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# Synthetic Applications of 2-(1,3-Dithian-2-yl)indoles. IV.[1] New Synthesis of the Tetracyclic ABED Ring System of *Strychnos* Alkaloids

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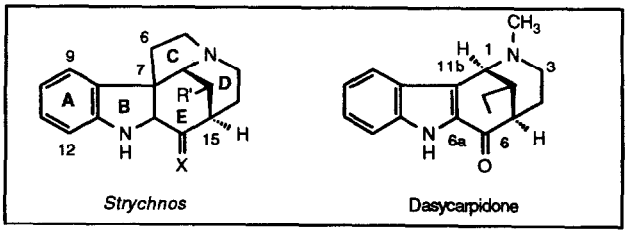
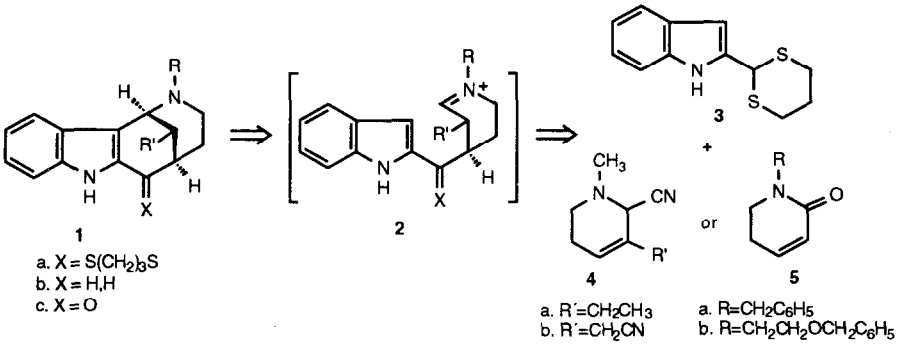
***Abstract***: A new and versatile synthesis of tetracyclic compounds **10**, **22** and **24** presenting the ABED ring system of *Strychnos* alkaloids is described by closure of the $C_1$-$C_{11b}$ bond in the key step. The intermediate tetrahydropyridinium salts **2** have been obtained from 2-(1,3-dithian-2-yl)indole (**3**) and either 2-cyano-3-ethyl-1-methyl-1,2,3,6-tetrahydropyridine (**4a**) or *N*-substituted $\Delta^3$-piperidein-2-ones (**5**).

Over the last few years several new and potentially general strategies have been devised for the synthesis of the pentacyclic framework of the *Strychnos* type indole alkaloids.[2-8] Among these, the approach wherein the ABED rings are first constructed and cyclization of the C ring by closure of the $C_6$-$C_7$ bond[9,10] is a late stage synthetic operation,[5,11,12] is the most commonly encountered. Therefore, efficient methods to the preparation of the dasycarpidone skeleton are required.[13-20] Along these lines, we have similarly been involved in the development and optimisation of a new methodology for the construction of the ABED rings of the *Strychnos* system, as found in the alkaloid dasycarpidone.




**Scheme 1**

Our initial entry to the 1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole system (**1**) was based on the condensation of a 2-(1,3-dithian-2-yl)indole,[21] as a nucleophilic synthetic equivalent of a 2-acylindole moiety, with *N*-methyl-4-piperidone and 1-benzyl-3-ethyl-3,4-epoxypiperidine, used as the electrophilic piperidine synthons.[20,22] However, subsequent $C_1$-$C_{11b}$ ring closure of the condensation products required additional steps to activate the C-2 center of the piperidine ring. This approach has now been improved, and we describe here the synthesis of several tetracyclic compounds, some of which are potential synthetic intermediates of pentacyclic *Strychnos* alkaloids. In the first approach, conjugate addition of the highly reactive dianion of indole dithiane **3** with the allylic amino nitriles **4a**[23] and **4b** also yielded products resulting from the competing of the indole dithiane component at the external C-1′ and the indole C-3 position. Further experiments were then conducted to examine the corresponding reaction of the dianion of dithiane **3** with the α,β-unsaturated lactams **5a** and **5b**. A subsequent study of the acid promoted cyclization of the addition products on the dithiane ring 2-position in both series established conditions for efficient formation of the dasycarpidone derivatives **22-24**.




**Scheme 2**

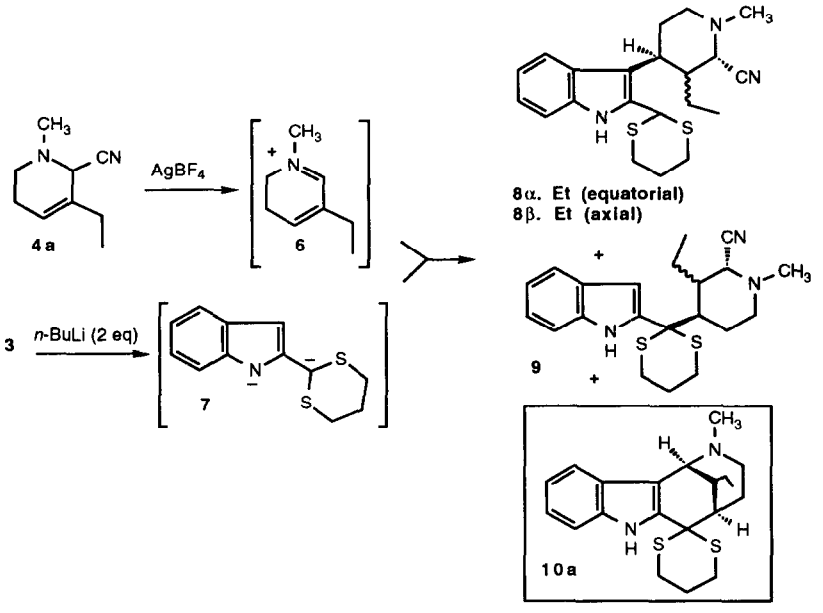
## RESULTS AND DISCUSSION

On the basis of our previous studies on the reactivity of 2-(1,3-dithian-2-yl)indoles diversely protected on the indole nitrogen atom,[24] we first designed an experiment in which the dianion of the unprotected indolyldithiane **3** would show both its chemoselectivity between the dithianyl ring 2-position or the indole 3-position, and its tendency to give conjugated addition on a 5,6-dihydropyridinium salt, which could be easily obtained from 2-cyano-$\Delta^3$-piperideine **4a**. Furthermore, if the condensation took place to furnish iminium salts type **2**, the desired tetracyclic structures of the dasycarpidone type could be directly obtained in a one pot reaction (Scheme 2).

For this purpose, 2-cyano-$\Delta^3$-piperideines **4a** and **4b** were chosen, and converted into the corresponding dihydropyridinium salts **6** and **12** by treatment with $AgBF_4$. Slow transfer of a cold solution of the dianion **7** to the dark coloured heterogeneous mixture containing the dihydropyridinium salt in THF (-10°C) and eventual warming to room temperature furnished a mixture of regioisomeric cyanopiperidines **8** and **9** together with the desired tetracyclic target **10a** (Scheme 3). Although the two epimers of compound **9** were not separated by silica gel flash chromatography, cyanopiperidines **8α**, **8β** and dasycarpidone type compound **10a** were isolated pure.[25]

The structure and stereochemistry of compounds **8α** and **8β** were inferred from their spectral data. The most characteristic features in their $^1H$ NMR spectra were a singlet at δ~5.5 due to the dithiane ring 2-H, narrow signals at δ 3.90

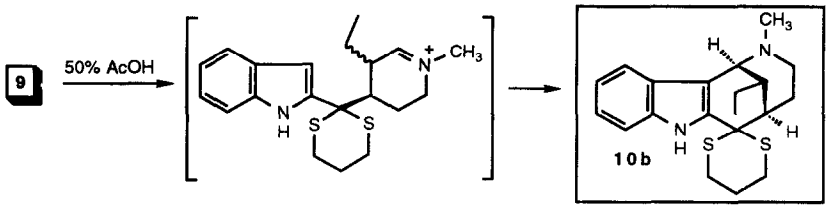
for 8β and δ 4.05 for 8α, corresponding to the piperidine 2-H equatorial proton, and the absence of the indole 3-H. Hence, the condensation had taken place on the indole 3-position, and the cyano group was in an axial disposition, as expected from 2-cyanopiperidines. Furthermore, the chemical shift values and coupling constants of the piperidine ring 4-H axial proton, unequivocally assigned by the correlation with the signal corresponding to C-4 (δ~35) in the COSY (H,C) experiment, were decisive in determining the orientation of the ethyl side chain, being a doublet of triplets at δ 3.55 when the ethyl side chain adopts an axial disposition (8β), and a triplet of doublets at δ 2.70 when equatorial (8α). Moreover, a shielding effect (Δδ 6.3 ppm) over C-5 was observed in 8β due to a "γ-gauche" effect promoted by the axial ethyl group.




**Scheme 3**

Similarly, the tetracyclic compound **10a** was identified from its spectroscopic data and elemental analysis. The most characteristic value in its $^1$H NMR spectrum was a broad singlet at δ 4.05 corresponding to the angular 1-H proton. This assignment was confirmed by the correlation with the signal of C-1 (δ 54.1) in the COSY (H,C) experiment. Also significant were the presence of three methine carbons and two methylenes in the aliphatic region of the $^{13}$C NMR spectrum whose chemical shift values corresponded to those described for similar systems.[26] On the other hand, the disposition of the ethyl chain on C-12 was shown to be axial by the chemical shift value of C-4 (δ 24.5), presenting a characteristic shielding (Δδ 7.6 ppm) due to the "γ-gauche" effect, in comparison with **10b** (see below). It should also be noted that there are two non-equivalent methylene groups adjacent to the sulphur atoms, as a consequence of the rigidity of this pentacyclic compound. Thus, in the $^1$H NMR spectrum, two double doublets of doublets centered at δ 2.97 and 3.15 were assigned to the dithiane ring 3-H and 5-H axial protons respectively, on the basis of the correlations observed in the COSY (H,H) and (H,C) experiments. The dasycarpidone type structure of compound **10a** was also confirmed by its fragmentation pattern in the mass spectrum. Thus, a fragment at m/z 230 (70%) characteristic of a carbazole $[C_{14}H_{15}NS]^{+\cdot}$ species was derived from the benzylic cleavage $C_1$-$N_2$ with simultaneous abstraction of the dithiane ring $SC_3H_6$ moiety.[27,28]

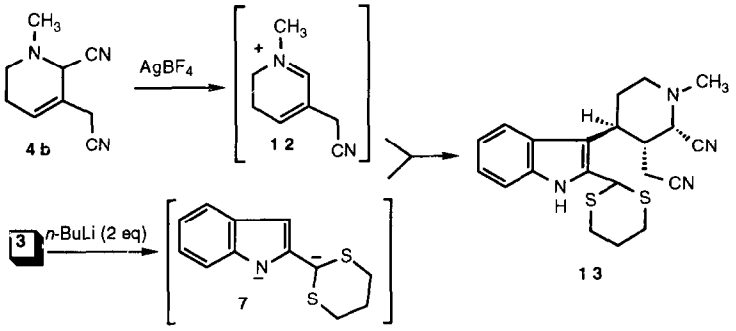
Finally, the mixture of cyanopiperidines **9** was directly submitted to treatment with 50% aqueous acetic acid, leading to the cyclized structure **10b**, which was also identified from its spectral data (Scheme 4). The most relevant signal in its $^1$H NMR spectrum was the broad singlet at δ 4.07 corresponding to the angular 1-H proton which correlates with the signal at δ 56.2 (C-1) in the COSY (H,C) experiment. The equatorial orientation of the ethyl side chain was confirmed by the chemical shift value (δ 32.1) of C-4 in the $^{13}$C NMR spectrum, as well as by the shielding (Δδ 0.2 ppm) observed for the signal of the methyl group in the $^1$H NMR spectrum (δ 0.90), now located in the anisotropic region of the aromatic ring.




**Scheme 4**

It is worth noting that in the reaction of dihydropyridinium salt **6** with dianion **7**, the only ABED ring system obtained is **10a**, presenting the ethyl chain on C-12 in an axial disposition, while the cyclization reaction from cyanopiperidines **9** leads only to isomer **10b**. This observation indicates that the less stable product can be kinetically formed, whereas in the hot aqueous acidic medium an evolution towards the thermodynamically most stable 1,2,3,4,5,6-hexahydro-1,5-methano-2-azocino[4,3-*b*]indole takes place. [29]

On the other hand, reaction of dihydropyridinium salt **12** with dianion **7** in the same experimental conditions yielded cyanopiperidine **13** as the only isolable product (27% yield), resulting from condensation on the indole 3-position (Scheme 5). Thus, the $^1$H NMR spectrum of **13** presented two singlets at δ 2.51 and 5.45 corresponding to the nitrogen methyl group and the dithiane ring 2-H proton respectively, a doublet (*J*=3.5 Hz) at δ 4.30 due to the equatorial piperidine ring 2-H, and a triplet of doublets at δ 2.80 assigned as the axial 4-H proton from its correlation observed with the signals at δ 1.84 and 2.40, corresponding to the two 5-H protons, in the COSY (H,H) experiment. The latter, together with the chemical shift at δ 31.0 for the piperidine C-5 carbon in the $^{13}$C NMR spectrum, clearly indicated an equatorial disposition of the cyanomethyl chain on C-3, since it was comparable to the data previously observed for the analogous compound **8**α. Therefore, cyanopiperidine **13** presented the most stable configuration, *i.e.* the cyano group on C-2 in an axial disposition and the other substituents equatorially oriented.

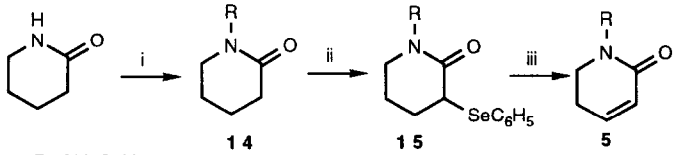



**Scheme 5**

These results demonstrated the feasibility of constructing the ABED ring system through combining the reactivities of α-aminonitriles and indolyldithianes, but also showed its limitations with regard to regioselectivity and to variety of substitutions on the piperidine ring. Considering the relative softness (HSAB principle)[30] of the two reactive sites of dianion **7** with respect to the soft γ-position of 5,6-dihydropyridinium salts **6** and **12**,[31,32] the major formation of compounds **8** and **13** shows that the indole 3-position of dianion **7** is slightly softer than its dithiane 2-position. This fact motivated the search for another piperidine compound which, while presenting similar synthetic usefulness, increased the hardness on position 4, thus facilitating the 1,4-addition on the dithiane ring.[33]

Therefore, we chose $\Delta^3$-piperidein-2-ones **5a**[34] and **5b** as the piperidine synthons, since their functionalization on positions 2 and 4 would allow us to pursue the same strategy by conjugate addition of the indolyldithiane anion followed by cyclization.

5,6-Dihydropyridones **5** were prepared in three steps by alkylation of commercial δ-valerolactam followed by phenylselenation with LDA and phenylselenyl chloride, and final oxidative elimination of the phenylselenide with MCPBA, as indicated in Scheme 6.




**14** **15** **5**

**a**. R=$CH_2C_6H_5$
**b**. R=$CH_2CH_2OCH_2C_6H_5$

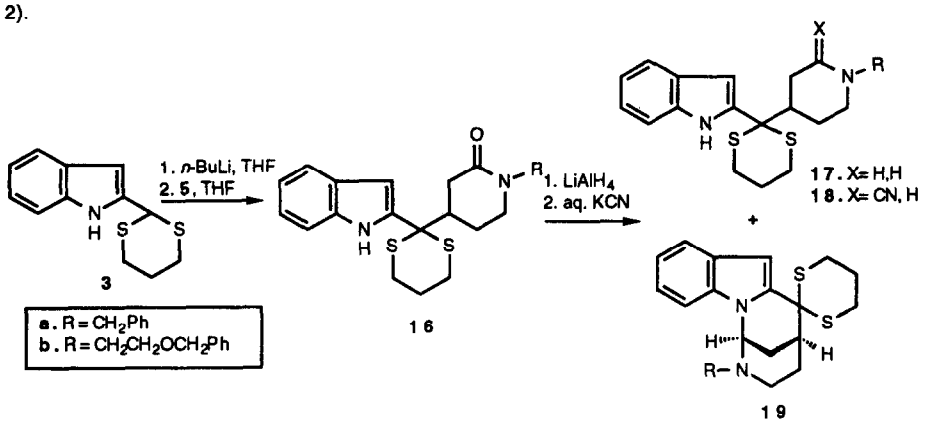
**Reagents and conditions**: i) 1. NaH (1.1 eq.), THF, 0°C, 30 min, room temperature. 2. $C_6H_5CH_2Cl$ (1 eq.) or $ICH_2CH_2OCH_2C_6H_5$ (1 eq.); ii) 1. LDA (2.1 eq.), THF, -78°C, 10 min. 2. $C_6H_5SeCl$ (1 eq.), HMPA (0.5 eq.), THF, -78°C (20 min) to room temperature; iii) MCPBA (1.2 eq.), $CH_2Cl_2$, 0°C to room temperature, 16 h.

**Scheme 6**

Lactams **5a** and **5b** were allowed to react separately with the dianion of the indolyldithiane (**7**), thus yielding the corresponding adducts **16a** (54%) and **16b** (67%) (Scheme 7). The conjugate addition on the dithiane 2-position was demonstrated by the presence of singlets at δ 6.65 and 6.75 for **16a** and **16b**, respectively, corresponding to indole 3-H in the $^1$H NMR spectra, and by the signal at δ~ 168 for the carbonyl group in the $^{13}$C NMR spectra.

Reduction of lactam **16a** with $LiAlH_4$ in the presence of potassium cyanide afforded a 4:3:1 mixture (60% yield) of piperidine **17a**, pentacyclic compound **19a**, and 2-cyanopiperidine **18a**, which were identified from their spectroscopic data. Thus, piperidine **17a** showed a characteristic symmetrical piperidine structure in its $^1$H and $^{13}$C NMR spectra.[35] The absence of carbonyl signals and the presence of cyano signals in the IR (2200 $cm^{-1}$) and $^{13}$C NMR (δ115.1) spectra of compound **18a**, together with the existence of a narrow triplet at δ 3.75 for the equatorial 2-H proton in the $^1$H NMR spectrum, confirmed the structure of the minor product. The $^1$H NMR spectrum of the second major product, compound **19a**, showed a singlet at δ 6.90 only assignable to indole 3-H, no indole NH signal, and a triplet ($J$ = 4 Hz) at δ 5.40, characteristic of an aminal proton. These data led us to conclude that the cyclization of the intermediate tetrahydropyridinium salt type **2**, formed in basic reduction conditions, occurred on the indole nitrogen atom to generate the corresponding 1,2,3,4,5,6-hexahydro-1,5-methano-2,11b-diazocino[4,3-*a*]indole (**19a**). A similar cyclization had been observed by Joule and co-workers in their synthesis of dasycarpidone and deethyldasycarpidone,[29] but in that

case the substrate possessed a 2-acylindole moiety which deactivated the indole 3-position (transformation **2c** to **1c** in Scheme 2).




**Scheme 7**

We confirmed the structure of compound **19a** from its X-Ray diffraction pattern[36] (Figure 1) and its 2D NMR spectra. Thus, the angular methine proton adjacent to the nitrogen atoms was correlated with the doublet of triplets at δ 2.40, assigned to the equatorial 12-H, which in turn was correlated with the broad singlet at δ 2.81 corresponding to the equatorial methine 5-H. The correlation of 5-H with the signals centered at δ 1.93 and 2.30 allowed the assigment of these to the axial and equatorial protons, respectively, of position 4. Again, the magnetic non equivalence of the dithiane ring protons next to the sulphur atoms was shown by the presence of two double doublets of doublets at δ 2.96 and 3.13 for the SCH axial protons. In the mass spectrum of **19a** the base peak at m/z 172 of the 1-benzyl-5,6-dihydropyridinium salt fragment was observed, indicating the easy initial fragmentation between the indole nitrogen atom and the aminal carbon.

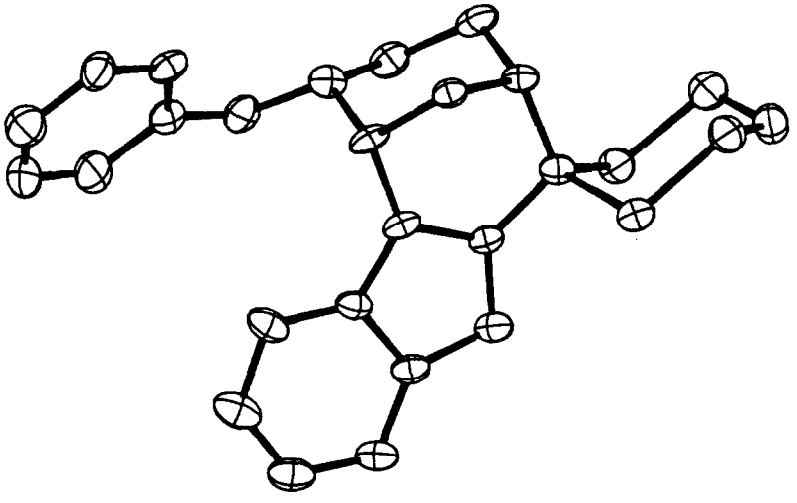
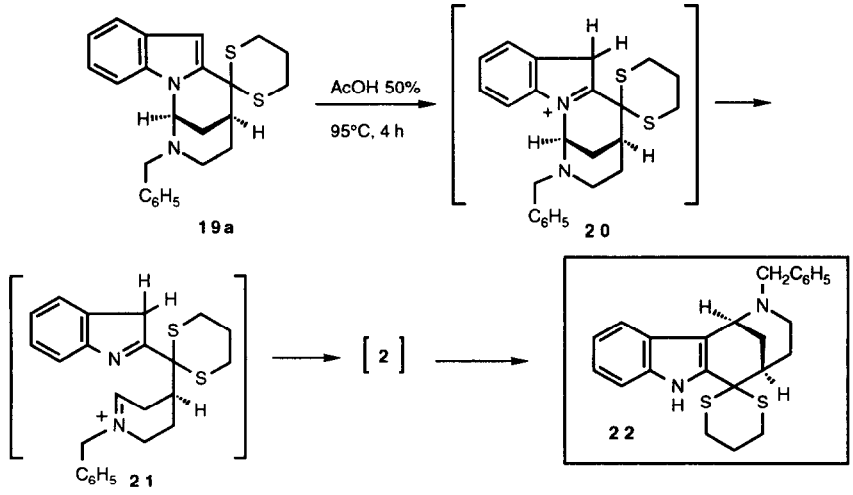


**Figure 1**. ORTEP plot of 1,5-methano-2,11b-diazocino[4,3-*a*]indole (**19a**)

At this point, we assayed the transformation of **19a** into hexahydro-1,5-methano-2-azocino[4,3-*b*]indole **22** in refluxing 50% aqueous acetic acid (Scheme 8). The product **22** showed an absorption at 3452 $cm^{-1}$ in the IR spectrum, and a singlet at δ 8.65 in the $^1H$ NMR spectrum, indicating an unsubstituted indole nitrogen. The absence of the signal at δ 6.90 characteristic of the indole proton at 3-position implied that this position was substituted. Therefore, the desired isomerization had taken place.




**Scheme 8**

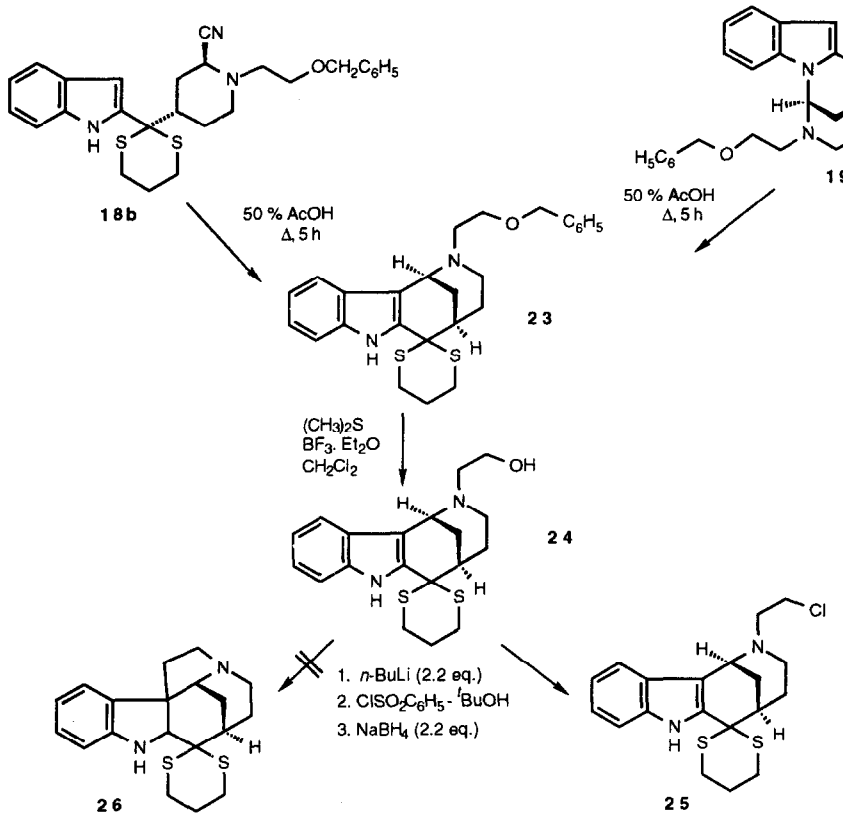
Unlike the case in which the reaction had been carried out on 2-acylindoles,[29] the mechanism we propose for our ring opening process is initiated by protonation of the reactive indole 3-position[37] and formation of the indoleninium salt **20**, followed by an elimination induced by the piperidine nitrogen lone pair. The intermediate tetrahydropyridinium salt **21**, whose tautomeric form is an intermediate type **2**, reacts only upon the indole 3-position. A particular advantage of this transformation is the consistently high yield.

Additional $^1H$ NMR data characterising compound **22** were: a singlet at δ 4.21 for the methine 1-H proton, which was correlated with the signal at δ 50.6 (C-1) in the COSY (H,C) experiment, and with the signals centered at δ 2.4 assignable to 12-H, in the COSY (H,H) experiment; the chemical shift of 1-H, shielded with respect to the aminal proton in **19a** (Δδ ~ 1.2 ppm), in accordance with that described for other dasycarpidone type compounds;[26,38] and two double doublets of doublets centered at δ 3.16 and 2.98 corresponding to the non-equivalent axial protons of positions 3 and 5 of the dithiane ring.

In parallel, we performed the same reactive sequence from lactam **16b** (Scheme 7). Further reduction of the dithiane ring would give tetracyclic compound **1b** (R′=H, R=$CH_2CH_2OH$; Scheme 2), which has already been used as the precursor of the basic pentacyclic skeleton of *Strychnos* alkaloids through a three step sequence.[39] Thus, when lactam **16b** was treated with $LiAlH_4$ in THF followed by addition of an aqueous solution of KCN, a 1:2.4:2.2 mixture of piperidine **17b**, 2-cyanopiperidine **18b**, and hexahydro-1,5-methanodiazocino[4,3-*b*]indole **19b** was obtained. These compounds were identified by their spectral data.

As in the preceding series, the most characteristic features of 2-cyanopiperidine **18b** were an absorption at 2200 $cm^{-1}$ and a signal at δ 116.4 due to the cyano group in the IR and the $^{13}C$ NMR spectra, respectively. The $^1H$ NMR record showed a signal at δ 4.05 for the equatorial methine proton on the 2-position, and a singlet at δ 4.48 for the benzyl

methylene group. With regard to compound **19b**, the data diagnostic of its structure were a triplet at δ 5.45 and a signal at δ 66.7, in its $^1H$ and $^{13}C$ NMR spectra respectively, characteristic of the aminal methine unit, together with a singlet at δ 6.90 in the $^1H$ NMR corresponding to the proton on indole 3-position, indicating that the cyclization had occurred on the indole nitrogen atom.




**Scheme 9**

As expected, treatment of 2-cyanopiperidine **18b** with refluxing 50% aqueous AcOH furnished the desired 1,5-methano-2-azocino[4,3-*b*]indole **23**, whose structure was assigned by the presence of a broad triplet at δ 4.15 characteristic of the angular 1-H methine proton, and by the absence of both the indole proton on position 3 and the aminal methine proton. Finally, the rearrangement of compound **19b** into **23** by cleavage of the $N_{12}$-$C_1$ bond was also carried out quantitatively by refluxing in 50% aqueous AcOH (Scheme 9).

Debenzylation of **23** was smoothly carried out by treatment with dimethylsulfide and $BF_3.Et_2O$ at room temperature, and was evidenced by the hydroxy absorption at 3450-3200 $cm^{-1}$ in the IR spectrum as well as by the disappearance of the benzyl group signals in the NMR spectra.

Finally, cyclization of compound **24** was assayed using the strategy that we previously applied for the conversion of 1-(2-hydroxyethyl)-2-[1-(phenylsulfonyl)indolyl]piperidines to indolo[2,3-*a*]quinolizidines,[40] consisting of the treatment of the alkoxy group generated in a base medium with *tert*-butyl benzenesulfonate.[41] In the present case, the latter was prepared from benzenesulfonylchloride and *tert*-butanol, and the only product of the reaction was the chloride

**25**, resulting from the attack of the chlorine ions present in the reaction medium. A similar result on a tetracyclic lactam was recently reported by Magnus[6] who explained the impossibility of transforming the chlorine derivative into the pentacyclic *Strychnos* skeleton. The structural assignment of chloride **25** was based on the presence of a signal at δ 41.8 in the $^{13}C$ NMR spectrum, corresponding to the β carbon of the chain on the nitrogen atom, and by its molecular peak at m/z 378 in the mass spectrum. The shielding of β carbon in **25** with respect to compound **24** (Δδ ~16 ppm) is characteristic of an exchange of the hydroxyl group by a chlorine atom.

## CONCLUSION

We have achieved an efficient new synthesis of dasycarpidone type tetracyclic systems, which not only demonstrates once again the usefulness of indolyldithianes in this field, but also overcomes the chemoselectivity problem, with which we had been dealing since the beginning of this research project. Furthermore, the simplicity and the overall yield of the three step approach presented in this paper is an improvement on the methods described so far.

The possibility of introducing diverse substituents on the piperidine ring, such as a hydroxyethyl chain, together with the fact that the transformation of such a substituent to a dimethyl dithioacetal followed by treatment with DMTSF is described as a pathway to obtain *Strychnos* alkaloids (Bosch's strategy),[5] give an additional interest to the synthetic approach presented here.

## EXPERIMENTAL

**General.** Melting points were determined in a capillary tube on a Büchi apparatus and are uncorrected. $^1H$ and $^{13}C$ NMR spectra were recorded on a Varian Gemini-200 instrument (200 MHz) and 2D NMR COSY experiments were performed on a Varian XL-500 instrument (500 MHz). Unless otherwise noted, NMR spectra were registered in $CDCl_3$, and chemical shifts are expressed in parts per million (δ) relative to internal $Me_4Si$. IR spectra were recorded on a Nicolet FT-IR spectrophotometer. Mass spectra were determined on a Hewlett-Packard 5988A mass spectrometer. Flash column chromatography was carried out on $SiO_2$ (silica gel 60, 40-63 mm, Macherey-Nagel). TLC was performed on $SiO_2$ (silica gel 60 F254, Merck) and developed with the solvent described in each case for flash chromatography. The spots were located by UV light and Draggendorff or hexachloroplatinate reagent. Purification of reagents and solvents was effected according to standard methods. Prior to concentration under reduced pressure, all extracts were dried over anhydrous $Na_2SO_4$ powder. Microanalyses were performed on a Carlo Erba 1106 analyzer by the Departament de Química Orgànica i Biològica, CID, Barcelona.

**Condensation of dihydropyridinium salts 6 with dianion 7.** To a solution of 2-cyano-$\Delta^3$-piperideine **4a** (500 mg, 3.33 mmol) in dry THF (30 ml), at -20°C and under argon atmosphere, $AgBF_4$ (650 mg, 1.8 mmol) was added, and the black slurry solution was stirred for 20 min. Simultaneously, to a solution of dithiane **3**[42] (784 mg, 3.33 mmol) in dry THF (30 ml) at -78°C and under argon atmosphere, 1.6 M *n*-BuLi (4.37 ml, 6.9 mmol) was added and the solution, which took a characteristic red coloration, was stirred for 20 min. Then, the solution of dianion **7** was slowly transferred *via* cannula upon the solution of dihydropyridinium salt and the reaction mixture was stirred at -10°C for 3 h and allowed to reach room temperature. After stirring for 16 h the reaction was quenched with aqueous ammonium chloride (20 ml), stirred for 6 h and extracted with ether. The organic extracts were dried and evaporated to give an oil which was purified by flash chromatography (1:1 ether-hexane): **2-Cyano-3-ethyl-4-[2-(2-indolyl)-1,3-dithian-2-yl]-1-methylpiperidine (9)** (Higher Rf, 102 mg, 8%) $^1H$ NMR (500 MHz) 0.75 (t, *J*= 7 Hz, 3H, $CH_2CH_3$), 1.62 (m, 1H, $CH_ACH_3$), 1.90-1.95 (m, 2H, $SCH_2CH_2$), 2.00 (m, 1H, 5-H), 2.12-2.18 (m, 1H, 6-$H_a$), 2.20 (m, 1H, $CH_BCH_3$), 2.25 (s, 3H, $NCH_3$), 2.62 (br d, *J*= 11 Hz,

2H, $SCH_e$), 2.76 (br d, $J$= 11 Hz, 1H, 6-$H_e$), 2.82 (t, $J$= 11 Hz, 1H, $SCH'_a$), 2.95 (t, $J$= 11 Hz, 1H, $SCH_a$), 3.65 (br s, 1H, 2-H), 6.75 (d, $J$= 2 Hz, 1H, In-3H), 7.13 (t, $J$= 7 Hz, 1H, In-6H), 7.18 (t, $J$= 7 Hz, 1H, In-5H), 7.37 (d, $J$= 7 Hz, 1H, In-7H), 7.55 (t, $J$ = 7 Hz, 1H, In-4H), 8.50 (br s, 1H, In-NH). **2-Cyano-4-[2-(1,3-dithian-2-yl)-3-indolyl]-3-ethyl-1-methylpiperidine (8β)** (254 mg, 28%): IR (NaCl) 2200 $cm^{-1}$ (CN); $^1H$ NMR (500 MHz) 0.74 (t, $J$ = 7 Hz, 3H, $CH_3CH_2$), 1.40 (m, 1H, $CH_ACH_3$), 1.80-1.90 (m, 3H, 5-$H_e$, $SCH_2CH_a$ and $CH_BCH_3$), 2.05 (m, 1H, 3-$H_e$), 2.18 (dm, $J$ = 14 Hz, 1H, $SCH_2CH_e$), 2.42 (s, 3H, $NCH_3$), 2.55 (td, $J$ = 12 and 2 Hz, 1H, 6-$H_a$), 2.60 (qd, $J$ = 12 and 5 Hz, 1H, 5-$H_a$), 2.88 (br d, $J$ = 12 Hz, 1H, 6-$H_e$), 2.95 (m, 2H, $SCH_e$), 3.15 (br t, $J$ = 14 Hz, 2H, $SCH_a$), 3.55 (dt, $J$ = 12 and 2 Hz, 1H, 4-$H_a$), 3.90 (s, 1H, 2-$H_e$), 5.61 (s, 1H, SCHS), 7.05 (t, $J$ = 7 Hz, 1H, In-5H), 7.15 (t, $J$ = 7 Hz, 1H, In-6H), 7.30 (d, $J$ = 7 Hz, 1H, In-7H), 7.64 (d, $J$ = 7 Hz, 1H, In-4H), 8.42 (s, 1H, In-NH); $^{13}C$ NMR 12.3 ($CH_3CH_2$), 18.5 ($CH_3CH_2$), 24.9 ($SCH_2CH_2$), 25.3 (C-5), 31.9 and 32.1 ($SCH_2$), 35.1 (C-4), 42.3 (SCHS), 44.4 ($NCH_3$), 46.3 (C-3), 51.9 (C-6), 56.9 (C-2), 111.2 (In-C7), 113.3 (In-C3), 117.8 (CN), 119.7 (In-C5), 120.7 (In-C4), 122.2 (In-C6), 127.2 (In-C3a), 131.3 (In-C2), 135.6 (In-C7a); MS (m/z, %) 386 ($M^+$+1, 10), 358 (40), 260 (11), 234 (13), 124 (15), 98 (100). High resolution MS calcd for $C_{21}H_{27}N_3S_2$: 385.1646. Found:385.1647. **2-Cyano-4-[2-(1,3-dithian-2-yl)-3-indolyl]-3-ethyl-1-methylpiperidine (8α)** (178 mg, 14 %): IR (NaCl) 3448 (NH), 2200 $cm^{-1}$ (CN); $^1H$ NMR 0.75 (t, $J$ = 7 Hz, 3H, $CH_3CH_2$), 1.20-1.40 (m, 2H, $CH_2CH_3$), 1.75 (d, $J$ = 12 Hz, 1H, 5-$H_e$), 1.90 (q, $J$ = 14 Hz, 1H, $SCH_2CH_a$), 2.19 (br d, $J$ = 14 Hz, 1H, $SCH_2CH_e$), 2.35 (qd, $J$ = 13 and 5 Hz, 1H, 5-$H_a$), 2.45 (br d, $J$ = 13 Hz, 1H, 3-$H_a$), 2.49 (s, 3H, $NCH_3$), 2.56 (td, $J$ = 13 and 2 Hz, 1H, 6-$H_a$), 2.70 (td, $J$ = 13 and 4 Hz, 1H, 4-$H_a$), 2.80-2.95 (m, 3H, $SCH_e$ and 6-$H_e$), 3.15 (t, $J$ = 14 Hz, 2H, $SCH_a$), 4.05 (d, $J$ = 5 Hz, 1H, 2-$H_e$), 5.54 (s, 1H, SCHS), 7.02 (t, $J$ = 7 Hz, 1H, In-5H), 7.15 (t, $J$ = 7 Hz, 1H, In-6H), 7.31 (d, $J$ = 7 Hz, 1H, In-7H), 7.68 (d, $J$ = 7 Hz, 1H, In-4H), 8.35 (s, 1H, In-NH); $^{13}C$ NMR 11.1 ($CH_3CH_2$), 23.5 ($CH_2CH_3$), 24.9 ($SCH_2CH_2$), 31.6 ($SCH_2$ and C-5), 36.4 (C-4), 41.0 (C-3), 42.9 (SCHS), 44.4 ($NCH_3$), 51.0 (C-6), 59.4 (C-2), 111.4 (In-C7), 113.4 (In-C3), 115.1 (CN), 119.4 (In-C5), 120.4 (In-C4), 122.4 (In-C6), 125.4 (In-C3a), 131.5 (In-C2), 136.1 (In-C7a); MS (m/z, %) 386 ($M^+$+1, 7), 385 ($M^+$, 24), 358 (39), 260 (11), 234 (38), 123 (11), 98 (100). High resolution MS calcd for $C_{21}H_{27}N_3S_2$: 385.1646. Found: 385.1653. **12β-Ethyl-*N*-methyl-6,6-propylenedithio-1,2,3,4,5,6-hexahydro-1,5-methano-2-azocino[4,3-*b*]indol (10a)** (Lower Rf, 140 mg, 12 %): $^1H$ NMR 1.05 (t, $J$ = 7 Hz, 3H, $CH_2CH_3$), 1.75 (m, 1H, $CH_ACH_3$), 1.95-2.04 (m, 1H, $SCH_2CH_a$), 2.08-2.20 (m, 4H, $SCH_2CH_e$, 4-H and $CH_BCH_3$), 2.29 (s, 3H, $NCH_3$), 2.33 (br t, $J$ =7 Hz, 1H, 12-$H_e$), 2.50 (br s, 2H, 3-$H_e$ and 4-$H_a$), 2.75 (ddd, $J$ = 13 and 3 Hz, 2H, $SCH_e$), 2.97 (ddd, $J$ = 13, 12 and 3 Hz, 2H, $SCH_a$), 3.14 (ddd, $J$ = 13, 12 and 3 Hz, 1H, $SCH'_a$), 4.05 (br s, 1H, 1-$H_e$), 7.10 (t, $J$ = 7 Hz, 1H, 10-H), 7.20 (t, $J$ = 7 Hz, 1H, 9-H), 7.35 (d, $J$ = 7 Hz, 1H, 8-H), 7.55 (d, $J$ = 7 Hz, 1H, 11-H), 8.60 (br s, 1H, In-NH); $^{13}C$ NMR 12.2 ($CH_3$), 23.6 ($SCH_2CH_2$), 24.5 (C-4 and $CH_2CH_3$), 26.8 ($SCH_2$), 29.3 ($SCH_2$), 36.8 (C-5), 40.9 (C-12), 44.5 ($NCH_3$), 44.6 (SCS), 45.1 (C-3), 54.1 (C-1), 111.3 (C-8), 119.4 (C-11), 120.1 (C-10), 122.6 (C-9), 126.0 (C-11a), 129.5 (C-11b), 136.5 (C-7a); MS (m/z, %) 358 ($M^+$, 3), 342 (1), 288 (29), 230 (70), 221 (15), 205 (60), 171 (55), 161 (27), 149 (60), 124 (55), 107 (72), 84 (54), 57 (100). Anal. Calcd for $C_{20}H_{26}N_2S_2$: C, 67.03; H, 7.26; N, 7.82. Found: C, 67.18; H, 7.45; N, 8.02. **2-Cyano-3-ethyl-4{2-[2-(3-ethyl-1-methyl-1,2,5,6-tetrahydro-2-pyridyl)-1,3-dithiane-2-yl]-3-indolyl}-1-methylpiperidine (11)** (50 mg, 2 %) $^1H$ NMR (500 MHz) 0.68 (br t, $J$= 7 Hz, 3H, $CH_2CH_3$), 0.77 (t, $J$= 7 Hz, 3H, $CH_2CH'_3$), 1.30 (m, 1H, $CH'_ACH_3$), 1.40-1.50 (m, 2H, $CH_2CH_3$), 1.63 (m, 1H, $CH'_BCH_3$), 1.69 ( dm, $J$= 12 Hz, 1H, 5-H'$_e$), 1.81 (dm, $J$= 12 Hz, 1H, 5-H), 1.92 (m, 2H, $SCH_2CH_2$), 2.15-2.24 (m, 1H, 5-H), 2.26 (qd, $J$= 12 and 4 Hz, 1H, 5-H'$_a$), 2.40-2.47 (m, 2H, $SCH'_2$), 2.44 (s, 3H, $NCH_3$), 2.48 (s, 3H , $NCH_3$), 2.52 (td, 1H, 6-H'$_a$), 2.58-2.67 (m, 2H, 3-H'$_a$ and 6-H), 2.83 (br d, $J$= Hz, 2H, 6-$H_e$ and $SCH_e$), 3.18 (m, 1H, $SCH_a$), 3.40 (br s, 1H, 2-H), 3.62 (m, 1H, 6-H), 3.82 (td, $J$=12 and 4 Hz, 1H, 4-H'$_a$), 4.05 (d, $J$= 4 Hz, 1H, 2-H'$_e$), 5.70 (br s, 1H, =CH), 7.03 (td, $J$= 8 and 1 Hz, 1H, In-5H), 7.14 (td, $J$= 8 and 1 Hz, 1H, In-6H), 7.36 (d, $J$= 8 Hz, 1H, In-7H), 7.72 (d, $J$=8 Hz, 1H, In-4H), 9.30 (br s, 1H, NH); $^{13}C$ NMR 11.8 ($CH_2CH'_3$), 12.4 ($CH_2CH_3$), 19.7 (C-5), 22.4 ($CH_2CH_3$), 25.0 ($SCH_2CH_2$), 27.8 ($CH'_2$ $CH_3$), 28.2 ($SCH'_2$), 31.2 ($SCH_2$), 31.8 (C-5'), 36.0 (C-4'), 43.2 ($NCH_3$), 44.0 (C-6, C-3' and

$NCH_3$), 51.5 (C-6'), 59.5 (C-2'), 71.0 (C-2), 110.5 (In-C7), 119.4 (In-C5), 121.1 (In-C4), 121.6 (In-C6), 123.5 (=CH).

**12α-Ethyl-*N*-methyl-6,6-propylenedithio-1,2,3,4,5,6-hexahydro-1,5-methano-2-azocino[4,3-*b*]-indol (10b).** A solution of 2-cyanopiperidine **9** (30 mg, 0.078 mmol) in 50% aqueous AcOH (10 ml) was refluxed for 4h. The reaction mixture was poured on a saturated aqueous $Na_2CO_3$ solution, basified with $Na_2CO_3$, and extracted with $CH_2Cl_2$. The organic extracts, dried and evaporated yielded an oil which was flash chromatografied ($CH_2Cl_2$) furnishing compound **10b** (15 mg, 54%): $^1$H NMR 0.90 (t, $J$ = 7 Hz, 3H, $CH_3$), 1.30-1.39 (m, 1H, $CH_ACH_3$), 1.50-1.60 (m, 1H, $CH_BCH_3$), 1.96-2.06 (m, 3H, 3-$H_a$, 4-$H_a$ and $SCH_2CH_a$), 2.11-2.18 (m, 1H, $SCH_2CH_e$), 2.26-2.28 (m, 1H, 4-$H_e$), 2.31 (s, 3H, $NCH_3$), 2.41 (br s, 1H, 12-$H_e$), 2.58 (br d, $J$ = 12 Hz, 1H, 3-$H_e$), 2.80 (ddd, $J$ = 12, 3 and 2 Hz, 1H, SCH'$_e$), 2.83-2.87 (m, 2H, 5-$H_a$ and $SCH_e$), 3.01 (ddd, $J$ = 12, 11 and 3 Hz, 1H, $SCH_a$), 3.22 (ddd, $J$ = 12, 11 and 3 Hz, 1H, SCH'$_a$), 4.07 (br s, 1H, 1-$H_e$), 7.05 (t, $J$ = 7 Hz, 1H, 10-H), 7.15 (t, $J$ = 7 Hz, 1H, 9-H), 7.30 (d, $J$ = 7 Hz, 1H, 8-H), 7.50 (d, $J$ = 7 Hz, 1H, 11-H), 8.60 (br s, 1H, In-NH); $^{13}$C NMR 12.5 ($CH_3$), 24.3 ($SCH_2CH_2$), 25.7 ($CH_2CH_3$), 28.1 ($SCH_2$), 29.1 (S'$CH_2$), 32.1 (C-4), 35.6 (C-5), 43.8 ($NCH_3$), 46.2 (C-3), 47.1 (C-12), 49.8 (SCS), 56.2 (C-1), 111.2 (C-8), 119.3 (C-11), 119.9 (C-10), 122.6 (C-9), 128.1 (C-11a), 135.0 (C-6a), 136.0 (C-7a). High resolution MS calcd for $C_{20}H_{26}N_2S_2$: 358.1532. Found: 358.1537.

**2-Cyano-3-cyanomethyl-4-[2-(1,3-dithian-2-yl)-3-indolyl]-1-methylpiperidine (13).** Operating as above, from dithiane **3** (186 mg, 0.79 mmol) and *n*-BuLi (1.05 ml, 1.66 mmol), in dry THF (10 ml), and 2-cyanopiperidine **4b**[43] (140 mg, 0.87 mmol) and $AgBF_4$ (130 mg, 0.37 mmol), in dry THF (10 ml), compound **13** was obtained ( 52 mg, 17 %): IR 3370 (NH), 2300 and 2290 cm$^{-1}$ (2 CN); $^1$H NMR 1.74-1.86 (m, 1H, 5-$H_a$), 1.94 (br t, $J$ = 13 Hz, 1H, $SCH_2CH_a$), 2.20 (br d, $J$ = 13 Hz, 1H, $SCH_2CH_e$), 2.28-2.32 (m, 2H, $CH_2CN$ ), 2.35-2.45 (m, 1H, 5-$H_e$), 2.51 (s, 3H, $NCH_3$), 2.60 (ddd, $J$ = 12, 10 and 2.5 Hz, 1H, 6-$H_a$), 2.80 (td, $J$ = 12 and 3 Hz, 1H, 4-$H_a$), 2.85-2.95 (m, 4H, 6-$H_e$, 3-$H_a$, and $SCH_e$), 3.10 (ddd, $J$ = 13, 12 and 2 Hz, 2H, $SCH_a$), 4.30 (d, $J$ = 3 Hz, 1H, 2-$H_e$), 5.45 (s, 1H, SCHS), 7.07 (t, $J$ = 7 Hz, 1H, In-5H), 7.19 (t, $J$ = 7 Hz, 1H, In-6H), 7.33 (d, $J$ = 7 Hz, 1H, In-7H), 7.61 (d, $J$ = 7 Hz, 1H, In-4H), 8.49 (s, 1H, In-NH); $^{13}$C NMR 19.4 ($CH_2CN$), 24.7 ($SCH_2CH_2$), 31.0 (C-5), 31.6 ($SCH_2$), 35.4 (C-4), 38.9 (C-3), 40.8 (SCHS), 44.2 ($NCH_3$), 50.6 (C-6), 59.4 (C-2), 110.9 (In-C3), 111.6 (In-C7), 113.9 (CN), 117.5 (CN), 119.8 (In-C4), 120.0 (In-C5), 122.9 (In-C6), 124.8 (In-C2), 132.0 (In-C3a), 136.0 (In-C7a); MS (m/z, %) 397 ($M^+$+1, 17), 370 (14), 262 (27), 261 (26), 260 (100), 254 (12), 248 (19), 234 (49), 223 (17), 186 (17). Anal. Calcd for $C_{21}H_{24}N_4S_2{\cdot}2H_2O$: C, 58.33; H, 6.48; N, 12.96. Found: C, 58.36; H, 6.54; N, 12.55.

***N*-Benzyl-2-piperidone (14a).** Sodium hydride dispersion in oil (60%, 2.08 g, 52.0 mmol) was washed with anhydrous hexane (3x10 ml) under argon atmosphere, resuspended in dry THF (50 ml), and cooled to 0°C. A solution of δ-valerolactam (97%, 4.65 g, 45.5 mmol) in dry THF (200 ml) was slowly added to the former suspension. The mixture was stirred at 0°C for 30 min, and at room temperature until cessation of hydrogen evolution. Benzyl chloride (5.2 ml, 45.4 mmol) was added dropwise under argon atmosphere, and the new mixture was refluxed until completion of the alkylation was observed on tlc (48 h). The reaction was quenched with $H_2O$ (200 ml), the layers were separated, and the aqueous phase was extracted first with $Et_2O$ then with $CH_2Cl_2$. The combined organic extracts were dried, and the solvent and the remaining benzyl chloride were evaporated under vacuum to furnish compound **14a**[34] (5.92 g, 69%), as a pale oil, which was used without further purification: IR (NaCl) 1638 cm$^{-1}$ (CO); $^1$H NMR 1.60-1.80 (m, 4H, 4-H and 5-H), 2.40-2.50 (m, 2H, 3-H), 3.10-3.20 (m, 2H, 6-H), 4.55 (s, 2H, $CH_2Ph$), 7.10-7.40 (m, 5H, Ph-H); $^{13}$C NMR 20.7 (C-5), 22.5 (C-4), 31.8 (C-3), 46.6 (C-6), 49.3 ($CH_2Ph$), 126.6 (Ph-*p*), 127.4 (Ph-*m*), 127.9 (Ph-*o*), 136.7 (Ph-*ipso*), 169.0 (CO); MS (m/z, %) 189 ($M^+$, 77), 147 (8), 106 (22), 105 (20), 104 (18), 98 (41), 92 (14), 91 (100).

***N*-(2-Benzyloxyethyl)-2-piperidone (14b)**. Operating as above, from δ-valerolactam (1.33 g, 13.28 mmol), 60% NaH dispersion in oil (0.61 g, 15.28 mmol), and benzyl 2-bromoethyl ether[44] (3 g, 13.95 mmol) in dry THF (100 ml), compound **14b** was obtained (3.10 g, 97%) as a yellow oil: IR (KBr) 1638 $cm^{-1}$ (CO); $^1H$ NMR 1.70-1.85 (m, 4H, 4-H and 5-H), 2.30-2.40 (m, 2H, 3-H), 3.35-3.45 (m, 2H, 6-H), 3.58 and 3.64 ($A_2B_2$ system, 4H, $NCH_2CH_2O$), 4.50 (s, 2H, $OCH_2Ph$), 7.20-7.40 (m, 5H, Ph-H); $^{13}C$ NMR 21.2 (C-5), 23.2 (C-4), 32.2 (C-3), 47.3 (C-6), 49.6 ($NCH_2$), 68.5 ($OCH_2CH_2$), 72.9 ($OCH_2Ph$), 127.4 and 127.6 (Ph-*o* and Ph-*p*), 128.2 (Ph-*m*), 138.1 (Ph-*ipso*), 169.7 (CO); MS (m/z, %) 234 ($M^+$+1, 4), 142 (84), 127 (78), 112 (79), 99 (13), 91 (100), 84 (82). Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.10; H, 8.15; N, 6.00. Found: C, 72.34; H, 8.40; N, 6.31.

***N*-Benzyl-3-phenylselenyl-2-piperidone (15a)**. To a solution of **14a** (2 g, 10.6 mmol) in dry THF (20 ml), cooled at -78°C and under argon atmosphere, a solution of LDA (1.5 M, 14.84 ml, 22.3 mmol) in dry THF (20 ml) was added dropwise. After stirring for 10 min, a solution of phenylselenyl chloride (97%, 2.09 g, 10.6 mmol) and HMPA (97%, 2.87 ml, 15.9 mmol) in dry THF (20 ml) was slowly added at -78°C. The resulting orange solution was maintained at -78°C for 20 min and left to reach room temperature. The reaction mixture was poured on $H_2O$ and extracted with $Et_2O$. The combined organic extracts were subsequently washed with 10% aqueous NaOH, $H_2O$, 10% aqueous HCl, and brine. The organic phase, dried and evaporated yielded an oil which was flash chromatographed ($Et_2O$) to obtain compound **15a**[33] as a transparent brown oil (2.52 g, 69%): IR (NaCl) 1638 $cm^{-1}$ (CO); $^1H$ NMR 1.65-2.20 (m, 4H, 4-H and 5-H), 3.20 (t, $J$ = 6 Hz, 2H, 6-H), 4.10 (t, $J$ = 5 Hz, 1H, 3-H), 4.50 (d, $J_{AB}$ = 15 Hz, 1H, $CH_APh$), 4.69 (d, $J_{AB}$ = 15 Hz, 1H, $CH_BPh$), 7.20-7.40 (m, 8H, Ph-H), 7.60-7.75 (m, 2H, Ph-H); $^{13}C$ NMR 20.3 (C-5), 28.3 (C-4), 42.4 (C-3), 46.5 (C-6), 49.8 ($CH_2Ph$), 126.7, 127.4, 127.9, 128.4, 134.4, and 136.4 (Ph), 168.3 (CO); MS (m/z, %) 345 ($M^+$, 8), 343 (4), 264 (6), 188 (100), 106 (18), 91 (90).

***N*-(2-Benzyloxyethyl)-3-phenylselenyl-2-piperidone (15b)**. Operating as above, from **14b** (607 mg, 2.60 mmol), LDA (3.64 ml, 5.46 mmol), phenylselenyl chloride (97%, 514 mg, 2.60 mmol), and HMPA (97%, 704 µl, 3.90 mmol), in dry THF (30 ml), compound **15b** was obtained (672 mg, 66%): IR (NaCl) 1638 $cm^{-1}$ (CO); $^1H$ NMR 1.60-1.80 (m, 1H, 4-H), 1.90-2.20 (m, 3H, 5-H and 4-H), 3.40 (t, $J$ = 7 Hz, 2H, 6-H), 3.55-3.65 (m, 4H, $NCH_2CH_2O$), 4.00 (t, $J$ = 7 Hz, 1H, 3-H), 4.50 (s, 2H, $OCH_2Ph$), 7.20-7.40 (m, 8H, Ar-H), 7.60-7.70 (m, 2H, Ar-H); $^{13}C$ NMR 20.9 (C-5), 28.7 (C-4), 42.7 (C-3), 47.8 (C-6), 49.5 ($NCH_2$), 68.3 ($OCH_2CH_2$), 72.8 ($OCH_2Ph$), 127.3, 127.7, 128.2, 128.8, 129.0, 134.9, and 138.0 (Ph), 168.7 (CO); MS (m/z, %) 391 ($M^+$+2, 54), 389 ($M^+$, 28), 387 (11), 386 (6), 298 (20), 283 (17), 232 (10), 202 (45), 126 (26). Anal. Calcd for $C_{20}H_{23}NO_2Se$: C, 61.85; H, 5.97; N, 3.61. Found: C, 62.09; H, 6.11; N, 3.51.

***N*-Benzyl-Δ$^3$-piperidein-2-one (5a)**. To a solution of **15a** (2.69 g, 7.82 mmol) in $CH_2Cl_2$ (35 ml), cooled at 0°C, a solution of MCPBA (50%, 3.37 g, 9.76 mmol) in $CH_2Cl_2$ (40 ml) was slowly added. The mixture was allowed to reach room temperature and was stirred overnight (16 h). The crude reaction mixture was poured on a saturated aqueous $NaHCO_3$ solution, dried and evaporated to yield an oil which was flash chromatographed (90:10 $Et_2O$-MeOH) to give pure **5a**[33] (1.32 g, 90%): IR (NaCl) 1666 (CO), 1610 $cm^{-1}$ (C=C); $^1H$ NMR 2.25-2.39 (m, 2H, 5-H), 3.31 (t, $J$ = 6 Hz, 2H, 6-H), 4.62 (s, 2H, $CH_2Ph$), 6.00 (dt, $J$ = 6 and 0.5 Hz, 1H, 3-H), 6.55 (dt, $J$ = 10 and 6 Hz, 1H, 4-H), 7.25 (s, 5H, Ph-H); $^{13}C$ NMR 23.7 (C-5), 44.1 (C-6), 49.2 ($CH_2Ph$), 124.7 (C-3), 126.9, (Ph-*p*), 127.5 (Ph-*m*), 128.1 (Ph-*o*), 136.9 (Ph-*ipso*), 139.3 (C-4), 164.0 (CO); MS (m/z, %) 187 ($M^+$, 32), 106 (12), 96 (31), 91 (100), 83 (77), 65 (50).

***N*-(2-Benzyloxyethyl)-$\Delta^3$-piperidein-2-one (5b).** Operating as above from **15b** (660 mg, 1.7 mmol), $CH_2Cl_2$ (20 ml) and MCPBA (50%, 733 mg, 2.12 mmol), enone **5b** was obtained (270 mg, 70%): IR 1608 (C=C), 1662 (CO) $cm^{-1}$ ; $^1H$ NMR 2.20-2.40 (m, 2H, 5-H), 3.50 (t, $J$ = 7 Hz, 2H, 6-H), 3.55-3.70 (m, 4H, $NCH_2CH_2O$), 4.45 (s, 2H, $OCH_2Ph$), 5.90 (dt, $J$= 8 and 2 Hz, 1H, 3-H), 6.50 (dt, $J$ = 8 and 5 Hz, 1H, 4-H), 7.20-7.30 (m, 5H, Ph-H); $^{13}C$ NMR 24.1 (C-5), 46.7 (C-6), 46.8 ($NCH_2$), 68.9 ($OCH_2CH_2$), 72.9 ($OCH_2Ph$), 125.2 (C-3) 127.3 (Ph-*p* and Ph-*o*), 128.2 (Ph-*m*), 138.0 (Ph-*ipso*), 139.4 (C-4), 164.3 (CO); MS (m/z, %) 232 ($M^+$+1, 24), 140 (31), 125 (48), 110 (100), 91 (68). Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.72; H, 7.36; N, 6.06. Found: C, 72.56; H, 7.44; N, 5.98.

***N*-Benzyl-4-[2-(2-indolyl)-1,3-dithian-2-yl]piperidin-2-one (16a).** To a solution of 2-(2-indolyl)-1,3-dithiane (**3**) (254 mg, 1.08 mmol) in dry THF (10 ml), cooled at -78°C and under argon atmosphere, *n*-BuLi (1.6 M, 1.49 ml, 2.38 mmol) was added dropwise. After 20 min, a solution of lactam **5a** (212 mg, 1.13 mmol) in dry THF (10 ml) was slowly added, and the mixture was maintained at -78°C for 1.5 h. The reaction was quenched by addition of saturated aqueous ammonium chloride (15 ml), the layers were separated, and the aqueous phase was extracted first with $Et_2O$ and then with $CH_2Cl_2$. The combined organic extracts, dried and evaporated furnished an oil, which after flash chromatography ($Et_2O$) yielded pure **16a** (246 mg, 54%) as a solid: mp: 192-193°C ($Et_2O$); IR (KBr) 1630 $cm^{-1}$ (CO); $^1H$ NMR 1.35-1.55 (m, 1H, 4-H), 1.65-1.85 (m, 2H, $SCH_2CH_2$), 2.10 (br d, $J$ = 12 Hz, 2H, 3-H), 2.25-2.45 (m, 2H, 5-H), 2.50-2.80 (m, 4H, $SCH_2$), 2.95-3.05 (m, 2H, 6-H), 4.30 (d, $J_{AB}$ = 15 Hz, 1H, $CH_APh$), 4.49 (d, $J_{AB}$ = 15 Hz, 1H, $CH_BPh$), 6.65 (s, 1H, In-3H), 6.90-7.25 (m, 9H, Ar-H), 7.49 (d, $J$ = 7 Hz, 1H, In-4H), 8.77 (s, 1H, In-NH); $^{13}C$ NMR 24.9 (C-5 and $SCH_2CH_2$), 28.0 ($SCH_2$), 34.2 (C-3), 44.9 (C-4), 46.2 (C-6), 49.8 ($CH_2Ph$), 57.7 (SCS), 105.6 (In-C3), 111.2 (In-C7), 120.0 (In-C-4), 120.6 (In-C5), 122.2 (In-C6), 127.4 (Ph-*p*), 128.0 (Ph-*m*), 128.6 (Ph-*o*), 128.7 (In-C3a), 136.0, 136.2, and 136.8 (In-C2 and In-C7a, and Ph-*ipso*), 168.8 (CO); MS (m/z, %) 422 ($M^+$, 3), 234 (25), 188 (7), 160 (15), 130 (11), 106 (11), 91 (100), 77 (10), 65 (29). Anal. Calcd for $C_{24}H_{26}N_2OS_2$: C, 68.20; H, 6.20; N, 6.63; S, 15.17. Found: C, 68.16; H, 6.20; N, 6.65; S, 15.11.

***N*-(2-Benzyloxyethyl)-4-[2-(2-indolyl)-1,3-dithian-2-yl]piperidin-2-one (16b).** Operating as above from dithiane **3** (282 mg, 0.856 mmol), THF (10 ml), *n*-BuLi (1.6 M, 1.18 ml, 1.883 mmol) and lactam **5b** (200 mg, 0.865 mmol), lactam **16b** (266 mg, 67%) was obtained : IR (KBr) 1627 (CO) $cm^{-1}$; $^1H$ NMR 1.70-2.00 (m, 2H, $SCH_2CH_2$), 2.40-2.80 (m, 4H, $SCH_2$), 3.30-3.70 (m, 6H, 6-H and $OCH_2CH_2$), 4.42 (s, 2H, $OCH_2Ph$), 6.75 (s, 1H, In-3H), 7.05-7.40 (m, 8H, Ar-H), 7.55 (d, $J$ = 7 Hz, 1H, In-4H), 8.70 (s, 1H, NH); $^{13}C$ NMR 24.8 ($SCH_2CH_2$), 27.7 ($SCH_2$), 33.8 (C-5), 44.5 (C-4), 46.8 and 48.4 (C-6 and $NCH_2$), 57.5 (SCS), 68.1 ($NCH_2CH_2O$), 72.6 ($OCH_2Ph$), 105.3 (In-C3), 110.9 (In-C7)119.6 (In-C4), 120.2 (In-C5), 121.8 (In-C6), 127.2, 128.1, 128.4, 135.9, and 137.8 (Ph), 168.6 (CO); MS (m/z,%) 466 ($M^+$, 10), 360 (3), 269 (4), 234 (100), 160 (19), 91 (72). Anal. Calcd for $C_{26}H_{30}N_2O_2S_2$: C, 66.91; H, 6.48; N, 6.00. Found: C, 66.61; H, 6.54; N, 5.85.

**$LiAlH_4$/KCN Reduction of 2-Piperidone 16a.** To a solution of **16a** (500 mg, 1.2 mmol) in dry THF (12 ml), a dispersion of $LiAlH_4$ (23 mg, 0.6 mmol) in dry THF (3 ml), was slowly added. The reaction mixture was refluxed for 45 min, and once cooled to room temperature, an aqueous solution of KCN (30 ml, 0.25 M, 0.77 mmol) was added. After stirring for 3 h at room temperature, the layers were separated and the aqueous phase extracted first with $Et_2O$ and then with $CH_2Cl_2$. The combined organic phases, dried and evaporated, yielded an oil which was flash chromatographed. On elution with hexane:$Et_2O$ (25:75) a 1:2.5 mixture of compounds **18a** and **19a** was obtained, from which a sample of pure***N*-benzyl-6-(1,3-dithian-2-yl)-1,2,3,4,5,6-hexahydro-1,5-methano-2,11b-diazocino[4,3-*a*]indole**

**(19a)** was obtained by further crystallization from $Et_2O$: (higher Rf, 89 mg, 22%): mp 200-201 °C ($Et_2O$); $^1H$ NMR 1.93 (tt, $J$ = 12 and 4 Hz, 1H, 4-$H_a$), 2.01 (br t, $J$ = 12 Hz, 1H, 3-$H_a$), 2.05 (qt, $J$ = 13 and 3 Hz, 1H, $SCH_2CH_a$), 2.12 (br d, $J$ = 13 Hz, 1H, $SCH_2CH_e$), 2.30 (dt, $J$ = 12 and 2 Hz, 1H, 4-$H_e$), 2.38 (dd, $J$ = 12 and 3 Hz, 1H, 3-$H_e$), 2.40 (dt, $J$ = 12 and 5 Hz, 1H, 12-$H_e$), 2.67 (dt, $J$ = 12 and 3 Hz, 1H, $SCSH_e'$), 2.67-2.75 (m, 2H, 12-$H_a$ and $SCH_e$), 2.81 (br s, 1H, 5-$H_e$), 2.96 (ddd, $J$ = 14, 12 and 3 Hz, 1H, $SCH_a'$), 3.13 (ddd, $J$ = 14, 12 and 3 Hz, 1H, $SCH_a$), 3.17 (d, $J_{AB}$ = 14 Hz, 1H, $CH_APh$), 3.98 (d, $J_{AB}$ = 14 Hz, 1H, $CH_BPh$), 5.40 (t, $J$ = 4 Hz, 1H, 1-H), 6.90 (s, 1H, 7-H), 7.10 and 7.11 (2 t, $J$ = 7 Hz, 1H each, 9-H and 10-H), 7.20-7.35 (m, 6H, Ar-H), 7.70 (d, $J$ = 7 Hz, 1H, 8-H); $^{13}C$ NMR 24.6 ($SCH_2CH_2$), 27.9 ( $SCH_2$), 28.5 (C-4), 29.8 ($SCH_2$), 31.2 (C-12), 31.3 (C-5), 42.8 (C-3), 51.9 (SCS), 60.3 ($CH_2Ph$), 66.1 (NCHN), 102.2 (C-7), 110.5 (C-11), 119.8 (C-8), 120.7 (C-9), 121.6 (C-10), 127.0 (Ph-*p*), 128.3 (Ph-*m*), 128.4 (Ph-*o*), 138.4 (C-11a), 138.8 (Ph-*ipso*); MS (m/z, %) 406 ($M^+$, 11), 300 (2), 234 (2), 209 (3), 173 (14), 172 (100), 91 (32). Anal. Calcd for $C_{24}H_{26}N_2S_2$: C, 70.89; H, 6.44; N, 6.89; S, 15.77. Found: C, 70.77; H, 6.43; N, 6.84; S, 15.60. ***N*-Benzyl-2-cyano-4-[2-(2-indolyl)-1,3-dithian-2-yl]piperidine (18a)** (35 mg, 7%): IR (NaCl) 3391 (NH), 2200 $cm^{-1}$ (CN); $^1H$ NMR 3.49 (d, $J_{AB}$ = 12 Hz, 1H, $CH_APh$), 3.65 (d, $J_{AB}$ = 12 Hz, 1H, $CH_BPh$), 3.75 (br t, $J$ =2 Hz, 1H, 2-$H_e$), 6.73 (d, $J$ = 0.5 Hz, 1H, In-3H), 7.05-7.40 (m, 8H, Ar-H), 7.60 (d, $J$ = 7 Hz, 1H, In-H4), 8.60 (s, 1H, In-NH); $^{13}C$ NMR 26.8 ($SCH_2CH_2$), 28.0 ($SCH_2$), 31.1 (C-5), 42.8 (C-3), 44.6 (C-4), 51.7 and 51.8 (C-6 and C-2), 60.1 ($CH_2Ph$), 105.5 (C-3), 111.1 (In-C7), 115.1 (CN), 119.8 (In-C4), 120.6 (In-C5), 121.6 (In-C6), 127.0 (Ph-*p*), 128.0 (Ph-*o*),128.5 (Ph-*m*), 136.5 (In-C7a), 138 (Ph-*ipso*); MS (m/z, %) 433 ($M^+$, 1), 406 (13), 300 (3), 234 (4), 209 (5), 172 (100), 91 (85). On elution with $Et_2O$:MeOH (98:2), ***N*-benzyl-4-[2-(2-indolyl)-1,3-dithian-2-yl]piperidine (17a)** (Lower Rf, 137 mg, 31%) was isolated: mp 146-147 °C ($Et_2O$); $^1H$ NMR 1.50 (dd, $J$ = 12 and 7 Hz, 1H, 4-H), 1.75-2.00 (m, 6H, $SCH_2CH_2$, 3-H and 5-H), 2.65 (dt, $J$ = 12 and 2 Hz, 2H, 2-H and 6-$H_e$), 2.70-2.95 (m, 6H, $SCH_2$, 2-$H_a$ and 6-$H_a$), 3.38 (s, 2H, $CH_2Ph$), 6.65 (s, 1H, In-3H), 7.05-7.35 (m, 8H, Ar-H), 7.55 (d, $J$ = 7 Hz, 1H, In-4H), 8.55 (s, 1H, In-NH); $^{13}C$ NMR 25.2 ($SCH_2CH_2$), 27.4 ($SCH_2$), 28.1 (C-3 and C-5), 48.6 (C-4), 53.6 (C-2 and C-6), 58.8 (SCS), 62.9 ($CH_2Ph$), 105.2 (In-C3), 110.9 (In-C-7), 119.8 (In-C4), 120.5 (In-C5), 121.8 (In-C6), 127.0 (Ph-*p*), 128.1 (Ph-*m*), 128.8 (In-C3a), 129.2 (Ph-*o*), 135.8, 137.3, and 137.7 (In-C7a, In-C2, and Ph-*ipso*). MS (m/z, %) 408 ($M^+$, 6), 333 (15), 291 (5), 234 (13), 200 (15), 172 (24), 160 (13), 146 (19), 91 (100). Anal. Calcd for $C_{24}H_{28}N_2S_2$: C, 70.54; H, 6.90; N, 6.85; S, 15.69. Found: C, 70.14; H,7.32; N, 6.82; S, 15.25.

**$LiAlH_4$/KCN Reduction of 2-Piperidone 16b**. Operating as above, from 2-piperidone **16b** (252 mg, 0.54 mmol), THF (10 ml), $LiAlH_4$ (10 mg, 0.27 mmol) and an aqueous solution of KCN (0.25 *M*, 14 ml), a mixture of piperidines **17b** and **18b**, and methanodiazocinoindole **19b** were obtained after flash chromatographic separation. On elution with $Et_2O$ compounds **18b** and **19b** were isoated. ***N*-(2-Benzyloxyethyl)-2-cyano-4-[2-(2-indolyl)-1,3-dithian-2-yl]piperidine (18b)** (Higher Rf, 100 mg, 39%) : $^1H$ NMR 2.55-2.85 (m, 4H, $NCH_2$ and 6-H), 3.50 (m, 2H, $OCH_2$), 4.05 (br s, 1H, 2-$H_e$), 4.48 (s, 2H, $OCH_2Ph$), 6.70 (d, $J$ =2 Hz, 1H, In-3H), 7.12 and 7.25 (2 t, $J$ = Hz, 1H each, In-5H and In-6H), 7.38 (d, $J$ = 7 Hz, 1H, In-4H), 7.60 (d, $J$ =7 Hz, 1H, In-4H), 8.55 (s, 1H, NH); $^{13}C$ NMR 25.0 ($SCH_2CH_2$), 26.7 and 28.1 ($SCH_2$), 30.3 (C-3), 44.4 (C-4), 49.6 (C-6), 53.0 (C-2), 55.1 ($NCH_2$), 58.1 (SCS), 67.6 ($OCH_2CH_2$), 73.0 ($OCH_2Ph$), 105.7 (In-C3), 111.1 (In-C7), 116.4 (CN), 120.0 (In-C4), 120.6 (In-C5), 122.2 (In-C6), 127.6 (Ph-*o*), 127.7 (Ph-*p*), 128.4 (Ph-*m*), 128.7 (In-C3a),136.0 (In-C7a), 138.0 (Ph-*ipso*); MS (m/z, %) 450 ($M^+$-HCN, 1), 216 (100), 167 (5), 124 (15), 91 (28). ***N*-(2-Benzyloxyethyl)-6-(1,3-dithian-2-yl)-1,2,3,4,5,6-hexahydro-1,5-methano-2,11b-diazocino[4,3-*a*]indole (19b)** (88 mg, 36%): $^1H$ NMR 3.15 (m, 1H, $SCH_a$), 4.55 (s, 2H, $OCH_2Ph$), 5.45 (t, $J$ =2 Hz, 1H, NCHN), 6.90 (s, 1H, 7-H), 7.05 and 7.10 (2 t, $J$ =7 Hz, 1H each, 9-H and 10-H), 7.30-7.35 (s, 5H, ArH), 7.45 and 7.55 (2 d, $J$ =7 Hz, 1H each, 8-H and 11-H); $^{13}C$ NMR 24.6 ($SCH_2CH_2$), 27.9 and 28.4 ($SCH_2$), 29.8 (C-4), 30.9 (C-12), 31.0 (C-5), 43.1 (C-3), 51.7 (SCS), 55.7 ($NCH_2CH_2$), 66.7 (C-1), 68.4 ($NCH_2CH_2$), 73.1 ($OCH_2Ph$), 102.2 (C-7), 110.6 (C-11), 119.7 (C-8),

120.6 (C-9), 121.7 (C-10), 127.6 (Ph-*o*), 128.4 (Ph-*m*), 138.0, 138.5 ; MS (m/z, %) 450 ($M^+$, 2), 345 (1), 216 (100), 124 (10), 91 (17). On elution with $Et_2O$-MeOH (95:5) ***N*-(2-benzyloxyethyl)-4-[2-(2-indolyl)-1,3-dithian-2-yl]piperidine (17b)** (40 mg, 16%) was obtained: IR (NaCl) 3436 $cm^{-1}$ (NH); $^1H$ NMR 1.55 (br t, $J$=12 Hz, 1H), 1.80-2.00 (m, 4H), 2.52 (t, $J$ = 5.5 Hz, 1H), 2.71 (ddd, $J$ = 11, 10 and 5 Hz, 1H), 2.95 (br d, $J$ = 8 Hz, 3.51 (t, $J$ = 5.5 Hz, 2 Hz), 4.47 (s, 2H, $OCH_2Ph$), 6.70 (d, $J$ = 1 Hz, 1H, In-3H), 7.05-7.35 (m, 7.55 (d, $J$=7 Hz, 1H, In-4H), 8.55 (br s, 1H NH); $^{13}C$ NMR 25.2 ($SCH_2CH_2$), 27.4 and 28.1 ($SCH_2$), 29.7 and 30.3 (C-3 and C-5), 48.7 (C-4), 54.3 (C-2 and C-6), 57.8 ($NCH_2$), 67.7 ($NCH_2CH_2$), 73.0 ($OCH_2Ph$), 105.2 (In-C3), 110.9 (In-C7), 119.8 (In-C4), 120.5 (In-C5), 121.8 (In-C6), 127.5 (Ph-*m*), 127.5, 128.3 (Ph-*o*), 136.5, 137.0; MS (m/z, %) 452 ($M^+$,20), 377 (43), 331 (100), 234 (52), 223 (15), 160 (19), 130 (24), 91 (72).

***N*-Benzyl-6-(1,3-dithian-2-yl)-1,2,3,4,5,6-hexahydro-1,5-methano-2-azocino[4,3-*b*]indol (22)**. A solution of a (1:1) mixture of compounds **18a** and **19a** (70 mg), in 50% aqueous AcOH (10 ml) was refluxed until completion of the reaction was observed by tlc (4 h). Once cooled, the mixture was basified with a saturated aqueous solution of $NaHCO_3$, and extracted with $CH_2Cl_2$. The organic extracts, dried and evaporated, furnished an oil which was flash chromatographed ($Et_2O$), to yield pure tetracycle **22** (61 mg, 75%) as a pale oil: IR (NaCl) 3452 $cm^{-1}$ (NH); $^1H$ NMR (500 MHz) 1.85-1.95 (m, 1H, 4-$H_a$), 1.99 (qt, $J$ = 12 and 3 Hz, 1H, $SCH_2CHa$), 2.02 (td, $J$ = 12 and 2 Hz, 1H, 3-$H_a$), 2.14 (dm, $J$ = 12 Hz, 1H, $SCH_2CH_e$), 2.24 (dm, $J$ = 12 and 2 Hz, 1H, 4-$H_e$), 2.31-2.46 (m, 3H, 12-$H_a$, 3-$H_e$ and 12-$H_e$), 2.74 (t, $J$ = 7 Hz, 2H, $SCH_a$), 2.78 (m, 1H, 5-$H_e$), 2.98 (ddd, $J$ = 14, 12 and 2 Hz, 1H, $SCH_e$), 3.16 (ddd, $J$ = 14, 12 and 2 Hz, 1H, $SCH_e'$), 3.20 (d, $J_{AB}$ = 13 Hz, 1H, $CH_APh$), 3.95 (d, $J_{AB}$ = 13 Hz, 1H, $CH_BPh$), 4.21 (s, 1H, 1-H), 7.08 (t, $J$ = 7 Hz, 1H, 10-H), 7.18 (t, $J$ = 7 Hz, 1H, 9-H), 7.23 (t, $J$ = 7 Hz, 1H, Ph-*p*), 7.30 (t, $J$ = 7 Hz, 2H, Ph-*m*), 7.37 (d, $J$ = 7 Hz, 2H, Ph-*o*), 7.36 (d, $J$ = 7 Hz, 1H, 8-H), 7. 49 (d, $J$ = 7 Hz, 1H, 11-H), 8.65 (s, 1H, In-NH); $^{13}C$ NMR 24.6 ($SCH_2CH_2$), 26.7 (C-4), 29.1 and 29.2 ($SCH_2$), 31.9 (C-12), 33.7 (C-5), 43.5 (C-3), 50.6 (C-1), 52.1 (SCS), 60.7 ($CH_2Ph$), 111.1 (C-8), 119.6 (C-11), 119.8 (C-10), 122.4 (C-9), 126.7 (Ph-*p*), 127.3 (C-11a), 128.1 (Ph-*m*), 128.7 (Ph-*o*), 135.6, 135.7 and 139.3 (C-6a, C-7a and Ph-*ipso*); MS (m/z, %) 406 ($M^+$, 26), 300 (26), 273 (63), 209 (20), 199 (24), 180 (20), 167 (50), 120 (22), 91 (100). Anal. Calcd for $C_{24}H_{26}N_2S_2$: C, 70.89; H, 6.45; N, 6.89; S, 15.77. Found: C, 70.56; H, 6.90; N, 6.55; S, 15.30.

***N*-(2-Benzyloxyethyl)-6-(1,3-dithian-2-yl)-1,2,3,4,5,6-hexahydro-1,5-methano-2-azocino[4,3-*b*]indol (23). Method A**. A solution of cyanopiperidine **18b** (50 mg, 0.105 mmol) in 50% aqueous AcOH (10 ml) was refluxed for 4 h. Once cooled, the mixture was basified with a saturated aqueous solution of $NaHCO_3$, and extracted with $CH_2Cl_2$. The organic extracts, dried and evaporated, furnished an oil which was flash chromatographed (95:5 $Et_2O$-MeOH), to yield pure **23** (35 mg, 70%): $^1H$ NMR 3.55 (td, $J$ = 12 and 6 Hz, 2H, $CH_2OBn$), 4.15 (br t, $J$ = 4 Hz, 1H, 1-H), 4.50 (s, 2H, $OCH_2Ph$), 6.95 (t, $J$ = 7 Hz, 1H, 9-H), 7.10 (t, $J$ = 7 Hz, 1H, 10-H), 7.2-7.3 (m, 6H, 8-H and ArH), 7.45 (d, $J$ = 7 Hz, 1H, 11-H), 8.50 (sa, 1H, NH); $^{13}C$ NMR 24.5 ($SCH_2CH_2$), 26.7 (C-4), 29.6 and 30.0 ($SCH_2$), 31.9 (C-12), 33.5 (C-5), 44.3 (C-3), 50.7 (C-1), 52.0 (SCS), 56.0 ($NCH_2$), 68.3 ($OCH_2$), 73.1 ($OCH_2Ph$), 111.0 (C-8), 119.7 (C-11), 119.8 (C-10), 122.4 (C-9), 127.5 (Ph-*p*), 127.7 (Ph-*m*), 128.3 (Ph-*o*), 135.6, 135.8, 138.4 (C-6a, C-7a and Ph-*ipso*); MS (m/z, %) 450 ($M^+$, 1), 446 (34), 344 (14), 329 (45), 316 (25), 223 (100), 194 (46), 167 (46), 91 (99).

**Method b**. Operating as above from diazocinoindole **19b** (58 mg, 0.128 mmol) and aqueous 50% AcOH (10 ml), compound **23** (48 mg, 82 %) was obtained, after flash chromatographic purification (95:5 $Et_2O$-MeOH).

***N*-(2-Hydroxyethyl)-6-(1,3-dithian-2-yl)-1,2,3,4,5,6-hexahydro-1,5-methano-2-azocino[4,3-*b*]indol (24)**. To a solution of compound **23** (48 mg, 0.11 mmol) in $CH_2Cl_2$ (5 ml), dimethyl sulfide (0.23 ml, 3.19 mmol) and

$BF_3.Et_2O$ (0.19 ml, 1,17 mmol) were added at room temperature. The reaction mixture was stirred at 35 °C for 7 h, the crude was poured on a saturated aqueous solution of $NaHCO_3$, and extracted with $CH_2Cl_2$. The organic extracts, dried and evaporated, furnished pure compound **24** (35 mg, 92%): IR ($CHCl_3$) 3450 (NH), 3450-3200 $cm^{-1}$ (OH); $^1H$ NMR 2.15 (td, $J$ = 12 and 2 Hz, 1H, 3-$H_a$) 2.20-2.30 (m, 2H, $SCH_2CHe$ and 4-$H_e$), 3.50-3.80 (m, 2H, $CH_2OH$), 4.30 (s, 1H, 1-H), 2.98 and 3.10 (2 td, $J$ = 12 and 2 Hz, $SCH_e$), 7.05 (t, $J$ = 7 Hz, 1H, 9-H), 7.10 (t, $J$ = 7 Hz, 1H, 10-H), 7.30 (d, $J$ = 7 Hz, 1H, 8-H), 7.40 (d, $J$ = 7 Hz, 1H, 11-H), 8.70 (br s, 1H, NH); $^{13}C$ NMR 24.4 ($SCH_2CH_2$), 26.7 (C-4), 28.2 and 29.6 ($SCH_2$), 30.7 (C-12), 33.2 (C-5), 43.8 (C-3), 51.5 (C-1), 57.1 and 58.1 ($NCH_2CH_2O$), 106.9 (C-11b), 111.5 (C-8), 119.0 (C-11), 120.6 (C-10), 123.0 (C-9), 126.3 (C-11a), 135.9 (C-6a), 136.7 ( C-7a). Anal. Calcd for $C_{19}H_{24}N_2S_2O$: C, 63.29; H, 6.71; N, 7.77. Found: C, 63.42; H, 6.84; N, 7.90.

***N*-(2-Chloroethyl)-6-(1,3-dithian-2-yl)-1,2,3,4,5,6-hexahydro-1,5-methano-2-azocino[4,3-*b*]indol (25)**. To a solution of *tert*-butanol (16 µl, 0.166 mmol) in anhydrous THF (2 ml) cooled at 0°C and under argon atmosphere, *n*-BuLi (6 *M*, 83 µl, 0.133 mmol) was added. After stirring for 5 min benzenesulfonylchloride (21 µl, 0.166 mmol) was added at 0°C, the ice bath was removed and the stirring continued for 2 h 30 min at room temperature. In the meantime, to a solution of alcohol **24** (40 mg, 0.11 mmol) in dry THF (10 ml) cooled at 0°C and under argon atmosphere, *n*-BuLi (1.6 *M*, 152 ml, 0.244 mmol) was added. The ice bath was removed and the stirring continued for 10 min at room temperature, before the previous solution containing *tert*-butylbenzenesulfonate was slowly transferred *via* cannula. After 2 h, $NaBH_4$ (8.6 mg, 22 mml) was added and the mixture was stirred for 45 min. The crude was poured in ice-water and extracted with $CH_2Cl_2$. The organic extracts, dried and evaporated, yielded an oil which was purified by flash chromatography (4:1 $Et_2O$-$CH_3OH$), to give pure **25** (10 mg): $^1H$ NMR 2.04 (br t, $J$=12 Hz, 1H, 3-$H_a$), 3.50-3.70 (m, 2H, $CH_2Cl$), 4.15 (br s, 1H, 1-H), 7.10 and 7.18 (2 t, $J$ = 7 Hz, 1H, 9-H and 10-H), 7.36 (d, $J$ = 7 Hz, 1H, 8-H), 7.52 (d, $J$ = 7 Hz, 1H, 11-H), 8.55 (br s, 1H, NH); $^{13}C$ NMR 24.5 ($SCH_2CH_2$), 26.7 (C-4), 29.0 and 29.3 ($SCH_2$), 31.7 (C-12), 33.6 (C-5), 41.8 ($CH_2Cl$), 44.0 (C-3), 50.8 (C-1), 58.2 ($NCH_2$), 106.8 (C-11b), 111.2 (C-8), 119.3 (C-11), 120.2 (C-10), 122.6 (C-9), 135.5 and 135.8 (C-11a and C-7a); MS (m/z,%) 380 ($M^+$+2, 5), 378 ($M^+$, 15), 329 (10), 273 (100 ), 255 (57), 199 (50), 167 (76), 143 (17 ).

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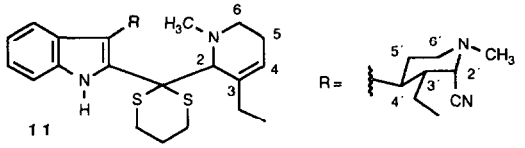


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36. Crystal data of compound **19a**: $C_{24}H_{26}N_2S_2$. Fw=406.61, monoclinic, **a**=11.376(2); **b**=14.232(3); **c**=13.677(3)Å; β=108.73(2). V=2097(1)Å$^3$, $P2_1/n$, Dx=1.287 g cm$^{-3}$. Z=4, F(000)=864.0, (Mo Kα)=0.71069 Å, μ (Mo Ka)=2.62 cm$^{-1}$. A prismatic crystal (0.1x0.1x0.2 mm) was selected and mounted on an ENRAF-NONIUS CAD4 diffractometer. Unit cell parameters were determined from automatic centring of 25 reflections ($12 \leq \theta \leq 21°$) and refined by least-squares method. Intensities were collected with graphite monochromatized Mo Kα radiation, using a ω/2θ scan technique. 6611 Reflections were measured in the range $2 \geq \theta \leq 30$. Rint (on F)=0.053, from which 4207 were assumed as observed applying the condition $I \geq 2.5\ \sigma(I)$. Three reflections were measured every two hours as orientation and intensity control, significant intensity decay was not observed. Lorentz-polarization, but not absorption corrections were made. The structure was solved by Patterson synthesis, using SHELXS computer program (Sheldrick, G. M. *Acta Cryst.*, **1990**, *A46*, 467-473) and refined by full-matrix least-squeares method, with the SHELX76 computer program (Sheldrick, G. M.; SHELX. A computer program for crystal structure determination, University of Cambridge, England). The minimized function was $\Sigma w\ |Fo| - |Fc|\ |^2$, where $w = (\sigma^2(Fo) + 0.010\ |Fo|^2)^{-1}$. f, f´And f´´were taken from International Tables of X-Ray Crystallography (International Tables of X-Ray Crystallography, (1974). Ed. Kynoch press, vol IV, pp 99-100 and 149). All H atoms were located from a difference synthesis and refined with an overall isotropic temperature factor. The final R factor was 0.066 (wR=0.072) for all observed reflections. The number of refined parameters was 332. max. shift/ e.s.d =0.4, Max. and min. peaks in the final difference synthesis was 0.4 and -0.3 eÅ$^{-3}$, respectively. Tables of atomic coordinates, bond lengths and angles, and thermal parameters (supplementary material) are available on request from the Cambridge Crystallographic Data Center.
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38. The 0.2 ppm difference between the methine 1-H proton in **22** with respect to compounds **10**, reported in this paper can be a consequence of the shielding effect (Δδ -0.2 to -0.4 ppm) of the ethyl group in C-12 of compounds **10**: see reference 34, Chapter 3.
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