A General Synthetic Route to Enantiopure Quinoline Alkaloids

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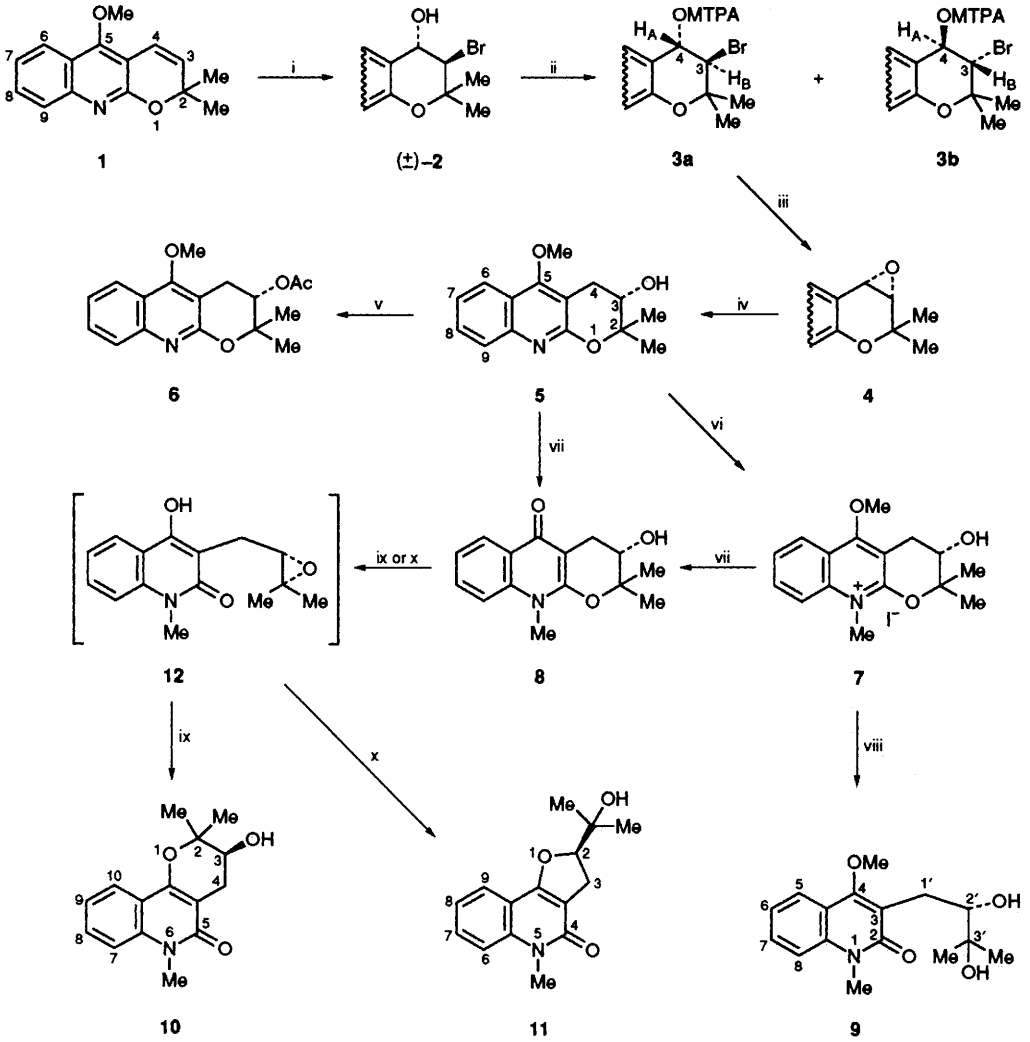
Enantiopure chromenoquinoline epoxides of established configuration are obtained by cyclization of their resolved bromomethoxy(trifluoromethyl)phenylacetates and provide a new route to geibalansine, *O*-acetylgeibalansine, ribalinine, araliopsine, edulinine and related quinoline alkaloids.

The Rutaceae family of plants contains a wide range of quinoline alkaloids with more than two hundred having been reported.[1] The majority of quinoline alkaloids contain one or more chiral centres but to date no methods for the synthesis of enantiopure quinoline alkaloids, and few reliable procedures for the assignment of their optical purity or absolute configuration, have been available. This communication outlines a new synthetic route which allows both enantiomeric excess (e.e.) and absolute configuration to be determined and for either enantiomer of a range of quinoline alkaloids to be synthesised.

The synthetic methodology is based upon the availability of 5-methoxy-2,2-dimethyl-(2*H*)-pyrano[2,3-b]quinoline **1** from earlier work.[2] Treatment of the latter chromenoquinoline with *N*-bromosuccinimide (NBS) to yield a *trans*-bromohydrin **2** and reaction with (+)-methoxy(trifluoromethyl)phenylacetyl chloride (MTPA-Cl) gave a mixture of diastereoisomers (**3a/3b**). Preparative TLC separation on silica gel (hexane : ethyl acetate : methanol; 8 : 1 : 1) gave the high R_f (**3a**, mp 156–158 °C, $[\alpha]_D$ +13.9 [*c* 0.6, $CHCl_3$]), and low R_f (**3b**, gum $[\alpha]_D$ −55.8 [*c* 0.13, $CHCl_3$]) diastereoisomers. The ^{1}H NMR spectra of **3a** and **3b** showed similar characteristics to those previously found for the analogous bromoMTPA diastereoisomers in the polycyclic aromatic hydrocarbon series,[3] *i.e.* the low R_f isomer showed a larger δ value for proton H_B (4.33) and a larger coupling constant J_{AB} (4.31 Hz), compared with the high R_f isomer (H_B δ 4.18, J_{AB} 3.88 Hz). This procedure provides an indirect method for % e.e. determination of the bromohydrin precursors and derivatives. Previous studies[3] have also shown that the benzylic configuration for the high R_f isomer (smaller δ value for H_B and smaller J_{AB} value) was consistently *S*. Extrapolation of this empirical method suggested a (3*R*,4*S*) configuration for the bromoester **3a**. This has been verified by X-ray crystallography.[4]

Treatment of the (+)-(3*R*,4*S*)-bromoester **3a** with potassium-*tert*-butoxide gave the (−)-(3*S*,4*S*)-epoxide **4** ($[\alpha]_D$ −132



Scheme 1 *Reagents and conditions*: i, NBS/aq.tetrahydrofuran (THF), 86%; ii, MTPA-Cl/pyridine, 98%; iii, KOBu^t/THF, 82%; iv, Pd/C MeOH/H_2, 87%; v, Ac_2O/pyridine, 95%; vi, MeI/benzene, room temp., 79%; vii, MeI, reflux, 97%; viii, aq. NH_3, room temp., 98%; ix, NaOH/MeOH, reflux, 88%; x, NaOMe/DMF, room temp., 92%.

Table 1 Optical rotations and absolute configurations of synthesised and isolated quinoline alkaloids or potential alkaloids

Alkaloid	$[\alpha]_D$[a] (configuration)	$[\alpha]_D$[b] (configuration)
5	−12 (*R*) + 12 (*S*)	[c]
6	−54 (*R*) + 58 (*S*)	[c]
7	−16 (*R*) + 15 (*S*)	[c]
8	+14 (*R*) − 14 (*S*)	−4 (*S*)[9]
9	+33[d] (*R*) − 31 (*S*)	−20[e] (*R*)[10,11]
10	−21 (*R*) + 21 (*S*)	[c]
11	−41 (*R*) + 42 (*S*)	+13 (*R*)[9]

[a] Enantiopure sample obtained by chemical synthesis, determined in MeOH solvent. [b] Isolated from plant sources or from asymmetric synthesis. [c] Not reported. [d] $[\alpha]_D$ +18 (*c* 1.59, $CHCl_3$). [e] In $CHCl_3$.

[*c* 0.95, $CHCl_3$]) as a viscous oil which was converted to (+)-(3*S*)-geibalansine **5** by catalytic hydrogenation. Similar treatment of the (−)-(3*S*,4*R*)-bromoester **3b** yielded (−)-(3*R*)-geibalansine **5**. Alkaloid **5** proved to be a versatile precursor to a range of related quinoline alkaloids using similar synthetic methods to those reported previously.[5–7] Thus, acetylation of (+)-(3*S*)-geibalansine **5** gave (+)-(3*S*)-*O*-acetylgeibalansine **6**. When (+)-(3*S*)-geibalansine **5** was treated wth MeI in benzene at room temp., the quaternary ammonium iodide **7** was isolated. The latter compound has not yet been detected as an alkaloid although the 7-hydroxy derivative, the rutalinium salt, has been isolated from *Ruta graveolens*.[8] By analogy with earlier quaternary alkaloids from the Rutaceae family, it should be described as (+)-(3*S*)-geibalansinium iodide **7**. When either (+)-(3*S*)-geibalansine **5** or the (+)-(3*S*)-geibalansinium iodide **7** was refluxed in neat iodomethane, (−)-(3*S*)-ribalinine **8** was produced in high yield. Treatment of (+)-(3*S*)-geibalansinium iodide with aqueous ammonia gave a quantitative yield of (−)-(2′*S*)-edulinine **9**.

In the synthetic sequence between epoxide **4** and the quinoline derivatives **5, 6, 7, 8** and **9**, the non-benzylic chiral *S* centre remains intact and thus all can be stereochemically correlated.

(−)-(3*S*)-Ribalinine **8** when refluxed with aqueous NaOH gave (+)-(3*S*)-ψ-ribalinine **10**, but when treated with NaOMe at room temp. gave (−)-(2*R*)-araliopsine **11**. Although this reaction has not previously been reported, the analogous alkaloids derived from 9-methoxy ribalinine (isobalfourodine), 7-methoxy-ψ-ribalinine (ψ-isobalfourodine) and 6-methoxy araliopsine (ψ-balfourodine), were formed by a pathway involving a postulated transient epoxide intermediate similar to **12**. On the assumption that (−)-(3*S*)-ribalinine **8** rearranges *via* the epoxide intermediate under basic conditions then the (+)-(3*S*) and (−)-(2*R*) configurations may be assigned to (+)-ψ-ribalinine **10** and (−)-araliopsine **11**, respectively. X-Ray crystallographic analysis of the camphanate ester of (−)-(3*R*)-ψ-ribalinine **10** confirmed this assignment.[4]

The $[\alpha]_D$ values and absolute configurations of the enantiopure quinoline alkaloids **5, 6, 8, 9** and **11**, and the potential alkaloids geibalansinium iodide **7** and ψ-ribalinine **10** and the previously reported configurations for alkaloids **8, 9** and **11** are shown in Table 1. Absolute configurations have not previously been assigned to geibalansine **5**, *O*-acetylgeibalansine **6**, ψ-ribalinine **10**, and geibalsinium iodide **7**. While the absolute configuration obtained for (−)-ribalinine **8** was in agreement with a previous assignment,[9] the reported configurations for (−)-edulinine **9**[10,11] and (+)-araliopsine **11**[9] appear to be incorrect.

Preliminary synthetic studies on the monomethoxylated analogues of the alkaloids shown in Scheme 1, *i.e.* isobalfourodine,[6] ψ-balfourodine,[7] ψ-isobalfourodine[7] and balfourolone,[6] indicate that this synthetic route may be generally applicable to a wide range of enantiopure quinoline alkaloids and that the absolute configurations previously reported in the literature[6,7] are often incorrect.

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