CSIRO PUBLISHING

Aust. J. Chem. **2013**, *66*, 30–39
http://dx.doi.org/10.1071/CH12473

Full Paper

Synthetic Studies Concerning the Crinine Alkaloid Haemultine

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The racemic form, (±)-**1**, of the structure originally assigned to the crinine alkaloid haemultine has been prepared for the first time. A key step involved the conversion of compound (±)-**4** into the isomeric *cis*-C3a-arylhexahydroindole (±)-**3** using a Pd^0-catalysed intramolecular Alder-ene reaction. The amino-alcohol (±)-**2** derived from the latter compound reacted with paraformaldehyde in the presence of trifluoroacetic acid to give, via a Pictet–Spengler reaction, the target (±)-**1**. The diastereoisomeric Mosher esters **15** and **16** obtained by coupling the racemate (±)-**1** with the *R*-form, **14**, of the Mosher acid could be separated chromatographically and then reductively cleaved to give the enantiomerically pure compounds (+)-**1** and (−)-**1**, respectively. The physical and spectroscopic data derived from the former enantiomer are consistent with the proposition that the title natural product is, in fact, a mixture of (+)-**1** and its $\Delta^{2,3}$-double bond isomer.

Manuscript received: 15 October 2012.
Manuscript accepted: 9 November 2012.
Published online: 14 January 2013.

Introduction

The colourful bush lily *Haemanthus multiflorus* Martyn is encountered in various parts of Africa and certain extracts of it have been used in traditional medicine in this region for centuries.[1] In 1958 Boit and Döpke reported[2] the isolation of the natural product haemultine (mp 174–175°C, $[\alpha]_D$ +147) from those extracts of the plant considered responsible for the observed pharmacological effects.[3] On the basis of various analytical and chemical correlation studies they assigned structure **1** (Fig. 1, no absolute stereochemistry implied) to haemultine and thereby categorised it as a member of the crinine family of alkaloids, albeit the only one lacking an oxygenated D-ring and, therefore, not fitting well with established biogenetic theories (Fig. 1).[4]

Independent work carried out around the same time[5] suggested that the chemical correlation studies employed by Boit and Döpke might have resulted in various undetected isomerisation processes and thus raised the possibility that the structure of the title alkaloid had been incorrectly assigned. Accordingly, in 1961 Fales and Wildman[4] reinvestigated matters and concluded that the semi-synthetic sample of haemultine that Boit and Döpke had obtained during the course of their correlation studies was, in fact, a mixture of compound **1** (mp 194–194.5°C, $[\alpha]_D$ +10) and its $\Delta^{2,3}$-double bond isomer (mp 201–202°C, $[\alpha]_D$ +199). They also examined the extracts of two different samples of *Haemanthus multiflorus* and could not detect haemultine in either of them. This raised questions about the existence of the title compound as a natural product. In the late 1980s a group lead by Itokawa reported[6] the isolation of haemultine from samples of *Haemanthus multiflorus* Martyn collected in Egypt. However, neither ^1H nor ^{13}C NMR spectroscopic data were reported for their material. Rather, this group simply stated that the compound was obtained as colourless needles with a melting range of 170–172°C and that 'its spectral data are similar with those reported' by Fales and Wildman.[4]

The rather unusual oxygenation pattern associated with haemultine[4] together with the lack of certainty about its existence as a natural product and the ambiguities surrounding its structure[4,7] suggests that carrying out synthetic studies in the area would be a worthwhile endeavour. Rather surprisingly, no such work appears to have been undertaken.[8,9] Accordingly, the main objective of the research described here was to develop unambiguous total syntheses of both enantiomeric forms of the structure, **1**, originally assigned to haemultine and to do so using methodology recently developed within our group.[10,11] A broader objective of such studies was to undertake various biological evaluations of these and other synthetically derived crinine-type systems for the purposes of establishing a comprehensive structure–activity relationship profile within the class.

The retrosynthetic analysis employed in developing syntheses of targets (+)-**1** and (−)-**1** is shown in Fig. 2. A key feature of the approach was to involve resolution of the racemic form of compound **1**, something considered achievable by either fractional crystallisation of the diastereoisomeric salts formed from reaction with chiral acids, or through chromatographic separation of the derived Mosher esters. The racemic material was to be prepared by subjecting the *cis*-C3a-arylhexahydroindole (±)-**2** to a Pictet–Spengler reaction so as to simultaneously establish the C6-methylene and B-ring of target **1**. Compound (±)-**2** would, in turn, be prepared using a new method for

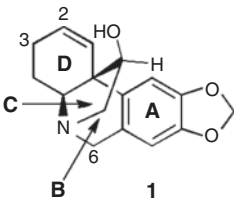


Fig. 1. Structure originally assigned to haemultine (**1**).

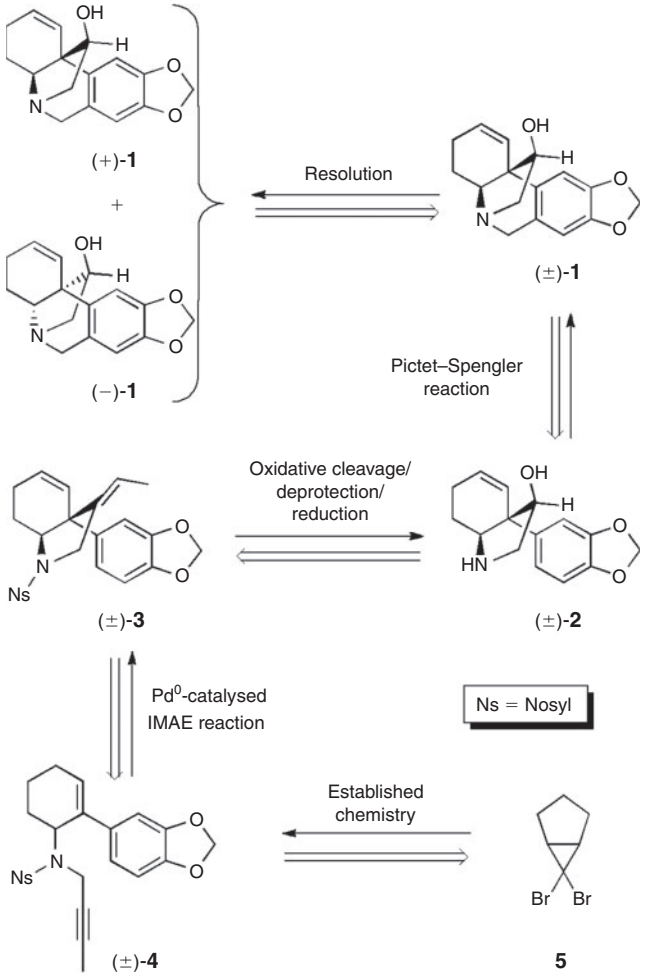


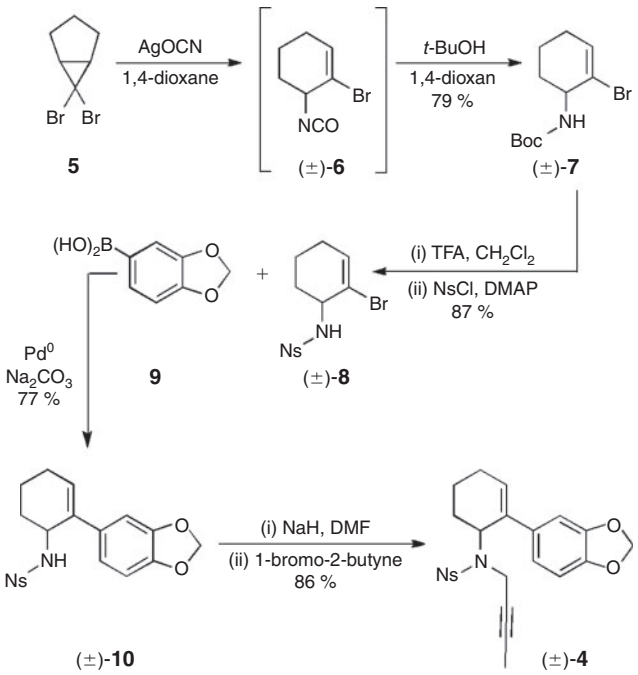
Fig. 2. The retrosynthetic analysis employed in developing syntheses of targets (+)-**1** and (−)-**1**. IMAE, intramolecular Alder-ene.

generating *cis*-C3a-arylhexahydroindoles developed by Banwell and coworkers,[10] specifically through the Pd-catalysed intramolecular Alder-ene (IMAE) reaction of the previously reported,[10] *N*-protected and propargylated 1-amino-2-aryl-2-cyclohexene (±)-**4** followed by selective oxidative cleavage of the exocyclic double bond within product (±)-**3**. Compound (±)-**4** itself was to be generated from the ring-fused *gem*-dibromocyclopropane **5** using established procedures as detailed in the following section.[12]

Results and Discussion

Synthesis of the Substrate Required for the IMAE Reaction

The synthesis of the *N*-protected and propargylated 1-amino-2-aryl-2-cyclohexene (±)-**4** required for the pivotal IMAE process

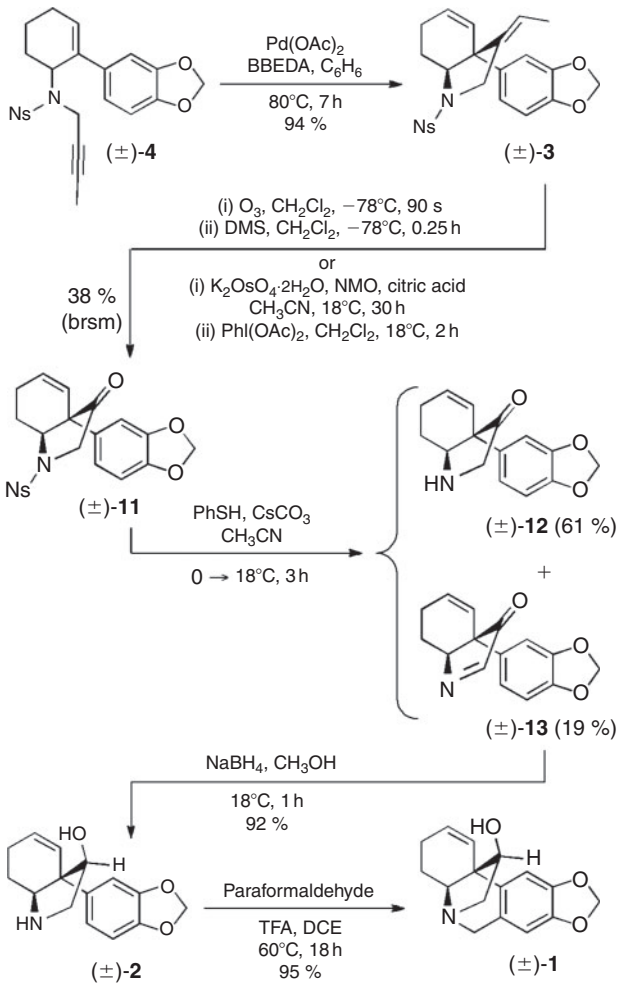


Scheme 1. DMAP, 4-(*N*,*N*-dimethylamino)pyridine; TFA, trifluoroacetic acid.

was achieved using the reaction sequence shown in Scheme 1 and as originally established by Banwell and coworkers.[10] Thus, the cyclopropane **5**, which is readily available in multigram quantities through addition of dibromocarbene to cyclopentene,[13] was treated with silver cyanate thus inducing electrocyclic ring-opening of the three-membered ring to give an allylic cation that was trapped, in situ, to form the allylic isocyanate (±)-**6**.[14] This last species was itself trapped by added *t*-butanol to give the carbamate (±)-**7**[14] in 79 % yield. Since carbamate-protected amines were considered likely to prevent appropriate orbital overlap of the reacting groups in the foreshadowed IMAE reaction,[10] compound (±)-**7** was deprotected using trifluoroacetic acid (TFA) in dichloromethane. The resulting primary amine was then treated with nosyl chloride in the presence of 4-(*N*,*N*-dimethylamino)pyridine and triethylamine thereby generating the sulfonamide (±)-**8**[10] in 87 % yield. Suzuki–Miyaura cross-coupling[15] of compound (±)-**8** with the commercially available aryl boronic acid **9** gave the arylated cyclohexene (±)-**10** (77 %) that was treated with sodium hydride followed by 1-bromo-2-butyne in DMF to provide substrate (±)-**4**[10] (86 %) required for the pivotal IMAE reaction. All the spectroscopic data obtained on the reaction products shown in Scheme 1 were in accord with the assigned structures and matched those reported previously.[10]

*Completion of the Synthesis of Racemic Haemultine [(±)-**1**]: Implementation of the IMAE and Pictet–Spengler Reactions*

With compound (±)-**4** to hand the pivotal IMAE reaction was examined. In the event, and in keeping with earlier observations,[10] upon subjecting this compound to reaction with $Pd(OAc)_2$ and the strongly σ-donating and bidentate ligand *N*,*N*′-bis(benzylidene)ethylenediamine (BBEDA) in refluxing benzene,[16] the required and previously reported[10] *cis*-C3a-arylhexahydroindole (±)-**3** was obtained as a white, crystalline solid in 94 % yield (Scheme 2).



Scheme 2. BBEDA, *N*,*N*′-bis(benzylidene)ethylenediamine; DMS, dimethyl sulphide; NMO, *N*-methylmorpholine *N*-oxide; TFA, trifluoroacetic acid; DCE, 1,2-dichloroethane.

The selective oxidative cleavage of the exocyclic double bond within compound (±)-**3** was a necessary step associated with obtaining the substrate, (±)-**2**, required for the Pictet–Spengler reaction. Accordingly, various methods for carrying out this conversion were explored on the basis that some selectivity should be observed in this type of transformation because the trisubstituted and exocyclic double bond should be the more nucleophilic of the two within substrate (±)-**3**. In the event, the desired selectivity was rather difficult to achieve. Under some of the best conditions identified thus far, and involving exposure of substrate (±)-**3** to ozone for 90 s at −78°C followed by rapid reductive work-up with dimethyl sulfide, the target and crystalline ketone (±)-**11** could be obtained in 38 % yield based on recovered starting material (brsm). Significant quantities of the ketodialdehyde arising from cleavage of both double bonds with substrate (±)-**3** seemed to be formed as a result of the ozonolysis but attempts to convert this very unstable material back into compound (±)-**11** by exposing it to the McMurry reagent[17] proved fruitless. The application of conditions used by us on a related substrate,[9c] namely $K_2OsO_4{\cdot}2H_2O$ and *N*-methylmorpholine *N*-oxide (NMO) in the presence of citric acid and then treating the resulting diols with $PhI(OAc)_2$, gave similar yields of ketone (±)-**11**. The spectroscopic data derived from ketone (±)-**11** were in complete

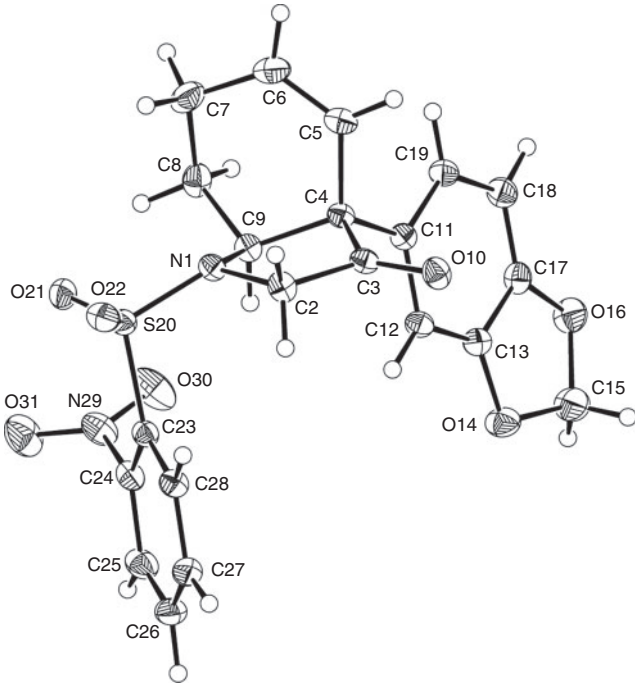


Fig. 3. *ORTEP* diagram derived from the single-crystal X-ray analysis of the ketone (±)-**11**. Thermal ellipsoids are drawn at the 30 % probability level. H atoms are shown as spheres of arbitrary radius.

accord with the assigned structure but final confirmation of this was secured by single-crystal X-ray analysis. The derived *ORTEP* diagram is shown in Fig. 3 while further details are provided in the Experimental section.

While various possible orderings of the steps required to effect the conversion (±)-**11** → (±)-**1** can be envisaged, several exploratory studies led us to conclude that the one shown in Scheme 2 would be the most effective. Accordingly, the ketone (±)-**11** was subjected to reaction with thiophenol in the presence of caesium carbonate, a reagent combination defined by Fukuyama et al.[18] for the cleavage of nosyl groups under mild conditions. As a consequence the deprotected and somewhat unstable amino-ketone (±)-**12** (61 %) was obtained together with its chromatographically separable dehydro-derivative (±)-**13** (19 %). In an alternate approach, treatment of compound (±)-**11** with magnesium in methanol gave azaenone (±)-**13** exclusively in 81–87 % yield. Exposure of compounds (±)-**12** and (±)-**13**, either separately or as a mixture, to sodium borohydride in methanol at 18°C afforded the diastereoisomerically pure and β-configured alcohol (±)-**2** in 96 % yield. The stereochemical outcome of this reduction process was presumed to be as illustrated on the basis that hydride would be delivered preferentially to the *exo*-face of the C-3 carbonyl group within the substrate. Confirmation of this was established by a single-crystal X-ray analysis of the final product (±)-**1** (see below). Successive treatment of the amino-alcohol (±)-**2** with paraformaldehyde followed by TFA resulted in a Pictet–Spengler reaction. As a consequence the racemic modification of the structure, **1**, assigned to haemultine, was obtained as a crystalline solid and in near quantitative yield.

The ^1H and ^{13}C NMR spectroscopic data obtained on compound (±)-**1** are presented in Table 1 and these were in complete accord with the assigned structure. In particular, the former spectrum displayed two one-proton singlets arising from the isolated protons of the aromatic ring, two mutually coupled

Table 1. ^{1}H and ^{13}C NMR spectroscopic data for (±)-haemultine [(±)-1] and the mixture of L-(+)-tartrate salts of (+)- and (−)-haemultine [(+)-1 and (−)-1]

^{1}H NMR [δ_H]		^{13}C NMR [δ_C]	
Synthetic (±)-**1**[A]	L-(+)-Tartrate salts of (+)-**1** and (−)-**1**[B]	Synthetic (±)-**1**[C]	L-(+)-Tartrate salts of (+)-**1** and (−)-**1**[D]
6.83, s, 1H	7.03, s, 1H	146.4	147.2 (C)
6.45, s, 1H	6.74, s, 1H	146.0	146.5 (C)
6.28, m, 1H	6.22, d, *J* 10.1, 1H	136.2	135.1 (C)
6.16, d, *J* 10.1, 1H	6.02, dd, *J* 10.1 and 5.7, 1H	134.6	130.8 (C)
5.88, m, 2H	5.97, s, 2H	126.8	123.3 (C)
4.30, d, *J* 16.7, 1H	4.50, d, *J* 16.0, 1H	122.3	122.6 (C)
3.90, m, 1H	4.03, d, *J* 16.0, 1H	106.8	107.5 (C)
3.70, d, *J* 16.7, 1H	3.91, m, 1H	103.3	104.2 (C)
3.30, m, 2H	3.67, dd, *J* 13.5 and 6.9, 1H	100.8	101.5 (CH_2)
3.10, dd, *J* 12.4 and 4.6, 1H	3.45, d, *J* 12.8, 1H and 3.34, d, *J* 12.8, 1H	79.9	77.3 (CH)
2.30–2.22, complex m, 2H	2.21–2.10, complex m, 2H	66.5	66.9 (CH_2)
2.21–2.00, complex m, 2H	2.11–2.02, complex m, 2H	63.0	61.2 (CH_2)
1.73, m, 1H	1.82, s, 1H	61.4	58.4 (CH)
–	2.48, s, 2H[E]	49.9	50.2 (C)
–	–	24.9	24.0 (CH_2)
–	–	23.7	21.6 (CH_2)
–	–	–	174.2 (C)[F]
–	–	–	72.4 (CH)[G]

[A]Recorded in $CDCl_3$ at 500 MHz.
[B]Recorded in $(CD_3)_2SO$ at 400 MHz.
[C]Recorded in $CDCl_3$ at 125 MHz.
[D]Recorded in $(CD_3)_2SO$ at 100 MHz.
[E]Signal due to methine protons of tartrate residue.
[F]Signal due to carbonyl carbons of tartrate residue.
[G]Signal due to methine carbons of tartrate residue.

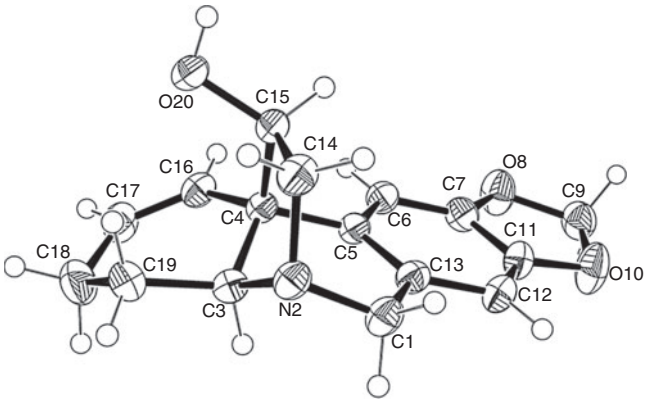


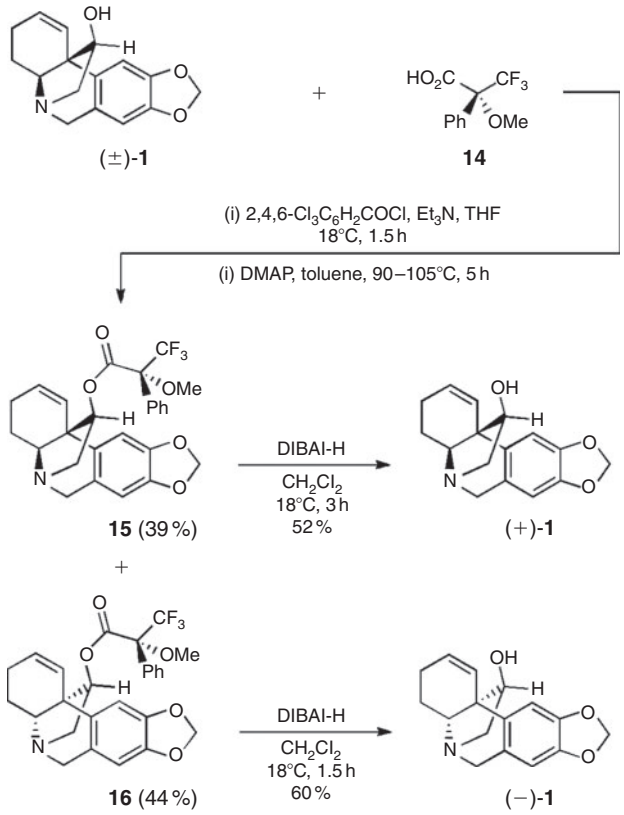
Fig. 4. *ORTEP* diagram derived from the single-crystal X-ray analysis of (±)-haemultine [(±)-**1**]. Thermal ellipsoids are drawn at the 50% probability level. H atoms are shown as spheres of arbitrary radius.

(*J* 10.1) one-proton multiplets due to the non-equivalent olefinic protons, and an AB spin-system (*J* 16.7) due to the geminally related methylene protons of the C-ring. The $\{^{1}H\}^{13}C$ NMR spectrum showed the expected seventeen signals including eight distinctly downfield of the resonances due to $CDCl_3$ and arising from the sp^2-hybridised carbons of the aromatic ring or of the double bond. The infrared spectrum showed no particularly distinguishing features while the 70 eV electron impact (EI) mass spectrum displayed a molecular ion at *m/z* 271 together with a significant daughter ion at *m/z* 227 [corresponding to the loss of $H_2C{=}C(H)OH$]. An accurate mass measurement on the molecular ion established that it was of the expected composition, that is $C_{16}H_{17}NO_3$. However, none of these data allowed for a definite assignment of the relative configuration at the hydroxy-bearing carbon. Accordingly, and given its crystalline form, the Pictet–Spengler product was subjected to single crystal X-ray analysis. The derived *ORTEP* diagram is shown in Fig. 4 while other details are presented in the Experimental section. This analysis clearly demonstrates that the hydroxy group attached to the C-ring sits over the D-ring rather than the B-ring as seen in structure, **1**, assigned to haemultine.

*Resolution of (±)-**1**: Isolation and Characterisation of the (+)- and (−)-Forms of Haemultine*

With the racemic form, (±)-**1**, of the structure assigned to haemultine in hand, methods for resolution into its constituent enantiomers could be investigated. In a first attempt, compound (±)-**1** was reacted with stoichiometric amounts of L-(+)-tartaric acid in order to form the corresponding pair of diastereoisomeric salts. The ^{1}H and ^{13}C NMR spectroscopic data obtained on the mixture so formed (see Table 1) displayed a single set of signals rather than the two that might have been expected given the formation of diastereoisomers. Nevertheless, the successful formation of the desired salts seems clear from, for example, a comparison of the ^{13}C NMR spectra of the free base and the corresponding salts. Specifically, the differences in chemical shifts due to the carbons surrounding the (protonated or unprotonated) nitrogen support this proposition. However, despite various attempts to do so, the salts could not be separated from one another.

As a result of the difficulties detailed above, the reaction sequence shown in Scheme 3 was used to provide compounds (+)-**1** and (−)-**1** in enantiomerically pure form. Thus, in the first step of this simple sequence, the racemic modification of compound **1** was reacted with the (*R*)-form, **14**, of the Mosher



Scheme 3. DMAP, 4-(*N*,*N*-dimethylamino)pyridine; DIBAl-H, diisobutylaluminium hydride.

acid in the presence of 2,4,6-trichlorobenzoyl chloride and triethylamine. After 1 h the reaction mixture was treated with 4-(*N*,*N*-dimethylamino)pyridine (DMAP) in toluene. The ensuing mixture of esters **15** and **16** could be cleanly separated from one another by flash chromatography and each was then characterised by the usual methods.

A comparison of the ^{1}H and ^{13}C NMR spectra derived from the diastereoisomeric Mosher esters **15** and **16** is presented in Table 2 and this reveals, generally speaking, only rather subtle differences between the two sets of data. The most notable and useful ones were encountered in the lower field regions of the ^{1}H NMR spectra. In particular, the signals due to the olefinic protons in compound **16** appear at lower field and are less well differentiated than those due to their counterparts in isomer **15** (see bold entries in Table 2).

On the basis that the significant conformation of the Mosher ester residue within each of compounds **15** and **16** is that in which the C(H)–O–C(=O)–C–CF_3 ensemble is co-planar[19] then, as illustrated in Fig. 5, it is the former diastereoisomer that would experience greater deshielding (and differentiation) of the olefinic protons. This is because these protons within diastereoisomer **15** are most readily exposed to the anisotropic magnetic shielding effect of the phenyl ring.

In order to confirm the above-mentioned assignments of the structures of compounds **15** and **16** each of them was subjected to ester cleavage using diisobutylaluminium hydride (DIBAl-H), thereby producing alcohols (+)-**1** (52 %) and (−)-**1** (60 %), respectively. The latter compounds were independently converted into the corresponding 2,5-dibromobenzoates and a single-crystal X-ray analysis was then undertaken on each, so

Table 2. ^{1}H and ^{13}C NMR spectroscopic data for Mosher esters 15 and 16

(Bold entries are signals due to the olefinic protons in compound **16** that appear at lower field and are less well differentiated than those due to their counterparts (also in bold) in isomer **15**)

^{1}H NMR [δ_H]		^{13}C NMR [δ_C]	
Compound **15**[A]	Compound **16**[B]	Compound **15**[C]	Compound **16**[C]
7.48, m, 2H	7.55, m, 2H	165.6	165.6
7.42, m, 3H	7.40, m, 3H	146.8	146.8
6.96, s, 1H	6.93, s, 1H	146.6	146.5
6.57, s, 1H	6.48, s, 1H	134.6	134.8
6.08, d, *J* 5.8, 1H	**6.17, d, *J* 10.2, 1H**	132.3	132.1
5.91, s, 2H	**5.94, m, 1H**	132.2	132.0
5.78, m, 1H	5.91, s, 2H	129.5	129.5
5.15, m, 1H	5.08, m, 1H	128.3	128.3
4.38, d, *J* 15.7, 1H	4.33, d, *J* 16.0, 1H	127.3	127.4
3.75, d, *J* 15.7, 1H	3.70, d, *J* 16.0, 1H	126.3	126.7
–	3.93, dd, *J* 14.0 and 7.0, 1H	123.3 (CF_3 quartet)	123.3 (CF_3 quartet)
3.52, s, 3H	3.51, s, 3H	121.7	122.4
3.42, m, 2H	3.28, dd, *J* 14.0 and 3.5, 1H	106.6	106.6
3.11, t, *J* 9.4, 1H	3.10, m, 1H	104.1	104.0
2.00, m, 2H	2.05, m, 2H	101.0	100.9
1.65, m, 2H	1.65, m, 2H	84.1 (C–CF_3 quartet)	84.5 (C–CF_3 quartet)
–	–	82.3	82.9
–	–	66.9	67.0
–	–	61.1	61.2
–	–	59.7	60.3
–	–	55.3	55.3
–	–	49.0	48.6
–	–	24.5	29.7
–	–	23.1	23.2

[A]Recorded in $CDCl_3$ at 300 MHz.
[B]Recorded in $CDCl_3$ at 500 MHz.
[C]Recorded in $CDCl_3$ at 125 MHz.

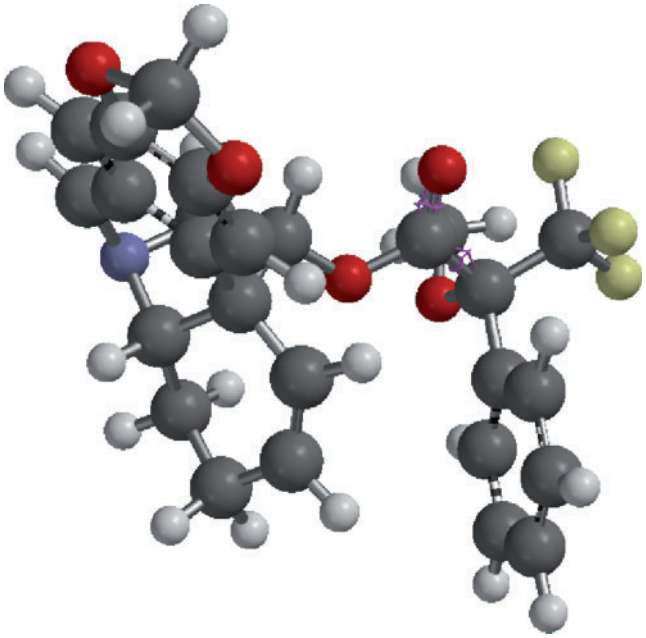


Fig. 5. Molecular model of compound **15** generated using *Spartan 10* (MMFF94-derived geometries) with the ester residue and associated oxymethine proton (top centre) constrained in the required *s-trans* and coplanar array and showing the consequent proximity of the olefinic hydrogens (bottom centre) to the shielding zone of the phenyl group (bottom right).

firmly establishing their absolute configurations. Details are presented in the Experimental section and the Supplementary Material. Spectroscopic analyses of the alcohols themselves revealed that the (+)-form was obtained from precursor **15** while its enantiomer was obtained from isomer **16**. The circular dichroism spectra recorded on each of the product enantiomers were essentially mirror images of one another (see Supplementary Material) while the melting points and signs of the specific rotations were consistent with those obtained by Fales and Wildman[4] from their synthetically derived sample of the former material. The discrepancy between the magnitudes of the specific rotation of our sample of (+)-**1** $[\alpha]_D$ +75 ($c = 0.1$, $CHCl_3$) and that reported for the material obtained by demethoxylation of haemanthamine[4] {$[\alpha]_D$ +10 ($c = 0.19$, solvent not specified)} may be attributed to the differences in solvent used for obtaining the optical rotation data. Accordingly, we agree with the suggestion[4] that the sample of haemultine obtained by Boit and Döpke is likely to be a mixture of compound (+)-**1** and its $\Delta^{2,3}$-double bond isomer. A similar interpretation could be applied to the results of the study carried out by Itokawa and coworkers.[6]

Conclusions

The studies reported here lend weight to the suggestion that the purported natural product haemultine may in fact be, as suggested by Fales and Wilman,[4] a mixture of compound (+)-**1** and its $\Delta^{2,3}$-double bond isomer. However, the only way to determine if this is truly so would be to reisolate the natural product (if this can be done) and then subject it to analysis using modern spectroscopic techniques. Despite these residual ambiguities, the present work demonstrates the utility of the IMAE/Pictet–Spengler reaction sequence outlined in Fig. 2 as a means for preparing crinine alkaloids, especially those bearing an oxygen functionality in the C-ring. The capacity to use such functionality for the purposes of resolving the racemic forms of such compounds into their constituent enantiomers is also noteworthy. Further applications of these protocols in natural products synthesis will be reported in due course as will the outcomes of the biological evaluations of compounds (+)-**1** and (−)-**1**.

Experimental

General Experimental Procedures

^1H and ^{13}C NMR spectra were recorded on a Varian Gemini machine operating at 300 or 75 MHz, respectively. Unless otherwise specified, spectra were acquired at 20°C in deuterochloroform ($CDCl_3$) that had been stored over anhydrous sodium carbonate. Chemical shifts are recorded as δ values in parts per million (ppm). Infrared spectra (ν_{max}) were normally recorded on a Perkin–Elmer 1800 Series FTIR Spectrometer and samples were analysed as thin films on KBr plates (for liquids) or as a KBr disk (for solids). Low-resolution electrospray ionisation (ESI) mass spectra were recorded in positive-ion mode on a Micromass–Waters LC-ZMD single quadrupole liquid chromatograph–mass spectrometer while low- and high-resolution EI mass spectra were recorded on a Fisons VG AUTOSPEC instrument. Melting points were measured on a Stanford Research Systems Optimelt-Automated Melting Point System and are uncorrected. Optical rotations were measured at the sodium-D line (λ 589 nm) between 17 and 20°C and at the concentrations (c, in g per 100 mL) indicated using spectroscopic grade chloroform ($CHCl_3$) as solvent. Analytical TLC was performed on aluminium-backed 0.2 mm thick silica gel 60 F254 plates as supplied by Merck. Eluted plates were visualised using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included a mixture of vanillin/sulfuric acid/ethanol (1 g : 1 g : 18 mL) or phosphomolybdic acid/ceric sulfate/sulfuric acid (conc.)/water (37.5 g : 7.5 g : 37.5 g : 720 mL). The retardation factor (R_F) values cited here have been rounded to the first decimal point. Flash chromatographic separations were carried out following protocols defined by Still et al.[20] with silica gel 60 (40–63 μm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. Starting materials and reagents were generally available from the Sigma–Aldrich, Merck, TCI, Strem, or Lancaster Chemical Companies and were either used as supplied or, in the case of liquids, distilled when required. Drying agents and other inorganic salts were purchased from the AJAX, BDH, or Unilab Chemical Companies. THF, dichloromethane, acetonitrile, and benzene were dried using a Glass Contour solvent purification system that is based upon a technology originally described by Grubbs et al.[21] Spectroscopic grade solvents were used for all analyses. Where necessary, reactions were performed under a nitrogen or argon atmosphere.

Specific Chemical Transformations

*Compound (±)-**11***

Method A: A magnetically stirred solution of diene (±)-**3**[10] (50 mg, 0.11 mmol) in dichloromethane/methanol (10 mL of a 1 : 1 v/v mixture) was cooled to −78°C then sparged with ozone generated using a 500 Model Fischer portable ozone generator. After 90 s the stream of ozone was replaced with nitrogen and the reaction mixture allowed to warm to 0°C and then treated with dimethyl sulfide (0.2 mL, 2.7 mmol). After a further 0.5 h the reaction mixture was concentrated under reduced pressure and the residue thus obtained subjected to flash chromatography (silica, 35 : 65 v/v ethyl acetate/hexane elution) to afford two fractions, A and B.

Concentration of fraction A (R_F 0.5 in 1 : 1 v/v ethyl acetate/hexane) afforded the *title compound (±)-**11*** (16 mg, 38 % brsm) as white crystals, mp 167–169°C (Found: $M^{+\bullet}$, 442.0837. $C_{21}H_{18}N_2O_7S$ requires: $M^{+\bullet}$, 442.0835). δ_H (300 MHz) 7.88 (d, *J* 8.0, 1H), 7.69 (m, 1H), 7.59 (m, 2H), 6.61–6.43 (complex m, 3H), 6.12 (dt, *J* 10.0 and 4.0, 1H), 5.91 (m, 2H), 5.56 (d, *J* 10.0, 1H), 4.39 (t, *J* 6.4, 1H), 4.16 (ABq, *J* 16.0, 2H), 2.13 (m, 2H), 1.95 (m, 2H). δ_C (125 MHz) 208.3, 148.1, 147.9, 147.1, 133.8, 133.1, 131.7, 131.6, 131.3, 130.7, 124.9, 124.1, 120.8, 108.2, 107.8, 101.2, 65.2, 60.4, 53.2, 24.7, 21.5. ν_{max} (KBr)/cm^{-1} 2917, 1757, 1543, 1505, 1486, 1437, 1371, 1243, 1162, 1126, 1068, 1038, 912. *m/z* (EI, 70 eV) 442 (10 %, $M^{+\bullet}$), 255 (7), 201 (20), 200 (100), 141 (15).

Concentration of fraction B (R_F 0.7 in 1 : 1 v/v ethyl acetate/hexane) gave the starting diene (±)-**3** (6 mg, 12 % recovery) that was identical, in all respects, with an authentic sample.

Method B: A magnetically stirred solution of diene (±)-**3** (321 mg, 0.71 mmol) in acetonitrile/water (15 mL of a 4 : 1 v/v mixture) maintained at 18°C was treated with $K_2OsO_4{\cdot}2H_2O$ (39 mg, 0.11 mmol), citric acid (1.4 g, 7.29 mmol), and NMO (579 mg, 4.94 mmol). After 30 h the reaction mixture was diluted with ethyl acetate (20 mL) followed by NH_4Cl (50 mL of a saturated aqueous solution), and the separated aqueous phase was extracted with ethyl acetate (3 × 15 mL). The combined organic phases were filtered through a short pad of TLC-grade silica gel and the filtrate concentrated under reduced pressure. The residue thus obtained was dissolved in dichloromethane and then treated, at 18°C and with magnetic stirring, with $PhI(OAc)_2$ (273 mg, 0.848 mmol). After 2 h the reaction mixture was filtered and the filtrate concentrated under reduced pressure to give a light-yellow oil that was subjected to flash chromatography (silica, 3 : 5 v/v ethyl acetate/hexane elution). Concentration of the relevant fractions (R_F 0.5 in 4 : 2.5 : 5.5 v/v/v ethyl acetate/dichloromethane/hexane) gave compound (±)-**11** (120 mg, 39 %) as a white, crystalline solid that was identical in all respects with the material produced by Method A.

*Compounds (±)-**12** and (±)-**13***

Method A: A magnetically stirred solution of ketone (±)-**11** (108 mg, 0.24 mmol) in acetonitrile (5 mL) maintained under a nitrogen atmosphere at 0°C was treated with thiophenol (74 mL, 0.73 mmol) and caesium carbonate (258 mg, 0.79 mmol). The ensuing mixture was allowed to warm to 18°C, stirred at this temperature for 1 h, and then treated with NH_4Cl (10 mL of a saturated aqueous solution) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic fractions were washed with NH_4Cl (1 × 10 mL of a saturated aqueous solution) and brine (1 × 10 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1 : 4 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_F 0.8 in 1 : 1 v/v ethyl acetate/hexane) afforded the *title compound (±)-**13*** (12 mg, 19 %) as a light-brown oil (Found: $M^{+\bullet}$, 255.0892. $C_{15}H_{13}NO_3$ requires: $M^{+\bullet}$, 255.0895). δ_H (500 MHz) 8.04 (s, 1H), 6.79 (d, *J* 8.6, 1H), 6.61 (m, 2H), 6.11 (m, 1H), 5.95 (s, 2H), 5.39 (d, *J* 9.8, 1H), 4.46 (br s, 1H), 2.38 (m, 1H), 2.14 (m, 1H), 1.89 (m, 2H). δ_C (125 MHz) 201.8, 164.9, 148.0, 146.8, 133.9, 132.9, 123.7, 121.0, 108.5, 108.0, 101.2, 77.3, 56.3, 23.1, 19.7. ν_{max} (KBr)/cm^{-1} 2917, 1735, 1504, 1489, 1439, 1246, 1234, 1210, 1039, 932. *m/z* (EI, 70 eV) 255 (60 %, $M^{+\bullet}$), 200 (100), 141 (30).

The column used in the chromatographic separation mentioned immediately above was stripped with methanol and the filtrate so obtained was concentrated under reduced pressure to give a light-brown oil. This was subjected to flash chromatography (silica, 0.3 : 99.7 v/v ammonia saturated methanol/dichloromethane elution) to afford, after concentration of the appropriate fractions (R_F 0.8 in 1 : 1 v/v ethyl acetate/hexane), the *title compound (±)-**12*** (38 mg, 61 %) as a brown oil (Found: $[M+H]^+$, 258.1132. $C_{15}H_{15}NO_3$ requires: $[M+H]^+$, 258.1130]. δ_H (400 MHz) 6.74 (d, *J* 8.1, 1H), 6.62 (m, 2H), 6.10 (m, 1H), 5.90 (s, 2H), 5.46 (d, *J* 9.9, 1H), 3.67 (d, *J* 18.6, 1H), 3.60 (broad s, 1H), 3.42 (d, *J* 18.6, 1H), 2.36 (br s, 1H), 2.17 (m, 2H), 1.84 (m, 1H), 1.70 (m, 1H). δ_C (100 MHz) 218.1, 147.8, 146.6, 135.3, 131.1, 124.0, 121.4, 108.4, 108.2, 101.1, 63.7, 58.7, 55.1, 20.5, 19.7. ν_{max} (KBr)/cm^{-1} 2921, 1742, 1503, 1488, 1440, 1243, 1038, 933, 811. *m/z* (ESI, +ve) 270 (23 %, $[M + Na]^+$), 258 (100, $[M + H]^+$), 240 (62).

Method B: Magnesium (91 mg, 3.74 g atom) was added to a magnetically stirred solution of compound (±)-**11** (166 mg, 0.38 mmol) in methanol (10 mL) maintained at 18°C. After 2 h the reaction mixture was filtered through a short pad of TLC-grade silica gel and the filtrate concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 3 : 5 v/v ethyl acetate/hexane elution) to give, after concentration of the appropriate fractions (R_F 0.5 in 2 : 2.5 : 5.5 v/v/v ethyl acetate/dichloromethane/hexane), compound (±)-**13** (80 mg, 83 %) as a light-yellow oil that was identical, in all respects, with the material obtained by Method A as detailed above.

*Compound (±)-**2***

Method A: A magnetically stirred solution of compounds (±)-**12** and (±)-**13** (50 mg, ~0.19 mmol of a ~3 : 1 mixture obtained as described immediately above) in THF/methanol (5 mL of a 1 : 1 v/v mixture) maintained at 0°C was treated with $NaBH_4$ (22 mg, 0.58 mmol). The resulting mixture was allowed to warm to 18°C over 1 h and then treated with NH_4Cl (10 mL of a saturated aqueous solution) and extracted with dichloromethane (3 × 10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash chromatography (silica, 15 : 85 v/v ammonia saturated methanol/dichloromethane elution) afforded, after concentration of the relevant fractions (R_F 0.5), the *title compound* (±)-***2*** (46 mg, 92 %) as a white, crystalline solid, mp 169–171°C (Found: $[M-H\bullet]^+$, 258.1135. $C_{15}H_{17}NO_3$ requires: $[M-H\bullet]^+$, 258.1130). δ_H (500 MHz) 6.89 (d, *J* 1.9, 1H), 6.82 (dd, *J* 8.2 and 1.9, 1H), 6.75 (d, *J* 8.2, 1H), 6.13 (m, 1H), 5.91 (s, 2H), 5.85 (d, *J* 10.4, 1H), 4.63 (t, *J* 7.1, 1H), 3.38 (m, 1H), 3.28 (m, 1H), 2.90 (m, 1H), 2.17 (m, 1H), 2.06 (m, 1H), 1.80 (br s, 2H) 1.70 (m, 1H), 1.60 (m, 1H). δ_C (125 MHz) 147.8, 146.0, 138.5, 130.5, 126.1, 120.1, 108.1, 107.6, 101.0, 79.5, 63.0, 52.7, 22.9, 20.1 (signal due to one carbon obscured or overlapping). ν_{max} (KBr)/cm^{-1} 3434, 3285, 3033, 2933, 2877, 1502, 1486, 1431, 1228, 1114, 1099, 1039, 937, 899, 873, 804. *m/z* (EI, 70 eV) 258 (1 %, $[M-H\bullet]^+$), 241 (5, $[M-H_2O]^+\bullet$), 201 (23), 200 (100).

Method B: $NaBH_4$ (16 mg, 3.743 mmol) was added to a magnetically stirred solution of compound (±)-**13** (56 mg, 0.22 mmol) in methanol (5 mL) maintained at 18°C. After 1 h the reaction mixture was concentrated under reduced pressure and the light-yellow oil thus obtained was subjected to flash chromatography (silica, ammonia-saturated methanol elution)

to give, after concentration of the appropriate fractions (R_F 0.4 in 1 : 9 v/v ammonia-saturated methanol/methanol), compound (±)-**2** (55 mg, 96 %) as a light-yellow, crystalline solid that was identical, in all respects, with the material obtained by Method A detailed immediately above.

*Compound (±)-**1***

A magnetically stirred solution of compound (±)-**2** (54 mg, 0.21 mmol) in 1,2-dichloroethane (10 mL) was treated with paraformaldehyde (32 mg, 1.06 mmol) and TFA (320 µL, 4.15 mmol). The resulting solution was heated at 60°C for 18 h and then cooled and concentrated under reduced pressure. The ensuing residue was subjected to flash chromatography (silica, 3 : 17 v/v ammonia-saturated methanol/methanol) to afford, after concentration of the relevant fractions (R_F 0.4 in methanol), the *title compound* (±)-***1*** (53 mg, 95 %) as a white, crystalline solid, mp 202–205°C (Found: $M^{+\bullet}$, 271.1208. $C_{16}H_{17}NO_3$ requires: $M^{+\bullet}$, 271.1208). δ_H (500 MHz) see Table 1. δ_C (125 MHz) see Table 1. ν_{max} (KBr)/cm^{-1} 2907, 1502, 1481, 1323, 1307, 1238, 1064, 1038, 935, 850. *m/z* (EI, 70 eV) 271 (76 %, $M^{+\bullet}$), 270 (50), 228 (53), 227 (100), 213 (56).

L-(+)-Tartrate Salts of (+)- and (−)-Haemultine

A magnetically stirred solution of compound (±)-**1** (10.0 mg, 0.04 mmol) in acetonitrile (2 mL) was treated with L-(+)-tartaric acid (5.5 mg, 0.04 mmol) and the resulting mixture heated at 50°C until all the solid had dissolved and then treated with water (~0.2 mL) and allowed to cool. The resulting solid was removed by filtration to give a mixture of the *title salts* (15.5 mg, 100 %) as clear, colourless crystals, mp 121–125°C (Found: $[M + H]^+$, 272.1287; $C_{16}H_{17}NO_3{\cdot}C_4H_6O_6$ requires $[M + H]^+$, 272.1287). δ_H (400 MHz) see Table 1. δ_C (100 MHz) see Table 1. ν_{max} (KBr)/cm^{-1} 3422, 2914, 1662, 1489, 1354, 1301, 1254, 1115, 1082, 841, 688. *m/z* (ESI, +ve) 272 (100 %, $[M + H]^+$).

*Compounds **15** and **16***

2,4,6-Trichlorobenzoyl chloride (78 µL, 0.50 mmol) was added to a magnetically stirred solution of (*R*)-(+)-MTPA-OH (**14**) (125 mg, 0.53 mmol) and triethylamine (230 µL, 1.65 mmol) in THF (4 mL) maintained at 18°C under a nitrogen atmosphere. After 1.5 h the reaction mixture was diluted with toluene (5 mL) and the solution thus obtained added by a syringe pump over 4 h to a magnetically stirred solution of compound (±)-**1** (90 mg, 0.33 mmol) and DMAP (405 mg, 3.32 mmol) in toluene (10 mL) maintained at 90°C under a nitrogen atmosphere. The ensuing mixture was stirred at 105°C for 1 h and then cooled and quenched with $NaHCO_3$ (50 mL of a saturated aqueous solution). The separated aqueous phase was extracted with ethyl acetate (2 × 10 mL) and the combined organic phases were washed with NH_4Cl (50 mL of a saturated aqueous solution) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Subjection of the yellow oil thus obtained to flash chromatography (silica, 1 : 20 : 20 → 1 : 10 : 10 v/v/v methanol/ethyl acetate/hexane gradient elution) afforded two fractions, A and B.

Concentration of fraction A (R_F 0.6 in 7 : 2 : 1 v/v/v ethyl acetate/hexane/methanol) afforded the *title compound **16*** (72 mg, 44 %) as a clear, colourless oil that solidified on standing, $[\alpha]_D$ −32 (*c* 0.1, $CHCl_3$) (Found: $M^{+\bullet}$, 487.1606. $C_{26}H_{24}F_3NO_5$ requires: $M^{+\bullet}$, 487.1607). δ_H (500 MHz) see Table 2. δ_C (125 MHz) see Table 2. ν_{max} (KBr)/cm^{-1} 2917, 1743, 1503, 1482, 1265, 1239, 1170, 1039, 1030, 938, 737. *m/z* (EI, 70 eV) 487 (100 %, $M^{+\bullet}$), 254 (45), 189 (43).

Concentration of fraction B (R_F 0.5 in 7 : 2 : 1 v/v/v ethyl acetate/hexane/methanol) afforded the *title compound **15*** (63 mg, 39 %) as a clear, colourless oil that solidified on standing, $[\alpha]_D$ +32 (*c* 0.2, $CHCl_3$) (Found: $M^{+\bullet}$, 487.1605. $C_{26}H_{24}F_3NO_5$ requires: $M^{+\bullet}$, 487.1607). δ_H (300 MHz) see Table 2. δ_C (125 MHz) see Table 2. ν_{max} (KBr)/cm^{-1} 2948, 2915, 1745, 1482, 1270, 1240, 1169, 1121, 1038, 1026, 847, 733, 714. *m/z* (EI, 70 eV) 487 (100 %, $M^{+\bullet}$), 254 (57), 189 (52).

*Compound (+)-**1***

DIBAl-H (1.1 mL of a 1.0 M solution in dichloromethane, 1.1 mmol) was added dropwise to a magnetically stirred solution of Mosher ester **15** (55 mg, 0.11 mmol) in dichloromethane (8 mL) maintained at 18°C under a nitrogen atmosphere. Stirring was continued for a further 3.0 h and then the reaction mixture was treated with methanol (2 mL) and additional dichloromethane (10 mL) before being poured into NH_4Cl (25 mL of a saturated aqueous solution). The separated aqueous phase was extracted with dichloromethane (2 × 10 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash chromatography (silica, 3 : 17 v/v ammonia-saturated methanol/methanol elution) gave, after concentration of the appropriate fractions (R_F 0.4 in methanol), the title compound (+)-**1**[4] (16 mg, 52 %) as a white, crystalline solid, mp 195–196°C (lit.[4] mp 194–194.5), $[\alpha]_D$ +75 (*c* 0.1, $CHCl_3$) {lit.[4] $[\alpha]_D$ +10 (*c* 0.19, solvent not specified)}. The ^{1}H NMR, ^{13}C NMR, IR, and mass spectroscopic data recorded on this material were identical with those reported above for racemic haemultine [(±)-**1**)].

*Compound (−)-**1***

Treatment of the Mosher ester **16** (54 mg, 0.11 mmol) with DIBAl-H (550 µL of a 1.0 M solution in dichloromethane, 0.55 mmol) in essentially the same manner as described above for the conversion **15** → (+)-**1** but using a reaction time of 1.5 h afforded, after work-up and flash chromatography, *compound (−)-**1*** (18 mg, 60 %) as a white, crystalline solid, mp 195–197°C, $[\alpha]_D$ −75 (*c* 0.25, $CHCl_3$). The ^{1}H NMR, ^{13}C NMR, IR, and mass spectroscopic data recorded on this material were identical with those reported above for racemic haemultine [(±)-**1**)].

*2,5-Dibromobenzoate of Compound (+)-**1***

A magnetically stirred solution of compound (+)-**1** (5.3 mg, 0.02 mmol) and 2,5-dibromobenzoic acid (11 mg, 0.04 mmol) in dichloromethane was treated with *N*,*N*′-dicyclohexylcarbodiimide (DCC, 12 mg, 0.06 mmol) and DMAP (11 mg, 0.06 mmol). After 16 h the reaction mixture was diluted with dichloromethane (10 mL) and the solution thus obtained treated with NH_4Cl (20 mL of a saturated aqueous solution). The separated aqueous phase was extracted with dichloromethane (2 × 10 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash chromatography (silica, 2 : 25 : 25 v/v/v methanol/ethyl acetate/hexane elution) gave, after concentration of the appropriate fractions (R_F 0.5 in 6 : 3 : 1 v/v/v ethyl acetate/hexane/methanol), the *title ester* (7.9 mg, 77 %), as a white, crystalline solid, mp 162–164°C. (Found: $M^{+\bullet}$, 532.9664. $C_{23}H_{19}{}^{79}Br^{81}BrNO_4$ requires $M^{+\bullet}$,

532.9660.) δ_H (600 MHz) 7.83 (d, *J* 3.0, 1H), 7.51 (d, *J* 8.4, 1H), 7.44 (dd, *J* 8.4 and 3.0, 1H), 6.96 (s, 1H), 6.52 (s, 1H), 6.20 (dm, *J* 10.2, 1H), 6.03 (m, 1H), 5.93 (m, 2H), 5.23 (m, 1H), 4.39 (d, *J* 16.8, 1H), 3.82 (d, *J* 16.8, 1H), 3.61 (d, *J* 13.8, 1H), 3.51 (dd, *J* 13.8 and 7.2, 1H), 3.24 (m, 1H), 2.28 (m, 1H), 2.21 (m, 1H), 2.01 (m, 1H), 1.90 (m, 1H). δ_C (150 MHz) 163.7, 147.0, 146.7, 135.8, 135.6, 134.6, 134.1, 133.4, 131.8, 122.6, 121.0, 120.6, 106.7, 104.1, 101.0, 81.4, 67.0, 60.9, 59.5, 49.4, 29.7, 23.4, 22.7. ν_{max} (KBr)/cm^{-1} 2917, 2849, 1730, 1483, 1456, 1282, 1234, 1112, 1095, 1042, 1027, 1006, 940. *m/z* (EI, 70 eV) 535, 533 and 531 (13, 26, and 13 %, all $M^{+\bullet}$), 270 (100), 253 (47), 97 (61).

*2,5-Dibromobenzoate of Compound (−)-**1***

Reaction of compound (−)-**1** (8.4 mg, 0.03 mmol) with 2,5-dibrombenzoic acid (17 mg, 0.06 mmol) in the presence of DCC (19 mg, 0.09 mmol) and DMAP (11 mg, 0.06 mmol) in the same manner as described above for enantiomer (+)-**1** afforded, after work-up and chromatographic purification, the *title ester* (13 mg, 79 %) as a white, crystalline solid, mp 162–164°C. The ^{1}H NMR, ^{13}C NMR, IR, and mass spectrometric data recorded on this material were identical with those reported above for its enantiomer.

Crystallographic Studies

*Data for Compound (±)-**1***

$C_{16}H_{17}NO_3$, *M* 271.32, *T* 200 K, monoclinic, space group $P2_1/n$, *Z* 4, *a* 7.5599(2), *b* 21.6876(5), *c* 8.0256(2) Å, β 96.1285 (16)°; *V* 1308.33(6) Å^3, D_x 1.377 g cm^{-3}, 2314 unique data ($2\theta_{max}$ 50°), *R* 0.035 [for 1835 reflections with $I > 2.0\sigma(I)$]; *Rw* 0.087 (all data), *S* 0.96. Crystals grown from dichloromethane.

*Data for Compound (±)-**11***

$C_{21}H_{18}N_2O_7S$, *M* 442.45, *T* 200 K, monoclinic, space group $P2_1/n$, *Z* 4, *a* 12.8018(2), *b* 11.8557(3), *c* 13.7369(3) Å, β 112.4650(12)°; *V* 1926.69(7) Å^3, D_x 1.525 g cm^{-3}, 4387 unique data ($2\theta_{max}$ 55°), *R* 0.035 [for 3903 reflections with $I > 2.0\sigma(I)$]; *Rw* 0.094 (all data), *S* 0.99. Crystals grown from dichloromethane/hexane.

*Data for the 2,5-Dibromobenzoate of Compound (+)-**1***

$C_{23}H_{19}Br_2NO_4$, *M* 533.22, *T* 200 K, monoclinic, space group $P2_1$, *Z* 12, *a* 7.4967(3), *b* 36.8043(12), *c* 21.8414(7) Å, β 90.5106(9)°; *V* 6026.0(4) Å^3, D_x 1.763 g cm^{-3}, 20816 unique data ($2\theta_{max}$ 50°), *R* 0.059 [for 11928 reflections with $I > 3.0\sigma(I)$]; *Rw* 0.068 [$I > 3.0\sigma(I)$], *S* 1.54. Crystals grown from chloroform/ethanol/ethyl acetate.

*Data for the 2,5-Dibromobenzoate of Compound (−)-**1***

$C_{23}H_{19}Br_2NO_4$, *M* 533.22, *T* 200 K, monoclinic, space group $P2_1$, *Z* 12, *a* 7.4853(3), *b* 36.7672(16), *c* 21.8086(3) Å, β 90.4044(15)°; *V* 6001.9(4) Å^3, D_x 1.770 g cm^{-3}, 26662 unique data ($2\theta_{max}$ 55.2°), *R* 0.070 [for 15459 reflections with $I > 3.0\sigma(I)$]; *Rw* 0.081 [$I > 3.0\sigma(I)$], *S* 1.88. Crystals grown from chloroform/methanol/ethyl acetate.

Structure Determination

Images were measured on a Nonius Kappa CCD diffractometer ($Mo_{K\alpha}$, graphite monochromator, λ 0.71073 Å) and data extracted using the *DENZO* package.[22] Structure solution was by direct methods (SIR92).[23] The structures of compounds (±)-**1** and (±)-**11** were refined using the *CRYSTALS* program package.[24] The crystallographic asymmetric unit for each of the 2,5-dibromobenzoate derivatives of compounds (+)-**1** and (−)-**1** contain six distinct molecules that vary in terms of the orientation of the benzoate residue with respect to the ABCD-ring system of the alkaloid framework. These molecules are arranged into pairs related by a non-crystallographic two-fold screw axis and the pairs related to one another by approximate *z*/3 translations. The data are twinned and the structures show pseudo-symmetry requiring the use of the specialist structure refinement program *RAELS*.[25] Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC nos. 828020, 828019, 860930, and 860929 for compounds (±)-**1**, (±)-**11**, and the 2,5-dibromobenzoate of compounds (+)-**1** and (−)-**1**, respectively). These data can be obtained free-of-charge from the Cambridge Crystallographic Data Centre 12 Union Road, Cambridge CB2 1EZ, UK via www.ccdc.cam.ac.uk/data_request/cif.

Supplementary Material

The X-ray crystal structures for the 2,5-dibromobenzoate of compounds (+)-**1** and (−)-**1**, ^{1}H and ^{13}C NMR spectra of compounds (±)-**1**, (±)-**2**, (±)-**11** to (±)-**13**, the L-(+)-tartrate salts of (+)- and (−)-haemultine, **15**, **16**, and the 2,5-dibromobenzoate of compound (+)-**1**, and circular dichroism spectra derived from (+)-**1** and (−)-**1** are available on the Journal's website.

Acknowledgements

The authors thank the Australian Research Council and the Institute of Advanced Studies for generous financial support.

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