Pergamon

Tetrahedron Vol. 50, No. 38, pp. 11219-11234, 1994

0040-4020/94 $7.00+0.00

0040-4020(94)00684-9

Resolution of Prenyl Bromohydrin Esters and Derivatives: Synthesis of the Quinoline Alkaloid (+)-(R)- and (-)-(S)-Lunacridine

Stephen A. Barr,[a] Derek R. Boyd,*[a] Narain D. Sharma,[a,b] Timothy A. Evans,[a] John F. Malone[a] and Vimal D. Mehta[b]

[a]School of Chemistry, The Queen's University of Belfast, Belfast, BT9 5AG, U.K.

[b]Department of Chemistry, University of Delhi, Delhi 110007, India.

Abstract: Chromatographic separation of the bromohydrin MTPA diastereoisomers formed at the prenyl group attached to quinoline and coumarin rings is reported; base catalysed cyclization of the bromo MTPA esters in the quinoline series yielded the corresponding prenyl epoxide enantiomers. This provides a synthetic route to the enantiopure quinoline alkaloid lunacridine **11** and to the dihydrofuroquinoline 8-methoxy-platydesmine **8**.

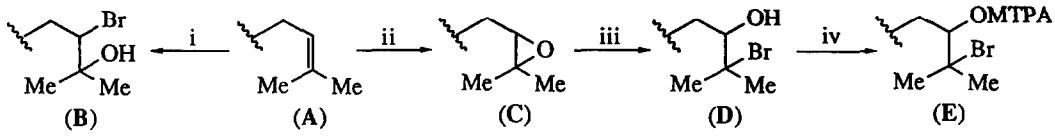
Epoxides of the prenyl (3,3-dimethylallyl) group are established intermediates in the synthesis and biosynthesis of many classes of compounds derived from plants *e.g.* flavanoids, quinoline alkaloids[1] and furanocoumarins.[2] Quinoline alkaloids have previously been obtained using chiral oxidants, *e.g.* peroxycamphoric acid,[3] *via* chiral prenyl epoxides having very low enantiomeric excess values (<10% e.e.). Alternative synthetic routes to enantiopure prenyl epoxide precursors of quinoline alkaloids are therefore required.

Recent reports on the synthesis of the optically pure prenyl epoxides, juvenile hormone III[4] and 10,11-epoxyfarnesol[5], involved an initial asymmetric dihydroxylation (AD) to yield the corresponding prenyl diol enantiomers (92-98% e.e.). Thus asymmetric dihydroxylation of the prenyl moiety, using osmium tetroxide and the chiral auxiliaries [$(DGQD)_2$-PHAL] (AD-mix β) and [$(DHQ)_2$-PHAL] (AD-mix α), followed by base-catalysed cyclization of the corresponding monomesylate derivatives gave juvenile hormone III[4] and 10,11-epoxyfarnesol[5] as single enantiomers. Prompted by the current interest in this area we now report our results on the production of enantiopure prenyl epoxides and derivatives by resolution of the prenyl bromohydrin precursors.

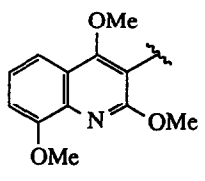
Two possible types of bromohydrin (**B** or **D**) may be formed by addition of a hydroxyl group and a bromine atom to the prenyl group of compound **A** (**Scheme 1**). In practice it is found that N-bromosuccinimide (NBS) in aqueous solution gives the bromohydrin **B** as the normal product. The isomeric bromohydrin **D** could only be obtained as the major product by an indirect method involving epoxidation (MCPBA) of the prenyl group in compound **A**, to yield the dimethylallyl epoxide **C**, followed by treatment with hydrogen bromide gas.

Enantiopure samples of cyclic bromohydrins have earlier been synthesised in these laboratories *via* chromatographic separation of the corresponding diastereoisomeric α-methoxytrifluoromethyl phenylacetate (MTPA) esters. These cyclic bromohydrin enantiomers were then used as precursors of optically pure epoxides and derivatives.[6,7] This resolution method has now been extended to bromohydrins of the prenyl group *e.g.* compound **D**. Type **D** bromohydrins were considered as more suitable candidates for resolution than type **B** due to: (i) the enhanced reactivity of the secondary OH relative to the tertiary OH group during MTPA ester formation, (ii) the proximity of the secondary OH to the chiral centre compared with the tertiary OH group.

The quinoline and coumarin prenyl epoxides (**1C-4C**) were readily obtained in racemic form by epoxidation (MCPBA) of the corresponding prenyl precursors (**1A-4A**).[8,9] Treatment of each of the racemic epoxides **1C**, **2C**, **3C** and **4C** in diethyl ether with hydrogen bromide gas yielded the bromohydrins **1D**, **5D**, **3D** and **4D** respectively in yields of *ca.* 60-70%, after chromatographic purification (**Scheme 1**).



Reagents : i NBS / H_2O ; ii MCPBA ; iii HBr / Et_2O ; iv MTPA-Cl / Pyridine ;



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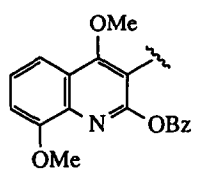

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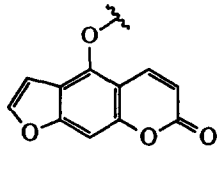

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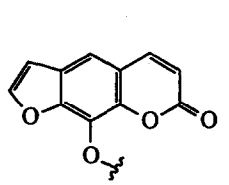

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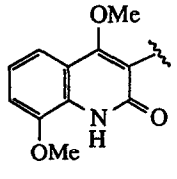

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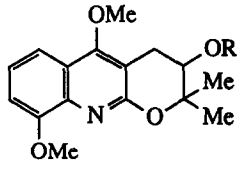
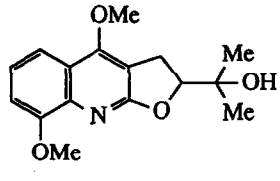


6 R = MTPA
7 R = H



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SCHEME 1

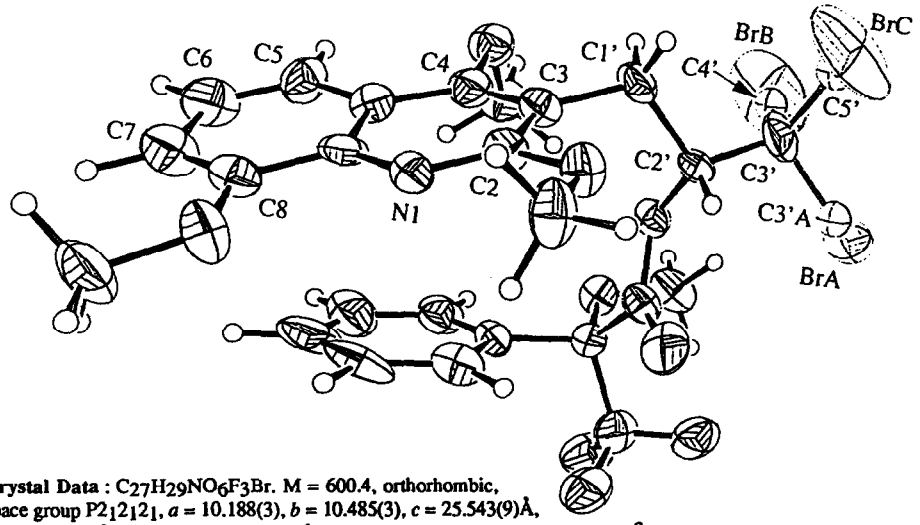
Esterification of the prenyl bromohydrins **1D**, **3D** and **4D**, using the specified MTPA chloride enantiomer in pyridine, yielded a diastereoisomeric mixture of the corresponding MTPA esters **1E**, **3E** and **4E** in good yield (>90%). Several of the bromo MTPA diastereoisomers proved to be crystalline ($1E_H$, $4E_E$, $3E_L$

and $4E_L$) (**Table 1**). The yield of the MTPA ester mixture **5E** obtained was much lower (42%) due to the concomitant formation of the tricyclic bromo MTPA ester **6**. Base catalysed hydrolysis (NaOH/MeOH) of the MTPA ester **6** yielded enantiopure 9-methoxygeibalansine **7**. As indicated by the results in **Table 1** the diastereoisomeric bromo MTPA esters $1E_H/1E_L$ were readily separated by multiple elution preparative TLC on silica-gel (R_f 0.20 and 0.16, $CHCl_3$).

TABLE 1 : *Physical Properties of the Prenyl Bromohydrin MTPA Esters* [a] *(1E, 3E, 4E, 5E)*

MORE POLAR DIASTEREOISOMER			LESS POLAR DIASTEREOISOMER		
Compound	m.p. (°C)	$[\alpha]_D^o$ ($CHCl_3$)	Compound	m.p. (°C)	$[\alpha]_D^o$ ($CHCl_3$)
$1E_H$ [a,b]	112-113	+21.1	$1E_L$ [a,b]	c	-6.8
$3E_E$ [d,e,f]	c	-6.0	$3E_L$ [d,e,f]	98-100	+1.5
$4E_E$ [d,e,g]	95-96	+69.4	$4E_L$ [d,e,g]	126-127	-16.5
$5E_E$ [a,e,h]	c	+41.0	$5E_L$ [a,e,h]	c	-50.0

[a] From (+)-MTPA acid;
[b] High R_f isomer ($1E_H$, 0.20 [$CHCl_3$]) and low R_f isomer ($1E_L$, 0.15 [$CHCl_3$]) after separation on silica-gel using hexane:diethyl ether (80:20 v/v, 6 elutions) as eluant;
[c] High b.p. oil or gum;
[d] From (-)-MTPA acid;
[e] HPLC separation on a Zorbax sil column using propan-2-ol:hexane (10:90 v/v) as eluant;
[f] α value 1.20 for the early ($3E_E$) and late ($3E_L$) eluting isomers;
[g] α value 1.19 for the early ($4E_E$) and late ($4E_L$) eluting isomers;
[h] α value 1.16 for the early ($5E_E$) and late ($5E_L$) eluting isomers;



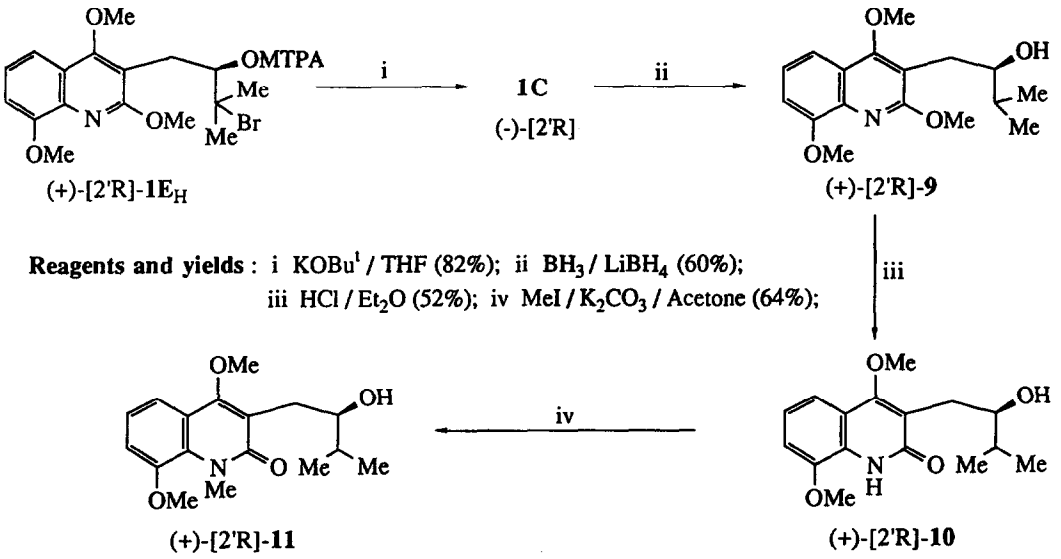
Crystal Data : $C_{27}H_{29}NO_6F_3Br$. M = 600.4, orthorhombic, space group $P2_12_12_1$, a = 10.188(3), b = 10.485(3), c = 25.543(9)Å, U = 2728(1)Å^3, μ(Mo-Kα) = 1.55 cm^{-1}, F(000) = 1232. Z = 4, D_C = 1.46 g cm^{-3}, Siemens P3/V2000 diffractometer, θ/2θ scan, range 3 < 2θ < 45°, 1905 unique reflections measured, direct methods solution, least squares refinement, non-hydrogen atoms anisotropic, -CMe_2Br group disordered, 1530 data with I > 2σ(I) gave R = .065, Rw = .063.

Figure 1 : A projection of the $1E_H$ molecule.
(The -CMe_2Br disorder is shown)

A baseline separation, of the bromo MTPA diastereoisomers $3E_E/3E_L$ (α 1.20) and $4E_E/4E_L$(α 1.19), was achieved by semi-preparative HPLC but the latter approach only provided a partial separation of the diastereoisomers $5E_E$/ $5E_L$ (α 1.16). As a result of the lower yield of the bromo MTPA esters ($5E_E$ and $5E_L$), coupled with the difficulty in obtaining a good separation by HPLC, only small samples (<10 mg) of pure material were available for base-catalysed cyclisation studies.

The bromo MTPA ester $1E_H$ proved to be a readily separable diastereoisomer ($[\alpha]_D$ +21.1°,$CHCl_3$) which crystallized from diisopropyl ether. A suitable crystal, by X-ray crystallographic analysis, showed that it had the (+)-[2'R] configuration (**Figure 1**).

Treatment of the [2'R] bromo MTPA ester $1E_H$ ($[\alpha]_D$ +21.1°), with $KOBu^t$ in THF, gave the [2'R] prenyl epoxide **1C** ($[\alpha]_D$ -26.0, $CHCl_3$). It was in turn reduced, with diborane and lithium borohydride, to the [2'R] secondary alcohol **9** ($[\alpha]_D$ +12°, MeOH) (**Scheme 2**).



SCHEME 2

Cleavage of the 2-methoxy group in compound (+)-**9** (dry HCl gas) yielded the [2'R] quinolinone **10** ($[\alpha]_D$ +18°, MeOH; 52% yield), which was subsequently N-methylated (MeI / K_2CO_3 / $(CH_3)_2CO$) to yield [2'R] lunacridine **11** ($[\alpha]_D$ +26°, MeOH; 64% yield). A similar reaction sequence was carried out on the alternative [2'S] bromo MTPA diastereoisomer $1E_L$ ($[\alpha]_D$ -6.8°, $CHCl_3$). The stereochemical correlation sequence, in **Scheme 2**, unequivocally establishes the [2'R] configuration for (+)-lunacridine **11** and is in agreement with an earlier assignment which was based upon a sample of low enantiomeric excess.[3]

Base-catalysed treatment ($KOBu^t$/THF) of the bromo MTPA diastereoisomer $5E_E$ ($[\alpha]_D$ +41°, $CHCl_3$) afforded 8-methoxyplatydesmine **8** (34% yield) presumably *via* the transient prenyl epoxide **5C**. A [2'R] configuration is assigned to the less polar bromo MTPA diastereoisomer $5E_E$ as its CD spectrum is similar to

that of bromo MTPA ester $\mathbf{1E_H}$ **(Figure 2A)** and hence a [2'S] configuration is assumed for the more polar diastereoisomer $\mathbf{5E_L}$ **(Figure 2B)**.

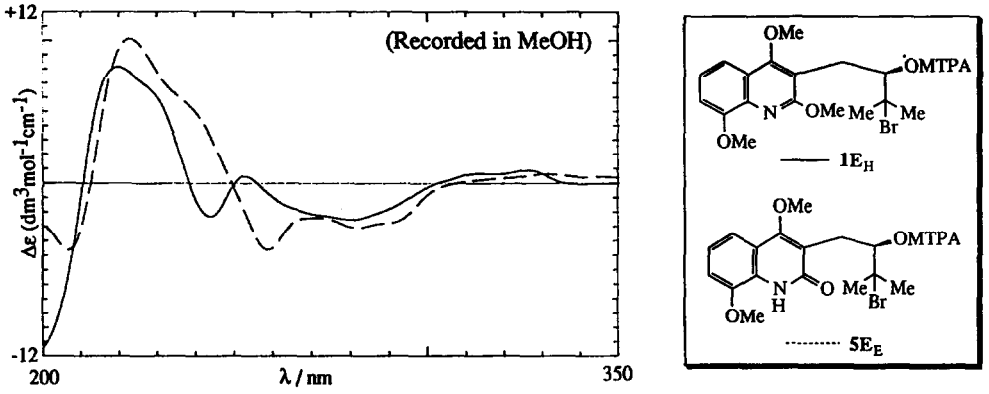


Figure 2A

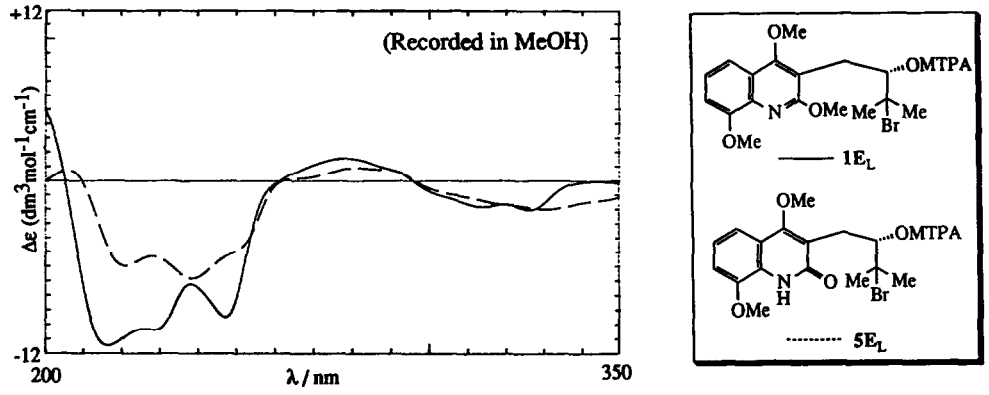
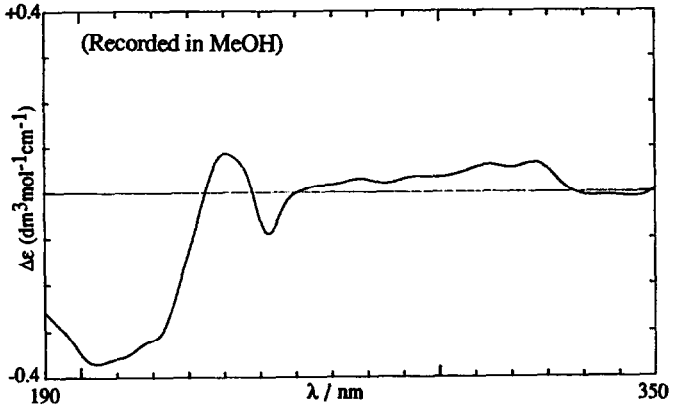


Figure 2B

The derivative, 8-methoxyplatydesmine **8**, should thus be of [2'S] configuration. Since only small samples of diastereoisomers $\mathbf{5E_E}$ and $\mathbf{5E_L}$ (*ca.*0.007g) were available, the quantity of derived enantiopure [2'R] and [2'S] 8-methoxyplatydesmine **8** (*ca.* 0.001-0.002 g) was insufficient for accurate $[\alpha]_D$ measurements. The CD spectrum of the enantiopure [2'R] dihydrofuroquinoline **8** is shown in **Figure 3**. This successful synthesis of

8-methoxyplatydesmine **8**, should thus provide a generally applicable route to a range of known enantiopure dihydrofuroquinoline alkaloids[1] which were unavailable from the cyclic bromohydrin precursors.[7]



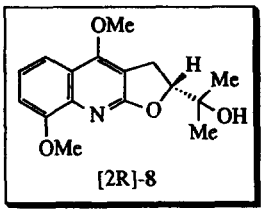


Figure 3

Preliminary attempts to convert the coumarin bromo MTPA diastereoisomers $3E_E$ (or $3E_L$) and $4E_E$ (or $4E_L$) to the corresponding coumarin epoxide enantiomers **3C** or **4C**, using basic conditions, resulted in either no reaction ($NaHCO_3$ or K_2CO_3) or opening of the lactone ring ($KOBu^t$ or NaOH). Further studies are thus required in order to establish the value of bromohydrin esters in the synthesis of coumarin epoxide enantiomers.

EXPERIMENTAL

Melting points were recorded using a Reichert block and are uncorrected. IR spectra were recorded on a Perkin-Elmer Model 983 G instrument coupled to a Perkin-Elmer 3700 Data station. ^{1}H-NMR spectra were recorded at 250MHz with a Bruker WH instrument, at 300 MHz with a General Electric QE 300 instrument and at 500 MHz with a General Electric GE 500 instrument. Mass spectra were recorded at 70 eV on an AEI-MS 902 instrument updated by VG Autospec instruments using a heated inlet system. Accurate molecular weights were determined by the peak-matching method using perfluorokerosene as standard reference and were accurate to within ± 0.000006 a.m.u. Optical rotations were determined on a Perkin-Elmer precision polarimeter Model 241, using specified solvent and concentration at the sodium D-line 589nm and at ambient temperature. Electronic CD spectra were recorded with a JASCO J-720 instrument. Analytical TLC was carried out on Merck Kieselgel 60_{254} plates and the spots visualized using a Hanovia Chromalite UV lamp. Preparative TLC was carried out with glass plates (20cm x 20cm) coated with Merck Kieselgel $PF_{254+366}$. Flash chromatography was effected using Merck Kieselgel 60 (230-400 mesh). HPLC analyses were carried out with a Perkin-Elmer series 3B

liquid chromatograph coupled to a Hewlett Packard 3380S integrator. Column types, conditions and solvents were as specified for individual separations. Pet. Ether refers to petroleum ether (40-60°C).

2,4,8-Trimethoxy-3-(3'-methylbut-2'-enyl)-2-quinolinone (**1A**) was prepared by the method of Grundon and co-workers[11] and was obtained as a pale yellow oil which solidified on standing. Recrystallization from pentane afforded **1A** as needles, m.p. 53-54°C (lit.[10] m.p. 59-60°C), R_f 0.75 ($CHCl_3$); δ_H (300MHz, $CDCl_3$), 1.68 (3H, s, $C(CH_3)_2$), 1.81 (3H, s, $C(CH_3)_2$), 3.45 (2H, d, J 6.5Hz, CH_2CHCMe_2), 3.94, 4.04, 4.14 (3 x 3H, 3 x s, 3 x OCH_3), 5.21 (1H, br t, J 6.5Hz, CH_2CHCMe_2), 6.99 (1H, d, J 7.7Hz, Ar*H*), 7.28 (1H, dd, J 8.3 and 7.7Hz, Ar*H*), 7.52 (1H, d, J 8.2Hz, Ar*H*);

(±)-3-(2',3'-Epoxy-3'-methylbutyl)-2,4,8-trimethoxyquinoline ((±)-**1C**)

Compound **1A** (465mg, 1.91mmol) was taken up in dichloromethane (50ml) and sodium hydrogen phosphate buffer solution (0.1M, pH8, 50ml) was added. *m*-Chloroperoxybenzoic acid (MCPBA)(560mg, 3.25mmol) was added in portions over 10 minutes to the stirred two-phase mixture at 0°C. The mixture was then allowed to rise to room temperature and stirred overnight. The two layers were separated and the organic layer washed with aqueous sodium metabisulphite (1M, 2 x 30ml), aqueous sodium bicarbonate (1M, 2 x 30ml), dried over $MgSO_4$ and reduced to give the crude epoxide as a yellow viscous oil. Purification by flash chromatography [$CHCl_3$-MeOH (99:1 v/v)] gave pure (±)-**1C** (483mg, 98%) as needles from pentane, m.p. 75-76°C (Lit.[3] m.p. 78-80°C); δ_H (300MHz, $CDCl_3$) 1.29 (3H, s, $C(CH_3)_2$), 1.44 (3H, s, $C(CH_3)_2$), 2.92 (1H, dd, J 12.9 and 5.3Hz, $CH^AH^BCHCMe_2$), 3.02-3.14 (2H, m, $CH^AH^BCHCMe_2$), 3.99, 4.05, 4.16 (3 x 3H, 3 x s, 3 x OCH_3), 7.02 (1H, d, J 7.6Hz, Ar*H*), 7.31 (1H, dd, J 8.5 and 7.6Hz, Ar*H*), 7.53 (1H, d, J 8.5Hz, Ar*H*); m/z (EI) 303 (M^+, 100%);

(±)-trans-3-(3'-Bromo-2'-hydroxy-3'-methylbutyl)-2,4,8-trimethoxyquinoline (**1D**)

The epoxide **1C** (557mg, 2.18mmol) was taken up in dry diethyl ether (50ml) and dry hydrogen bromide gas bubbled through the solution at 0°C for 10 minutes. The solution was left to stand for 30 minutes at room temperature and then the ether was evaporated under a stream of nitrogen. The oily residue was dispersed in dichloromethane (30ml), shaken with aqueous sodium bicarbonate (1M, 2 x 20ml) and the organic extracts were then dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave the crude products as a viscous brown oil. Separation of the mixture by preparative TLC [EtOAc:$CHCl_3$ (1:4 v/v)] gave the desired reverse bromohydrin **1D** (416mg, 59%) as a colourless viscous oil, R_f 0.60; δ_H (500MHz, $CDCl_3$) 1.876 (3H, s, $C(CH_3)_2$), 1.881 (3H, s, $C(CH_3)_2$), 3.00 (1H, dd, J 13.6 and 9.9Hz, $CH^AH^BCH(OH)$), 3.16 (1H, dd, J 13.6 and 2.1Hz, $CH^AH^BCH(OH)$), 3.66 (1H, dd, J 9.9 and 2.1Hz, $CH_2CH(OH)$), 4.01, 4.04, 4.15 (3 x 3H, 3 x s, 3 x OCH_3), 7.01 (1H, dd, J 7.8 and 1.1Hz, Ar*H*), 7.31 (1H, dd, J 8.3 and 7.8Hz, Ar*H*), 7.51 (1H, dd, J 8.3 and 1.1Hz, Ar*H*); m/z (EI), 385 (M^+, ^{81}Br, 34%), 383 (M^+, ^{79}Br, 34%) and 232 (100%); (Found: M^+, 383.0722 $C_{17}H_{22}NO_4{}^{79}Br$ requires M^+, 383.0732, 34%);

(+)-(2'R)- and (-)-(2'S)-trans-3-[3'-bromo-2'-(2"-methoxy-2"-phenyl-2"-trifluoromethylacetoxy)-3'-methylbutyl]-2,4,8-trimethoxyquinoline (**1E**$_H$ and **1E**$_L$)

The acyclic bromohydrin **1D** (70mg, 0.18mmol) was taken up in dry pyridine (5ml) containing a trace of dimethylaminopyridine (DMAP), and (+)-MTPA-chloride (60mg, 0.24mmol) was added to the stirred solution at room temperature and stirring continued for 48h. Another portion of (+)-MTPA-chloride (20mg, 7.9 x 10^{-5}mol) was then added and stirring was continued for another 24h. The pyridine was removed under reduced pressure (aided by addition of toluene) and the crude product then purified initially by preparative TLC ($CHCl_3$) to give the bromoester diastereoisomers **1E**$_H$ and **1E**$_L$ as a colourless viscous oil (103mg, 94%). The two bromoester diastereoisomers **1E**$_H$ and **1E**$_L$ were then separated by multiple elution preparative TLC [Pet. ether:Et_2O (4:1 v/v)]. The high R_f (R)-isomer **1E**$_H$ was obtained as a white solid which crystallized from isopropylether, m.p. 112-113°C; $[\alpha]_D$ +21.1° (*c* 0.76 in $CHCl_3$); δ_H (500MHz, $CDCl_3$) 1.89 (3H, s, C(C*H*$_3$)$_2$), 1.93 (3H, s, C(C*H*$_3$)$_2$), 3.13 (1H, dd, J 13.9 and 2.8Hz, C*H*^{A}H^{B}CH(OMTPA)), 3.42 (1H, dd, J 13.9 and 10.5Hz, CH^A*H*^{B}CH(OMTPA)), 3.43 (3H, s, OC*H*$_3$ [MTPA]), 3.70, 4.08, 4.13 (3 x 3H, 3 x s, 3 x OC*H*$_3$), 5.89 (1H, dd, J 10.6 and 2.8Hz, CH_2C*H*(OMTPA)), 6.75-6.79 (2H, m, Ar*H*), 6.91 (2H, d, J 7.7Hz, Ar*H*), 6.95-6.99 (1H, m, Ar*H*), 7.03-7.04 (1H, m, Ar*H*), 7.25-7.27 (2H, m, Ar*H*); m/z (EI) 601 (M^+, ^{81}Br, 47%), 599 (M^+, ^{79}Br, 45%) and 286 (100%); (Found: C, 54.2; H, 4.85; N, 2.1; $C_{27}H_{29}BrF_3NO_4$ requires C, 54.0; H, 4.9; N, 2.3%);

The low R_f (S)-isomer **1E**$_L$ was obtained as a colourless viscous oil; $[\alpha]_D$ -6.8° (*c* 0.89 in $CHCl_3$); δ_H (500MHz, $CDCl_3$) 1.81 (3H, s, C(C*H*$_3$)$_2$), 1.85 (3H, s, C(C*H*$_3$)$_2$), 3.26 (1H, dd, J 14.2 and 3.0Hz, C*H*^{A}H^{B}CH(OMTPA)), 3.29 (3H, s, OC*H*$_3$ [MTPA]), 3.45 (1H, dd, J 14.2 and 10.1Hz, CH^A*H*^{B}CH(OMTPA)), 3.84, 4.06, 4.14, (3 x 3H, 3 x s, 3 x OC*H*$_3$), 5.94 (1H, dd, J 10.1 and 3.2Hz, CH_2C*H*(OMTPA)), 6.92 (2H, m, Ar*H*), 7.02-7.06 (3H, m, Ar*H*), 7.12-7.15 (1H, m, Ar*H*), 7.30-7.33 (1H, m, Ar*H*), 7.46 (1H, dd, J 8.4 and 1.1Hz, Ar*H*); m/z (EI) 601 (M^+, ^{81}Br, 49%), 599 (M^+, ^{79}Br, 50%) and 286 (100%); (Found: M^+, 599.1137 $C_{27}H_{29}NO_6{}^{79}BrF_3$ requires M^+, 599.1130);

(-)-(2'R)-3-(2',3'-Epoxy-3'-methylbutyl)-2,4,8-trimethoxyquinoline ((-)-**1C**)

The (+)-(2'R)-bromoester **1E**$_H$ (100mg, 0.167mmol) was taken up in dry freshly distilled tetrahydrofuran (15ml) and potassium *tert*-butoxide (56mg, 0.499 mmol) was added. The solution was stirred under reflux overnight, cooled, filtered through a pad of celite and evaporated under reduced pressure to yield the crude epoxide as a pale yellow gum. Purification by preparative TLC ($CHCl_3$) gave the pure (-)-**1C** (40mg, 82%) as needles from pentane, m.p. 88-89°C (Lit.[11], m.p. 78-80° for (-)); $[\alpha]_D$ -26° (*c* 0.66 in $CHCl_3$); (Found: C, 66.7; H, 6.8; N, 4.6; $C_{17}H_{21}NO_4$ requires C, 67.3; H, 7.0; N, 4.6%);
(NMR and MS as for (±)-**1C**)

(+)-(2'S)-3-(2',3'-Epoxy-3'-methylbutyl)-2,4,8-trimethoxyquinoline ((+)-**1C**)

The (-)-(2'S)-bromoester **1E**$_L$ (125mg, 0.21mmol) was treated exactly as described for the (+)-(R)-isomer **1E**$_H$ to give pure (+)-**1C** (38mg, 60%) in needles from pentane, m.p. 93-94°C (Lit.[11], m.p. 78-80°C for (-)); $[\alpha]_D$ +27° (*c* 0.61 in $CHCl_3$);
(NMR and MS as for (±)-**1C**)

(+)-(2'R)-3-(2'-Hydroxy-3'-methylbutyl)-2,4,8-trimethoxyquinoline ((+)-**9**)

The (-)-(2'R)-epoxide (-)-**1C** (28mg, 9.24 x 10^{-5}mol) was taken up in a borane-THF solution (1.0M soln., 3ml) and $LiBH_4$ added (large excess). The solution was stored at 0°C for 24h. then a mixture of aqueous sulphuric acid and THF (1M H_2SO_4:THF, 1:1 v/v, 5ml) added dropwise and stirred for 15 minutes. The THF was removed under reduced pressure, a little water was added and the aqueous phase extracted with ether (3 x 5ml). The organic extracts were dried over $MgSO_4$ and reduced to give the crude product as an oil. Preparative TLC [EtOAc:$CHCl_3$ (1:4 v/v)] gave pure (+)-**9** as a colourless viscous oil (17mg, 60%) which was spectrally identical to a reported sample[11]; $[\alpha]_D$ +12° (*c* 1.60 in MeOH); δ_H (500MHz, $CDCl_3$) 1.05 (3H, d, J 3.0Hz, $CHCH_3^A$), 1.07 (3H, d, J 2.7Hz, $CHCH_3^B$), 1.78-1.82 (1H, m, CH(OH)C*H*CMe_2), 2.87 (1H, dd, J 13.6 and 9.4Hz, C*H*^{A}H^{B}CH(OH)), 3.02 (1H, dd, J 13.6 and 3.0Hz, CH^{A}C*H*^{B}CH(OH)), 3.67-3.71 (1H, m, CH_2CH(OH)$CHMe_2$), 4.01, 4.07, 4.17 (3 x 3H, 3 x s, 3 x OCH_3), 7.04 (1H, dd, J 7.8 and 1.0Hz, Ar*H*), 7.34 (1H, dd, J 8.3 and 7.8Hz, Ar*H*), 7.54 (1H, dd, J 8.3 and 1.0Hz, Ar*H*); m/z (EI) 305 (M^+, 52%), 233 (73%) and 218 (100%);

(-)-(2'S)-3-(2'-Hydroxy-3'-methylbutyl)-2,4,8-trimethoxyquinoline ((-)-**9**)

The (+)-(2'S)-epoxide (+)-**1C** (29mg, 9.57 x 10^{-5}mol) was treated exactly as described for the (-)-(R)-epoxide (-)-**1C** to give pure (-)-**9** as a colourless viscous oil (24mg, 82%); $[\alpha]_D$ -13° (*c* 2.04 in MeOH); (NMR and MS as for (+)-**9**)

(+)-(2'R)-3-(2'-Hydroxy-3'-methylbutyl)-4,8-dimethoxy-2-quinolinone ((+)-**10**)

The (+)-(2'R)-trimethoxy compound (+)-**9** (14mg, 4.59 x 10^{-5} mol) was taken up in dry ether (10ml), the solution was saturated with dry hydrogen chloride gas and allowed to stand at room temperature for 24h. The solvent was removed under a stream of nitrogen and the oily residue dispersed in dichloromethane (10ml). This solution was washed with aqueous sodium bicarbonate (1M, 2 x 10ml), dried over $MgSO_4$ and reduced to give the crude product as a gum. Purification by preparative TLC [$CHCl_3$-MeOH (95:5 v/v)] gave alcohol (+)-**10** as a white solid (7mg, 52%) which recrystallized from EtOAc in colourless needles, m.p. 154-155°C (Lit.[11], m.p. 163-165°C); $[\alpha]_D$ +18° (*c* 0.10 in MeOH); $\upsilon_{max.}$ (KBr) 3374 cm^{-1} (OH, NH), 1627 cm^{-1} (2-quinolinone); δ_H (500MHz, $CDCl_3$) 1.03 (3H, d, J 3.7Hz, $CHCH_3^A$), 1.04 (3H, d, J 3.7Hz, $CHCH_3^B$), 1.78-1.82 (1H, m, CH(OH)C*H*CMe_2), 2.74 (1H, dd, J 14.0 and 9.5Hz, C*H*^{A}H^{B}CH(OH)), 3.00 (1H, dd, J 14.0 and 2.1Hz, CH^{A}C*H*^{B}CH(OH)), 3.59-3.62 (1H, m, CH_2CH(OH)$CHMe_2$), 3.95, 3.99 (2 x 3H, 2 x s, 2 x OCH_3), 6.98 (1H, dd, J 8.0 and 1.0Hz, Ar*H*), 7.19 (1H, dd, J 8.2 and 8.0Hz, Ar*H*), 7.36 (1H, dd, J 8.2 and 0.9Hz, Ar*H*), 9.33 (1H, br s, N*H*); m/z (EI) 291 (M^+, 3%), 273 (M^+ -H_2O, 4%) and 219 (100%);

Unreacted starting material (+)-**9** was also isolated (5mg, 36%).

(-)-(2'S)-3-(2'-Hydroxy-3'-methylbutyl)-4,8-dimethoxy-2-quinolinone ((-)-**10**)

The (-)-(S)-trimethoxy compound (-)-**9** (20mg, 6.56 x 10^{-5} mol) was treated exactly as described for (+)-**9** and on purification gave unreacted starting material (-)-**9** (11mg, 55%) and pure (-)-**10** as a white solid

(7mg, 37%) which recrystallized from EtOAc, m.p. 151-152°C (Lit.[11], m.p. 163-165°C); $[\alpha]_D$ -20° (*c* 0.46 in MeOH);
(IR, NMR and MS as for (+)-**10**)

(+)-(2'R)-Lunacridine ((+)-**11**)

The (+)-(2'R)-2-quinolinone (+)-**10** (6mg, 2.06 x 10^{-5} mol) was taken up in dry acetone (10ml), dry potassium carbonate (0.5g) and methyl iodide (0.5ml, 8.03mmol) were added and the mixture was stirred under reflux for 1h. The solution was cooled, filtered, and evaporated under reduced pressure. The crude product was purified by preparative TLC [$CHCl_3$-MeOH (95:5 v/v)] to give pure (2'R)-lunacridine (+)-**11** as the major product as a colourless viscous oil (4mg, 64%) which was identical by spectroscopic and chromatographic comparison with racemic material prepared by using the literature procedure[11]; $[\alpha]_D$ +26° (*c* 0.48 in MeOH); $\upsilon_{max.}$ (neat) 3463 cm^{-1} (OH), 1628 cm^{-1} (2-quinolinone); δ_H (500MHz, $CDCl_3$), 1.02 (3H, d, J 3.3Hz, $CHCH_3^A$), 1.04 (3H, d, J 2.9Hz, $CHCH_3^B$), 1.77-1.81 (1H, m, $CH(OH)CHCMe_2$), 2.74 (1H, dd, J 13.6 and 9.5Hz, $CH^AH^BCH(OH)$), 2.99 (1H, dd, J 13.8 and 2.3Hz, $CH^ACH^BCH(OH)$), 3.58-3.61 (1H, m, $CH_2CH(OH)CHMe_2$), 3.90, 3.91 (2 x 3H, 2 x s, 2 x OCH_3), 4.55 (1H, br s, OH), 7.07 (1H, dd, J 8.2 and 1.2Hz, ArH), 7.21 (1H, dd, J 8.2 and 8.2Hz, ArH), 7.45 (1H, dd, J 8.2 and 1.2Hz, ArH); m/z (EI) 305 (M^+, 6%), 262 (66%), 233 (84%) and 218 (100%);

A minor by-product of the reaction was the trimethoxy compound (+)-**9** (1mg, 17%).

(-)-(2'S)-Lunacridine ((-)-**11**)

The (-)-(2'S)-2-quinolinone (-)-**10** (7mg, 2.41 x 10^{-5} mol) was treated exactly as described for (+)-**10** to give pure (S)-lunacridine (-)-**11** as a colourless viscous oil (6mg, 82%); $[\alpha]_D$ -28° (*c* 0.84 in MeOH); (IR, NMR, MS as for (+)-**11**)

2-Benzyloxy-3-(3'-methylbut-2'-enyl)-4,8-dimethoxyquinoline (**2A**)

Glycolone **5A**, prepared by the literature method[12], (100mg, 0.37mmol) was taken up in dry acetone (20ml), dry potassium carbonate (1.0g), benzyl chloride (60mg, 0.47mmol) and potassium iodide (5mg) were added and the mixture stirred under reflux for 24h. The solution was cooled, filtered and the solvent evaporated under reduced pressure to give the crude product as a viscous oil. Analytical TLC showed the presence of two main products which were separated by preparative TLC ($CHCl_3$) to give alkene **2A**, as the minor product, as a colourless viscous oil which solidified to a white solid overnight at 0°C (37mg, 28%) and crystallized from an isopropylether-methanol mixture, m.p. 79-81°C, R_f 0.75 ($CHCl_3$); δ_H (300MHz, $CDCl_3$), 1.66 (3H, s, $C(CH_3)_2$), 1.69 (3H, s, $C(CH_3)_2$), 3.49 (2H, d, J 6.4Hz, CH_2CHCMe_2), 3.94, 4.05 (2 x 3H, 2 x s, 2 x OCH_3), 5.22 (1H, br t, J 6.4Hz, CH_2CHCMe_2), 5.61 (2H, s, OCH_2Ph), 7.00 (1H, d, J 7.7Hz, ArH), 7.25-7.40 (4H, m, ArH), 7.52-7.55 (3H, m, ArH); m/z (EI) 363 (M^+, 40%), 272 (M^+-CH_2Ph, 67%) and 91 (100%); (Found: C, 75.7; H, 6.75; N, 3.6; $C_{23}H_{25}NO_3$ requires C, 76.0; H, 6.9; N, 3.9%);

The major product was identified as the N-protected isomeric *1-benzyl-3-(3'-methylbut-2'-enyl)-4,8-dimethoxyquinoline* and was obtained as a colourless viscous oil (77mg, 58%), R_f 0.56 ($CHCl_3$); $\upsilon_{max.}$ (neat) 1636cm^{-1} (2-quinolinone); δ_H (300MHz, $CDCl_3$) 1.70 (3H, s, C(C*H*$_3$)$_2$), 1.81 (3H, s, C(C*H*$_3$)$_2$), 3.44 (2H, d, J 6.4Hz, C*H*$_2$CHCMe$_2$), 3.54, 3.91 (2 x 3H, 2 x s, 2 x OC*H*$_3$), 5.29 (1H, t, J 6.3Hz, CH$_2$C*H*CMe$_2$), 5.87 (2H, s, NC*H*$_2$Ph), 6.94 (1H, d, J 7.9Hz, Ar*H*), 7.09-7.36 (6H, m, Ar*H*), 7.48 (1H, d, J 7.7Hz, Ar*H*); m/z (EI) 363 (M^+, 40%) and 272 (M^+-CH_2Ph, 100%) (Found: M^+, 363.1837 $C_{23}H_{25}NO_3$ requires M^+, 363.1834);

(±)-2-Benzyloxy-3-(2',3'-epoxy-3'-methylbutyl)-4,8-dimethoxyquinoline (2C)

The benzyl ether 2A (117mg, 0.32mmol) was taken up in dichloromethane (15ml) and sodium hydrogen phosphate buffer solution (1M, pH8, 15ml) added. MCPBA (130 mg, 0.75mmol) was added to the stirred two-phase mixture at 0°C. Stirring was continued for 30 minutes at this temperature and then the solution was allowed to rise to ambient temperature and stirred overnight. The two phases were separated and the organic phase was washed with aqueous sodium metabisulphite (1M, 2 x 10ml), aqueous sodium bicarbonate (1M, 2 x 10ml), dried over $MgSO_4$ and reduced to yield the crude epoxide as a pale yellow viscous oil (113mg, 93%). Inspection of the crude product by NMR and TLC showed it to be sufficiently pure for the next step in the synthesis. A small proportion of the total sample was purified by preparative TLC ($CHCl_3$) to give epoxide 2C as a clear viscous oil, R_f 0.17 ($CHCl_3$); δ_H (300MHz, $CDCl_3$) 1.22 (3H, s, C(C*H*$_3$)$_2$), 1.32 (3H, s, C(C*H*$_3$)$_2$), 2.94 (1H, dd, J 12.5 and 4.7Hz, C*H*^{A}H^{B}CHCMe$_2$), 3.05-3.98 (2H, m, CH^A*H*^{B}C*H*CMe$_2$), 3.99, 4.07 (2 x 3H, 2 x s, 2 x OC*H*$_3$), 5.62 (2H, s, OC*H*$_2$Ph), 7.04 (1H, d, J 7.7Hz, Ar*H*), 7.30-7.41 (4H, m, Ar*H*), 7.53-7.56 (3H, m, Ar*H*); m/z (EI) 379 (M^+, 45%), 322 (47%), 230 (60%) and 49 (100%) (Found: M^+, 379.1798 $C_{23}H_{25}NO_4$ requires M^+, 379.1783);

(±)-trans-3-(3'-Bromo-2'-hydroxy-3'-methylbutyl)-4,8-dimethoxy-2-quinolinone (5D)

The crude protected epoxide 2C (113mg, 0.30mmol) was taken up in dry diethyl ether (20ml) and dry hydrogen bromide gas was bubbled through the solution at 0°C for 10 minutes. The solution was left to stand for 30 minutes at room temperature and then the ether solvent was removed under a stream of nitrogen. The solid residue was dispersed in dichloromethane (10ml) and shaken with aqueous sodium bicarbonate (1M, 2 x 10ml). The organic phase was then dried over $MgSO_4$ and evaporated under reduced pressure to give the crude product as a light brown solid. Purification by preparative TLC [$CHCl_3$-EtOAc (4:1 v/v)], gave pure bromohydrin 5D as a light brown solid (61mg, 55%) which crystallized in needles from an isopropylether-methanol mixture, m.p. 126-128°C, R_f 0.23 (EtOAc:$CHCl_3$); $\upsilon_{max.}$ (KBr) 3417 cm^{-1} (OH, NH), 1625 cm^{-1} (2-quinolinone); δ_H (500MHz, $CDCl_3$) 1.87 (3H, s, C(C*H*$_3$)$_2$), 1.89 (3H, s, C(C*H*$_3$)$_2$), 2.86 (1H, dd, J 13.8 and 10.0Hz, C*H*^{A}H^{B}CH(OH)), 3.42 (1H, dd, J 13.8 and 1.9Hz, CH^A*H*^{B}CH(OH)), 3.74 (1H, dd, J 10.0 and 1.9Hz, CH$_2$C*H*(OH)CMe$_2$Br), 3.99, 4.02 (2 x 3H, 2 x s, 2 x OC*H*$_3$), 6.99 (1H, dd, J 7.7 and 0.8Hz, Ar*H*), 7.20 (1H, dd, J 8.1 and 7.7Hz, Ar*H*), 7.38 (1H, dd, J 8.1 and 0.8Hz, Ar*H*), 9.47 (1H, br s, N*H*); m/z (EI) 371 (M^+, ^{81}Br, 0.2%), 369 (M^+, ^{79}Br, 0.5%) and 290 (100%); (Found: C, 52.0; H, 5.3; N, 3.5; $C_{16}H_{20}BrNO_4$ requires C, 51.9; H, 5.45; N, 3.8%);

(+)-(R)- and (-)-(S)-trans-3-[3'-bromo-2'-(2"-methoxy-2"-phenyl-2"-trifluoromethyl-acetoxy)-3'-methylbutyl]-4,8-dimethoxy-2-quinoline (**5E**$_E$ and **5E**$_L$)

The (±)-bromohydrin **5D** (35mg, 9.43 x 10^{-5}mol) was taken up in dry pyridine (3ml), DMAP (trace) added and (+)-MTPA-chloride (40mg, 0.16mmol) added dropwise to the stirred solution at room temperature. The solution was stirred for two days, another portion of (+)-MTPA-chloride (40mg, 0.16mmol) was added, and stirring continued for a further two days before the solvent was removed (aided by addition of toluene) under reduced pressure. The crude products were purified by preparative TLC [$CHCl_3$-MeOH (99.9:0.1 v/v)] and gave the desired bromoester diastereoisomers **5E**$_E$ and **5E**$_L$ (inseparable by preparative TLC) as a colourless viscous oil (23mg, 42%); (Found: M^+, 585.0970 $C_{26}H_{27}NO_6{}^{79}BrF_3$ requires M^+, 585.0974); The bromoesters were repurified by multiple elution preparative TLC (Et_2O) before being separated by semi-preparative HPLC (Zorbax sil, 9.4mm x 25cm; 10% ^iPrOH in hexane; flow rate 6ml min^{-1}, uv detection at 390nm). The early (high R_f) diastereoisomer **5E**$_E$ was identified as the (+)-(R)-bromoester and was obtained as a colourless viscous oil (6.6mg); $[\alpha]_D$ +41° (*c* 0.66 in $CHCl_3$); δ_H (300MHz, $CDCl_3$) 1.89 (3H, s, $C(CH_3)_2$), 1.95 (3H, s, $C(CH_3)_2$), 3.04 (1H, dd, J 13.8 and 2.8Hz, CH^AH^BCH(OMTPA)), 3.35 (1H, dd, J 13.7 and 10.6Hz, CH^AH^BCH(OMTPA)), 3.55 (3H, s, OCH_3 [MTPA]), 3.77, 4.02 (2 x 3H, 2 x s, 2 x OCH_3), 5.84 (1H, dd, J 10.6 and 2.8Hz, CH_2CH(OMTPA)), 6.83-6.99 (4H, m, Ar*H*), 7.10-7.33 (4H, m, Ar*H*), 8.92 (1H, br s, N*H*); m/z (EI) 587 (M^+, ^{81}Br, 1%), 585 (M^+, ^{79}Br, 1%), 505 (25%) and 272 (80%);

The late (low R_f) diastereoisomer **5E**$_L$ was identified as the (-)-(S)-bromoester and obtained as a colourless viscous oil (7.2mg); $[\alpha]_D$ -50° (*c* 0.72 in $CHCl_3$); δ_H (300MHz, $CDCl_3$) 1.78 (3H, s, $C(CH_3)_2$), 1.87 (3H, s, $C(CH_3)_2$), 3.17 (1H, dd, J 14.0 and 2.7Hz, CH^AH^BCH(OMTPA)), 3.35 (1H, dd, J 14.0 and 9.8Hz, CH^AH^BCH(OMTPA)), 3.44 (3H, s, OCH_3 [MTPA]), 3.90, 3.99 (2 x 3H, 2 x s, 2 x OCH_3), 5.85 (1H, dd, J 9.8 and 2.7Hz, CH_2CH(OMTPA)), 6.98 (1H, d, J 7.8Hz, Ar*H*), 7.08-7.40 (7H, m, Ar*H*), 9.02 (1H, br s, N*H*); (MS as for **5E**$_E$);

One other high R_f fluorescent band was seen on preparative TLC of the crude reaction product. This was obtained and identified as the cyclized mono-MTPA ester diastereoisomers *(+)-(S)-* and *(-)-(R)-3-(2'-methoxy-2'-phenyl-2'-trifluoro-methylacetoxy)-3,4-dihydro-5,9-di-methoxy-2,2-dimethyl-2H-pyrano[2,3-b] quinoline* (+)-**6** and (-)-**6** and obtained as a colourless viscous oil (10mg, 21%), R_f 0.64 [$CHCl_3$-MeOH (98:2 v/v)]; (Found: M^+, 505.1706. $C_{26}H_{26}F_3NO_6$ requires M^+, 505.1712). These mono-MTPA diastereoisomers were separated by multiple elution preparative TLC (CH_2Cl_2) to give the high R_f (S)-diastereoisomer (+)-**6** as a colourless viscous oil; $[\alpha]_D$ +18° (*c* 0.28 in $CHCl_3$); δ_H (300MHz, $CDCl_3$) 1.32 (3H, s, $C(CH_3)_2$, 1.40 (3H, s, $C(CH_3)_2$), 3.18 (1H, dd, J 17.7 and 5.1Hz, CH^AH^BCH(OMTPA)), 3.32 (1H, dd, J 17.8 and 4.8Hz, CH^AH^BCH(OMTPA)), 3.41 (3H, s, OCH_3 [MTPA]), 3.94, 4.01 (2 x 3H, 2 x s, 2 x OCH_3), 5.26 (1H, dd, J 5.1 and 4.8Hz, CH_2CH(OMTPA)), 6.99 (1H, d, J 7.6Hz, Ar*H*), 7.23-7.51 (7H, m, Ar*H*); m/z (EI) 505 (M^+, 2%) and 189 (100%);

The low R_f (R)-diastereoisomer (-)-**6** was obtained as a colourless viscous oil; $[\alpha]_D$ -9° (*c* 0.32 in $CHCl_3$); δ_H (300MHz, $CDCl_3$) 1.40 (3H, s, $C(CH_3)_2$), 1.44 (3H, s, $C(CH_3)_2$), 3.02 (1H, dd, J 17.7 and 5.4Hz, CH^AH^BCH(OMTPA)), 3.31 (1H, dd, J 17.7 and 4.9Hz, CH^AH^BCH(OMTPA)), 3.46 (3H, s, OCH_3 [MTPA]), 3.90, 4.00 (2 x 3H, 2 x s, 2 x OCH_3), 5.26 (1H, dd, J 5.4 and 4.9Hz, CH_2CH(OMTPA)), 6.97 (1H, d, J 7.7Hz, Ar*H*), 7.30-7.34 (4H, m, Ar*H*), 7.45-7.49 (3H, m, Ar*H*); (MS as for (+)-**6**);

(+)-(S)-3-Hydroxy-3,4-Dihydro-5,9-dimethoxy-2,2-dimethyl-2H-pyrano-[2,3-b]quinoline (9-Methoxygeibalansine) ((+)-7)

The (+)-(S)-mono-MTPA diastereoisomer (+)-**6** (15mg, 2.97 x 10^{-5} mol) was taken up in methanol (4ml) and aqueous potassium hydroxide (10%, 2ml) was added dropwise to the stirred solution at room temperature. After stirring for 3h. the methanol was removed under reduced pressure, brine was added (5ml) and the aqueous mixture extracted with chloroform (3 x 5ml). The extracts were dried over $MgSO_4$, concentrated and the crude product was purified by preparative TLC [$CHCl_3$:EtOAc (4:1 v/v)] to give the optically pure alkaloid (+)-7 (8mg, 93%), as a colourless viscous oil spectrally identical with the literature values[12]; $[\alpha]_D$ +23.7° (*c* 2.27 in EtOH), +17.9° (*c* 1.04 in MeOH); δ_H (300MHz, $CDCl_3$) 1.42 (6H, s, $C(CH_3)_2$), 2.94 (1H, dd, J 17.2 and 6.5Hz, $CH^AH^BCH(OH)$), 3.16 (1H, dd, J 17.2 and 5.0Hz, $CH^AH^BCH(OH)$), 3.92 (1H, dd, J 6.5 and 5.0Hz, $CH^AH^BCH(OH)$), 3.97 (3H, s, OCH_3), 3.99 (3H,s, OCH_3), 6.95 (1H, d, J 7.7Hz, Ar*H*), 7.26 (1H, dd, J 8.3 and 7.7Hz, Ar*H*), 7.47 (1H, d, J 8.3Hz, Ar*H*); m/z (EI) 289 (M^+, 11%) and 83 (100%);

(R)-2,3-Dihydro-2-(1'-hydroxyisopropyl)-4,8-dimethoxyfurano[2,3-b]- quinoline ((R)-**8**)

The (-)-(S)-acyclic bromoester $\mathbf{5E_L}$ (7.2mg, 1.23 x 10^{-5} mol) was taken up in dry tetrahydrofuran (5ml) and potassium *tert*-butoxide (10mg, 8.9 x 10^{-5} mol) added in one portion. The mixture was stirred under reflux overnight, cooled, filtered through a pad of celite and the solvent evaporated under reduced pressure. The crude product was purified by multiple elution preparative TLC [$CHCl_3$-MeOH (99:1 v/v)] and gave pure (R)-**8** as the major product (1mg, 31%), R_f 0.29 (5% MeOH in $CHCl_3$), spectrally identical with a racemic sample and with the literature[12]; δ_H (300MHz, $CDCl_3$) 1.25 (3H, s, $C(CH_3)_2$), 1.39 (3H, s, $C(CH_3)_2$), 3.57 (2H, d, J 8.2Hz, $CH_2CH(CMe_2OH)$), 3.99, 4.20 (2 x 3H, 2 x s, 2 x OCH_3), 4.60 (1H, t, J 8.3Hz, $CH_2CH(CMe_2OH)$), 6.97 (1H, d, J 7.7Hz, Ar*H*), 7.22 (1H, dd, J 8.4 and 7.7Hz, Ar*H*), 7.60 (1H, d, J 8.4Hz, Ar*H*); m/z (EI) 289 (M^+, 76%), 204 (54%) and 69 (100%);

(S)-2,3-Dihydro-2-(1'-hydroxyisopropyl)-4,8-dimethoxyfurano[2,3-b]- quinoline ((S)-**8**)

The (+)-(R)-acyclic bromoester $\mathbf{5E_E}$ (6.6mg, 1.13 x 10^{-5} mol) was treated exactly as described for the $\mathbf{5E_L}$ diastereoisomer to give pure (S)-**8** (1mg, 34%); (Spectral details as for (R)-**8**);

(±)-Heraclenin (**3C**)

Imperatorin **3A** (500mg, 1.85mmol), synthesised by literature methods[2], was taken up in chloroform (25ml) and MCPBA (400mg, 2.32mmol) added in portions to the stirred solution at 0°C. After 2h. the solution was washed with aqueous sodium bicarbonate (5%, 2 x 25ml), water (1 x 25ml), dried over Na_2SO_4 and the solvent removed under reduced pressure to yield the crude product. Purification by column chromatography on neutral alumina yielded pure heraclenin **3C** (400mg, 76%) which crystallized from a chloroform-pet. ether mixture as colourless crystals, m.p. 113-115°C (lit.[2], m.p. 114-115°C); δ_H (250MHz, $CDCl_3$) 1.28 (3H, s, $C(CH_3)_2$), 1.34 (3H, s, $C(CH_3)_2$), 3.32 (1H, t, J 7Hz, CH_2CHCMe_2), 4.59 (2H, d, J 7Hz, CH_2CHCMe_2),

6.38 (1H, d, J 10Hz, OCOC*H*CHC), 6.84 (1H, d, J 2.5Hz, OCHC*H*C), 7.41 (1H, s, Ar*H*), 7.70 (1H, d, J 2.5Hz, OC*H*CHC), 7.78 (1H, d, J 10Hz, OCOCHC*H*C); (Found: C, 72.1; H, 5.3; $C_{16}H_{14}O_5$ requires C, 72.2; H, 5.3%);

(±)-Oxypeucedanin (**4C**)

Isoimperatorin **4A** (500mg, 1.85mmol), synthesised by literature methods[2], was treated exactly as described previously for imperatorin **3A** to yield pure oxypeucedanin **4C** (450mg, 85%) which crystallized from a chloroform-pet. ether mixture as white crystals, m.p. 142-143°C (lit.[2], m.p. 142-143°C); δ_H (250MHz, $CDCl_3$) 1.36 (3H, s, $C(CH_3)_2$), 1.44 (3H, s, $C(CH_3)_2$), 3.28 (1H, t, J 7Hz, CH_2CHCMe_2), 4.41-4.68 (2H, m, CH_2CHCMe_2), 6.35 (1H, d, J 10 Hz, OCOC*H*CHC), 6.98 (1H, d, J 2.5Hz, OCHC*H*C), 7.20 (1H, s, Ar*H*), 7.63 (1H, d, J 2.5Hz, OC*H*CHC), 8.23 (1H, d, J 10Hz, OCOCHC*H*C); (Found: C, 72.1; H, 5.3; $C_{16}H_{14}O_5$ requires C, 72.2; H, 5.3%);

(±)-8-(3"-Bromo-2"-hydroxy-3"-methylbutanoxy)-psoralen (**3D**)

Dry hydrogen bromide gas was passed through a solution of heraclenin **3C** (500mg, 1.75mmol) in dry diethyl ether:benzene (90:10 v/v) (25ml) until the solution became saturated. After stirring for 1h. at 5°C the reaction mixture was washed with water (2 x 25ml), dried over Na_2SO_4 and the solvent evaporated under reduced pressure to yield crude bromohydrin **3D** (450mg, 70%) as a viscous oil, which was sufficiently pure to be used for the next step; δ_H (250MHz, $CDCl_3$) 1.76 (6H, s, $C(CH_3)_2$), 3.38 (1H, s, O*H*), 3.95 (1H, q, $CH^AH^BCH(OH)$), 4.35 (1H, q, CH_2CHCMe_2), 4.67 (1H, q, $CH^AH^BCH(OH)$), 6.20 (1H, d, J 10Hz, OCOC*H*CHC), 6.70 (1H, d, J 2.5Hz, OCCHC*H*C), 7.25 (1H, s, ArH), 7.60 (1H, d, J 2.5 Hz, OC*H*CHC), 7.65 (1H, d, J 10Hz, OCOCHC*H*C); (Found: C, 52.3; H, 4.1; $C_{16}H_{15}O_5Br$ requires C, 52.3; H, 4.1%);

(±)-5-(3"-Bromo-2"-hydroxy-3"-methylbutanoxy)-psoralen (**4D**)

The epoxide **4C** (500mg, 1.75mmol) was treated with dry hydrogen bromide gas exactly as described previously for heraclenin **3C** to yield the crude bromohydrin **4D** (450mg, 70%) as a viscous oil, which was sufficiently pure to be used for the next step; δ_H (250MHz, $CDCl_3$) 1.60 (6H, s, $C(CH_3)_2$), 4.28 (1H, q, $CH^AH^BCH(OH)$), 4.70 (1H, q, CH_2CHCMe_2), 4.90 (1H, s, O*H*), 5.02 (1H, q, $CH^AH^BCH(OH)$), 6.22 (1H, d, J 10Hz, OCOC*H*CHC), 7.05 (1H, d, J 2.5Hz, OCCHC*H*C), 7.15 (1H, s, ArH), 7.68 (1H, d, J 2.5 Hz, OC*H*CHC), 8.25 (1H, d, J 10Hz, OCOCHC*H*C); (Found: C, 52.3; H, 4.2; $C_{16}H_{15}O_5Br$ requires C, 52.3; H, 4.1%);

(-)- and (+)-8-[3"-Bromo-2"-(2-methoxy-2-phenyl-2-trifluoromethylacetoxy)-3"-methyl-butanoxy]-psoralen (**$3E_E$** and **$3E_L$**)

The bromohydrin **3D** (100mg, mmol) was taken up in dry pyridine (0.1ml) and (-)-MTPA-chloride (760mg, 3.0mmol) added dropwise to the stirred solution. After stirring for 24h. at room temperature water was added

and the mixture extracted with diethyl ether (2 x 25ml), the combined extracts dried over Na_2SO_4 and the solvent removed under reduced pressure to yield the crude products as a viscous brown oil (150mg). The two bromo-MTPA diastereoisomers **3E**$_E$ and **3E**$_L$ were purified by flash chromatography before being separated by semi-preparative HPLC (Zorbax sil, 9.4mm x 25cm; 6% ethyl acetate in hexane; flow rate 3ml min^{-1}, uv detection at 254nm), (96% yield, α 1.20); (Found: C, 53.5; H, 3.7; $C_{26}H_{22}O_7BrF_3$ requires C, 53.5; H, 3.8%); The early (high R_f) diastereoisomer **3E**$_E$ was obtained as a solid foam; $[\alpha]_D$ -6.0 ($CHCl_3$); δ_H (250MHz, $CDCl_3$) 1.76 (3H, s, C(C*H*$_3$)$_2$), 1.82 (3H, s, C(C*H*$_3$)$_2$), 3.70 (3H, s, OC*H*$_3$), 4.70-5.07 (2H, m, OC*H*$_2$CH(OMTPA)), 5.76 (1H, dd, J 7 and 2Hz, OCH$_2$C*H*(OMTPA)), 6.37 (1H, d, J 10Hz, OCOC*H*CHC), 6.83 (1H, d, J 2.5Hz, OCHC*H*C), 7.25-7.71 (7H, m, Ar*H*, OC*H*CHC), 7.77 (1H, d, J 10Hz, OCOCHC*H*C);

The late (low R_f) diastereoisomer **3E**$_L$ was obtained as a solid which crystallized from a pet.ether-ether mixture in colourless needles, m.p.98-100°C; $[\alpha]_D$ +1.5° ($CHCl_3$); δ_H (250MHz, $CDCl_3$) 1.91 (3H, s, C(C*H*$_3$)$_2$), 1.95 (3H, s, C(C*H*$_3$)$_2$), 3.64 (3H, s, OC*H*$_3$), 4.68-4.97 (2H, m, OC*H*$_2$CH(OMTPA), 5.75 (1H, dd, J 7 and 2Hz, OCH$_2$C*H*(OMTPA)), 6.36 (1H, d, J 10Hz, OCOC*H*CHC), 6.80 (1H, d, J 2.5Hz, OCHC*H*C), 7.23-7.68 (7H, m, Ar*H*, OC*H*CHC), 7.75 (1H, d, J 10Hz, OCOCHC*H*C);

(-)- and (+)-5-[3"-Bromo-2"-(2-methoxy-2-phenyl-2-trifluoromethylacetoxy)-3"-methyl-butanoxy]-psoralen (**4E**$_E$ and **4E**$_L$)

The bromohydrin **4D** (100mg, 0.27mmol) was treated with (-)-MTPA-chloride exactly as described previously for bromohydrin **3D** to yield the crude diastereoisomers **4E**$_E$ and **4E**$_L$ (150mg). These were purified as previously to yield the pure esters and then separated by semi-preparative HPLC (as previously described), (95% yield, α 1.18); (Found: C, 53.5; H, 3.8; $C_{26}H_{22}O_7BrF_3$ requires C, 53.5; H, 3.8; The early (high R_f) diastereoisomer **4E**$_E$ was obtained as a solid which crystallized from a pet.ether-ether mixture as white crystals, m.p. 95-96°C; $[\alpha]_D$ +69.4° ($CHCl_3$); δ_H (250MHz, $CDCl_3$) 1.77 (3H, s, C(C*H*$_3$)$_2$), 1.84 (3H, s, C(C*H*$_3$)$_2$), 3.55 (3H, s, OC*H*$_3$), 4.75-5.06 (2H, m, OC*H*$_2$CH(OMTPA), 5.77 (1H, dd, J 7 and 2Hz, OCH$_2$C*H*(OMTPA)), 6.17 (1H, d, J 10Hz, OCOC*H*CHC), 6.94 (1H, d, J 2.5Hz, OCHC*H*C), 7.10-7.55 (6H, m, Ar*H*), 7.63 (1H, d, J 2.5Hz, OC*H*CHC), 7.88 (1H, d, J 10Hz, OCOCHC*H*C);

The late (low R_f) diastereoisomer **4E**$_L$ was obtained as a solid which crystallized from a pet.ether-ether mixture as an amorphous powder, m.p. 126-127°C; $[\alpha]_D$ -16.5° ($CHCl_3$); δ_H (250MHz, $CDCl_3$) 1.82 (3H, s, C(C*H*$_3$)$_2$), 1.87 (3H, s, C(C*H*$_3$)$_2$), 3.55 (3H, s, OC*H*$_3$), 4.70-4.96 (2H, m, OC*H*$_2$CH(OMTPA), 5.70 (1H, dd, J 7 and 2Hz, OCH$_2$C*H*(OMTPA)), 6.22 (1H, d, J 10Hz, OCOC*H*CHC), 6.88 (1H, d, J 2.5Hz, OCHC*H*C), 7.20-7.50 (6H, m, Ar*H*), 7.60 (1H, d, J 2.5Hz, OC*H*CHC), 7.94 (1H, d, J 10Hz, OCOCHC*H*C);

ACKNOWLEDGEMENTS

We thank the Department of Education, Northern Ireland for a Distinction Award (to S.A.B) and a Quota Award (to T.A.E), and the Industrial Research and Technology Unit, Northern Ireland for financial support (to N.D.S).

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(*Received in UK* 25 *May* 1994; *revised* 1 *August* 1994; *accepted* 4 *August* 1994)