Synthesis of an Enantiomerically Pure Indolosesquiterpene[1]

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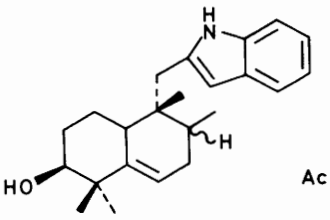
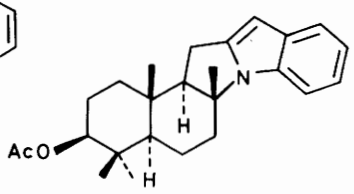
The preparation of a chiral indolosesquiterpene from sclareol is described. The main reaction involves coupling a homosesquiterpene intermediate with *o*-toluidine or its *N*-trimethylsilyl derivative.

The indolosesquiterpene family consists of a small group of new secondary metabolites, which have been isolated from the medicinal African species of *Greenwayodendron*, and are exemplified by neopolyalthenol (**1**),[2] greenwayodendrin-β-yl acetate (**2**),[3] *etc.*[4] The only cited preparation of this class of sesquiterpenes involves the cyclization of 3-ω-epoxyfarnesylindoles.[2]

We have thus embarked on the synthesis of compound (**3**) so as to try to develop a general synthetic route adaptable to compounds (**1**) and (**2**) and other 2-substituted indolosesquiterpenes. The target molecule (**3**) can, on a biogenetic basis, also be visualized as the intermediate carbon skeleton in the biosynthesis of compounds (**1**) and (**2**). Analogous reasoning has been used with respect to the biogenetic precursor of polyalthenol (**4**).[5] The chirality of compound (**3**) is a desirable characteristic, taking into consideration that the absolute configuration of only one member of this class, compound (**5**),[6] has been determined by *X*-ray crystallography.



(**1**)



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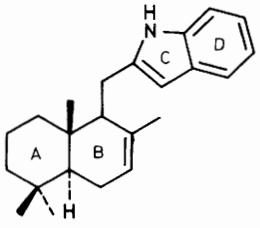
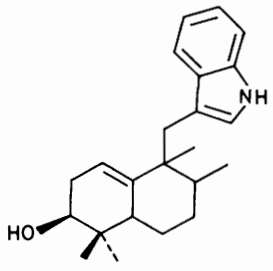
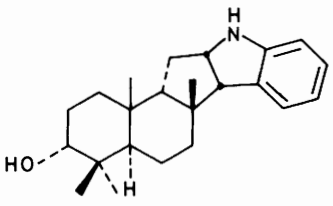


(**3**)

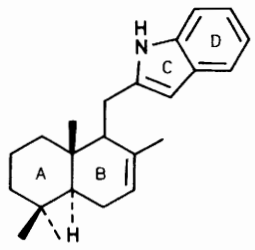


(**4**)



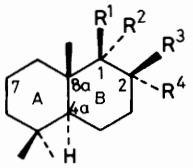
(**5**)

Our first attempts to assemble the tetracyclic nucleus of compound (**3**) took form *via* route a (AB + CD→ABCD). Key compounds in this retrosynthetic analysis were suitably activated chiral derivatives of (**6**). The α,β-unsaturated ketone



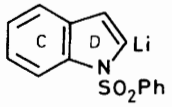
(**3**)

route *a*



(**6**)

+



(**7**)

a; R^1, R^2 = CH_2 ; R^3, R^4 = O
b; R^1 = CH_2OTs ; R^2 = H ; R^3, R^4 = O

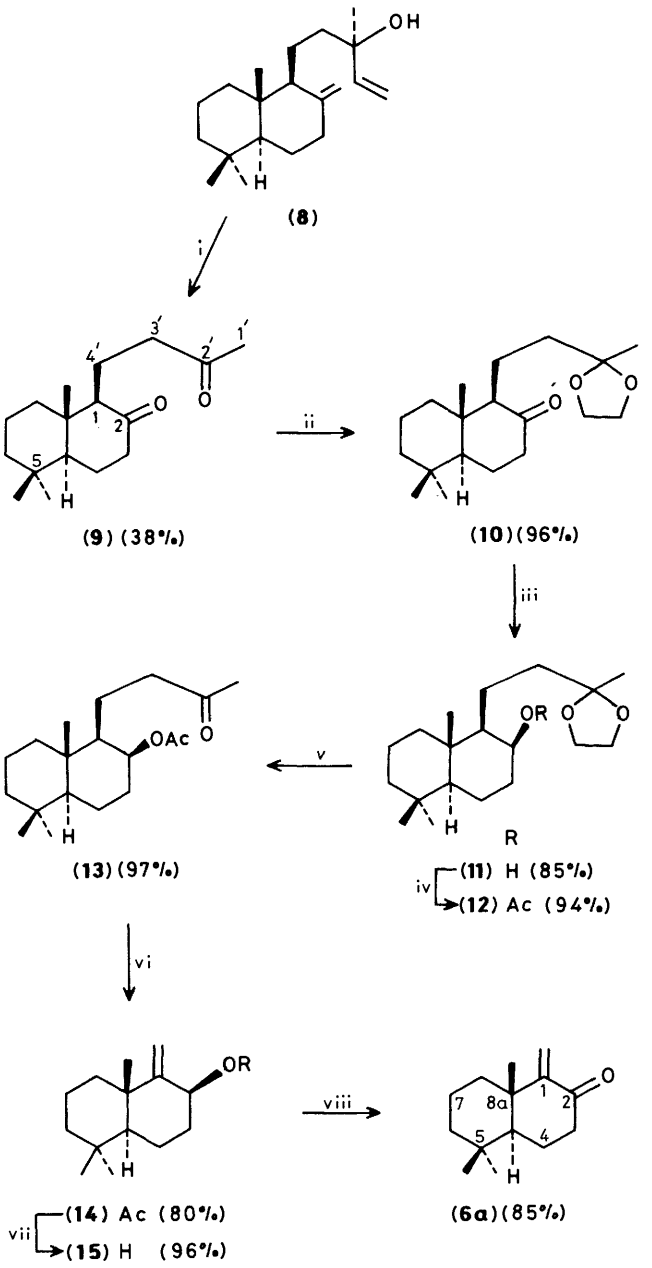
(**6a**) was considered to be an attractive chiron. Our approach to the synthesis of the ketone (**6a**), using manool (**8**) as a chiral template involved the elimination of six carbon atoms (Scheme 1).

The first carbons were easily eliminated by the oxidation of manool (**8**) with $KMnO_4$–$MgSO_4$, which upon work-up furnished the diketone (**9**).[7] Further loss of three carbon atoms were achieved when compound (**13**) underwent a type II photoelimination.[8] For better yields this reaction had to be interrupted after 5 h to recover the unchanged ketone (**13**), which was then recycled. This step had to be repeated several times. The conversion of compound (**14**) into the target molecule was carried out by treating (**14**) with DBU,† followed by oxidation with CrO_3–pyridine, to yield the chiron (**6a**) in 19% overall yield from manool. (**8**).

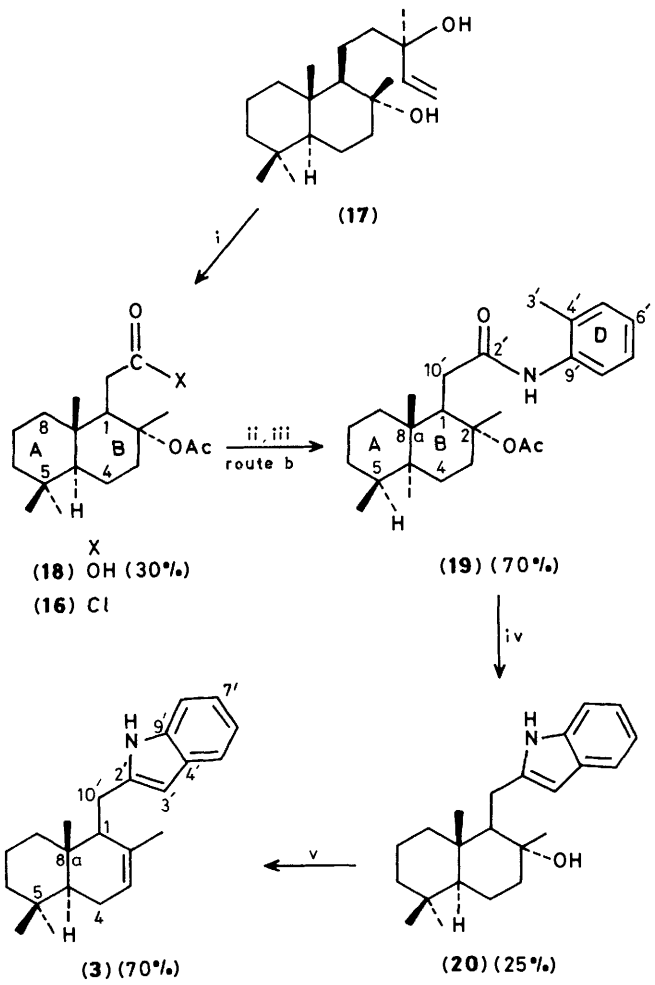
The conjugate addition of the ketone (**6a**) to the indole (**7**) could not be brought about either by the use of mixed organocopper, $R^2Cu(CN)Li_2$,[9] or organozinc, R^2Zn, derivatives[10] of (**7**).

The failure of this strategy could not be associated with the lack of reactivity of (**6a**), since the reaction between the ketone (**6a**) and methyl acetoacetate has been reported.[11] Therefore we decided to test the 2-indolyl anion (**7**) as a nucleophile for a simple Michael reaction with methyl vinyl ketone. The addition product was not detected and the reactivity of (**7**) with α,β-unsaturated ketones was not investigated further. The use of

† The use of DBU as a selective deprotection agent for the acetyl group will be published elsewhere.



Scheme 1. *Reagents and conditions:* i, $KMnO_4$, $MgSO_4$, acetone; ii, $(CH_2OH)_2$, PPTs, C_6H_6; iii, $NaBH_4$, MeOH; iv, Ac_2O, py; v, PPTs, acetone, water; vi, light petroleum, *hv*; vii, MeOH, DBU; viii, CrO_3, py



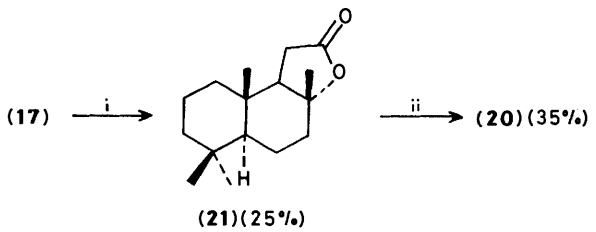
Scheme 2. *Reagents and conditions:* i, $RuCl_3$, $NaIO_4$; ii, $SOCl_2$; iii, *o*-toluidine, PhMe, K_2CO_3; iv, $NaNH_2$, $PhNEt_2$, 150 °C; v, $SnCl_4$, CH_2Cl_2, 0 °C

compounds (**6b**) and (**7**) was considered as an alternative method to form compound (**3**). In order to test this pathway quickly, we used the readily available racemic (**6b**),[11] bearing in mind that enantiomerically pure (**6b**) could be obtained later. Exposure of (**6b**) to the indolyl anion (**7**) did not produce the desired indolosesquiterpene intermediate, probably due to steric hindrance at C-9 of (**6b**).

An alternative strategy bypassing all dependence on C-9 as the reactive site and (**7**) as the nucleophile was visualized as route b (AB + D→ABD→ABCD). The formation of the indole moiety following Madelungs indole approach[12] appeared to be a suitable method to provide 2-substituted indolosesquiterpenes.

Intermediate (**18**) was obtained in one step by the oxidation of sclareol (**17**) with ruthenium chloride and sodium periodate (30%) (Scheme 2). This method provides a better alternative than that previously reported (14% yield).[13] Treatment of compound (**18**) with thionyl chloride followed by work-up and treatment of the crude product with *o*-toluidine gave a crystalline product in 70% yield which showed spectral data consistent with the formation of the amide (**19**). The indole moiety was formed by treating the amide (**19**) with $NaNH_2$.[12] However, attempts to use BuLi instead of $NaNH_2$[14] did not lead to the indolosesquiterpene (**20**).

An alternative synthesis of compound (**20**) was achieved using the homosesquiterpene lactone (**21**) and *N*-trimethylsilyl-*o*-toluidine.[15] Dehydration was accomplished by treating (**20**)



Scheme 3. *Reagents:* i, $RuCl_3$, $NaIO_4$; ii, *N*-trimethylsilyl-*o*-toluidine, BuLi

with $SnCl_4$. Finally, the ease of formation of the indolosesquiterpene described herein points to the the possibility of using this pathway for the synthesis of compounds (**1**) and (**2**).

Experimental

All m.p.s were determined on a Reichert hot stage microscope and are uncorrected. Optical rotations were measured in a Carl Zeiss photoelectric polarimeter. I.r. spectra were run on a Perkin-Elmer 399 B spectrophotometer using thin films or KBr pellets, calibrated with polystyrene (1 601 cm^{-1}). ^1H N.m.r. spectra were determined on a Varian T-60, Bruker AW80, or Varian XL-100 spectrometer using Me_4Si as an internal reference. ^{13}C N.m.r. spectra were measured at 22.5 MHz on a Varian XL-100 instrument in $CHCl_3$ or CCl_4 solutions and the chemical shifts (δ) are reported using the 77.2 or 96.0 p.p.m. resonance of chloroform or carbon tetrachloride, respectively, as internal reference. Low resolution mass spectra were obtained with a Varian MAT 311A.

(−)-(4aS,8aS)-1-*Methylene*-5,5,8a-*trimethyldecahydronaphthalen*-2-*one* (**6a**).—Small portions of a mixture of potassium permanganate (15.9 g) and magnesium sulphate (13.8 g) were added to a solution of manool (**8**) $[\alpha]_D$ +32.0° (*c* 1.2 in $CHCl_3$) (4.4 g, 15 mmol) in acetone (800 ml) over 9 h. The mixture was stirred at room temperature for 12 h, filtered through a Celite pad, and concentrated under reduced pressure. Chromatography on silica gel with hexane–diethyl ether gradient as eluant yielded the diketone (**9**) (1.5 g, 38%) as an oil; $[\alpha]_D^{25}$ −8.0° (*c* 1.0 in $CHCl_3$) (lit.,[7] −11.0°); $\nu_{max.}$(film) 1 710 cm^{-1} (C=O); δ_H(60 MHz; CCl_4) 0.72 (3 H, s, 8a-Me), 0.86 (3 H, s, 5-Me_{ax}), 0.96 (3 H, s, 5-Me_{aq}), and 2.03 (3 H, s, 2′-Me).

Product (**9**) (1.6 g, 6.0 mmol) was refluxed with ethylene glycol (400 mg, 6.4 mmol) and pyridinium toluene-*p*-sulphonate (PPTs) (150.0 mg, 0.6 mmol) in dry benzene (50 ml) in a Dean and Stark apparatus for 5 h. The solution was washed with aqueous sodium hydrogen carbonate (5%), water, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography on silica gel with hexane–diethyl ether (49:1) as eluant yielded the pure ketone (**10**) (1.67 g, 95%); $[\alpha]_D^{25}$ −24.0° (*c* 1.0 in $CHCl_3$); $\nu_{max.}$(film) 1 705 cm^{-1} (C=O); δ_H(60 MHz; CCl_4) 0.70 (3 H, s, 8a-Me), 0.85 (3 H, s, 5-Me_{ax}), 0.97 (3 H, s, 5-Me_{eq}), 1.23 (3 H, s, 2′-Me), and 3.80 [4 H, s, $C(OCH_2)_2$]; *m/z* 308 ($M^{+\bullet}$, 14%), 264 (40), 248 (100), and 137 (30).

Compound (**10**) (1.5 g, 5.0 mmol) in methanol at 0 °C was treated with small portions of sodium borohydride (250.0 mg). The mixture was then stirred for 10 h after which it was poured into cold water (50 ml) and extracted with diethyl ether (3 × 30 ml). The organic layer was washed with water, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography on silica gel with hexane–diethyl ether gradient as eluant yielded the pure alcohol (**11**) (1.1 g, 85%); $\nu_{max.}$(KBr) 3 500 cm^{-1} (OH); δ_H(60 MHz; CCl_4) 0.87 (6 H, s, 5-Me), 0.98 (3 H, s, 8a-Me), 1.23 (3 H, s, 2′-Me), and 3.86 [4 H, br s, $C(OCH_2)_2$].

Compound (**11**) (1.1 g, 3.5 mmol) in pyridine (1.5 ml) was treated with a mixture of acetic anhydride (1.5 ml) and pyridine (1.5 ml) and stirred at room temperature for 72 h. The mixture was then poured into cold water. The organic layer was washed with HCl (1%; 50 ml), water, dried ($MgSO_4$), and concentrated under reduced pressure to yield the pure 2-acetoxy compound (**12**) (1.2 g, 94%) as an oil (Found: C, 71.4; H, 10.1. $C_{20}H_{34}O_4$ requires C, 70.97; H, 10.12%); $[\alpha]_D^{25}$ +32.0° (*c* 1.0 in $CHCl_3$); $\nu_{max.}$(KBr) 1 740 (OAc) and 1 030 cm^{-1} (O–C); δ_H(60 MHz; CCl_4) 0.86 (6 H, s, 5- and 2-Me), 0.95 (3 H, s, 8a-Me), 1.22 (3 H, s, 2′-Me), 1.98 (3 H, s, AcO), 3.83 [4 H, s, $C(OCH_2)_2$], and 5.06 (1 H, m, C*H*OAc).

Compound (**12**) (1.2 g, 3.3 mmol) in water (3 drops) and acetone (30 ml) was treated with pyridinium toluene-*p*-sulphonate (150.0 mg, 0.6 mmol) and refluxed for 3 h. The solvent was evaporated and the residue treated with diethyl ether and water. The organic layer was dried with Na_2SO_4 and evaporated under reduced pressure to give the pure ketone (**13**) (1.0 g, 97%) as an oil (Found: C, 73.7; H, 10.4. $C_{19}H_{32}O_3$ requires C, 73.98; H, 10.46%); $[\alpha]_D^{25}$ +49.0° (*c* 0.7 in $CHCl_3$); $\nu_{max.}$(film) 1 735 (O=C–O) and 1 720 cm^{-1} (C=O); δ_H(60 MHz; CCl_4) 0.90 (6 H, s, 5- and 2-Me), 0.98 (3 H, s, 8a-Me), 2.00 (3 H, s, OAc), 2.06 (3 H, s, Ac), and 5.05 (1 H, m, C*H*OAc).

Product (**13**) (1.0 g, 3.4 mmol) in pentane (100 ml) was irradiated with a medium pressure mercury lamp (125 W) under argon in a quartz apparatus. The temperature of the solution was kept between 0 and 10 °C. The reaction was monitored by t.l.c. and was interrupted when 20% of the substrate was transformed. The solvent was evaporated under reduced pressure and chromatography on silica gel with hexane–diethyl ether gradient as eluant yielded unchanged compound (**13**) (800 mg) and the pure 1-methylene compound (**14**) (129.0 mg, 80% based on the reaction starting material); $[\alpha]_D^{25}$ −29.0° (*c* 1.6 in $CHCl_3$); $\nu_{max.}$(KBr) 1 740 (O=C–O), 1 635 (C=C), and 1 030 cm^{-1} (O–C); δ_H(100 MHz; CCl_4) 0.90 (6 H, s, 5- and 2-Me), 1.13 (3 H, s, 8a-Me), 1.96 (3 H, s, AcO), 4.83 (1 H, d, *J* 1 Hz, C=CH_2), 4.95 (1 H, d, *J* 1 Hz, C=CH_2), and 5.28 (1 H, m, C*H*OAc); *m/z* 250 ($M^{+\bullet}$, 4%), 190 (99), and 174 (100).

Product (**14**) (70.0 mg, 0.3 mmol) in methanol (10 ml) and DBU (700 mg) was stirred at room temperature for 16 h. The solvent was removed under reduced pressure and chromatography on silica gel with hexane–diethyl ether gradient as eluant yielded the pure alcohol (**15**) as an oil (56.0 mg, 96%); $[\alpha]_D^{25}$ −21.0° (*c* 0.8 in $CHCl_3$); $\nu_{max.}$(KBr) 3 400 (OH) and 1 630 cm^{-1} (C=C); δ_H(60 MHz; CCl_4) 0.90 (6 H, s, 5- and 2-Me), 1.23 (3 H, s, 8a-Me), 4.22 (1 H, m, C*H*OH), and 4.72 (2 H, m, C=CH_2); *m/z* 208 ($M^{+\bullet}$, 41%), 191 (29), 189 (60), 175 (65), 125 (88), and 123 (100).

Product (**15**) (40.0 mg, 0.2 mmol) in pyridine (1 ml) was treated with CrO_3 (17.0 mg). The mixture was stirred at room temperature for 3 h, dissolved in ether, and filtered on a SiO_2 pad. The solution was then washed with HCl (1%), water, dried ($MgSO_4$), and evaporated under reduced pressure to yield the pure *title compound* (**6a**) (33.0 mg, 85%) which crystallized from benzene, m.p. 54.0—55.5 °C; $[\alpha]_D^{25}$ −52.0° (*c* 0.8 in $CHCl_3$), lit.,[16] −69.6°; $\nu_{max.}$(KBr) 1 720 and 1 690 cm^{-1} (αβ unsat. C=O); δ_H(100 MHz; CCl_4) lit.,[11,16] 0.94 (3 H, s, 5-Me_{ax}), 0.98 (3 H, s, 5-Me_{eq}), 1.04 (3 H, s, 8a-Me), 5.04 (1 H, d, *J* 1 Hz, C=CH_2), and 5.58 (1 H, d, *J* 1 Hz, C=CH_2); *m/z* 206 ($M^{+\bullet}$, 71%) 191 (47), 163 (58), 135 (60), and 122 (100).

(−)-(1R,4aS,8aS)-1-(1H-*Indol*-2-*ylmethyl*)-2,5,5,8a-*tetramethyl*-1,4,4a,5,6,7,8,8a-*octahydronaphthalene* (**3**).—Sclareol (**17**) {$[\alpha]_D^{25}$ −5.5° (*c* 1.3 in $CHCl_3$), lit.,[17] −5.0°}; (2.2 g, 7.2 mmol) in carbon tetrachloride (15 ml), acetonitrile (15 ml), and water (20 ml) was treated with a mixture of sodium periodate (10.0 g, 50.0 mmol) and ruthenium(III) chloride trihydrate (150 mg). The mixture was stirred at room temperature for 4 h and then dissolved in dichloromethane. The organic layer was washed with water, aqueous sodium thiosulphate (5%), water, dried (Na_2SO_4), and concentrated under reduced pressure. Chromatography on silica gel with hexane–diethyl ether gradient as eluant yielded the pure lactone (**21**) (443 mg, 25%), m.p. 123—125 °C (lit.,[13] 123—124 °C); $\nu_{max.}$(KBr) 1 770 cm^{-1} (*C*OOR); δ_H(80 MHz; CCl_4) 0.82, 0.86 (6 H, 2 s, 5- and 2-Me), 0.90 (3 H, s, 8a-Me), and 1.30 (3 H, s, 2-Me); *m/z* 235 ($M^{+\bullet}$, 75%), 206 (60), and 123 (100), followed by the pure acid (**18**) (690.0 mg, 30%), m.p. 156—158 °C (lit.,[13] 155—157 °C); $[\alpha]_D^{25}$ −23.4° (*c* 3.7 in $CHCl_3$); $\nu_{max.}$(KBr) 3 500—2 540 (*C*O*O*H), 1 730 (*C*OOR), and 1 700 cm^{-1} (*C*OOH); δ_H(60 MHz; $CDCl_3$) 0.83 (3 H, s, 8a-Me_{ax}), 0.86 (3 H, s, 5-Me_{ax}), 0.90 (3 H, s, 5-Me_{eq}), 1.53 (3 H, s, 2-Me), 1.88 (3 H, s, Ac), and 2.35 (2 H, m, CH_2C=O).

Product (**18**) (1.0 g, 3.3 mmol) in anhydrous diethyl ether (15 ml), pyridine (0.5 ml), and thionyl chloride (3 ml) was stirred for 2 h at 0 °C. The solvents and reagents were removed under reduced pressure without heating. The residue was dissolved in toluene and treated with anhydrous potassium carbonate (469.0

mg, 34 mmol) and *o*-toluidine (500.0 mg, 4.6 mmol). The reaction was stirred at 0 °C for 2 h and then poured into cold water and extracted with diethyl ether. The organic layer was washed with water, dried (Na_2SO_4), and concentrated under reduced pressure. Recrystallization (hexane–dichloromethane) gave compound (**19**) (950 mg, 70%), m.p. 184—186 °C (Found: C, 74.1; H, 9.3; N, 3.8. $C_{25}H_{37}NO_3$ requires C, 75.15; H, 9.33; N, 3.51%); $[\alpha]_D^{25}$ +14.0° (*c* 1.0 in $CHCl_3$); $\lambda_{max.}$(EtOH) 233.4 nm (log ε 2.98); $\nu_{max.}$(KBr) 3 260 (NH), 1 735 (*COOR*), 1 665 cm^{-1} (O=C–NH); δ_H(100 MHz; $CDCl_3$) 0.80 (3 H, s, 5-Me), 0.90 (6 H, s, 5- and 8a-Me), 1.52 (3 H, s, 2-Me), 1.90 (3 H, s, AcO), 2.32 (3 H, s, MePh), 2.46 (2 H, br s, CH_2CONHR), 6.92—7.34 (4 H, m, ArH), and 7.86 (1 H, m, CONHR); δ_C(25.2 MHz; $CHCl_3$) 171.8 (s, C=O), 169.9 (s, CON), 135.8 (s, C-9′), 130.2 (d, C-5′), 128.8 (s, C-4′), 126.4 (d, C-7′), 124.7 (d, C-6′), 123.1 (d, C-8′), 86.9 (s, C-2), 55.3 (s, C-4a; d, C-1), 41.5 (t, C-6), 39.0 (t, C-8), 38.6 (t, C-3), 33.6 (t, C-9), 33.2 (s, C-5), 33.0 (q, 5-Me_{eq}), 22.8 (q, 2-Me), 21.4 (q, 5-Me_{ax}), 20.4 (t, C-4), 19.8 (q, C-3′), 18.2 (t, C-7), 17.8 (q, *Me*C=O), and 15.7 p.p.m. (q, 8a-Me); *m/z* 399 ($M^{+\bullet}$, 7%) and 107 (100).

Product (**19**) (250.0 mg, 0.6 mmol) in diethylaniline (5 ml) was treated with sodium amide (150 mg, 3.8 mmol) under argon. The reaction was stirred at 150 °C for 1 h, after which it was poured into cold water (0 °C) (50 ml). The mixture was extracted with diethyl ether, washed with HCl (5%), water, dried (Na_2SO_4), and concentrated under reduced pressure. After column chromatography (SiO_2, hexane–diethyl ether gradient) the pure alcohol (**20**) (53 mg, 25%) was obtained: m.p. 226—227 °C (hexane–dichloromethane) (Found: C, 81.1; H, 9.7; N, 4.3. $C_{23}H_{33}NO$ requires C, 81.37; H, 9.80; N, 4.13%); $[\alpha]_D^{25}$ −44.0° (*c* 1.3 in $CHCl_3$); $\lambda_{max.}$(EtOH) 218.3 (log ε 4.39) and 271.3 nm (2.83); $\nu_{max.}$(KBr) 3 540 (OH) and 3 300 cm^{-1} (NH); δ_H(100 MHz; $CDCl_3$) 0.80 (3 H, s, 8a-Me), 0.84 (3 H, s, 5-Me_{ax}), 0.90 (3 H, s, 5-Me_{eq}), 1.34 (3 H, s, 2-Me), 2.80 (2 H, m, 10′-H), 6.18 (1 H, m, 3′-H), 7.02—7.60 (4 H, m, ArH), and 9.02 (1 H, m, NH); δ_C(25.2 MHz; $CHCl_3$) 142.2 (s, C-2′), 135.1 (s, C-9′), 127.8 (s, C-4′), 119.0 (d, C-7′), 118.3 (d, C-6′), 117.8 (d, C-5′), 109.5 (d, C-8′), 97.5 (d, C-3′), 71.9 (s, C-2), 60.7 (d, C-1), 55.3 (d, C-4a), 43.4 (t, C-3), 40.9 (t, C-6), 38.5 (t, C-8), 32.6 (q, 5-Me_{eq}), 32.2 (s, C-5), 23.1 (t, C-10′), 23.1 (q, 2-Me), 20.7 (q, 5-Me), 19.7 (t, C-4), 17.4 (t, C-7), and 14.5 p.p.m. (q, 8a-Me); *m/z* 339 ($M^{+\bullet}$, 15%), 322 (13), 307 (5), and 130 (100).

Product (**20**) (15 mg, 0.05 mmol) in dichloromethane and water (5 ml) was treated with $SnCl_4$ (130.0 mg, 0.5 mmol) at 0 °C under argon. The mixture was stirred at 0 °C for 5 min and then poured into ice–water (10 ml). The organic layer was washed with water, dried (Na_2SO_4), and concentrated under reduced pressure. Chromatography on silica gel (SiO_2, hexane–diethyl ether gradient) yielded the pure *title compound* (**3**) (10 mg, 70%), m.p. 172 °C (hexane) (Found: C, 85.6; H, 9.6; N, 4.3. $C_{23}H_{31}N$ requires C, 85.92; H, 9.72; N, 4.36%); $[\alpha]_D^{25}$ −13.3° (*c* 0.6 in $CHCl_3$); $\lambda_{max.}$(EtOH) 220.6 (log ε 3.95), 270.9 nm (2.93); $\nu_{max.}$(KBr) 3 415 cm^{-1} (NH); δ_H(100 MHz; $CDCl_3$) 0.87 (3 H, s, 8a-Me_{ax}), 0.89 (3 H, s, 5a-Me_{ax}), 0.92 (3 H, s, 5-Me_{eq}), 1.59 (3 H, s, 2-Me), 5.47 (1 H, m, 3-H), 6.30 (1 H, m, 3′-H), 7.05—7.69 (4 H, m, ArH), and 7.92 (1 H, m, NH); δ_C(25.2 MHz; $CDCl_3$) 141.1 (s, C-2′), 134.6 (s, C-2), 134.4 (s, C-9′), 128.8 (s, C-4′), 122.8 (s, C-3), 120.7 (d, C-7′), 119.5 (d, C-6′), 110.1 (d, C-8′), 99.9 (d, C-3′), 54.3 (d, C-1), 50.2 (d, C-4a), 42.3 (t, C-6), 39.7 (t, C-8), 36.7 (s, C-8a), 33.3 (q, 5-Me), 33.1 (s, C-5), 26.2 (t, C-4), 23.8 (t, C-10′), 22.3 (q, 2-Me), 21.9 (q, 5-Me), 18.9 (t, C-7), and 13.8 p.p.m. (q, 8a-Me); *m/z* 321 ($M^{+\bullet}$, 21%), 191 (7), and 130 (100).

BuLi (2.4 ml, 2.5M in hexane) was added to *N*-trimethylsilyl-*o*-toluidine (477.7 mg, 2.66 mmol) in dry hexane (19 ml). The resultant pale yellow solution was heated under reflux for 6.5 h, cooled to −78 °C, and the lactone (**21**) (593.7 mg, 2.37 mmol) in dry THF added *via* a cannula. The mixture was allowed to warm to room temperature, quenched with brine, and extracted with diethyl ether (3 × 50 ml). The combined ethereal fractions were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography on silica gel with hexane–diethyl ether gradient as eluant yielded the pure alcohol (**20**) (256.85 mg, 32%).

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