Total Synthesis of (±)- and (+)-Latifine

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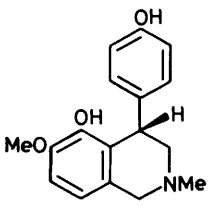
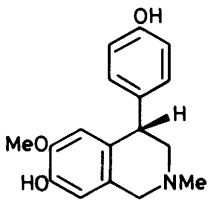
Racemic latifine (+)-(**1**), a new representative of the rare phenolic Amaryllidaceae alkaloids, has been synthesized by employing the Claisen rearrangement of 4-benzyloxycinnamyl 2-methoxyphenyl ether (**11**) as a key step. Based on the racemic synthesis, (*R*)-(+)-latifine (*R*)-(**1**), the unnatural enantiomer, has also been synthesized from (*S*)-*O*-benzylglycidol (*S*)-(**3**) *via* (*S*)-1-benzyloxy-3-phenylthiopropan-2-ol (*S*)-(**4**) as a key intermediate.

The isolation, structure, and absolute configuration of (−)-latifine, an Amaryllidaceae alkaloid, has recently been reported by Kobayashi and co-workers.[1] The structure determination has revealed latifine (**1**) to be the first isoquinoline alkaloid possessing a 4-phenyl-5,6-dioxygenated substitution pattern and isomeric with cherylline (**2**) which is the only 4-phenyl-6,7-dioxygenated isoquinoline alkaloid so far known.[2] We now describe the first total synthesis of latifine (**1**) in racemic and unnatural enantiomeric forms as a part of our synthetic studies utilizing an optically active glycidol (hydroxymethyloxirane) derivative.[3]



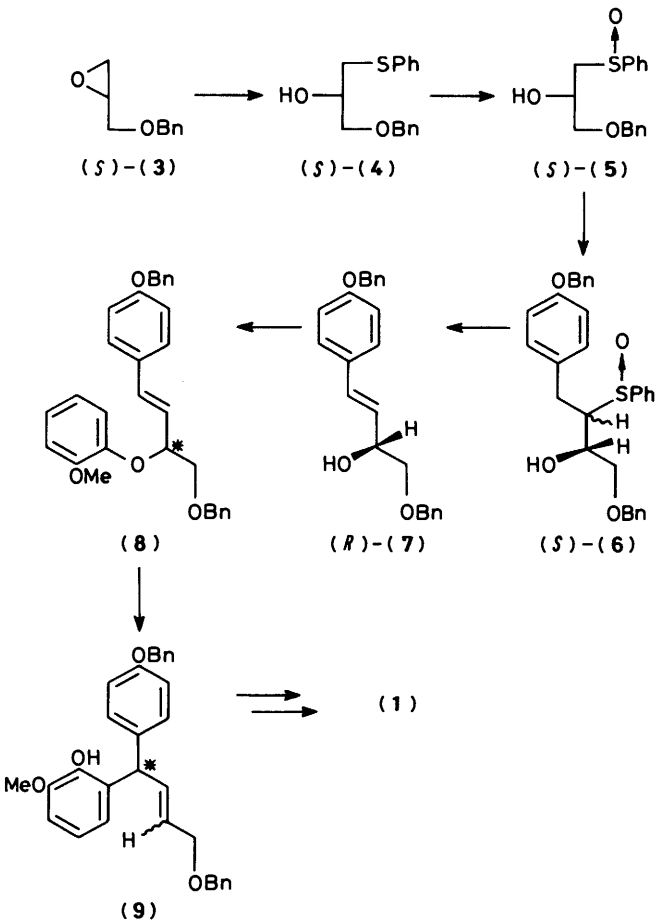
(**1**)



(**2**)

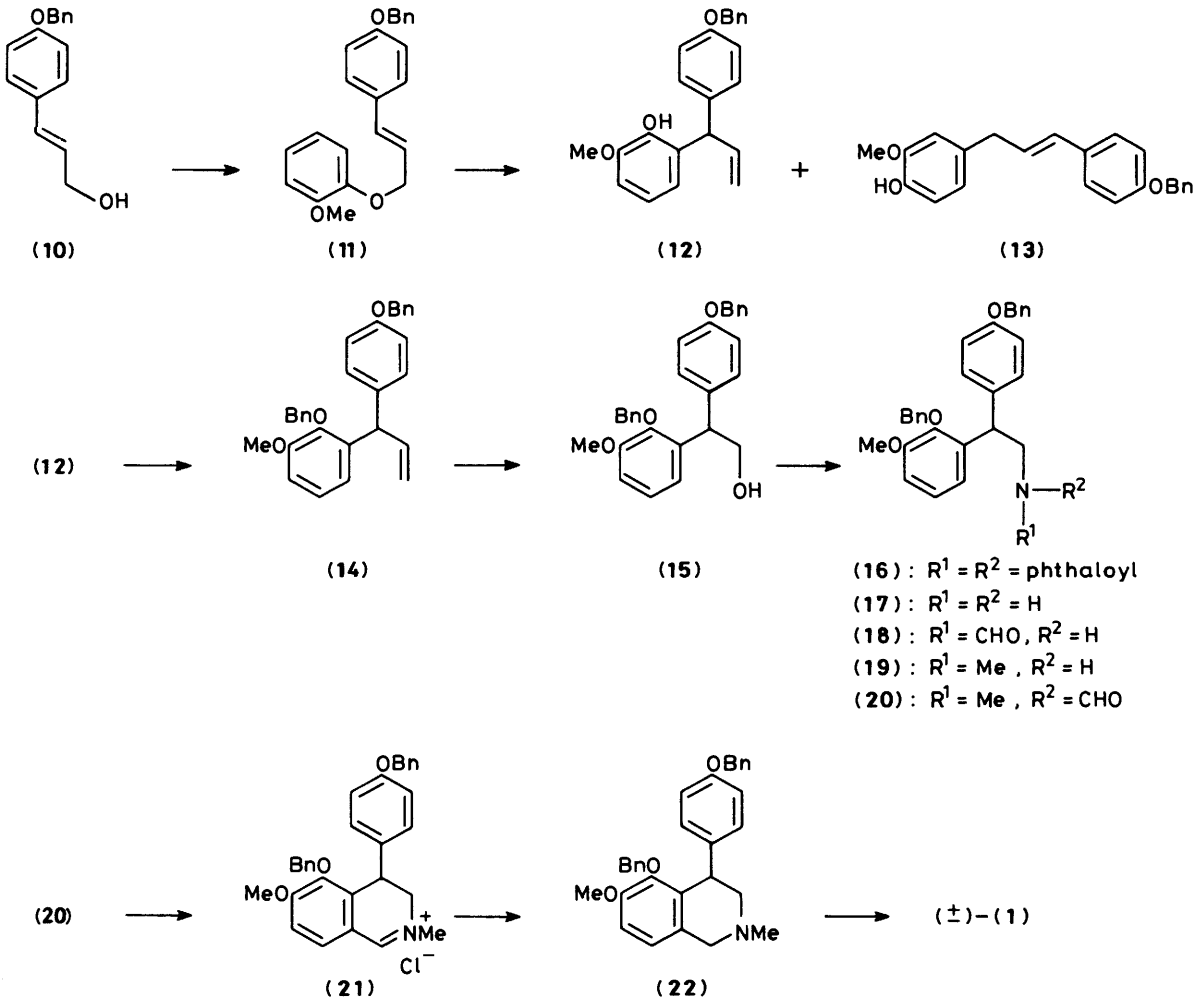
The general approach which was conceived for the chiral synthesis of latifine (**1**) using the chiral sulphide (**4**) is outlined in Scheme 1. The critical feature of this plan focused upon the potential success in synthesizing the optically active allyl aryl ether (**8**) and its stereochemical behaviour in the Claisen rearrangement, since very few examples involving chirality transfer of chiral allyl aryl ether substrates are known.[4] The availability of both enantiomers of the chiral epoxide (**3**) from the same precursor, D-mannitol, encouraged us to exploit this compound as the key chiral building block.[5]

Reaction of the (*S*)-epoxide (*S*)-(**3**)[5] with sodium benzenethiolate at 0 °C in tetrahydrofuran (THF) smoothly gave (*S*)-1-benzyloxy-3-phenylthiopropan-2-ol (*S*)-(**4**) in 89% yield. Since the sulphide (*S*)-(**4**) was found to be inactive to alkylating agents under basic conditions, it was converted into the corresponding sulphoxide (*S*)-(**5**) upon treatment with hydrogen peroxide in aqueous methanol for 3 days at room temperature. The product (*S*)-(**5**) obtained in 100% yield appeared to be a single epimer in its chromatographic behaviour; however, its ^{1}H n.m.r. spectrum revealed that it existed as a *ca.* 1:1 mixture of epimers at the newly generated sulphoxide centre. It was gratifying to find that when the sulphoxide (**5**) was allowed to react with 2.1 mol equiv. of n-butyl-lithium for 2 h at between −60 and 0 °C in THF containing 2.1 mol equiv. of *N,N,N',N'*-tetramethylethylenediamine followed by 1 mol equiv. of 4-benzyloxybenzyl chloride for 20 h at from 0 °C to room temp. it gave the alkylated product (*S*)-(**6**) as a mixture of epimers. Although both epimers could be separated on silica gel plates, the mixture gave the desired allyl alcohol (*R*)-(**7**) directly in 87% yield from sulphoxide (**5**) as a single product upon refluxing in toluene in the presence of calcium carbonate.[6] The ^{1}H n.m.r. spectrum confirmed that compound (**7**) possessed the *E* configuration, since its olefin signals appeared at δ 5.98 and 6.58 with a coupling constant of 17.0 Hz.



Scheme 1.

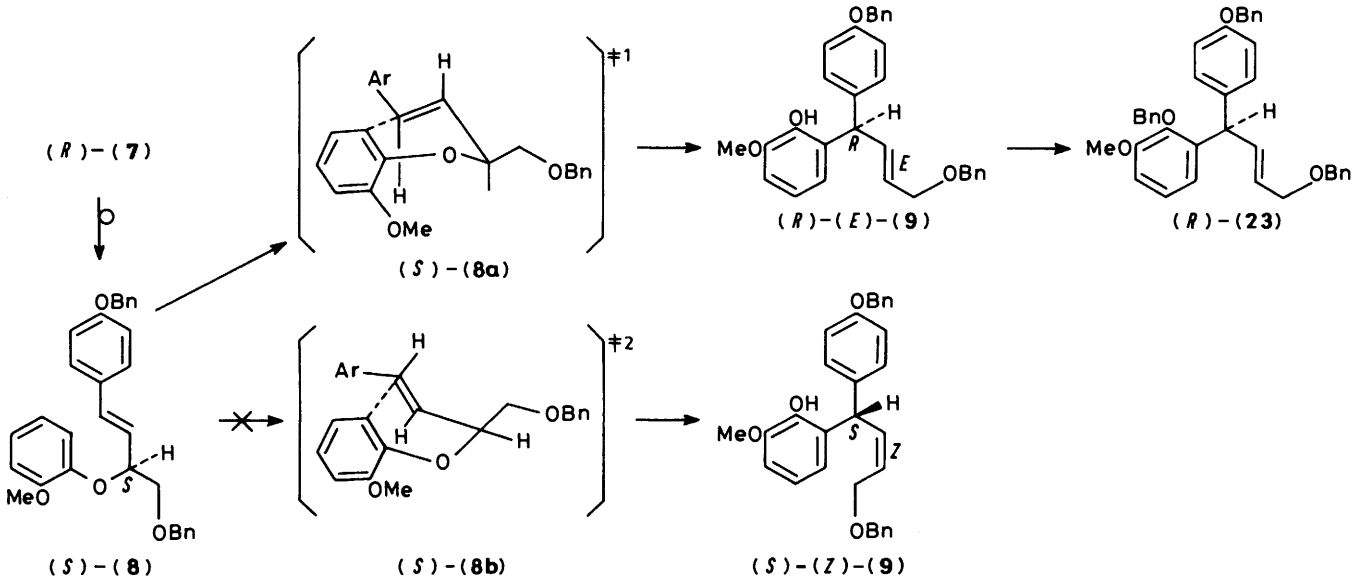
Having obtained the chiral allyl alcohol (*R*)-(**7**) as shown in Scheme 1, we first examined the Claisen rearrangement and the subsequent conversion into the target alkaloid using a non-chiral substrate as a model study shown in Scheme 2. Mitsunobu reaction[7,8] of 4-benzyloxycinnamyl alcohol (**10**) and guaiacol (2-methoxyphenol) with diethyl azodicarboxylate and triphenylphosphine afforded the requisite ether (**11**) in 34% yield, though the yield was greatly reduced by concomitant formation of an unidentified compound which is believed to be



Scheme 2.

an adduct of (**11**) and diethyl azodicarboxylate. When the ether (**11**) was heated in xylene at reflux temperature or in Carbitol[9] at 150 °C, decomposition occurred and no rearranged product could be detected. However, smooth rearrangement occurred in *N,N*-dimethylaniline[10] at reflux temperature to give the desired phenolic compound (**12**) in 75% yield, accompanied by the doubly rearranged product (**13**) in 16% yield which could be separated by silica gel column chromatography. The phenolic group of compound (**12**) was alkylated with benzyl bromide at 80 °C in *N,N*-dimethylformamide (DMF) in the presence of potassium carbonate to give the triether (**14**), in 83% yield, whose newly introduced benzylic methylene protons appeared at δ 4.67 and 4.92 with *J* 11.0 Hz in the ^{1}H n.m.r. spectrum, reflecting its highly congested environment. Ozonization at −78 °C in methanol, followed by reduction in the same flask with sodium borohydride at the same temperature, gave the primary alcohol (**15**) in 87% yield. Mitsunobu reaction[7,11] of compound (**15**) with phthalimide afforded the imide (**16**), in 86% yield, which was deacylated with hydrazine hydrate in refluxing ethanol to give the primary amine (**17**) in 96% yield. Acylation of compound (**17**) with acetic formic anhydride[12] in pyridine at 0 °C gave the formamide (**18**) in 90% yield. Very curiously, the *N*-substituted primary amide (**18**) gave only intractable tars under Bischler–Napieralski conditions using phosphoryl trichloride ($POCl_3$) in refluxing benzene, during which reaction the starting material was consumed. However, the *N,N*-disubstituted amide (**20**), obtained in 76% overall yield from compound (**18**) *via* the secondary amine (**19**) by sequential reduction with lithium aluminium hydride and acylation with acetic formic anhydride, allowed smooth cyclization to afford the desired 3,4-dihydroisoquinolinium chloride (**21**) on treatment with phosphoryl trichloride for 45 min in refluxing benzene. Without purification compound (**21**) was immediately reduced with sodium borohydride in aqueous methanol to give di-*O*-benzyl-latifine (**22**) in 51% yield from the amide (**20**). Conversion of (**22**) into racemic latifine (±)-(**1**) was simply carried out in 85% yield by hydrogenolysis in ethanol at 55 °C in the presence of 10% palladized charcoal. Synthetic material thus obtained showed identical ^{1}H n.m.r. (in deuteriomethanol) and mass spectra with those reported for the natural product.[1]

Following the racemic synthesis, we next investigated the chiral synthesis using the chiral allyl alcohol (*R*)-(**7**) obtained as above. Mitsunobu reaction of (*R*)-(**7**) with guaiacol using di-isopropyl azodicarboxylate in place of the diethyl ester resulted in some improvement to give the desired ether (*S*)-(**8**) in 48% yield with inversion of chirality. Upon Claisen rearrangement in refluxing *N,N*-dimethylaniline the ether (*S*)-(**8**) gave a 76% yield of the rearranged product (*R*)-(*E*)-(**9**), accompanied by an 8% yield of another product, probably formed by double rearrangement to the *para* position with respect to the phenolic group. The ^{1}H n.m.r. spectrum of the former product (after benzylation) revealed that its olefin bond had the *E* configuration based on the large coupling constant (15.7 Hz). Since formation of the *E* configuration could be expected only from



Scheme 3.

the chair transition state (**8a**) and not from the boat transition state (**8b**), it may be concluded that a chair transition state is preferred over a boat transition state in an allyl aryl ether, in a similar way .o that in an allyl vinyl system. This also suggested the absolute chirality of the product which should have the *R* configuration with the *E* olefin structure [(*R*)-(*E*)-(**9**)] but not the *S* configuration with *Z* olefin structure [(*S*)-(*Z*)-(**9**)] (Scheme 3).

The olefin (*R*)-(*E*)-(**9**) was treated with benzyl bromide at 80 °C in DMF using potassium carbonate as base to give the benzyl ether (**23**) in 89% yield. Sequential ozonization and reduction with sodium borohydride in methanol at −78 °C in the same flask afforded the optically active primary alcohol (*R*)-(**15**), in 64% yield, which was identical with the racemic material obtained above in all respects except optical rotation. The following transformation was carried out in completely identical manner with the racemic synthesis described above. Thus, (+)-latifine (*R*)-(**1**) was obtained in 36% overall yield from the primary alcohol (*R*)-(**15**) *via* 8 steps. These indicated that natural (−)-latifine (*S*)-(**1**) may be synthesized if we use the (*R*)-epoxide (*R*)-(**8**) as a chiral starting material. However, it was disappointing to find that the observed specific rotation of the synthetic material, $[\alpha]_D$ +9.9° (MeOH), was unexpectedly lower than that of the natural product (*S*)-(**1**), $[\alpha]_D$ −27.9° (MeOH),[1] even after repeated recrystallization. We are currently investigating the synthesis of (−)-latifine (*S*)-(**1**) with high optical purity based on the present methodology.

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-PMX 60 and JEOL-FX 100 spectrometers. Mass spectra were measured with Hitachi M-52 and JEOL-JMS-OISG-2 spectrometers. Optical rotations were measured with a JASCO-DIP-4 automatic polarimeter. Light petroleum refers to that fraction boiling in the range 30—60 °C.

(S)-1-*Benzyloxy*-3-*phenylthiopropan*-2-*ol* (S)-(**4**).—To a stirred suspension of sodium hydride (1.39 g, 69.2 mmol) in THF (80 ml) at 0 °C was added dropwise thiophenol (5.92 ml, 69.2 mmol) and after 30 min a solution of (*S*)-*O*-benzylglycidol-benzyloxymethyloxirane (*S*)-(**3**) (9.44 g, 57.7 mmol) in THF (20 ml) was added dropwise at the same temperature. After 20 min methanol (5 ml) was added to the reaction mixture and the mixture was diluted with ether (250 ml). The mixture was washed successively with water (100 ml × 3) and brine (100 ml), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was chromatographed on a silica gel column (200 g) with n-hexane–ether (4:1) as eluant to give the *sulphide* (*S*)-(**4**) (14.14 g, 89%) as an oil, $[\alpha]_D$ −14.37° (*c* 4.176 in $CHCl_3$); $\nu_{max.}$(neat) 3 450 cm^{-1}; δ 2.77 (1 H, br d, exchangeable, CHO*H*), 3.05 (2 H, d, *J* 6.0 Hz, CH_2), 3.53 (2 H, d, *J* 5.0 Hz, CH_2), 3.90 (1 H, m, CH), 4.44 (2 H, s, CH_2Ph), 7.23 (5 H, s, Ph), and 7.02—7.51 (5 H, m, Ph); *m/z* 274 (M^+) and 91 (100%) (Found: M^+, 274.1040; C, 69.9; H, 6.45; S, 11.9. $C_{16}H_{18}O_2S$ requires *M*, 274.1028; C, 70.04; H, 6.61; S, 11.69%).

(S)-1-*Benzyloxy*-3-*phenylsulphinylpropan*-2-*ol* (S)-(**5**).—A mixture of the sulphide (*S*)-(**4**) (9.72 g, 35.5 mmol) and 30% aqueous hydrogen peroxide (6.03 ml, 53.3 mmol) in methanol (40 ml) was stirred for 3 days at room temperature. After removal of the solvent under reduced pressure, the residue was dissolved in methylene dichloride (50 ml) and the solution was washed with brine (50 ml), dried ($MgSO_4$), and evaporated under reduced pressure to give the *sulphoxide* (*S*)-(**5**) (10.34 g, 100%) as a practically pure, semi-solid; $\nu_{max.}$(neat) 3 320 cm^{-1}; δ 2.97 (2 H, m, CH_2), 3.48 (2 H, m, CH_2), 4.02 (1 H, br s, exchangeable, OH), 4.28 (1 H, m, CH), 4.45 (2 H, 2 × s, CH_2Ph), 7.16 (5 H, s, Ph), and 7.96 (5 H, m, Ph); *m/z* 290 (M^+) and 91 (100%) (Found: M^+, 290.1007; C, 65.9; H, 6.1; S, 11.3. $C_{16}H_{18}O_3S$ requires *M*, 290.0977; C, 66.18; H, 6.25; S, 11.04%).

(R)-(E)-1-*Benzyloxy*-4-(4-*benzyloxyphenyl*)*but*-3-*en*-2-*ol* (R)-(**7**).—To a mixture of the sulphoxide (*S*)-(**5**) (4.89 g, 16.0 mmol) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (2.4 ml, 34.0 mol) in THF (62 ml) at −55 °C was added 15% (w/w) n-butyl-lithium in n-hexane (21.7 ml, 34.0 mmol) and the temperature was gradually raised to room temperature. After 1 h, the mixture was cooled to 0 °C and to this mixture was added a solution of 4-benzyloxybenzyl chloride (3.74 g, 16.0 mmol) in THF (10 ml). After 30 min at the same temperature, the reaction was

quenched by addition of saturated aqueous ammonium chloride (10 ml) and the mixture was evaporated under reduced pressure. The residue was extracted with methylene dichloride (40 ml × 2) and the extract was washed successively with 10% hydrochloric acid, saturated aqueous sodium hydrogen carbonate (30 ml), and brine (30 ml), and was then dried ($MgSO_4$) and evaporated under reduced pressure to give the crude sulphoxide (*S*)-(**6**) (8.54 g).

A solution of the crude sulphoxide (*S*)-(**6**) (8.54 g) in toluene (150 ml) was refluxed with calcium carbonate (4.82 g, 48 mmol) for 2 h and the mixture was washed successively with saturated aqueous sodium hydrogen carbonate (30 ml × 2) and brine (30 ml), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was chromatographed on a silica gel column (150 g) with methanol–methylene dichloride (5:95) as eluant to give crystals on work-up. Recrystallization from light petroleum–diethyl ether gave the *allylic alcohol* (*R*)-(**7**) (5.03 g, 87%) as prisms, m.p. 81—82 °C; $[\alpha]_D$ +18.31° (*c* 1.966 in ethanol); $\nu_{max.}$(Nujol) 3 450 and 3 050 cm^{-1}; δ 2.16 (1 H, br s, exchangeable, OH), 3.23—3.69 (2 H, m, $CHCH_2O$), 4.48 (1 H, m, $CHCH_2O$), 4.56 (2 H, s, CH_2OCH_2Ph), 5.02 (2 H, s, $ArOCH_2Ph$), 5.98 (1 H, dd, *J* 17 and 6 Hz, CHCH=CH), 6.58 (1 H, d, *J* 17 Hz, CH=CHAr), 6.86 (2 H, m, ArH), 7.30 (10 H, s, 2 × Ph), and 7.04—7.51 (2 H, m, ArH); *m/z* 360 (M^+) and 91 (100%) (Found: M^+, 360.1768; C, 79.9; H, 6.5. $C_{24}H_{24}O_3$ requires *M*, 360.1725; C, 79.97; H, 6.71%).

4-*Benzyloxycinnamyl Alcohol* (**10**).—Sodium hydride (60% in oil; 0.48 g, 12.0 mmol), washed with n-hexane (10 ml × 4), was suspended in a mixture of DMF (10 ml) and THF (30 ml). To this stirred suspension at 0 °C was added triethyl phosphonoacetate [ethyl (diethoxyphosphoryl)acetate] (2.38 ml, 12.0 mmol) dropwise. After 30 min, a solution of 4-benzyloxybenzaldehyde (2.12 g, 10.0 mmol) in THF (10 ml) was added dropwise at the same temperature and the mixture was stirred for 10 min. The reaction mixture was diluted with ether (100 ml) and the extract was washed successively with water (40 ml × 2), saturated aqueous hydrogen carbonate (40 ml × 2), and brine (50 ml), and was then dried ($MgSO_4$) and evaporated under reduced pressure. The crystalline residue was crystallized from ethanol (50 ml) to give *ethyl 4-benzyloxycinnamate* (2.31 g, 82%) as needles, m.p. 61—62 °C; $\nu_{max.}$(Nujol) 1 712 cm^{-1}; δ 1.31 (3 H, t, *J* 7.0 Hz, CH_2CH_3), 4.23 (2 H, q, *J* 7.0 Hz, CH_2CH_3), 5.04 (2 H, s, CH_2Ph), 6.27 and 7.07 (each 1 H, d, *J* 16.0 Hz, CH=CH), 7.33 (5 H, s, Ph), and 6.85—7.77 (4 H, m, ArH); *m/z* 282 (M^+) and 91 (100%) (Found: M^+, 282.1258; C, 76.5; H, 6.55. $C_{18}H_{18}O_3$ requires *M*, 282.1256; C, 76.57; H, 6.43%).

A solution of ethyl 4-benzyloxycinnamate (846 mg, 3.00 mmol) in methylene dichloride (10 ml) was cooled to 0 °C. To this stirred mixture was added dropwise 1.0M di-isobutylaluminium hydride in methylene dichloride (6.6 ml, 6.6 mmol). After 30 min, 15% aqueous sodium hydroxide (3 ml) was added to the reaction mixture to decompose the unchanged hydride reagent. The mixture was extracted with methylene dichloride (15 ml × 2) and the extract was washed successively with water (15 ml) and brine (15 ml), dried ($MgSO_4$), and evaporated under reduced pressure to give crystals. Recrystallization from isopropyl alcohol (20 ml) gave pure *4-benzyloxycinnamyl alcohol* (**10**) (698 mg, 97%) as needles, m.p. 113—115 °C; $\nu_{max.}$(Nujol) 3 320 and 1 602 cm^{-1}; δ 1.51 (1 H, br s, exchangeable, OH), 4.28 (2 H, d, *J* 5 Hz, CH_2O), 5.03 (2 H, s, CH_2Ph), 5.95—6.53 (2 H, m, CH=CH), 7.34 (5 H, s, Ph), and 6.71—6.57 (4 H, m, ArH); *m/z* 240 (M^+) and 91 (100%) (Found: M^+, 240.1152; Found: C, 79.9; H, 6.6. $C_{16}H_{16}O_2$ requires *M*, 240.1150; C, 79.97; H, 6.71%).

4-*Benzyloxycinnamyl 2-Methoxyphenyl Ether* (**11**).—To a stirred mixture of the alcohol (**10**) (2.06 g, 8.58 mmol) and triphenylphosphine (2.70 g, 10.30 mmol) in THF (100 ml) at 0 °C was added guaiacol (1.0 ml, 9.01 mmol) followed by diethyl azodicarboxylate (1.63 ml, 10.30 mmol). After 2 h, the solvent was evaporated off under reduced pressure and the residue was triturated with cold ether (10 ml) to separate out triphenylphosphine oxide which was removed by filtration. The filtrate was evaporated under reduced pressure and the residue was chromatographed on a silica gel column (160 g) with n-hexane–ether (9:1) as eluant to give a crystalline mass which was recrystallized from n-hexane to give the *ether* (**11**) (1.02 g, 34%) as granules, m.p. 91—93 °C; δ 3.86 (3 H, s, OMe), 4.74 (2 H, d, *J* 5 Hz, $=CHCH_2$), 5.06 (2 H, s, CH_2Ph), 6.14—6.79 (2 H, m, CH=CH), 6.83—7.62 (8 H, m, ArH), and 7.37 (5 H, s, Ph); *m/z* 346 (M^+) and 91 (100%) (Found: M^+, 346.1582; C, 80.1; H, 6.2. $C_{23}H_{22}O_3$ requires *M*, 346.1569; C, 79.74; H, 6.40%).

rac-6-(4-*Benzyloxy-α-vinylbenzyl*)*guiacol* (±)-(**12**).—A solution of the ether (**11**) (987 mg, 2.85 mmol) in *N,N*-dimethylaniline (5 ml) was refluxed for 50 min. After having cooled, the mixture was diluted with ether and the solution was washed successively with 10% hydrochloric acid (10 ml × 3) and brine (20 ml), dried ($MgSO_4$), and evaporated under reduced pressure to leave a yellow oil (1.03 g). The residual oil was chromatographed on a silica gel column (30 g) with n-hexane–ethyl acetate (15:1) as eluant to give the *phenol* (±)-(**12**) (737 mg, 75%) as an oil, $\nu_{max.}$(neat) 3 520 and 1 610 cm^{-1}; δ 3.80 (3 H, s, OMe), 4.99 (2 H, s, CH_2Ph), 4.75—5.33 (3 H, m, $CH=CH_2$), 5.71 (1 H, s, exchangeable, OH), 6.02—6.40 (1 H, m, CHCH=), 6.68—7.50 (7 H, m, ArH), and 7.33 (5 H, s, Ph); *m/z* 346 (M^+) and 91 (100%) (Found: M^+, 346.1566. $C_{23}H_{22}O_3$ requires *M*, 346.1567) and the *para*-phenol (**13**) (158 mg, 16.0%); $\nu_{max.}$(neat) 3 540 and 1 605 cm^{-1}; δ 3.45 (2 H, d, *J* 5.0 Hz, $=CHCH_2$), 3.81 (3 H, s, OMe), 5.02 (2 H, s, CH_2Ph), 5.53 (1 H, m, $CH=CHCH_2$), 6.30 (1 H, m, $CH=CHCH_2$), 6.32 (1 H, s, exchangeable, OH), 6.46—7.66 (7 H, m, ArH), and 7.33 (5 H, s, Ph); *m/z* 346 (M^+) and 91 (100%).

rac-3-(4-*Benzyloxyphenyl*)-3-(2-*benzyloxy*-3-*methoxy phenyl*)*prop*-1-*ene* (±)-(**14**).—A mixture of the phenol (±)-(**12**) (337 mg, 0.974 mmol), benzyl bromide (0.29 ml, 2.44 mmol), and potassium carbonate (202 mg, 2.92 mmol) in DMF (5 ml) was heated at 80 °C for 10 h. To the reaction mixture was added water (10 ml) and the mixture was extracted with ether (20 ml × 2). The extract was washed successively with water (10 ml × 2) and brine (10 ml), dried ($MgSO_4$), and evaporated under reduced pressure to leave a yellow oil (0.47 g). The residual oil was chromatographed on a silica gel column (15 g) with n-hexane–ethyl acetate (30:1) as eluant to give the *bis*(*benzyl ether*) (±)-(**14**) (352 mg, 83%) as an oil, $\nu_{max.}$(neat) 1 610 cm^{-1}; δ 3.87 (3 H, s, OMe), 4.67 and 4.92 (each 1 H, d, *J* 11.0 Hz, together CH_2Ph), 4.97 (2 H, s, CH_2Ph), 4.63—5.34 (3 H, m, $CH=CH_2$), 5.90—6.27 (1 H, m, CH), 6.62—7.56 (7 H, m, ArH), and 7.31 (10 H, s, 2 × Ph); *m/z* 436 (M^+) and 91 (100%) (Found: M^+, 436.2028. $C_{30}H_{28}O_3$ requires *M*, 436.2036).

rac-2-*Benzyloxy*-β-(4-*benzyloxyphenyl*)-3-*methoxyphenethyl Alcohol* (±)-(**15**).—To a solution of the ether (±)-(**14**) (1.07 g, 2.45 mmol) in a mixture of methanol (30 ml) and methylene dichloride (10 ml) at −78 °C was introduced ozone for 12 min. After excess of ozone had been expelled by bubbling nitrogen into the reaction mixture for 20 min, the mixture was treated with a solution of sodium borohydride (0.93 g, 24.5 mmol) in water (4 ml) at the same temperature and was gradually warmed to room temperature. The reaction mixture was evaporated under reduced pressure and the residue was extracted with ether (50 ml). The extract was washed successively with water (20 ml) and brine (20 ml), dried ($MgSO_4$), and evaporated to give the *alcohol* (±)-(**15**) (0.97 g, 87%) as an oil which was used for the

next reaction without further purification. A small sample was purified for analysis on a silica gel plate [n-hexane–ether (1:1)]; $\nu_{max.}$(neat) 3 450 cm^{-1}; δ 1.53 (1 H, br s, exchangeable, OH), 3.86 (3 H, s, OMe), 4.01 (2 H, d, *J* 7.0 Hz, CH_2OH), 4.56 (1 H, t, *J* 7.0 Hz, $CHCH_2$), 4.71 and 4.99 (each 1 H, d, *J* 11.0, together CH_2Ph), 6.70—7.50 (7 H, m, ArH), and 7.33 (10 H, s, Ph); *m/z* 440 (M^+) and 91 (100%) (Found: M^+, 440.1998. $C_{29}H_{28}O_4$ requires *M*, 440.1988).

rac-N-[2-*Benzyloxy*-β-(4-*benzyloxyphenyl*)-3-*methoxyphenethyl*]*phthalimide* (±)-(**16**).—To a mixture of the alcohol (±)-(**15**) (315 mg, 0.670 mmol), phthalimide (148 mg, 1.01 mmol), and triphenylphosphine (228 mg, 0.871 mmol) in THF (8 ml) at 0 °C was added diethyl azodicarboxylate (0.18 ml, 1.14 mmol). After the mixture had been stirred for 3 h, the solvent was removed under reduced pressure and the residue was triturated with cold ether (2 ml) to separate out triphenylphosphine oxide which was removed by filtration. The filtrate was evaporated under reduced pressure and the residue was chromatographed on a silica gel column (30 g) with n-hexane–ethyl acetate (5:1) as eluant to give the *imide* (±)-(**16**) (315 mg, 83.0%) as a semi-solid, $\nu_{max.}$(neat) 1 768 and 1 708 cm^{-1}; δ 3.66 (3 H, s, OMe), 4.18 (2 H, d, *J* 8.0 Hz, $CHCH_2$) 4.65 and 4.93 (each 1 H, d, *J* 11.0 Hz, together CH_2Ph), 4.88 (2 H, s, CH_2Ph), 5.17 (1 H, t, *J* 8.0 Hz, $CHCH_2$), 6.53—7.86 (11 H, m, ArH), and 7.24 (10 H, s, 2 × Ph); *m/z* 569 (M^+) and 404 (100%) (Found: M^+, 569.2216. $C_{37}H_{31}NO_5$ requires *M*, 569.2200).

rac-2-*Benzyloxy*-β-(4-*benzyloxyphenyl*)-3-*methoxyphenethylamine* (±)-(**17**).—A solution of the imide (±)-(**16**) (314 mg, 0.552 mmol) in ethanol (5 ml) was refluxed with 90% hydrazine hydrate (96 mg, 1.66 mmol) for 2 h. After the solution had cooled, the separated material was removed by filtration and the filtrate was evaporated under reduced pressure. The residue was chromatographed on a silica gel column (10 g) with ammonia-saturated methanol–chloroform (1:30) as eluant to give the amine (±)-(**17**) (235 mg, 97%) as an oil, $\nu_{max.}$(neat) 3 380 cm^{-1}; δ 1.54 (2 H, br s, exchangeable, NH_2), 3.12 (2 H, d, *J* 8.0 Hz, CH_2NH_2), 3.82 (3 H, s, OMe), 4.33 (1 H, t, *J* 8.0 Hz, $CHCH_2$), 4.68 and 4.99 (each 1 H, d, *J* 11.0 Hz, together CH_2Ph), 4.97 (2 H, s, CH_2Ph), 6.65—7.45 (7 H, m, ArH), and 7.30 (10 H, s, 2 × Ph); *m/z* 422 [$M - NH_3)^+$] and 91 (100%) [Found: *m/z* 422.1869. $C_{29}H_{29}NO_3$ requires ($M - NH_3$), 422.1880].

rac-N-[2-*Benzyloxy*-β-(4-*benzyloxyphenyl*)-3-*methoxyphenethyl*]*formamide* (±)-(**18**).—To a stirred solution of the amine (±)-(**17**) (233 mg, 0.531 mmol) in pyridine (5 ml) at 0 °C was added acetic formic anhydride (0.1 ml, 2.12 mmol). After 45 min, the solvent was removed under reduced pressure and the residue was extracted with ether (20 ml). The extract was washed successively with 10% hydrochloric acid (10 ml × 2), saturated aqueous hydrogen carbonate (10 ml), and brine (10 ml), and was then dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on a silica gel column (10 g) with n-hexane–ethyl acetate (1:1) as eluant to give the *amide* (±)-(**18**) (222 mg, 90%) as a glass, $\nu_{max.}$(neat) 3 290 and 1 670 cm^{-1}; δ 3.36 (2 H, m, CH_2NH), 3.81 (3 H, s, OMe), 4.47 (1 H, dd, *J* 9.0 and 7.0 Hz, $CHCH_2$), 4.95 (2 H, s, CH_2Ph), 4.71 and 4.99 (each 1 H, d, *J* 11.0 Hz, together CH_2Ph), 5.53 (1 H, br s, NHCHO), 6.53—7.50 (7 H, m, ArH), 7.29 (10 H, s, 2 × Ph), and 7.96 (1 H, br d, NHCHO); *m/z* 467 (M^+) and 91 (100%) (Found: M^+, 467.2110. $C_{30}H_{29}NO_4$ requires *M*, 467.2097).

rac-2-*Benzyloxy*-β-(4-*benzyloxyphenyl*)-3-*methoxy*-N-*methylphenethylamine* (±)-(**19**).—A mixture of the amide (±)-(**18**) (224 mg, 0.480 mmol) and lithium aluminium hydride (91 mg, 240 mmol) in THF (5 ml) was refluxed for 3 h. After the mixture had cooled, 33% ammonium hydroxide (2 ml) was added to the reaction mixture to decompose the unchanged hydride reagent and the mixture, suspended with ether (20 ml), was filtered through Celite. The filtrate was dried ($MgSO_4$) and evaporated under reduced pressure to give the *amine* (±)-(**19**) (194 mg, 89%) as an oil which was used for the next reaction without further purification. A small sample was purified for analysis on a silica gel plate [methanol–chloroform (1:99)]; $\nu_{max.}$(neat) 3 350 cm^{-1}; δ 1.93 (1 H, br s, exchangeable, NHMe), 2.35 (3 H, s, NH*Me*), 3.08 (2 H, d, *J* 8.0 Hz, CH_2NH), 3.81 (3 H, s, OMe), 4.60 (1 H, t, *J* 8.0 Hz, $CHCH_2$), 4.97 (2 H, s, CH_2Ph), 4.69 and 4.98 (each 1 H, d, *J* 11.0 Hz, together CH_2Ph), 6.63—7.56 (7 H, m, ArH), and 7.32 (10 H, s, 2 × Ph); *m/z* 453 (M^+) and 91 (100%) (Found: M^+, 453.2277. $C_{30}H_{31}NO_3$ requires *M*, 453.2302).

rac-N-[2-*Benzyloxy*-β-(4-*benzyloxyphenyl*)-3-*methoxyphenethyl*]-N-*methylformamide* (±)-(**20**).—To a stirred solution of the amine (±)-(**19**) (93 mg, 0.20 mmol) in pyridine (1.5 ml) at 0 °C was added acetic formic anhydride (0.04 ml, 0.80 mmol). After 40 min the solvent was removed under reduced pressure and the residue was extracted with ether (10 ml). The extract was washed successively with 10% hydrochloric acid (5 ml × 2), saturated aqueous hydrogen carbonate, and brine (5 ml), and was then dried ($MgSO_4$) and evaporated under reduced pressure to give a glass. Purification on a silica gel plate [n-hexane–ethyl acetate (2:1)] gave the pure *amide* (±)-(**20**) (80 mg, 85%) as a glass, $\nu_{max.}$(neat) 1 678 cm^{-1}; δ 2.60 and 2.66 (3 H, each s, together NMe), 3.64 (2 H, d, *J* 8.0 Hz, CH_2N), 3.82 (3 H, s, OMe), 4.53 (1 H, t, *J* 8.0 Hz, $CHCH_2$), 4.96 (2 H, s, CH_2Ph), 4.70 and 4.96 (each 1 H, d, *J* 11.0 Hz, together CH_2Ph), 6.63—7.50 (7 H, m, ArH), 7.31 (10 H, s, 2 × Ph), and 7.67 and 7.82 (1 H, each br s, together NCHO); *m/z* 481 (M^+) and 91 (100%) (Found: M^+, 481.2227. $C_{31}H_{31}NO_4$ requires *M*, 481.2262).

rac-*Di*-O-*benzyl-latifine* (±)-(**22**).—A mixture of the amide (±)-(**20**) (32 mg, 0.067 mmol) and phosphoryl trichloride (0.04 ml, 0.34 mmol) in benzene (1.5 ml) was refluxed for 45 min. After the solvent had been evaporated off under reduced pressure, the residue was washed with hot n-hexane (2 ml × 3) to remove unchanged phosphoryl trichloride. The residue, dissolved in 10% aqueous methanol (2 ml), was then treated with solid sodium borohydride (25 mg, 0.67 mmol) at 0 °C for 1 h. The reaction mixture was evaporated under reduced pressure and the residue was extracted with ether (10 ml). The extract was washed successively with water (5 ml) and brine (5 ml), dried ($MgSO_4$), and evaporated under reduced pressure to leave a viscous oil (27 mg). Purification on a silica gel plate [methanol–chloroform (5:95)] gave the pure *base* (±)-(**22**) (16 mg, 51%) as a viscous oil, δ 2.26 (3 H, s, NMe), 2.68 (2 H, d, *J* 4.0 Hz, $CHCH_2N$), 3.30 and 3.85 (each 1 H, d, *J* 14.0, together $ArCH_2N$), 3.80 (3 H, s, OMe), 3.91 and 4.80 (each 1 H, d, *J* 10.0 Hz, together CH_2Ph), 4.23 (1 H, t, *J* 4.0 Hz, $CHCH_2$), 4.92 (2 H, s, CH_2Ph), 6.60—7.45 (6 H, m, ArH), and 7.21 (10 H, s, 2 × Ph); *m/z* 465 (M^+) and 91 (100%) (Found: M^+, 465.2295. $C_{31}H_{31}NO_3$ requires *M*, 465.2302).

rac-*Latifine* (±)-(**1**).—A solution of racemic di-*O*-benzyl-latifine (±)-(**22**) (94 mg, 0.202 mmol) in ethanol (5 ml) was hydrogenated in the presence of 10% palladized charcoal (25 mg) for 24 h at 55 °C. After removal of the catalyst by filtration through Celite, the filtrate was evaporated under reduced pressure to give pale brown crystals. Recrystallization from hot ethanol (3 ml) gave pure racemic latifine (±)-(**1**) (49 mg, 85%), m.p. 212—215 °C (decomp.) (natural,[1] m.p. 215—217 °C), as prisms. The spectral data (i.r., ^1H n.m.r. in CD_3OD, and mass) obtained were virtually identical with those reported for the natural product.[1]

(S)-(E)-1-*Benzyloxy*-4-(4-*benzyloxyphenyl*)*but*-3-*en*-2-*yl* 2-*Methoxyphenyl Ether* (S)-(**8**).—To a stirred mixture of the allyl alcohol (*R*)-(**7**) (1.67 g, 4.64 mmol) and triphenylphosphine (1.83 g, 6.96 mmol) in THF (70 ml) at 0 °C was added guaiacol (0.77 ml, 6.96 mmol) followed by di-isopropyl azodicarboxylate (1.37 ml, 6.96 mmol). After 2 h, the solvent was evaporated off under reduced pressure and the residue was dissolved in ether (70 ml). The ether layer was washed successively with 15% aqueous sodium hydroxide (20 ml), water (20 ml), and brine (20 ml), and was then dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on a silica gel column (75 g) with n-hexane–ethyl acetate (10:1) as eluant to give the ether (*S*)-(**8**) (1.04 g, 48%) as an oil, $[\alpha]_D$ +13.87° (*c* 2.264 in $CHCl_3$); δ 3.77 (2 H, d, *J* 6.0 Hz, $CHCH_2$), 3.84 (3 H, s, OMe), 4.64 (2 H, s, CH_2OCH_2Ph), 4.96 (1 H, m, $CHCH_2$), 5.02 (2 H, s, $ArOCH_2Ph$), 6.11 (1 H, dd, *J* 16.0 and 6.0 Hz, CH=C*H*CH), 6.58 (1 H, d, *J* 16.0 Hz, C*H*=CHCH), 6.72—7.02 (8 H, m, ArH), and 7.04—7.48 (10 H, m, 2 × Ph); *m/z* 374 [$(M - 92)^+$] and 91 (100%).

(R)-(E)-6-[4-*Benzyloxy*-1-(4-*benzyloxyphenyl*)*but*-2-*enyl*]-*guiacol* (R)-(**9**).—A solution of the ether (*S*)-(**8**) (1.04 g, 2.22 mmol) in *N*,*N*-dimethylaniline (8 ml) was refluxed for 20 min. After having cooled, the mixture was diluted with ether (50 ml) and the solution was washed successively with 10% hydrochloric acid (20 ml × 3), saturated aqueous sodium hydrogen carbonate (20 ml), and brine (20 ml), and was then dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on a silica gel column (40 g) with n-hexane–ether (5:1) as eluant to give the *phenol* (*R*)-(**9**) (782 mg, 76%) as an oil, $[\alpha]_D$ +5.11° (*c* 1.88 in $CHCl_3$); $\nu_{max.}$(neat) 3 530 cm^{-1}; δ 3.73 (3 H, s, OMe), 4.02 (2 H, d, $=CHCH_2O$), 4.44 (2 H, s, CH_2OCH_2Ph), 4.94 (2 H, s, $ArOCH_2Ph$), 5.03 (1 H, m, $CHCH=CH$), 5.67 (1 H, m, CH=), 5.73 (1 H, br s, exchangeable, OH), 6.19 (1 H, m, =CH), and 6.58—7.52 (17 H, m, ArH and 2 × Ph); *m/z* 466 (M^+) and 91 (100%) (Found: M^+, 466.2134. $C_{31}H_{30}O_4$ requires *M*, 466.2142) (Found: C, 78.6; H, 6.4. $C_{31}H_{30}O_4 \cdot 0.5H_2O$ requires C, 78.29; H, 6.57%) and a by-product, 4-[3-benzyloxymethyl-1-(4-benzyloxyphenyl)-prop-1-enyl]guiacol (8.2 mg, 7.9%) as an oil, $\nu_{max.}$(neat) 3 525 and 1 608 cm^{-1}; δ 3.28 (3 H, s, OMe), 3.76 (2 H, d, *J* 6.0 Hz, $CHCH_2O$), 3.77 (1 H, m, $=CHCHCH_2$), 4.50 (2 H, s, CH_2OCH_2Ph), 4.99 (2 H, s, $ArOCH_2Ph$), 5.51 (1 H, m, CH=C*H*CH), 6.22 (1 H, m, C*H*=CHCH), 6.26 (1 H, s, exchangeable, OH), 6.40—7.53 (7 H, m, ArH), and 7.25 (10 H, s, 2 × Ph); *m/z* 466 (M^+) and 91 (100%).

(R)-(E)-4-*Benzyloxy*-1-(4-*benzyloxyphenyl*)-1-(2-*benzyloxy*-3-*methoxyphenyl*)*but*-2-*ene* (R)-(**23**).—A mixture of the phenol (*R*)-(**9**) (782 mg, 1.68 mmol), benzyl bromide (0.30 ml, 2.52 mmol), and potassium carbonate (929 mg, 6.72 mmol) in DMF (15 ml) was heated at 80 °C for 15 h. To the reaction mixture was added water (15 ml) and the mixture was extracted with ether (30 ml × 2). The extract was washed successively with water (20 ml) and brine (20 ml), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was chromatographed on a silica gel column (35 g) with n-hexane–ethyl acetate (15:1) as eluant to give the *ether* (*R*)-(**23**) (829 mg, 89%) as a syrup, $[\alpha]_D$ + 15.95° (*c* 1.868 in $CHCl_3$); $\nu_{max.}$(neat) 3 050 and 1 615 cm^{-1}; δ 3.84 (3 H, s, OMe), 3.99 (2 H, d, *J* 6.0 Hz, $=CHCH_2O$), 4.55 (2 H, s, CH_2OCH_2Ph), 4.66 and 4.90 (each 1 H, d, *J* 11.0 Hz, together 2′-OCH_2Ph), 4.98 (2 H, s, OCH_2Ph), 5.14 (1 H, d, *J* 6.8 Hz, $CHCH=$), 5.64 (1 H, dt, *J* 15.7 and 6.0 Hz, CH=C*H*CH_2), 6.07 (1 H, dd, *J* 15.7 and 6.8 Hz, CHC*H*=CH), 6.64—7.14 (7 H, m, ArH), and 7.08—7.44 (15 H, m, 3 × Ph); *m/z* 556 (M^+) and 465.91 (100%) (Found: M^+, 556.2604; C, 81.8; H, 6.6. $C_{38}H_{36}O_4$ requires *M*, 556.2612; C, 81.98; H, 6.52%).

(R)-2-*Benzyloxy*-β-(4-*benzyloxyphenyl*)-3-*methoxyphenethyl Alcohol* (R)-(**15**).—To a solution of the ether (*R*)-(**23**) (829 mg, 1.49 mmol) in a mixture of methanol (30 ml) and methylene dichloride (10 ml) at −74 °C was introduced ozone for 35 min. After excess of ozone had been expelled by bubbling nitrogen into the reaction mixture, the mixture was treated with sodium borohydride (564 mg, 14.9 mmol) in water at the same temperature and was gradually warmed to room temperature. The reaction mixture was evaporated under reduced pressure and the residue was extracted with ether (50 ml). The extract was washed successively with water (20 ml) and brine (20 ml), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was chromatographed on a silica gel column (25 g) with n-hexane–ether (1:1) as eluant to give the alcohol (*R*)-(**15**) (422 mg, 64%), $[\alpha]_D$ +34.48° (*c* 1.978 in $CHCl_3$). Spectral (^1H n.m.r. and mass) and chromatographic properties of this compound were identical in all respects with those of the racemic material (±)-(**15**).

(R)-N-2-*Benzyloxy*-[β-(4-*benzyloxyphenyl*)-3-*methoxyphenethyl*]*phthalimide* (R)-(**16**).—Following the procedure described for the racemic material (±)-(**16**), (*R*)-alcohol (*R*)-(**15**) (422 mg, 0.959 mmol) was transformed into the optically active imide (*R*)-(**16**) (519 mg, 95%), $[\alpha]_D$ +14.35° (*c* 1.714 in $CHCl_3$). Spectral (^1H n.m.r. and mass) and chromatographic properties of this compound were identical in all respects with those of the racemic material.

(R)-2-*Benzyloxy*-β-(4-*benzyloxyphenyl*)-3-*methoxyphenethylamine* (R)-(**17**).—Following the procedure described for the racemic material (±)-(**17**), (*R*)-imide (*R*)-(**16**) (519 mg, 0.912 mmol) was transformed into the optically active amine (*R*)-(**17**) (374 mg, 93%), $[\alpha]_D$ +29.76° (*c* 1.942 in $CHCl_3$). Spectral (^1H n.m.r. and mass) and chromatographic properties were identical in all respects with those of the racemic material.

(R)-N-2-*Benzyloxy*-[β-(4-*benzyloxyphenyl*)-3-*methoxyphenethyl*]*formamide* (R)-(**18**).—Following the procedure described for the racemic material (±)-(**18**), (*R*)-amine (*R*)-(**17**) (312 mg, 0.711 mmol) was transformed into the optically active amide (*R*)-(**18**) (297 mg, 89%), $[\alpha]_D$ +25.31° (*c* 2.284 in $CHCl_3$). Spectral (^1H n.m.r. and mass) and chromatographic properties of this compound were identical in all respects with those of the racemic materials.

(R)-2-*Benzyloxy*-β-(4-*benzyloxyphenyl*)-3-*methoxy*-N-*methylphenethylamine* (R)-(**19**).—Following the procedure described for the racemic material (±)-(**19**), (*R*)-amide (*R*)-(**18**) (297 mg, 0.636 mmol) was transformed into the optically active amine (*R*)-(**19**) (217 mg, 75%), $[\alpha]_D$ +28.76° (*c* 1.794 in $CHCl_3$). Spectral (^1H n.m.r. and mass) and chromatographic properties of this compound were identical in all respects with those of the racemic material.

(R)-N-2-*Benzyloxy*-[β-(4-*benzyloxyphenyl*)-3-*methoxyphenethyl*]-N-*methylformamide* (R)-(**20**).—Following the procedure described for the racemic material (±)-(**20**), (*R*)-amine (*R*)-(**19**) (217 mg, 0.479 mmol) was transformed into the optically active amide (*R*)-(**20**) (179 mg, 80%), $[\alpha]_D$ +32.64° (*c* 0.772 in $CHCl_3$). Spectral (^1H n.m.r. and mass) and chromatographic properties of this compound were identical in all respects with those of the racemic material.

(R)*Di*-O-*benzyl-latifine* (R)-(**22**).—Following the procedure described for the racemic material (±)-(**22**), (*R*)-amide (*R*)-(**20**) (179 mg, 0.383 mmol) was transformed into the optically active base (*R*)-(**22**) (132 mg, 76%), $[\alpha]_D$ +4.31° (*c* 0.882 in $CHCl_3$). Spectral (^1H n.m.r. and mass) and chromatographic properties

of this compound were identical in all respects with those of the racemic material.

(R)-(+)-*Latifine* (R)-(**1**).—Following the procedure described for the racemic material (±)-(**1**), (*R*)-benzyl-latifine (*R*)-(**22**) (132 mg, 0.291 mmol) was transformed into optically active latifine (*R*)-(**1**) (75 mg, 100%), m.p. 213—217 °C (decomp.) (natural,[1] m.p. 215—217 °C), $[\alpha]_D$ +9.78° (*c* 1.35 in MeOH) (one recrystallization), $[\alpha]_D$ +9.94° (*c* 0.644 in MeOH) (two recrystallizations), $[\alpha]_D$ +9.39° (*c* 0.362 in MeOH) (three recrystallizations {natural product,[1] $[\alpha]_D$ −27.9° (*c* 0.32 in MeOH)}. Spectral (^{1}H n.m.r. and mass) and chromatographic properties of this compound were identical in all respects with those of the racemic materials.

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