Chiral Synthesis of (+)-Eburnamine, (−)-Eburnamenine, and (−)-Eburnamonine

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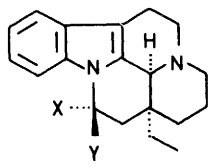
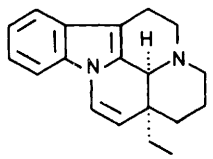
The (*S*)-trityl-lactone (**6**), easily prepared from L-glutamic acid or D-mannitol, has been stereoselectively converted into (+)-eburnamine (**3**), (−)-eburnamenine (**4**), and (−)-eburnamonine (**2**), *via* the dithiane-lactone (**15**).

Because of the medicinal importance of some of the Vincamine–Eburnamine indole alkaloids, such as (+)-vincamine (**1**) and (−)-eburnamonine (**2**), many attempts have been made to develop an efficient synthesis of these compounds.[1,2] We report here a new chiral synthesis of the latter alkaloid (**2**) and its congeners, (+)-eburnamine (**3**) and (−)-eburnamenine (**4**).[3] Our synthesis uses the readily available (*S*)-trityl-lactone (**6**) with a stereoselective double alkylation reaction as the key chirality transfer step.[4,5]



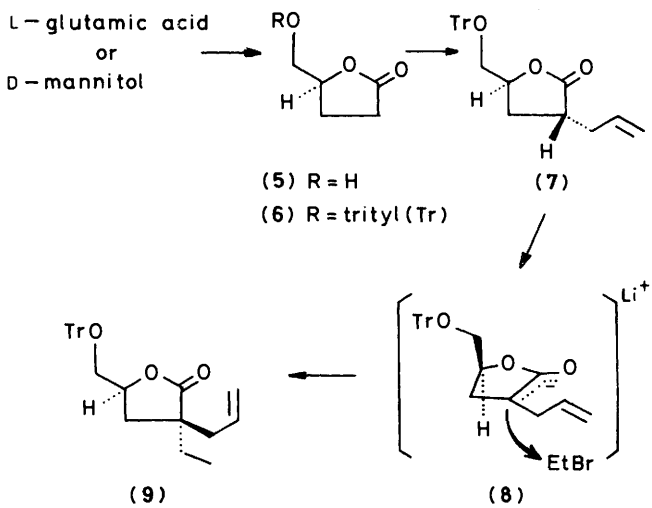
(1) X = CO_2Me, Y = OH, (+)—vincamine
(2) X,Y = O, (−)—eburnamonine
(3) X = OH, Y = H, (+)—eburnamine



(4) (−)—eburnamenine

Results and Discussion

Stereoselective Double Alkylation.—The chiral synthon of the present synthesis, the trityl-lactone (**6**),[5,6] was prepared by a standard method from the hydroxylactone (**5**) which can be prepared from L-glutamic acid[7] or D-mannitol.[8] The alkylation of the trityl-lactone (**6**) was carried out highly stereoselectively using lithium di-isopropylamide (LDA) in tetrahydrofuran (THF) to form a new chiral centre at the α position under the influence of the existing chiral centre. Thus, treatment of the lithium enolate, generated *in situ* in THF from compound (**6**) in the presence of a slight excess of LDA, with a small excess of allyl bromide for 1.5 h at −78 °C gave the allyl-lactone as a major (**7**) and a minor epimer (5~3:1). As the ratio of the two epimers was found to depend on the amount of base present, we believe that the minor epimer may be formed from the major one (**7**) *via* re-enolization followed by stereoselective protonation.[9] The allyl-lactone mixture was again treated with LDA to generate the enolate (**8**) which on alkylation with ethyl bromide for 13 h at room temperature yielded a single product (**9**)† in good yield and with virtually complete diastereoselectivity (Scheme 1). This observation clearly indicates that the trityl group consistently directs the approach of the incoming group to the opposite side. Consequently, the stereochemistry of the newly generated chiral centre may be arbitrarily controlled merely by changing the alkylation sequence.

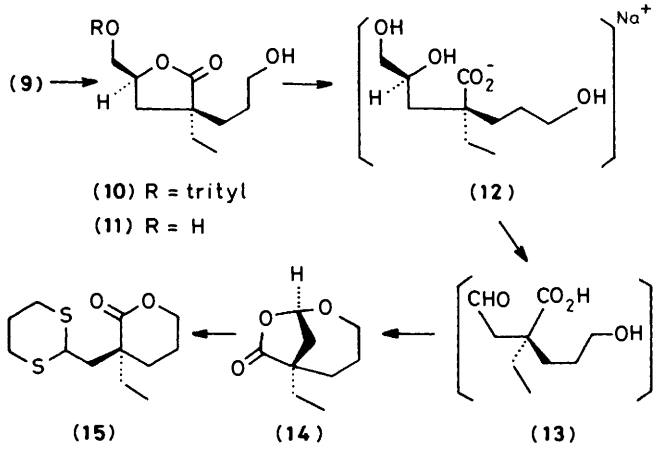


Scheme 1.

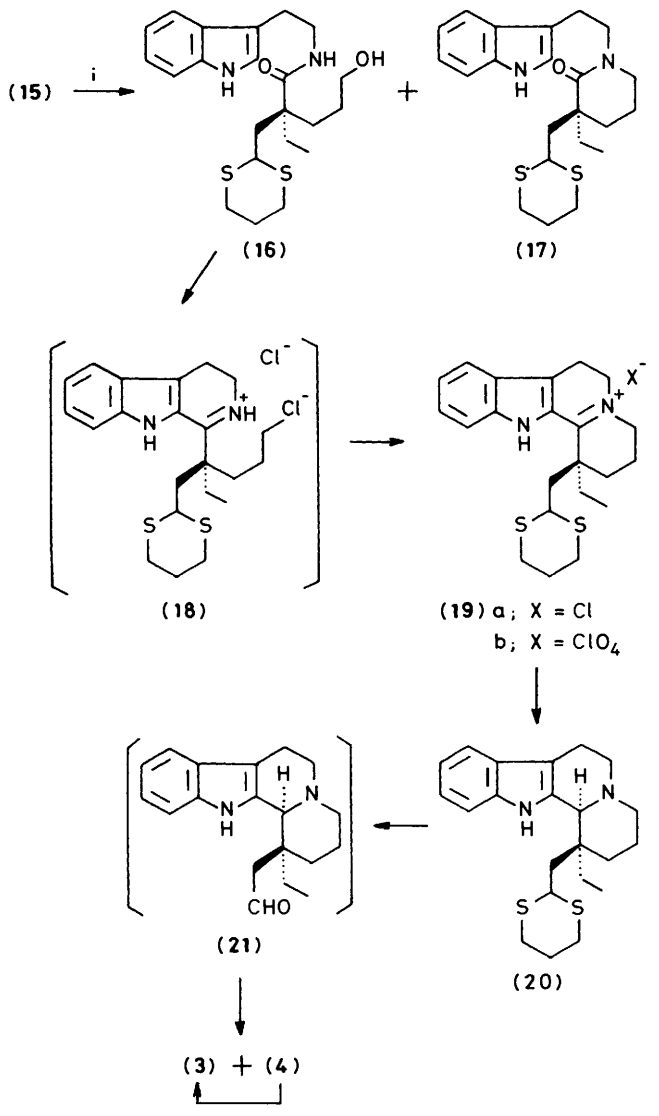
Conversion of the Dialkyl-lactone into the Dithiane-lactone.—In order to functionalize the dialkyl-lactone (**9**), we first introduced a primary hydroxy group at the vinylic position; this was achieved by hydroboration using dicyclohexylborane,[10]‡ followed by oxidation with alkaline hydrogen peroxide afforded the primary alcohol (**10**) selectively. Next, the 1,2-glycol moiety of the alcohol (**10**) was cleaved after detritylation. Thus, compound (**10**) was stirred in methanol containing a trace of hydrochloric acid for 5 h at room temperature to give the hydroxylactone (**11**) in excellent yield accompanied by insoluble methyl trityl ether which could be easily removed by filtration. Compound (**11**) was then hydrolysed with aqueous sodium hydroxide at room temperature, and the reaction mixture was made weakly alkaline (pH *ca.* 9) with carbon dioxide, and treated with aqueous sodium periodiate at 0 °C to cleave the 1,2-glycol function. Under acidic work-up conditions, the expected compound (**13**) underwent a further spontaneous reaction to furnish the crystalline bicyclo[3.2.1]nonane acetal (**14**) in an excellent overall yield. The bicyclic compound (**14**) was then treated with propane-1,3-dithiol in boiling benzene in the presence of a catalytic amount of toluene-*p*-sulphonic acid to give the key dithiane-lactone (**15**), in 98% yield, appropriately functionalized for the non-tryptamine moiety of the target alkaloids (Scheme 2).[11]

† This compound was also used in the chiral synthesis of the Aspidosperma indole alkaloids (+)- and (−)-quebrachamines, see refs. 4*a* and 4*b*.

‡ The use of diborane resulted in concomitant reduction of the lactone carbonyl group.



Scheme 2.



Scheme 3. *Reagents:* i, tryptamine, heat

Transformation of the Dithiane-lactone (**15**) *into the Target Alkaloids.*—In order to assemble the target alkaloids using the non-tryptamine moiety already obtained, compound (**15**) was heated with tryptamine for 5 h at 160 °C to give the secondary amide (**16**) and the δ-lactam (**17**)* in yields of 81 and 14%. Cyclization of the amide (**16**) with boiling phosphoryl chloride yielded the iminium salt (**19**); the perchlorate of (**19**) was then stereoselectively reduced with lithium tri-t-butoxyaluminium hydride[1g,l] in THF at 0 °C to give the tertiary amine (**20**), in 62% overall yield, with the desired configuration (11-Et and 12b-H *cis*). After the amine (**20**) had been converted into the hydrochloride, it was treated with an excess of methyl iodide in acetonitrile containing a small amount of water (50:1)[1g] for 70 h at room temperature to hydrolyse the dithiane group without affecting the tertiary nitrogen; thus (+)-eburnamine (**3**) (27%) and (−)-eburnamenine (**4**) (3%) were obtained *via* spontaneous cyclization of the formylamine (**21**) under the reaction conditions (Scheme 3). Prolonged treatment was found to increase the proportion of the latter alkaloid (**21**); however, this reverted to the former on treatment with dilute hydrochloric acid (0.5%) for 16 h at room temperature.[1a] The medicinally more important (−)-eburnamonine (**2**)[12] could be obtained in 75% yield from (+)-eburnamine (**3**) on oxidation with pyridinium dichromate in methylene dichloride at room temperature. This conversion has also been carried out using chromium trioxide in pyridine.[1a] Except in the case of (−)-eburnamenine (**4**) (Synthetic $[\alpha]_D$ − 151°, natural $[\alpha]_D$ − 183°), the observed specific optical rotations are in good agreement with the reported data for the natural products.

The overall yields of (**2**)—(**4**) from the chiral lactone (**15**) were 5.7, 0.6, and 4.3%, respectively.

Conclusions

Three of the Eburnamine-type indole alkaloids including a medicinally important one (**2**) were synthesized in optically active forms from the chiral lactone (**6**). The results indicate that the present method may be widely applicable to other Eburnamine-type alkaloids, though the hydrolysis of the dithiane function of compound (**20**) could be improved. The naturally occurring enantiomers of these alkaloids may also be synthesized from the same synthon (**6**) by reversing the alkylation sequence.

Experimental

All the reactions were carried out under argon. M.p.s were determined on a Yanagimoto MP-S2 apparatus and are uncorrected. I.r. spectra were recorded on a JASCO A-102 instrument, and ^{1}H n.m.r. spectra were measured for solutions in deuteriochloroform on JEOL PS 100 and PMX 60 spectrometers with tetramethylsilane as internal reference. Mass spectra were measured with a JEOL-D 300 spectrometer. Optical rotations were measured with a JASCO-DIP-4L automatic polarimeter.

(+)-(3R,5S)-3-*Allyl*-5-*trityloxymethyltetrahydrofuran*-2-*one* (**7**).—To a solution of di-isopropylamine (19.6 ml, 140 mmol) in THF (140 ml) was added 10% (w/v) n-butyl-lithium in n-hexane (90 ml, 140 mmol) at − 78 °C with stirring; after 10 min (+)-(5*S*)-5-trityloxymethyltetrahydrofuran-2-one (**6**)[6] (40 g, 112 mmol) in THF (230 ml) was added during 25 min and the stirring was continued for 1 h at the same temperature. Allyl bromide (11.6 ml, 134 mmol) was then added in one portion and the mixture was stirred for 1.5 h at −78 °C. The reaction mixture was treated with saturated aqueous sodium sulphate, the organic layer was separated, and the aqueous layer was extracted with benzene. The combined organic layer was washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure to leave an oil (47 g) which was crystallized from methanol to give

* This compound may also be converted into the amine (**20**), see ref. 1*g*.

the *allyl-lactone* (**7**) (29.1 g, 65.3%) as colourless needles, m.p. 89—90 °C; $[\alpha]_D$ + 24.8° (*c* 1.96; $CHCl_3$); $\nu_{max.}$ (Nujol) 1 755 cm^{-1}; δ 1.70—2.60 (5 H, m), 3.00—3.40 (2 H, m, CH_2OTr), 4.50 (1 H, m, CHOCO), 4.90—6.20 (3 H, m, $CH{=}CH_2$), and 7.00—7.70 (15 H, m, ArH); *m/z* 398 (M^+) and 243 (100%) (Found: C, 81.2; H, 6.6. $C_{27}H_{26}O_3$ requires C, 81.38; H, 6.58%).

(+)-(3S,5S)-3-*Allyl*-3-*ethyl*-5-*trityloxymethyltetrahydrofuran*-2-*one* (**9**).—To a solution of lithium di-isopropylamide prepared as above from di-isopropylamine (7.05 ml, 50.3 mmol) and 10% (w/v) n-butyl-lithium in n-hexane (32.3 ml, 50.3 mol) in THF (50 ml) was added the allyl-lactone (**7**) (10 g, 25.1 mmol) in THF (30 ml) during 10 min at −78 °C with stirring. After 40 min, ethyl bromide (5.62 ml, 75.4 mmol) was added to the solution at −78 °C and the stirring was continued for 18 h at room temperature. The reaction mixture was treated with saturated aqueous sodium sulphate, the organic layer was separated, and the aqueous layer was extracted with benzene. The combined organic layer was washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure to give a pale yellow crystalline residue (10.86 g) which was recrystallized from methanol to give the dialkyl-lactone (**9**) (9.14 g, 85.8%) as colourless needles, m.p. 144—145 °C; $[\alpha]_D$ + 30.8° (*c* 2.0, CH_2Cl_2); $\nu_{max.}$ (Nujol) 1 760 cm^{-1}; δ 0.97 (3 H, t, *J* 7 Hz, CH_2CH_3), 1.67 (2 H, q, CH_2CH_3), 1.87—2.23 (2 H, m, CH_2CHO), 2.35 (2 H, d, *J* 7 Hz, $CH_2CH{=}CH_2$), 3.28 (2 H, d, *J* 5 Hz, CH_2OTr), 4.53 (1 H, m, CHOCO), 4.90—6.27 (3 H, m, $CH{=}CH_2$), and 7.20—7.73 (15 H, m, ArH); *m/z* 426 (M^+), 243 (100%) (Found: C, 81.5; H, 7.0. $C_{29}H_{30}O_3$ requires C, 81.69; H, 7.04%).

(+)-(3S)-3-*Ethyl*-5-*hydroxymethyl*-3-(3-*hydroxypropyl*)-*tetrahydrofuran*-2-*one* (**11**).—To a solution of cyclohexene (3.5 ml, 34.5 mmol) in THF (10 ml) was added 2M-diborane–dimethyl sulphide complex in THF (8.6 ml, 17.2 mmol) at 0 °C with stirring. After 1 h, the dialkyl-lactone (**9**) (4.87 g, 11.4 mmol) in THF (15 ml) was added to the reaction mixture at the same temperature with stirring, and the stirring was continued for 1 h at room temperature. The reaction mixture was then treated with ethanol (8.6 ml), followed by 3N-aqueous sodium hydroxide (5.7 ml) and 30% aqueous hydrogen peroxide (5.8 ml, 51.2 mmol) at 0 °C, and the mixture was warmed to 50 °C for 1 h with stirring. Cold water (30 ml) was then added, the mixture was extracted with ether, and the extract was washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure to leave a colourless oil (6.20 g). The oil was dissolved in aqueous methanol (MeOH–H_2O, 10:1) (22 ml) and was refluxed with sodium hydroxide (1.80 g) for 1 h. After evaporation of the solvent the residue was extracted with water and the aqueous extract was washed with ether, acidified with acetic acid, and extracted with methylene dichloride. The organic extract was washed with brine, dried (Na_2SO_4), and evaporated to give the crude alcohol (**10**) (4.92 g). The crude compound (**10**) was dissolved in methanol (40 ml) containing a trace amount of concentrated hydrochloric acid (0.4 ml) and the mixture was stirred at room temperature for 3.5 h. After evaporation of the solvent, the crystalline residue was extracted with n-hexane which dissolved the trityl methyl ether leaving the desired dihydroxylactone (**11**) in the residue. The oily residue was dissolved in methylene dichloride, filtered through Celite, and evaporated. The oily residue was then chromatographed on a silica gel column (200 g) using chloroform–methanol (85:15 v/v) as eluant to give the pure *diol* (**11**) (1.79 g, 78%) as colourless prisms, m.p. 36—38 °C; $[\alpha]_D$ + 26.8° (*c* 1.195, MeOH); $\nu_{max.}$ (Nujol) 3 350, 1 740 cm^{-1}; δ 0.98 (3 H, t, *J* 7 Hz, CH_2CH_3), 1.50—1.90 (6 H, m), 2.00—2.30 (2 H, m), 2.85 (2 H, br, exchangeable, 2 × OH), 3.50—4.00 (4 H, m, 2 × OCH_2), and 4.30—4.75 (1 H, m, OCHO); *m/z* 202 (M^+), 99 (100%) (Found: *m/z* 202.1188. $C_{10}H_{18}O_4$ requires *M* 202.1204) (Found: C, 59.0; H, 9.2. $C_{10}H_{18}O_4$ requires C, 59.38; H, 8.97%).

(+)-(1S,4S)-1-*Ethyl*-3,5-*dioxabicyclo*[4.2.1]*nonan*-2-*one* (**14**).—A solution of the diol (**11**) (10.1 g, 50 mmol) and sodium hydroxide (6.0 g, 150 mmol) in aqueous methanol (MeOH–H_2O, 4:1) (100 ml) was refluxed for 2.5 h with stirring. Carbon dioxide was introduced at 0 °C to make the solution weakly basic (pH *ca.* 9) and the mixture was treated with sodium periodate (12.8 g, 60 mmol) in water (100 ml) at the same temperature with stirring. After 2 h, the reaction mixture was filtered through Celite and the filtrate was evaporated at room temperature under reduced pressure. The residue was dissolved in brine (200 ml) and was made acidic by the addition of concentrated hydrochloric acid with ice-cooling. The aqueous solution was extracted with methylene dichloride and the extract was washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure. The oily residue was chromatographed on a silica gel column (150 g) using a mixture of n-hexane and ether (2:1) as an eluant to give the *bicyclic acetal* (**14**) (8.29 g, 97.8%) as colourless prisms, m.p. 82—85 °C; $[\alpha]_D$ + 6.7° (*c* 0.42, CH_2Cl_2); $\nu_{max.}$ (Nujol) 1 750 cm^{-1}; δ 0.93 (3 H, t, *J* 7 Hz, CH_2CH_3), 1.50—2.00 (6 H, m), 2.20—2.50 (2 H, m), 3.85—4.00 (2 H, m, OCH_2), 5.80 (1 H, dd, *J* 5 and 2 Hz, OCHO); *m/z* 171 (M^+ + 1), 97 (100%) (Found: C, 63.5; H, 8.1. $C_9H_{14}O_3$ requires C, 63.51; H, 8.29%).

(+)-(2S)-2-(1,3-*Dithian*-2-*yl*)*methyl*-2-*ethyl*-δ-*valerolactone* (**15**).—A mixture of the bicycloacetal (**14**) (2.26 g, 13.3 mmol), propane-1,3-dithiol (4.0 ml, 39.8 mmol), and toluene-*p*-sulphonic acid monohydrate (76 mg) in toluene (100 ml) was refluxed for 40 h with azeotropic removal of water using a Dean–Stark apparatus. The reaction mixture was washed with 5% aqueous sodium hydrogen carbonate, dried ($MgSO_4$), and evaporated under reduced pressure. The residue was chromatographed on a silica gel column (100 g) using n-hexane–ether (1:1) as eluant to give the *dithianelactone* (**15**)* (3.40 g, 98.0%) as colourless prisms, m.p. 32—33 °C; $[\alpha]_D$ + 37.6° (*c* 1.53, $CHCl_3$); $\nu_{max.}$ (Nujol) 1710 cm^{-1}; δ 0.93 (3 H, t, *J* 7 Hz, CH_2CH_3), 1.50—3.05 (14 H, m), 3.90 (1 H, dd, *J* 7 and 6 Hz, SCHS), and 4.29 (2 H, m, OCH_2); *m/z* 260 (M^+), 133 (100%) (Found: *m/z* 260.0919. $C_{12}H_{20}O_2S_2$ requires *M* 260.0904) (Found: C, 53.9; H, 7.5; S, 23.0. $C_{12}H_{20}O_2S_2 \cdot 1/2H_2O$ requires S, 53.50; H, 7.86; S. 23.80%.

Condensation of the Lactone (**15**) *with Tryptamine*.—A mixture of the bicyclic lactone (**15**) (6.00 g, 23.1 mmol) and tryptamine (4.3 g, 27.7 mmol) was heated for 5 h at 160 °C. The reaction mixture was chromatographed on a silica gel column (200 g) using chloroform as eluant to give the δ-lactam (**17**)* (1.30 g, 14%) as colourless crystals and the secondary amide (**16**)* (7.80 g, 81%) as a pale yellow gum: 3-{2-[3-(1,3-*dithian*-2-*ylmethyl*)-3-*ethyl*-2-*oxopiperidino*]*ethyl*}*indole* (**17**) had m.p. 152—153 °C, $[\alpha]_D$ + 2.0° (*c* 0.99, $CHCl_3$); $\nu_{max.}$ (Nujol) 3 250, 1 605 cm^{-1}; δ 0.85 (3 H, t, *J* 7 Hz, CH_2CH_3), 1.50—3.80 (11 H, m), 4.13 (1 H, m, SCHS), 6.80—7.80 (5 H, m, ArH), and 8.56 (1 H, br s, exchangeable, N*H*); *m/z* 402 (M^+), 270 (100%) (Found: *m/z* 402.1810. $C_{22}H_{30}N_2OS_2$ requires *M* 402.1800); 3-{2-[2-(1,3-dithian-2-ylmethyl)-2-ethyl-5-hydroxypentanamido]ethyl}indole (**16**), $[\alpha]_D$ + 1.5° (*c* 1.53, CH_2Cl_2); $\nu_{max.}$ (film) 3 300, 1 625 cm^{-1}; δ 0.76 (3 H, t, *J* 7 Hz, CH_2CH_3), 1.00—2.20 (11 H, m), 2.30—3.15 (6 H, m), 3.25—4.10 (5 H, m), 5.95 (1 H, br s, exchangeable, OH), 6.80—7.70 (5 H, m, ArH), and 8.60 (1 H, br s, exchangeable, N*H*); *m/z* 420 (M^+), 143

* The compound was identical in all respects except the optical rotations with the corresponding racemic material.[1g]

(100%) [Found: (M^+ + 1) 421.2002. Calc. for $C_{22}H_{30}N_2OS_2$: (M^+ + 1) 421.1982].

Dithianamine (**20**) *from the Amide* (**16**).—The amide (**16**) (11.10 g, 26.4 mmol) was dissolved in phosphoryl chloride (60 ml) and the mixture was refluxed for 4 h. After the removal of volatile material under reduced pressure, the residue was washed with n-hexane, made basic with saturated aqueous sodium hydrogen carbonate, extracted with methylene dichloride, and dried (K_2CO_3). After removal of the drying agent, the filtrate was refluxed for 2.5 h and to the reaction mixture was added 2M-aqueous lithium perchlorate (200 ml) dropwise at 0 °C and the mixture was stirred for 1 h at room temperature. The organic layer was separated, washed with 0.1M-aqueous lithium perchlorate, dried ($MgSO_4$), and evaporated under reduced pressure to give the crude perchlorate (**19b**) (12.45 g) as yellow crystals; this was used for the next reaction without further purification.

To a suspension of lithium aluminium hydride (8.64 g, 227 mmol) in THF (200 ml) was added t-butyl alcohol (64.6 ml, 681 mmol) dropwise at 0 °C with stirring and the stirring was continued for 2 h at the same temperature. The above crude perchlorate (11.00 g) was added in portions at 0 °C and the mixture was stirred for 4 h at the same temperature, then treated with 30% ammonium hydroxide to decompose the remaining reducing agent and filtered through Celite. The organic layer was separated and the aqueous layer was extracted with methylene dichloride. Each organic layer was washed with brine, dried (K_2CO_3), and the combined layer evaporated under reduced pressure. The residual oil was chromatographed on a silica gel column (200 g) using chloroform as eluant to give the tertiary amine (**20**)* (5.59 g, 62%) as pale yellow crystals: m.p. 183—185 °C, $[\alpha]_D$ − 58.8° (*c* 1.03, $CHCl_3$); $\nu_{max.}$ (Nujol) 3 480 cm^{-1}; δ 1.17 (3 H, t, *J* 7 Hz, CH_2CH_3), 1.20—3.20 (20 H, m), 3.33 (1 H, s, NC*H*), 3.80 (1 H, t, *J* 5 Hz, SCHS), 6.90—7.60 (4 H, m, ArH), and 7.80 (1 H, br s, exchangeable, N*H*); *m/z* 386 (M^+), 267 (100%) (Found: *m/z* 386.1838. Calc. for $C_{22}H_{30}N_2S_2$: *M* 386.1838).

(+)-*Eburnamine* (3) *and* (−)-*Eburnamenine* (**4**) *from the Dithianamine* (**20**).—The dithianamine (**20**) (500 mg, 1.30 mmol) in methanol (10 ml) was treated with saturated methanolic hydrogen chloride at 0 °C. After removal of the solvent under reduced pressure, the residual amine (**20**) hydrochloride was dissolved in acetonitrile containing a small amount of water (50:1; 51 ml) and the solution was stirred with methyl iodide (2.4 ml, 39.0 mmol) for 70 h at room temperature. After removal of the solvent under reduced pressure, the residue was made basic with saturated aqueous sodium hydrogen carbonate, and extracted with methylene dichloride. The extract was washed with saturated aqueous sodium hydrogen carbonate, 1% aqueous sodium thiosulphate, and brine, dried (K_2CO_3), and evaporated under reduced pressure. The residue was chromatographed on a silica gel column (15 g) using methylene dichloride as eluant to give (−)-eburnamenine (**4**) (11 mg, 3%) as a pale yellow amorphous powder and (+)-eburnamine (**3**) (102 mg, 27%) as colourless needles after recrystallization from ethanol: (−)-eburnamenine (**4**), $[\alpha]_D$ −151° (*c* 0.16, $CHCl_3$) {for (+)-enantiomer, lit.,[13] $[\alpha]_D$ + 183° (*c*, $CHCl_3$)}; $\nu_{max.}$ (film) 1635 cm^{-1}; δ 1.00 (3 H, t, *J* 7 Hz, CH_2CH_3), 4.27 (1 H, s, NC*H*), 5.05 (1 H, d, *J* 8 Hz, NCH=C*H*), 6.88 (1 H, d, *J* 8 Hz, NC*H*=CH), and 6.95—7.60 (4 H, m, Ar*H*); *m/z* 278 (M^+), 249 (100%); (+)-eburnamine (**3**), m.p. 178—180 °C, $[\alpha]_D$ + 96.0° (*c* 0.10, $CHCl_3$) {for (−)-enantiomer, lit.,[13] m.p. 179—181 °C, $[\alpha]_D$ − 98.2° ($CHCl_3$)}; $\nu_{max.}$ (Nujol) 3 300 cm^{-1}; δ 0.87 (3 H, t, *J* 7 Hz, CH_2CH_3), 3.70 (1 H, s, NC*H*), 3.87 (1 H, br s, exchangeable, O*H*), 5.50 (1 H, dd, *J* 10 and 5 Hz, OC*H*), and 7.00—7.82 (4 H, m, Ar*H*); *m/z* 296 (M^+), 249 (100%). The both compounds were identical with authentic samples (i.r. ^1H n.m.r., and mass spectra, and t.l.c.).

Conversion of (−)-*Eburnamenine* (**4**) *into* (+)-*Eburnamine* (**3**).—A solution of (−)-eburnamenine (**4**) (35 mg, 0.13 mmol) in 0.5% hydrochloric acid (2 ml) was stirred for 16 h at room temperature. The reaction mixture was made basic with saturated aqueous sodium hydrogen carbonate and was extracted with ether. The extract was washed with brine, dried (K_2CO_3), and evaporated. The residual gum was separated on a silica gel plate (1 mm), developing with methanol–chloroform (7:93) to give (+)-eburnamine (**3**) (15 mg) accompanied by starting (−)-eburnamenine (**4**) (10 mg).

(−)-*Eburnamonine* (**2**) *from* (+)-*Eburnamine* (**3**).—To a stirred solution of pyridinium dichromate (47 mg, 0.22 mmol) in methylene dichloride (4 ml) was added (−)-eburnamine (**3**) (50 mg, 0.17 mmol) in methylene dichloride (4 ml) at room temperature. After being stirred for 3 h at the same temperature, the reaction mixture was treated with saturated aqueous sodium hydrogen carbonate (5 ml) for 30 min with stirring and was filtered using Celite. The organic layer was separated and the aqueous layer was extracted thoroughly with methylene dichloride. The combined organic layer was washed with saturated aqueous sodium hydrogen carbonate, brine, dried (K_2CO_3), and evaporated under reduced pressure. The residual gum was separated on a silica gel plate (1 mm) developing with methanol–chloroform (4:96) to give (−)-eburnamonine (**2**) (37 mg, 75%) as colourless prisms after recrystallization from methanol: m.p. 164—165 °C, $[\alpha]_D$ − 97.6° (*c* 0.082, $CHCl_3$) {lit.,[2] m.p. 175 °C, $[\alpha]_D$ − 97.6° ($CHCl_3$)} $\nu_{max.}$ (film) 1 700 cm^{-1}; δ 0.93 (3 H, t, *J* 7 Hz, CH_2CH_3), 1.10—3.60 (14 H, m), 3.93 (1 H, br s, NC*H*), and 7.20—7.50, 8.20—8.50 (4 H, m, Ar*H*); *m/z* 294 (M^+), 168 (100%).

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References

1 Racemic synthesis: (*a*) M. F. Bartlett and W. I. Taylor, *J. Am. Chem. Soc.*, 1960, **82**, 5941; (*b*) E. Wenkert and B. Wickberg, *ibid.*, 1965, **87**, 1580; (*c*) J. E. D. Barton, J. Harley-Mason, and K. C. Yates, *Tetrahedron Lett.*, 1965, 3669; (*d*) A. Buzas, C. Herisson, and G. Lavielle, *C. R. Acad. Sci. Ser. C.*, 1976, **283**, 763; (*e*) D. Cartier, J. Levy, and J. LeMen, *Bull. Soc. Chim. Fr.*, 1976, 1961; (*f*) J. L. Herrmann, G. R. Kieczykowski, S. E. Normandin, and R. H. Schlessinger, *Tetrahedron Lett.*, 1976, 801; (*g*) S. Takano, S. Hatakeyama, and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, 1977, 68; *idem., J. Chem. Soc., Perkin Trans., 1*, 1980, 457; (*h*) L. Novak, J. Rohaly, and C. Szantay, *Heterocycles*, 1977, **6**, 1149; (*i*) F. Klatte, U. Rosentreter, and E. Winterfeldt, *Angew. Chem., Int. Ed. Engl.*, 1978, **16**, 878; (*j*) E. Wenkert, T. Hudlicky, and H. D. Showalter, *J. Am. Chem. Soc.*, 1978, **100**, 4893; (*k*) G. Kalaus, P. Gyory, L. Szabo, and C. Szantay, *Acta Chim. Acad. Sci. Hung.*, 1978, **97**, 429; (*l*) J. L. Herrmann, R. J. Cregge, J. E. Richman, G. R. Kieczykowski, S. N. Normandin, M. L. Quesada, C. L. Semmelhack, A. J. Poss, and R. H. Schlessinger, *J. Am. Chem. Soc.*, 1979, **101**, 1540; (*m*) E. Bolsing, F. Klatte, U. Rosentreter, and E. Winterfeldt, *Chem. Ber.*, 1979, **112**, 1902; (*n*) A. Buzas, J.-P. Jacquet, and G. Lavielle, *J. Org. Chem.*, 1980, **45**, 32; (*o*) K. Irie, M. Okita, T. Wakamatsu, and Y.

* See footnote on p. 307.

Ban, *Nouv. J. Chem.*, 1980, **4**, 275; (*p*) K. Irie and Y. Ban, *Heterocycles*, 1981, **15**, 201; (*q*) E. Wenkert, T. D. J. Halls, L. D. Kwart, G. Magnusson, and H. D. H. Showalter, *Tetrahedron*, 1981, **37**, 4017; (*r*) A.-ur-Rahman and M. Sultana, *Z. Naturforsch.*, 1982, **37b**, 793; (*s*) T. Imanishi, K. Miyashita, A. Nakai, M. Inoue, and M. Hanaoka, *Chem. Pharm. Bull.*, 1983, **30**, 1521; *idem.*, *ibid.*, 1983, **31**, 1191.

2 Chiral synthesis: L. Szabo, J. Sapi, G. Kalaus, G. Argay, A. Kalman, E. Baitz-Gacs, J. Tamas, and C. Szantay, *Tetrahedron*, 1983, **39**, 3737.

3 A part of the present work was published in a preliminary communication: S. Takano, M. Yonaga, and K. Ogasawara, *Heterocycles*, 1982, **19**, 1391.

4 Employing the same methodology the following natural products have been synthesized in chiral forms from the trityl-lactone (**6**): (*a*) (+)-quebrachamine: S. Takano, K. Chiba, M. Yonaga, and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, 1980, 616; (*b*) (−)-velbanamine: S. Takano, M. Yonaga, K. Chiba, and K. Ogasawara, *Tetrahedron Lett.*, 1980, **21**, 3697; (*c*) (+)- and (−)-quebrachamines: S. Takano, M. Yonaga, and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, 1981, 1253; (*d*) (−)-antirhine: S. Takano, N. Tamura, and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, 1981, 1155; (*e*) gibbane framework: S. Takano, C. Kasahara, and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, 1981, 637; (*f*) carbapenem synthon: S. Takano, C. Kasahara, and K. Ogasawara, *Chem. Lett.*, 1982, 631; (*g*) (+)-cleavamine: S. Takano, W. Uchida, S. Hatakeyama, and K. Ogasawara, *Chem. Lett.*, 1982, 733; (*h*) (−)-semburin: S. Takano, N. Tamura, K. Ogasawara, Y. Nakagawa, and T. Sakai, *Chem. Lett.*, 1982, 933; (*i*) (+)- and (−)-mevalonolactones: S. Takano, M. Morimoto, and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, 1984, 82.

5 The use of the lactone (**6**) and its congeners as a chiral synthon was first reported by Koga and his co-workers: see, K. Tomioka, H. Mizuguchi, and K. Koga, *Chem. Pharm. Bull.*, 1982, **30**, 4304 and earlier references cited therein.

6 S. Takano, M. Yonaga, and K. Ogasawara, *Synthesis*, 1981, 265.

7 M. Taniguchi, K. Koga, and S. Yamada, *Tetrahedron*, 1974, **30**, 3574.

8 S. Takano, E. Goto, M. Hirama, and K. Ogasawara, *Heterocycles*, 1981, **16**, 951.

9 This finding was successfully extended to the stereocontrolled synthesis of some natural products with a secondary asymmetric carbon: (*a*) (+)-cleavamine: see, ref. 2*g*; (*b*) (+)-nuciferol and (+)-nuciferal: S. Takano, E. Goto, and K. Ogasawara, *Tetrahedron Lett.*, 1982, **23**, 5567; (*c*) (−)-desmosterol: S. Takano, S. Yamada, H. Numata, and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, 1983, 760; (*d*) 20-epicholanate esters: S. Takano, H. Numata, S. Yamada, S. Hatakeyama, and K. Ogasawara, *Heterocycles*, 1983, **20**, 2159; (*e*) irregular monoterpenes: S. Takano, M. Tanaka, K. Seo, M. Hirama, and K. Ogasawara, *J. Org. Chem.*, in press.

10 H. C. Brown, 'Organic Syntheses *via* Boranes,' Wiley, New York, 1975, pp. 28—29.

11 The racemic compound was synthesized by a completely different method, see: ref. 1*g* and S. Takano, S. Hatakeyama, and K. Ogasawara, *J. Am. Chem. Soc.*, 1979, **101**, 6414.

12 *Cf.* C. Szantay, L. Szabo, G. Kalaus, P. Gyory, J. Sapi, and K. Nogradi, 'Organic Synthesis Today and Tomorrow,' eds. B. M. Trost and C. R. Hutchinson, Pergamon, Oxford, 1981, pp. 285—298.

13 J. Mokry, I. Kompis, and G. Spiteller, *Collect. Czech. Chem. Commun.*, 1967, **32**, 2523.

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