Synthesis and absolute stereochemistry assignment of enantiopure dihydrofuro- and dihydropyrano-quinoline alkaloids

Derek R. Boyd,* Narain D. Sharma, Stephen A. Barr, Jonathan G. Carroll, Donald Mackerracher and John F. Malone

School of Chemistry, The Queen's University of Belfast, Belfast, UK BT9 5AG

Received (in Cambridge, UK) 3rd July 2000, Accepted 14th August 2000
First published as an Advance Article on the web 2nd October 2000

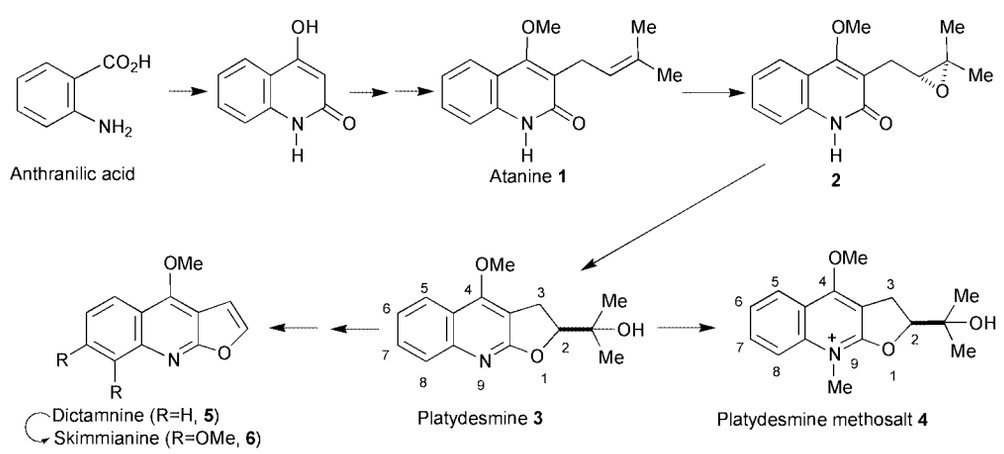
The chiral quinoline alkaloids platydesmine **3**, platydesmine methosalt **4** and edulinine **9**, have been synthesised in enantiopure form *via* asymmetric dihydroxylation of the achiral alkaloid atanine **1**. Chromatographic separation of MTPA diastereoisomers **20** formed from racemic bromohydrin derivatives of atanine **1** was a key step in the synthesis of geibalansine **7**, edulinine **9**, ribalinine **10**, Ψ-ribalinine **11** and araliopsine **12** as single enantiomers. The absolute configurations of (+)-platydesmine methosalt **4** and (−)-Ψ-ribalinine **11** were unequivocally determined by X-ray crystallography while stereochemical correlation and circular dichroism spectroscopy methods were used to assign absolute configurations to platydesmine **3**, geibalansine **7**, ribalinine **10**, araliopsine **12** and edulinine **9**. Possible errors which earlier led to the incorrect assignment of absolute configurations of the quinoline alkaloids platydesmine **3**, platydesmine methosalt **4**, edulinine **9**, araliopsine **12** and other related chiral quinoline alkaloids are discussed.

Introduction

The *Rutaceae* family of plants has yielded a large number (>500) of alkaloids with quinoline alkaloids being the most common type (>200).[1,2] The pharmacological properties of quinoline alkaloids have been investigated to a limited degree and thus evidence of anti-bacterial, anti-fungal, and anti-viral (HIV) activity has been observed.[1,2] Several quinoline alkaloids have also been found to show cytotoxic, phototoxic and mutagenic activity and to form cycloadducts with DNA.[1–5] Although many quinoline alkaloids have been synthesised in racemic form, prior to the publication of a part of this work, as a preliminary report,[6] the individual enantiomers of chiral quinoline alkaloids have not been synthesised and thus have not been available for comparative studies of their biological activity.

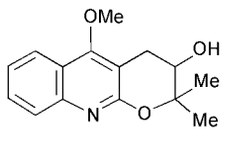
Our initial approach[6] provided a diastereoisomeric separation route to the synthesis of enantiopure quinoline alkaloids and also indicated that several of the absolute configuration assignments in the literature[7–10] may have been incorrect. This comprehensive study has been undertaken in order to explore the potential of an asymmetric synthesis approach to the enantiopure quinoline alkaloids platydesmine **3**, platydesmine methosalt **4** and edulinine **9**, and to assign or re-examine the absolute stereochemistry of these alkaloids along with the chemically synthesised enantiopure samples of geibalansine **7**, geibalansine methosalt **8**, ribalinine **10**, Ψ-ribalinine **11**, and araliopsine **12** using unequivocal methods.

The majority of quinoline alkaloids appear to be derived from anthranilic acid *via* a biosynthetic pathway of the type shown in Scheme 1.[1,2] Platydesmine **3** has been shown to play a central role in the biosynthesis of a much wider range of alkaloids including platydesmine methosalts **4**, furoquinolines *e.g.* dictamnine **5** and skimmianine **6** which occur in the ornamental shrub *Skimmia japonica*[9] (Scheme 1). The chirality introduced during enzyme-catalysed epoxidation of atanine **1** to form the oxirane intermediate **2**, is followed by an inversion of configuration during cyclisation to yield platydesmine **3** and other chiral plant alkaloids. The metabolic pathway linking anthranilic acid, platydesmine **3**, platydesmine methosalt **4**, dictamnine **5** and skimmianine **6** (Scheme 1) has been established from biosynthetic labelling studies.[1,2] This study describes biomimetic methods for the synthesis of alkaloids **3**, **4**, **7**–**12** in enantiopure form and provides unequivocal assignments of their absolute stereochemistry.

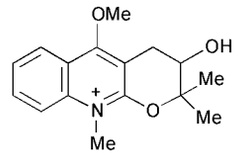


Scheme 1

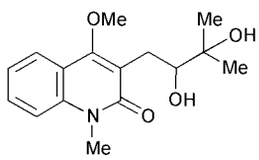
DOI: 10.1039/b005285j



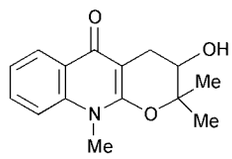
Geibalansine **7**



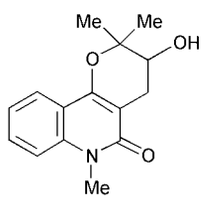
Geibalansine methosalt **8**



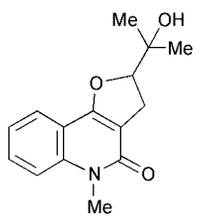
Edulinine **9**



Ribalinine **10**



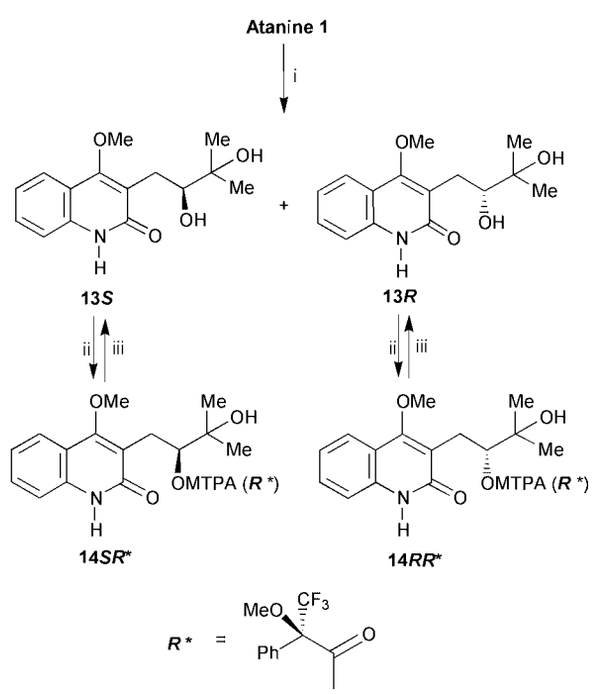
Ψ-Ribalinine **11**



Araliopsine **12**

Results and discussion

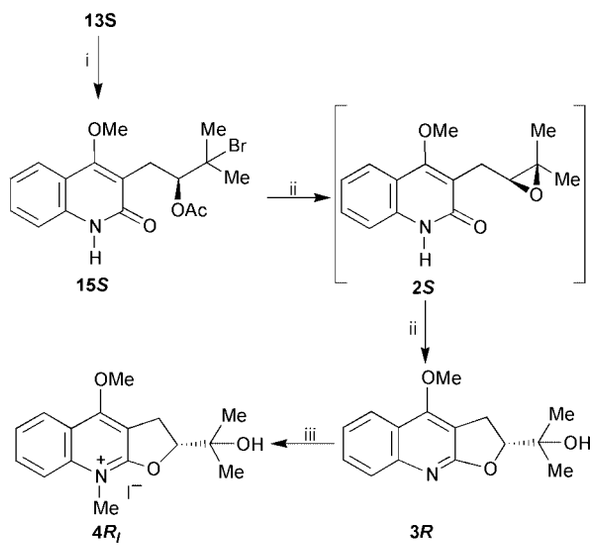
Atanine **1**, a quinoline alkaloid containing a dimethylallyl group, was obtained by synthesis using the literature method.[11] It was asymmetrically dihydroxylated to yield an enantiomerically enriched mixture of diols **13*S*–13*R*** using a catalytic amount of osmium tetraoxide in the presence of $K_3Fe(CN)_6$ and the chiral ligand ($(DHQ)_2$-PHAL, AD-mix-α)[12] (Scheme 2).



Scheme 2 *Reagents*: i AD-α or AD-β mix, t-BuOH, H_2O; ii (+)-*S*-MTPA-Cl; iii MeOH, K_2CO_3.

Formation of the corresponding diastereoisomeric mono-MTPA esters [MTPA = methoxy(trifluoromethyl)phenylacetic acid] **14*SR**** (97%) or **14*RR**** (3%) after treatment with the (+)-(*S*)-MTPA chloride (derived from (+)-(*R*)-MTPA, *R**), followed by ^{1}H-NMR analysis, confirmed that diol **13*S*** was the major enantiomer (enantiomeric excess, ee, 94%). Chromatographic separation of the mono-MTPA diastereoisomers **14*SR**/14*RR**** on silica gel (50% Et_2O in hexane) yielded a pure sample of the major mono-MTPA ester **14*SR**** which was hydrolysed (K_2CO_3, MeOH) to yield enantiopure diol **13*S*** ($[\alpha]_D$ −42, MeOH). When the procedure was repeated using the β-form of AD-mix the opposite enantiomer **13*R*** ($[\alpha]_D$ +43, MeOH) was obtained as the major product (94% ee). Application of the stereochemical mnemonic model developed by Sharpless *et al.* for the asymmetric dihydroxylation of trisubstituted alkenes,[12] using the β-form of AD-mix, to the alkene atanine **1**, allowed an (*R*) configuration to be tentatively assigned to the major enantiomer of diol **13** (**13*R***). Conversely the use of the α-form of AD-mix was expected to yield the configuration **13*S*** preferentially.

Reaction of diol **13*S*** with acetoxyisobutyryl bromide yielded the corresponding bromoacetate **15*S*** in 75% yield (Scheme 3).



Scheme 3 *Reagents*: i $MeCO_2CMe_2COBr$, MeCN; ii t-BuOK, THF; iii MeI, EtOH.

This reaction has been widely used in these and other laboratories with a range of *vicinal* diol enantiomers and has been consistently found to yield a bromo ester where the configuration remained unchanged at the chiral centre bearing an oxygen atom.[13] Treatment of bromo acetate **15*S*** with potassium *tert*-butoxide in THF yielded platydesmine **3*R*** (67% yield, $[\alpha]_D$ −47, MeOH) *via* the intermediate epoxide **2*S*** which was not isolated. Treatment of platydesmine **3*R*** with methyl iodide yielded the platydesmine methiodide **4*R*$_I$** (56% yield, $[\alpha]_D$ −31, MeOH). This (−)-(*R*) absolute configuration proved to be opposite to that reported earlier[7,8] for the naturally occurring (+)-sample of platydesmine methosalt **4** which was also given an (*R*) configuration.

Using the enantiopure diol **13*R*** and a similar reaction sequence (**13*R*→15*R*→2*R*→3*S*→4*S*$_I$**) to that shown in Scheme 3 for diol **13*S*** gave platydesmine **3*S*** ($[\alpha]_D$ +47, MeOH) and the platydesmine methiodide **4*S*$_I$** ($[\alpha]_D$ +31, MeOH). This sample of platydesmine methiodide proved to be indistinguishable from a sample of the alkaloid ($[\alpha]_D$ +31, MeOH) which was re-isolated from the *Rutaceous* shrub *Skimmia japonica* as the reineckate anion during the current study. Using an anion exchange resin (Amberlite IRA-420, ClO_4^-) the reineckate anion was replaced by the perchlorate anion.

Recrystallisation of the perchlorate salt **4*S*$_P$** from methanol gave suitable crystals ($[\alpha]_D$ +33, MeOH) for X-ray crystallographic determination of absolute structure using the anomalous X-ray scattering (Bijvoet) method. The (+)-configuration of perchlorate **4*S*$_P$** was unequivocally assigned as (*S*) from the absolute structure parameter $x = -0.01(4)$ and therefore the earlier (*R*) configurations assigned to the (+)-platydesmine methosalt **4** from *S. japonica*[1,7,8,14] and to (+)-platydesmine **3**[1,14]

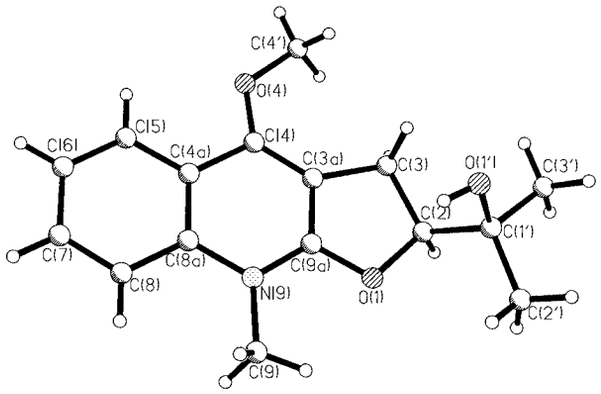


Fig. 1 X-Ray structure of one of the two independent molecules of $4S_P$.

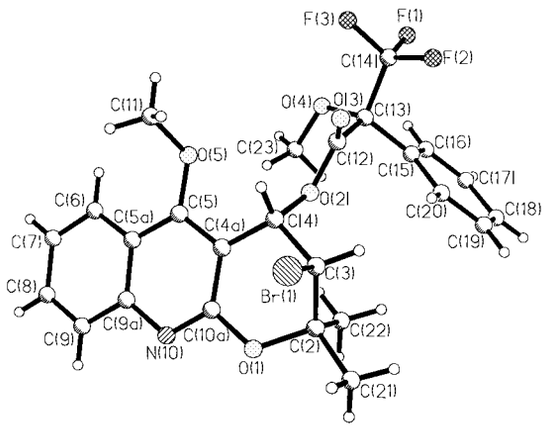
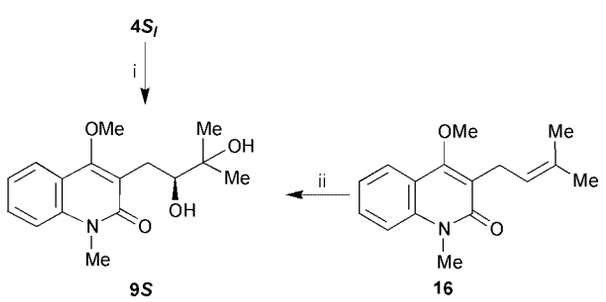


Fig. 2 X-Ray structure of **20*RSR****.

were incorrect. The structure consists of two crystallographically independent but chemically and conformationally equivalent molecules, one of which is shown in Fig. 1. There is no evidence of intermolecular hydrogen bonding.

Cleavage of the dihydrofuran ring in platydesmine methiodide **4*S*$_I$** ($[\alpha]_D$ +31, MeOH) under mild alkaline conditions (NH_3, MeOH) was found to yield edulinine **9*S*** (85% yield, $[\alpha]_D$ −32, MeOH) (Scheme 4). The configuration of the chiral centre

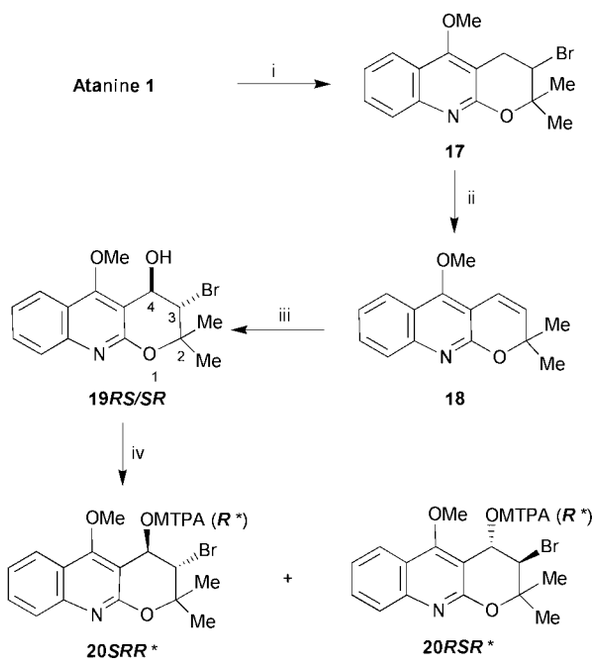


Scheme 4 *Reagents*: i NH_3, MeOH; ii AD-mix-α.

in alkaloids **4*S*** and **9*S*** remained unchanged since the nucleophilic ring opening process occurred at C-9a. Further evidence of this absolute stereochemistry was obtained when the *N*-methyl derivative **16** of atanine **1**, obtained as a by-product during the synthesis of atanine **1**,[10] was treated with the α-form of AD-mix in the same manner as atanine **1** (Scheme 4). The isolated diol, edulinine **9** ($[\alpha]_D$ −29, MeOH, 94% ee), was predicted to have the (*S*) configuration using the Sharpless model.[12] This (*S*) configuration was confirmed when the circular dichroism spectra of the diol products **13*S*** and **9*S*** obtained by asymmetric dihydroxylation (using AD-mix-α) of alkenes **1** and **16** respectively were found to be virtually identical.

Pyranoquinoline **18**, obtained from atanine **1** *via* the bromodihydropyranoquinoline intermediate **17**,[15] was found to react with *N*-bromosuccinimide under aqueous conditions (Scheme 5) to yield the racemic *trans*-bromohydrin **19*RS*/*SR*** in good yield (86%). Treatment with the (+)-(*S*)-MTPA chloride derived from (+)-(*R*)-MTPA (***R****) gave a mixture of diastereoisomers **20*RSR***–**20*SRR**** (Scheme 5) which was separated by PLC (hexane–ethyl acetate–methanol; 8 : 1 : 1). The bromo-MTPA diastereoisomers **20*RSR**** (R_f 0.5, $[\alpha]_D$ +14) and **20*SRR**** (R_f 0.35, $[\alpha]_D$ −56) were tentatively assigned the (3*R*,4*S*) and (3*S*,4*R*) configurations respectively on the basis of their ^{1}H-NMR spectra. This NMR method had earlier been applied successfully to a similar series of cyclic *trans*-bromo-MTPA esters.[16]

The assignment of absolute configuration was unequivocally confirmed by X-ray crystallography on the bromo-MTPA ester **20*RSR**** which showed the OMTPA group at C-4 to have adopted a pseudoaxial conformation *trans* to the axial bromine

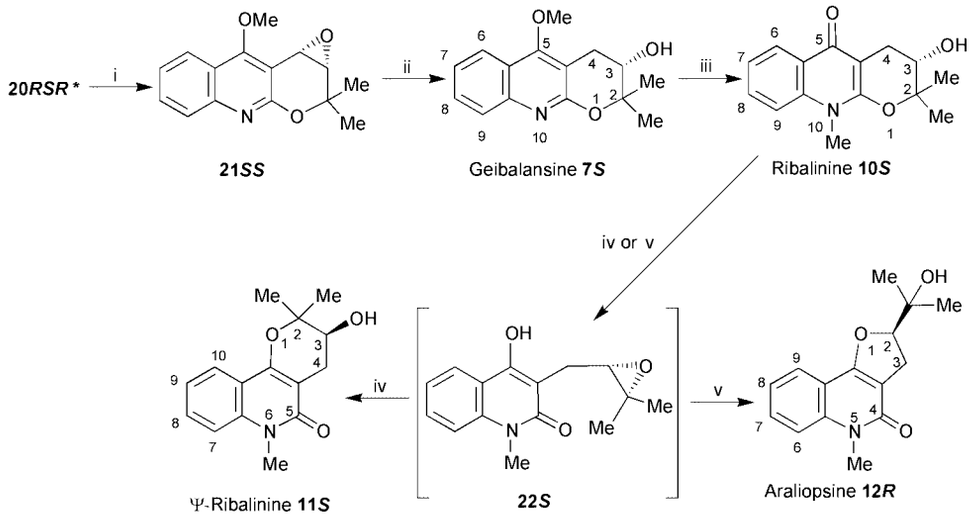


Scheme 5 *Reagents*: i NBS, Et_2O; ii NaOMe, MeOH; iii NBS, THF, H_2O; iv (+)-(*S*)-MTPA-Cl.

atom at C-3. The absolute configuration of compound **20*RSR**** was thus found to be (3*R*,4*S*) relative to the known (*R*) configuration of the OMTPA group (Fig. 2). It was *independently* confirmed as (3*R*,4*S*) from the anomalous X-ray scattering of the Mo-K_α X-radiation by the bromine atom in the molecule (absolute structure parameter $x = -0.03(2)$).

Treatment of the bromo-MTPA ester **20*RSR**** with potassium *tert*-butoxide yielded the epoxide **21*SS*** (82% yield, $[\alpha]_D$ −142, $CHCl_3$) as an unstable oil where the (*S*) absolute configuration at C-4 remained unchanged (Scheme 6). Similarly the bromo-MTPA ester **20*SRR**** yielded the other epoxide enantiomer **21*RR*** ($[\alpha]_D$ +144, $CHCl_3$). The epoxides **21*SS*** and **21*RR***, which showed evidence of decomposition during PLC purification, were hydrogenated (Pd-C) to yield the alkaloids geibalansine **7*S*** (78% yield, $[\alpha]_D$ +12, MeOH) and **7*R*** (87% yield, $[\alpha]_D$ −12, MeOH) respectively which were spectrally indistinguishable from the natural alkaloid ($[\alpha]_D$ −2).[17]

The quinoline alkaloid ribalinine **10** (also described as folifine) has been isolated from at least nine plant members of the *Rutaceae* family and is unusual in being isolated either as a racemate or having an excess of either enantiomer. Previous studies[11] have shown that racemic ribalinine **10** could be obtained by refluxing racemic geibalansine **7** with methyl iodide. Similar treatment of geibalansine enantiomers **7*S*** ($[\alpha]_D$ +12) and **7*R*** ($[\alpha]_D$ −12) gave the corresponding enantiomers of

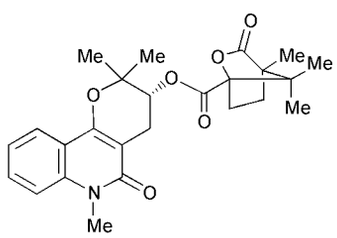


Scheme 6 *Reagents*: i KOt-Bu, THF; ii Pd-C–H_2; iii MeI; iv NaOH, MeOH; v NaOMe, DMF.

ribalinine **10*S*** (97% yield, $[\alpha]_D$ −14) and **10*R*** (99% yield, $[\alpha]_D$ +14) respectively (Scheme 6). An earlier synthesised sample of (−)-ribalinine **10** of low enantiopurity was correctly reported[10] to have an (*S*) configuration.

The alkaloid ribalinine **10*S*** ($[\alpha]_D$ −14) was found to undergo base-catalysed rearrangements to yield the angular alkaloids araliopsine **12** and Ψ-ribalinine **11** (Scheme 6). Thus, treatment of alkaloid **10*S*** with NaOMe in DMF gave araliopsine **12*R*** (92% yield, $[\alpha]_D$ −41) while refluxing with NaOH in MeOH gave Ψ-ribalinine **11*S*** (87% yield, $[\alpha]_D$ +21). Alkaloid **10*R*** ($[\alpha]_D$ +14) when treated in an identical manner yielded araliopsine **12*S*** ($[\alpha]_D$ +42) and Ψ-ribalinine **11*R*** ($[\alpha]_D$ −21). Although this particular type of base-catalysed rearrangement had not previously been reported on ribalinine **10**, a similar process had earlier been reported[18,19] on the alkaloid 9-methoxy-ribalinine (isobalfourodine **29**) to yield 6-methoxyaraliopsine **12** (Ψ-balfourodine **27**) and 7-methoxy-Ψ-ribalinine **11** (Ψ-isobalfourodine **28**). The reported mechanism for the 9-methoxy analogues[20] involved base-catalysed cleavage of the O–C-2 bond and rearrangement to yield a transient epoxide similar to intermediate **22**. On this basis, spontaneous ring opening and cyclisation of the transient epoxide **22*S*** will yield the dihydrofuran araliopsine **12*R*** (with inversion of configuration during epoxide ring opening) or the dihydropyran Ψ-ribalinine **11*S*** (with retention of configuration during epoxide ring opening). On the assumption that this mechanism is correct then the alkaloids (−)-araliopsine **12*R*** and (+)-Ψ-ribalinine **11*S*** derived from (−)-ribalinine **10*S*** should have the (*R*) and (*S*) configurations respectively. It was considered important to obtain additional support for the rearrangement mechanism of ribalinine **10*S*** to yield Ψ-ribalinine **11** and araliopsine **12** (Scheme 6).

X-Ray crystallographic analysis of the camphanate† ester derivative **23*RS**** ($[\alpha]_D$ −34) of (−)-Ψ-ribalinine **11**, obtained by reaction with (−)-(1*S*)-camphanic chloride in pyridine solution, confirmed that (−)-Ψ-ribalinine **11** had an (*R*) configuration (Fig. 3). The camphanate ester group adopts an axial conformation in the crystalline state. Since absolute configurations of both ribalinine **10*S*** (indirectly from **20*RSR**** and Ψ-ribalinine **11*S*** have been independently established by X-ray crystallography, the proposed mechanism of rearrangement of the alkaloid **10*S*** to **11*S*** is consistent with that proposed for the rearrangement of the 8-methoxyquinoline alkaloid isobalfourodine to yield Ψ-balfourodine and Ψ-isobalfourodine.[18,19] Ribalinine **10*S*** was thus assumed to have rearranged to araliopsine **12*R***, as indicated in Scheme 6.



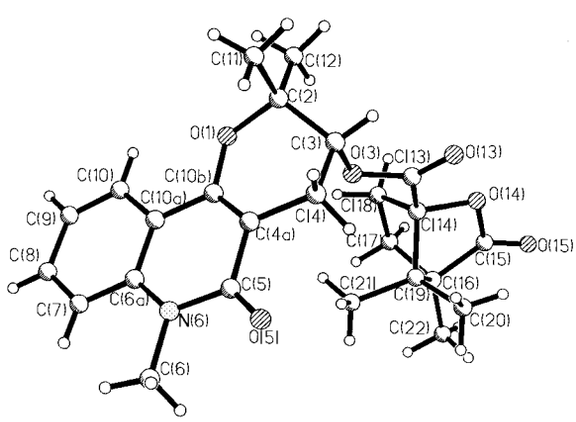
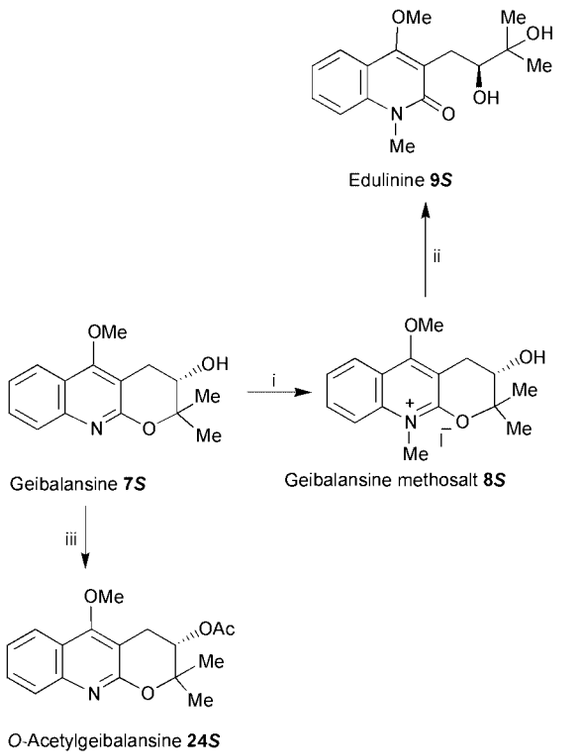


Fig. 3 X-Ray structure of **23*RS****.

N-Methylation of geibalansine **7*S*** ($[\alpha]_D$ +12) occurred after stirring for several days with MeI in benzene solvent at ambient temperature to give the methosalt **8*S*** (geibalansine methiodide) in good yield (78%, $[\alpha]_D$ +15, MeOH). Similarly the other enantiomer of the quaternary salt **8*R*** ($[\alpha]_D$ −16.0, MeOH) was also obtained from geibalansine **7*R*** ($[\alpha]_D$ −12). The geibalansine methosalt **8*S*** does not yet appear to have been isolated as a naturally occurring alkaloid. However, treatment of the quaternary salt **8*S*** ($[\alpha]_D$ +15.3) with ammonia, as described for the platydesmine methosalt **4*S*** (Scheme 4), also yielded the alkaloid edulinine **9*S*** ($[\alpha]_D$ −32) (Scheme 7). The ester derivatives *O*-acetylgeibalansine **24*S*** ($[\alpha]_D$ +58) and **24*R*** ($[\alpha]_D$ −54), obtained by acetylation of the corresponding geibalansine enantiomers **7*S*** and **7*R***, were of interest in view of a literature report[17] on the isolation of *O*-acetylgeibalansine as an alkaloid from *Geijera balansae*. Unfortunately no $[\alpha]_D$ value was given for the alkaloid isolated from the plant[17] so it is not possible to identify its absolute configuration.

† The IUPAC name for camphanic acid is 4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxylic acid.



Scheme 7 *Reagents*: i MeI, C_6H_6; ii NH_4OH; iii Ac_2O, pyridine.

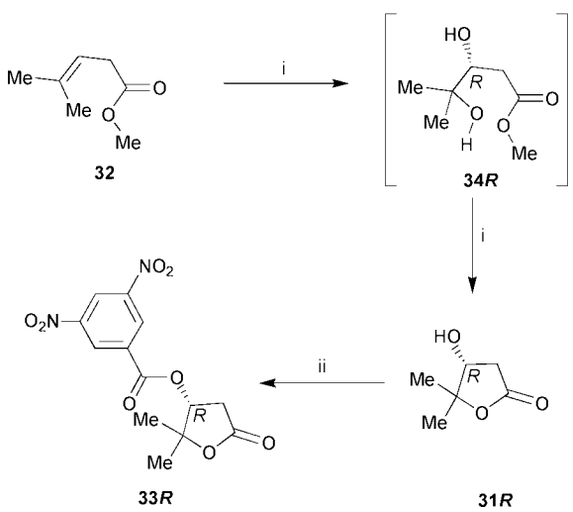
The results provided in the preceding section indicate that two approaches, asymmetric synthesis and chromatographic separation of bromo-MTPA diastereoisomers, can be adopted for the synthesis of single enantiomers of the quinoline alkaloids *e.g.* platydesmine **3**, platydesmine methosalt **4**, geibalansine **7** (and the *O*-acetyl derivative **24**), edulinine **9**, ribalinine **10**, Ψ-ribalinine **11** and araliopsine **12**. The general applicability of both these routes to enantiopure alkaloids has recently been established in our laboratories by the synthesis of more than twenty quinoline alkaloids including lunacridine **25**,[21] balfourolone **26**,[22] Ψ-balfourodine **27**,[22] Ψ-isobalfourodine **28**,[22] isobalfourodine **29**[22] and orixine **30**.[22]

The absolute configurations of the eleven quinoline alkaloids **3**, **4**, **9**, **10**, **12**, **25**–**30** have been assigned in the literature.[8,9,10,14,23] However, our results for alkaloids **3**, **4**, **9**, **10**, and **12**, clearly show that only the absolute configuration of ribalinine **10** has been correctly determined. Similarly, out of the absolute configurations of the synthesised enantiopure alkaloids **25**–**30** recently assigned by using unequivocal methods including X-ray crystallography and CD correlation,[21,22] only the configuration of lunacridine **25** was found to be correct. In view of the high proportion of incorrect stereochemical assignments, possible sources of error in the absolute configurations reported for the alkaloids **3**, **4**, **9**, **12**, **26**–**30** were examined.

The literature syntheses of alkaloids **3**, **4**, **9**, **10**, **12**, **25**–**30** in all cases involved chiral epoxidation with (+)-peroxycamphoric acid as oxidant[7,8,10,20,23] and generally resulted in a small enrichment (2–10%) of one enantiomer. The insensitivity of polarimetric equipment may have resulted in less accurate and reliable optical rotation values which were often very low ($[\alpha]_D$ <1.0).

Exhaustive ozonolysis of the enantiomerically enriched alkaloids **26**–**29** to yield 3-hydroxy-4,4-dimethyl-4-butyrolactone **31** of known absolute configuration was used to assign absolute stereochemistry.[7,8,10,20,23] Using this method, a sample of lactone **31** was obtained as a viscous oil ($[\alpha]_D$ +7, $CHCl_3$) from enantiopure (+)-platydesmine methosalt **4** (isolated from *S. japonica*).[8] Since this $[\alpha]_D$ value was significantly lower than that of a previously reported[24] sample ($[\alpha]_D$ −11, $CHCl_3$) the former sample appears to have been impure. The sample of lactone **31** of higher $[\alpha]_D$ value (+11) gave a crystalline 3,5-dinitrobenzoate derivative **33** ($[\alpha]_D$ +5).[24] In addition, it would have been much more difficult to obtain reliable $[\alpha]_D$ values for the samples of lactone **31** ($[\alpha]_D$ <1.0) derived from alkaloids whose ee values were often *ca.* 5% or less without a similar purification procedure. The generally low $[\alpha]_D$ values obtained for samples of lactone **31**, the limited accuracy of measurement, and the purity of samples, may thus have been important factors in the incorrect assignments.

A further possible source of error in the stereochemistry of the quinoline alkaloids under discussion was the reliability of the earlier assignment of absolute configuration to lactone **31**.[24–26] Since the (*R*) configurational assignment to the (+)-enantiomer of lactone **31** involved a lengthy (>10 steps) stereochemical correlation sequence,[24–26] an independent method for assigning the absolute stereochemistry to lactone **31** was developed. Thus ester **32**, which contains a dimethylallyl group, was treated with AD-mix-β to yield the corresponding diol **34**. The latter diol was not isolated since it appeared to spontaneously cyclize to the required lactone **31** and was purified by PLC ($[\alpha]_D$ +11.5) and converted into the 3,5-dinitrobenzoate derivative **33** ($[\alpha]_D$ +5, $CHCl_3$) (Scheme 8). The $[\alpha]_D$



Scheme 8 *Reagents*: i AD-mix-β, t-BuOH, H_2O; ii 3,5-dinitrobenzoyl chloride, pyridine.

values compare favourably with the reported values of compounds **31** and **33** ($[\alpha]_D$ −11 and +5).[24] The absolute configuration of the (+)-lactone **31** based on the Sharpless mnemonic[12] was in accord with that reported in the literature.[24–26]

Conclusion

New synthetic routes to enantiopure samples of the chiral quinoline alkaloids platydesmine **3**, platydesmine methosalt **4**, geibalansine **7**, edulinine **9**, ribalinine **10**, Ψ-ribalinine **11** and araliopsine **12** have been developed. The absolute configurations of the latter alkaloids have been unequivocally established by X-ray crystallography. The incorrect configurational assignments previously reported for the majority of these alkaloids appear to be a consequence of (i) the purity of the samples including 3-hydroxy-4,4-dimethyl-4-butyrolactone **31**, a key compound in stereochemical correlation obtained from ozonolysis of the alkaloids, and (ii) the generally low $[\alpha]_D$ values and enantiomeric purities obtained from earlier asymmetric synthesis, allied to the inaccuracy of available methods. The results presented here form the first part of a comprehensive reappraisal of earlier literature reports on the absolute configurations of quinoline alkaloids. Further results will be discussed elsewhere.[22]

Experimental

^{1}H NMR spectra were recorded at 300 MHz (Bruker Avance DPX-500) and at 500 MHz (Bruker Avance DRX-500) in $CDCl_3$ solvent unless stated otherwise. Chemical shifts (δ) are reported in ppm relative to $SiMe_4$ and coupling constants (J) are given in Hz. Mass spectra were recorded at 70 eV on a VG Autospec Mass Spectrometer, using a heated inlet system. Accurate molecular weights were determined by the peak matching method with perfluorokerosene as standard. Elemental microanalyses were obtained on a Perkin-Elmer 2400 CHN microanalyser. Circular dichroism spectra were recorded on a JASCO J-720 instrument in acetonitrile solvent.

Atanine **1** and 5-methoxy-2,2-dimethyl-2*H*-pyrano[2,3-*b*]-quinoline **18** were synthesised by the literature procedures.[11,15] Dictamnine **5** (1.52 g), skimmianine **6** (1.2 g), and the platydesmine methosalt **4** were isolated as the major quinoline alkaloids from the leaves (3400 g) of *S. japonica* using the reported method.[9] The water soluble quaternary alkaloid platydesmine methosalt **4** was first isolated as the insoluble reineckate salt (1.55 g) and was subsequently converted to (**2*S***) platydesmine methoperchlorate **4*S*$_P$** and methiodide **4*S*$_I$** salts by the reported method.[12] PLC was carried out on glass plates (20 × 20 cm) coated with Merck Kieselgel $PF_{254+366}$.

(+)-(2*S*)-Platydesmine methoperchlorate (4*S*$_P$)

(0.9 g, 0.27%) Mp 200 °C (from MeOH) [lit.,[9] 200–202 °C]; $[a]_D$ +33.0 (*c* 0.42, MeOH) [lit.[9] +33, MeOH]; ^{1}H NMR (500 MHz, CD_3OD) δ 1.21 (3 H, s, Me), 1.37 (3 H, s, Me), 3.84 (1 H, dd, $J_{3a,3b}$ 15.6, $J_{3a,2}$ 6.9, H-3$_a$), 3.92 (1 H, dd, $J_{3b,3a}$ 15.6, $J_{3b,2}$ 9.3, H-3$_b$), 4.00 (3 H, s, NMe), 4.42 (3 H, s, OMe), 5.16 (1 H, dd, $J_{2,3a}$ 6.9, $J_{2,3b}$ 9.3, H-2), 7.60 (1 H, dd, $J_{6,5}$ 8.3, $J_{6,7}$ 7.2, H-6), 7.88 (1 H, dd, $J_{7,6}$ 7.2, $J_{7,8}$ 8.3, H-7), 7.93 (1 H, d, $J_{8,7}$ 8.3, H-8), 8.22 (1 H, d, $J_{5,6}$ 8.3, H-5); ^{13}C NMR (125 MHz, CD_3OD) δ 24.0, 25.2, 29.1, 33.6, 59.6, 71.1, 94.8, 102.7, 116.9, 120.1, 124.7, 127.0, 134.0, 137.3, 163.6, 167.3.

(+)-(2*S*)- Platydesmine methiodide (4*S*$_I$)

The perchlorate salt **4*S*$_P$** (0.05 g, 0.13 mmol) was converted into the corresponding iodide **4*S*$_I$** by passing its methanolic solution through a column of Amberlite IRA-420 (iodide) resin (0.035 g, 87%); mp 156 °C (EtOH) [lit.,[9] 155–156 °C], $[a]_D$ +31.0 (*c* 0.53, MeOH) [lit.,[9] $[a]_D$ +30, MeOH].

(−)-(*S*)-Edulinine (9*S*)

A solution of the iodide salt **4*S*$_I$** (0.025 g, 0.08 mmol) in methanolic NH_3 (32% w/w, 2 cm^3) was stirred (24 h) at room temperature. The reaction mixture was diluted with water and extracted with $CHCl_3$ (3 × 5 cm^3). The combined extracts were dried ($MgSO_4$) and concentrated to yield edulinine (**9*S***) (0.02 g, 85%) as a viscous oil which solidified on standing; mp 140 °C (from i-Pr_2O–MeOH) [lit.,[9] 139–141 °C]; $[a]_D$ −32.0 (*c* 0.52, MeOH); ^{1}H NMR (500 MHz; $CDCl_3$) δ 1.34 (6 H, s, 2 × Me), 2.76 (1 H, dd, $J_{1a,1b}$ 13.7, $J_{1a,2'}$ 10.3, H-1′a), 3.15 (1 H, dd, $J_{1'b,1'a}$ 13.7, $J_{1'b,2'}$ 1.7, H-1′b), 3.64 (1 H, dd, $J_{2',1'a}$ 10.3, $J_{2',1'b}$ 1.7, H-2′), 3.79 (3 H, s, NMe), 4.00 (3 H, s, OMe), 5.08 (1 H, br, OH), 7.33 (1 H, dd, $J_{6,7}$ 7.3, $J_{6,5}$ 8.0, H-6), 7.43 (1 H, dd, $J_{8,7}$ 8.4, H-8), 7.61 (1 H, dd, $J_{7,8}$ 8.4, $J_{7,6}$ 7.3, H-7), 7.85 (1 H, d, $J_{5,6}$ 8.0, H-5); *m*/*z* 291 (100). The ee (>98%) was determined by the formation of MTPA esters.

Synthesis of platydesmine 3 and platydesmine methiodide 4*S*$_I$ from atanine 1 using AD-mix-α as oxidant

To a stirring mixture of AD-mix-α (12 g), *t*-BuOH (40 cm^3) and water (40 cm^3) was added methanesulfonamide (0.79 g, 8.3 mmol) at 0 °C. Atanine **1** (2.0 g, 8.3 mmol) was then added to the mixture and the heterogeneous slurry vigorously stirred at 0 °C. On completion of the reaction (~24 h), monitored by TLC (5% MeOH–$CHCl_3$, R_f 0.25), sodium sulfite (1 g) was added and the reaction mixture further stirred at room temperature (0.5 h). The crude diol was extracted with EtOAc (2 × 50 cm^3), the extract washed with water (25 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure to yield diols **13*S*/13*R*** as a light yellow coloured solid (1.84 g, 80%). Reaction of the diols **13*S*/13*R***, in pyridine, with (+)-MTPA chloride gave the corresponding MTPA esters **14*SR**/14*RR**** (97 : 3) indicating a 94% enantiomeric excess (ee) of **13*S***. A pure sample of diastereoisomer **14*SR**** was obtained by multiple elution PLC on silica gel (Et_2O–hexane, 1 : 1) as a gum, $[a]_D$ +30 (*c* 0.9, MeOH).

To a solution of mono-MTPA ester **14*SR**** (0.5 g, 1.0 mmol, $[a]_D$ +30) in MeOH (10 cm^3) was added water (1 cm^3) and K_2CO_3 (0.5 g, 3.6 mmol). The reaction mixture was stirred (~12 h) at room temperature. The diol product **13*S*** was obtained from the ethyl acetate extract of the diluted reaction mixture (0.24 g, 86%), R_f 0.4 (5% MeOH–$CHCl_3$); mp 155–158 °C (from EtOAc–hexane) (Found: C, 65.2; H, 6.7; N, 4.9. $C_{15}H_{19}NO_4$ requires C, 65.0; H, 6.6; N, 5.15%); $[a]_D$ −42.0 (*c* 0.45, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35 (6 H, s, $C(Me)_2$), 1.70 (1 H, br, OH), 2.76 (1 H, dd, $J_{1'a,1'b}$ 14.1, $J_{1'a,2'}$ 9.9, H-1′a), 3.18 (1 H, dd, $J_{1'b,1'a}$ 14.1, $J_{1'b,2'}$ 1.9, H-1′b), 3.47 (1 H, dd, $J_{2',1'a}$ 9.9, $J_{2',1'b}$ 1.9, H-2′), 4.00 (3 H, s, OMe), 5.28 (1 H, br, OH), 7.28 (1 H, dd, $J_{6,5}$ 8.2, $J_{6,7}$ 7.2, H-6), 7.37 (1 H, d, $J_{8,7}$ 8.2, H-8), 7.53 (1 H, dd, $J_{7,8}$ 8.2, $J_{7,6}$ 7.2, H-7), 7.79 (1 H, d, $J_{5,6}$ 8.2, H-5), 11.87 (1 H, br, NH); ^{13}C NMR (125 MHz, $CHCl_3$) δ 24.2, 25.8, 27.4, 62.5, 73.0, 79.3, 116.2, 117.2, 121.1, 123.0, 123.1, 130.9, 137.3, 163.8, 167.6; *m*/*z* 277 (7%), 218 (100).

Atanine **1** (1.9 g, 7.8 mmol) on reaction with AD-mix-β (11 g), under identical conditions to those mentioned earlier, yielded diol mixture **13*R*** and **13*S*** (1.8 g, 83%). Formation of MTPA esters **14*RR****–**14*SR**** indicated that the diol **13*R*** had an ee value of 94%. Separation of the MTPA esters **14*RR****–**14*SR**** by PLC gave the major diastereoisomer **14*RR**** as a gum; $[a]_D$ +10 (*c* 0.8, MeOH) which on hydrolysis furnished the diol **13*R*** ($[a]_D$ +43 (*c* 0.8, MeOH).

(−)-(*S*)-4-Methoxy-3-(2′-acetoxy-3′-bromo-3′-methylbutyl)-quinolin-2(1*H*)-one (15*S*)

Diol (−)-**13*S*** (0.2 g, 0.72 mmol, $[a]_D$ −42) was dissolved in dry MeCN (10 cm^3) at 0 °C and 1-bromocarbonyl-1-methylethyl acetate (0.21 g, 1.0 mmol) was carefully added to the solution. After stirring the cooled reaction mixture (3 h) most of the MeCN was removed under reduced pressure and EtOAc (25 cm^3) was added to the residue; the EtOAc solution was washed with 5% aqueous $NaHCO_3$ (2 × 10 cm^3), dried (Na_2SO_4) and concentrated to yield bromoacetate **15*S*** (0.32 g, 93%). Purification by PLC (35% EtOAc–hexane, R_f 0.3) gave the title compound as a colourless oil; $[a]_D$ −35 (*c* 0.70, MeOH) (Found: M^+ 381.05608. $C_{17}H_{20}BrNO_4$ requires 381.05757); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.57 (3 H, s, Me), 1.63 (3 H, s, Me), 1.97 (3 H, s, Me), 3.53 (1 H, dd, $J_{1'a,1'b}$ 15.9, $J_{1'a,2'}$ 7.0, H-1′a), 3.64 (1 H, dd, $J_{1'b,1'a}$ 15.9, $J_{1'b,2'}$ 9.2, H-1′b), 4.23 (3 H, s, OMe), 4.98 (1H, dd, $J_{2',1'a}$ 7.0, $J_{2',1'b}$ 9.2, H-2′), 7.32 (1 H, dd, $J_{6,5}$ 8.2, $J_{6,7}$ 6.9, H-6), 7.57 (1 H, dd, $J_{7,6}$ 6.9, $J_{7,8}$ 8.4, H-7), 7.75 (1 H, d, $J_{8,7}$ 8.4, H-8), 8.03 (1 H, d, $J_{5,6}$ 8.2, H-5); *m*/*z* 381 (2%), 226 (100).

(+)-(*R*)-4-Methoxy-3-(2′-acetoxy-3′-bromo-3′-methylbutyl)-quinolin-2(1*H*)one (15*R*)

Diol (+)-**13*R*** (0.2 g, 0.72 mmol, $[a]_D$ +43) was similarly converted to the (*R*)-bromoacetate **15*R***, a colourless oil (0.29 g, 85%), $[a]_D$ +34 (*c* 0.7, MeOH).

(−)-(*R*)-Platydesmine (3*R*)

A solution of bromoacetate **15*S*** (0.07 g, 0.18 mmol, $[a]_D$ −35) in dry THF (5 cm^3) was treated with KOt-Bu (0.1 g, 0.89 mmol) and the mixture stirred at room temperature (3 h). The reaction

mixture was filtered and the filtrate concentrated to give crude dihydrofuranoquinoline (−)-**3*R*** which on purification by PLC (EtOAc–hexane, 1:1, R_f 0.5) yielded the title compound (0.027 g, 57%); mp 136–138 °C (Et_2O–MeOH) [lit.,[27] 137–138 °C]; $[\alpha]_D$ −47.0 (*c* 0.76, MeOH) (lit.,[27] $[\alpha]_D$ +44, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.28 (3 H, s, Me), 1.45 (3 H, s, Me), 1.66 (1 H, br, OH), 3.58 (1 H, dd, $J_{3a,3b}$ 15.5, $J_{3a,2}$ 8.8, H-3_a), 3.65 (1 H, dd, $J_{3b,3a}$ 15.5, $J_{3b,2}$ 7.9, H-3_b), 4.21 (3 H, s, OMe), 4.64 (1 H, dd, $J_{2,3a}$ 8.8, $J_{2,3b}$ 7.9, H-2), 7.29 (1 H, dd, $J_{6,5}$ 8.2, $J_{6,7}$ 7.0, H-6), 7.55 (1 H, dd, $J_{7,6}$ 7.0, $J_{7,8}$ 8.3, H-7), 7.73 (1 H, d, $J_{8,7}$ 8.3, H-8), 8.01 (1 H, d, $J_{5,6}$ 8.2, H-5); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.3, 26.2, 29.0, 58.2, 71.5, 86.4, 101.6, 120.0, 122.1, 123.4, 126.7, 129.8, 147.3, 159.0, 168.7; *m*/*z* 259 (53%), 200 (100).

(+)-(*S*)-Platydesmine (3*S*)

Treatment of bromoacetate **15*R*** (0.1 g, 0.26 mmol, $[\alpha]_D$ +34) with KOt-Bu, as described for bromoacetate **15*S***, gave platydesmine **3*S*** (0.045 g, 67%), $[\alpha]_D$ +47 (*c* 0.71, MeOH) (lit.,[27] $[\alpha]_D$ +44, MeOH).

(−)-(2*R*)-Platydesmine methiodide (4R_I)

A solution of (−)-platydesmine **3*R***, (0.02 g, 0.08 mmol, $[\alpha]_D$ −47) in EtOH (3 cm^3), containing a few drops of MeI, was refluxed (1.5 h). The reaction mixture was cooled and the solid iodide salt (−)-**4R_I** (0.018 g, 56%) was collected by filtration, $[\alpha]_D$ −31 (*c* 0.64, MeOH) [lit.,[9] $[\alpha]_D$ +30, MeOH]. The sample was spectrally indistinguishable from the sample of iodide salt obtained from *S. japonica*.

(+)-(2*S*)-Platydesminium methiodide (4S_I)

(+)-Platydesmine **3*S*** (0.02 g, 0.08 mmol) ($[\alpha]_D$ +47) was converted to the (−)-iodide **4R_I** (0.02 g, 63%), $[\alpha]_D$ +31 (*c* 0.74, MeOH) by the procedure given for the (−)-enantiomer **3*R***.

(+)-(3*R*)-3-Hydroxy-4,4-dimethyl-4-butyrolactone (31)

Methyl 4-methylpent-3-enoate (1.0 g, 7.8 mmol) on reaction with AD-mix-β (11.0 g) yielded crude lactone **31** (0.6 g, 59%) under identical conditions to those used earlier. PLC purification (Et_2O, R_f 0.25) gave butyrolactone **31** as a colourless oil, spectrally identical with literature values;[24] $[\alpha]_D$ +11.5 (*c* 2.2, $CHCl_3$) [lit.[8] $[\alpha]_D$ +7.1, $CHCl_3$]. The 3,5-dinitrobenzoate derivative **33** of (+)-lactone **31** was obtained as colourless crystals, mp 151 °C (from hexane–$CHCl_3$) [lit.,[24] 151–152 °C]; $[\alpha]_D$ +5 (*c* 1.0, $CHCl_3$) (lit.,[24] $[\alpha]_D$ +5) ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.55 (3 H, s, $C(Me)_2$), 1.60 (3 H, s, $C(Me)_2$), 2.80 (1 H, dd, $J_{2a,3}$ 2.0, $J_{2a,2b}$ 18.7, H-2_a), 3.26 (1 H, dd, $J_{2b,3}$ 6.7, $J_{2b,2a}$ 18.7, H-2_b), 5.55 (1 H, dd, $J_{3,2a}$ 2.0, $J_{3,2b}$ 6.7, H-3), 9.15 (2 H, t, *J* 2.1, Ar), 9.28 (1 H, t, *J* 2.1, Ar-H).

(±)-*trans*-3-Bromo-4-hydroxy-3,4-dihydro-5-methoxy-2,2-dimethyl-2*H*-pyrano[2,3-*b*]quinoline (19*RS*/*SR*)

To a stirring solution (~5 °C) of 5-methoxy-2,2-dimethyl-2*H*-pyrano[2,3-*b*]quinoline **18** (0.762 g, 3.16 mmol) in aqueous tetrahydrofuran (THF, 100 cm^3–H_2O, 10 cm^3) was added, in small portions, *N*-bromosuccinimide (0.62 g, 3.48 mmol). After stirring (24 h) at ambient temperature, the solution was concentrated, diluted with water and the product extracted into chloroform (3 × 30 cm^3). The organic extracts were dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give the crude product. PLC purification ($CHCl_3$) yielded racemic bromohydrin **19** (1.655 g, 78%) (R_f 0.57, $CHCl_3$–EtOAc, 4:1); mp 164–165 °C (from i-Pr_2O–MeOH) (Found: C, 53.1; H, 4.6; N, 4.9; Br, 23.8. $C_{15}H_{16}NO_3Br$ requires C, 53.3; H, 4.8; N, 4.2; Br, 23.6%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.56 (3 H, s, $C(Me)_2$), 1.74 (3 H, s, $C(Me)_2$), 4.16 (3 H, s, OMe), 4.31 (1 H, d, $J_{3,4}$ 7.1, H-3), 5.41 (1 H, d, $J_{4,3}$ 7.1, H-4), 7.38–7.43 (1 H, m, H-8), 7.62–7.67 (1 H, m, H-7), 7.87 (1 H, d, $J_{6,7}$ 8.5, H-6), 7.94 (1 H, d, $J_{9,8}$ 8.3, H-9); *m*/*z* 339 (^{81}Br, 100%) and 337 (^{79}Br, 100).

(+)-(3*R*,4*S*)- and (−)-(3*S*,4*R*)-*trans*-3-Bromo-4-(2-methoxy-2-phenyl-2-trifluoromethylacetoxy)-3,4-dihydro-5-methoxy-2,2-dimethyl-2*H*-pyrano[2,3-*b*]quinolines (20*RSR** and 20*SRR**)

Racemic bromohydrin **19** (0.585 g, 1.05 mmol) was converted into the corresponding MTPA esters [(+)-MTPA-chloride, 0.49 g, 1.94 mmol]. Separation of the esters by multiple elution PLC (hexane–EtOAc–MeOH; 8:1:1) gave the high R_f diastereoisomer **20*RSR**** (0.038 g, 40%), mp 156–158 °C (from i-Pr_2O–MeOH), $[\alpha]_D$ +13.9 (*c* 0.6, $CHCl_3$) (Found: C, 54.1; H, 4.2; N, 2.5. $C_{25}H_{23}BrF_3NO_5$ requires C, 54.1; H, 4.2; N, 2.5%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.26 (3 H, s, $C(Me)_2$), 1.59 (3 H, s, $C(Me)_2$), 3.59 (3 H, s, OMe), 4.09 (3 H, s, OMe), 4.18 (1 H, d, $J_{3,4}$ 3.8, H-3), 6.78 (1 H, d, $J_{4,3}$ 3.8, H-4), 7.38–7.47 (4 H, m, Ar-H), 7.60–7.72 (3 H, m, Ar-H), 7.93 (2 H, dd, *J* 8.5, 16.2, Ar-H); *m*/*z* 555 (^{81}Br, 19%), 553 (^{79}Br, 20) and 226 (100). The low R_f diastereoisomer **20*SRR**** was obtained as a colourless gum (0.0346 g, 36%); $[\alpha]_D$ −55.8 (*c* 1.3, $CHCl_3$) (Found: C, 53.5; H, 4.8; N, 2.6. $C_{25}H_{23}BrF_3NO_5$ requires C, 54.1; H, 4.2; N, 2.5%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.57 (3 H, s, $C(Me)_2$), 1.66 (3 H, s, $C(Me)_2$), 3.49 (3 H, s, OMe), 4.03 (3 H, s, OMe), 4.33 (1 H, d, $J_{3,4}$ 4.3, H-3), 6.81 (1 H, d, $J_{4,3}$ 4.3, H-4), 7.39–7.44 (4 H, m, Ar-H), 7.62–7.70 (3 H, m, Ar-H), 7.87–7.92 (2 H, m, Ar-H); *m*/*z* 555 (^{81}Br, 18), 553 (^{79}Br, 18) and 226 (100).

(−)-(3*S*,4*S*)-3,4-Dihydro-3,4-epoxy-5-methoxy-2,2-dimethyl-2*H*-pyrano[2,3-*b*]quinoline (21*SS*)

A solution of (+)-bromo-MTPA ester **20*RSR**** (0.69 g, 1.24 mmol) in dry THF (20 cm^3) was treated with KOt-Bu (0.42 g, 3.74 mmol) at room temperature (24 h). The reaction mixture was filtered, the filtrate concentrated, and the product purified by PLC ($CHCl_3$–EtOAc; 4:1, R_f 0.64) to yield the epoxide **21*SS*** as a viscous oil (0.262 g, 81%), $[\alpha]_D$ −142 (*c* 0.95, $CHCl_3$) (Found: M^+, 257.1050. $C_{15}H_{15}NO_3$ requires M^+, 257.1052); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.42 (3 H, s, $C(Me)_2$), 1.69 (3 H, s, $C(Me)_2$), 3.60 (1 H, d, $J_{3,4}$ 4.4, H-3), 4.16 (3 H, s, OMe), 4.49 (1 H, d, $J_{4,3}$ 4.3, H-4), 7.40–7.45 (1 H, m, H-8), 7.62–7.67 (1 H, m, H-7), 7.85 (1 H, d, $J_{5,6}$ 8.3, H-6), 7.99 (1 H, d, $J_{9,8}$ 8.1, H-9); *m*/*z* 257 (100).

(+)-(3*R*,4*R*)-3,4-Dihydro-3,4-epoxy-5-methoxy-2,2-dimethyl-2*H*-pyrano[2,3-*b*]quinoline (21*RR*)

(−)-Bromo-MTPA ester **20*SRR**** (0.735 g, 1.33 mmol) was treated as described for the (+)-bromo-MTPA ester **20*RSR**** to yield epoxide **21*RR*** as an oil (0.279 g, 82%). $[\alpha]_D$ +144.0 (*c* 1.47, $CHCl_3$).

(+)-(*S*)-Geibalansine (7*S*)

(−)-Epoxide **21*SS*** (0.047 g, 0.18 mmol) was hydrogenated in MeOH solution (10 cm^3) using Pd-C (10%) catalyst at ambient temperature. The crude hydrogenated product was purified by PLC ($CHCl_3$–EtOAc; 4:1) to give (+)-(*S*)-geibalansine **7*S*** as a colourless oil which solidified on standing (0.037 g, 78%); mp 181–182 °C (from i-Pr_2O–MeOH) (lit.,[17] mp 179 °C); $[\alpha]_D$ +12.0 (*c* 0.86, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.46 (3 H, s, $C(Me)_2$), 1.49 (3 H, s, $C(Me)_2$), 3.00 (1 H, dd, $J_{4a,3}$ 6.2, $J_{4a,4b}$ 17.2, H-4_a), 3.20 (1 H, dd, $J_{4b,3}$ 5.1, $J_{4b,4a}$ 17.3, H-4_b), 3.95–3.99 (1 H, m, H-3), 3.99 (3 H, s, OMe), 7.32–7.38 (1 H, m, H-8), 7.56–7.61 (1 H, m, H-7), 7.82 (1 H, d, $J_{6,7}$ 8.4, H-6), 7.89 (1 H, d, $J_{9,8}$ 8.3, H-9); *m*/*z* 259 (100%).

(−)-(*R*)-Geibalansine (7*R*)

(+)-Epoxide **21*RR*** (0.071 g, 0.27 mmol) was treated as described for (−)-(3*S*,4*S*)-epoxide **21*SS*** and yielded (−)-(*R*)-geibalansine **7*R*** (0.062 g, 87%); mp 180–181 °C (from i-Pr_2O–MeOH); $[\alpha]_D$ −12.0 (*c* 1, MeOH).

(+)-(*S*)-*O*-Acetylgeibalansine (24*S*)

A solution of (+)-geibalansine **7*S*** (0.02 g, 0.08 mmol) in dry pyridine (1 cm^3) containing acetic anhydride (0.2 cm^3) was refluxed (2.5 h). The solvent was removed under reduced pressure and the residue purified by PLC ($CHCl_3$–EtOAc; 4:1) to yield (+)-*O*-acetylgeibalansine **24*S*** as a gum (0.023 g, 98%), spectrally identical to literature values;[17] $[\alpha]_D$ +58 (*c* 1.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.46 (3 H, s, $C(Me)_2$), 1.48 (3 H, s, $C(Me)_2$), 2.06 (3 H, s, OCOMe), 3.07 (1 H, dd, $J_{4a,3}$ 4.8, $J_{4a,4b}$ 17.7, H-4_a), 3.26 (1 H, dd, $J_{4a,3}$ 4.9, $J_{4b,4a}$ 17.7, H-4_b), 4.01 (3 H, s, OMe), 5.16 (1 H, dd, $J_{3,4a} = J_{3,4b}$ 4.8, H-3), 7.36–7.41 (1 H, m, H-8), 7.59–7.64 (1 H, m, H-7), 7.86 (1 H, d, $J_{6,7}$ 8.5, H-6), 7.94 (1 H, d, $J_{9,8}$ 8.3, H-9); *m*/*z* 301 (16%), 241 (16), 226 (100).

(−)-(*R*)-*O*-Acetylgeibalansine (24*R*)

(−)-Geibalansine **7*R*** (0.025 g, 0.1 mmol) was treated as described for (+)-geibalansine **7*S*** and gave (−)-*O*-acetylgeibalansine **24*R*** (0.022 g, 76%); $[\alpha]_D$ −54.0 (*c* 1.3, $CHCl_3$).

(−)-(*S*)-Ribalinine (10*S*)

A solution of (+)-geibalansine **7*S*** (0.060 g, 0.23 mmol) in methyl iodide (5 cm^3) was refluxed (15 h). Purification of the reaction product by PLC ($CHCl_3$–EtOAc; 4:1) gave (*S*)-ribalinine **10** as a white solid (0.058 g, 97%); mp 220–222 °C (from i-Pr_2O–MeOH) (lit.,[28] mp 222 °C); $[\alpha]_D$ −14.0 (*c* 0.5, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30 (3 H, s, $C(Me)_2$), 1.54 (3 H, s, $C(Me)_2$), 2.87 (1 H, dd, $J_{4a,4b}$ 17.1, $J_{4a,3}$ 4.7, H-4_a), 3.00 (1 H, dd, $J_{4b,4a}$ 17.2, $J_{4b,3}$ 4.1, H-4_b), 3.43 (3 H, s, NMe), 3.90 (1 H, dd, $J_{3,4a}$ 4.8, $J_{3,4b}$ 4.1, H-3), 7.09 (1 H, d, $J_{9,8}$ 8.6, H-9), 7.18–7.23 (1 H, m, H-8), 7.43–7.49 (1 H, m, H-7), 8.22 (1 H, d, $J_{6,7}$ 8.0, H-6); *m*/*z* 259 (50%) and 188 (100).

(+)-(*R*)-Ribalinine (10*R*)

(−)-(*R*)-Geibalansine **7** (0.078 g, 0.30 mmol) was treated in the manner described for (+)-(*S*)-geibalansine **7** and gave (*R*)-ribalinine **10** as a white solid (0.078 g, 100%); mp 218–220 °C (from i-Pr_2O–MeOH) (lit.,[28] mp 222 °C); $[\alpha]_D$ +14.1 (*c* 0.6, MeOH).

(+)-(*S*)-3-Hydroxy-3,4,5,6-tetrahydro-2,2,6-trimethyl-5-oxo-2*H*-pyrano[3,2-*c*]quinoline (Ψ-ribalinine, 11*S*)

A solution of (−)-(*S*)-ribalinine **10*S*** (0.053 g, 0.20 mmol) in MeOH (3 cm^3) and aqueous sodium hydroxide (30%, 5 cm^3) was refluxed (8 h) under nitrogen. The cooled reaction mixture was diluted with water and then extracted with chloroform (2 × 10 cm^3); the extracts were dried ($MgSO_4$) and the crude product, obtained after removal of solvent, was purified by PLC (2% MeOH–$CHCl_3$) to give the title compound **11*S*** as a white solid (0.046 g, 87%); mp 213–214 °C (from i-Pr_2O–MeOH); $[\alpha]_D$ +21.4 (*c* 0.6, MeOH) (Found: M^+ 259.1204, $C_{15}H_{17}NO_3$ requires 259.1208); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.39 (3 H, s, $C(Me)_2$), 1.48 (3 H, s, $C(Me)_2$), 2.24 (1 H, br s, OH), 2.73 (1 H, dd, $J_{4a,4b}$ 17.9, $J_{4a,3}$ 5.1, H-4_a), 2.93 (1 H, dd, $J_{4a,4b}$ 17.9, $J_{4a,3}$ 5.0, H-4_b), 3.64 (3 H, s, NMe), 3.93 (1 H, dd, $J_{3,4a} = J_{3,4b}$ 5.0, H-3), 7.21–7.28 (2 H, m, H-8, H-10), 7.50–7.56 (1 H, m, H-9), 7.99 (1 H, d, $J_{7,8}$ 8.0, H-7); *m*/*z* 259 (67%) and 188 (100).

(−)-(*R*)-3-Hydroxy-3,4,5,6-tetrahydro-2,2,6-trimethyl-5-oxo-2*H*-pyrano[3,2-*c*]quinoline (Ψ-ribalinine, 11*R*)

(+)-Ribalinine **10*R*** (0.043 g, 0.17 mmol) was treated in the manner described for (−)-ribalinine **10*S*** and yielded (−)-Ψ-ribalinine **11*R*** as a white solid (0.040 g, 93%); mp 215 °C (from i-Pr_2O–MeOH); $[\alpha]_D$ −21.3 (*c* 0.7, MeOH).

(−)-(*R*)-3-(4,7,7-Trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptylcarbonyloxy)-3,4,5,6-tetrahydro-2,2,6-trimethyl-5-oxo-2*H*-pyrano[3,2-*c*]quinoline (23*RS)**

4-Dimethylaminopyridine (DMAP, 0.01 g) was added to a solution of (−)-Ψ-ribalinine **11*R*** (0.015 g, 0.058 mmol) in dry pyridine (2 cm^3) and (−)-(1*S*)-camphanic chloride (0.016 g, 0.074 mmol) and the reaction mixture stirred at room temperature (24 h). The crude product, obtained after removal of pyridine, was purified by PLC (R_f 0.2, $CHCl_3$–EtOAc; 4:1) to furnish compound **23*RS**** as colourless crystals (0.022 g, 87%); mp 190–191 °C (from Et_2O) (Found: M^+, 439.2012. $C_{25}H_{29}NO_6$ requires M^+, 439.1995); $[\alpha]_D$ −34.0 (*c* 0.4, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (3 H, s, Me, camphanyl), 0.93 (3 H, s, Me, camphanyl), 1.07 (3 H, s, Me, camphanyl), 1.42 (3 H, s, $C(Me)_2$), 1.46 (3 H, s, $C(Me)_2$), 1.60–1.69 (1 H, m, CH, camphanyl), 1.81–1.90 (1 H, m, CH, camphanyl), 1.95–2.10 (1 H, m, CH, camphanyl), 2.32–2.42 (1 H, m, CH, camphanyl), 2.79 (1 H, dd, $J_{4a,4b}$ 18.3, $J_{4a,3}$ 4.8, H-4_a), 3.23 (1 H, dd, $J_{4b,4a}$ 18.3, $J_{4b,3}$ 5.1, H-4_b), 3.71 (3 H, s, NMe), 5.27 (1 H, dd, $J_{3,4a} = J_{3,4b}$ 4.9, H-3), 7.23–7.28 (1 H, m, H-8), 7.36 (1 H, d, $J_{10,9}$ 8.4, H-10), 7.55–7.60 (1 H, m, H-9), 7.98 (1 H, d, $J_{7,8}$ 8.0, H-7); *m*/*z* 439 (10%), 226 (100).

(+)-(*S*)-3-(4,7,7-Trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptylcarbonyloxy)-3,4,5,6-tetrahydro-2,2,6-trimethyl-5-oxo-2*H*-pyrano[3,2-*c*]quinoline (23*SS)**

(+)-Camphanate ester **23*SS**** was prepared as described earlier for the (−)-isomer **23*RS****; $[\alpha]_D$ +20 (*c* 1.1, MeOH) (Found: M^+, 439.1979. $C_{25}H_{29}NO_6$ requires M^+, 439.1995); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (3 H, s, Me, camphanyl), 1.00 (3 H, s, Me, camphanyl), 1.07 (3 H, s, Me, camphanyl), 1.42 (3 H, s, $C(Me)_2$), 1.44 (3 H, s, $C(Me)_2$), 1.63–1.69 (1 H, m, CH, camphanyl), 1.83–1.88 (1 H, m, CH camphanyl), 1.90–2.03 (1 H, m, CH, camphanyl), 2.33–2.45 (1 H, m, CH, camphanyl), 2.73 (1 H, dd, $J_{4a,4b}$ 18.1, $J_{4a,3}$ 5.3, H-4_a), 3.04 (1 H, dd, $J_{4b,4a}$ 18.1, $J_{4b,3}$ 5.2, H-4_b), 3.71 (3 H, s, NMe), 5.26 (1 H, dd, $J_{3,4a} = J_{3,4b}$ 5.2, H-3), 7.23–7.28 (1 H, m, H-8), 7.35 (1 H, d, $J_{10,9}$ 8.5, H-10), 7.55–7.61 (1 H, m, H-9), 7.98 (1 H, d, $J_{7,8}$ 7.9, H-7); *m*/*z* 439 (8%) and 226 (100).

(+)-(*S*)-Araliopsine (12*S*)

Sodium methoxide (0.10 g, 0.185 mmol) was added to a stirred solution of (+)-(*R*)-ribalinine (+)-**10*R*** (0.042 g, 0.16 mmol) in dry DMF (2 cm^3). After stirring for 16 h the reaction mixture was diluted with water, extracted with chloroform and the extracts dried ($MgSO_4$). The solvent was evaporated and the crude product purified by PLC ($CHCl_3$–EtOAc; 4:1) to yield (*S*)-araliopsine **12** (0.038 g, 91%), mp 142–144 °C (from i-Pr_2O–MeOH) (lit.,[29] mp 152 °C); $[\alpha]_D$ +42 (*c* 0.43, MeOH) (lit.,[29] $[\alpha]_D$ +40); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (3 H, s, $C(Me)_2$), 1.38 (3 H, s, $C(Me)_2$), 2.23 (1 H, br s, OH), 3.11–3.27 (2 H, m, H-4_a, H-4_b), 3.68 (3 H, s, NMe), 4.88 (1 H, dd, $J_{3,4a} = J_{3,4b}$ 9.4, H-3), 7.21–7.27 (1 H, m, H-7), 7.36 (1 H, d, $J_{9,8}$ 8.6, H-9), 7.55–7.60 (1 H, m, H-8), 7.78 (1 H, d, $J_{6,7}$ 8.1, H-6); *m*/*z* 259 (56%), 226 (53), 200 (100).

(−)-(*R*)-Araliopsine (12*R*)

(−)-Ribalinine **10*S*** (0.036 g, 0.14 mmol) was converted into araliopsine **12*R*** as described for (+)-ribalinine **10*R***, white solid (0.033 g, 92%); mp 136–138 °C (from i-Pr_2O–MeOH); $[\alpha]_D$ −41 (*c* 0.5, MeOH).

(+)-(*S*)-Geibalansine methiodide (8S_I)

(+)-Geibalansine **7*S*** (0.039 g, 0.15 mmol) was dissolved in a mixture of methyl iodide (2 cm^3) and benzene (2 cm^3) and the solution left at room temperature for 4 days. The precipitated solid salt **8S_I** was filtered off and washed several times with

portions of dry benzene (0.047 g, 79%), R_f 0.17 (10% MeOH in $CHCl_3$); mp 199–201 °C (Found: M^+, 259.1211. $C_{16}H_{20}NO_3I - CH_3I$ requires M^+, 259.1208); $[\alpha]_D$ +15.0 (*c* 0.81, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.57 (3 H, s, $C(Me)_2$), 1.73 (3 H, s, $C(Me)_2$), 3.30 (1 H, dd, $J_{4a,4b}$ 17.2, $J_{4a,3}$ 3.8, H-4_a), 3.74 (1 H, dd, $J_{4b,4a}$ 17.3, $J_{4b,3}$ 4.0, H-4_b), 4.14 (3 H, s, NMe), 4.39 (1 H, dd, $J_{3,4a} = J_{3,4b}$ 4.0, H-3), 4.43 (3 H, s, OMe), 7.68–7.73 (1 H, m, H-8), 7.88–8.00 (2 H, m, H-6, H-7), 8.27 (1 H, d, $J_{9,8}$ 8.1, H-9); *m*/*z* 259 (7%), 188 (25), 142 (100).

(−)-(*R*)-Geibalansine methiodide (**8*R*$_I$**)

(−)-Geibalansine **7*R*** (0.048 g, 0.185 mmol) was treated as described for (+)-geibalansine **7*S*** and to yield compound **8*R*$_I$** (0.057 g, 77%); mp 198–200 °C; $[\alpha]_D$ −16.0 (*c* 0.76, MeOH).

(−)-(*S*)-Edulinine (**9*S***)

(+)-Geibalansine methiodide **8*R*$_I$** (0.038 g, 0.0948 mmol) was converted into (−)-edulinine **9*S*** following the procedure described from iodide salt **4*S*$_I$** (0.028 g, 98%); $[\alpha]_D$ −32.0 (*c* 1.41, MeOH).

(+)-(*R*)-Edulinine (**9*R***)

(−)-Geibalansine methiodide **8*R*$_I$** (0.059 g, 0.15 mmol) similarly gave (+)-edulinine **9*R*** (0.043 g, 100%); $[\alpha]_D$ +33.0 (*c* 1.22, MeOH).

X-Ray crystal structure analyses

Crystal data. *(i) Compound* **4*S*$_P$**. $C_{16}H_{20}ClNO_7$, $M_r = 373.8$, orthorhombic, space group $P2_12_12_1$, $a = 8.715(2)$, $b = 18.175(5)$, $c = 21.948(5)$ Å, $V = 3476.4(15)$ Å^3, $Z = 8$, $T = 293$ K, $D_x = 1.428$ g cm^{-3}, $F(000) = 1568$, μ(Cu-K$_\alpha$) = 2.30 mm^{-1}. Measured/independent reflections: 5026/4384, $R1 = 0.089$, $wR2 = 0.251$, GoF = 1.01.

(ii) Compound ***20RSR****. $C_{25}H_{23}BrF_3NO_5$, $M_r = 554.4$, orthorhombic, space group $P2_12_12_1$, $a = 10.330(3)$, $b = 11.287(4)$, $c = 21.203(6)$ Å, $V = 2472.2(13)$ Å^3, $Z = 4$, $T = 293$ K, $D_x = 1.489$ g cm^{-3}, $F(000) = 1128$, μ(Mo-K$_\alpha$) = 1.72 mm^{-1}. Measured/independent reflections: 3221/3221, $R1 = 0.069$, $wR2 = 0.153$, GoF = 0.90.

(iii) Compound ***23RS****. $C_{25}H_{29}NO_6$, $M_r = 439.5$, monoclinic, space group $P2_1$, $a = 8.120(21)$, $b = 12.457(19)$, $c = 12.139(19)$ Å, $\beta = 101.2(2)°$, $V = 1204.4(4)$ Å^3, $Z = 2$, $T = 293$ K, $D_x = 1.212$ g cm^{-3}, $F(000) = 468$, μ(Mo-K$_\alpha$) = 0.09 mm^{-1}. Measured/independent reflections: 2313/2210, $R1 = 0.101$, $wR2 = 0.320$, GoF = 0.95.

Data collection, structure analysis and refinement. All data were collected on a Siemens P3/V2000 diffractometer using graphite-monochromated Cu-K$_\alpha$ (**4*S*$_P$**) or Mo-K$_\alpha$ (**20*RSR****, **23*RS***) radiation. Lorentz and polarisation correction factors were applied. All structures were solved by direct methods and refined by full matrix on F^2. All hydrogens in **4*S*$_P$** and **20*RSR**** were located in difference Fouriers but the poorer quality crystals of **23*RS*** gave data which yielded a high *R*1 value and did not reveal hydrogens. In the final cycles for all three structures hydrogen atoms were included at positions calculated from the geometry of the molecule, riding on the atoms to which they are attached. Crystallographic computations were carried out using the SHELX-97 suite of programs.[30]

Additional crystallographic tables comprising crystal data, atomic coordinates, anisotropic displacement parameters, bond lengths, angles and torsion angles for **4*S*$_P$**, **20*RSR****, and **23*RS*** are available. CCDC reference number 207/469. See http://www.rsc.org/suppdata/p1/b0/b005285j/ for crystallographic files in .cif format.

Acknowledgements

We thank the BBSRC (N. D. S), DENI (S. A. B.), ESF (D. M., J. G. C.), QUESTOR Centre (J. G. C.) and the Queen's University of Belfast (J. G. C.) for funding, and Dr V. N. Ramachandran for helpful discussions.

References

1 M. F. Grundon, in *The Alkaloids: Quinoline Alkaloids Related to Anthranilic Acid*, Academic Press, London, 1988, vol. 32, 341.
2 J. P. Michael, *Nat. Prod. Rep.*, 1998, **61**, 595.
3 M. Rideau, C. Verchere and P. Hibon, *Phytochemistry*, 1979, **18**, 155.
4 K. A. El Sayed, *Nat. Prod. Rep.*, 1998, **61**, 149.
5 J. L. McCormick, T. C. McKee, J. H. Cardinella and M. R. Boyd, *J. Nat. Prod.*, 1996, **59**, 469.
6 S. A. Barr and D. R. Boyd, *J. Chem. Soc.*, *Chem. Commun.*, 1994, 153.
7 J. F. Collins and M. F. Grundon, *J. Chem. Soc.*, *Chem. Commun.*, 1969, 1078.
8 J. F. Collins and M. F. Grundon, *J. Chem. Soc.*, *Perkin Trans. 1*, 1973, 161.
9 D. R. Boyd and M. F. Grundon, *J. Chem. Soc.* (*C*), 1970, 556.
10 M. F Grundon and. S. A. Surgenor, *J. Chem. Soc.*, *Chem. Commun.*, 1978, 624.
11 R. M. Bowman and M. F. Grundon, *J. Chem. Soc.* (*C*), 1966, 1504.
12 H. C. Kolb, M. S. van Nieuwenhze and K. B. Sharpless, *Chem. Rev.*, 1994, **94**, 2483.
13 S. Greenberg and J. G. Moffatt, *J. Am. Chem. Soc.*, 1973, **95**, 4016.
14 M. F. Grundon, *Tetrahedron*, 1978, **50**, 143.
15 M. F Grundon, D. M. Harrison, M. D. Magee, M. J. Rutherford and S. Surgenor, *Proc. R. Ir. Acad.*, *Sect. B*, 1983, **83**, 103.
16 S. K. Balani, D. R. Boyd, E. S. Cassidy, G. I. Devine, J. F. Malone, K. M. McCombe, N. D. Sharma and W. B. Jennings, *J. Chem. Soc.*, *Perkin Trans. 1*, 1983, 2751.
17 A. Ahond, C. Poupat and J. Pusset, *Phytochemistry*, 1979, **18**, 1415.
18 H. Rapoport and K. G. Holden, *J. Am. Chem. Soc.*, 1959, **81**, 3738.
19 H. Rapoport and K. G. Holden, *J. Am. Chem. Soc.*, 1960, **80**, 4395.
20 K. J. James and M. F. Grundon, *J. Chem. Soc.*, *Perkin Trans. 1*, 1979, 1467.
21 S. A. Barr, D. R. Boyd, N. D. Sharma, T. A. Evans, J. F. Malone and V. D. Mehta, *Tetrahedron*, 1994, **50**, 11219.
22 S. A. Barr, D. R. Boyd, N. D. Sharma and P. L. Loke, unpublished results.
23 R. M. Bowman, J. F. Collins and M. F. Grundon, *J. Chem. Soc.*, *Perkin Trans. 1*, 1973, 626.
24 J. Lemmich and B. Eichstedt Nielsen, *Tetrahedron Lett.*, 1969, 3.
25 B. Eichstedt Nielsen and J. Lemmich, *Acta Chem. Scand.*, 1964, **18**, 2111.
26 G. Buchi, L. Crombie, P. J. Godin, K. S. Kaltenbronn, K. S. Siddalingaiah and D. A Whiting, *J. Chem. Soc.*, 1961, 2843.
27 J. A. Diment, E. Ritchie and W. C. Taylor, *Aust. J. Chem.*, 1967, **20**, 565.
28 F. Fish, I. A Meshel and P. G. Waterman, *Planta Med.*, 1976, **29**, 310.
29 J. Vaquette, M. S. Hifnawy, J. L. Pousset, A. Fournet, A. Bouquet and A. Cave, *Phytochemistry*, 1976, **15**, 743.
30 G. M. Sheldrick, SHELX-97, University of Göttingen, Germany, 1997.