Total Synthesis of (−)-Kopsinilam, (−)-Kopsinine, and the Bis-indole Alkaloids (−)-Norpleiomutine and (−)-Pleiomutine

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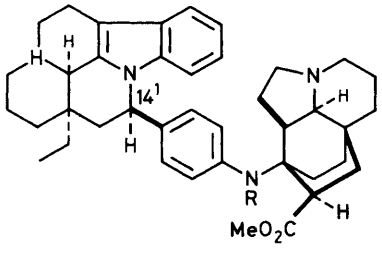
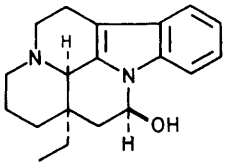
The racemic tetracyclic amine (**5**) was resolved and converted into (−)-kopsinine (**16**); subsequent coupling to (−)-eburnamine (**2**) gave (−)-norpleiomutine (**4**).

In 1966 Schmid, Hesse, and Biemann[1] reported the isolation of (−)-pleiomutine (**1**) from *Pleiocarpa mutica* Benth. Its structure was established through chemical degradation, high resolution mass spectroscopy, and by partial synthesis from (−)-eburnamine (**2**), and (−)-pleiocarpinine (**3**). Here we report the total synthesis of (−)-norpleiomutine (**4**), which has been converted into (−)-pleiomutine (**1**) using a modified Eschweiler–Clark *N*-methylation procedure.[2] It should be noted that bis-indole alkaloids have been synthesized where both components are achiral; one component is chiral, the other achiral; and both are chiral, but identical. The only syntheses of unsymmetrical chiral bis-indole alkaloids, such as vinblastine, or the alstonia alkaloids, are partial syntheses from the naturally occurring (or slightly modified) monomeric components. There is no reported total synthesis of an unsymmetrical chiral bis-indole alkaloid where both parts are completely synthetic.[3]

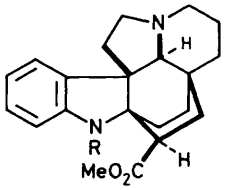
The racemic tetracyclic amine (**5**) was coupled to (*R*)-(+)-*p*-tolylsuphinylacetic acid using the modified carbodi-imide reagent 1-cyclohexyl-3-(2-morpholinoethyl)carbodi-imide metho-*p*-toluene sulphonate[4] to give the readily separated diastereoisomers (**6a**) and (**6b**) (47% of each).[5] The diastereoisomer (**6a**) was treated with trifluoroacetic anhydride (TFAA)–CH_2Cl_2, 0 °C, then heated to 130 °C (in PhCl) to



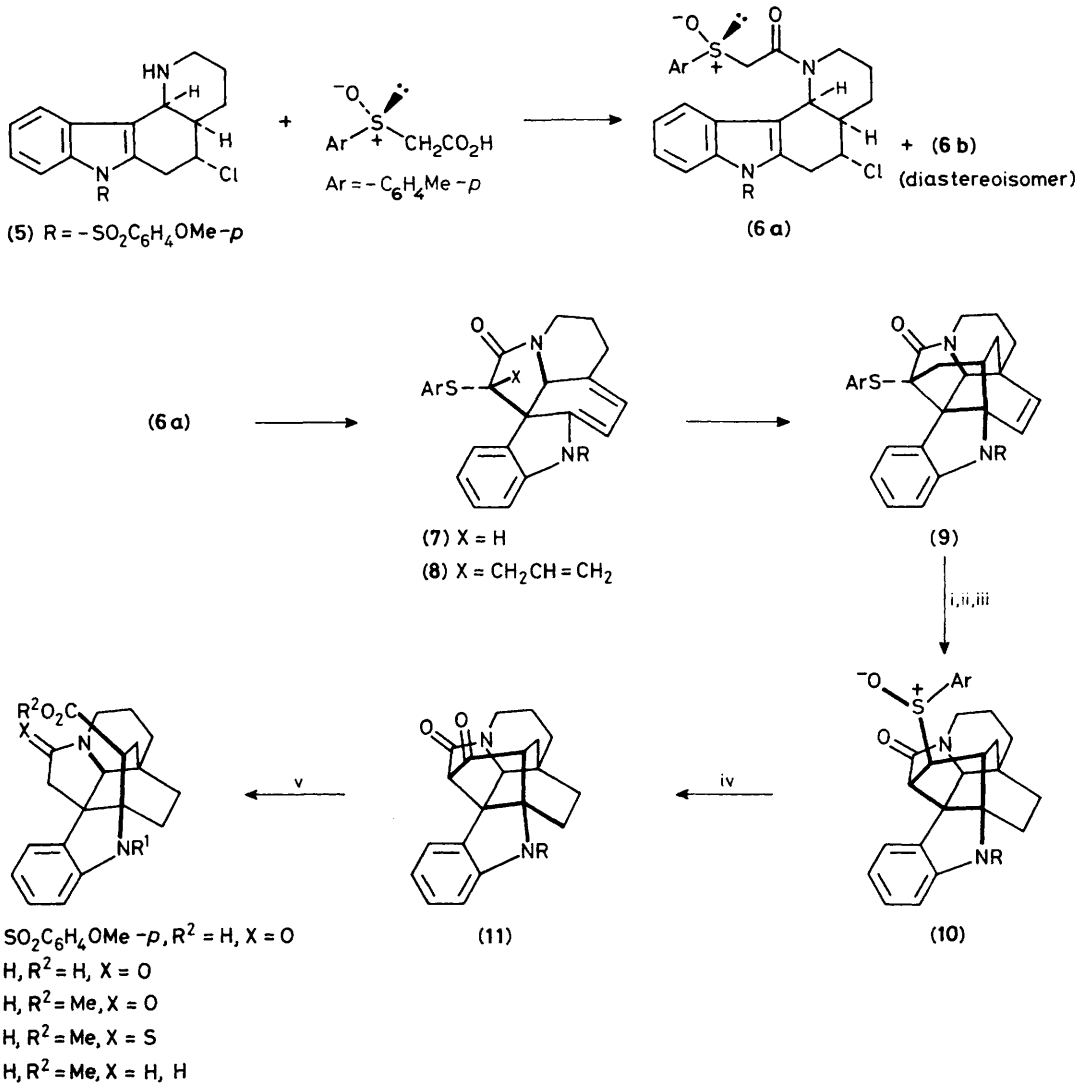
(**1**) R = Me
(**4**) R = H



(**2**) β-OH isomer



(**3**) R = Me
(**16**) R = H



Reagents and conditions: i, HN=NH; ii, *m*-chloroperbenzoic acid; iii, 240 °C; iv, TFAA; v, KOH.

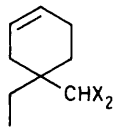
give the homoannular diene (**7**) (69%). Its absolute configuration was assigned using the Weiss homoannular diene rule,[6] and subsequently confirmed by a single crystal *X*-ray structure determination on (**10**).† The diene (**7**) was converted into (**8**) (81%) by treatment with $KN(SiMe_3)_2$–allyl bromide, 0 °C, and heated at 100 °C for 4 h to give (**9**) (73%), n.m.r. (360 MHz) δ 6.05 (2H, AB, *J* 8.3 Hz), 4.21 (1H, dd, *J* 3.8 and 13.4 Hz), 3.90(3H,s), 3.37(1H,s), 3.09(1H, d, *J* 5.0 Hz), and 2.89(1H, dt, *J* 4.3 and 12.3 Hz); $[\alpha]_D^{25}$ + 111.8° (*c* 15.4, in $CHCl_3$). Proceeding through the sequence (**9**) and (**10**) using the chemistry developed previously[5] we arrived at (**11**), m.p. 257—258 °C (MeOH), $[\alpha]_D^{25}$ + 61.4° (*c* 5, in $CHCl_3$).

† *Crystal data* for (**10**): $C_{34}H_{34}N_2O_5S_2$, *M* = 614.77, orthorhombic, space group $P2_12_12_1$, *a* = 16.427(10), *b* = 18.194(12), *c* = 9.675(4) Å, *U* = 2891 Å^3, D_c = 1.412 g cm^{-3}, *Z* = 4. *R* = 0.0575, R_w = 0.0590 for 2904 independent reflections, $6 < 2\theta < 50°$. The absolute configuration of (**10**) was determined by the largest Bijvoet differences, and the enantiomer depicted is correct.

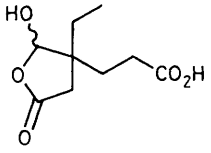
The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Rd., Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

Treatment of (**11**) with KOH–MeOH, 20 °C, cleaved the non-enolisable β-ketoamide functionality resulting in the acid (**12**) (96%). Removal of the *p*-methoxyphenylsulphonyl group in (**12**) was achieved by Li–NH_3, −78 °C reduction, and the resulting acid-amine (**13**) esterified with MeOH–HCl to give kopsinilam (**14**);[7] n.m.r. (360 MHz) δ 7.05(2H, m), 6.80(1H, t, *J* 7.4 Hz), 6.73(1H, d, *J* 7.6 Hz), 4.30(1H, dd, *J* 4.5 and 13.3 Hz), 3.77(3H, s), 3.61(1H, s), 3.40(1H, part of AB system, *J* 18.6 Hz), 2.99(1H, t, *J* 9.8 Hz), 2.77(1H, dd, *J* 2.5 and 12.7 Hz), 2.35(2H, m), 2.02(1H, part of AB system, *J* 18.6 Hz), and 2.00—1.20(10H, m). The amide carbonyl in (**14**) was reduced by conversion into the thioamide using Lawesson's reagent,[8] followed by Raney nickel desulphurisation to give (−)-kopsinine (**16**) (67%), $[\alpha]_D^{21}$ −43.1° (*c* 1.8, in $CHCl_3$), lit.[9] $[\alpha]_D$ −69.0 ±3° (c 0.856, in $CHCl_3$), n.m.r. (360 MHz) δ 7.47(1H, dd, *J* 1.3 and 5.7 Hz), 7.23(1H,d), 6.99(1H,t), 6.75(1H,t), 6.66(1H,d, *J* 7.3 Hz), 6.21(1H,dd, *J* 2.0 and 5.8 Hz), 5.15(1H,m), 4.00(1H, a part of ABX system, J_{AB} 12.2, J_{AX} 3.8 Hz), 3.79(1H, J_{AB} 12.2, J_{BX} 5.1 Hz), 3.76(3H,s), 3.37(1H,q), 3.2—2.60(5H,m), and 2.00—1.10(8H,m).

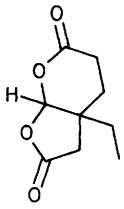
The second component needed for the synthesis of (−)-norpleiomutine (**4**) is (−)-eburnamine (**2**). A modified version of the Taylor synthesis[10] was used to synthesise (**2**). The



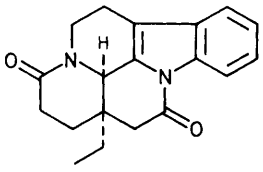
(17) X = OMe



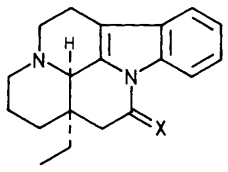
(18)



(19)



(20)



(21) X = H, OH

(22) X = O

Diels–Alder adduct (**17**)‡ was exposed to the Starks[11] phase-transfer oxidation conditions ($KMnO_4$–H_2O–tri-n-decylmethylammonium chloride–benzene) followed by 2 M HCl to give a mixture of the lactol (**18**) and lactone (**19**) (58% overall). Heating a mixture of (**18**) and (**19**) and tryptamine in acetic acid at 100 °C, followed by polyphosphoric acid at 110 °C gave (±)-eburnamonine lactam (**20**) (27%), m.p. 210—211 °C. Reduction of (**20**) ($LiAlH_4$–Et_2O) gave (±)-eburnamine (**21**), which directly oxidized (CrO_3–pyridine) to (±)-eburnamonine (**22**). Resolution of (**22**) using the Szántay procedure[12] [(+)-di-*O*-benzoyltartaric acid monohydrate in MeOH, followed by liberation of the free base with 1 M NaOH] gave (+)-eburnamonine (**22**), $[\alpha]_D^{24}$ + 94.9° (*c* 3.5, in $CHCl_3$).[12] Reduction of (+)-eburnamonine with $LiAlH_4$ in tetrahydrofuran (THF) gave (−)-eburnamine (**2**) and (+)-epi-eburnamine (**2**) (α-OH isomer). When a mixture of (−)-kopsinine (**16**) and (−)-eburnamine (**2**) (and its α-OH isomer) in 2% aqueous HCl was heated at reflux for 7 h, (−)-norpleiomutine (**4**) (16.5%) was obtained {$[\alpha]_D^{19}$ −65.5° (*c* 0.7, in $CHCl_3$), lit.[2] $[\alpha]_D$ −65° (*c* 0.5, in $CHCl_3$), compared with an authentic sample, ^{1}H n.m.r. (360 MHz), t.l.c., i.r.}. The configuration depicted at C-14[1] is based upon the ABX system at δ 4.95, *J* 12 and 5 Hz. Since (−)-norpleiomutine (**4**) has been previously converted into (−)-pleiomutine (**1**), this completes the total synthesis.§

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Added in proof: Recently (+)-kopsoffine has been isolated and differs from (**1**) in that it is antipodal in the eburnamine position, X. Z. Feng, C. Kan, H. P. Husson, P. Potict, S. K. Kan, and M. Lounasmaa, *J. Nat. Prod.*, 1984, **47**, 117.

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‡ The compound (**17**) was made from 2-ethylacrolein–buta-1,3-diene–$AlCl_3$, and the resulting aldehyde converted by standard methods into its dimethoxyacetal (**17**).

§ All new compounds gave satisfactory i.r., n.m.r., and mass spectral and/or microanalytical data in agreement with the assigned structures. All structures, where relevant, are written in their correct absolute configuration.