1** (see supplementary material).

With these data, the entire structure of maitotoxin (**1**) is disclosed for the first time: It is a C142 carbon chain of composition $C_{164}H_{256}O_{68}S_2Na_2$ (molecular weight of 3422 in nominal mass as disodium salt),[10] encompassing 32 ether rings, 28 hydroxyl groups,[11] and two sulfate esters. Most of the ether rings are probably trans-fused as is the case with brevetoxin[12] except for rings L/M and N/O, for which NOE data suggested cis-fusion (see supplementary material).

Severe overlapping of both ^{13}C and ^{1}H NMR signals was overcome by repeated spectral measurements in different solvents[6,8] and by application of new NMR methods (e.g., 2D HMQC-TOCSY or HSQC). Even so, assignment of NMR signals was sometimes imperfect with only 10 mM of **1** or with 3 mM of **2**. Three-dimensional ^{1}H–^{13}C–^{1}H NMR experiments will be attempted with a ^{13}C-enriched sample, which should help to confirm the structure of MTX. Synthesis of labeled MTX in *G. toxicus* culture will also shed light on mechanisms of action, and on the intriguing relationship of MTX to its companion ciguatoxin.[13]

Acknowledgment. We are grateful to Messrs. H. Ohmura, T. Kaneta, K. Hokii, and M. Satake as well as to Misses E. Iwama, N. Furuya, and A. Sato in Yasumoto's laboratory for the assistance in isolating maitotoxin and in culturing the dinoflagellate; to Prof. T. Kusumi of Tokushima University, Dr. M. Wälchli of Japan Bruker, and Dr. A. Ueno of Tohoku University for measuring 500-MHz and 600-MHz NMR spectra; to Dr. M. Ohyabu of Shimadzu Ltd. for performing 2D/3D HMQC-TOCSY experiments; and to Prof. P. J. Scheuer of the University of Hawaii for critical reading of the manuscript.

Supplementary Material Available: Summary of NMR experiments showing connectivities assigned by NMR, stereochemical assignments of rings K–O of **1**, ^{1}H NMR assignments of **2** and its acetyl derivative, partial ^{1}H NMR assignments of **1**, NOESY and TOCSY of **2**, TOCSY of the acetyl derivative of **2**, negative FAB MS/MS of **2**, ^{1}H NMR 1D spectrum of **1**, NOESY of **1**, DQF-COSY of **1** in two different solvents, HMBC of **1** (21 pages). ^{1}H–^{1}H COSY, TOCSY, and NOESY of **1** in CD_3OD and 2D HMQC-TOCSY (^{13}C–^{1}H HOHAHA) of **1** in CD_3CN–D_2O, 1:1, are available as supplementary material to a previous paper.[5] Ordering information is given on any current masthead page.

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[9] Naoki, H.; Murata, M.; Yasumoto, T. *Rapid Commun. Mass Spectrom.*, in press.

[10] The presence of nitrogen suggested in a previous paper[2] was ruled out by elementary analyses with **1**.

[11] The number of hydroxyl groups was determined on the basis of deuterium shifts in ^{13}C NMR signals between spectra obtained in CD_3CN–D_2O and in CD_3CN–H_2O, and of comparison of **2** with its acetyl derivative in ^{1}H NMR chemical shifts.

[12] (a) Lin, Y.-Y.; Risk, M.; Ray, S. M.; Van Engen, D.; Clardy, J.; Golik, J.; James, J. C.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 6773–6775. (b) Shimizu, Y.; Chou, H.-N.; Bando, H.; Duyne, G. V.; Clardy, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 514–515.

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ESR Spectrum of a Stable Triplet π Biradical: Trioxytriangulene

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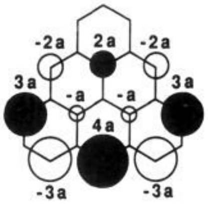
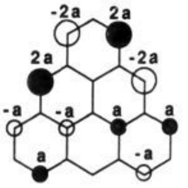
We report the first observation of the ESR spectrum of a non-Kekulé polynuclear aromatic compound: a derivative of triangulene **1**.[1-3] Like the non-Kekulé polyenes[4] and the non-Kekulé quinodimethanes,[5] the non-Kekulé polynuclear aromatics[6] are π biradicals for which it is impossible to write a structure in which each π electron is paired with one on a neighboring carbon. The non-Kekulé polyenes and non-Kekulé quinodimethanes have been known for some time. However, although attempts to make non-Kekulé polynuclear aromatics date back to the work of Clar in the 1950s,[1,7] so far they have escaped detection. Hückel molecular orbital calculations show that the simplest non-Kekulé polynuclear aromatic, triangulene, has a pair of nondisjoint[8] degenerate nonbonding molecular orbitals and as such should have a triplet ground state.

1



Ψ_{11} a = $66^{-1/2}$



Ψ_{12} a = $22^{-1/2}$

Our route to compounds of this type is based on the two-electron reduction of the diketone **2**.[1] The single-crystal structure of this compound, which has a vivid blue color, shows that the molecule is essentially planar with a 3-fold axis of symmetry.[9] Cyclic voltammetry[10] shows that the monoanion **2** undergoes two reversible one-electron additions ($E_{R1} = -2.04$ V, $E_{R2} = -2.37$ V) and hence that the dianion monoradical **3** and the trianion bi-

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[8] Borden, W. T.; Davidson, E. R. *J. Am. Chem. Soc.* **1977**, *99*, 4587.

[9] The small deviations from planarity and 3-fold symmetry seem to be attributable to lattice effects. Allinson, G.; Bushby, R. J.; Paillaud, J.-L.; Thornton-Pett, M. To be published.

[10] In DMF at a mercury drop cathode under an atmosphere of nitrogen with tetrabutylammonium tetrafluoroborate as the supporting electrolyte and a silver/silver nitrate reference electrode.

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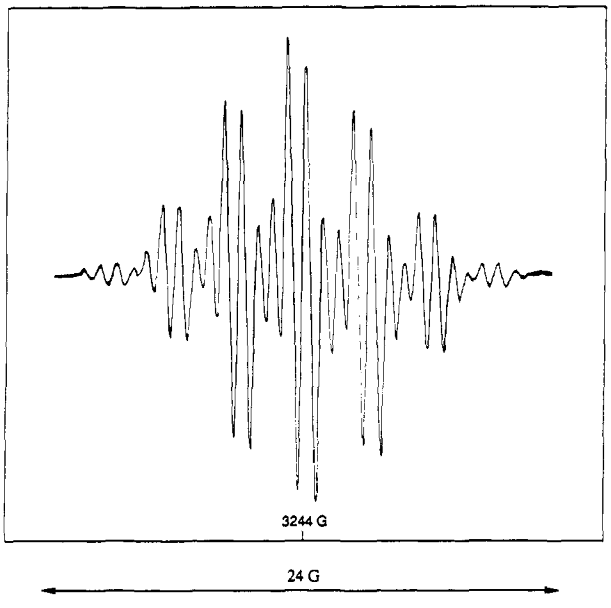
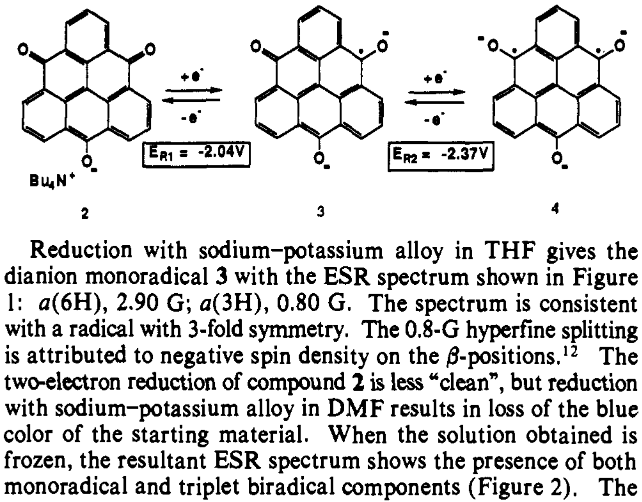


Figure 1. The ESR spectrum of the monoradical dianion **3** at room temperature produced by reduction of the monoanion **2** in THF with Na/K alloy.

radical **4** are reasonably stable in solution. However, they are very oxygen sensitive, and preparative reactions need to be carried out in a reaction vessel sealed under vacuum (ca. 10^{-5} mmHg).[11]



Reduction with sodium–potassium alloy in THF gives the dianion monoradical **3** with the ESR spectrum shown in Figure 1: *a*(6H), 2.90 G; *a*(3H), 0.80 G. The spectrum is consistent with a radical with 3-fold symmetry. The 0.8-G hyperfine splitting is attributed to negative spin density on the β-positions.[12] The two-electron reduction of compound **2** is less "clean", but reduction with sodium–potassium alloy in DMF results in loss of the blue color of the starting material. When the solution obtained is frozen, the resultant ESR spectrum shows the presence of both monoradical and triplet biradical components (Figure 2). The relative proportions of these vary slightly from run to run.

The biradical component is believed to be due to the trioxy derivative **4** of triangulene **1**. The assignment rests on the (probable) 3-fold symmetry of the triplet, the size of the zero-field splitting, and the fact that the spectrum is associated with a triplet-ground-state molecule. The spectrum shown in Figure 2 can be simulated assuming that the doublet and triplet components have slightly different *g* values and that the triplet is uniaxial (i.e., that the molecule has ~3-fold symmetry and $|E/hc| = 0$); triplet $g = 2.0034$, $|D/hc| = 0.0064$ cm^{-1}; doublet $g = 2.0029$. If no assumption is made concerning the symmetry of the triplet species and the value of $|E/hc|$ is allowed to "float" in the calculation, a very small nonzero value results, but the improvement in the fit is also small and may not be significant; triplet $g = 2.0034$, $|D/hc| = 0.0064$ cm^{-1}, $|E/hc| = 0.0003$ cm^{-1}; doublet $g = 2.0030$.[13]

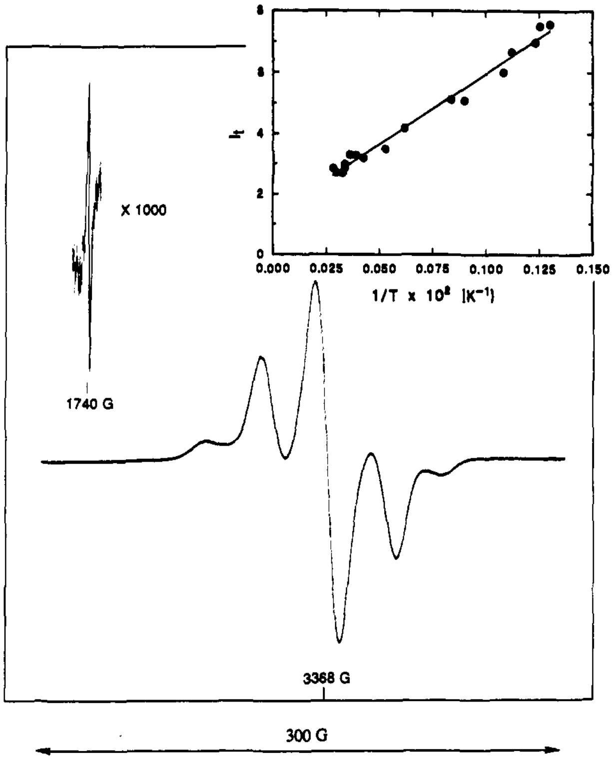


Figure 2. The ESR spectrum of the triplet biradical trianion **4** (together with monoradical impurities) in a frozen glassy matrix at 13 K. Produced by reduction of the monoanion **2** in DMF with Na/K alloy. Inset top left: The "half-field" line recorded at increased gain (×1000) and increased sweep width (×20). Inset top right: The "Curie law" plot of the intensity of the triplet component (I_t, arbitrary units) versus $1/T$ (K^{-1}) between 13 and 37 K.

As is expected for a triplet with a small zero-field splitting, the half-field ($\Delta m = 2$) transition is extremely weak, although it can be detected at high gain (Figure 2).[14] For planar π biradicals the zero-field splitting $|D/hc|$ can be calculated using the point charge model of McWeeney.[15] When, as is normal, these calculations are based on Hückel molecular orbitals, the absolute values obtained are almost uniformly a factor of 2 too large but the relative values are not too bad.[4,16] In the case of biradical **4** such calculations yield $|D/hc|$ values of 0.015–0.016 cm^{-1},[17] close to those expected. "Curie law" studies of triplet species by ESR spectroscopy[18] are normally based on the temperature dependence of the intensity of the $\Delta m = 2$ transition. In this case, however, the signal/noise ratio in the $\Delta m = 2$ region of the spectrum is too low for this purpose, and so our studies are based on the intensity of the $\Delta m = 1$ transition using the simulation to disentangle the contributions of the triplet and doublet components. The resultant plot is consistent with the view that the triplet spectrum arises from a triplet-ground-state species, i.e., the trioxytriangulene **4**.

The biradical is remarkably stable, and we have found that samples can be stored at room temperature for up to 5 months without loss in the intensity of the ESR signal. It is one of only a handful of organic triplet-ground-state molecules which are

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(11) Bushby, R. J.; Ferber, G. *J. Chem. Soc., Perkin Trans. 2* **1976**, 1688.

(12) It is instructive to compare this spectrum with that obtained on reduction of phenalenone. Rabold, G. P.; Bar-Eli, K. H.; Reid, E.; Weiss, K. *J. Chem. Phys.* **1965**, *42*, 2438.

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(16) Rule, M.; Matlin, A. R.; Seeger, D. E.; Hilinski, E. F.; Dougherty, D. A.; Berson, J. A. *Tetrahedron* **1982**, *38*, 787.

(17) Calculations were based on an assumed regular planar geometry with all C–C bond lengths 1.395 Å, C–O bond lengths 1.43 Å, and each p orbital represented by a pair of points 0.68 Å above and below the plain. For Hückel MOs with $h_O = 2.0$, $|D/hc|_{\text{calcd}} = 0.0150$ cm^{-1}; with $h_O = 1.0$, $|D/hc|_{\text{calcd}} = 0.0160$ cm^{-1}.

(18) Bushby, R. J.; Jarecki, C.; Oduwole, D.; Sales, K. D. *Tetrahedron Lett.* **1987**, *28*, 6501. Ayscough, P. B.; Bushby, R. J.; Jarecki, C.; Sales, K. D.; Oduwole, D.; Tann, J. *Tetrahedron Lett.* **1988**, *29*, 2719 and references therein.

stable at room temperature. We attribute this stability, first, to the extended conjugation present, and, second, to the fact that it is a triplet with "nowhere to go". Either dimerization of the triplet or valence isomerization of the singlet (for example, a reaction like the isomerization of *m*-quinodimethane to a bicyclo[3.1.0] system[5]) would lead to highly strained products.[19] The biradical is, however, very sensitive to oxygen, and as soon as the sample tube is opened, there is an instant oxidation and the bright blue color of the starting material **2** is restored.

Acknowledgment. We thank the SERC for financial assistance and N. Taylor for assistance with the cyclic voltammetry.

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[19] A referee has suggested that Coulombic factors may also contribute in making dimerization unfavorable.

A New, General Synthetic Pathway to *Strychnos* Indole Alkaloids. First Total Synthesis of (±)-Echitamidine

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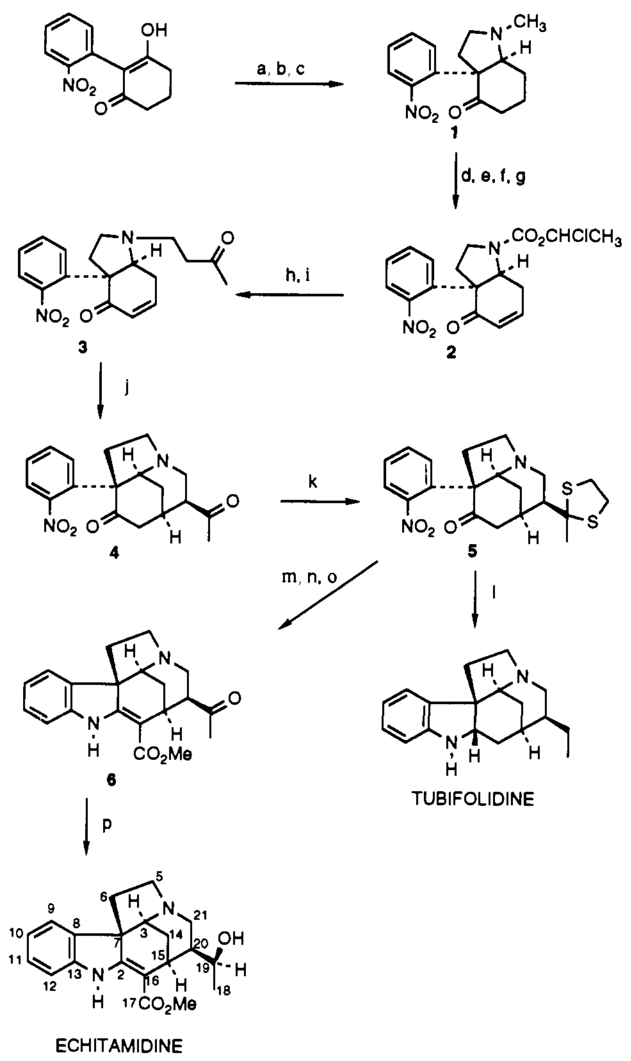
New strategies for the synthesis of pentacyclic *Strychnos* indole alkaloids have appeared during the last two years,[1] showing a renewed interest in this area since the initial synthetic work by Harley-Mason.[2] However, only about 10 of the vast array of alkaloids with this skeletal type have been synthesized so far.[3]

We report now a new, general synthetic entry to *Strychnos* alkaloids of both the norcuran (tubifolidine,[4] for instance) and the curan (echitamidine,[5] for instance) skeleton through a synthetic sequence with a high degree of flexibility involving the *o*-nitrophenyl azatricyclic ketone **4** as a pivotal intermediate. Two important features of **4** are (i) the presence of a two-carbon chain at C-20 which can be elaborated to the variety of C-20 substituents present in *Strychnos* alkaloids and (ii) the activation at C-16, which allows the introduction of the C-17 oxidized one-carbon appendage characteristic of curan alkaloids.

The crucial steps of the synthesis (Scheme I) are (i) the elaboration of the *cis*-3a-(*o*-nitrophenyl)octahydroindolone **1** through a double (inter- and intramolecular) reductive amination from a symmetric cyclohexanedione derivative,[6] (ii) closure of the piperidine ring by an intramolecular Michael process, and (iii) formation of the indoline ring in the last synthetic steps by reductive cyclization.[7]

Scheme I[a]



[a] (a) $BrCH_2CH{=}CH_2$ (1.1 equiv), K_2CO_3 (4 equiv), acetone, reflux, 3 h. (b) Toluene, sealed tube, 180 °C, 12 h. (c) O_3 (1 equiv), CH_2Cl_2, −78 °C, 2 h; then $CH_3NH_2{\cdot}HCl$ (4 equiv), $NaBH_3CN$, MeOH, room temperature, 4 h. (d) $ClCO_2CHClCH_3$ (1 equiv), $ClCH_2CH_2Cl$, reflux, 3 h. (e) HMDS (3 equiv), $ISiMe_3$ (2 equiv), CH_2Cl_2/pentane (1:1), −20 °C, 6 h. (f) PhSeCl (1 equiv), $(PhSe)_2$ (1 equiv), THF, −35 °C, 90 min. (g) O_3 (1 equiv), CH_2Cl_2, −78 °C, 3 min; then iPr_2NH (1 equiv), 15 min. (h) MeOH, reflux, 3 h. (i) Methyl vinyl ketone (1.1 equiv), Et_3N (1.1 equiv), MeOH, room temperature, 1 h, 45 min. (j) (*R*)-α-methylbenzylamine (2 equiv), 3-Å molecular sieves, THF, room temperature, 4 days; then aqueous AcOH (20%), room temperature, 4 h. (k) $(HSCH_2)_2$ (8 equiv), AcOH, $BF_3{\cdot}Et_2O$ (5 equiv), room temperature, 24 h. (l) Bu_3SnH (15 equiv), AIBN, benzene, 80 °C, 16 h. (m) LDA (2.1 equiv), HMPA (5 equiv), THF, −78 °C, 30 min; then $CNCO_2Me$, room temperature, 3 h. (n) HgO (2 equiv), $BF_3{\cdot}Et_2O$ (4 equiv), H_2O/THF, room temperature, 30 min. (o) H_2, Pd/C, HCl (1 equiv), MeOH, room temperature. (p) $NaBH_4$ (2 equiv), MeOH, room temperature, 3 h.

Starting from the multigram available octahydroindolone **1**,[6] formation of the corresponding chloroethyl carbamate,[8] followed by selenation at the ketone α-position via a silyl enol ether and further oxidation, gave the enone **2** in 50% yield from **1**. Deprotection of the pyrrolidine nitrogen of **2** gave a secondary amine, which was treated with methyl vinyl ketone to provide the alkylated hexahydroindolone **3** in 74% yield. Base-catalyzed cyclization of **3** gave (67%) a 4:1 mixture of **4**, having the natural relative stereochemistry, and its epimer at C-20. The latter was transformed into **4** by treatment with KF/MeOH. Tricyclic ketone

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[1] (a) Amat, M.; Linares, A.; Bosch, J. *J. Org. Chem.* **1990**, *55*, 6299. (b) Kuehne, M. E.; Frasier, D. A.; Spitzer, T. D. *J. Org. Chem.* **1991**, *56*, 2696. (c) Nkiliza, J.; Vercauteren, J.; Lēger, J.-M. *Tetrahedron Lett.* **1991**, *32*, 1787. (d) Fevig, J. M.; Marquis, R. W., Jr.; Overman, L. E. *J. Am. Chem. Soc.* **1991**, *113*, 5085. (e) Kraus, G. A.; Bougie, D. *Synlett* **1992**, 279. (f) Magnus, P.; Giles, M.; Bonnert, R.; Kim, C. S.; McQuire, L.; Merritt, A.; Vicker, N. *J. Am. Chem. Soc.* **1992**, *114*, 4403.

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[5] (a) Isolation: Goodson, J. A. *J. Chem. Soc.* **1932**, 2626. (b) Constitution: Djerassi, C.; Nakagawa, Y.; Budzikiewicz, H.; Wilson, J. M.; LeMen, J.; Poisson, J.; Janot, M.-M. *Tetrahedron Lett.* **1962**, 653. (c) Configuration: Zēches, M.; Ravao, T.; Richard, B.; Massiot, G.; LeMen-Olivier, L.; Guilhem, J.; Pascard, C. *Tetrahedron Lett.* **1984**, *25*, 659.

[6] Solê, D.; Bonjoch, J. *Tetrahedron Lett.* **1991**, *32*, 5183. The minor trans isomer could be converted to the cis isomer by treatment of the corresponding *N*-oxide with TFAA and further $NaCNBH_3$ reduction of the resulting iminium salt.

[7] For an approach to the pentacyclic *Strychnos* framework by elaboration of the indolenine nucleus in the last step, see ref 1d. For a previous unsuccessful approach by Fischer indolization, see: Bonjoch, J.; Casamitjana, N.; Quirante, J.; Rodríguez, M.; Bosch, J. *J. Org. Chem.* **1987**, *52*, 267.

[8] All new compounds were characterized by IR, ^1H NMR, ^{13}C NMR, HRMS, and/or microanalysis.

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