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The Synthesis of (-)-Dihydroaszonalenin from *L*-Tryptophan; the Relative and Absolute Configuration of Aszonalenin

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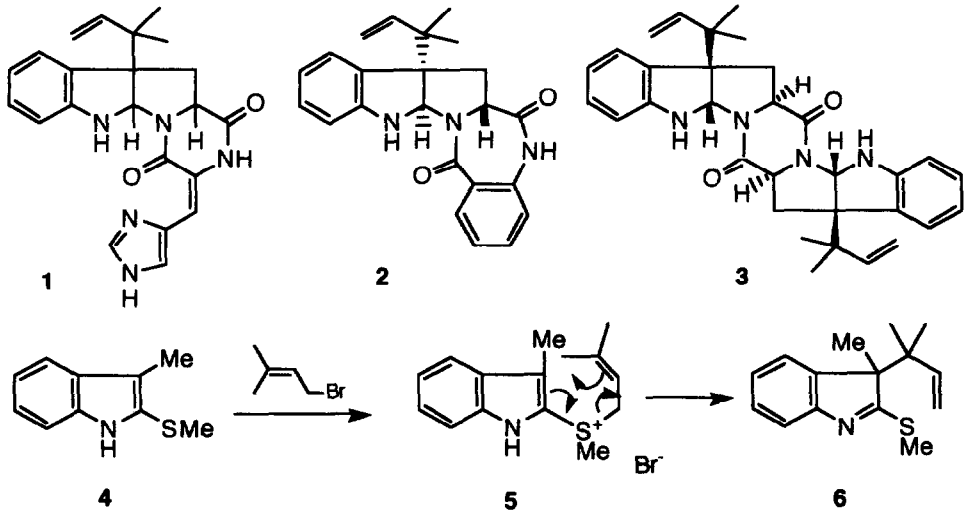
Abstract The enantiomer of dihydroaszonalenin has been synthesised from *L*-tryptophan, aszonalenin **2** has been assigned the relative and absolute configuration indicated

INTRODUCTION

Alkaloids that contain a 1,1-dimethylallyl substituent at the 3a-position of a hexahydropyrrolo[2,3-b]indole moiety constitute a small but biosynthetically important group of natural products Such compounds include the mould metabolites roquefortine[1] **1**, aszonalenin[2] **2**, amauromine[3] **3**, and the marine



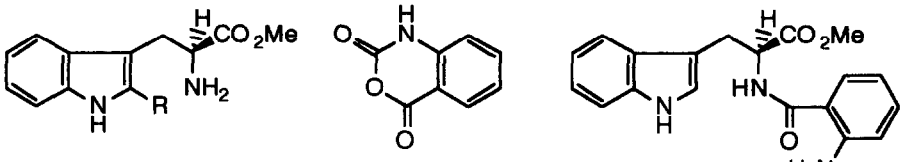
Scheme 1

alkaloids flustramines A[4] and C [5] Prior to the recognition of this class of natural product, Bycroft and Landon had reported that 3-methyl-2-(thiomethyl)indole **4** was alkylated by 3,3-dimethylallyl bromide to furnish the indolenine **6**, *via* thio-Claisen rearrangement of an intermediate sulphonium salt **5** (**Scheme 1**), in a reaction sequence of possible biosynthetic relevance [6] Our interest in the biosynthesis of mould metabolites[7] prompted us to explore the scope of this thio-Claisen rearrangement in the synthesis of

aszonalenin, whose stereochemistry was unknown We now report the synthesis of (-)-dihydroaszonalenin and assign the relative and absolute configuration shown **2** to aszonalenin Part of this work has been the subject of a preliminary communication [8] While our work was in progress Takase *et al* reported the synthesis of an analogue of dihydroflustramine C,[9] and the total synthesis of amauromine,[10] utilising the same thio-Claisen rearrangement Plate *et al* [11] have also explored the synthetic utility of this rearrangement while Hino *et al* [12] have described an alternative approach to the construction of the 3a-(1,1-dimethylallyl)hexahydropyrrolo[2,3-b]indole system

RESULTS AND DISCUSSION

Initially our aim was the total synthesis of aszonalenin *via* *S*-alkylation of the substituted benzodiazepine **10b** with 3,3-dimethylallyl bromide, and thio-Claisen rearrangement[6] of the derived sulphonium salt To this end *L*-tryptophan methyl ester **7a** was condensed with isatoic anhydride **8** to furnish the amide **9** which readily cyclised with pyridine hydrochloride in refluxing pyridine to give the benzodiazepine **10a** The latter benzodiazepine was prepared in one step by the condensation of *L*-tryptophan methyl ester hydrochloride with isatoic anhydride in pyridine [13] However attempts to prepare the required benzodiazepine **10b** by treatment of **10a** with methanesulphenyl chloride led to intractible mixtures Alternatively *L*-tryptophan methyl ester hydrochloride reacted with methanesulphenyl chloride under Wieland's conditions[14] to furnish the 2-(methylthio) derivative **7b** in 65% yield, which represents a substantial improvement over the route described by Takase *et al* [10] Condensation of **7b** with isatoic anhydride in pyridine, in the presence of pyridine hydrochloride, gave the desired benzodiazepine **10b** in 40% yield



7 a, R = H
b, R = SMe

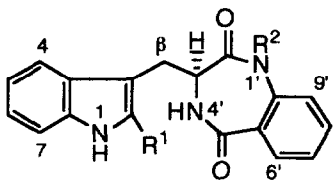
8

9

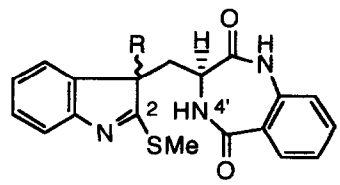
The course of alkylation of the benzodiazepine **10b** with an excess of 3,3-dimethylallyl bromide, in the presence of anhydrous potassium carbonate, showed an unexpected dependence on the concentration of the reactants Thus alkylation of a dilute solution (typically 0 05 *M*) of the benzodiazepine in anhydrous acetone or dimethylformamide at room temperature gave an *N*-(3,3-dimethylallyl) derivative as the major product The ^{1}H-NMR spectrum of the latter showed the presence of the spin-coupled system CH_2CHNH and it was concluded that alkylation had occurred either at N-1 or at N-1' The changes observed in the carbonyl region of the IR spectrum upon alkylation of **10b** (experimental) suggested that the *N*-alkyl derivative had structure **10d** This structure was confirmed by the ^{1}H-NMR difference-NOE spectra performed on the *N*-alkyl derivative In particular a 7% enhancement observed for H-9' upon irradiation of the methylene protons of the dimethylallyl group is consistent only with structure **10d** Critical assignments of aromatic resonances, especially that of H-9', were made by appropriate spin-decoupling experiments The parent benzodiazepine **10a** also gave an *N*-(dimethylallyl) derivative under the same conditions The latter compound was assigned structure **10c** mainly on the basis of the ^{1}H-NMR spectrum which showed *inter alia* a one-proton doublet at δ7 12, which collapsed to a sharp singlet on irradiation of the NH at δ8 21, and which could be assigned only to H-2 of an indole with an unsubstituted N-1 The assignments of the aromatic proton resonances of **10c** were confirmed by means of the COSY spectrum

Alternatively alkylation of a more concentrated solution (typically 1 5 *M*) of benzodiazepine **10b** in acetone with an excess of dimethylallyl bromide furnished the diastereoisomeric 3-(1,1-dimethylallyl)indolenines **11a** and **11b** as the main products, and only a trace of the *N*-(3,3-dimethylallyl)indole

10d was detected The structures but not the stereochemistry of the 3-(1,1-dimethylallyl)indolenines **11a** and **11b** follow unexceptionally from analysis of the spectroscopic data (experimental) and require no further comment The major (less polar) indolenine was assigned the configuration **11a** and the minor (more polar) indolenine was assigned the diastereoisomeric configuration **11b** on the basis of the work that is presented below The concentration-dependence of the alkylation of **10b** suggests that there are two competing reactions, one leading to **10d**, the other to **11a** and **11b**, and that the latter pathway has the higher kinetic order [15]

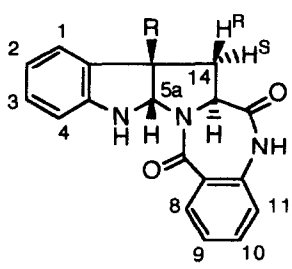


10 a, $R^1 = R^2 = H$
b, $R^1 = SMe$, $R^2 = H$
c, $R^1 = H$, $R^2 = CH_2CH{=}CMe_2$
d, $R^1 = SMe$, $R^2 = CH_2CH{=}CMe_2$

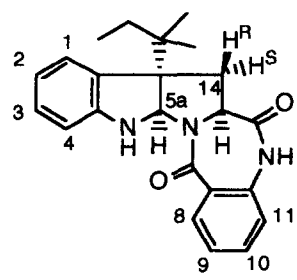


11 a, R =

b, R =



12 a, R = $CMe_2CH{=}CH_2$
b, R = CMe_2CH_2Me



13

All our attempts to selectively remove the methylthio-group from **11a** or from **11b** were unsuccessful, including application of the titanium tetrachloride/lithium aluminium hydride desulphurisation procedure,[16] that had been used successfully in the total synthesis of amauromine [10] Furthermore, neither diastereomer could be persuaded to undergo cyclisation from N-4' onto C-2 [cf 10] Finally we had recourse to desulphurisation of the less polar indolenine **11a** with deactivated Raney nickel which gave an inseparable mixture (^{1}H-NMR and mass spectrum) of the desired product **12a** and its dihydro-derivative **12b** This mixture was hydrogenated over Adams' catalyst to furnish **12b**, mp 254-255°C, $[\alpha]_D$ -50 4° Application of the same desulphurisation-hydrogenation sequence to the more polar indolenine **11b** furnished the isomeric pentacycle **13**, mp 125°C, $[\alpha]_D$ +800° The relative configurations depicted for pentacycles **12b** and **13** (and the configurations of the precursor indolenines **11a** and **11b** respectively) were assigned with the aid of NOE difference spectra (experimental) which gave mutually consistent results for the two pentacycles For example, irradiation of either quaternary methyl in **12b** resulted in enhancement only of resonances due to the following protons 5a-H (7%), 1-H (4%), and 14-H^R (4%), the equivalent NOE experiment on **13** resulted in enhancement of the resonances due to 5a-H (5%), 1-H (3%), and 14-H^S (2%) alone

Authentic aszonalenin was hydrogenated over Adams' catalyst to yield the dihydro-derivative, mp 254-255°C, $[\alpha]_D$ +59 7°, which showed identical chromatographic and spectroscopic behaviour to compound **12b** but showed a mixed mp depression with the latter We conclude that the two specimens of dihydroaszonalenin are enantiomers and that natural aszonalenin has the stereochemistry depicted in **2**

EXPERIMENTAL

General directions are as reported earlier [17] In particular, except where stated otherwise, ^{1}H-NMR spectra were recorded at 90 MHz with a Perkin Elmer R32 spectrometer for dilute solutions in $CDCl_3$ with internal tetramethylsilane ^{1}H-NMR were recorded also at 360 MHz on a Bruker WH 360 spectrometer or at 400 MHz on a Bruker ACP 400 spectrometer Optical rotations were measured at 25°C and IR spectra were recorded for KBr discs

Benzodiazepine (10a)

(a) A solution of *L*-tryptophan methyl ester hydrochloride (3 75 g) and triethylamine (1 9 g) in dimethylformamide (10 ml) was added over 40 m to a stirred solution of isatoic anhydride (2 44 g) in dimethylformamide (10 ml) at 50°C After 5 h at 50°C the solution was poured into ice-cold water (100 ml) then the resultant mixture was brought to pH 9 by addition of dilute alkali, and extracted with ethyl acetate The organic phase was washed with water, dried over anhydrous magnesium sulphate, and evaporated to dryness *in vacuo* The solid residue was recrystallised from ethyl acetate/petroleum ether to furnish *Nb-(2-aminobenzoyl)-L-tryptophan methyl ester* **9**, (4.00 g, 80 4%), as fine needles mp 132°C, $[\alpha]_D$ +73 9° (c 1 0, $CHCl_3$) (Found C, 67 6, H, 5 7, N, 12 3%, M^+, 337 142 $C_{19}H_{19}N_3O_3$ requires C, 67 6, H, 5 7, N, 12 45%, M, 337 143), ν_{max} 3425 (s, NH), 3330 (s, NH), 3250 (m, NH), 1745 (s, ester C=O), 1642 (s, amide C=O), 1613 (m), 1582 (s) cm^{-1}, δ_H 3 42 (2H, m, CH_2), 3 69 (3H, s, OMe), 4 55 (2H, br, NH_2), 5 08 (1H, dt, J~7 5 and 5 5 Hz, α-H), 6 60 (2H, m, arom), 6 96 (1H, d, J ~2 5 Hz, indole H-2), 7 0-7 5 (5H, m, arom), 7 57 (1H, m, arom), 8 25 (1H, br, indole NH), δ_C 27 7 (t), 52 4 (q), 53 1 (d), 110 1 (s), 111 3 (d), 115.3 (s), 116 6 (d), 117 3 (d), 118 7 (d), 119 7 (d), 122 3 (d), 122 8 (d), 127 5 (s+d), 132 5 (d), 136 2 (s), 148 9 (s), 168 8 (s), 172 5 (s)

A solution of the aminobenzamide **9** (0 505 g) and pyridine hydrochloride (0 231 g) in dry pyridine (10 ml) was refluxed with vigorous stirring for 18 h The solution was concentrated *in vacuo*, then diluted with water The crystalline precipitate was isolated by filtration and washed sequentially with 0 2 *M* hydrochloric acid and water Crystallisation from methanol and ethyl acetate furnished the *title benzodiazepine* **10a** (0 301 g, 65 9%), mp 245°C, $[\alpha]_D$ +142 9° (c 1 0, ethanol) (Found C, 70 7, H, 5 1, N, 13 7%, M^+, 305 117 $C_{18}H_{15}N_3O_2$ requires C, 70 8, H, 4 95, N, 13.8%, M, 305 116), ν_{max} 3450 (m, NH), 1678 (s, C=O), 1660 (s, C=O), 1605 (m), 1580 (m) cm^{-1}, δ_H (d_6-dmso) 3 08 (1H, dd, J 9 5 and 16 Hz, CH_AH_BCHNH), 3 34 (1H, dd, J 6 and 16 Hz, CH_AH_BCHNH), 3 72 (1H, s, NH), 3 96 (1H, ddd, J 5 5, 6, and 9.5 Hz, CH_2CHNH), 6 8-7 9 (10H, m, aromatic + NH), 8 44 (1H, d, J 5 5 Hz, CH_2CHNH), δ_C (d_6-dmso) 23 6 (t), 52 8 (d), 109 7 (s), 111 4 (d), 118 2 (d), 118 4 (d), 121 0 (2C, d), 124 0 (d), 124 3 (d), 126 2 (s), 127 0 (s), 130.3 (d), 132 2 (d), 136 1 (s), 136.8 (s), 167 7 (s), 171 5 (s)

(b) A solution of *L*-tryptophan methyl ester hydrochloride (2 00 g) and isatoic anhydride (1 61 g) in pyridine (20 ml) was refluxed with vigorous stirring for 18 h [13] Work-up as described above furnished the benzodiazepine **10a** (1 72 g, 70.8%), mp 245°C

Reaction of Benzodiazepine (10a) with 3,3-Dimethylallyl bromide.

A solution of 3,3-dimethylallyl bromide (0 551 g) in anhydrous acetone (30 ml) was added to a well-stirred suspension of the benzodiazepine **10a** (1 02 g) and anhydrous potassium carbonate (0 690 g) in acetone (35 ml) The mixture was stirred for 2 days under nitrogen, then fresh 3,3-dimethylallyl bromide (0 250 g) and potassium carbonate (0 275 g) were added and stirring continued for 2 more days At the end

of this time TLC (eluted with $CHCl_3$/ethyl acetate, 1 1 by volume) showed only one significant product, (Rf 0 6) and complete loss of the starting benzodiazepine (Rf 0 3) The reaction mixture was filtered and the filtrate evaporated to dryness *in vacuo* Flash chromatography furnished the *N-(3,3-dimethylallyl) derivative* **10c**, (0 850 g, 69 6%), mp 108-109°C, $[\alpha]_D$ +226 1° (c 1 0, chloroform) (Found. C, 73 7, H, 6 2, N, 11 2%; M^+, 373 179 $C_{23}H_{23}N_3O_2$ requires C, 74 0, H, 6 2, N, 11 25%, M, 373 179), ν_{max} 3400 (m, NH), 3320 (m, br, NH), 1655 (s, br, C=O), 1600 (m), 1570 (w) cm^{-1}, δ_H (400 MHz) 1 65 (3H, s, Me), 1 67 (3H, s, Me), 3 26 (1H, dd, J 8 4 and 15 3 Hz, CH_AH_BCHNH), 3 49 (1H, dd, J 5 8 and 15 3 Hz, CH_AH_BCHNH), 4.07 (1H, dt, J 8 4 and 5 7 Hz, CH_2CHNH), 4 5 (2H, AB part of ABX, δ_A 4 47, δ_B 4 50, J_{AB} ~15 4, J_{AX} ~6 2, J_{BX} ~6 8 Hz, CH_2CH=), 5 22 (1H, br t, J ~5 8 Hz, X part of ABX, CH_2CH=), 6 57 (1H, d, J ~5 5 Hz, CH_2CHNH), 7 06 (1H, dt, J ~0 8 and 7 5 Hz, H-5), 7 12 [1H, br d, J ~2 1 Hz (collapsed to sharp singlet on irrad at δ8 21), H-2], 7 16 (1H, dt, J 1 0 and 7 6 Hz, H-6), 7 23 [1H, t, J 7 4 Hz, (partly obscured by $CHCl_3$ resonance at δ7 25), H-7'], 7 28 (1H, d, J 8 0 Hz, H-9'), 7 32 (1H, d, J 8 1 Hz, H-7), 7 48 (1H, dt, J ~1 6 and 7 7 Hz, H-8') overlapping with 7.49 (1H, d, J ~7 3 Hz, H-4), 7 74 (1H, dd, J 1 6 and 7 8 Hz, H-6'), 8 21 (1H, br s, H-1), δ_C 18 0 (q), 24 5 (t), 25 6 (q), 47 2 (t), 52 5 (d), 109 8 (s), 111 4 (d), 118 2 (d), 119 4 (d), 119 9 (d), 122 1 (d), 122 2 (d), 123 8 (d), 125 8 (d), 127 2 (s), 128 6 (s), 130 3 (d), 132 4 (d), 135 8 (s), 136 2 (s), 140 3 (s), 168 8 (s), 169 9 (s)

Benzodiazepine (10b)

Trichloroacetic acid (3 00 g) was added to a vigorously stirred suspension of *L*-tryptophan methyl ester hydrochloride (10 00 g) in chloroform (150 ml) under an atmosphere of dry nitrogen The flask contents were cooled to -70°C whereupon a solution of methanesulphenyl chloride [freshly prepared from dimethyldisulphide (3 70 g) and sulphuryl chloride (5.30 g)] in chloroform (15 ml) was added slowly, ensuring that the temperature of the reaction mixture did not rise above -60°C After the addition was complete the reaction mixture was allowed to stirr at room temperature under nitrogen for an additional 72 h The solvent was removed under reduced pressure and the residue was partitioned between 10% aqueous sodium bicarbonate solution and ethyl acetate The organic phase was washed with water and dried over anhydrous magnesium sulphate Solvent was removed under reduced pressure to afford the tryptophan derivative **7b** as a thick gum (9 01 g, 65%) [δ_H (60 MHz) 1 9 (2H, v br, NH_2), 2 32 (3H, s, SMe), 3 0-3 5 (2H, m, CH_2CH), 3 67 (3H, s, OMe), 3 85 (1H, dd, J 5 5 and 8 Hz, CH_2CH), 6 8-7 75 (4H, m, arom), 8 66 (1H, br, NH)] which was used in the next step without purification

A solution of the crude amine **7b** (13 52 g), isatoic anhydride (8 25 g), and pyridine hydrochloride (7 51 g), in dry pyridine (100 ml) was refluxed with vigorous stirring under an atmosphere of nitrogen for 72 h Most of the solvent was removed under reduced pressure and the residue was partitioned between water and ethyl acetate The organic extract was washed with water, dried over magnesium sulphate, and evaporated to dryness *in vacuo* The crude product was purified by flash chromatography on silica gel, eluting with benzene/ethyl acetate (1 1 by volume), the resultant solid (Rf 0 3) was crystallised from ethyl acetate/petroleum ether to furnish the benzodiazepine **10b**, (7 16 g, 40%), mp 157-159°C, $[\alpha]_D$ +181 0° (c 1 0, chloroform) (Found M^+, 351 1045 $C_{19}H_{17}N_3O_2S$ requires M, 351 104), ν_{max} 3260 (m, br, NH), 1687 (s, C=O), 1645 (s, C=O), 1607 (m), 1577 (w) cm^{-1}, δ_H 2 31 (3H, s, SMe), ~3 45 (2H, m, CH_2CH), 4 18 (1H, m, CH_2CH), 6 9-7 65 (~8H, arom H + NH), 7 90 (1H, m, arom), 8 91 (1H, s, NH), 9 40 (1H, s, NH), δ_C 19 8 (q), 23 8 (t), 53 1 (d), 111 1 (d), 114 1 (s), 118 2 (d), 119 9 (d), 121 1 (d), 123 0 (d), 125 1 (d), 125 2 (s), 127 4 (s), 128 4 (s), 131 5 (d), 133 1 (d), 135 8 (s), 136 8 (s), 168 9 (s), 172 5 (s)

Reaction of Benzodiazepine (10b) with 3,3-Dimethylallyl Bromide

(a) 3,3-Dimethylallyl bromide (68 mg) in anhydrous acetone (5 ml) was added to a stirred solution of the benzodiazepine **10b** (150 mg) in acetone (5 ml) Anhydrous potassium carbonate (276 mg) was added

and the mixture was stirred under an atmosphere of nitrogen for 3 days The inorganic residue was removed by filtration and washed with acetone TLC (ethyl acetate/benzene, 1 1 by volume) on the combined acetone phase showed one major component, with Rf 0 6, and traces of the starting benzodiazepine, Rf 0 35 The solvent was removed *in vacuo* to leave a viscous oil which was submitted to flash chromatography over silica gel, eluting with benzene/ethyl acetate (7 3 by volume) The solid product was recrystallised from ethyl acetate/petroleum ether to yield the *N-(3,3-dimethylallyl) derivative* **10d** (110 mg, 61%), mp 103-104°C, $[\alpha]_D$ +211° (c 1 0, $CHCl_3$) (Found C, 68 15, H, 6 2, N, 9 8%, M^+, 419 169 $C_{24}H_{25}N_3O_2S$ requires C, 68 7, H, 6 0, N, 10 0%, M, 419 167), ν_{max} 3300 (m, br, NH), 1655 (s, C=O), 1600 (m) cm^{-1}, δ_H (400 MHz) 1 68 (3H, s, Me), 1 69 (3H, s, Me), 2 37 (3H, s, SMe), 3 44 (2H, m, $C\underline{H}_2CHNH$), 4 06 [1H, m, (approx dt, J ~ 8 6 and 5 5 Hz), $CH_2C\underline{H}NH$], 4.49 (1H, dd, J 15 3 and 6 1 Hz, $C\underline{H}_A\underline{H}_BCH$=), 4 57 (1H, dd, J 15 3 and 6 9 Hz, $CH_A\underline{H}_BCH$=), 5 27 (1H, br t, J ~ 6 5 Hz, $CH_2C\underline{H}$=), 6.56 (1H, d, J 5 2 Hz, $CH_2CHN\underline{H}$), 7 03 (1H, dt, J ~0 8 and 7 5 Hz, H-5), 7 17 [1H, dt, J~1 0 and 7 6 Hz, (collapsed to d, J~7 6 Hz, on irrad. at δ7 03), H-6], 7 22 [1H, dt, J~0 8 and 7 5 Hz, (collapsed to d, J~7 5 Hz, on irrad at δ7 47 or 7 72), H-7'], 7 29 [1H, d, J~8 1 Hz, (sharpened on irrad at δ7 03), H-7] overlapping with 7 31 [1H, d, J~7 4, collapsed to s on irrad at δ7 47), H-9'], 7 40 [1H, d, J 7 9 Hz, (collapsed to s on irrad at δ7 03), H-4], 7 47 [1H, dt, J~1 6 and 7 8, (collapsed to t, J~7 8, on irrad at δ7 72), H-8'], 7 72 [1H, dd, J 1 6 and 7 8 Hz, (collapsed to d, J~7 8 Hz, on irrad at δ7 47), H-6'], 8 61 (1H, s, H-1), δ_C 18 1 (q), 20 0 (q), 23 9 (t), 25 6 (q), 47 3 (t), 52 9 (d), 111 1 (d), 114.5 (s), 118 0 (d), 119 8 (2C, d), 122 1 (d), 123 0 (d), 125 9 (d), 127 5 (s), 128 2 (s), 128 4 (s), 130 4 (d), 132 4 (d), 136 0 (s), 136 7 (s), 140 2 (s), 168 6 (s), 170 1 (s)

(b) 3,3-Dimethylallyl bromide (68 mg) was stirred with the benzodiazepine **10b** (150 mg) and anhydrous potassium carbonate (276 mg) in dimethylformamide (10 ml) for 2 days to furnish the same product **10d**, (112 mg, 63%)

(c) Anhydrous potassium carbonate (1 57 g), and 3,3-dimethylallyl bromide (3 39 g) in dry acetone (5 ml), were added to a well-stirred solution of the benzodiazepine **10b** (4 00 g) in anhydrous acetone (15 ml) under an atmosphere of nitrogen After stirring for 65 h additional aliquots of 3,3-dimethylallyl bromide (0 89 g) and anhydrous potassium carbonate (0 39 g) were added and stirring was continued for a further 24 h The reaction mixture was filtered and the filtrate evaporated *in vacuo* to give a non-crystalline residue which on TLC, eluted with benzene/ethyl acetate (1 1 by volume) showed components with the following Rf values 0 7 (minor), 0 6 (minor), 0 4 [major, **10b**], 0 3 [major, **11a**], 0 2 [major, **11b**], 0.15 (minor), and 0 0 (minor). Careful flash chromatography, eluting with benzene/ethyl acetate (1·1 by volume), furnished the starting compound **10b**, (0 73 g, 17 5%), followed by the indolenine **11a** (2 1 g, 42%), a mixture of indolenines **11a** and **11b** (0 60 g, 12 5%), the indolenine **11b** (0 93 g, 19%), and a mixture of the latter indolenine with more polar material (0 22 g)

Indolenine **11a** had mp 127-128°C (from benzene/ethyl acetate), $[\alpha]_D$ -24.2° (c 0 5, ethanol) (Found C, 68 4, H, 6 0, N, 9 8%, M^+, 419 166 $C_{24}H_{25}N_3O_2S$ requires C, 68 7, H, 6 0, N, 10 0%, M, 419 167), ν_{max} 3430 (br shoulder, NH), 3220 (m, br, NH), 1685 (s, C=O), 1655 (s, C=O), 1608 (m), 1580 (w) cm^{-1}, δ_H 1 01 (3H, s, CH_3), 1 12 (3H, s, CH_3), 2 70 (~3H, s, SCH_3) superimposed on 2 25-3 07 (~3H, m, $C\underline{H}_2C\underline{H}NH$), 5 03 (d, J 17 Hz) and 5 13 (d, J 11 Hz) (total 2H, $CH{=}C\underline{H}_2$), 6 01 (1H, dd, J 17 and 11 Hz, $C\underline{H}{=}CH_2$), 6 51 (1H, d, J 5 5 Hz, $CH_2CHN\underline{H}$), ~6 75-7 55 (7H, m, arom), 7 73 (1H, d, J 8 Hz, arom), 8 60 (1H, s, NH), δ_C 14 9 (q), 22 6 (q), 23 0 (q), 31 1 (t), 40 9 (s), 50.3 (d), 68 2 (s), 115 0 (t), 118 9 (d), 120 6 (d), 123 5 (d), 124 7 (d), 125 0 (s+d), 128 5 (d), 130 9 (d), 132 8 (d), 135 3 (s), 138 6 (s), 143 1 (d), 155 4 (s), 167 8 (s), 171 7 (s), 184 9 (s)

Indolenine **11b** had mp 116-117°C (from tetrachloromethane/ethyl acetate), $[\alpha]_D$ +187° (c 1 0, ethanol) (Found C, 68 4, H, 6 15, N, 9 8%, M^+, 419 168 $C_{24}H_{25}N_3O_2S$ requires C, 68 7, H, 6 0, N, 10 0%, M, 419 167), δ_H (250 MHz) 1 17 (3H, s, CH_3), 1 42 (3H, s, CH_3), 2 54 (3H, s, SCH_3), 2 79 (2H, m, $C\underline{H}_2CH$), 3 16 (1H, m, $CH_2C\underline{H}$), 5 26 (d, J 18 Hz) overlapping with 5 31 (d, J 11 Hz) (total 2H,

CH=C$\underline{H}_2$), 6 23 (1H, dd, J 17 3 and 10 8 Hz, C$\underline{H}$=CH$_2$), 6 9-7 2 (3H, m, arom), 7 3-7 45 (3H, m, arom), 7 51 (1H, d, J 7 8 Hz, arom), 7 65 (1H, d, J 7 4 Hz, arom), 8 2 (1H, br, NH), 10 5 (1H, br, NH), δ_C (62 9 MHz) 14 6, 23 4 (2C?), 30 4, 41 0, 49 7, 69 1, 114 8, 118 6, 120 9, 123 1, 124 7, 125 0, 126 0, 128 4, 130 2, 132 7, 136 1, 139 5, 143 0, 155 0, 168 8, 172 4, 184 9

Natural Dihydroaszonalenin

A solution of aszonalenin (7 5 mg) in ethyl acetate (10 ml) was hydrogenated at atmospheric pressure over Adams' catalyst (1 5 mg) for 2 h Filtration and evaporation of the filtrate furnished dihydroaszonalenin, mp 254-255°C, $[\alpha]_D$ +59 7°, $[\alpha]_{578}$ +61 3°, $[\alpha]_{546}$ +75 4°, $[\alpha]_{436}$ +218 5° (c 0 1, $CHCl_3$)

(-)-Dihydroaszonalenin (12b)

A slurry of freshly prepared W2 Raney nickel in ethanol (1 ml) was added to a well-stirred solution of the indolenine **11a** (100 mg) in vigorously refluxing benzene (5 ml) After refluxing for 10 m the mixture was cooled, filtered, and the filtrate evaporated to dryness TLC of the residue, eluted with benzene/ethyl acetate (3 7 by volume), showed components with Rf 0 8 (major), 0 45 (minor), 0 4 [minor, compound **11a**], and 0 25 (major) The main components of the mixture were isolated by flash chromatography The fraction with Rf 0 25 furnished benzodiazepine **10a**, mp 245°C, IR and ^{1}H-NMR spectra and TLC behaviour identical to those of authentic material The fraction with Rf 0 8 gave needles (22 mg), mp 247°C (from chloroform/methanol) This substance was shown by ^{1}H-NMR and mass spectrometry to be a mixture of (-)-aszonalenin and its dihydro-derivative Qualitatively similar results were obtained when the desulphurisation was performed with various different grades of deactivated Raney nickel

A solution of the substance described above (50 mg) in ethyl acetate (30 ml) was hydrogenated for 2 h, at atmospheric pressure over Adams' catalyst (5 mg) Filtration and evaporation of the filtrate furnished *(-)-dihydroaszonalenin* **12b**, mp 254-255°C (depressed upon mixed mp with natural dihydroaszonalenin), $[\alpha]_D^{23°}$ -50 4°, $[\alpha]_{578}$ -53 1°, $[\alpha]_{546}$ -65 1°, $[\alpha]_{436}$ -185 4° (c 0 5, $CHCl_3$), TLC behaviour, IR and ^{1}H-NMR spectra identical to those of natural dihydroaszonalenin (Found C, 73 5, H, 6 7, N, 10 8%, M$^+$, 375 194 $C_{23}H_{25}N_3O_2$ requires C, 73 6, H, 6 7, N, 11 2%, M, 375 195), ν_{max} (KBr) 3380 (m, NH), 3250 (m, NH), 1683 (s, C=O), 1617 (s, C=O), 1600 (s), 1570 (m) cm^{-1}, δ_H (360 MHz) 0 82 (3H, t, J 7 5 Hz, C$\underline{H}_3$CH$_2$), 0 97 (3H, s, CH$_3$), 0 99 (3H, s, CH$_3$), 1 27 and 1 61 (each 1H, each m, CH$_3$C$\underline{H}_2$), 2 42 (1H, dd, J 13 9 and 9 1 Hz, H-14-*pro-S*), 3 48 (1H, dd, J 13 9 and 7 4 Hz, H-14-*pro-R*), 4 00 (1H, dd, J 9 1 and 7 4 Hz, H-13a), 5 61 (1H, s, H-5a), 6 15 (1H, s, H-5), 6 60 (1H, m, ^{3}J~7 8 Hz, H-4), 6 71 (1H, dt, J 1 1 and 7 5 Hz, H-2), 6 92 (1H, dd, J 1 1 and 8 0 Hz, H-11), 7 06 (1H, m, ^{3}J~7 6 Hz, H-3), 7 15 (1H, dd, J 0 8 and 7 5 Hz, H-1), 7 20 (1H, ddd, J 1 1, 7 4, and 7 9 Hz, H-9), 7 43 (1H, ddd, J 1 6, 7 4, and 8 0 Hz, H-10), 7 83 (1H, dd, J 1 6 and 7 9, H-8), 8 25 (1H, s, H-12)

Desulphurisation and Hydrogenation of (11b)

Compound **11b** (100 mg) was submitted to desulphurisation over Raney nickel as described above to furnish *inter alia* a mixture of the desired compound and its dihydro-derivative Hydrogenation of the latter mixture over Adams' catalyst gave *the pentacycle* **13** (15 mg) mp 125°C (from benzene/petroleum ether), $[\alpha]_D$ +800° (c 0 2, chloroform) (Found M$^+$, 375 193 $C_{23}H_{25}N_3O_2$ requires M, 375 195), δ_H (360 MHz) 0 81 (3H, t, J 7 5 Hz, C$\underline{H}_3$CH$_2$), 0 94 (3H, s, CH$_3$), 0.98 (3H, s, CH$_3$), 1 29 and 1 58 (each 1H, each m, CH$_3$C$\underline{H}_2$), 2 57 (1H dd, J 13 4 and 9 6 Hz, H-14-*pro-S*), 3 13 (1H, d, J 13 5 Hz, H-14-*pro-R*), 4 13 (1H, dd, J 9 5 and 1 0 Hz H-13a), 5 17 (1H, s, H-5), 5 67 (1H, s, H-5a), 6 46 (1H, m, ^{3}J~7 8 Hz, H-4), 6 63 (1H, dt, J 1 0 and 7 5 Hz, H-2), 6 82 (1H, dd, J 1 0 and 8 1 Hz, H-11), 6 97 (1H, dt, 1 2 and 7 6 Hz, H-3), 7 24 (1H, ddd, J 1 0, 7 3 and 7 9 Hz, H-9), 7 28 (1H, dd, J 0 8 and 7 5 Hz, H-1), 7 45 (1H, ddd, J 1 7, 7 3, and 8 1 Hz, H-10), 7 82 (1H, s H-12), 7 98 (1H, dd, J 1 7 and 7 9 Hz, H-8)

Selected Results of Difference NOE Spectroscopy (360 Mz) on (12b) and (13)

Compound	Irradiate/δ	NOE Observed/δ
12b	0 97 (Me)	0.82 (2%), 1 28 (2%), 3 48 (4%), 5 61 (7%), 7 15 (5%)
	0 99 (Me)	1 61 (2%), 3 48 (4%), 5 61(8%), 7 15 (4%)
	2 42 (14-H^S)	3 48 (15%, 14-H^R), 4 00 (12%, 13a-H), 7 15 (4%, 1-H)
	3 48 (14-H^R)	2 42 (10%, 14-H^S)
	4 00 (13a-H)	2 42 (4%, 14-H^S)
	6 15 (5-H)	5 61 (7%, 5a-H), 6 60 (10%, 4-H)
	8 25 (12-H)	6 92 (16%, 11-H)
13	0 94 & 0 98 (Me_2)	2 57 (2%, 14-H^S), 5 67 (5%, 5a-H), 7 29 (3%, 1-H)
	2 57 (14-H^S)	0 94 & 0 98 (each 1%, Me_2), 3 14 (13%, 14-H^R), 4 13 (8%, 13a-H)
	5 17 (5-H)	5 67 (6%, 5a-H), 6 46 (8%, 4-H)
	7 79 (12-H)	6 82 (13 5%, 11-H)

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REFERENCES AND FOOTNOTES

1 Scott, P M , Merrien, M-A , Polonsky, J *Experientia*, 1976, **32**, 140, Scott, P M , Polonsky, J, Merrien, M-A *J Agric Food Chem* , 1979, **27**, 201

2 Kimura, Y ; Hamasaki, T , Nakajima, H , Isogai, A *Tetrahedron Lett* , 1982, **23**, 225

3 Takase, S , Kawai, Y., Uchida, I , Tanaka, H , Aoki, H *Tetrahedron Lett* , 1984, **25**, 4673, *Tetrahedron*, 1985, **41**, 3037

4 Carlé, J S , Christophersen, C *J Am Chem Soc* , 1979, **101**, 4012

5 Carlé, J S , Christophersen, C *J Org Chem* , 1981, **46**, 3440

6 Bycroft, B W , Landon, W *J Chem Soc , Chem Commun* , 1970, 967

7 Bhat, B , Harrison, D M., Lamont, H M *J Chem Soc , Chem Commun* , 1990, 1518, *Tetrahedron*, accompanying paper

8 Bhat, B , Harrison, D M *Tetrahedron Lett* , 1986, **27**, 5873

9 Takase, S , Uchida, I , Tanaka, H , Aoki, H *Heterocycles*, 1984, **22**, 2491, *Tetrahedron*, 1986, **42**, 5879

10 Takase, S , Itoh, Y , Uchida, I , Tanaka, H , Aoki, H *Tetrahedron Lett* , 1985, **26**, 847, *Tetrahedron*, 1986, **42**, 5887

11 Plate, R , Theunisse, A W G , Ottenheijm, H. C J *J Org Chem* , 1987, **52**, 370

12 Hino, T , Hasumi, K , Yamaguchi, H , Taniguchi, M , Nakagawa, M *Chem Pharm Bull* , 1985, **33**, 5202

13 cf Dong Han Kim, *J Het Chem* , 1975, **12**, 1323

14 Wieland, T , de Urries, M P J , Indest, H , Faulstich, H *Annalen*, 1974, 1570

15 It is likely that *S*-alkylation of **10b** is the rate-determining step in the formation of **11a** and **11b**, and that this step is 1st order in both **10b** and dimethylallyl bromide In contrast, the formation of **10d** must involve alkylation of the amide anion derived from **10b** If the dissolution of K_2CO_3 in acetone is rate-limiting in the deprotonation of **10b**, then the rate of formation of **10d** will be zero order in both **10b** and dimethylallyl bromide

16 Mukaiyama, T , Hayashi, M , Narasaka, K *Chem Lett* , 1973, 291

17 Harrison, D M , Sharma, R B *Tetrahedron*, 1993, **49**, 3165