A Synthesis of Micandrol-C a Novel Methylthiophenanthrenediol Isolated from the Trunkwood of *Micandropsis scleroxylon*

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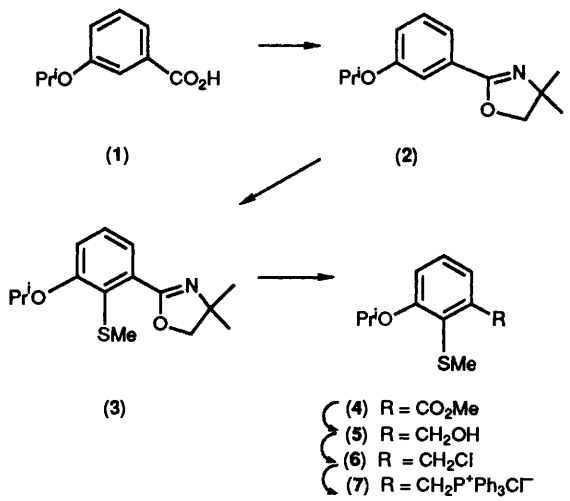
The structure of the unusual phenanthrene micandrol-C (7-methyl-1-methylthiophenanthrene-2,6-diol) (**16**), isolated from the trunkwood of the Amazonian tree, *Micandropsis scleroxylon* W. Rodr., is confirmed by synthesis. The key step involved the cyclization of a *cis*-2-chlorostilbene in the presence of activated magnesium.

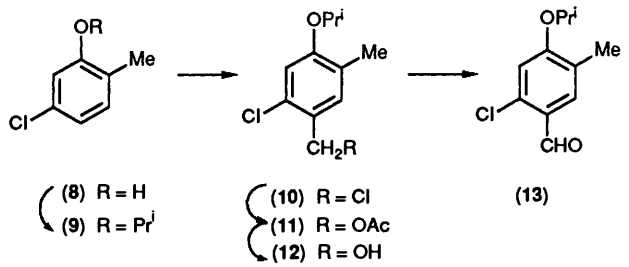
In continuation of our interest in the synthesis of phenanthrenoid natural products[1] we were attracted to the problem of the synthesis of micandrol-C (**16**) (see Scheme 3), an unusual methylthiophenanthrenediol isolated from the trunkwood of the Amazonian Euphorbiaceous tree, *Micandropsis scleroxylon* W. Rodr., by de Alvarenga and Gottlieb.[2] The initial structural assignment for micandrol-C was based on a misinterpretation of the ^{1}H NMR spectra of micandrol-C and its derivatives, but spectra were obtained at higher field, and the structural proposal was later amended.[3]

We have now confirmed this structural revision by the synthesis of 7-methyl-1-methylthiophenanthrene-2,6-diol (**16**). For this purpose we adopted the phenanthrene synthesis which we have described previously,[4,5] and which depends on the cyclization of a *cis*-2-chlorostilbene by the agency of activated magnesium.[6] In consequence, we required the stilbene (**14**) (see Scheme 3) as the key intermediate, and we planned to synthesize this by a Wittig reaction between the known aldehyde (**13**)[5] and the phosphonium salt (**7**).



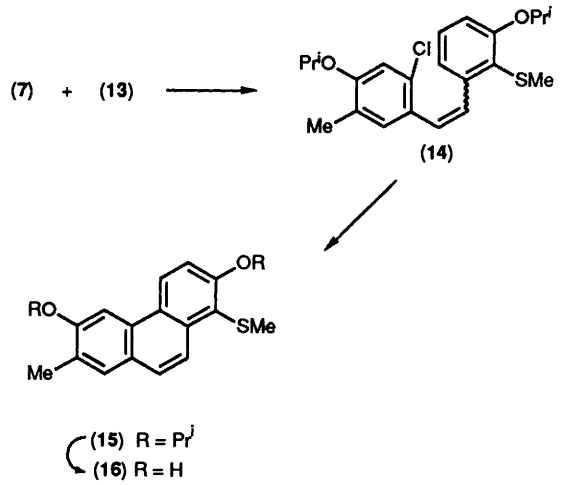
Scheme 1.

3-Isopropoxybenzoic acid (**1**)[7] (Scheme 1) was therefore converted into the dihydro-oxazole (**2**) by the standard method.[8] Meyers and Mihelich[9] have shown that such 2-aryldihydro-oxazoles may be lithiated in the *ortho*-position of the aromatic ring, and that the resultant *ortho*-lithiated species undergo efficient reactions with electrophiles. Treatment of the dihydro-oxazole (**2**) with butyl-lithium followed by dimethyl disulphide smoothly gave the methylthio compound (**3**) which was converted by standard functional group manipulations into



Scheme 2.

the phosphonium salt (**7**). The aldehyde (**13**)[5] (see Scheme 2) was conveniently prepared from the chlorocresol (**8**),[10] which was first converted into the isopropyl ether (**9**). On Blanc chloromethylation this intermediate supplied the benzyl chloride (**10**) which was converted into the alcohol (**12**), *via* the acetate (**11**), and this on oxidation with manganese dioxide yielded the aldehyde (**13**).



Scheme 3.

A Wittig reaction between the aldehyde (**13**) (see Scheme 3) and the phosphonium salt (**7**) was carried out by the *in situ* method with *N*,*N*-dimethylformamide as solvent. These conditions are known to give predominantly the *cis*-stilbene.[11] The resultant stilbene (**14**), rich in the *cis*-isomer, was allowed to react with activated magnesium in boiling tetrahydrofuran and a moderate yield of the phenanthrene (**15**) was secured.

Selective *O*-deprotection of the phenanthrene (**15**) was achieved with boron trichloride in dichloromethane and this

reaction gave synthetic micandrol-C, the spectral properties of which were in accord with those recorded in the literature[2,3] so that structure (**16**) is correct.

Experimental

General directions have been given before.[1,2]

2-(3-*Isopropoxyphenyl*)-4,4-*dimethyl*-4,5-*dihydro-oxazole* (**2**).—3-Isopropoxybenzoic acid[7] (**1**) (23.8 g) and thionyl chloride (32 ml) were stirred together for 24 h and the excess of thionyl chloride was removed by evaporation under reduced pressure, and finally by azeotropic distillation with carbon tetrachloride. A solution of the crude acid chloride in dichloromethane (75 ml) was added dropwise to a stirred solution of 2-amino-2-methylpropan-1-ol (31 ml) in dichloromethane (50 ml) at 0 °C. The mixture was stirred at room temperature for 2 h and next the precipitated hydrochloride was separated by filtration and washed with dichloromethane. The volume of dichloromethane was reduced to 75 ml and this solution was stirred and treated with thionyl chloride (40 ml), first at 0 °C, and then at room temperature for 30 min. The solution was poured on ice, the organic phase was extracted twice with hydrochloric acid (2M), the combined aqueous phases were basified with dilute sodium hydroxide solution. The *dihydro-oxazole* (**2**) was isolated by extraction with ethyl acetate and next distilled under dinimished pressure whereupon it was obtained as an oil, (19.3 g, 63%), b.p. 120 °C at 0.01 mmHg (Kugelrohr) (Found: C, 72.3; H, 8.45%; M^+, 233. $C_{14}H_{19}NO_2$ requires C, 72.05; H, 8.2% *M*, 233); δ(80 MHz) 1.32 (6 H, d, OCH*Me*$_2$), 1.36 (6 H, s, Me_2), 4.06 (2 H, s, CH_2), 4.60 (1 H, septet, CH), and 6.87–7.66 (4 H, m, 4 × ArH).

2-(3-*Isopropoxy*-2-*methylthiophenyl*)-4,4-*dimethyl*-4,5-*dihydro-oxazole* (**3**).—A solution of butyl-lithium (1.26M) in hexane (25 ml) was added dropwise to a stirred solution of the dihydro-oxazole (**2**) (3.6 g) in anhydrous tetrahydrofuran (200 ml) under argon at −45 °C. The solution was stirred at −45 °C for 2 h, dimethyl disulphide (3 ml) was added dropwise, and the solution was allowed to warm to room temperature and stirred for 26 h. The usual work up gave an oil which was filtered through a short column of neutral alumina with 20% ethyl acetate–light petroleum as eluant which gave the *dihydro-oxazole* (**3**) (3.2 g, 74%) as an oil, a sample of which had b.p. 120 °C at 0.01 mmHg (Kugelrohr) (Found: C, 64.35; H, 7.55; S, 11.15%; M^+, 279. $C_{15}H_{21}NO_2S$ requires C, 64.5; H, 7.6; S, 11.45%; *M*, 279); δ(80 MHz) 1.34 (6 H, d, OCH*Me*$_2$), 1.31 (6 H, s, Me_2), 2.25 (3 H, s, SMe), 3.90 (2 H, s, CH_2), 4.44 (1 H, septet, CH), and 6.57–7.15 (3 H, m, 3 × ArH).

Methyl 3-*Isopropoxy*-2-*methylthiobenzoate* (**4**).—A solution of the dihydro-oxazole (**3**) (6.35 g) and iodomethane (5 ml) in nitromethane (50 ml) was stirred at 55 °C (bath) for 24 h. The solvent was removed under diminished pressure and the crude methiodide was boiled under reflux with sodium hydroxide (10 g), water (10 ml), and methanol (50 ml) for 42 h. The usual work up gave the crude acid which was esterified in the usual way with iodomethane and potassium carbonate in *N,N*-dimethylformamide at room temperature. The *ester* (**4**) (3.1 g, 57%) was obtained as an oil, b.p. 70 °C at 0.01 mmHg (Kugelrohr) (Found: C, 60.35; H, 6.7; S, 13.15%; M^+, 240. $C_{12}H_{16}O_3S$ requires C, 60.0; H, 6.7; S, 13.35%; *M*, 240); δ(80 MHz) 1.39 (6 H, d, Me_2), 2.39 (3 H, s, SMe), 3.91 (3 H, s, OMe), 4.63 (1 H, septet, CH), and 6.89–7.36 (3 H, s, 3 × ArH).

3-*Isopropoxy*-2-*methylthiophenylmethanol* (**5**).—A solution of the ester (**4**) (18.6 g) in anhydrous tetrahydrofuran (200 ml) was added dropwise to a stirred solution of lithium aluminium hydride (3.7 g) in tetrahydrofuran (200 ml) and the solution was stirred at room temperature for 30 min. The solution was cooled to 0 °C and treated with an excess of saturated sodium sulphate solution. The usual work up gave the alcohol (**5**) as an oil (15.4 g, 94%), b.p. 80 °C at 0.01 mmHg (Kugelrohr); δ(300 MHz) 1.40 (6 H, d, Me_2), 2.39 (3 H, s, SMe), 2.48 (1 H, br s, OH), 4.64 (1 H, septet, CH), 4.80 (2 H, s, CH_2), 6.85 (1 H, dd, $J_{6,5}$ 7.5, $J_{6,4}$ 1.2 Hz, 6-H), 6.96 (1 H, dd, $J_{4,5}$ 7.5, $J_{4,6}$ 1.2 Hz, 4-H), and 7.24 (1 H, dd, $J_{5,4} = J_{5,6}$ = 7.5 Hz, 5-H); *m/z* 212 (M^+).

3-*Isopropoxy*-2-*methylthiobenzyl Chloride* (**6**).—A stirred solution of the alcohol (**5**) (15.4 g) in anhydrous benzene (500 ml) and pyridine (7 ml) was treated dropwise with thionyl chloride (5 ml) at room temperature and then stirred for 2 h, and next washed with water and with saturated brine. The solvent was removed under reduced pressure to leave the *chloride* (**6**) (14.1 g, 84%) as an oil b.p. 45 °C at 0.01 mmHg (Found: C, 64.7; H, 6.95; Cl, 19.35%; M^+, 230/232. $C_{10}H_{13}ClO$ requires C, 65.05; H, 7.1; Cl, 19.2%; *M*, 230/232); δ(300 MHz) 1.40 (6 H, d, Me_2), 2.39 (3 H, s, SMe), 4.63 (1 H, septet, CH), 4.89 (2 H, s, CH_2), 6.87 (1 H, dd, $J_{4,5}$ 7.8, $J_{4,6}$ 1.3 Hz, 4-H), 7.03 (1 H, dd, $J_{6,5}$ 7.8, $J_{6,4}$ 1.3 Hz, 6-H), and 7.23 (1 H, dd, $J_{5,6} = J_{5,4}$ = 7.8 Hz, 5-H).

1-*Chloro*-3-*isopropoxy*-4-*methylbenzene* (**9**).—A solution of 5-chloro-2-methylphenol[10] (**8**) (5.0 g) in anhydrous *N,N*-dimethylformamide (80 ml) was stirred at 55 °C (bath) with 2-bromopropane (5.35 ml), anhydrous potassium carbonate (12.5 g), and potassium iodide (9.5 g) under an atmosphere of argon for 24 h. The cooled mixture was then diluted with water and the crude product isolated by extraction with ether, passed through a short column of neutral alumina with light petroleum as eluant, and finally distilled under diminished pressure whereupon the *ether* (**9**) (5.66 g, 87%) was obtained as an oil, b.p. 45 °C at 0.01mmHg (Kugelrohr) (Found: C, 64.7; H, 6.55; Cl, 19.35%; M^+, 184/186. $C_{10}H_{13}ClO$ requires C, 65.05; H, 7.1; Cl, 19.2%; *M*, 184/186); δ(80 MHz) 1.31 (6 H, d, Me_2), 2.13 (3 H, s, Me), 4.45 (1 H, septet, CH), and 6.73–7.14 (3 H, m, 3 × ArH).

1-*Chloro*-2-*chloromethyl*-5-*isopropoxy*-4-*methylbenzene* (**10**).—Hydrogen chloride was passed through a stirred mixture of the foregoing ether (**9**) (5.25 g), aqueous formaldehyde (37%, 3.7 ml), zinc chloride (0.5 g), sodium chloride (40 mg), and ether (20 ml) with cooling in an ice–salt bath so that the internal temperature remained below 37 °C. When no further rise in temperature occurred the reaction mixture was set aside for 2 h and then poured into water. The crude product was isolated by extraction with ether and the extract was washed in turn with water, aqueous sodium hydrogen carbonate, and finally saturated brine. The product (**10**) was distilled under reduced pressure and was obtained as an *oil* (5.15 g, 78%), b.p. 80 °C at 0.01 mmHg (Found: C, 56.85; H, 5.95; Cl, 30.45%; M^+, 232/234/236. $C_{11}H_{14}Cl_2O$ requires C, 56.65; H, 6.05; Cl, 30.4%; *M*, 232/234/236); δ(80 MHz) 1.33 (6 H, d, Me_2), 2.14 (3 H, s, Me), 4.49 (1 H, septet, CH), 4.63 (2 H, s, CH_2), and 6.83 and 7.17 (each 1 H, s, ArH).

2-*Chloro*-4-*isopropoxy*-5-*methylbenzyl Acetate* (**11**).—The foregoing chloride (**10**) (4.68 g) and anhydrous sodium acetate (16.4 g) were stirred at room temperature in anhydrous *N,N*-dimethylformamide (35 ml) for 68 h, and then at 90 °C (bath) for 22 h. The usual work up gave the *acetate* (**11**) (5.10 g, 99%) as an oil, b.p. 110 °C at 0.01 mmHg (Kugelrohr) (Found: C, 60.75; H, 6.5; Cl, 13.8%; M^+, 256/258. $C_{13}H_{17}ClO_3$ requires C, 60.8; H, 6.65; Cl, 13.8%; *M* 256/258); δ(80 MHz) 1.33 (6 H, d, Me_2), 2.09 (3 H, s, COMe), 2.15 (3 H, s, Me), 4.49 (1 H, septet,

CH), 5.11 (2 H, s, CH_2), and 6.84 and 7.16 (each 1 H, s, ArH).

2-Chloro-4-isopropoxy-5-methylphenylmethanol (**12**).—The foregoing acetate (**11**) (5.1 g) and sodium hydroxide (3.2 g) were stirred at 0 °C with water (35 ml) and methanol (65 ml) for 30 min. The usual work up gave the alcohol (**12**) (3.9, 92%) as an oil, b.p. 120 °C at 0.01 mmHg (Kugelrohr); δ(80 MHz) 1.33 (6 H, d, Me_2), 1.85 (1 H, br s, OH), 2.15 (3 H, s, Me), 4.48 (1 H, septet, CH), 4.66 (2 H, s, CH_2), and 6.83 and 7.18 (each 1 H, s, ArH); *m/z* 214/216 (M^+).

2-Chloro-4-isopropoxy-5-methylbenzaldehyde (**13**).—The foregoing alcohol (**12**) (5.88 g) was stirred and heated under reflux in benzene (400 ml) with activated manganese dioxide (37 g) in a Dean–Stark apparatus for 1 h. The manganese dioxide was separated by filtration and washed thoroughly with boiling chloroform. Removal of the solvents left the aldehyde as an oil which was distilled under reduced pressure, b.p. 140 °C at 0.01 mmHg (Kugelrohr), and next crystallized from light petroleum whereupon it was obtained as needles (4.66 g, 80%), m.p. 43–45 °C (lit.,[5] 43–45 °C).

2-Chloro-3′,4-di-isopropoxy-2′-methylthiostilbene (**14**).—The chloride (**6**) (2.8 g) was heated under reflux in anhydrous toluene (100 ml) with triphenylphosphine (6.0 g) for 66 h. The solvent was then decanted from the gummy salt (**7**) which was triturated under boiling benzene whereupon it crystallized (5.5 g, 86%) but proved to be too hygroscopic to be isolated by filtration; it was therefore used without delay. A solution of the salt (**7**) (1.40 g) and the aldehyde (**13**) (600 mg) in anhydrous *N*,*N*-dimethylformamide was stirred and heated at 90 °C (bath) under nitrogen during the dropwise addition of lithium methoxide (0.83M) in methanol (3.7 ml) during 10 min. The solution was stirred at 90 °C for 1 h and then poured into water. The crude product was isolated by extraction with ether and purified by radial chromatography with 5% ethyl acetate–light petroleum as eluant. The stilbene (**14**) (710 mg, 68%) was obtained as an oily mixture of isomers; *m/z* 390/392 (M^+). A portion of this mixture (151 mg) was heated under reflux in toluene (10 ml) with a crystal of iodine for 4 days. The crude product was purified by radial chromatography with 5% ethyl acetate–light petroleum as eluant which gave the (*E*)-isomer (130 mg, 86%) as an oil; δ_H(300 MHz) 1.35 and 1.41 (each 6 H, d, Me_2), 2.22 (3 H, s, Me), 2.37 (3 H, s, SMe), 4.51 and 4.62 (each 1 H, septet, CH), 6.83 (1 H, s, 3-H), 7.17–7.39 (3 H, m, 4′-, 5′-, and 6′-H), 7.32 and 7.80 (2 H, AB, *J* 16.2 Hz, olefinic H), and 7.55 (1 H, s, 6-H); λ_{max}(MeOH) 311 nm (log ε 4.29); *m/z* 390/392 (M^+).

2,6-Di-isopropoxy-7-methyl-1-methylthiophenanthrene (**15**).—Clean potassium (380 mg) was added in portions under dry argon to a stirred suspension of anhydrous magnesium chloride (460 mg) and finely ground potassium iodide (400 mg) in boiling anhydrous tetrahydrofuran (15 ml) under an atmosphere of argon. The suspension was boiled and stirred under reflux for 2.5 h when a solution of the foregoing stilbene (**14**) (941.5 mg) in tetrahydrofuran (10 ml) was added to the stirred and heated mixture during 40 min. Stirring and heating under reflux were continued for 19 h, the reaction mixture was cooled to 0 °C, and water was cautiously added dropwise. The crude product was isolated by extraction with ethyl acetate and purified by radial chromatography with 5% ethyl acetate–light petroleum as eluant. The *phenanthrene* (**15**) (236 mg, 28%) crystallized from methanol as needles, m.p. 119 °C (Found: C, 74.45; H, 7.55; S, 8.8%; M^+, 354. $C_{22}H_{26}O_2S$ requires C, 74.55; H, 7.4; S, 9.05%; *M* 354); δ(300 MHz) 1.46 and 1.47 (each 6 H, d, Me_2), 2.38 (3 H, d, $J_{Me,8}$ 0.6 Hz, Me), 2.43 (3 H, s, SMe), 4.80 and 4.82 (each 1 H, septet, CH), 7.30 and 8.51 (2 H, AB, $J_{3,4}$ 9.1 Hz, 3- and 4-H), 7.62 (1 H, s, $w_{\frac{1}{2}}$ 2.7 Hz, 8-H), 7.69 and 8.49 (each 1 H, AB, $J_{9,10}$ 9.1 Hz, 9- and 10-H), and 7.89 (1 H, s, 5-H).

7-Methyl-1-methylthiophenanthrene-2,6-diol (*Micandrol-C*) (**16**).—A solution of boron trichloride (192 mg) in dichloromethane (0.4 ml) was added to a stirred solution of the foregoing phenanthrene (**15**) (83 mg) in dichloromethane (4 ml) at −10 °C and the solution was stirred under argon for 5 h. The usual work up gave the crude product which was purified by radial chromatography with 40% ethyl acetate–light petroleum as eluant. The phenanthrene (**16**) (34 mg 54%) crystallized from benzene as needles, m.p. 157–158 °C (lit.,[2] 151–152 °C) (Found: C, 69.7; H, 5.7; S, 11.2. Calc. for $C_{16}H_{14}O_2$: C, 71.1; H, 5.2; S, 11.85%); δ(300 MHz) 2.31 (3 H, s, SMe), 2.46 (3 H, d, $J_{Me,8}$ 0.6 Hz, Me), 5.13 (1 H, br s, OH), 7.34 and 8.47 (2 H, AB, $J_{3,4}$ 9.0 Hz, 3- and 4-H), 7.41 (1 H, s, OH), 7.64 (1 H, s, $w_{\frac{1}{2}}$ 3 Hz, 8-H), 7.75 and 8.22 (2 H, AB, $J_{9,10}$ 9.2 Hz, 9- and 10-H), and 7.87 (1 H, s, 5-H); irradiation at the frequency of the 4-H caused collapse of the 3-H signal to a singlet, and irradiation at the frequency of the methyl signal sharpened the 8-H signal; λ_{max}(MeOH) 231, 246, 256, 270, 294, 344, and 361 nm (log ε 4.32, 4.34, 4.44, 4.20, 4.07, 3.28, and 3.15 respectively; ν_{max}(KBr) 1 630, 1 594, 1 500, 1 470, 1 420, 1 400, 1 384, 1 260, 1 210, 1 180, 1 140, 1 115, 1 000, 890, and 815 cm^{-1}; *m/z* 271 (19%), 270 (100, M^+), 255 (44), 227 (32), and 165 (25).

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