2,3,4,9-Tetrahydrothiopyrano[2,3-*b*]indoles: Synthesis *via* an Intramolecular Indole Grignard Reaction† and Conformational Study by ^1H and ^{13}C NMR Spectroscopy

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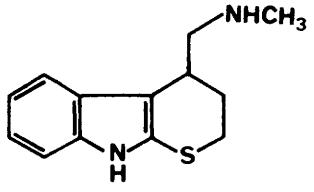
Cycloalkylation reactions of 2-alkylthioindoles, (**2**; X = OSO_2R, halogens, or epoxy) to 2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indoles (**3**) *via* the corresponding metallated indole intermediates have been studied. Compound (**2**) could be cyclized to (**3**) in good yield and regioselectivity on treatment with a Mg or Zn reagent, whereas Li, Na, and K reagents afforded (**3**) and/or its regioisomer. The leaving group (X) and the solvent were shown to be crucial for reactivity. The reaction of (**2**; X = OSO_2R as leaving group) and a Grignard reagent in non-polar solvents effectively afforded (**3**). The cyclization was demonstrated to proceed *via* an S_N2 process. Analyses of the ^1H and ^{13}C NMR spectra of (**3**) revealed that the thiopyrano ring entity of (**3**) was anchored in a half-chair conformation which ensured that any C-4 substituent introduced was in the pseudoaxial position. Assignments for the ^1H and ^{13}C signals of (**3**) are also reported.

4-Methylaminomethyl-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]-indole (**1**) acts on the central nervous system as a non-narcotic analgesic of high potency.[1] The sulphur-containing tricyclic indole ring system (**1**) is structurally rare and unrelated to any other potent analgesics reported. In order to obtain further insights into the structure–activity relationships, we had to develop a method to prepare the analogues of (**1**). Scheme 1 illustrates two fundamental strategies employed so far to



(**1**)

construct the parent tetrahydrothiopyrano[2,3-*b*]indole‡ ring system (**3**). Route A represents the initial introduction of a suitably functionalized side chain into the C-3 position of indole, followed by cyclization at C-2 by means of C–S linkages to give (**3**).[2] Route B is a reversal of route A.[1]

The problem with both of these approaches for the preparation of the compounds represented by general formula (**3**) is the regio- and stereo-selective introduction/cyclization of a functionalized alkyl side chain into the C-3 position of indole. It has been well documented that the regioselectivity, *i.e.*, the relative ratio between carbon *vs.* nitrogen alkylation, and the stereoselectivity, which mainly depends on the reaction mechanism, are dramatically affected by various factors due to the typical 'ambident nucleophilic' characteristics of indoles.[3] Although a number of methods can be adopted for selective *N*-alkylation,[4] there are few that can afford effective *C*-alkylation.

Indoles react directly with Grignard reagents to form magnesium salts. The reactions of these salts with various nucleophiles, generally called indole Grignard reactions, have been used to introduce substituents into the C-3 position of indoles.[3] Many indole derivatives have been synthesized using this reaction, but the yields are often disappointingly low.[5] Nevertheless, some systematic surveys have been done so far to obtain practical results. Bearing in mind the exceptional regioselectivity of the indole Grignard reaction, we decided to study this reaction as a hitherto unknown intramolecular reaction. We describe here a simple and efficient method for synthesizing tetrahydrothiopyrano[2,3-*b*]indoles (**3**) by cycloalkylation[6] of 2-alkylthioindoles (**2**) *via* the corresponding indolylmagnesium intermediates. Conformational studies of (**3**) by means of ^1H and ^{13}C NMR spectroscopy are also reported.

Studies of Cyclization Reactions

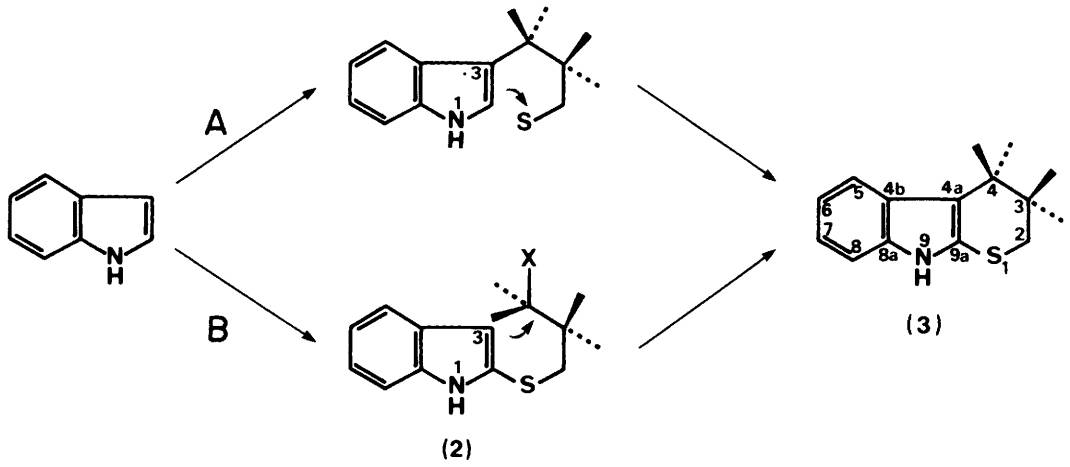
(1) *Effects of Metal Cation.*—The indolyl sulphide (**4**), carrying a methylsulphonyloxy (OMs) group at the γ-position of the sulphide, was prepared as a model compound to examine the reaction conditions for cycloalkylation. On treatment with an appropriate metallating reagent, (**4**) was expected to give the tricyclic indole (**8**) and/or its regioisomer (**9**) *via* metallated indole intermediates (Scheme 2).

The reaction of (**4**) with ethylmagnesium bromide (EtMgBr) was examined first. A commercially available ether solution of EtMgBr (*ca.* 3 M) was added to a stirred solution of (**4**) in benzene at 8 °C dropwise. A viscous gummy precipitate appeared immediately. The reaction was completed within a few minutes and afforded the cyclized products in 90% yield accompanied by a small amount of the bromide (**5**). Analysis of the products by NMR and high-performance liquid chromatography (HPLC) revealed that 95% of the cyclized products was the desired isomer (**8**). Comparable results were obtained by the reaction with diethylmagnesium (Et_2Mg).[7] The unexpected ease of cyclization prompted us to further examine the reaction conditions.

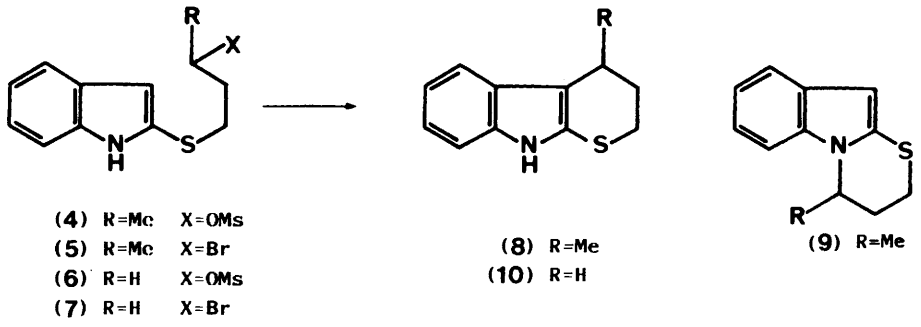
Treatment of (**4**) with butyl-lithium (BuLi) in ether at 25 °C afforded (**8**) and (**9**) in a ratio of 78:22 in 76% yield. Similar homogeneous reactions of (**4**) and sodium hexamethyldisilazane (NaHMDS),[8] or lithium hexamethyldisilazane (Li-

† This work was presented in part at the 9th International Congress of Heterocyclic Chemistry, Tokyo, Japan, August 21–26, 1983. See: Abstracts of Papers, 1983, p. 397.

‡ The descriptors 2,3,4,9- of tetrahydrothiopyrano[2,3-*b*]indoles are omitted hereafter.



Scheme 1.



Scheme 2.

Table 1. Cyclization reaction of (4)

RM(equiv.)		Temp. (°C)	Time	Yield (%)	Ratio[a]
EtMgBr (1.1)	C_6H_6	8	5 min	90	95:5
EtMgBr (1.1)	Et_2O	0	5 min	85	98:2
EtMgBr (1.1)	$CHCl_3$	0	5 min	76	96:4
EtMgBr (1.1)	THF	25	6 h	76	99:1
EtMgBr (1.1)	DME	25	1 d	0	—
Et_2Mg (1.1)	C_6H_6	25	5 min	67	95:5
Et_2Mg (1.3)	THF	25	10 h[b]	86	98:2
EtMgBr (1.3)–HMPA (3.0)	THF	25	2 d	3	65:35
BuLi (1.2)–$ZnCl_2$ (1.5)	Et_2O	25	22 h	65	100:0
BuLi (1.2)	Et_2O	25[c]	1 h	76	78:22
BuLi (1.2)	THF	25[c]	2 h	95	43:57
NaHMDS (1.4)	C_6H_6	25	1 h	95	78:22
LiHMDS (1.1)	C_6H_6	25	1 h	95	73:27
KH (1.3)	C_6H_6	25	5 min	95	58:42
KH (1.2)	THF	−13	8 h	75	9:91
LDA (1.2)–HMPA (4.0)	THF	25[c]	2 h	95	1:99

[a] The ratios of (8) and (9) were determined by analytical HPLC. See Experimental section. [b] 5% of (4) was recovered unchanged. [c] Reaction was initiated at −78 °C and then allowed to warm to 25 °C (see Experimental section).

HMDS)[9] in benzene gave 95% yields of cyclized products. The ratios of the isomers in these reactions were essentially the same as that of BuLi. Potassium hydride (KH)[10] in benzene under heterogeneous conditions at 25 °C gave a 58:42 mixture of (8) and (9) in 95% yield. On the other hand, the reagent prepared from $ZnCl_2$ and BuLi[11] in ether resulted in exclusive *C*-alkylation, though the rate of reaction was significantly reduced.

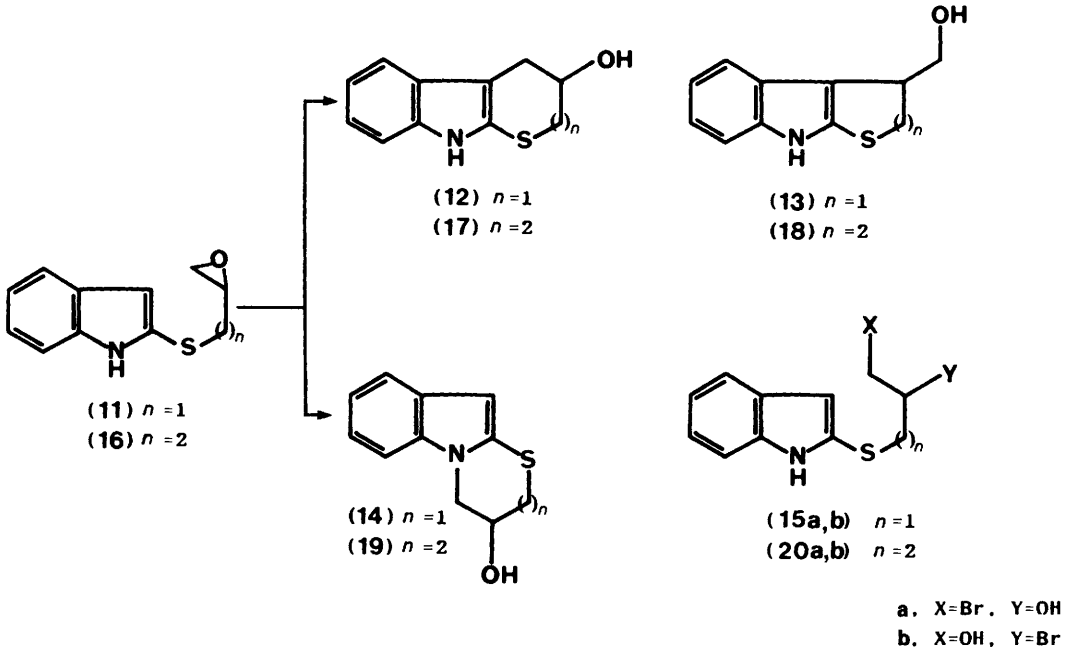
The general significance of a position of alkylation of metallated indoles has been rationalized in terms of the 'hard-soft acid-base' theory, that is, the alkali metals of harder cations lead to more *C*-alkylation.[3] Our results generally agreed with this rationale and the findings of intermolecular reactions.[12] The results are summarized in Table 1.

(2) *Solvent Effects.*—The reactions of (4) with Grignard reagents in ether or benzene afforded similar satisfactory results. The reaction proceeded even in $CHCl_3$. Unexpectedly, however, when the reactions were carried out in more polar solvents, the reactivity was significantly diminished. In THF, it took much longer for completion than in ether or benzene. Dimethoxy-

Table 2. Reaction of compounds (5)–(7) and EtMgBr in C_6H_6

Compd	X	RLGA[a]	Temp. (°C)	Time (min)	Yield (%)
(5)	Br	10^{-2}–10^{-3}	80	150	78
(6)	OMs	1	8	5	70
(7)	Br	10^{-2}–10^{-3}	80	80	83
(4)	$OS(O)_2C_6H_4NO_2$-*p*	13	10	10	51

[a] Relative Leaving Group Ability: values were estimated from Table 1, and 2 of ref. 13.



Scheme 3.

ethane could not afford a detectable amount of cyclized products. Addition of the hard co-ordinating agent hexamethylphosphoric triamide (HMPA) to the reaction medium gave rise to predominant *N*-alkylation due to separation of ion pairs even with the magnesium salts derived from indole or pyrrole.[12] However, addition of HMPA to a solution of (4) and EtMgBr in THF resulted in a mixture of (8) and (9) in a ratio of 65:35 with a very low yield, the major isolated product being the bromide (5). In contrast, the reactions of (4) and lithium or potassium reagents proceeded smoothly to give good yields of the cyclized products. The ratios of (9) were improved in THF. Addition of HMPA to a solution of (4) and lithium di-isopropylamide (LDA) in THF resulted in exclusive formation of (9) in 95% yield as was expected from the results of Guida *et al.*[4]

These results suggest that the N–Mg–solvent association remained to affect both the *C*- and *N*-alkylation and the use of non-polar solvents is crucial for sufficient reactivity when a Grignard reagent is used for cyclization. The results are summarized in Table 1.

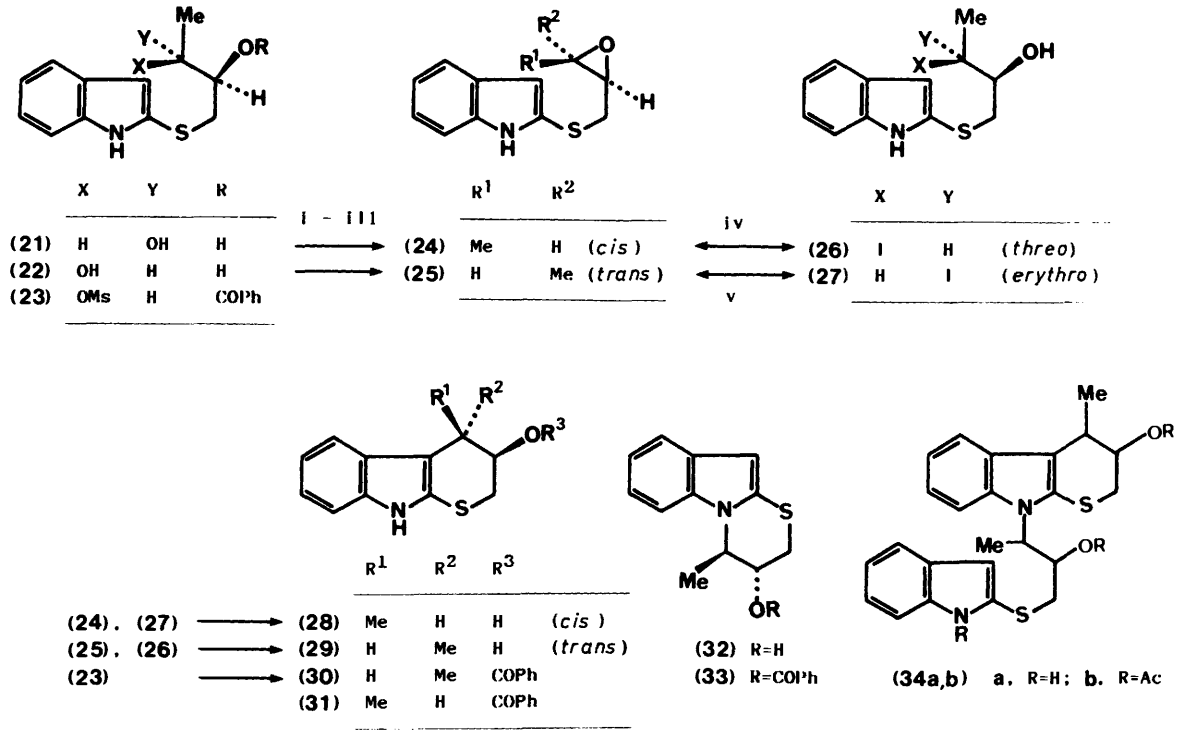
(3) *Effects of the Leaving Group.*—Halogens have most commonly been employed as alkylating agents. The reaction of the bromide (5) and EtMgBr afforded (8) in refluxing benzene in 78% yield. Similarly, while the terminal mesylate (6) smoothly cyclized to (10) at 8 °C, the corresponding bromide (7) cyclized to (10) in refluxing benzene. The conditions required for bromides were much more rigorous than those for mesylates. The reactivity of bromides was obviously less efficient than the corresponding mesylates. The difference in reactivity could be rationalized in terms of the difference in the relative leaving group ability (RLGA) between mesylates and bromides, since the estimated RLGA of bromide is *ca.* 0.01–0.001 times less than that of the former.[13] Unfortunately, replacement of the *O*-mesyl group with more active leaving groups [*e.g.* (4): $X = OS(O)_2C_6H_4$–NO_2-*p*] resulted in a poorer yield mainly due to the increased instability of the compounds themselves. The results are summarized in Table 2.

Epoxides could also act as the leaving group. Treatment of the primary expoxide (11) with EtMgBr in ether at 25 °C afforded (12) in 78% yield accompanied by a small amount of the isomeric bromohydrins (15a) (0.5%), (15b) (5%), and the regioisomer (14) (3.5%). The five-membered compound (13) was not detected.

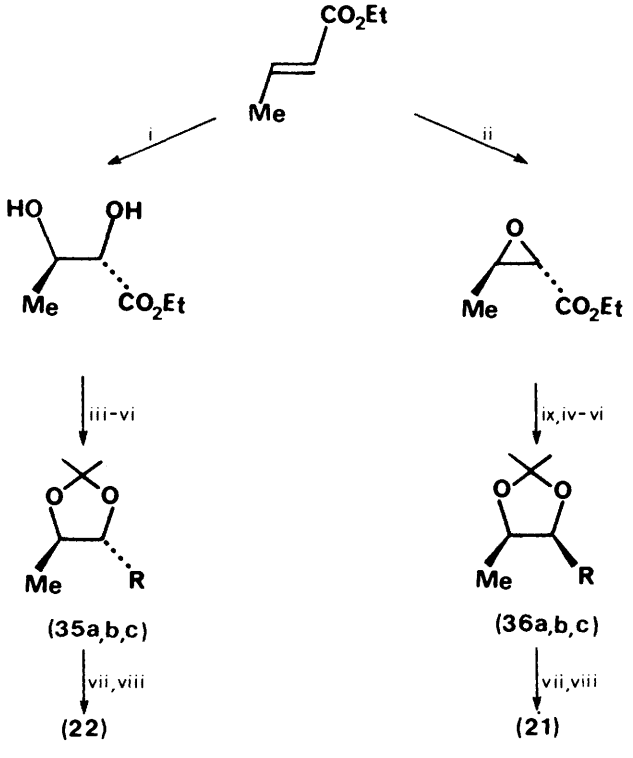
Under identical reaction conditions, the homologous epoxide (16) cyclized to (17) and (18) in a ratio of *ca.* 1:1 in 43% yield after isolation as a mixture of the corresponding acetates. Although the reaction proceeded even at −25 °C, the ratio of (17) and (18) did not change significantly, and an increasing amount of bromohydrins (20) was isolated. Compound (19) was not detected (Scheme 3).

(4) *Stereochemical Outcome.*—The mechanism of cyclization was examined next using two epimeric epoxides (24) (*cis*) and (25) (*trans*) and two epimeric iodohydrins (26) (*threo*) and (27) (*erythro*). These compounds were subjected to the reactions with Grignard reagents. They were expected to afford *cis*-(28) and/or *trans*-(29) depending on the mechanism of cyclization (Scheme 4).

Since both sulphide and indole entities are sensitive to



Scheme 4. *Reagents:* i, $CH(OMe)_3$, $C_6H_5CO_2H$, C_6H_6; ii, TMSCl, CH_2Cl_2; iii, 20% NaOH, MeOH–H_2O; iv, NaI–NaOAc, AcOH–$EtCO_2H$; v, 2M-NaOH, MeOH.



Scheme 5. *Reagents:* i, OsO_4–Bu^{t}OOH–Et_4NOAC, Me_2CO–THF[30]; ii, MCPBA, $Cl(CH_2)_2Cl$; iii, TsOH, Me_2CO; iv, $LiAlH_4$, ether; v, TsCl, pyridine; vi, LiBr, Me_2CO; vii, indole-2-(1*H*)-thione, K_2CO_3, acetone; viii, HCl, MeOH–H_2O; ix, $SnCl_4$, Me_2CO–CCl_4.

oxidative conditions and, further, it was necessary to establish unambiguously the relative configurations, the starting materials were prepared from ethyl crotonate as illustrated in Scheme 5. The key intermediates were the diols *erythro*-(**21**) and *threo*-(**22**). Each diol was converted into the epoxides *cis*-(**24**) and *trans*-(**25**), respectively, by the method of Newman *et al.*[14] These diols could also be converted into epoxides by monomesylation, demesylation sequences. In the latter method, inversion of the configuration occurred during epoxidation, and (**21**) afforded *trans*-(**25**), and *vice versa*.[15] Subsequently, the *cis*-epoxide (**24**) was converted into the pure *threo*-iodohydrin (**26**) by the method of Cornforth *et al.*[16] In a similar manner, *erythro*-(**27**) was obtained from *trans*-(**25**). The relative configurations of these epimeric iodohydrins were confirmed by restoring them to the starting epoxides by treatment with NaOH.[15] These epimeric epoxides and iodohydrins were readily distinguished by NMR spectroscopy.

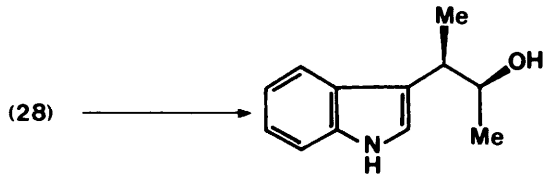
The reaction of the *cis*-epoxide (**24**) with EtMgBr in ether was completed smoothly at 0 °C, and exclusively afforded (**28**) in 92% yield. However, the reaction of the *trans*-epoxide (**25**) was sluggish, giving a 36% yield of (**29**) and a 32% yield of a dimeric product (**34**) after 6 h at 25 °C.

Cyclization of iodohydrins was conducted using commercially available methylmagnesium iodide (MeMgI) instead of EtMgBr in order to avoid complication by halogen exchange.

threo-Iodohydrin (**26**), which had the reverse configuration to (**24**), was treated with MeMgI in ether at ambient temperature (32–33 °C) for 16 h. The products were (**29**) (33% yield) and (**32**) (55% yield), respectively. Compound *erythro*-(**27**) afforded complex products under identical reaction conditions, with a 35% yield of (**28**) being isolated as the major product by silica gel chromatography.

The ratio of the products [(**28**):(**29**)] in each reaction was determined by HPLC analysis or by comparison of the intensities of methyl signals at C-4 of ^1H NMR in C_6D_6 solution after isolation as an inseparable mixture of stereoisomers (Table 3). Except for the last case, satisfactory stereoselectivities were realized.

Similar cyclization was also effected with mesylate as the



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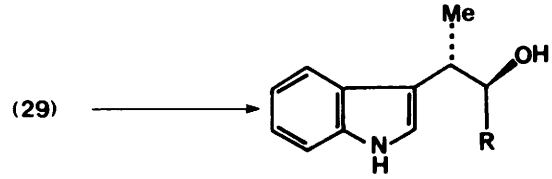


(38) R=Me
(39) R=CO_2H
(40) R=CO_2Et
(41) R=CH_2OH

Scheme 6.

Table 3. Reactions of compounds (**24**)–(**27**) with Grignard reagents

Compound	Conditions	(**28**):(**29**)	Yield[a]	
(**24**)	0 °C 8 min	99:1[b]	92	
(**25**)	25 °C 6 h	7:93[b]	36	(**34a**):32%
(**26**)	32 °C 20 h[c]	9:91[b]	33	(**32**):55%
(**27**)	33 °C 16 h[c]	78:22[d]	35	(**27**):13%[e]

[a] Isolated yield (%). [b] Determined by HPLC. See Experimental section. [c] 3.0–3.2 eq. of MeMgI was used in ether. [d] Determined by ^{1}H NMR in C_6D_6. [e] At least, six compounds were detected on TLC.

leaving group. Selective mono-benzoylation of *threo*-(**22**) followed by *in situ* *O*-mesylation afforded the mesylate (**23**). Treatment of (**23**) with EtMgBr in benzene afforded the benzoate (**30**) and its regioisomer (**33**) in 42 and 2% yield, respectively. The stereoisomer (**31**), the reference compound of which was obtained by benzoylation of (**28**), was not detected on TLC. Base hydrolysis of (**30**) yielded (**29**).

The relative configurations between the hydroxy group at C-3 and the methyl group at C-4 of (**28**) and (**29**) were unambiguously established as follows (Scheme 6).

Compounds (**28**) and (**29**) were desulphurized with Raney nickel (W4) in refluxing ethanol to provide (**37**) and (**38**), respectively. Compound (**38**) could also be obtained by the consecutive reduction of the ethyl ester of α-indolmycenic acid (**39**), of which the relative as well as absolute configurations had been firmly established.[17–18]* Compound (**38**) was identical in all respects with that obtained from (**29**). Both (**37**) and (**38**) were readily distinguished by ^{1}H NMR spectroscopy. These results clearly demonstrated that the relative configuration between the two asymmetric centres of (**29**) should be a *trans* configuration. The structures of the starting and final materials were thus established, and the cyclization mechanism could be unequivocally demonstrated as being cycloalkylation proceeding *via* an S_N2 process with a single inversion of configuration.

NMR Studies of Tetrahydrothiopyrano[2,3-b]*indoles*

(1) ^{13}C *NMR Spectra.*—Numerous reviews and articles have reported on the ^{13}C NMR studies of natural and synthetic indoles. However, only limited data are available on the chemical-shift assignment of indoles carrying a sulphur atom at the C-2 position because these compounds are rare. Further, papers describing them have not included the ^{13}C NMR data, or had not assigned the chemical shifts irrespective of whether they were synthetic or natural compounds.[19] Thus, ^{13}C NMR chemical shifts assignments were made for a series of tetrahydrothiopyrano[2,3-*b*]indoles. Results for the compounds studied are tabulated in Table 4.

The aromatic carbons in the indole ring were assigned in the order of increasing chemical shifts, C-8 < C-5 < C-6 < C-7 for protonated carbons, and C-4a < C-4b < C-9a < C-8a for quaternary carbon atoms based on the references to assignments reported for indole derivatives,[20–22] and substituent effects on ^{13}C chemical shifts (SCS) induced by electron donating/withdrawing substituents[20,23] at N-9 and C-4. Comparison of the spectra of the sulphide (**4**; X = OH) and the regioisomers (**9**) and (**14**) were also considered.

The resonances of aromatic carbons of tetrahydrothiopyrano[2,3-*b*]indoles are closely related to those of 2,3-dimethylindole and indole alkaloids, especially 1,2,3,4-tetrahydro-9*H*-carbazole[20,21] and yohimbine alkaloids,[20,22] except for the C-9a positions which are shielded by a sulphur atom.[24]

Assignments of aliphatic carbons were determined by the single-frequency off-resonance decoupling method (SFORD), comparison of ^1J(C,H), and SCS. C-2 and C-3 could be differentiated owing to their different ^1J(C,H) values. Namely, those of one of the secondary carbon atoms of the selected compounds were consistently larger (140 Hz) than the others (*ca.* 130 Hz), and they were assigned to C-2.[23] Discrimination between C-3 and C-4 of compound (**10**) was made by ^{13}C,^{1}H selective decoupling experiments. The assignments were confirmed by comparison with the spectra of [4-$^2H_2$]-(**10**).

(2) ^{1}H *NMR Spectra of Thiopyrano Ring Hydrogens.*—The ^{1}H NMR spectra were analyzed only on the thiopyrano ring (c ring) hydrogens at C-2 to C-4. Compounds (**18**) and (**42**)—(**45**)† were measured at 90 MHz in $CDCl_3$ solution. These spectra were difficult to interpret owing to several overlapping resonances. [10-^{2}H]- and/or [4,10-^{2}H]-Labelled compounds were prepared as depicted in Scheme 7; this allowed complete analyses of the 2-H, 3-H, and 4-H signals of these compounds. Compounds (**8**), (**10**), and (**28**)–(**31**) were measured at 200 MHz.

Each of the CH_2 fragments in the CH_2CH_2CH or CH_2CHCH entities of all of the 4-substituted compounds gave rise to an AB type spectrum, the geminal coupling constant of which was 12.5–13.1 Hz for ^2J(2,2) and 13.9–14.1 Hz for ^2J(3,3), respectively.

In 4-monosubstituted compounds, the large vicinal coupling constants (*ca.* 11 Hz) were commonly observed as one of the ^3J(2,3), indicating an *antiperiplanar*‡ relationship between two vicinal hydrogens. Thus, 2_{ax}-H and 3_{ax}-H, and therefore 2_{eq}-H and 3_{eq}-H, were assigned, respectively. The initial parameters were obtained by hand-calculated analyses, and then refined by the LAOCN3 program.[25] The results satisfactorily reproduced the experimental spectra and are summarized in Table 5.

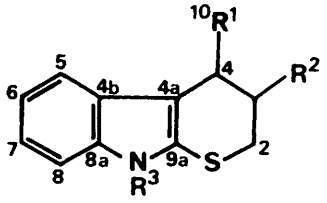
3,4-Disubstituted compounds (**28**)–(**31**) exhibited an ABMX system. A and B denote methylene protons at C-2, and M and X

* IR and NMR spectra of optically active (**39**), which had been kindly provided by Prof. T. Mukaiyama, Univ. of Tokyo, agreed well with our data. See ref. 18*c*.

† The methods of preparation of compounds (**42**)–(**45**) were reported in ref. 1.

‡ For nomenclature and definition of these terms, see: W. Klyne and V. Prelog, *Experientia*, 1960, **16**, 521.

Table 4. ^{13}C NMR data for 2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole derivatives[a]



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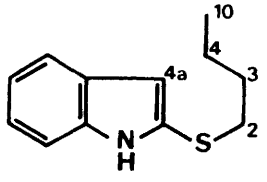

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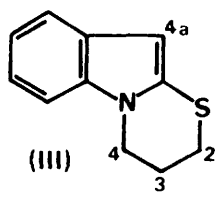


(III)

Compd. R^1	R^2	R^3	C-2	C-3	C-4	C-4a	C-4b	C-5	C-6	C-7	C-8	C-8a	C-9a	C-10
(10) H	H	H	28.2	23.6	20.5	107.2	125.9	116.3	119.5	120.8	109.9	135.7	128.5	—
			(140)	(130)	(130)			(160)	(160)	(160)	(160)[b]			
(10) H	H	Me	28.2	23.7	20.8	106.0	128.3	116.6	119.2	120.5	108.2	137.2	129.0	—[c]
(10) H	H	Ac	29.1	22.6	20.8	114.0	129.9	116.9	123.2	123.5	114.3	135.2	131.9	—[c]
(8) Me	H	H	24.6	31.8	26.0	112.4	125.7	117.1	119.4	120.6	110.1	135.9	128.0	21.4
			(140)	(130)	(125)			(160)	(160)	(160)	(160)			(125)[b]
(8) Me	H	Me	24.6	31.8	26.2	111.3	127.9	117.3	119.1	120.4	108.3	137.4	128.8	21.8[c]
(8) Me	H	Ac	24.9	30.2	25.6	118.3	129.4	117.3	122.7	123.0	114.1	135.2	131.1	20.9[c]
			(140)	(130)	(125)			(160)	(160)	(160)	(160)[b]			
(18) CH_2OH	H	H	24.7	25.9	34.0	106.3	127.9	116.8	119.6	120.8	110.2	135.9	128.2	65.3
			(140)	(130)	(130)			(161)	(161)	(161)	(161)			(145)[b]
(42) CHO	H	H	25.4	23.1	45.0	101.5	127.7	116.5	120.2	121.4	110.4	135.8	128.8	200.3
(43) CN	H	H	25.3	27.6	23.9	100.5	126.8	116.3	120.2	121.9	110.3	135.6	128.1	120.5
(44) CH_2NH_2	H	H	24.7	26.5	34.8	108.2	127.3	116.8	119.6	120.8	110.2	135.9	128.1	46.0
(45) CH_2NHCO_2Me	H	H	24.5	26.4	32.2	107.6	128.0	117.2	120.1	121.2	110.4	136.2	128.1	44.7[c]
(12) H	OH	H	34.7	63.4	29.7	105.5	124.0	116.5	119.8	121.5	110.1	136.5	129.3	—
(28) Me	OH	H	31.6	68.6	32.9	111.4	123.7	117.6	119.6	121.0	110.3	136.6	128.1	15.4
(29) Me	OH	H	30.6	67.6	34.5	109.9	123.1	116.8	119.6	121.2	110.3	136.3	128.3	20.5
(4)[d,e]			32.9	38.7	66.9	108.4	128.6	120.1	120.1	122.4	110.6	137.2	128.6	23.5[c]
			(140)	(126)	(128)	(176)		(160)	(160)	(160)	(160)			(140)[b]
(9)[d,f]			20.2	29.9	46.3	98.3	127.9	118.9	119.8	120.0	108.1	136.7	128.3	19.0
(14)[d,f]			32.4	62.4	48.6	99.8	125.9	119.2	120.5	120.7	108.0	138.2	128.3	—

[a] All the spectra were measured in $CDCl_3$. [b] Parentheses indicate $^1J(C,H)$. [c] Other signals: 10: 29.6 (R^3, Me); 10: 26.8, 169.8 (R^3, Ac); 8: 29.6 (R^3, Me); 8: 26.7, 169.4 (R^3, Ac); 45: 52.3, 157.9 (CO_2Me); 46: 23.6 (Me). [d] Atom numbers were modified for the convenience of comparison. [e] X = OH, structure (II). [f] Structure (III).

are 3-H, and 4-H protons, respectively. Procedures similar to those described for the 4-monosubstituted compounds were followed for the analyses of these compounds. The results are summarized in Table 6.

Compound (**10**), which lacks a substituent at C-4, exhibited symmetrical signals at the centres 3.12, 2.24, and 2.85 ppm for 2-H, 3-H, and 4-H methylenes, respectively. The 2-H and 3-H signals of [4-$^2H_2$]-(**10**) also afford highly symmetrical signals, although the latter is somewhat broadened probably due to the small coupling with ^2H at C-4.

(3) *Conformational Properties of the Thiopyrano Rings.*—The averaged spectrum of (**10**) indicates that the C ring of (**10**) undergoes rapid conformational interconversion,[26] whereas, each of the geminal and vicinal coupling constants of 4-substituted derivatives, (**8**), (**18**), (**42**)–(**45**), converged to similar values. This feature is in marked contrast to that of (**10**), suggesting that the conformational properties of the C rings of these compounds are quite similar to each other, but significantly different from that of (**10**).

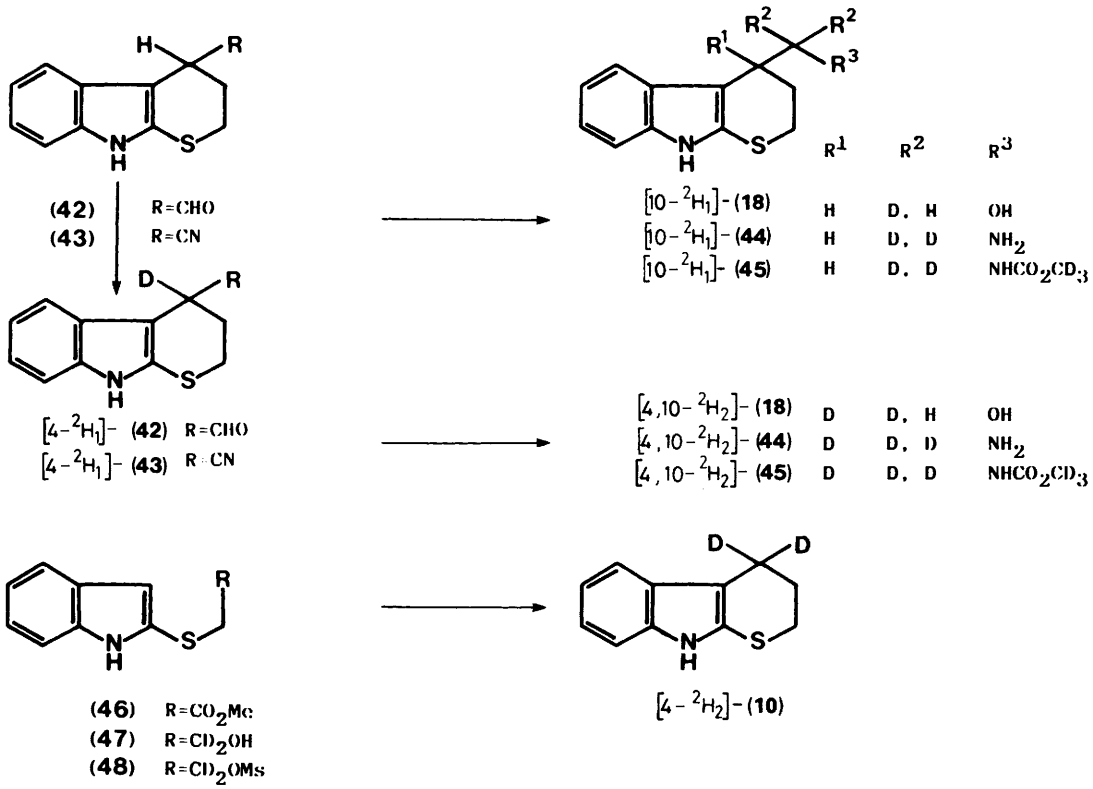
In the case of 4-substituted compounds, the conformers may be represented by two extreme structures (**A**) and (**B**) (Figure 1). Conformer (**A**) stands for a half-chair/envelope conformation where C-3 is below the mean plane of the aromatic atoms, the C-4 substituent (C-10 group) and C-2 are *synclinal*,* and the C-10 group occupies a pseudoaxial† position. On the other hand, ring flipping of conformer (**A**) affords conformer (**B**), which is a complete reversal of (**A**), and C-10 and C-2 are *antiperiplanar* with a pseudoequatorial† orientation of the C-10 group.

The values of the $^3J(2,3)$ vicinal coupling constants of 10.7–11.4 Hz and 2.1–2.6 Hz for 2-H_{ax}, and 6.3–7.0 Hz and 2.5–3.1 Hz for 2-H_{eq} indicate that the C ring of 4-substituted compounds adopts either one of the conformers represented by (**A**) or (**B**). Almost equal values of $^3J(3,4)$ (4.2–4.8 Hz and 5.4–6.0 Hz), however, strongly suggest that 4-H bisects the angle formed by 3-H, C-3, and 3′-H and, therefore, that conformer (**A**) is the preferred one. Figure 2 illustrates the Newman representations of relevant hydrogens with arithmetic means of ^2J and ^3J coupling constants.

Support for the existence of a preferred conformation was obtained from the ^{13}C NMR data. Introduction of a substituent into the 4-position of (**10**) resulted in consistent shielding of C-2 in ^{13}C NMR chemical shifts when compared with the corresponding resonance of (**10**). They were −3.3 to −3.6 ppm for the methyl or methylene group, and *ca.* −2.8 ppm for the aldehyde and nitrile groups, respectively. These shieldings

* See footnote ‡ on p. 817.

† Inspection of the Dreiding model showed that introduction of C–S bonds modified the ring geometry when compared to the corresponding C, N, or O bonds, so as to push either C-2 or C-3 more out of the mean plane of the aromatic atoms. Thus, the terms 'pseudoaxial' or 'pseudoequatorial' might not be necessarily suitable for designating the orientation of the C-4 substituent due to the probable distortion of the C ring. However, these terms are conventionally used in relation to cyclohexenes: see G. M. Kellie and F. G. Riddell, 'Topics in Stereochemistry', ed. E. L. Eliel, and N. L. Allinger, Wiley, New York, 1974, vol. 8, p. 225.



Scheme 7.

Table 5. ^{1}H NMR chemical shifts and coupling constants of 2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indoles[a].

	Chemical shifts					Coupling constants[b]							
Compd.	2e-H	2a-H	3e-H	3a-H	4-H	2e,2a	2e,3e	2e,3a	2a,3a	2a,3e	3e,3a	3e,4	3a,4
(8)[c]	2.97	3.23	2.03	2.23	3.27	12.5	7.0	2.5	10.7	2.2	13.9	4.6[d]	5.5
(18)	2.92	3.27	2.40	2.08	3.27	12.9	6.3	2.9	11.4	2.5	14.1	4.3	5.4
(42)	3.00	3.16	2.66	2.12	4.76	12.7	6.6	2.9	10.6	2.3	13.9	4.2	6.0
(43)	3.00	3.27	2.49	2.30	3.93	13.1	6.7	2.7	10.7	2.1	14.1	4.8	5.4
(44)	2.94	3.20	2.31	2.10	3.16	12.7	6.7	3.1	10.7	2.6	14.2	4.8	5.4
(45)	2.92	3.20	2.22	2.07	3.29	12.9	6.5	2.8	11.0	2.3	14.4	4.2	5.4
Mean[e]						12.8	6.6	2.8	10.9	2.3	14.1	4.5	5.5

[a] The parameters were refined by LAOCN3. Except for (8), these compounds were measured at 90 MHz in $CDCl_3$ after partial deuteriation. [b] Absolute value. [c] Measured at 200 MHz. [d] $^4J(2,4) = 0.1$ was observed. [e] Arithmetic mean of each of the coupling constant.

Table 6. ^{1}H NMR chemical shifts and coupling constants of 3,4-disubstituted 2,3,4,9-tetrahydrothiopyrano[2,3 *b*]indoles[a]

	Chemical shifts					Coupling constants[b]				
Compd.	2e-H	2a-H	3e-H	4-H	Me	2e,2a	2e,3	2e,4	2a,3	3,4
(28)	3.06	3.28	4.34	3.29	1.43	12.3	2.1	0.7	8.0	4.5
(31)	3.09	3.53	5.68	3.63	1.47	12.3	2.8	0.8	10.1	5.1
(29)	2.99	3.34	4.23	3.45	1.32	12.3	5.8	0.9	1.6	3.0
(30)	3.24	3.36	5.59	3.42	1.40	13.1	6.2	0.4	2.1	3.9

[a] Measured at 200 MHz in $CDCl_3$. Parameters were refined by LAOCN3. [b] Absolute values.

could be explained by the steric interaction (γ-*gauche* effect) induced by introduction of C-4 substituents. The γ-*gauche* effect is expected only from the predominant conformer (**A**).

The $^3J(2,3)$ and $^3J(3,4)$ values of *cis*-3,4-disubstituted compounds, (**28**), (**31**), indicate that one of the 2-H methylene protons and 3-H (^3J 8.0–10.1 Hz) are in *antiperiplanar* relationships, and the other 2-H, 3-H (2.1–2.8 Hz), and 3-H, 4-H (4.5–5.1 Hz) are in *synclinal* relationships. The corresponding vicinal coupling constants of *trans*-isomers, (**29**), (**30**), indicate that all of these hydrogens are located synclinally (Table 6). Furthermore, small couplings (<0.9 Hz) are commonly observed in one of the 2-H methylene protons in all of these

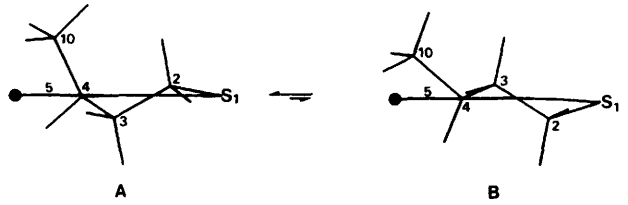


Figure 1. Two extreme C ring geometries (**A**, **B**). ● denotes 5-H. Atoms at 6–8, 8a, and 9 are removed for clarity.

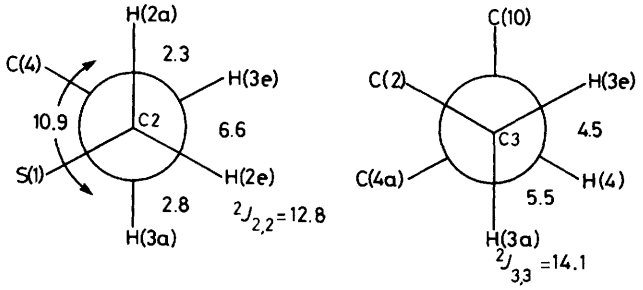


Figure 2. Newman projections of the C ring hydrogens. Numbers indicate the arithmetic means of coupling constants of the respective positions. See Table 5 and text.

isomers. We assumed the existence of coplanar W-type ^4J couplings between 2-H_{eq} and 4-H. Similar long-range couplings were reported by Cotterill *et al.* for two 1,3-diequatorial hydrogens in the structurally related 3,4-disubstituted dihydrobenzothiopyrans.[27] In the ^{13}C NMR spectra, similar shieldings of C-2 are also observed in compounds (**28**) (−3.1 ppm) and (**29**) (−4.1 ppm) when compared with (**12**) which lacks a substituent at C-4.

These results are best exemplified by C ring geometries similar to those of 4-monosubstituted compounds [conformer (**A**)]; methyl groups at C-4 of both isomers are located in pseudo-axial positions, while hydroxy/benzoyloxy groups at C-3 are located equatorially in *cis*- and axially in *trans*-isomers, respectively.

The restricted conformation of 4-substituted compounds must result from the steric interactions between the 5-H *peri* hydrogen and the C-10 group. Inspection of a CPK model suggests that in a pseudoequatorial disposition the C-10 group would suffer from severe van der Waals contacts with the C-5 region, which would force the C-10 group into a pseudoaxial rather than a pseudoequatorial position.

In summary, we have demonstrated a novel method of cycloalkylation of (**2**) to give tetrahydrothiopyranol[2,3-*b*]-indoles (**3**) *via* indolylmagnesium intermediates. The reactions proceeded most effectively in non-polar media using a Grignard reagent and a sulphonate ester as the metallating agent and the internal leaving group, respectively. A hitherto unknown intramolecular application of the classical indole Grignard reaction provided regio- and stereo-selective cycloalkylation to the C-3 position of indole with remarkable simplicity.

Assignments of ^{13}C NMR signals should offer insight into the pattern of chemical shifts in these rare compounds. ^1H and ^{13}C NMR analyses demonstrated that the conformational properties of the tetrahydrothiopyran ring entity is considerably modified when a substituent there is a C-4 substituent. Clearly, the presence of a substituent at C-4 characterizes the conformational properties of 2,3,4,9-tetrahydrothiopyranol[2,3-*b*]indoles and conformer (**A**) should be the preferred conformation for C-4 substituted thiopyranoindoles.

The synthetic potential of this method and significance of the conformational properties will be demonstrated in the following paper.[28]

Experimental

M.p.s and b.p.s were uncorrected. IR spectra were recorded on a Hitachi 260-10. ^1H NMR spectra were recorded on a Varian XL-200 (200 MHz), EM-390 (90 MHz), or EM-360 (60 MHz). Tetramethylsilane (TMS) was used as an internal standard. ^{13}C NMR spectra were recorded on a Varian XL-100-12A FT-NMR spectrometer operating at 25.16 MHz. Samples were spun in 10-mm tubes at 31 °C. Spectra were measured as 0.1–0.2 M solutions in [^2H] chloroform with TMS as internal standard. Typical FT-NMR measurement parameters were as follows: spectral width, 6 016 Hz; pulse width, 7.5 μs (flipping angle = 18°); acquisition time, 0.7–0.8 s; pulse delay, 0.2–0.4 s; number of data points, 9 625. Analytical HPLC was performed on a Waters 600A instruments with an UV detector (254 nm). GLC was performed on a Shimadzu GC-7AG. A glass column (1.5 m) with SE-30 on Gas Chrom Q was used. Merck silica gel 60 (230–400 mesh) was used for column chromatography. Medium-pressure liquid chromatography (MPLC) was performed on a Merck LiChroprep Si 60 prepacked column (size A: 240 × 10 mm or size B: 310 × 25 mm). Merck $60F_{254}$ (0.25 mm) pre-coated plates were used for TLC. Reactions were run under positive pressure of nitrogen. THF and ether were distilled from sodium benzophenone ketyl. Other solvents were dried over molecular sieves and used without further purifications. Commercially available ether solutions of EtMgBr and MeMgI, and a hexane solution of butyl-lithium were used as received. These reagents and Et_2Mg were titrated prior to use.[29] Unless otherwise stated, organic extracts were washed with saturated NaCl (brine), dried over $MgSO_4$, and concentrated under reduced pressure. The LAOCN3 program was performed on a FACOM M-150 or VAX-11/780. The fit between experimental and calculated spectra were considered satisfactory when the RMS deviation between them were less than 0.2.

2-(3-Methylsulphonyloxybutylthio)indole (**4**).—1-Bromobutan-3-ol (6.3 g, 41 mmol), indole-2(1*H*)-thione (the thione)[1] (5 g, 33 mmol), and K_2CO_3 (5 g, 36 mmol) were stirred in acetone (50 ml) for 2.5 h at 25 °C. The solvent was removed, and the residue was extracted with ether. The organic layer was washed, dried and concentrated. The residue was purified by silica gel (140 g; ether–hexane, 4:6) to give the sulphide alcohol (7.3 g, 97%) as a colourless oil; $\nu_{max}(CHCl_3)$ 3 600 (OH), 3 450 (NH), and 3 300 cm^{-1} (OH); δ_H(90 MHz; $CDCl_3$) 1.15 (3 H, d, *J* 6 Hz, Me), 1.73 (2 H, m, CH_2), 2.06 (1 H, br s, OH), 2.92 (2 H, t, *J* 7.5 Hz, SCH_2), 3.97 (1 H, m, CH), 6.60 (1 H, d, *J* 2 Hz, NC=CH), and 6.9–7.6 (4 H, m, ArH).

Methanesulphonic anhydride (MSA) (4.2 g, 24 mmol) was added at −13 °C to a solution of the above alcohol (4.9 g, 22 mmol) in triethylamine (6 ml, 43 mmol) and CH_2Cl_2 (50 ml). The mixture was stirred for 15 min and then poured into ice. The layers were separated, and the aqueous phase was extracted with ether. The combined organic extracts were washed, dried, and concentrated. Chromatography of the residue on silica gel (30 g; CH_2Cl_2) gave (**4**) (6.0 g, 91%) as a colourless oil: δ_H(90 MHz; $CDCl_3$) 1.40 (3 H, d, *J* 6 Hz, Me), 1.78–2.2 (2 H, m, CH_2), 2.91 (2 H, t, *J* 7.5 Hz, SCH_2), 2.99 (3 H, s, Me), 5.07 (1 H, m, CH), 6.66 (1 H, br s, NC=CH), and 7.0–7.6 (4 H, m, ArH).

2-(3-Methylsulphonyloxypropylthio)indole (**6**).—In a similar manner, (**6**) was prepared from the thione and 3-bromopropan-1-ol as a colourless oil; δ_H(90 MHz; $CDCl_3$) 2.03 (2 H, m, CH_2), 2.93 (2 H, t, *J* 7 Hz, SCH_2), 2.98 (3 H, s, Me), 4.38 (2 H, t, *J* 6 Hz, OCH_2), 6.65 (1 H, d, *J* 2 Hz, NC=CH), 7.05–7.6 (4 H, m, ArH), and 8.30 (1 H, br s, NH).

Bromides (**5**) *and* (**7**).—Compound (**4**) (1.0 g, 3.34 mmol) and anhydrous LiBr (0.9 g, 10 mmol) were heated in DMF (10 ml)

at 80 °C for 4 h. The reaction mixture was poured into ice, and the layer was extracted with ether. The organic extracts were washed, dried, and concentrated. The residue was purified by silica gel (30 g; EtOAc–hexane, 1:8) and afforded (**5**) (760 mg, 80%) as a colourless oil; δ_H(60 MHz; $CDCl_3$) 1.63 (3 H, d, *J* 7 Hz, Me), 1.8–2.2 (2 H, m, CH_2), 2.8–3.0 (2 H, m, SCH_2), 6.62 (1 H, d, *J* 2 Hz, NC=CH), 6.9–7.6 (4 H, m, ArH), and 8.2 (1 H, br s, NH).

In a similar manner, compound (**7**) was prepared as a colourless oil; ν_{max}($CHCl_3$) 3 450 cm^{-1} (NH); δ_H(60 MHz; $CDCl_3$) 1.8–2.3 (2 H, m, CH_2), 2.93 (2 H, m, SCH_2), 3.47 (2 H, t, *J* 6 Hz, CH_2Br), 6.63 (1 H, d, *J* 2 Hz, NC=CH), 6.9–7.6 (4 H, m, ArH), and 8.0 (1 H, br s, NH).

2-[3-(4-*Nitrophenylsulphonyloxy*)*butylthio*]*indole*.—In a similar manner, the alcohol (4; X = OH); (0.5 g, 2.26 mmol) was treated with 4-nitrobenzenesulphonyl chloride (0.55 g, 2.48 mmol) in pyridine (5 ml) at 0 °C for 30 min to give the titled compound as a dark red oil (520 mg, 57%); δ_H(60 MHz; $CDCl_3$) 1.32 (3 H, d, *J* 6 Hz, Me), 1.7–2.1 (2 H, m, CH_2), 2.70–2.86 (2 H, m, CH_2), 4.20 (1 H, m, CHBr), 5.03 (1 H, m, CH), 6.59 (1 H, d, *J* 2 Hz, NC=CH), 7.0–7.6 and 7.98–8.35 (8 H, m, ArH).

2-(2,3-*Epoxypropylthio*)*indole* (**11**).—Epichlorohydrin (2.8 g, 30.3 mmol) was added to a solution of thione (3.0 g, 20.1 mmol) and K_2CO_3 (5.50 g, 40.2 mmol) in acetone (30 ml), and the mixture was stirred at 25 °C for 4 h. All the volatiles were removed under reduced pressure and the residue was extracted with ether. The organic layer was washed, dried, and concentrated. The residue was chromatographed on silica gel (50 g; benzene) and gave (**11**) (3.7 g, 90%) as a colourless oil; δ_H(60 MHz; $CDCl_3$) 2.6–3.3 (4 H, m, CH_2CHCH), 6.60 (1 H, d, *J* 2 Hz, NC=CH), 6.9–7.6 (4 H, m, ArH), and 8.80 (1 H, br s, NH); *m/z* 205 (65%) and 148 (100).

2-(3,4-*Epoxybutylthio*)*indole* (**16**).—Tosyl chloride (3.2 g, 17 mmol) was added to a solution of 2-(3,4-dihydroxybutylthio)-indole[28] (3.3 g, 14 mmol) in pyridine (33 ml) at 5 °C. The mixture was left at 0 °C for 16 h. The solvent was removed under reduced pressure and the residue was extracted with ether. The organic layer was washed with 1M HCl, aqueous $NaHCO_3$, and brine, and then dried and concentrated to give the monotosylate (5.8 g). This was treated with 2M NaOH (8 ml) in MeOH (50 ml) at 0 °C for 5 min. Work-up and purification by silica gel (100 g; benzene) afforded (**16**) (1.45 g, 48%) as a yellow oil; δ_H(60 MHz; $CDCl_3$) 1.5–2.1 (2 H, m, CH_2), 2.4–3.2 (5 H, m, SCH_2, $CHCH_2$), 6.65 (1 H, d, *J* 2 Hz, NC=CH), 7.1–7.7 (4 H, m, ArH), and 8.42 (1 H, br s, NH).

General Procedures for Cyclizations of (**4**)–(**7**).—The reaction was continued until the starting material was not detectable on TLC. The reaction was quenched by dropwise addition of aqueous NH_4Cl, and the mixture was extracted with ether. The products were purified by silica gel (20–25 g; EtOAc–hexane, 1:10), and the fractions containing (**8**) and (**9**) were collected. The products were analyzed by HPLC (Waters μ-Porasil, $CHCl_3$–hexane–EtOH, 100:400:1, 2.0 ml/min). Typical retention times for (**8**), (**9**), and (**5**) were 3.5, 2.3, and 4.1 min. respectively. The results are tabulated in Table 1.

Compound (**8**): (Found: C, 71.0; H, 6.6; N, 6.9; S, 15.5%; M^+, 203. $C_{12}H_{13}NS$ requires C, 70.89; H, 6.45; N, 6.89; S, 15.77%; *M*, 203).

Compound (**9**): δ_H(90 MHz; $CDCl_3$) 1.36 (3 H, d, *J* 6.0 Hz, Me), 2.3 (2 H, m, CH_2), 2.76 (1 H, dt, *J* 13.0 and *J* 4 Hz, SCH), 3.28 (1 H, ddd, *J* 13.0, 10.5, and 5.0 Hz, SCH), 4.67 (1 H, m, CH), 6.22 (1 H, s, NC=CH), and 6.95–7.45 (4 H, m, ArH); *m/z*: 203 (M^+, 100%), 188 (20), and 160 (10) (Found: C, 71.1; H, 6.75; N, 6.9; S, 15.6. $C_{12}H_{13}NS$ requires C, 70.89; H, 6.45; N, 6.89; S, 15.77%).

Compound (**10**): m.p. 147–149 °C (from EtOH) (lit.,[2] 148–149 °C) (Found: C, 69.8; H, 5.85; N, 7.2; S, 17.2. $C_{11}H_{11}NS$ requires C, 69.80; H, 5.86; N, 7.40; S, 16.93%); ν_{max}($CHCl_3$) 3 450 cm^{-1} (NH); *m/z*: 189 (M^+, 100%), 161 (90), and 117 (35).

Reaction of (**4**) *with* EtMgBr. EtMgBr (2.8M; 0.2 ml, 0.56 mmol) was added to a rapidly stirred solution of (**4**) (155 mg, 0.52 mmol) in benzene (2 ml) at 8 °C. A viscous gummy mass was precipitated immediately. The mixture was stirred for 5 min to give a yellow oil (95 mg, 90%). In a similar manner, reactions were carried out in ether, chloroform, THF, and dimethoxyethane.

Reaction of (**6**) *with* EtMgBr. Compound (**6**) was treated with EtMgBr in benzene as described above.

Reaction of (**4**) *with* Et_2Mg. An ether solution of Et_2Mg (1.1M)[7] was allowed to react with (**4**) as described above.

Reaction of (**4**) *with* EtMgBr–HMPA. EtMgBr (2.8M; 0.22 ml, 0.62 mmol) was added to a solution of (**4**) (140 mg, 0.468 mmol) in THF (2 ml) at −13 °C. After the mixture had been stirred for 5 min, HMPA (0.25 ml, 1.44 mmol) was added dropwise. The mixture was stirred at −13 °C for 2 h and then 25 °C for 2 days to give an oily product (54 mg).

Reaction of (**4**) *with* BuLi–$ZnCl_2$ *in ether*. BuLi (1.35M; 0.6 ml, 0.81 mmol) was added to an ether solution of anhydrous $ZnCl_2$ (0.4M; 2.5 ml, 1 mmol) at 25 °C. The resultant cloudy solution was allowed to react for 20 min, and then (**4**) (200 mg, 0.67 mmol) in ether (3.5 ml) was added. The mixture was stirred for 22 h at 25 °C to give an oily product (88 mg, 65%).

Reaction of (**4**) *with* BuLi. BuLi (1.35M; 0.6 ml, 0.81 mmol) was added to a solution of (**4**) (206 mg, 0.69 mmol) in ether (4 ml) at −78 °C, and the mixture was stirred for 30 min at −78 °C and then 1 h at 25 °C to give the product (106 mg, 76%). In a similar manner, the reaction was carried out in THF (95% yield).

Reaction of (**4**) *with* LDA *in* HMPA-THF. To a solution of LDA (0.48 mmol) in THF (1 ml) were added a solution of (**4**) (125 mg, 0.418 mmol) in THF (2.5 ml) followed by HMPA (0.3 ml, 1.73 mmol). The mixture was stirred at −78 °C for 30 min and 25 °C for 2 h to give on work-up (**9**) (80 mg, 95% yield).

Reaction of (**4**) *with* KH. A solution of (**4**) (144 mg, 0.48 mmol) in THF (2.8 ml) was added to an oil-free suspension of KH[10] (32 mg, 0.56 mmol) in THF (1.5 ml) at 13 °C. The mixture was stirred for 8 h to give the product (73 mg, 75%). In a similar manner, the reaction was conducted in benzene.

Reaction of (**4**) *with* LiHMDS/NaHMDS. A mixture of (**4**) (132 mg, 0.44 mmol) and LiHMDS[9] (80 mg, 0.48 mmol) was stirred in benzene (2 ml) at 25 °C for 1 h to give an oily product (85 mg, 95%). In a similar manner, (**4**) was treated with NaHMDS[8].

Reaction of (**5**) *with* EtMgBr. EtMgBr (2.8M; 0.4 ml, 1.12 mmol) was added to a solution of (**5**) (230 mg, 0.81 mmol) in benzene (3 ml). The mixture was refluxed for 150 min and then worked up and purified to give (**8**) (129 mg, 78%).

Reaction of (**7**) *with* EtMgBr. Compound (**7**) (1.65 g, 6.11 mmol) was refluxed with EtMgBr (2.8M; 3.4 ml, 9.6 mmol) in benzene (16 ml) for 80 min and then worked up to give (**10**) (962 mg, 83%).

Reaction of (**11**) *with* EtMgBr. EtMgBr (3.0M; 2.3 ml, 6.9 mmol) was added to a stirred solution of (**11**) (570 mg, 2.78 mmol) in ether (7 ml) at 0 °C. The mixture was stirred at 0 °C for 10 min and then at 23 °C for 2 h to give after work-up a yellow solid (750 mg). Recrystallization of this from acetone–light petroleum afforded (**12**) (310 mg, 54%), m.p. 148.5–150 °C (Found: C, 64.45; H, 5.45; N, 6.8; S, 15.65. $C_{11}H_{11}NOS$ requires C, 64.36; H, 5.40; N, 6.82; S, 15.62%); *m/z* 205 (M^+, 30%), 162

(100), 161 (65), and 128 (65); $\nu_{max}(CHCl_3)$ 3 580, 3 530, and 3 450 cm^{-1} (NH).

The mother liquor was concentrated and purified by MPLC (size B, EtOAc–benzene, 5:95). The products were as follows in the order of elution (1) (**15a**) (5 mg, 0.5%): colourless oil; $\nu_{max}(CHCl_3)$ 3 550, 3 450 (NH), and 3 350 cm^{-1}; δ_H(60 MHz; $CDCl_3$) 2.6–3.2 (2 H, m, SCH_2), 3.09 (1 H, br s, OH), 3.37 (2 H, d, *J* 4 Hz, CH_2Br), 3.83 (1 H, m, *J* 6 and 4 Hz, CHO), 6.58 (1 H, d, *J* 2 Hz, NC=CH), 6.95–7.65 (4 H, m, ArH), and 8.4 (1 H, br s, NH).

(2) (**15b**) (40 mg, 5%): colourless oil; which was characterized as acetate (X=OAc): $\nu_{max}(CHCl_3)$ 3 450 (NH), 3 335, and 1 735 cm^{-1} (C=O); δ_H(60 MHz; $CDCl_3$) 2.03 (3 H, s, Me), 3.1–3.7 (2 H, m, SCH_2), 3.9–5.0 (3 H, m, $CHCH_2$), 6.72 (1 H, d, *J* 2 Hz, NC=CH), and 7.1–7.6 (4 H, m, ArH); *m/z* 329 (M^+, 16%), 327 (17), 181 (17), 179 (16), and 148 (100).

(3) (**14**) (20 mg, 3.5%); m.p. 113–114 °C (acetone–light petroleum) (Found: C, 64.55; H, 5.4; N, 6.75; S, 15.8. $C_{11}H_{11}NOS$ requires C, 64.36; H, 5.40; N, 6.82; S, 15.62%); *m/z*: 205 (M^+, 85%), 161 (45), and 117 (100); $\nu_{max}(CHCl_3)$ 3 550, 3 450, and 3 350 cm^{-1}; δ_H(60 MHz; $CDCl_3$) 2.67–3.25 (2 H, m, SCH_2), 3.90 (2 H, d, *J* 4 Hz, CH_2), 4.32 (1 H, br, CH), 6.30 (1 H, s, NC=CH), and 6.95–7.55 (4 H, m, ArH).

(**4**) Finally (**12**) (135 mg) was eluted. The total yield of (**12**) was 78%.

Reaction of (**16**) *with* EtMgBr *in ether at* −25 °C. EtMgBr (3.0M; 2.80 ml, 8.4 mmol) was added to a solution of (**16**) (600 mg, 2.74 mmol) in ether (7 ml) at −25 °C. Stirring was continued for 2 h at −25 °C after which the mixture was worked up. The residue (580 mg) was purified by MPLC (size B; EtOAc–hexane, 3:97). The following products were obtained in this order of elution (1) (**20a**) (95 mg, 13%): colourless oil; δ_H(60 MHz; $CDCl_3$) 1.78 (2 H, m, CH_2), 2.52 (1 H, br, OH), 2.93 (2 H, t, *J* 7 Hz, SCH_2), 3.12–3.58 (2 H, m, CH_2Br), 3.7–4.2 (1 H, m, C*H*OH), 6.60 (1 H, d, *J* 2 Hz, NC=CH), 6.9–7.6 (4 H, m, ArH), and 8.33 (1 H, br s, NH); $\nu_{max}(CHCl_3)$ 3 550, 3 450 (NH), and 3 300 cm^{-1}.

(2) (**18**) (55 mg, 10%): colourless oil: $\nu_{max}(CHCl_3)$ 3 580, 3 450 (NH), and 3 270 cm^{-1}. Acetate of (**18**): m.p. 128–130 °C (from MeOH) (Found: C, 64.3; H, 5.8; N, 5.35; S, 12.0. $C_{14}H_{15}NO_2S$ requires C, 64.34; H, 5.79; N, 5.36; S, 12.27%); $\nu_{max}(CHCl_3)$ 3 445 (NH), 3 300, and 1 730 cm^{-1} (C=O); δ_H(60 MHz; $CDCl_3$) 2.13 (3 H, s, COMe), *ca.* 2.0–3.7 (5 H, m, SCH_2, and CH_2CH), 3.88–4.72 (2 H, m, CH_2OAc), and 6.9–7.7 (4 H, m, ArH).

(3) A 6:4 mixture of (**18**) and (**17**) (60 mg, 11%).

(4) (**17**) (74 mg, 13%): colourless oil: $\nu_{max}(CHCl_3)$ 3 570, 3 450 (NH), and 3 280 cm^{-1}; δ_H(60 MHz; $CDCl_3$) 1.87 (1 H, br s, OH), 2.1–2.5 (2 H, m, CH_2), 2.5–3.2 (4 H, m, SCH_2CH_2), 3.7–4.1 (1 H, m, C*H*OH), 6.9–7.5 (4 H, m, ArH), and 8.17 (1 H, br s, NH). Acetate of (**17**) gave the following data: m.p. 140–142 °C (from MeOH) (Found: C, 61.5; H, 6.45; N, 4.8; S, 10.95. $C_{14}H_{15}NO_2S$·MeOH requires C, 61.41; H, 6.53; N, 4.77; S, 10.93%); *m/z*: 261 (M^+, 55%), 201 (90), 186 (35), and 173 (100); $\nu_{max}(CHCl_3)$ 3 650, 3 480, 3 450 (NH), and 1 725 cm^{-1}; δ_H (60 MHz; $CDCl_3$) 1.97 (3 H, s, COMe), 2.0–2.9 (4 H, m, SCH_2CH_2), 3.22 (2 H, d, *J* 6 Hz, CH_2), 4.90 (1 H, m, C*H*OAc), 6.9–7.5 (4 H, m, ArH), and 8.23 (1 H, br s, NH).

Reaction of (**16**) *with* EtMgBr *at* 25 °C. EtMgBr (3.0M; 0.5 ml, 1.5 mmol) was added to a solution of (**16**) (306 mg, 1.40 mmol) in ether (6 ml) at 25 °C. The mixture was stirred for 60 min and then worked up. The products were immediately acetylated with acetic anhydride (0.3 ml) in pyridine (3 ml) at 0 °C for 3 h. ^1H NMR spectra indicated that this was a 1:1 mixture of (**17**) and (**18**). Purification by silica gel afforded the acetates (158 mg, 43%).

Reaction of the cis-*epoxide* (**24**) *with* EtMgBr. EtMgBr (3.0M; 2.0 ml, 6 mmol) was added to a rapidly stirred solution of (**24**) (420 mg, 1.92 mmol) in ether (6 ml) at 0 °C, and the mixture was stirred for an additional 3 min. Work-up and purification by silica gel (30 g; EtOAc–benzene, 1:99) afforded (**28**) (340 mg, 92%) as a colourless oil (Found: C, 65.75; H, 6.1; N, 6.45; S, 14.6. $C_{12}H_{13}NOS$ requires C, 65.72; H, 5.98; N, 6.39; S, 14.62%); *m/z* 219 (M^+, 40%), 175 (100), 130 (15), and 78 (60); $\nu_{max}(CHCl_3)$ 3 570 (OH), 3 440 (NH), and 3 300sh cm^{-1}; δ_H(60 MHz; C_6D_6) 1.29 (3 H, d, *J* 7 Hz, Me), 2.12 (1 H, br s, OH), 2.47, and 2.92 (2 H, AB of ABX, *J* 12, 8, and 2 Hz, SCH_2), 2.7–3.2 (1 H, m, C*H*Me), 3.93 (1 H, br s, $W_{\frac{1}{2}}$ 17 Hz, C*H*OH), and 6.85–7.55 (4 H, m, ArH).

Reaction of trans-*epoxide* (**25**) *with* EtMgBr. EtMgBr (3.0M; 2.1 ml, 6.2 mmol) was added to a rapidly stirred solution of (**25**) (435 mg, 2 mmol) in ether (6 ml) at 0 °C. The mixture was stirred for 30 min at 0 °C and then allowed to react at 25 °C for 6 h. Work-up gave a residue which was purified by chromatography (40 g). Elution with EtOAc–benzene (5:95) afforded (**29**) (155 mg, 36%) as a colourless oil: *m/z* 219 (M^+, 43%), 175 (100), and 130 (20); $\nu_{max}(CHCl_3)$ 3 580 (OH), 3 530, 3 440 (NH), and 3 280 cm^{-1}; δ_H(60 Hz; C_6D_6) 0.99 (3 H, d, *J* 7 Hz, Me), 2.3–3.4 (3 H, m, SCH_2, and C*H*Me), 3.67 (1 H, br s, $W_{\frac{1}{2}}$ 11 Hz, C*H*OH), and 6.85–7.55 (4 H, m, ArH).

Continued elution with EtOAc–benzene (20:80) afforded (**34a**) (140 mg, 32%): colourless oil, which was characterized as the peracetate (**34b**) on treatment with acetic anhydride in pyridine–DMAP (5 mg) at 23 °C for 16 h: δ_H(60 MHz; $CDCl_3$) 1.33 (3 H, d, *J* 7 Hz, Me), 1.70 (3 H, d, *J* 6 Hz, Me), 1.78 (3 H, s, OAc), 1.98 (3 H, s, OAc), *ca.* 2.0–2.4 (1 H, m), 2.78 (3 H, s, NAc), 2.9–3.5 (4 H, m), 4.73 (1 H, m, NCH), 5.10 (1 H, m, C*H*OAc), 5.70 (1 H, m, C*H*OAc), 6.52 (1 H, d, *J* 2 Hz, NC=CH), and 6.95–8.0 (8 H, m, ArH).

Reaction of the threo-*iodohydrin* (**26**) *with* MeMgI. MeMgI (2.0M; 2.0 ml, 4 mmol) was added to a solution of (**26**) (442 mg, 1.27 mmol) in ether (5 ml) at 0 °C. The mixture was stirred at 32 °C for 20 h and then worked up. The oily product obtained (333 mg) was purified by MPLC (size A; EtOAc–benzene, 1:500). Compound (**32**) (153 mg, 55%) eluted first: colourless oil: $\nu_{max}(CHCl_3)$ 3 600 and 3 530 cm^{-1}; δ_H(60 MHz; $CDCl_3$) 1.23 (3 H, d, *J* 7 Hz, Me), 2.79, and 3.40 (2 H, AB of ABX, *J* 15.0, 3.0, and 1.0 Hz, SCH_2), 4.07 (1 H, br s, $W_{\frac{1}{2}}$ 10 Hz, C*H*OH), 4.50 (1 H, qd, *J* 7 and 3 Hz, NCH), 6.28 (1 H, s, NC=CH), and 6.95–7.60 (4 H, m, ArH). Next (**29**) (90 mg, 33%) was obtained.

Reaction of the erythro-*iodohydrin* (**27**) *with* MeMgI. In a similar manner, (**27**) (390 mg, 0.98 mmol) was allowed to react with MeMgI (2.0M; 2.0 ml, 4 mmol) in ether (4 ml) at 32 °C for 16 h. At least six compounds were detected on TLC. Purification by MPLC (size A; EtOAc–benzene, 1:500) yielded starting material (**27**) (50 mg, 13%), and a mixture of (**28**) and (**29**) (75 mg, 35%). The rest of the products could not be identified.

Reaction of (**23**) *with* EtMgBr.—EtMgBr (2.9M; 0.6 ml, 1.74 mmol) was added to (**23**) (710 mg, 1.69 mmol) in benzene (12 ml) dropwise at 25 °C. A thick gummy orange product formed immediately, and the mixture was rapidly stirred for 3 h at 25 °C. The reaction was quenched by dropwise addition of aqueous NH_4Cl, then diluted with ether. The layers were separated, and the aqueous phase was extracted twice with ether. The combined organic layers were washed, dried, and concentrated. The residue was purified by silica gel chromatography (50 g; CH_2Cl_2–hexane, 1:1) to afford (**33**) (10 mg, 2%), (**30**) (300 mg, 55%), and starting material (50 mg) in this order of elution.

Benzoate (**30**): $\nu_{max}(CHCl_3)$ 3 450 (NH), 1 710, and 1 270 cm^{-1}; TLC (CH_2Cl_2–hexane, 7:3), R_F 0.47.

Compound (**33**): $\nu_{max}(CHCl_3)$ 1 710 and 1 270 cm^{-1}; δ_H(90 MHz; $CDCl_3$) 1.53 (3 H, d, *J* 6.6 Hz, Me), 3.17 [1 H, part A of ABX, *J* 13.7, 4.7, and 0.8 Hz, $SC(2)H_{eq}$], 3.56 (1 H, part B of ABX, *J* 13.7 and 2.7 Hz, $SC(2)H_{ax}$], 5.25 (1 H, m, C*H*Me), 5.61 (1 H, m, C*H*OBz), 6.35 (1 H, s, NC=CH), and 6.95–7.95 (9 H, m, ArH); TLC (CH_2Cl_2–hexane, 7:3), R_F 0.65.

cis-3-*Benzoyloxy*-4-*methyl*-2,3,4,9-*tetrahydrothiopyrano*[2,3-b]*indole* (**31**).—Benzoyl chloride (97 mg, 0.69 mmol) was added to a stirred solution of the *cis*-alcohol (**28**) (130 mg, 0.59 mmol) in triethylamine (0.17 ml, 1.22 mmol) and CH_2Cl_2 (2 ml) at 25 °C. After 3 h, the solution was concentrated under reduced pressure and the residue was directly adsorbed on silica gel (20 g; CH_2Cl_2–hexane, 1:1) to give the *cis*-benzoate (**31**) (153 mg, 80%) as a colourless oil; $\nu_{max}(CHCl_3)$ 3 450 (NH), 1 715 (C=O), and 1 270 cm^{-1}; TLC (CH_2Cl_2–hexane, 7:3), R_F 0.37.

Determination of the Ratio of (**28**) *and* (**29**).—The ratio of (**28**) and (**29**) was determined by HPLC (μ-Porasil, $CHCl_3$, 1 ml/min). Typical retention times for (**28**) and (**29**) were 6.4 and 6.0 min, respectively. The ratio could also be determined from the relative intensity of the methyl signals, 1.29 and 0.99 ppm, respectively, from ^1H NMR in C_6D_6. Both methods gave comparable results.

Ethyl threo-2,3-O-*Isopropylidenedioxybutyrate* (**35a**).—*threo*-Ethyl 2,3-dihydroxybutyrate (80 g)[30] and TsOH (1 g, 5.26 mmol) were stirred at 20 °C for 16 h in acetone (400 ml) after which excess of $NaHCO_3$ (10 g) was added. The solvent was removed under atmospheric pressure and the residue was extracted with ether. The organic layer was washed, dried and concentrated under atmospheric pressure to leave an oil (79 g). Distillation gave (**35a**): b.p. 87–90 °C (15 mmHg); GLC (5% SE30, 100 °C), t_R 2.8 min; δ_H (60 MHz; $CDCl_3$) 1.30 (3 H, t, *J* 7 Hz, Me), *ca.* 1.4 (3 H, d, Me), 1.47 (3 H, s, Me), 1.48 (3 H, s, Me), 3.9–4.1 (2 H, m, CHCH), and 4.25 (2 H, q, *J* 7 Hz, CH_2); $\nu_{max}(CHCl_3)$ 1 755 and 1 730 cm^{-1}.

threo-2,3-O-*Isopropylidenedioxybutan*-1-*ol* (**35b**).—A solution of unpurified (**35a**) (79 g) in ether (800 ml) was added to a suspension of $LiAlH_4$ (16 g, 0.47 mol) in ether (200 ml) at 10–15 °C over 50 min. Stirring was continued for 45 min at 10 °C. Work-up and distillation afforded (**35b**) (40.0 g, 43% yield from ethyl crotonate): b.p. 83–85 °C (16 mmHg); GLC (5% SE30, 80 °C), t_R 2.2 min; δ_H (60 MHz; $CDCl_3$) 1.28 (3 H, d, *J* 7 Hz, Me), 1.40 (6 H, s, Me_2C), and 3.5–4.3 (4 H, m, CH_2CHCH); $\nu_{max}(CHCl_3)$ 3 440 cm^{-1} (OH).

Ethyl trans-2,3-*Epoxybutyrate*.—Ethyl crotonate (24.9 g, 0.22 mol) and 3-chloroperbenzoic acid (80% purity; 58 g, 0.28 mol) were refluxed in 1,2-dichloroethane (60 ml) for 6 h. The mixture was cooled, and the precipitate was filtered off. The filtrate was washed in turn with aqueous $Na_2S_2O_3$, aqueous $NaHCO_3$, and brine, dried, and concentrated under atmospheric pressure. The residue was distilled to afford the title epoxy ester (23.9 g, 84%) as a colourless oil: b.p. 70–72 °C (15 mmHg); GLC (20% SE30, 100 °C), t_R 4.7 min; δ_H (60 MHz; $CDCl_3$) 1.27 (3 H, t, *J* 7 Hz, Me), 1.40 (3 H, d, *J* 5 Hz, Me), 3.1–3.4 (2 H, m, CHCH), and 4.23 (2 H, q, *J* 7 Hz, CH_2).

Ethyl erythro-2,3-O-*Isopropylidenedioxybutyrate* (**36a**).—A solution of $SnCl_4$ (6 ml, 52 mmol) in CCl_4 (12 ml) was added to a rapidly stirred solution of the epoxy ester (6.0 g, 46 mmol) in CCl_4 (50 ml)–acetone (20 ml) at −13 °C over 15 min. The reaction was continued for 30 min and then quenched by aqueous $NaHCO_3$ (19 g). The phases were centrifuged, and the aqueous layer was extracted with ether. The solid mass was washed with ether. The combined organic layers were washed, dried, and concentrated under atmospheric pressure. The residue was distilled to yield (**36a**) (7.2 g, 83%) as a colourless oil: b.p. 100 °C (22 mmHg); GLC (5% SE30, 100 °C), t_R 3.5 min; δ_H (60 MHz; $CDCl_3$) 1.30 (3 H, t, *J* 7 Hz, Me), 1.33 (3 H, d, *J* 5 Hz, Me), 1.38 (3 H, s, Me), 1.60 (3 H, s, Me), 4.20 (2 H, q, *J* 7 Hz, CH_2), and 4.4–4.65 (2 H, m, CHCH); $\nu_{max}(CHCl_3)$ 1 755 and 1 730 cm^{-1}.

erythro-2,3-O-*Isopropylidenedioxybutan*-1-*ol* (**36b**).—In a similar manner as described for (**35a**) to (**35b**), (**36a**) (6.8 g, 36 mmol) was reduced to (**36b**) (4.5 g, 85%): colourless viscous oil: b.p. 98–100 °C (28 mmHg); GLC (5% SE30, 80 °C), t_R 3.0 min; δ_H (60 MHz; $CDCl_3$) 1.23 (3 H, d, *J* 7 Hz, Me), 1.37 (3 H, s, Me), 1.47 (3 H, s, Me), 3.60 (2 H, dd, *J* 6, and 5 Hz, CH_2), 4.0–4.6 (2 H, m, CHCH); $\nu_{max}(CHCl_3)$ 3 440 cm^{-1} (OH).

threo-1-*Bromo*-2,3-O-*isopropylidenedioxybutane* (**35c**).—Tosyl chloride (60 g, 31.5 mmol) and (**35b**) (39 g, 0.267 mol) were stirred in pyridine (390 ml) at 23 °C for 4 h. The solvent was removed and the residue was extracted with ether. The combined organic layers were washed with 1M HCl, aqueous $NaHCO_3$, and brine, dried, and concentrated to provide the crude tosylate (87 g), which was immediately dissolved in acetone (600 ml). Anhydrous LiBr (50 g, 0.57 mol) was added to the mixture which was then refluxed for 40 h. The solvent was removed under atmospheric pressure, and the residue was extracted with ether. The extracts were washed, dried, and concentrated under atmospheric pressure. Distillation of the residue gave (**35c**) (41.8 g, 75%) as a colourless oil: b.p. 73–75 °C (15 mmHg); GLC (1% SE30, 60 °C), t_R 2.7 min; δ_H (60 MHz; $CDCl_3$) 1.37 (3 H, d, *J* 6 Hz, Me), 1.42 (6 H, s, Me_2C), 3.45–3.55 (2 H, m, CH_2), and 3.65–4.20 (2 H, m, CH–CH).

erythro-1-*Bromo*-2,3-O-*isopropylidenedioxybutane* (**36c**).—In a similar manner, (**36c**) (26 g, 41%) was obtained from (**36b**) (45 g, 0.3 mol): b.p. 103–105 °C (52 mmHg); GLC (1% SE30, 60 °C), t_R 3.3 min; δ_H (60 MHz; $CDCl_3$) 1.30 (3 H, d, *J* 7 Hz, Me), 1.37 (3 H, s, Me), 1.47 (3 H, s, Me), and 3.3–3.6 and 4.1–4.6 (4 H, m, $CHCHCH_2$).

2-(threo-2,3-*Dihydroxybutylthio*)*indole* (**22**).—Compound (**35c**) (5.9 g, 28 mmol), the thione (4.1 g, 27.5 mmol), and K_2CO_3 (4.1 g, 28 mmol) were stirred in acetone (40 ml) at 25 °C for 4 h. The solvent was removed and the residue was extracted with ether. The organic layer was washed, dried, and concentrated to give a dark oil (8.9 g). This material was immediately dissolved in MeOH (90 ml) and 3M HCl (20 ml) was added. The solution was stirred at 25 °C for 90 min after which the solvent was removed under reduced pressure and the residue was extracted with EtOAc. The organic layer was washed, dried, and concentrated to give a viscous yellow oil, which was purified by chromatography on silica gel (60 g). Elution with EtOAc–hexane (1:4) afforded non-polar products, which were discarded. Continued elution with EtOAc–hexane (2:1 to 1:1) afforded the diol (**22**) (4.6 g, 67%) as a colourless viscous oil; $\nu_{max}(CHCl_3)$ 3 550 (OH), 3 450 (NH), and 3 330 cm^{-1}; δ_H(90 MHz; $CDCl_3$) 1.13 (3 H, d, *J* 6.3 Hz, Me), 2.82, and 2.97 (2 H, AB of ABX, *J* 13.8, 8.7, and 3.2 Hz, SCH_2), 3.48 (1 H, m, C*H*OH), 3.71 (1 H, m, *J* 6.3, and 5.4 Hz, C*H*OH), 6.60 (1 H, dd, *J* 2.2, and 0.8 Hz, NC=CH), 6.95–7.6 (4 H, m, ArH), and 9.03 (1 H, br s, NH).

2-(erythro-2,3-O-*Dihydroxybutylthio*)*indole* (**21**).—In a similar manner, (**36c**) (18 g, 0.12 mol) was converted into (**21**) (13.4 g): colourless viscous oil: $\nu_{max}(CHCl_3)$ 3 550 (OH), 3 450 (NH), and 3 400–3 320br cm^{-1} (OH); δ_H(60 MHz; $CDCl_3$) 1.05 (3 H, d, *J* 6 Hz, Me), 2.7–4.0 [6 H, m, CH(OH)CH(OH)CH_2], 6.60 (1 H, d, *J* 2 Hz, NC=CH), 6.9–7.6 (4 H, m, ArH), and 8.97 (1 H, br s, NH).

2-(threo-2-*Benzoyloxy*-3-*methylsulphonyloxybutylthio*)*indole* (**23**).—Benzoyl chloride (386 mg, 2.74 mmol) was added at −30 °C to a solution of the *threo*-diol (**22**) (590 mg, 2.49 mmol) and ethyldi-isopropylamine (1.3 ml, 7.48 mmol) in CH_2Cl_2 (12 ml). The mixture was allowed to react at −20 °C for 16 h after which methanesulphonic anhydride (519 mg, 2.98 mmol) was

added in one portion. Stirring was continued for an additional 15 min at −13 °C after which the mixture was poured into ice–water. The aqueous layer was extracted twice with ether and the combined organic layers were washed in turn with 10% NaOH and brine, dried, and concentrated. The dark residue was purified by silica gel chromatography (30 g; CH_2Cl_2) and to give (**23**) (750 mg, 72%) as a pale yellow oil: δ_H(90 MHz; $CDCl_3$) 1.42 (3 H, d, *J* 6.6 Hz, Me), 2.93 (3 H, s, Me), 3.10 (2 H, d, *J* 6.3 Hz, SCH_2), 5.03 (1 H, m, C*H*OMs), 5.37 (1 H, m, C*H*OBz), 6.70 (1 H, dd, *J* 2.4, and 0.8 Hz, *N*-C=CH), 6.95–7.6 and 8.0–8.12 (total 9 H, m, ArH), and 8.94 (1 H, br s, NH).

2-(trans-2,3-*Epoxybutylthio*)*indole* (**25**).—The method of Newman[14] was applied. Compound (**22**) (1.72 g, 7.26 mmol), trimethyl orthoformate (1.3 ml, 10.4 mmol), and benzoic acid (25 mg) were heated to reflux in benzene (30 ml) for 2 h. The mixture was cooled and a slight excess of $NaHCO_3$ was added in portions. The volatiles were removed under reduced pressure, and the residue was extracted with ether. The organic layer was washed, dried, and concentrated to give the ortho ester (1.4 g) as a dark yellow oil. Without purification, this material was dissolved in CH_2Cl_2 (40 ml), and trimethylchlorosilane (4 ml, 32 mmol) was added. The mixture was refluxed for 60 min after which the volatiles were removed under reduced pressure to leave the chloroacetate as a dark red oil, which was treated with 20% NaOH (20 ml) in MeOH (40 ml) at 25 °C for 15 min. The solvent was evaporated under reduced pressure, and the residue was extracted with ether. The organic layer was washed, dried, and concentrated. The residue was purified by silica gel chromatography (40 g; EtOAc–benzene, 2:98) to afford the *trans*-epoxide (**25**) (400 mg, 25%) as a colourless oil. Analytical HPLC (μ-Porasil; $CHCl_3$–hexane, 1:5, 3 ml/min) indicated that the unpurified material contained 2% of the *cis*-epoxide (**24**) (t_R 5.9 min). The desired compound (**25**) (t_R 3.8 min) was readily isolated by chromatography on silica gel (40 g; EtOAc–benzene, 2:98); ν_{max}($CHCl_3$) 3 445 (NH) and 3 320 cm^{-1}; δ_H(60 MHz; $CDCl_3$) 1.27 (3 H, d, *J* 5 Hz, Me), 2.7–3.2 (4 H, m, CH_2CHCH), 6.62 (1 H, d, *J* 2 Hz, NC=CH), 6.9–7.6 (4 H, m, ArH), and 8.9 (1 H, br s, NH).

2-(cis-2,3-*Epoxybutylthio*)*indole* (**24**).—In a manner similar to that described for the preparation of (**25**), the *erythro*-diol (**21**) (5.3 g, 22.4 mmol) was converted into the *cis*-epoxide (**24**) (820 mg, 17%). The crude material contained *ca.* 8% (HPLC analysis) of *trans*-(**25**), which was removed by silica gel chromatography; δ_H(60 MHz; $CDCl_3$) 1.03 (3 H, d, *J* 5 Hz, Me), 2.7–3.3 (4 H, m, CH_2CHCH), 6.65 (1 H, d, *J* 2 Hz, NC=CH), 6.9–7.7 (4 H, m, ArH), and 8.8 (1 H, br s, NH).

In this reaction, *N*-cyclized product (830 mg, 17%) was also isolated: colourless oil; δ_H(60 MHz; $CDCl_3$) 1.30 (3 H, d, *J* 7 Hz, Me), 2.30 (1 H, br s, OH), 2.74 and 3.16 (2 H, AB of ABX, *J* 12, 4, and 10 Hz, SCH_2), 4.50 (2 H, m, CH × 2), 6.23 (1 H, s, NC=CH), and 6.95–7.50 (4 H, m, ArH).

2-(threo-2-*Hydroxy*-3-*iodobutylthio*)*indole* (**26**).—The method of Cornforth was applied.[16] A pre-cooled solution of NaI (890 mg, 6 mmol) and NaOAc (97 mg, 1.2 mmol) in acetic acid (2 ml)–propionic acid (3 ml) mixture was added to (**24**) (440 mg, 2.01 mmol) placed in a cold flask (−13 °C). The solution was stirred at −10 °C for 45 min, and 0 °C for 30 min; it was then allowed to warm to 23 °C over 15 min. The reaction mixture was poured into ice, neutralized with $NaHCO_3$, and extracted with ether. The organic layer was washed, dried, and concentrated. Chromatography of the residue (620 mg) on silica gel (100 g; EtOAc–benzene, 2:98) gave (**26**) (442 mg, 63%) as a colourless oil; δ_H(60 MHz; $CDCl_3$) 1.93 (3 H, d, *J* 7 Hz, Me), 2.9–3.2 (3 H, m, CH_2CHO), 4.40 (1 H, qd, *J* 7, and 4 Hz, CHI), 6.65 (1 H, d, *J* 2 Hz, 1 H, NC=CH), 6.95–7.65 (4 H, m, ArH), and 9.0 (1 H, br s, NH). Continued elution afforded an isomeric mixture of iodohydrins (114 mg, 16%).

Treatment of (**26**) (88 mg) with 2M NaOH (0.3 ml) in MeOH (2 ml) at 25 °C for 10 min afforded exclusively the starting epoxide (**24**) (46 mg), whereas the latter mixture afforded a 1:2 (HPLC) mixture of (**24**) and (**25**) under identical reaction conditions.

2-(erythro-2-*Hydroxy*-3-*iodobutylthio*)*indole* (**27**).—In a similar manner, (**25**) (600 mg, 2.74 mmol) was converted into (**27**) (478 mg, 46%); δ_H(60 MHz; $CDCl_3$) 1.80 (3 H, d, *J* 7 Hz, Me), 2.67–3.33 (2 H, m, CH_2S), 3.4–3.8 (1 H, m, CHO), 4.28 (1 H, qd, *J* 7 and 4 Hz, CHI), 6.67 (1 H, d, *J*, 2 Hz, NC=CH), and 7.0–7.7 (4 H, m, ArH). A mixture of iodohydrins (185 mg) was also isolated.

Ethyl Ester of α-*Indolmycenic Acid* (**40**).—Compound (**40**) was prepared by the method of von Wittenau *et al.*[17]: δ_H(60 MHz; $CDCl_3$) 1.23 (3 H, t, *J* 7 Hz, Me), 1.29 (3 H, d, *J* 7 Hz, Me), 2.83 (1 H, br s, OH), 3.60 (1 H, dq, *J* 7, and 3 Hz, CH), 4.18 (2 H, q, *J* 7 Hz, CH_2), 4.45 (1 H, d, *J* 3 Hz, C*H*OH), 6.95–7.75 (5 H, m, ArH), and 8.20 (1 H, br s, NH); ν_{max}($CHCl_3$ 3 520(OH), 3 460 (NH), 3 350sh, and 1 725 cm^{-1}.

α-*Indolmycenic Acid* (**39**).—According to the literature procedure, compound (**40**) was hydrolysed to (**39**): m.p. 168 °C (lit.,[18a] 169—170 °C); δ_H(60 MHz; CD_3OD) 1.36 (3 H, d, *J* 7 Hz, Me), 3.62 (1 H, qd, *J* 7, and 4 Hz, CH), 4.43 (1 H, d, *J* 4 Hz, C*H*OH), and 6.85–7.75 (5 H, m, ArH); ν_{max}(KBr) 3 450 (NH), 3 410, and 1 725 cm^{-1}. The spectral properties of (**39**) were identical with those reported.[18]

(2R*,3S*)-3-*Indol*-3-*ylbutane*-1,2-*diol* (**41**).—Compound (**40**) (500 mg, 2.02 mmol) and $LiAlH_4$ (150 mg) were stirred in ether (10 ml) at 23 °C for 3 h. Work-up afforded (**41**) as a pale yellow oil (415 mg): ν_{max}($CHCl_3$) 3 570, 3 470, and 3 320sh cm^{-1}; δ_H(90 MHz; $CDCl_3$) 1.34 (3 H, d, *J* 7.2 Hz, Me), 3.13 (1 H, qd, *J* 7.2, and 7.2 Hz, C*H*Me), 3.4–3.65 (2 H, m, CH_2), 3.88 (1 H, m, C*H*OH) 6.70 (1 H, d, *J* 2 Hz, NCH=C), 6.9–7.6 (4 H, m, ArH), and 8.16 (1 H, br s, NH).

(2S*,3S*)-3-*Indol*-3-*ylbutan*-2-*ol* (**38**).—Unpurified diol (**41**) (415 mg, 2.02 mmol) was treated with tosyl chloride (420 mg, 2.2 mmol) in pyridine (4 ml) at −13 °C for 5 h. Solvent was removed under reduced pressure and the residue was extracted with ether. The ether extracts were washed, dried, and concentrated to yield the mono-tosylate (431 mg) as a dark oil, which was used without purification. The mixture of $LiAlH_4$ (100 mg, 2.9 mmol) and tosylate in THF (8 ml) was refluxed for 2 h. Work-up and purification by silica gel (20 g, EtOAc–benzene, 5:95) afforded (**38**) (270 mg, 70%): colourless oil: ν_{max}($CHCl_3$) 3 600sh, 3 560, 3 470, and 3 320 cm^{-1}; δ_H(60 MHz; $CDCl_3$) 1.18 (3 H, d, *J* 6 Hz, Me), 1.37 (3 H, d, *J* 7 Hz, Me), 1.55 (1 H, br s, OH), 3.15 (1 H, qd, *J* 7 and 4 Hz, CH), 4.07 (1 H, qd, *J* 6 and 4 Hz, C*H*OH), 6.96 (1 H, d, *J* 2 Hz, NCH=C), 7.0–7.7 (4 H, m, ArH), and 8.20 (1 H, br s, NH).

Desulphurization of (**29**).—A mixture of (**29**) (85 mg, 0.39 mmol) and W4 Ra–Ni in EtOH (3 ml) was refluxed for 2 h. The catalyst was filtered off and the solvent was evaporated. The residue was purified by silica gel (10 g; EtOAc–benzene, 3:97) to give (**38**) (45 mg, 62%).

Desulphurization of (**28**).—The same procedure as described above was followed, starting with (**28**) (310 mg, 1.41 mmol) and (**37**) (180 mg, 68%) was obtained as a colourless oil: ν_{max}($CHCl_3$) 3 600sh, 3 550, 3 470(NH), and 3 310 cm^{-1}; δ_H(60 MHz; $CDCl_3$) 1.20 (3 H, d, *J* 6 Hz, Me), 1.31 (3 H, d, *J* 7 Hz, Me),

1.93 (1 H, br s, OH), 2.99 (1 H, qd, *J* 7 and 7 Hz, C*H*Me), 3.95 (1 H, qd, *J* 7 and 6 Hz, C*H*OH), 6.88 (1 H, d, *J* 2 Hz, NCH=C), 6.95–7.35, and 7.5–7.7 (4 H, m, ArH), and 8.40 (1 H, br s, NH).

2,3,4,9-*Tetrahydrothiopyrano*[2,3-b]*indole-4-carbaldehyde* (**42**).—Dimethyl sulphide (0.2 ml, 2.7 mmol) was added at 0 °C to a solution of NCS (268 mg, 2.0 mmol) in toluene (13 ml). The mixture was cooled to −25 °C, and then a solution of (**18**) (220 mg, 1.0 mmol) in toluene (1 ml) was added dropwise. After 2.5 h, Et_3N (0.5 ml, 3.6 mmol) in toluene (1 ml) was added, and the mixture was allowed to warm to room temperature. The volatiles were removed under reduced pressure and the residue was purified by silica gel chromatography (5 g; C_6H_6), to give (**42**) (130 mg, 60%) as a colourless oil.[1]

[4-$^2H_1$]-2,3,4,9-*Tetrahydrothiopyrano*[2,3-*b*]*indole-4-carbaldehyde* [4-$^2H_1$]-(**42**).—To a solution of LDA (1.2 mmol) in THF (3 ml) at −78 °C was added a solution of (**42**) (108 mg, 0.50 mmol) in THF (1.5 ml) followed by HMPA (0.2 ml). The mixture was stirred for an additional 20 min, after which 20% DCl–D_2O was added. After being stirred for 20 min, the mixture was extracted with ether. Work-up followed by silica gel (15 g; EtOAc–hexane, 1:5) purification afforded [4-$^2H_1$]-(**42**) (80 mg, 73%). More than 95% of the hydrogen had been replaced.

[4-$^2H_1$]-2,3,4,9-*Tetrahydrothiopyrano*[2,3-b]*indole-4-carbonitrile* [4-$^2H_1$]-(**43**).—In a similar manner, (**43**) was treated with LDA–HMPA in THF, followed by DCl–D_2O to afford isotopically pure [4-$^2H_1$]-(**43**): m.p. 114–116 °C (from EtOH).

[4-$^2H_1$]-*Hydroxy*[$^2H_1$]*methyl*-2,3,4,9-*tetrahydrothiopyrano*-[2,3-b]*indole* [4,10-$^2H_2$] (**18**).—$NaBD_4$ (41 mg, 0.1 mmol) was added at −13 °C to a stirred solution of [4-$^2H_1$]-(**42**) (50 mg, 0.23 mmol) in MeOH (1 ml). After 10 min, the mixture was partitioned between ether and water, and the aqueous layer was extracted with ether. The crude product was purified by silica gel (10 g; EtOAc–hexane, 1:3) to afford [4,10-$^2H_2$]-(**18**) (48 mg) as a colourless oil; [10-$^2H_1$]-(**18**) was prepared from (**42**) similarly.

Preparation of [10-$^2H_1$]-(**44**), [4,10-$^2H_2$]-(**44**), [10-$^2H_1$]-(**45**), *and* [4,10-$^2H_2$]-(**45**).—These compounds were prepared from (**42**), [4-$^2H_1$]-(**42**), (**43**), and [4-$^2H_1$]-(**43**), respectively by the method described elsewhere[1,28] except that $LiAlD_4$ was used instead of $LiAlH_4$.

[4-$^2H_2$]-2,3,4,9-*Tetrahydrothiopyrano*[2,3-b]*indole* [4-$^2H_1$]-(**10**).—Compound (**46**) (695 mg, 2.94 mmol), which had been prepared from the thione and methyl 3-bromopropionate by a method similar to that described for the preparation of (**4**), was reduced by $LiAlD_4$ (250 mg, 6.0 mmol) in ether (6 ml) at 0 °C for 15 min. After work-up, the crude material was purified by silica gel chromatography (20 g; EtOAc–hexane, 1:4) to give the alcohol (**47**) (380 mg) as a colourless oil. To a solution of (**47**) (315 mg, 1.51 mmol) in CH_2Cl_2 (4 ml) at −13 °C were added triethylamine (0.5 ml, 3.6 mmol) and MSA (390 mg, 2.2 mmol). After 10 min, an ether solution of EtMgBr (3.0M; 0.8 ml, 2.4 mmol) was added dropwise, and stirring was continued for an additional 8 min. Following work-up similar to that described for the reaction of (**4**), the crude material was purified by silica gel (40 g; CH_2Cl_2–hexane, 1:2) and gave a colourless solid (250 mg). Recrystallization from EtOH afforded isotopically homogeneous [4-$^2H_2$]-(**10**): m.p. 150–151 °C.

9-*Methyl and* 9-*Acetyl Analogues of* (**8**) *and* (**10**).—These compounds were prepared by the method described elsewhere.[1]

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References

1 S. Takada, N. Ishizuka, T. Sasatani, Y. Makisumi, H. Jyoyama, H. Hatakeyama, F. Asanuma, and K. Hirose, *Chem. Pharm. Bull.*, 1984, **32**, 877, and references therein.
2 T. Hino, H. Miura, R. Murata, and M. Nakagawa, *Chem. Pharm. Bull.*, 1978, **26**, 3659.
3 R. A. Jones, 'Comprehensive Heterocyclic Chemistry', ed. A. R. Katrizky and C. W. Rees, Pergamon Press, Oxford, 1984, vol. 4, p. 235.
4 W. C. Guida and D. J. Mathre, *J. Org. Chem.*, 1980, **45**, 3172, and references therein.
5 For examples: J. I. DeGraw, J. G. Kennedy, and W. A. Skinner, *J. Heterocycl. Chem.*, 1966, **3**. 67; T. Kametani, T. Suzuki, K. Takahashi, Y. Ichikawa, and K. Fukumoto, *J. Chem. Soc., Perkin Trans. 1*, 1975, 413; M. Sainsbury and R. F. Schinazi, *ibid.*, 1976, 1155; T. Kametani, Y. Ichikawa, T. Suzuki, and K. Fukumoto, *Tetrahedron*, 1974, **30**, 3713; R. P. Joyce, J. A. Gainor, and S. M. Weinreb, *J. Org. Chem.*, 1987, **52**, 1177.
6 S. K. Taylor, G. H. Hockerman, G. L. Karrick, S. B. Lyle, and S. B. Schramm, *J. Org. Chem.*, 1983, **48**, 2449, and references therein.
7 W. Schlenk and W. Schlenk, Jr., *Chem. Ber.*, 1929, **62B**, 920; G. E. Coates and D. Ridley, *J. Chem. Soc.*, 1967, 56.
8 U. Wannagat and H. Niederprüm, *Chem. Ber.*, 1961, **94**, 1540; C. A. Brown, *Synthesis*, 1974, 427.
9 E. H. Amonoo-Neizer, R. A. Shaw, D. O. Skovlin, and B. C. Smith, *J. Chem. Soc.*, 1965, 2997.
10 C. A. Brown, *J. Org. Chem.*, 1974, **39**, 3913.
11 E. Negishi, 'Organometallics in Organic Synthesis,' John Wiley & Sons, New York, 1980, vol. 1, p. 91.
12 B. Cardillo, G. Casnati, A. Pochini, and A. Ricca, *Tetrahedron*, 1967, **23**, 3771; M. G. Reinecke, J. F. Sebastian, H. W. Johnson, Jr., and C. Pyun, *J. Org. Chem.*, 1972, **37**, 3066; N.-C. Wang, K.-E. Teo, and H. J. Anderson, *Can. J. Chem.*, 1977, **55**, 4112.
13 P. J. Stang, M. Hanack, and L. R. Subramanian, *Synthesis*, 1982, 85.
14 M. S. Newman and D. R. Olson, *J. Org. Chem.*, 1973, **38**, 4203.
15 G. Berti, 'Topics in Stereochemistry,' ed. N. L. Allinger and E. L. Eliel, John Wiley & Sons, New York, 1973, vol. 7, p. 93.
16 J. W. Cornforth, R. H. Cornforth, and K. K. Mathew, *J. Chem. Soc.*, 1959, 112.
17 M. S. von Wittenau and H. Els, *J. Am. Chem. Soc.*, 1963, **85**, 3425.
18 (*a*) M. N. Preobrazhenskaya, E. G. Balashova, K. F. Turchin, E. N. Padeiskaya, N. V. Uvarova, G. N. Pershin, and N. N. Suvorov, *Tetrahedron*, 1968, **24**, 6131; (*b*) M. R. Harnden and N. D. Wright, *J. Chem. Soc., Perkin Trans. 1*, 1977, 1012; (*c*) T. Takeda and T. Mukaiyama, *Chem. Lett.*, 1980, 163.
19 Ref. 1; Ref. 2; R. Plate and H. C. J. Ottenheijm, *Tetrahedron*, 1986, **42**, 4511; R. Plate, R. J. F. Nivard, and H. C. J. Ottenheijm, *ibid.*, 1986, **42**, 4503; K. Goerlitzer and D. Hoelscher, *Arch. Pharm.*, 1986, **319**, 120; J. Levy, D. Royer, J. Guilhem. M. Cesario, and C. Pascard, *Bull. Soc. Chim. Fr.*, 1987, 193; J.-B. Baudin, S. A. Julia, R. Lorne, *Bull. Soc. Chim. Fr.*, 1987, 181; G. Zanotti, B. Beijer, and T. Wieland, *Int. J. Pept. Protein Res.*, 1987, **30**, 323; M. Takasugi, K. Monde, N. Katsui, and A. Shirata, *Bull. Chem. Soc. Jpn.*, 1988, **61**, 285.
20 M. S. Morales-Ríos, J. Espiñeira, and P. Joseph-Nathan, *Magn. Reson. Chem.*, 1987, **25**, 377.
21 M. S. Morales-Ríos and P. Joseph-Nathan, *Magn. Reson. Chem.*, 1989, **27**, 75; A. R. Katrizky, G. W. Rewcastle, L. M. Vazquez de Miguel, and Z. Wang, *Magn. Reson. Chem.*, 1988, **26**, 347; G. Burton, A. A. Ghini, and E. G. Gros, *Magn. Reson. Chem.*, 1986, **24**, 829.
22 K. Honty, E. Baitz-Grács, G. Blaskó, and C. Szántay, *J. Org. Chem.*, 1982, **47**, 5111.
23 H.-O. Kalinowski, S. Berger, and S. Braun, 'Carbon-13 NMR Spectroscopy,' John Wiley & Sons, Chichester, 1988, ch. 4.
24 L. Laitem, L. Christiaens, and M. Renson, *Org. Magn. Reson.*, 1980, **13**, 319.

25 A. A. Bothner-By and S. M. Castellano, 'Computer Programs for Chemistry', ed. D. F. DeTar, W. A. Benjamin Inc., New York, vol. 1, pp. 10–53 (1968).
26 D. M. Fatheree, G. L. Deeg, D. M. Matthews, and J. G. Russell, *Org. Magn. Reson.*, 1982, **18**, 92.
27 D. C. Cotterill, J. Cottam, and R. Livingstone, *J. Chem. Soc.*, 1972, 787.
28 N. Ishizuka, M. Shiro, and Y. Makisumi, submitted for publication for *J. Chem. Soc., Perkin Trans. 1*, 1990, following paper.
29 D. E. Bergbreiter and E. Pendergrass, *J. Org. Chem.*, 1981, **46**, 219.
30 K. Akashi, R. E. Palermo, and K. B. Sharpless, *J. Org. Chem.*, 1978, **43**, 2063.

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