Total synthesis and establishment of the absolute stereochemistry of (+)-mostueine. Addition of chiral nucleophiles to 3,4-dihydro-2-methyl-9-(*p*-toluenesulfonyl)-β-carbolinium iodide[1]

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A highly convergent synthesis of the pentacyclic indole alkaloid (+)-mostueine (**1**) is described. The key step involved the coupling of the dianion derived from (1′*S*)-3-(1′-hydroxyethyl)-4-methylpyridine (**4**) with the iminium salt 3,4-dihydro-2-methyl-9-(*p*-toluenesulfonyl)-β-carbolinium iodide (**3**). Low asymmetric induction (15% de) at the C-1 position of the β-carboline ring system (C-3 of mostueine) was obtained. The nonfermenting baker's yeast-mediated reduction of 3-acetyl-4-methylpyridine provided the hydroxyethylpyridine component in acceptable yield (67%) and high optical purity (99.0% ee). This synthesis of **1** has established that the absolute stereochemistry of mostueine is (3*S*,19*R*).

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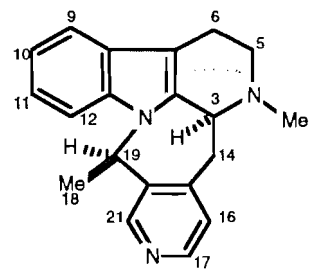
On décrit une synthèse hautement convergente de l'alcaloïde indolique pentacyclique (+)-mostuéine (**1**). L'étape clé implique le couplage du dianion dérivé de la (1′*S*)-3-(1′-hydroxyéthyl)-4-méthylpyridine (**4**) avec le sel iminium (**3**), l'iodure de 3,4-dihydro-2-méthyl-9-(*p*-toluènesulfonyl)-β-carbolinium. On a obtenu une faible induction asymétrique (15% de) à la position C-1 du système cyclique β-carboline (C-3 de la mostuéine). La réduction de la 3-acétyl-4-méthylpyridine, sous l'influence de la levure pâtissière qui ne fermente pas, fournit la portion hydroxyéthylpyridine avec un rendement acceptable (67%) et une grande pureté optique (99,0% ee). Cette synthèse du composé **1** a établi que la stéréochimie absolue de la mostuéine est (3*S*,19*R*).

[Traduit par la rédaction]

Introduction

The structurally interesting pentacyclic indole alkaloid mostueine (**1**) (also referred to as 3,14-dihydrodecussine) is composed of a β-carboline skeleton possessing an azepino ring attached to a pyridine ring. Mostueine, a weak muscle relaxant, was originally isolated from the leaves of *Mostuea brunonis* (2). It has also been found to be a constituent in the root and stem bark of *Strychnos decussata, S. dale, S. elaecarpa* (3) and, most recently, *S. johnsonii* (4). The pharmacologically more active compound decussine (**2**) is identical with mostueine except for a site of unsaturation at C-3—C-14. It is noteworthy that mostueine has been reported to be converted into decussine (3, 5) on storage (3).



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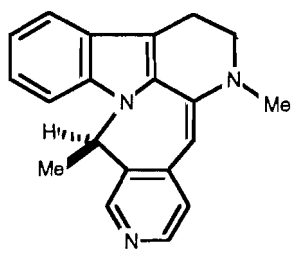

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The total synthesis of (±)-mostueine was accomplished by McGee *et al.* (6) and by Onanga and Khuong-Huu (7), and their combined studies have established the relative configuration at C-3 and C-19 to be 3*SR*,19*RS*. These syntheses are strategically similar in that they both rely upon the alkylation of the indole nitrogen to close the azepino ring as the last step. Herein we report another more convergent and enantioselective synthesis of mostueine.

The addition of nucleophiles to iminium salt electrophiles has been effectively exploited by us and others for the synthesis of a variety of alkaloids (8). It became apparent that this reaction may permit an efficient synthesis of mostueine as shown retrosynthetically in Scheme 1. Furthermore, this strategy would establish the absolute stereochemistry at C-3. Another more general and synthetically interesting question was the extent of asymmetric induction at the C-1 position of the β-carboline ring system (C-3 of mostueine) upon addition of the chiral nucleophile **4**. In any event, the diastereomeric-adduct mixture should be readily resolvable by chromatography, thereby providing an enantioselective route to mostueine.

Results and discussion

Synthesis of **4**

The synthesis of (1′*S*)-3-(1′-hydroxyethyl)-4-methylpyridine (**4**) is outlined in Scheme 2. The starting material, 3-cyano-4-methylpyridine (**6**), was prepared in gram quantities using the 3-step procedure developed by Bobbitt and Scola (9). The conversion of **6** into 3-acetyl-4-methylpyridine (**8**) was originally accomplished by Webb and Corwin (10). However, this transformation necessitated 3 steps and the overall yield was 30%. Another higher-yielding but longer sequence involved conversion of **6** into 4-methylnicotinaldehyde (3 steps, 71% yield) (10, 11). This aldehyde was then converted into the desired methyl ketone **8** by way of its trimethysilylcyanohydrin derivative in 63% yield (12). In

[1]A preliminary account of a part of this work has appeared (1).
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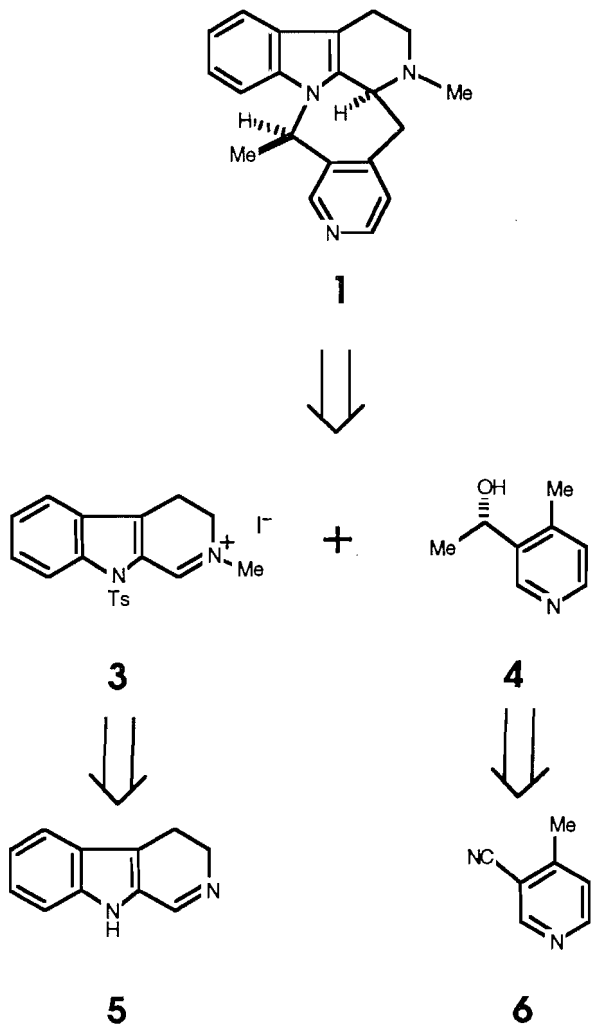
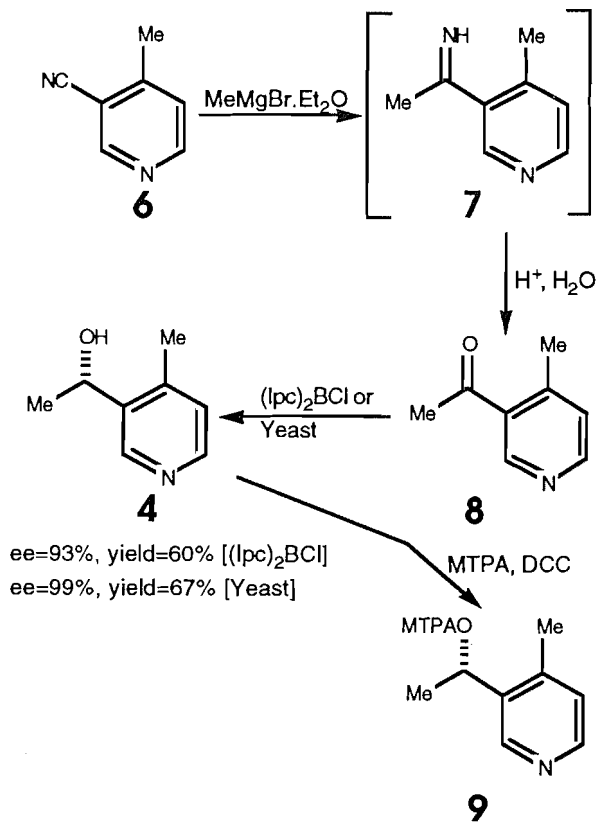


SCHEME 1



SCHEME 2

contrast to these methods, we have found that a more direct route was the Grignard addition of methylmagnesium bromide (3.0 M solution in diethyl ether) to the nitrile **6** followed by *in situ* acid-catalyzed hydrolysis of the presumed imine intermediate **7**. This protocol, based upon work done by Canonne *et al.* (13), conveniently furnished 3-acetyl-4-methylpyridine in 83% yield.

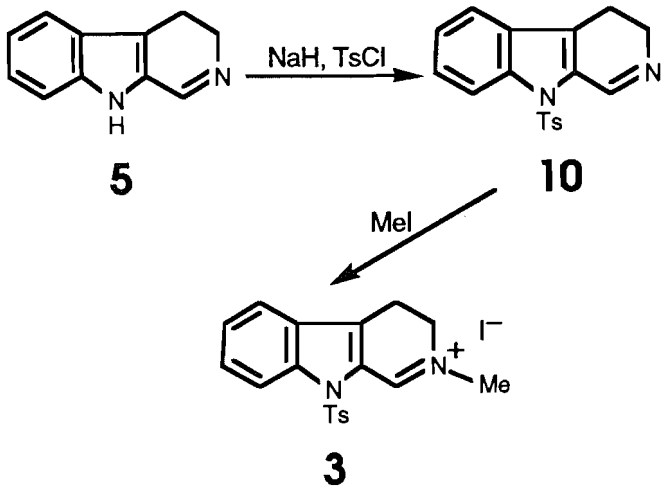
With acetylpyridine **8** in hand, the next challenge was the stereoselective reduction to form the (*S*)-alcohol **4**. Our initial notion was to employ methodology developed by Brown and co-workers (14) for the asymmetric reduction of aralkyl ketones. Thus, treatment of 3-acetyl-4-methylpyridine with (−)-*B*-chlorodiisopinocampheylborane [(−)-$(Ipc)_2BCl$], and subsequent removal of the boron moiety with diethanolamine, gave (1′*S*)-3-(1′-hydroxyethyl)-4-methylpyridine (**4**). The overall yield was 60% and the enantiomeric excess was 93%. This result is consistent with Brown and co-workers' (14) reduction of 3-acetylpyridine (65% yield and 92% ee). It is pertinent to note that, in each case, 2.3 equivalents of the (−)-$(Ipc)_2BCl$ reagent were required, presumably because of complex formation.

Owing to the expense of the (−)-$(Ipc)_2BCl$ reagent, we examined the possibility of a yeast-mediated reduction. Thus, treatment of the substrate **8** with Fleischmann's Baker's yeast (170:1 yeast to **8** ratio (w/w)) for 4 days at 32°C provided **4** in 67% yield and 99.0% ee ($[\alpha]_D$ −53.5; *c* 1.0, $CHCl_3$). The product was isolated by extractive processing, and the reaction was performed on a 5-gram scale. Another salient feature was that this reduction was accomplished using nonfermenting yeast (i.e., glucose or sucrose was *not* added), thereby facilitating processing. This modification was based upon work done by Bucciarelli *et al.* (15) and by Rasor and Rüchardt (16). An interesting point is that, under almost identical conditions, Takeshita *et al.* (17) found that the yeast-mediated reduction of 3-acetylpyridine gave (1′*S*)-3-(1′-hydroxyethyl)pyridine in 40% yield and 67% ee. Clearly, the 4-methyl group in substrate **8** has a profound effect on the stereochemical outcome of this reduction.

The enantiomeric excesses were determined by conversion of the crude alcohol products into their corresponding diastereomeric (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetate derivatives (**9**) using *S*-MTPA (Aldrich) and *N*,*N*′-dicyclohexylcarbodiimide as the coupling agent. The ee was then assessed by high-resolution ^1H nmr (400 MHz) integration of the well-resolved signals ($\Delta\delta$ = 20 Hz) of the diastereomeric 4-methyl protons.

The absolute stereochemistry of **4** was ascertained to be *S* by ^1H nmr analysis of its *S*-MTPA and *R*-MTPA esters (18). This conclusion is consistent with Brown and co-workers' observation (14) that reduction of similar compounds with (−)-$(Ipc)_2BCl$ leads to the *S* enantiomer. Furthermore, yeast reductions of aralkyl ketones give predominantly the *S*-alcohol (19).

It has not escaped our attention that the enantiopure compound, (1′*S*)-3-(1′-hydroxyethyl)-4-methylpyridine, may be of value as a synthetic intermediate in the synthesis of various pyrido-alkaloids and other natural products. Further-



SCHEME 3

more, its *N*-benzyl salt may be of therapeutic value (20) as a possible antineoplastic agent.

Synthesis of ***3***

The synthesis of the intermediate of which the β-carboline portion of mostueine is comprised, specifically the iminium salt, 3,4-dihydro-2-methyl-9-(*p*-toluenesulfonyl)-β-carbolinium iodide (**3**), is depicted in Scheme 3. The starting material was the known 3,4-dihydro-β-carboline (or norharmalan) (**5**), which is readily accessible by way of the Bischler–Napieralski reaction of N^b-formyltryptamine (21). Protection of the indole nitrogen as its tosylamide presented some difficulty. Initially, phase-transfer catalytic methods (22) were examined; however, the yields were low (<30%) owing to formation of side products. Finally, reproducible yields (65%) of the desired 3,4-dihydro-9-(*p*-toluenesulfonyl)-β-carboline (**10**) were obtained by formation of the sodium salt of the indole (sodium hydride, DMF, −10°C, 30 min) followed by addition of *p*-toluenesulfonyl chloride (−60°C, 1.5 h). The major by-product resulted from sulfonylation at the C-3 position of the indole nucleus (C-7 of mostueine). This procedure is an adaptation of a method developed by Langlois *et al.* (23) for the *N*-benzylation of **5**. Methylation of the imine nitrogen of **10** by treatment with iodomethane (THF, room temperature, 12 h) and subsequent filtration provided the iminium salt **3** in 91% yield.

Coupling of ***3*** *and* ***4*** *and completion of the synthesis of* ***1***

The remaining steps in this convergent synthesis of mostueine are shown in Scheme 4. The critical coupling of **3** and **4** went as predicted and afforded adducts **11***a* (3*S*, 19*S*) and **11***b* (3*R*, 19*S*) as a 1.35:1.00 mixture, respectively, and in 62% yield. Considerable effort was spent optimizing this reaction and it was found that the use of a combination of potassium *tert*-butoxide and lithium diisopropylamide afforded the highest yield. A 30-min reaction time at −78°C was found to be sufficient; longer reaction periods led to a reduced yield. The diastereomeric compounds **11***a* and **11***b* were readily separable by silica gel flash chromatography.

We were somewhat disappointed by the low degree of asymmetric induction (de = 15%) obtained for the addition of enantiopure **4** to the iminium salt **3**. Preliminary efforts were made to improve the diastereoselection of this process by varying the hydroxyl protecting group (*tert*-butyldimethylsilyl ether and methoxymethyl ether) on **4** and the indole protecting group (benzyl and free indole). No improvement in the asymmetric induction was obtained for the coupling of these modified compounds (all combinations were tried). These results suggest that the stereocenter on **4** is too remote to offer significant stereoinduction upon addition of this nucleophile.

Compounds **11***a* and **11***b* in racemic form were also isolated by McGee *et al.* (6) in their synthesis of (±)-mostueine. Of significance is that our high-resolution ^{1}H nmr data obtained for (+)-**11***a* and (−)-**11***b* correspond exactly with the literature (6). Their work demonstrated that the racemic modifications of the (3*S*,19*S*) diastereomer **11***a* can be cyclized under forcing conditions (potassium *tert*-butoxide in THF) to provide (±)-mostueine. Mechanistically, this reaction is consistent with the transfer of the *p*-toluenesulfonyl group from the indole nitrogen to the C-19 alkoxide followed by S_N2 displacement of the *p*-toluenesulfonyloxy group by the indole nitrogen (for a related example of this type of cyclization, see ref. 24). Thus, treatment of **11***a* with potassium *tert*-butoxide in anhydrous THF provided (+)-mostueine in 13.5% yield. The major product of the reaction was the imine **12** (40% yield) presumably formed by *C*-alkylation of the intermediary C-19 tosylate. Our results are consistent with those obtained by others (6, 7). The relative (and in this case the absolute) configuration of **12** was established by ^{1}H nmr nOe experiments. For instance, a significant enhancement (6.8%) of the H-14ax signal was observed upon presaturation at the signal for H-19. Additionally, presaturation at the signal for the H-18 methyl protons gave a 7.5% intensity enhancement of the H-21 signal.

Attempts to improve the yield of mostueine were unsuccessful. For instance, the adduct corresponding to **11***a* deprotected at N-9 was oxidized (MnO_2, CH_2Cl_2, reflux, 36 h, 42%) at C-19 to provide the ketone. Unfortunately, conditions to reductively aminate the indole nitrogen with the ketone were not found.

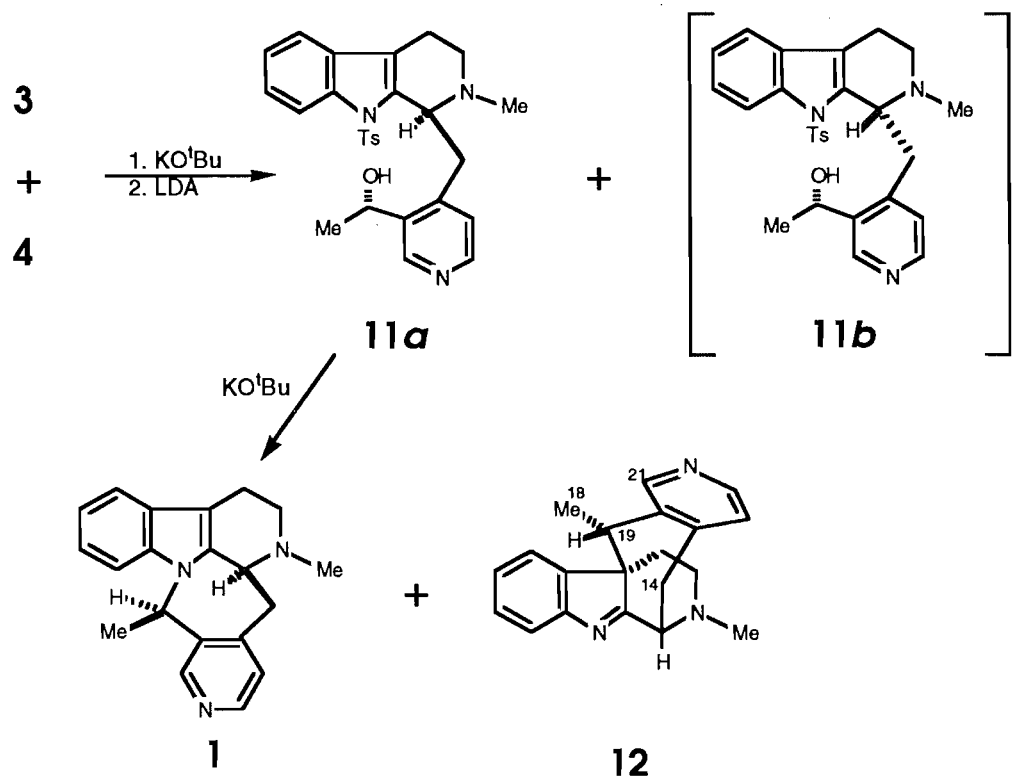
The spectral data for the synthetically prepared (+)-mostueine were identical with the data for a sample of the natural product that was kindly provided by Prof. F. Khuong-Huu. Also, the optical rotation for mostueine synthesized by this method was +186 (*c* 1.0, $CHCl_3$), a value that closely corresponds to the optical rotation of natural mostueine (+196 (2)). This result unambiguously demonstrates that the absolute stereochemistry of **1** is (3*S*,19*R*), an assignment that is consistent with the proposed biosynthesis (4) of mostueine from strictoside.

In summary, the enantioselective synthesis of the indole alkaloid mostueine has been accomplished in a convergent and efficient manner. This work shows that the absolute configuration of mostueine is (3*S*,19*R*) as depicted.

Experimental

Apparatus, materials, and methods

The ^{1}H nmr spectra were recorded at 200 MHz and 400 MHz (as indicated) on Bruker AC-F200 and AM-400 spectrometers, respectively. The samples were dissolved in either $CDCl_3$ or DMSO-d_6 (as indicated). The proton chemical shifts are quoted in parts per million (ppm) downfield relative to the internal standard, tetramethylsilane (δ scale). The ^{13}C nmr spectra were recorded at 50.3 MHz on a Bruker AC-F200 spectrometer. The carbon chemical shifts are quoted in ppm with reference to $CDCl_3$ (77.00 ppm). The multiplicities of signals were determined by JMOD experiments. The analyses were done as a first-order ap-



SCHEME 4

proximation. The ir spectra were determined using KBr disks or taken from films on sodium chloride plates (as indicated) on a BOMEM MB-120 ft-ir spectrophotometer at room temperature.

EI (electron ionization) mass spectra were recorded at 70 eV on a VG Analytical ZAB-E mass spectrometer equipped with a VG 11-250 data system. CI (chemical ionization) spectra were recorded on the same instrument using NH_3 at ~1 Torr (1 Torr = 133.3 Pa) as reagent gas. The peak intensities are given as a percent of the base peak (100%) intensity. High-resolution mass spectra (hrms) measurements were performed on the above instrument under EI conditions.

Melting points were determined using a Fisher–Johns apparatus and are uncorrected. Optical rotations were measured on a Perkin–Elmer 241 polarimeter and were run at room temperature (~23°C). Thin-layer chromatography was performed using silica gel 60-F_{254} plates (E. Merck No. 5714) of 0.25 mm thickness. Preparative-layer chromatographic (ptlc) separations were accomplished on silica gel 60-F_{254} plates (E. Merck No. 5717) of 2 mm thickness. For flash chromatography, silica gel 60 (230–400 mesh, E. Merck No. 9385-5) was employed.

All reactions involving lithiation were performed in apparatus dried in the oven at 140°C for at least 12 h and assembled hot under a stream of argon. Septa and syringes were used for transfer of reagents. Solvents and reagents were reagent grade and, when required, further purifications were accomplished following published procedures (25). Titrations of the organolithium reagents were done using diphenylacetic acid (26).

3-Acetyl-4-methylpyridine (8)

To a stirred solution of 3-cyano-4-methylpyridine (**6**) (5.01 g, 42.5 mmol) (prepared according to ref. 9) in benzene (30 mL) at 0°C and under an argon atmosphere was added a 3.0 M solution of MeMgBr in diethyl ether (42.0 mL, 126 mmol). The solution was stirred at 0°C for 2 h, the temperature was then raised to room temperature, and the stirring was continued a further 16 h. The mixture was cooled to 0°C, the excess of MeMgBr was carefully quenched, and the solution acidified to pH ~2 by addition of 4 M HCl. This solution was stirred for 2 h, at which point it was basified to pH ~10 using concentrated NH_4OH solution (aq.). The aqueous layer was extracted with ethyl acetate (6 × 60 mL), the combined organic extracts were dried over $MgSO_4$ (anhydrous), and the solvent was removed *in vacuo*. The crude red oil (5.14 g) was purified by silica gel flash chromatography (ethyl acetate – hexane (2:3, v/v)) to furnish the acetylpyridine **8** (4.75 g, 83% overall yield from **6**) as a colorless oil (this material is slightly volatile and, thus, should not be exposed to reduced pressure for prolonged periods); bp 57–58°C (1–2 Torr); ν_{max} (film): 3052, 2979, 2928, 1687, 1592, 1358, 1270 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$) δ: 2.53 (3H, s, CH_3CO), 2.62 (3H, s, CH_3 at C-4), 7.17 (1H, d, J = 5.0 Hz, H-5), 8.51 (1H, d, J = 5.0 Hz, H-6), 8.92 (1H, s, H-2); ^{13}C nmr (50.3 MHz, $CDCl_3$) δ: 20.8 (CH_3 at C-4), 29.1 (CH_3CO), 126.6 (C-5), 132.8 (C-4), 147.8 (C-3), 150.2 (C-6), 151.5 (C-2), 199.2 (CH_3CO); ms (EI), m/z (%): 135 (52) $[M]^+$, 120 (100), 92 (82), 65 (37). Exact Mass calcd. for C_8H_9NO $[M]^+$: 135.0684; found (hrms): 135.0692.

(1′S)-3-(1′-Hydroxyethyl)-4-methylpyridine (4)

Method 1. (−)-(Ipc)$_2$BCl reduction

To a solution of (−)-*B*-chlorodiisopinocampheylborane ((−)-(Ipc)$_2$BCl, Aldrich, 5.95 g, 18.5 mmol) in THF (20 mL) at −20°C and under an argon atmosphere was added 3-acetyl-4-methylpyridine (**8**) (1.00 g, 7.41 mmol). The reaction mixture was stirred for 17 h and the volatiles were removed under vacuum. The residue was dissolved in diethyl ether (30 mL) and diethanolamine (4.29 g, 40.8 mmol) was added. This mixture was stirred for 3 h and the solid that precipitated was removed by filtration through a sintered-glass funnel (medium porosity). The filter cake was washed twice with pentane and the combined filtrate and washings were concentrated *in vacuo*. To remove the remaining α-pinene, the oil was taken up in 0.2 M HCl (40 mL) and washed with ethyl acetate (60 mL). The aqueous layer was basified with $NaHCO_3$ (s) and extracted with ethyl acetate (5 × 50 mL). The combined extracts

were dried over $MgSO_4$ and the solvent removed *in vacuo*. The remaining oil was purified by silica gel flash chromatography (ethyl acetate – methanol (95:5, v/v)) to yield 0.61 g (60% yield) of the chiral alcohol **4** (ee = 93.0%) as a colorless oil; $[\alpha]_D$ −50.2 (*c* 1.0, $CHCl_3$).

Method 2. Yeast reduction

Six 500-mL side-arm Erlenmeyer flasks, each containing a mixture of the ketone **8** (0.85 g, 6.3 mmol) and dry baker's yeast (Fleischmann's Yeast Limited, "Traditional Active Dry Yeast") (145 g) in tap water (250 mL), were shaken on a wrist-action shaker for 4 days at 32°C. The solutions were combined and centrifuged (13,000 rpm, 10 min, 4°C). The supernatant aqueous layers were decanted, more water was added to the centrifuge tubes, and the yeast re-suspended. This mixture was centrifuged as above and the supernatant aqueous layers were collected. All aqueous extracts were combined and passed through a 2-cm bed of Celite. Extraction of the aqueous phase with ethyl acetate (6 × 400 mL), followed by drying of the combined organic layers over Na_2SO_4 and removal of the solvent *in vacuo*, gave a slightly-yellow oil. This material was further purified by silica gel flash chromatography (ethyl acetate – methanol (95:5, v/v)) to provide 3.45 g (67% yield) of the (*S*)-alcohol **4** (ee = 99.0%) as a colorless oil; $[\alpha]_D$ −53.5 (*c* 1.0, $CHCl_3$); ν_{max} (film): 3296, 2975, 2926, 1603, 1449, 1416, 1373, 1096, 1071 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$) δ: 1.46 (3H, d, *J* = 6.5 Hz, C-2′ H's), 2.30 (3H, s, CH_3 at C-4), 4.80 (1H, br s, D_2O-exchangeable, OH), 5.06 (1H, q, *J* = 6.5 Hz, H-1′), 6.98 (1H, d, *J* = 4.8 Hz, H-5), 8.18 (1H, d, *J* = 4.8 Hz, H-6), 8.51 (1H, s, H-2); ^{13}C nmr (50.3 MHz, $CDCl_3$) δ: 18.1 (C-2′), 23.4 (CH_3 at C-4), 64.5 (C-1′), 125.0 (C-5), 140.0 (C-4), 144.3 (C-3), 145.7 (C-6), 146.3 (C-2); ms (EI), *m/z* (%): 137 (28) $[M]^+$, 122 (100), 94 (50), 93 (13), 92 (12), 65 (14). Exact Mass calcd. for $C_8H_{11}NO$ $[M]^+$: 137.0841; found (hrms): 137.0851.

(1′S)-3-[1′-O-(S-MTPA)ethyl]-4-methylpyridine (9)

To *S*-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (101 mg, 0.430 mmol) in dichloromethane (15 mL) were added *N*,*N*′-dicyclohexylcarbodiimide (114 mg, 0.553 mmol), 4-dimethylaminopyridine (10 mg, 0.082 mmol), and the chiral alcohol **4** (42.0 mg, 0.306 mmol), and the solution was stirred for 16 h. The white precipitate was removed by filtration through a sintered-glass funnel (fine porosity) and washed with pentane (2 × 15 mL). The filtrate was diluted with dichloromethane (20 mL) and sequentially washed with saturated aqueous solutions of $NaHCO_3$ and NaCl (15 mL of each). The organic layer was dried over $MgSO_4$ and the solvent removed *in vacuo* to afford 76.8 mg (71% yield) of the acetate **9** as a colorless oil (the spectral data for the (1′*S*,*R*) diastereomer are given in parentheses if they are different from those of the (1′*S*,*S*) diastereomer); ^1H nmr (400 MHz, $CDCl_3$) δ: 1.56 (1.63) (3H, d, *J* = 6.7 Hz, C-2′ H's), 2.38 (2.33) (3H, s, CH_3 at C-4), 3.45 (3.55) (3H, q, *J* = 1.2 Hz, OCH_3), 6.27 (6.23) (1H, q, *J* = 6.7 Hz, H-1′), 7.06 (7.03) (1H, d, *J* = 5.0 Hz, H-5), 7.30–7.45 (5H, m, Ph), 8.39 (8.37) (1H, d, *J* = 5.0 Hz, H-6), 8.53 (8.35) (1H, s, H-2); ^{13}C nmr (50.3 MHz, $CDCl_3$) δ: 18.4 (18.3) (C-2′), 21.1 (21.0) (CH_3 at C-4), 55.3 (55.5) (OCH_3), 70.5 (70.4) (C-1′), 120.4 (*C*CF_3), 125.4 (125.2) (C-5), 126.2 (CF_3), 127.2, 128.3, 129.6, 131.8 (127.0, 128.4) (Ph), 134.4 (134.3) (C-3), 144.2 (C-4), 147.6 (147.4) (C-6), 149.1 (149.0) (C-2), 165.6 (165.8) (R*C*O_2R′); ms (EI), *m/z* (%): 354 (5) $[M + H]^+$, 224 (12), 189 (65), 143 (14), 120 (100); ms (CI), *m/z* (%): 354 (100) $[M + H]^+$, 120 (15). Exact Mass calcd. for $C_{18}H_{19}NO_3F_3$ $[M + H]^+$: 354.1316; found (hrms): 354.1322.

4,9-Dihydro-9-(p-toluenesulfonyl)-3H-pyrido-[3,4-b]indole (10)

At −10°C, the 3,4-dihydro-β-carboline **5** (see ref. 21 for preparation, 1.40 g, 8.23 mmol) was added slowly to a suspension of NaH (0.58 g, 60% in mineral oil, 14.6 mmol) in DMF (20 mL) and under an argon atmosphere. (**Caution**: various 3,4-dihydro-β-carbolines and 3,4-dihydro-2-methyl-β-carbolinium salts have recently been implicated in provoking the neuronal degeneration underlying idiopathic Parkinson's disease (27).) The mixture was stirred for 30 min and then cooled to −60°C at which time *p*-toluenesulfonyl chloride (3.15 g, 16.5 mmol) was added. The reaction mixture was acidified after 1.5 h using 0.2 M HCl (40 mL) and extracted with diethyl ether (2 × 30 mL). The combined organic layers were extracted with 0.2 M HCl (25 mL) and the combined aqueous extracts made basic with concentrated NH_4OH solution (aq.). Extraction with dichloromethane (2 × 60 mL) and subsequent drying over $MgSO_4$ and removal of the solvent *in vacuo* provided a solid amorphous material. This solid was purified by silica gel flash chromatography (ethyl acetate – hexane (7:3 v/v)) to yield 1.74 g (65%) of the tosylamide **10**, which was recrystallized from ethyl acetate – hexane; mp 143–145°C; ν_{max} (KBr): 3048, 2936, 2849, 1596, 1554, 1444, 1365, 1230, 1167 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$) δ: 2.31 (3H, s, Ts-CH_3), 2.75 (2H, app t, *J* = 8.7 Hz, H-4), 3.84 (2H, td, *J* = 2.2, 8.8 Hz, H-3), 7.16 (2H, d, *J* = 8.2 Hz, Ts), 7.28 (1H, t, *J* = 7.5 Hz, H-6), 7.43 (1H, t, *J* = 7.8 Hz, H-7), 7.47 (1H, d, *J* = 7.9 Hz, H-5), 7.65 (2H, d, *J* = 8.2 Hz, Ts), 8.18 (1H, d, *J* = 8.3 Hz, H-8), 8.99 (1H, app s, H-1); ^{13}C nmr (50.3 MHz, $CDCl_3$) δ: 18.7 (C-4), 21.4 (Ts-CH_3), 47.1 (C-3), 115.1 (C-8), 120.1 (C-5), 124.1 (C-6), 125.6 (C-4a), 126.5 (Ts), 127.3 (C-7), 127.8 (C-4b), 128.6, 129.8 (Ts), 134.7 (C-9a), 136.8 (C-8a), 145.1 (Ts), 150.9 (C-1); ms (EI), *m/z* (%): 324 (24) $[M]^+$, 169 (100), 142 (22), 115 (21), 91 (19). Exact Mass calcd. for $C_{18}H_{16}N_2O_2S$ $[M]^+$: 324.0932; found (hrms): 324.0926.

4,9-Dihydro-2-methyl-9-(p-toluenesulfonyl)-3H-pyrido-[3,4-b]indolinium iodide (3)

To a solution of the tosylamide **10** (501 mg, 1.54 mmol) in tetrahydrofuran (25 mL) was added iodomethane (0.49 mL, 7.7 mmol) with stirring and at room temperature, and the mixture was allowed to stand overnight. The solid precipitate **3** was isolated by filtration through Whatman filter paper (hardened) and the filter cake washed with hexane (2 × 20 mL) to provide 0.653 g (91% yield) of the bright-yellow crystalline 3,4-dihydro-2-methyl-β-carbolinium salt **3**; mp 195–197°C; ν_{max} (KBr): 3077, 3035, 2994, 2970, 1640, 1540, 1434, 1370, 1171, 1096 cm^{-1}; ^1H nmr (200 MHz, DMSO-d_6) δ: 2.31 (3H, s, Ts-CH_3), 3.37 (2H, app t, *J* = 9.0 Hz, H-4), 3.89 (3H, s, *N*-CH_3), 4.16 (2H, t, *J* = 9.1 Hz, H-3), 7.16 (2H, d, *J* = 8.4 Hz, Ts), 7.45 (1H, app t, *J* = 7.9 Hz, H-6 or H-7), 7.70 (1H, app t, *J* = 7.9 Hz, H-6 or H-7), 7.87 (1H, d, *J* = 7.9 Hz, H-5), 7.99 (2H, d, *J* = 8.4 Hz, Ts), 8.07 (1H, d, *J* = 8.6 Hz, H-8), 9.47 (1H, s, H-1); ^{13}C nmr (50.3 MHz, DMSO-d_6) δ: 19.0 (C-4), 21.0 (Ts-CH_3), 47.7 (*N*-CH_3), 49.8 (C-3), 114.6 (C-8), 123.2 (C-5), 125.4 (C-6), 125.8, 125.9 (C-4a, C-4b), 127.4, 130.4 (Ts), 131.6 (C-7), 132.5 (C-9a), 134.1 (Ts), 138.7 (C-8a), 146.5 (Ts), 155.1 (C-1); ms (EI), *m/z* (%): 340 (17) $[M - I + H]^+$, 185 (100), 184 (73), 183 (36), 157 (18), 156 (18), 142 (61), 139 (24), 92 (51), 91 (64). Exact Mass calcd. for $C_{19}H_{20}N_2O_2S$ $[M - I + H]^+$: 340.1245; found (hrms): 340.1234.

Tosylamide adducts 11a[(1S,1″S)-2,3,4,9-tetrahydro-1-{[3′-(1″-hydroxyethyl)-4′-pyridinyl]methyl}-2-methyl-9-(p-toluenesulfonyl)-1H-pyrido[3,4-b]indole] and 11b[(1R,1″S)-2,3,4,9-tetrahydro-1-{[3′-(1″-hydroxyethyl)-4′-pyridinyl]methyl}-2-methyl-9-(p-toluenesulfonyl)-1H-pyrido[3,4-b]indole]

Under an argon atmosphere and at −10°C, the hydroxypyridine **4** (228 mg, 1.66 mmol) in tetrahydrofuran (20 mL) was treated with potassium *tert*-butoxide (1.5 M in tetrahydrofuran, 1.44 mL, 2.16 mmol). The solution was stirred at this temperature for 10 min at which time it was cooled to −78°C and lithium diisopropylamide (1.5 M in tetrahydrofuran, 1.44 mL, 2.16 mmol) was added; the solution became yellow. After 25 min, the solution was added dropwise using a cannula to a vigorously stirred suspension of the 2-methyl-β-carbolinium salt **3** (519 mg, 1.11 mmol) in tetrahydrofuran (20 mL) at −78°C. The reaction was quenched after 0.5 h by addition of saturated NaCl (aq.) (2 mL) and then diluted with dichloromethane (40 mL). This mixture was washed sequentially with saturated $NaHCO_3$ (aq.) (15 mL) and saturated NaCl (aq.) (15 mL), dried over $MgSO_4$, and the solvent removed *in vacuo*. The

residual oil was purified by silica gel chromatography (ethyl acetate – methanol (95:5, v/v)) Silica gel flash chromatography (dichloromethane – 95% ethanol (20:1, v/v)) afforded the diastereomers **11***a* (188 mg) and **11***b* (139 mg) (62% overall yield) as slightly yellowish crystals. (The numbering system used for both ^{1}H nmr and ^{13}C nmr assignments for **11***a* and **11***b*, and for the following two compounds (**12** and **1**), refers to mostueine numbering, as shown in the structural formula for **1**.)

11*a*: mp 85–90°C; $[\alpha]_D$ +68 (*c* 1.0, $CHCl_3$); ν_{max} (KBr): 3363, 2967, 2933, 2847, 1597, 1450, 1366, 1170, 754 cm^{-1}; ^{1}H nmr (400 MHz, $CDCl_3$) δ: 1.60 (3H, d, *J* = 6.6 Hz, C-18 H's), 2.29 (3H, s, Ts-C*H*$_3$), 2.35 (3H, s, *N*-C*H*$_3$), 2.31–2.40 (1H, m, H-5 or H-6), 2.48–2.83 (3H, m, C-5 H's, C-6 H's), 3.34 (1H, dd, A of ABX, *J* = 7.4, 14.2 Hz, H-14), 3.53 (1H, dd, B of ABX, *J* = 3.5, 14.2 Hz, H-14′), 4.46 (1H, dd, *J* = 3.2, 7.3 Hz, H-3), 5.15 (1H, q, *J* = 6.6 Hz, H-19), 7.11 (2H, d, *J* = 8.4 Hz, Ts), 7.22 (1H, d, *J* = 5.1 Hz, H-16), 7.29–7.41 (3H, m, H-9, H-10, H-11), 7.50 (2H, d, *J* = 8.1 Hz, Ts), 8.22 (1H, d, *J* = 7.8 Hz, H-12), 8.32 (1H, d, *J* = 5.1 Hz, H-17), 8.61 (1H, s, H-21); ^{13}C nmr (50.3 MHz, $CDCl_3$) δ: 15.9 (C-6), 19.9 (Ts-*C*H$_3$), 21.4 (C-18), 36.5 (C-14), 41.3 (*N*-*C*H$_3$), 43.1 (C-5), 62.5, 62.9 (C-3, C-19), 115.7 (C-12), 118.6 (C-9), 118.9 (C-7), 124.2 (C-10), 125.2 (C-11), 125.7 (C-16), 126.1, 129.5, 130.0 (Ts), 134.5 (C-8), 137.1 (C-2), 137.2 (C-13), 138.8 (C-20), 144.9 (C-15), 146.9 (C-17), 147.0 (Ts), 148.7 (C-21); ms (EI), *m*/*z* (%): 476 (<1) $[M + H]^+$, 339 (100), 184 (47), 183 (36), 122 (23), 91 (35). Exact Mass calcd. for $C_{27}H_{30}N_3O_3S$ $[M + H]^+$: 476.1993; found (hrms): 476.2008.

11*b*: $[\alpha]_D$ −149 (*c* 1.0, $CHCl_3$); ν_{max} (KBr): 3378, 2969, 2935, 2849, 2801, 1596, 1450, 1368, 1170, 753 cm^{-1}; ^{1}H nmr (400 MHz, $CDCl_3$) δ: 1.68 (3H, d, *J* = 6.5 Hz, C-18 H's), 2.25 (3H, s, *N*-C*H*$_3$), 2.29 (3H, s, Ts-C*H*$_3$), 2.51–3.40 (4H, m, C-5 H's, C-6 H's), 3.16 (1H, dd, A of ABX, *J* = 10.0, 14.2 Hz, H-14), 3.37 (1H, d, *J* = 14.2 Hz, H-14′), 4.23 (1H, br d, *J* = 9.8 Hz, H-3), 5.02 (1H, q, *J* = 6.5 Hz, H-19), 7.10 (2H, d, *J* = 8.0 Hz, Ts), 7.26–7.41 (3H, m, H-9, H-10, H-11), 7.49 (2H, d, *J* = 8.4 Hz, Ts), 7.88 (1H, d, *J* = 5.2 Hz, H-16), 8.24 (1H, d, *J* = 8.1 Hz, H-12), 8.55 (1H, d, *J* = 5.1 Hz, H-17), 8.76 (1H, s, H-21); ^{13}C nmr (50.3 MHz, $CDCl_3$) δ: 16.4 (C-6), 21.4 (Ts-*C*H$_3$), 23.1 (C-18), 36.6 (C-14), 42.3 (*N*-*C*H$_3$), 44.1 (C-5), 61.4 (C-3), 65.4 (C-19), 115.7 (C-12), 118.6 (C-9), 119.9 (C-7), 124.2 (C-10), 125.0 (C-11), 126.0 (C-16), 126.2, 129.5, 130.2 (Ts), 134.4 (C-8), 134.8 (C-2), 137.2 (C-13), 139.5 (C-20), 144.8 (C-15), 146.3 (Ts), 148.0 (C-17), 148.1 (C-21).

Imine ***12*** *[(6*S*, 12*R*)-5,12-dihydro-12,15-dimethyl-6*H*-6,11b-(iminoethano)pyrido[3′,4′:4,5]cyclohept[1,2-*b*]indole] and (+)-mostueine (**1**) [(8*R*, 13a*S*)-1,2,3,8,13,13a-hexahydro-1,8-dimethyl-1,7b,10-triazabenzo[5,6]cyclohepta[1,2,3-jk]fluorene]*

To a stirred solution of the tosylamide **11***a* (163 mg, 0.343 mmol) in tetrahydrofuran (15 mL) at 0°C was added potassium *tert*-butoxide (231 mg, 2.06 mmol). The medium was allowed to warm slowly to room temperature and, after 5 h, was diluted with dichloromethane (40 mL) and washed with saturated NaCl (aq.) (20 mL). The organic layer was dried over $MgSO_4$ and the solvent removed *in vacuo*. The residual solid was purified by ptlc (diethyl ether – 95% ethanol – diethylamine (90:3:7, v/v)). The major product isolated was the imine **12** (40.3 mg, 40%) along with mostueine **1** (14.0 mg, 13.5%).

12: $[\alpha]_D$ −42.8 (*c* 1.0, $CHCl_3$); ν_{max} (KBr): 2930, 2859, 2794, 1593, 1451, 1325, 1143, 920 cm^{-1}; ^{1}H nmr (200 MHz, $CDCl_3$) δ: 1.72 (3H, d, *J* = 7.2 Hz, C-18 H's), 1.96–2.37 (4H, m, C-5 H's, C-6 H's), 2.38 (3H, s, *N*-C*H*$_3$), 2.78 (1H, q, *J* = 7.2 Hz, H-19), 3.11 (1H, dd, A of ABX, *J* = 6.3, 14.9 Hz, H-14), 3.47 (1H, dd, B of ABX, *J* = 1.9, 14.9 Hz, H-14′), 4.12 (1H, dd, *J* = 2.0, 6.4 Hz, H-3), 7.23 (1H, td, *J* = 1.2, 7.3 Hz, H-10 or H-11), 7.24 (1H, d, *J* = 4.8 Hz, H-16), 7.37 (1H, td, *J* = 1.3, 7.5 Hz, H-10 or H-11), 7.46 (1H, d, *J* = 7.5 Hz, H-9), 7.64 (1H, d, *J* = 7.3 Hz, H-12), 8.47 (1H, d, *J* = 4.8 Hz, H-17), 8.58 (1H, s, H-21); ^{13}C nmr (50.3 MHz, $CDCl_3$) δ: 18.5 (C-18), 30.6 (C-6), 36.0 (C-14), 38.2 (*N*-C*H*$_3$), 42.1 (C-7), 42.3 (C-19), 47.1 (C-5), 60.7 (C-3), 121.0 (C-12), 124.9 (C-11), 125.1 (C-10), 125.8 (C-9), 128.1 (C-16), 137.1 (C-20), 144.9 (C-8), 148.2 (C-17), 148.3 (C-15), 148.7 (C-21), 154.2 (C-13), 187.3 (C-2); ms (EI), *m*/*z* (%): 303 (82) $[M]^+$, 288 (8), 260 (23), 184 (100); ms (CI), *m*/*z* (%): 304 (100) $[M + H]^+$, 184 (18), 183 (18). Exact Mass calcd. for $C_{20}H_{21}N_3$ $[M]^+$: 303.1735; found (hrms): 303.1741.

1:[3] $[\alpha]_D$ +186 (c 1.0, $CHCl_3$); ν_{max} (KBr): 2920, 2850, 2790, 1596, 1457, 1320, 1192, 1051, 747 cm^{-1}; ^{1}H nmr (200 MHz, $CDCl_3$) δ: 1.67 (3H, d, *J* = 7.0 Hz, C-18 H's), 2.54 (3H, s, *N*-C*H*$_3$), 2.62–2.79 (1H, m, H-6), 2.90–3.00 (1H, m, H-5 or H-6), 3.10–3.38 (2H, m, C-5 H's or C-6 H's), 3.15 (1H, dd, *J* = 2.1, 13 Hz, H-14), 3.52 (1H, t, *J* = 12.7 Hz, H-14′), 3.85 (1H, dd, *J* = 2.1, 12.7 Hz, H-3), 5.79 (1H, q, *J* = 7 Hz, H-19), 7.19 (1H, t, *J* = 7.0 Hz, H-10), 7.28 (1H, d, *J* = 4.9 Hz, H-16), 7.29 (1H, t, *J* = 7.0 Hz, H-11), 7.47 (1H, d, *J* = 8.3 Hz, H-9), 7.52 (1H, d, *J* = 7.5 Hz, H-12), 8.55 (1H, d, *J* = 4.9 Hz, H-17), 8.62 (1H, s, H-21); ^{13}C nmr (50.3 MHz, $CDCl_3$) δ: 18.7 (C-6), 22.8 (C-18), 36.8 (C-14), 37.3 (*N*-C*H*$_3$), 53.1 (C-5), 55.3 (C-19), 60.8 (C-3), 108.2 (C-7), 109.5 (C-12), 118.4 (C-11), 119.6 (C-10), 121.8 (C-9), 125.1 (C-16), 126.8 (C-8), 133.7, 134.8 (C-2, C-20), 136.3 (C-13), 147.1 (C-15), 149.4, 150.2 (C-17, C-21); ms (EI), *m*/*z* (%): 303 (100) $[M]^+$, 288 (33), 260 (56), 184 (74); ms (CI), *m*/*z* (%): 304 (100) $[M + H]^+$, 183 (37). Exact Mass calcd. for $C_{20}H_{21}N_3$ $[M]^+$: 303.1735; found (hrms): 303.1738.

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1. A. W. Rey, W. A. Szarek, and D. B. MacLean. 13th International Congress of Heterocyclic Chemistry, Corvallis, Oreg. 1991.
2. M. Onanga and F. Khuong-Huu. C. R. Seances Acad. Sci. Sér. C: **291**, 191 (1980).
3. W. N. A. Rolfsen, A. A. Olaniyi, R. Verpoorte, and L. Bohlin. Nat. Prod. **44**, 415 (1981).
4. G. Massiot, P. Thépenier, M.-J. Jacquier, L. Le Men-Olivier, R. Verpoorte, and C. Delaude. Phytochemistry, **26**, 2839 (1987).
5. W. N. A. Rolfsen, A. A. Olaniyi, F. Sandberg, and A. H. Kvick. Acta Pharm. Suec. **17**, 105 (1980).
6. L. R. McGee, G. S. Reddy, and P. N. Confalone. Tetrahedron Lett. **25**, 2115 (1984).
7. M. Onanga and F. Khuong-Huu. Tetrahedron Lett. **24**, 3627 (1983).
8. A. W. Rey, W. A. Szarek, and D. B. MacLean. Heterocycles, **32**, 1143 (1991); M. Nakagawa, T. Kawate, H. Yamazaki, and T. Hino. J. Chem. Soc. Chem. Commun. 991 (1990); D. B. Repke, Jahangir, R. D. Clark, J. T. Nelson, and D. B. MacLean. Tetrahedron, **45**, 2541 (1989); D. B. Repke, Jahangir, R. D. Clark, and J. T. Nelson. Heterocycles, **27**, 2289 (1988); D. B. Repke, Jahangir, R. D. Clark, and D. B. MacLean. J. Chem. Soc. Chem. Commun. 439 (1988); Jahangir, M. A. Brook, D. B. MacLean, and H. L. Holland.

[3]In the present work **1** was isolated as a low-melting solid. Of the five publications (2–4, 6, 7) in which the isolation of mostueine has been reported, only in the case of ref. 3 has a melting point been cited (mp 78–82°C).

Tetrahedron, **43**, 5761 (1987); Jahangir, M. A. Brook, D. B. MacLean, and H. L. Holland. J. Chem. Soc. Chem. Comm. 1608 (1986).
9. J. M. Bobbit and D. A. Scola. J. Org. Chem. **25**, 560 (1960).
10. J. L. Webb and A. H. Corwin. J. Am. Chem. Soc. **66**, 1456 (1944).
11. A. Shariff and S. McLean. Can J. Chem. **61**, 2813 (1983).
12. K. Deuchert, U. Hertenstein, and S. Hünig. Synthesis, 777 (1973).
13. P. Canonne, G. B. Foscolos, and G. Lemay. Tetrahedron Lett. **21**, 155 (1980).
14. J. Chanrasekharan, P. V. Ramachandran, and H. C. Brown. J. Org. Chem. **50**, 5446 (1985).
15. M. Bucciarelli, A. Forni, I. Moretti, and G. Torre. Synthesis, 897 (1983).
16. J. P. Rasor and C. Rüchardt. Chem. Ber. **122**, 1375 (1989).
17. M. Takeshita, K. Terada, N. Akutsu, S. Yoshida, and T. Sato. Heterocycles, **26**, 3051 (1987).
18. I. Ohtani, T. Kusumi, Y. Kashman, and H. Kakisawa. J. Am. Chem. Soc. **113**, 4092 (1991), and references cited therein.
19. R. Csuk and B. I. Glänzer. Chem. Rev. **91**, 49 (1991).
20. A. C. Lovesey. J. Med. Chem. **13**, 693 (1970).
21. N. Whittaker. J. Chem. Soc. (C), 85 (1969).
22. Y. Kikugawa. Synthesis, 460 (1981); V. O. Illi. Synthesis, 136 (1979); V. Bocchi, G. Casnati, A. Dossena, and F. Villani. Synthesis, 414 (1976).
23. Y. Langlois, A. Pouilhès, D. Génin, R. Z. Andriamialisoa, and N. Langlois. Tetrahedron, **39**, 3755 (1983).
24. M. Rubiralta, A. Diez, J. Bosch, and X. Solans. J. Org. Chem. **54**, 5591 (1989).
25. D. D. Perrin, W. L. F. Armarego, and D. R. Perrin. *In* Purification of laboratory compounds. 2nd ed. Pergamon Press, London. 1980.
26. W. G. Kofron and L. M. Baclawski. J. Org. Chem. **41**, 1879 (1976).
27. G. Druker, K. Raikoff, E. J. Neafsey, and M. A. Collins. Brain Res. **509**, 125 (1990).