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PAPER

Total synthesis of the Amaryllidaceae alkaloid clivonine†

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Two syntheses of the Amaryllidaceae alkaloid clivonine (**1**) are described. Both employ previously reported 7-arylhydrindane **6** as an intermediate but differ in the method employed for subsequent introduction of what becomes the ring-B lactone carbonyl carbon (C7). The synthesis featuring a Bischler–Napieralski reaction for this transformation constitutes the first asymmetric synthesis of natural (+)-clivonine. Crystal structures for compounds (±)-**13**, (±)-**16**, (–)-**20** and (±)-**28** are also reported.

Introduction

The Amaryllidaceae are herbaceous perennials that produce a diverse array of alkaloid secondary metabolites. These alkaloids can mostly be classified as belonging to one of eight skeletally distinct subclasses all derived biosynthetically from a common precursor, norbelladine.[1–3] Clivonine (**1**), along with homolycorine (**2**), hippeastrine (**3**) and lycorenine (**4**) are prominent members of the lycorenine subclass; these alkaloids feature a tetracyclic 2-benzopyrano-[3,4-g]indole skeleton and display growth inhibition of various tumour cells,[4–6] DNA binding properties,[7] anti-viral activity,[8,9] antifungal activity,[10] and insect antifeedant activity[11] (Fig. 1).[12]

(+)-Clivonine (**1**) was first isolated as white prisms in 0.0007% yield from an ethanolic extract of freshly collected rhizomes and leaves of *Clivia miniata* Regel in 1956 by Wildman, who also tentatively proposed the correct gross topology of the molecule.[13] In 1965 Mehlis suggested relative (and absolute) stereochemistry for (+)-clivonine but assigned the stereochemistry of the C5/5a *cis*-diol centres relative to the others incorrectly.[14] In 1967 the stereochemical assignment of these centres was revised by Döpke *et al.* from ^{1}H NMR data of the C5 acetate derivative[15] and in 1971 these assignments and the absolute stereochemistry were confirmed by Jeffs *et al. via* chemical correlation with α-dihydrohippeastrine§.[16–19]

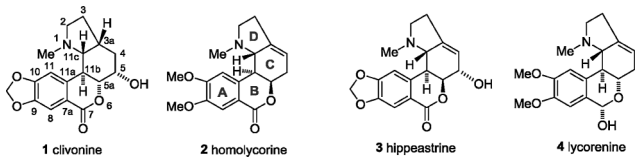

Fig. 1 Structures of the lycorenine-class Amaryllidaceae alkaloids clivonine (**1**), homolycorine (**2**), hippeastrine (**3**) and lycorenine (**4**). Also showing atom numbering/ring designations and correct absolute stereochemistry for natural (+)-clivonine (*i.e.* 3a*R*,5*S*,5a*R*,11b*S*,11c*R*).

Irie developed the first total synthesis of (±)-clivonine in 1973[20–22] (17 steps, 0.43% overall yield from piperonal) and we have recently described the second[23] (12 steps, 6.1% overall yield from enone **5**). Our synthesis featured the use of a thermal *retro*-Cope elimination reaction[24] to install the B-C and C-D ring-junction stereochemistry in a 7-arylhydrindane advanced intermediate **6**.[25] This compound was then converted into a lycorine-type iminium salt having a 1*H*-pyrrolo[3,2,1-d,e]phenanthridine/galanthan skeleton, which by sequential hydration, methylation and oxidation underwent a biomimetic 'ring-switch' to give clivonine (**1**) (Scheme 1).

Herein, we describe two alternative syntheses of clivonine (**1**), from 7-arylhydrindane **6**, one *via* a lycorine-type intermediate but featuring a non-biomimetic sequence of reactions to effect the 'ring-switch' and the other not proceeding *via* a lycorine-type intermediate. These syntheses were primarily developed to deliver authentic samples of clivonine (**1**) in order to aid development of the biomimetic 'ring-switch' approach and have therefore not been fully optimised. The first of these syntheses was carried out from

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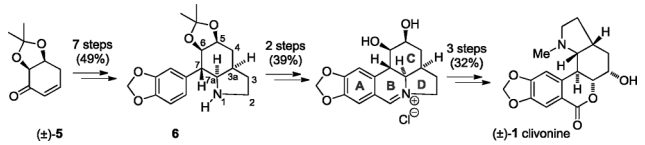
† Electronic supplementary information (ESI) available: crystallographic analyses for compounds (±)-**13**, (±)-**16**, (-)-**20** and (±)-**28** including CIF files. Details of the DFT modelling for compound **11** and its C3a epimer and NMR spectra for compounds **1**, **8**, **9**, **11–13**, **16** and **25–31**. CCDC reference numbers 792816–792819. For ESI and crystallographic data in CIF or other electronic format see DOI: http://dx.doi.org/10.1039/c0ob00895h/

‡ Deceased March 15, 1996.

§ The absolute stereochemistry of (+)-α-dihydrohippeastrine was secured from chemical correlation to dihydrolycorine hydrobromide, which had been subject to anomalous dispersion single crystal X-ray structure determination (see ref.16. T. Kitagawa, S. Uyeo and N. Yokoyama, *J. Chem. Soc.*, 1959, 3741–3751. and 17. M. Shiro, T. Sato and H. Koyama, *Chem. Ind.*, 1966, 1229.).



Scheme 1 Our previous synthesis of (±)-clivonine (**1**) from enone (±)-**5** (see ref.[23]). Also showing atom numbering for 7-arylhydrindane (octahydroindole) **6** and ring designations for the subsequent lycorine-type (galanthan) salt.

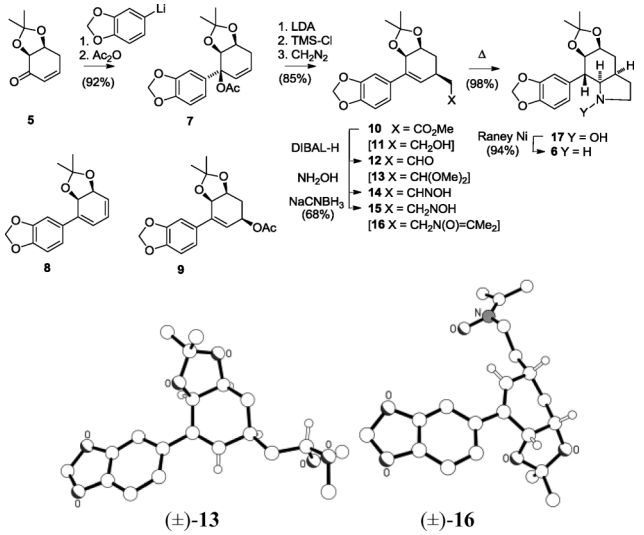
enantiomerically pure enone (+)-**5** and therefore constitutes the first asymmetric synthesis of natural (+)-clivonine (**1**).

Results and discussion

For the synthesis of enone (±)-**5** two routes were used both starting from *meso*-cyclohexa-3,5-dienyl-1,2-diol acetonide.¶ [26–29] The first was *via* a telescoped variant[23] of the method described by Hudlicky[30] and by Borchardt[31] involving epoxidation then Pd(0)/acid-mediated rearrangement, and the second was *via* singlet oxygen addition[27] then Kornblum–DeLaMare rearrangement.[32,33] Both afforded similar overall yields of enone (±)-**5** but the former was preferred on step-count and reaction duration grounds. Synthesis of enone (+)-(5*S*,6*S*)-**5** was from commercially available *Pseudomonas putida* derived (+)-(2*S*,3*S*)-1-chloro-4,6-cyclohexadiene-2,3-diol acetonide *via* a modification[34] of the method described by Oppolzer[35] involving singlet oxygen addition, polystyrene-supported thiourea mediated hydrogenolysis/acetate protection then Pd(0)/TMDS mediated reduction.

These enones were converted through to 7-arylhydrindanes (±)-**6** and (+)-**6** according to our published procedure;[23] the following summary draws attention to some synthetic details that were not previously highlighted for this sequence of steps (Scheme 2).

1,2-Aryl lithium addition and acetate trapping (**5** → **7**, 92% yield) requires 2 h at −78 °C in THF, followed by warming to RT, and then addition of freshly distilled acetic anhydride. Development of the Ireland–Claisen rearrangement (**7** → **10**) required some optimisation as it was found that use of *n*-BuLi as a base led to exclusive formation of diene **8** (95% yield) and use of too dilute solutions of LDA led simply to rearrangement to the 1,3-transposed allylic acetate **9** (43% yield). However, the optimised Ireland–Claisen conditions could even be performed on the crude acetate **7** and the resulting acid reacted directly with diazomethane following work-up to give the methyl ester **10** on a large scale (~20 g) in yields of 65–85% over the 3 steps. Conversion of this ester to the aldehyde **12** was carried out either directly using DIBAL-H at low temperature or by reduction to alcohol **11** using $LiBH_4$ then re-oxidation using the Dess–Martin periodinane; yields were comparable (80–85%). Interestingly, attempted conversion of aldehyde **12** into the corresponding oxime **14** using hydroxylamine hydrochloride and magnesium sulfate in



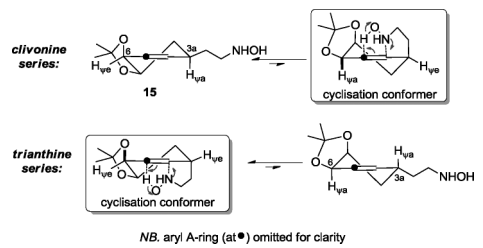
Scheme 2 Synthesis of 7-arylhydrindane **6** and the molecular structures of acetal (±)-**13** and nitrone (±)-**16** (X-ray).

MeOH led to formation of the dimethylacetal **13** (39% yield) on which a single crystal X-ray structure determination was performed to confirm the relative stereochemistry in the racemic series. Omission of the dehydrating agent and use of thermally milder conditions however gave the oxime **14** as a ~1.2 : 1 mixture of (*E*)- and (*Z*)-isomers in 82% yield. The Borch reduction of this mixture using $NaCNBH_3$/HCl required precise control of the dilution and pH (using methyl orange) of the reaction medium and the duration of the reaction. A range of unidentified products formed when HCl addition was too slow (*i.e.* pH >4) and nitrone **16**, the structure of which was secured by a single crystal X-ray structure determination, was the unexpected major product when HCl addition was too fast (*i.e.* pH <3). This product presumably arises from partial deprotection of the acetonide under the acidic conditions and condensation of the released acetone with hydroxylamine **15** (the yield never exceeded 48%). However, under optimised conditions the labile hydroxylamine **15** could be obtained in 83% yield. Direct thermolysis of this compound in degassed toluene effected the *retro*-Cope elimination reaction to give the *N*-hydroxy-7-arylhydrindane **17** almost quantitatively (98% yield). Relatively high dilution is important in this reaction to preclude competing disproportionation to the corresponding amine and nitro derivatives and degassing is required to prevent radical coupling to an azoxydimer. Raney®-Ni hydrogenolysis of *N*-hydroxy-7-arylhydrindane **6** in wet ethanol gave the 7-arylhydrindane **6** in 94% yield.

A particular aspect of the above synthesis that intrigued us was the fact that the *retro*-Cope elimination reaction of hydroxylamine **15** proceeded significantly more rapidly than that of its C3a epimer, which we had previously studied *en route* to lycorine-type alkaloid (+)-trianthine, when compared under identical conditions (*i.e.* **15** → **17**, 91% yield after 14 h *vs.* 93% after 70 h for its C3a epimer, both in degassed benzene at 0.01 M).[35] Inspection of the ^{1}H NMR spectra of pre-cyclisation intermediates in both series (*i.e.* compounds **10**, **11**, **12**, **14** and **15**[23] *cf*. their C3a epimers[35]) reveals that the protons in their respective cyclohexene C-rings display systematic differences indicating that the two series adopt

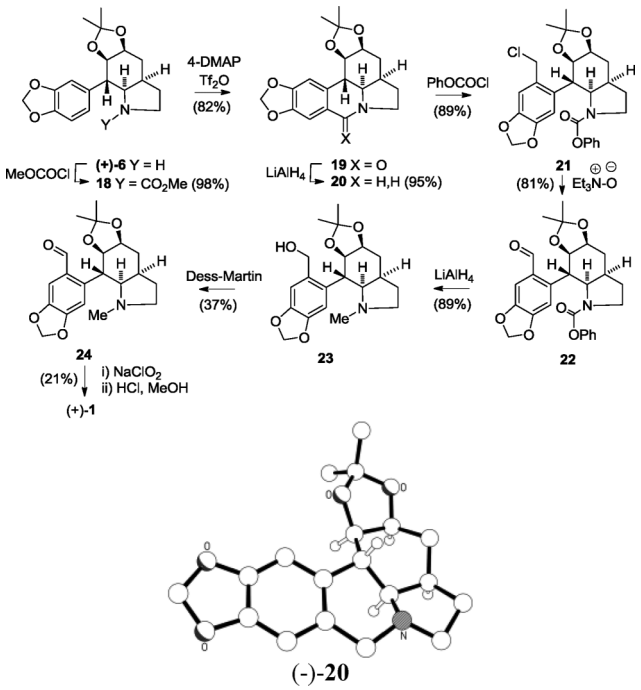
¶ This compound is commercially available or can be prepared from 1,4-cyclohexadiene (4 steps, 87% yield, see ref. 26. C. R. Johnson, P. A. Ple and J. P. Adams, *J. Chem. Soc., Chem. Commun.*, 1991, 1006–1007, 27. Y. Sutbeyaz, H. Secen and M. Balci, *J. Chem. Soc., Chem. Commun.*, 1988, 1330–1331, 28. N. C. Yang, M.-J. Chen and P. Chen, *J. Am. Chem. Soc.*, 1984, **106**, 7310–7315.) or from *myo*-inositol (3 steps, 36% yield, see ref. 29 F. Fabris, E. Rosso, A. Paulon and O. De Lucchi, *Tetrahedron Lett.*, 2006, **47**, 4835–4837.).

conformationally distinct half-chair structures in solution.‖ However, the relative positions of H3a suggest that in the clivonine series this proton is *pseudo*-axial (and hence the C3a side chain *pseudo*-equatorial) and in the trianthine series it is *pseudo*-equatorial (and the C3a side-chain *pseudo*-axial) indicating that both their fused-bicyclic (dioxolane/cyclohexene) cores adopt conformations in which the allylic C6a–O bond is *pseudo*-axial (*e.g.* for alcohol **11** H3a is at δ 2.45 ppm *cf*. its epimer at δ 2.63 ppm)[36] These conformational preferences were corroborated by DFT molecular modelling at the 6-31G(d,p) level in the gas phase. The crystal structures of compounds **13** and **16** (Scheme 2) reveal that, at least in the clivonine series, this conformation persists also in the solid phase. Since *retro*-Cope elimination is geometrically precluded unless the C3a side chain adopts a *pseudo*-axial conformation this means that the faster cyclising epimer **15**, leading to clivonine, must ring-flip in order to react. This places the aforementioned allylic C–O bond *pseudo*-equatorial and the corresponding allylic C–H bond *pseudo*-axial. Strain-release, or a favourable H-bonding interaction between the hydroxylamine hydroxyl and one of the *syn* dioxolane oxygens in the transition state[24] might explain the higher rate of cyclisation but it likely reflects more facile cyclisation on the alkene face *anti* to the *pseudo*-axial allylic σ_{C-H} bond (*i.e.* the best donor, *cf.* a Cieplak effect, Scheme 3)[37–39]**.



Scheme 3 Conformational analysis of the *retro*-Cope elimination substrate **15** (clivonine series) and its C3a epimer (trianthine series)[35] showing the relative orientations of the CH and CO bonds at their respective allylic C6 stereocentres. A favourable $\sigma_{CH} \rightarrow \pi^*_{CC}$ Cieplak stereoelectronic interaction (*cf.* $\sigma_{CH} \rightarrow \pi^*_{CC}$) may account for the more facile cyclisation in the clivonine series.

Based on precedent from the work of Mizukami,[42] Kotera *et al.*,[43] and Harken *et al.*[44] who have reported multi-step conversions of isolated natural lycorine-type alkaloids to lycorenine-type congeners exploiting the classical von Braun reaction[45] (using cyanogen bromide), we envisaged that a related strategy could be deployed to access clivonine (**1**) from lycorine-type progenitor **20**. The synthesis of 1*H*-pyrrolo[3,2,1-d,e]phenanthridine **20** from 7-arylhydrindane **6** was envisaged *via* a Pictet–Spengler reaction to form ring-B based on our successful use of this approach in the synthesis (+)-trianthine from a diastereomeric 7-arylhydrindane[35] (Scheme 4).



Scheme 4 Synthesis of clivonine (+)-**1** using a von Braun-type reaction as a key step and the molecular structure of amine (–)-**20** (X-ray).

In the event, direct Pictet–Spengler ring closure to give amine **20** using Eschenmoser's salt (*N*,*N*-dimethyliminium iodide)[46,47] proved to be less high yielding than in the trianthine series (53% *cf*. 92%[35]). Since this yield could not be improved by the use of the corresponding *N*,*N*-dimethyliminium triflate,[48] we employed a three-step approach *via* methyl carbamate formation (→**18**, 98% yield), a Bischler–Napieralski reaction using Banwell's conditions[49,50] (4-DMAP/Tf_2O, → **19**, 82% yield) and then lactam reduction ($LiAlH_4$, → **20**, 95% yield).†† A single crystal X-ray structure determination on amine **20** confirmed the introduction of the desired *trans* B-C and *cis* C-D ring-junction stereochemistry by the *retro*-Cope elimination reaction and the successful completion of the required galanthan skeleton (Scheme 4). The stage was now set for the von Braun-type cleavage of the benzylic C-N bond in ring-B. The optimum reagent for this key step was found to be phenylchloroformate,[51] which proved superior to both ethylchloroformate[52] and α-chloroethylchloroformate[53] and gave the ring-opened benzyl chloride **21** in 89% yield when used in conjunction with $NaHCO_3$ in refluxing CH_2Cl_2. Conversion of this chloride to an oxygen-based function turned out to be challenging: attempted silver-salt assisted nucleophilic substitution resulted in reclosure of ring-B to give amine **20** and treatment with KOAc/TMEDA,[54] polymer-supported carbonate,[55] and CrO_3,[56]

‖ Specifically, in the clivonine series H5 appears at δ 4.2–4.3 ppm as a ddd or q (J ~5 Hz) and H6 at δ ~4.8 ppm as a d (J ~5 Hz), whereas in the trianthine series the corresponding protons are downfield shifted: H5 at δ 4.5–4.6 ppm and H6 at δ 4.9 ppm.

** Knight and Salter have proposed that allylic oxygenation favours *retro*-Cope elimination reactions but a strong conformational dependence for this has not been noted previously (see ref. 40, D. W. Knight, R. Salter, *Tetrahedron Lett.*, 1999, **40**, 5915–5918). That the *retro*-Cope elimination proceeds *via* a dissymmetric concerted pathway in which the hydroxylamine nitrogen has some nucleophilic character and the alkene some electrophilic character is supported by computational studies by Tronchet (see ref. 41. I. Komaromi and J. M. J. Tronchet, *J. Phys. Chem. A*, 1997, **101**, 3554–3560) and by our own observations that these reactions are facilitated by electron withdrawing substituents on the alkene.

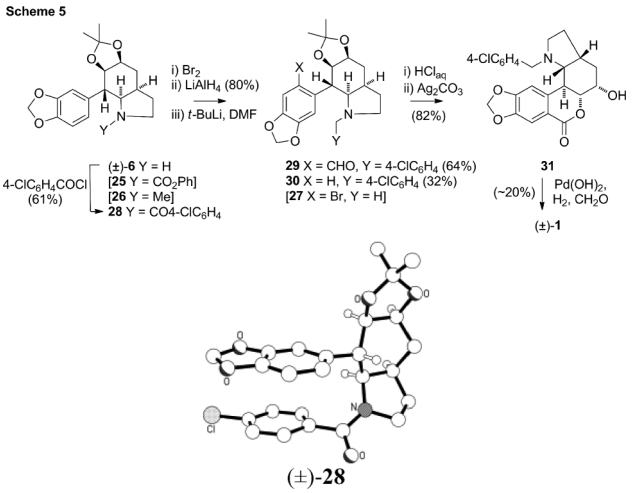
†† Lactam **19** and amine **20** were explored as precursors to the corresponding lactamol (hemiaminal) *via* 'half-reduction' (using $LiEt_3BH$) and oxidation (using Polonovski–Poitier chemistry) respectively in our development of the biomimetic approach to clivonine (see ref. 23. C. Giro-Manas, V. L. Paddock, C. G. Bochet, A. C. Spivey, A. J. P. White, I. Mann and W. Oppolzer, *J. Am. Chem. Soc*, 2010, **132**, 5176–5178.).

gave multiple unidentified products. Finally, introduction of oxygen at the benzylic position could be achieved by oxidation with trimethylamine-*N*-oxide[57] giving aldehyde **22** in 81% yield. Treatment of this compound with $LiAlH_4$ effected conversion of the carbamate to the desired *N*-methyl function albeit with concomitant aldehyde to alcohol reduction giving aminoalcohol **23** in 89% yield. A reversed order of events was also explored but all attempts at carbamate reduction directly on benzyl chloride **21** using a variety of hydride reagents (*e.g.* $LiAlH_4$) effected reclosure of ring-B to give amine **20** exclusively. Reoxidation of alcohol **23** could not be realized *via* various Swern-type protocols[58] but conversion to aldehyde **24** was achieved, albeit in a disappointing yield of 37% using the Dess–Martin periodinane.[59]‡‡ Finally, treatment with $NaClO_2$ in *t*-BuOH/H_2O[60] gave the carboxylic acid which upon immediate treatment with HCl in MeOH (to remove the acetonide and induce lactone formation) gave (+)-clivonine (**1**), with spectroscopic data identical to that reported for the natural product, in 21% yield. The overall yield from 7-arylindoline (+)-**6** was therefore 3.8% over the 8 steps [*i.e.* 1.9% over the 15 steps from enone (+)-**5**)] although there is clearly room for optimisation of the final oxidation steps.

We also explored routes towards clivonine (**1**) from arylindoline (±)-**6** that did *not* involve the introduction of C7 (ultimately the lactone carbonyl carbon) concomitant with closure to a lycorine-type galanthan ring system [*cf.* the aforementioned Pictet–Spengler (**6** → **20**) and Bischler–Napieralski reactions (**18** → **19**)] but rather by initial *N*-functionalisation and then formylation or sequential bromination/carbonylation. Our initial plan was to start by introducing the methyl group onto the nitrogen then perform S_EAr functionalisaton of the aryl ring-A but when this proved problematic, due to the nucleophilicity of the tertiary amine function, we opted to protect the nitrogen as an amide during the S_EAr functionalisaton. This allowed bromination and subsequent carbonylation and provided efficient access to an *N*-benzyl analogue of clivonine **31** but left a difficult final FGI to replace this group with the *N*-methyl group found in (±)-clivonine itself (Scheme 5).

Protection of 7-arylindoline (±)-**6** with phenylchloroformate gave the corresponding carbamate **25** in 72% yield. This compound could be reduced cleanly to the *N*-methyl derivative **26** using $LiAlH_4$ (99% yield). However, all attempts to effect electrophilic formylation (*e.g.* using DMF/$POCl_3$ or $TiCl_4$/Cl_2CHOMe) or bromination of this compound (*e.g.* using Br_2 or NBS) gave intractable mixtures of multiple products apparently arising from reaction of these reagents at nitrogen. To circumvent this, we opted to perform bromination on the carbamate prior to reduction to the *N*-methyl derivative. Our initial attempts at bromination utilised methyl carbamate **18** and also resulted in very unpromising mixtures of multiple products. By contrast, the bromination of phenyl carbamate **25** using Br_2 was somewhat cleaner but the desired brominated *N*-methyl derivative **27** was obtained in just 21% yield following $LiAlH_4$ reduction due to partial C–Br bond hydrogenolysis concomitant with the carbamate reduction.

‡‡ This oxidation appears to be difficult, Irie *et al.* obtained just a 10% yield of clivonine by oxidation of the same substance but lacking the acetonide protecting group using MnO_2 (see ref. 20. H. Irie, Y. Nagai, K. Tamoto and H. Tanaka, *J. Chem. Soc., Chem. Commun.*, 1973, 302–303, 21. H. Tanaka, H. Irie, S. Babu, S. Uyeo, A. Kuno and Y. Ishiguro, *J. Chem. Soc., Perkin Trans. 1*, 1979, 535–538, 22. H. Tanaka, Y. Nagai, H. Irie, S. Uyeo and A. Kuno, *J. Chem. Soc., Perkin Trans. 1*, 1979, 874–878.).



Scheme 5 Synthesis of clivonine (±)-**1** directly from 7-arylhydrindane (±)-**6** and the molecular structure of 4-chlorobenzamide (±)-**28** (X-ray).

Intrigued by the difference in reactivity towards electrophilic bromination between the alkyl and aryl carbamate derivatives **18** and **25**, and cognisant that the latter (and also the structurally related phenyl carbamate derivatives **21** and **22**, Scheme 4) showed distinct peak-broadning in their ^{1}H NMR spectra at RT, which we attributed to restricted mutual rotation of the carbamate and 7-indoline aryl groups,§§ we hypothesised that intramolecular π–π interactions could be positively influencing the outcome of our attempted bromination reactions. To test this notion, *N*-(4-chlorobenzoyl) derivative **28** was prepared from 7-arylindoline **6** in 61% yield. A single crystal X-ray structure determination on this compound revealed that in the solid state the amide and 7-indoline aryl groups are orientated for face-to-face π–π stacking (Scheme 5). Pleasingly, amide **28** underwent relatively clean bromination to give the corresponding bromo-*N*-(4-chlorobenzyl) derivative in 80% yield following amide reduction with $LiAlH_4$. Subsequent bromine-lithium exchange using *t*-BuLi at −78 °C followed by reaction with DMF afforded a separable mixture of aldehyde **29** (64% yield) and the debrominated product **30** (32% yield). Upon acetonide deprotection using aqueous HCl, a crude lactol/aldehyde containing mixture was obtained which on treatment with Fetizon's reagent (*i.e.* Ag_2CO_3–Celite®)[61] furnished lactone **31** in 82% yield. Finally, *N*-debenzylation/methylation of lactone **31** was accomplished using Overman's one-pot procedure[62] to afford (±)-clivonine (**1**) in an unoptimised ~20% yield (by ^{1}H NMR). The overall yield from 7-arylindoline (±)-**6** *via* this route was therefore ~5.1% over the 6 steps [*i.e.* ~2.5% over the 13 steps from enone (±)-**5**)] although again there is clearly room for optimisation of the final *N*-debenzylation/methylation procedure.

Conclusions

In summary, we have reported the total synthesis of the lycorine-type Amaryllidaceae alkaloid clivonine (**1**) *via* two routes. Both

§§ The broad peaks in the ^{1}H NMR spectra of carbamates **21**, **22** and **25** at RT became sharp when recorded at ~330 K. By contrast, the broad peaks in the ^{1}H NMR spectrum of amide **27** remained unchanged at 328 K suggesting higher barriers to aryl/aryl mutual rotation in this latter derivative.

routes employ previously reported 7-arylhydrindane **6**, which is prepared using a *retro*-Cope elimination as the key step, as an intermediate. They differ in the method employed for subsequent introduction of what becomes the ring-B lactone carbonyl carbon (C7). The first route described (Scheme 4) features a Bischler–Napieralski reaction for this transformation and constitutes the first asymmetric synthesis of natural clivonine [(+)-**1**] as it was prepared from enantiomerically pure enone (+)-**5** (15 steps, 1.9% overall yield). The second route described (Scheme 5), which employs bromination/carbonylation for C7 introduction, however provides more efficient access to racemic clivonine (**1**) from enone (±)-**5** on both a step-count and yield basis (13 steps, ~2.5% overall yield). Moreover, this second approach potentially provides access to a range of clivonine analogues having alternative *N*-substituents following *N*-debenzylation. The fact that neither synthesis exceeds the efficiency of our previously described route to (±)-clivonine (**1**) utilising a biomimetic ring-switch approach (Scheme 1; 12 steps, 6.1% overall yield) underscores the efficiency of that approach but also reflects to some extent the fact that the final steps of these latest approaches remain to be fully optimised.

Experimental section

General Directions. All reactions were performed under anhydrous conditions and an inert atmosphere of N_2 in the oven or flame dried glassware. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogenous materials, unless otherwise indicated. Reagents were used as obtained from commercial sources or purified according to known procedures.[63] Flash chromatography (FC) was carried out using Merck Kiesegel 60 F_{254} (230–400 mesh) silica gel. Only distilled solvents were used as eluents. Thin layer chromatography (TLC) was performed on Merck DC-Alufolien or glass plates pre-coated with silica gel 60 F_{254} which were visualised either by quenching of ultraviolet fluorescence (λ_{max} = 254 nm) or by charring with 5% w/v phosphomolybdic acid in 95% EtOH, 10% w/v ammonium molybdate in 1 M H_2SO_4, or 10% $KMnO_4$ in 1 M H_2SO_4. Observed retention factors (R_f) are quoted to the nearest 0.05. All reaction solvents were distilled before use and stored over activated 4 Å molecular sieves, unless otherwise indicated. Anhydrous CH_2Cl_2 was obtained by refluxing over CaH_2. Anhydrous THF and Et_2O were obtained by distillation, immediately before use, from sodium/benzophenone ketyl under an inert atmosphere of N_2. Anhydrous DMF was obtained by distillation from CaH_2 under reduced pressure. Ethylene glycol was distilled immediately prior to use. Petrol refers to the fraction of light petroleum boiling between 40–60 °C. NMR *J* values are given in Hz. High Resolution Mass Spectrometry (HRMS) measurements are valid to ±5 ppm. Microanalyses were performed by Mr Stephen Boyer (Microanalysis Service, London Metropolitan University).

Detailed procedures for the syntheses of (±)-**5**, (±)-**6**, (±)-**7**, (±)-**10**, (±)-**12**, (±)-**14**, (±)-**15** and (±)-**17** can be found in the Supplementary Material for ref.23 Enantiomerically pure (+)-(5*S*,6*S*)-**5**[35] {white needles: Mp 82–83 °C (EtOAc/pentane), $[\alpha]_D$ +107.0 (*c.* 1.00, MeOH, 20 °C)} was prepared from enantiopure chlorodiene derivative (+)-(2*S*,3*S*)-1-chloro-4,6-cyclohexadiene-2,3-diol (CSS-Almac, Craigavon, Northern Ireland) *via* a modification[34] of the method described by Oppolzer.[35] The subsequent enantiopure intermediates **7**, **10**, **12**, **14**, **15**, **17** and **6** were prepared in an identical fashion to the above racemates, in the same yields and had identical spectroscopic characteristics but the following physical properties and optical rotations: (+)-(1*S*,5*S*,6*S*)-**7**[35] white solid: Mp 115–116 °C (Et_2O), $[\alpha]_D$ +6.5 (*c.* 1.00, MeOH, 20 °C); (+)-(3*R*,5*S*,6*R*)-**10** colourless oil: $[\alpha]_D$ +19.5 (*c.* 1.00, $CHCl_3$, 20 °C); (+)-(3*R*,5*S*,6*R*)-**12** white solid: Mp 79 °C (Et_2O/pentane), $[\alpha]_D$ +26.4 (*c.* 0.95, $CHCl_3$, 20 °C); (+)-(*E*,3*R*,5*S*,6*R*)-**14** white solid: Mp 139 °C (Et_2O/pentane), $[\alpha]_D$ +11.4 (*c.* 0.98, $CHCl_3$, 20 °C); (–)-(*Z*,3*R*,5*S*,6*R*)-**14** white solid: Mp 141 °C (Et_2O/pentane), $[\alpha]_D$ –9.8 (*c.* 0.84, $CHCl_3$, 20 °C); (+)-(3*R*,5*S*,6*R*)-**15** white solid: Mp 99–102 °C (MeOH/Et_2O), $[\alpha]_D$ +14.6 (*c.* 1.16, $CHCl_3$, 20 °C); (+)-(3a*R*,5*S*,6*R*,7*S*,7a*R*)-**17** white solid: Mp 61–65 °C (Et_2O), $[\alpha]_D$ +65.0 (*c.* 0.50, $CHCl_3$, 20 °C); (+)-(3a*R*,5*S*,6*R*,7*S*,7a*R*)-**6** colourless oil, $[\alpha]_D$ +13.3 (*c.* 0.25, $CHCl_3$, 20 °C).

Clivonine (1)

Method 1 [(+)-***1*** *via oxidation then hydrolysis of aldehyde* (+)-**24**]: To a solution of aldehyde (+)-**24** (11 mg, 0.031 mmol) in *t*-BuOH (1.3 mL) was added 2-methyl-2-butene (167 µL, 111 mg, 1.578 mmol) dropwise followed by a solution of 85% w/w $NaClO_2$ (33 mg, 0.31 mmol) and $NaH_2PO_4{\cdot}2H_2O$ (27 mg, 0.173 mmol) in H_2O (500 µL). The reaction mixture was stirred for 14 h at RT, partitioned between CH_2Cl_2 (10 mL) and brine (10 mL), the phases separated, the aqueous phase re-extracted with CH_2Cl_2 (4 × 10 mL), the combined organic phases dried over Na_2SO_4 and concentrated *in vacuo*. The solid yellow residue (crude acid, ~10 mg) was then dissolved in MeOH (2 mL) and cooled to 0 °C. To this solution was added dropwise a solution of acetyl chloride (200 µL) in MeOH (2 mL) also at 0 °C. The resulting solution was stirred for 10 min at 0 °C and then 4 h at RT before concentrating *in vacuo*. The residue was dissolved in CH_2Cl_2 (10 mL), washed with sat. aq. $NaHCO_3$, (15 mL), the phases separated, the aqueous phase re-extracted with CH_2Cl_2 (5 × 5 mL) and the combined organic phases dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by FC (SiO_2; pentane/Et_2O/MeOH (NH_3 sat.), 50 : 45 : 5] to give clivonine [(+)-**1**] [13,15,18,19,64,65] as a colourless solid (2 mg, 21%).[23] Mp 198–200 °C (Lit. 199–200 °C);[13] R_f 0.7 ($CHCl_3$/MeOH, 9 : 1); ν_{max}/cm^{-1} (neat): 1036, 1274, 1477, 1710, 2924, 3420; δ_H (400 MHz, $CDCl_3$): 1.80 (1H, ddd, *J* 15.3, 6.3, 3.9, C_4HH), 2.05–2.15 (1H, m, C_4HH), 2.22–2.31 (2H, m, C_2HH & C_3HH), 2.48–2.58 (5H, m, NCH_3, $C_{3a}H$, C_3HH), 2.89 (1H, dd, *J* 10.0, 6.7, $C_{11c}H$), 3.22 (1H, dd, *J* 12.3, 10.0, $C_{11b}H$), 3.25–3.32 (1H, m, C_2HH), 4.09 (1H, dd, *J* 12.3, 2.7, $C_{5a}H$), 4.24 (1H, dd, *J* 6.3, 2.7, C_5H), 6.02 (2H, *AB*, *J* 5.0, OCH_2O), 7.46 (1H, s, C_8H), 7.74 (1H, s, $C_{11}H$), OH absent;); δ_C (125 MHz, $CDCl_3$) 28.73 (t), 30.82 (t), 33.12 (d), 33.43 (d), 45.22 (q), 52.95 (t), 67.41 (d), 69.50 (d), 81.81 (d), 101.82 (t), 107.15 (d), 109.34 (d), 118.69 (s), 140.77 (s), 146.68 (s), 152.67 (s), 164.68 (s); *m*/*z* (ESI$^+$) 318 (MH$^+$, 28%), 282 (70); Found *m*/*z* MH$^+$, 318.1345, $C_{17}H_{20}NO_5$, requires 318.1341 (Δ = 1.3 ppm). Unfortunately, we were unable to obtain an optical rotation on our synthetic sample; the natural material is reported to have $[\alpha]_D$ +41.2 (*c.* 1.11, $CHCl_3$, 23 °C)[13]

Method 2 [(±)-***1*** *via hydrogenolysis/reductive amination of 4-chlorobenzylamine* (±)-**31**]: Under an atmosphere of H_2, Pearlman's catalyst [$Pd(OH)_2$/C] (5 mg, 10 mol%) and formaldehyde (37% aq., 2 mL) were added to a solution of 4-chlorobenzylamine (±)-**31** (10 mg, 0.02 mmol) in EtOAc/MeOH (1 : 10, 2 mL) at RT. After stirring for 5 h, the suspension was filtered and concentrated

in vacuo to give a mixture of compounds including clivonine [(±)-**1**, ~20% by ^{1}H NMR] which was not isolated.

(5*S,6*R**)-5,6-Di-*O*-isopropyldiene-1-[3,4-(methylenedioxy)phenyl]cyclohex-1,3-diene 8.** In a flame-dried 2-neck flask equipped with a condenser, *n*-BuLi (0.19 mL, 2.26 M in hexanes, 0.43 mmol) was added dropwise to a solution of acetate (±)-**7** (120 mg, 0.36 mmol) in THF (12 mL) at −78 °C. After stirring for 10 min, freshly distilled TMSCl (55 µl, 0.433 mmol) was added dropwise. After stirring for further 10 min, the dry ice bath was removed and the solution was allowed to reach RT over 3 h. The solution was then refluxed for 7 h, cooled to RT and partitioned between Et_2O (50 mL) and brine (50 mL). The organic phase was extracted with Et_2O (3 × 20 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a dark orange solid, which was purified by FC (SiO_2; Et_2O/petrol, 4 : 1) to give diene (±)-**8** as a light yellow solid (93 mg, 95%): Mp 65.7–69.2 °C (Et_2O/petrol); R_f 0.65 (Et_2O/petrol, 1 : 1); ν_{max}/cm^{-1} (KBr) 1039, 1248, 1490, 1506, 1608, 1732, 2895, 2984; δ_H ($CDCl_3$, 400 MHz) 1.43 (3H, s, CH_3), 1.51 (3H, s, CH_3), 4.93 (2H, br s, C_5H & C_6H), 5.89 (1H, dd, *J* 9.0, 1.0, C_4H), 6.00 (2H, s, OCH_2O), 6.12 (1H, dd, *J* 9.0, 6.0, C_3H), 6.35 (1H, d, *J* 6.0, C_2H), 6.85 (1H, d, *J* 7.5, $C_{ar}H$), 7.13 (2H, m, 2 × $C_{ar}H$); δ_C ($CDCl_3$, 100 MHz) 25.34 (q), 26.97 (q), 72.19 (d), 73.05 (d), 101.13 (t), 105.78 (d), 106.10 (d), 108.38 (d), 119.62 (d), 119.82 (d), 123.47 (d), 125.79 (d), 133.14 (s), 134.50 (s), 147.35 (s), 147.98 (s); *m*/*z* (CI$^+$) 273 (MH^+, 60), 290 (MNH_4^+, 21), 215 (100); Found: *m*/*z* MH^+, 273.1118, $C_{16}H_{17}O_4$, requires 273.1115 (Δ = +0.5 ppm); Calculated for $C_{16}H_{16}O_4$ C, 70.57%; H, 5.92%; O, 23.50%, found C, 70.09%; H, 5.92%; O, 23.99%.

(3*R,5*S**,6*R**)-5,6-Di-*O*-isopropyldiene-3-acetoxy-1-[3,4-(methylenedioxy)phenyl]cyclohex-1-ene 9.** In a flame-dried 2-neck flask equipped with a condenser, acetate (±)-**7** (0.30 mg, 0.88 mmol) was dissolved in THF (10 mL) and cooled to −78 °C. A solution of LDA [9 mL, 0.10 M in THF, prepared by dropwise addition of *n*-BuLi (2.5 M in hexanes, 1 equiv) to a stirred solution of diisopropylamine (1 equiv) in THF at 0 °C followed by stirring for 20 min at 0 °C] was then added *via* syringe and the mixture was stirred at −78 °C for 10 min. Freshly distilled TMSCl (136 µl, 1.06 mmol) was added dropwise. After stirring for further 10 min, the dry ice bath was removed and the solution was allowed to reach RT over 3 h. The solution was then refluxed for 12 h, cooled to RT and partitioned with Et_2O (50 mL) and brine (50 mL). The organic phase was extracted with Et_2O (3 × 20 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by FC (SiO_2; Et_2O/petrol, 1 : 4) to afford rearranged acetate (±)-**9** as a white solid (130 mg, 43%): Mp 78.5–79.7 °C (Et_2O/petrol); R_f 0.7 (Et_2O/petrol, 1 : 1); ν_{max}/cm^{-1}(KBr) 1023, 1241, 1375, 1508, 1720 (C═O), 2883, 2995; δ_H ($CDCl_3$, 400 MHz) 1.37 (3H, s, CH_3), 1.51 (3H, s, CH_3), 1.80 (1H, dt, *J* 12.0, 9.5, C_4HH), 2.02 (3H, s, CH_3O), 2.16 (1H, dt, *J* 12.0, 5.5, C_4HH), 4.33 (1H, dt, *J* 9.5, 5.5, C_5H), 4.47 (1H, d, *J* 5.5, C_6H), 5.34 (1H, m, C_3H), 5.89 (2H, s, OCH_2O), 6.06 (1H, d, *J* 6.5, C_2H), 6.71 (1H, d, *J* 8.5, $C_{ar}H$), 7.01 (2H, m, 2 × $C_{ar}H$); δ_C ($CDCl_3$, 100 MHz) 21.25 (q), 26.39 (q), 28.44 (d), 31.68 (t), 68.36 (d), 72.21 (d), 72.51 (d), 100.96 (t), 106.74 (d), 108.30 (d), 109.9 (s), 120.15 (d), 126.88 (d), 132.36 (s), 136.09 (s), 147.63 (s), 147.94 (s), 179.69 (s); *m*/*z* (CI$^+$) 273 {[M-(AcOH)+H]$^+$, 56}; Found: *m*/*z* [M-(AcOH)+H]$^+$, 273.1127, $C_{16}H_{17}O_4$, requires 273.1124 (Δ = +0.3 ppm); Calculated for $C_{18}H_{20}O_6$, C, 65.05%; H, 6.07%; O, 28.88%, found C, 64.97%; H, 6.09%; O, 28.94%.

(3*R,5*S**,6*R**)-5,6-Di-*O*-isopropylidene-3-(2-oxoethyl)-1-[3,4-(methylenedioxy)phenyl]cyclohex-1-ene 12.[23].** To a stirred solution of methyl ester (±)-**10** (6.73 g, 19.43 mmol) in THF (150 mL) at 0 °C was added $LiBH_4$ (68.02 mL, 2 M in THF, 136.04 mmol) and the mixture warmed to RT. After stirring for 40 h the reaction was quenched with H_2O (100 mL) and the organic phase extracted with EtOAc (4 × 100 ml). The combined organic phases were washed with brine (200 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give alcohol (±)-**11** as a yellow foam (5.34 g, 86%): R_f 0.39 (Et_2O/petrol, 3 : 1); ν_{max}/cm^{-1} (neat) 3427, 2924, 1720, 1504, 1488, 1371, 1244, 1215, 1038, 935, 749; δ_H ($CDCl_3$, 400 MHz) 1.44 (1H, m, C_4HH), 1.47 (3H, s, CH_3), 1.52 (3H, s, CH_3), 1.61 (1H, br s, OH), 1.73 (1H, td, *J* 13.9, 6.5, C_3HH), 1.86 (1H, td, *J* 13.5, 6.5, C_3HH), 2.01 (1H, *app* dt, *J* 12.1, 4.7, C_4HH), 2.45 (1H, m, $C_{3a}H$), 3.84 (2H, m, $C_{3b}H_2$), 4.32 (1H, *app* dt, *J* 10.5, 5.0, C_5H), 4.83 (1H, d, *J* 5.0, C_6H), 5.98 (2H, s, OCH_2O), 6.17 (1H, d, *J* 2.3, C_2H), 6.82 (1H, d, *J* 8.3, $C_{Ar}H$), 7.07–7.10 (2H, 2 × $C_{Ar}H$); δ_C ($CDCl_3$, 100 MHz) 26.26 (q), 28.64 (q), 31.54 (d), 32.48 (t), 38.09 (t), 60.03 (t), 72.38 (d), 74.41 (d), 101.65 (t), 106.38 (d), 108.24 (d), 108.79 (d), 119.50 (d), 132.91 (d), 133.33 (s), 133.36 (s), 147.00 (s), 147.82 (s); *m*/*z* (EI$^+$) 318 (M^+, 32), 260 (46), 215 (52), 91 (100); Found: *m*/*z* MNH_4^+, 336.1811, $C_{18}H_{26}NO_5$, requires 336.1811 (Δ = 0.0 ppm). To a suspension of Dess–Martin periodianane (21.4 g, 50.4 mmol) in CH_2Cl_2 (60 mL) at RT was added a solution of alcohol **11** (5.34 g, 16.8 mmol) in CH_2Cl_2 (20 mL) dropwise *via* cannula. After stirring for 23.5 h the reaction mixture was filtered through Celite® and the filtrate treated with $NaHCO_3$ (sat. aq., 100 mL). The organic phase was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic phases were washed with $NaHCO_3$ (sat. aq., 50 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give aldehyde (±)-**12** (5.04 g, 95%).[23] Mp 80.2–81.3 °C; R_f 0.70 (Et_2O/petrol, 1 : 1); ν_{max}/cm^{-1} ($CHCl_3$): 754, 850, 927, 1063, 1103, 1224, 1372, 1434, 1485, 1507, 1723, 3020; δ_H ($CDCl_3$, 400 MHz) 1.41 (3H, s, CH_3), 1.45 (3H, s, CH_3), 1.48–1.52 (1H, m, C_4HH), 1.98 (1H, *app* dt, *J* 12.6, 5.3, C_4HH), 2.66–2.68 (2H, m, C_3H_2), 2.80–2.89 (1H, m, $C_{3a}H$), 4.33 (1H, *app* quintet, *J* 5.3, C_5H), 4.78 (1H, d, *J* 5.3, C_6H), 5.93 (2H, s, OCH_2O), 6.03 (1H, d, *J* 2.8, C_2H), 6.76 (1H, d, *J* 8.7, $C_{Ar}H$), 7.00–7.03 (2H, m, 2 × $C_{Ar}H$), 9.83 (1H, s, CHO); δ_C ($CDCl_3$, 100 MHz) 26.16 (q), 28.49 (q), 29.02 (d), 31.98 (t), 49.34 (t), 72.25 (d), 73.89 (d), 101.05 (t), 106.57 (d), 108.24 (d), 108.94 (s), 119.71 (d), 130.47 (d), 133.31 (s), 134.92 (s), 147.16 (s), 147.82 (s), 201.02 (d); *m*/*z* (EI$^+$) 316 (M^+, 76%); Found *m*/*z* M^+, 316.1318, $C_{18}H_{20}O_5$, requires 316.1305 Δ = +4.1 ppm).

(3*R,5*S**,6*R**)-5,6-Di-*O*-isopropylidene-3-(2-dimethyalcetalethyl)-1-[3,4-(methylenedioxy)phenyl]cyclohex-1-ene 13.** To a solution of aldehyde (±)-**12** (377 mg, 1.06 mmol) in MeOH (15 mL) at RT was added $NH_2OH{\cdot}HCl$ (111.12 mg, 1.59 mmol), $NaOAc_{(anh.)}$ (140.42 mg, 1.59 mmol) and $MgSO_4$ (190 mg, 1.59 mol) and the resulting suspension was then refluxed overnight. $MgSO_4$ was filtered and reaction mixture concentrated *in vacuo*. The solid residue was then partitioned between CH_2Cl_2 (10 mL) and brine (5 mL). The organic phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by FC (SiO_2; petrol/Et_2O, 1 : 1) to give acetal (±)-**13** as colourless needles (95 mg, 39%): Mp 102.3–104.1 °C (Et_2O/petrol); R_f 0.75

(Et_2O/petrol, 1 : 1); ν_{max}/cm^{-1} (KBr) 980, 1039, 1253, 1494, 1510, 1612, 1742, 2901, 2959; δ_H ($CDCl_3$, 400 MHz) 1.47 (3H, s, CH_3), 1.52 (3H, s, CH_3), 1.75 (1H, ddd, *J* 12.0, 10.5, 6.0, C_4HH), 1.89 (2H, m, C_3H_2), 2.01 (1H, dt, *J* 12.0, 5.5, C_4HH), 2.39 (1H, m, $C_{3a}H$), 3.38 (6H, s, 2 × OCH_3), 4.31 (1H, dt, *J* 10.5, 5.5, C_5H), 4.58 (1H, t, *J* 6.0, C_2HH), 4.82 (1H, d, *J* 5.5, C_6H), 5.98 (2H, s, OCH_2O), 6.17 (1H, d, *J* 2.5, C_2HH), 6.82 (1H, d, *J* 8.5, $C_{ar}H$), 7.09 (2H, m, 2 × $C_{ar}H$); δ_C ($CDCl_3$, 100 MHz) 26.26 (q), 28.65 (q), 31.16 (t), 32.80 (d), 38.13 (t), 52.78 (d), 53.06 (2 × CH_3), 72.28 (d), 74.29 (d), 101.03 (t), 102.84 (d), 106.46 (d), 108.26 (d), 108.80 (s), 119.54 (d), 132.62 (s), 133.55 (s), 147.01 (s), 147.81 (s); *m*/*z* (CI$^+$) 380 (MNH_4^+, 40), 273 (100); Found: *m*/*z* MNH_4^+, 380.2074, $C_{20}H_{30}NO_6$, requires 380.2073 (Δ = +0.2 ppm); Calculated for $C_{20}H_{16}O_6$ C, 66.28%; H, 7.23%; O, 26.49%, found C, 66.53%; H, 7.28%; O, 26.19%. For a single crystal X-ray structure determination on this compound see ESI.†

Crystal data for **13**: $C_{20}H_{26}O_6$, *M* = 362.41, monoclinic, $P2_1/c$ (no. 14), *a* = 14.5941(4), *b* = 9.4049(2), *c* = 13.8121(3) Å, *β* = 91.949(2)°, *V* = 1894.70(8) Å^3, *Z* = 4, D_c = 1.270 g cm^{-3}, *μ*(Mo-Kα) = 0.093 mm^{-1}, *T* = 173 K, colourless plates, Oxford Diffraction Xcalibur 3 diffractometer; 6105 independent measured reflections (R_{int} = 0.0455), F^2 refinement, R_1(obs) = 0.0448, wR_2(all) = 0.1191, 3310 independent observed absorption-corrected reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta_{max}$ = 64°], 235 parameters. CCDC 792816.

(3*R,5*S**,6*R**)-5,6-Di-*O*-isopropylidene-3-(2-dimethylnitronylethyl)-1-[3,4-(methylenedioxy)phenyl]cyclohex-1-ene 16.** A mixture of oxime isomers (±)-**14** (636 mg, 1.92 mmol) were transferred into a flask containing $NaBH_3CN$ (236 mg, 3.84 mmol) using dry MeOH (80 mL) *via* a cannula. The suspension was heated gently until a clear solution was obtained, and then cooled to 0 °C. 6 drops of methyl orange indicator were added and the solution was titrated rapidly dropwise with a mixture of MeOH:HCl $_{(conc.)}$ 3.0 mL, 10 : 1). The cooling bath was removed and the solution was stirred for 5 min at RT, cooled again to 0 °C and treated with NaOH (8 mL, 2 M). After stirring for 10 min at 0 °C, the mixture was partitioned between CH_2Cl_2 (15 mL) and $NaHCO_3$ (sat. aq., 15 mL) and extracted with CH_2Cl_2 (4 × 15 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by FC [SiO_2; Et_2O/petrol, 1 : 1 → Et_2O/MeOH (NH_3 sat.), 97 : 3] to give nitrone (±)-**16** as colourless needles (344 mg, 48%): Mp 82.6–88.9 °C (Et_2O/petrol); R_f 0.35 [Et_2O/MeOH (NH_3 sat.), 9 : 1]; ν_{max}/cm^{-1} (neat) 980, 1041, 1253, 1586 (C═N–OH), 2930, 2984; δ_H ($CDCl_3$, 400 MHz) 1.45 (3H, s, CH_3), 1.47 (1H, m, C_4HH), 1.49 (3H, s, CH_3), 1.98 (1H, dt, *J* 12.5, 5.0, C_4HH), 2.05–2.22 (2H, m, $C_{3b}HH$ $C_{3a}H$), 2.14 (3H, s, CH_3), 2.16 (3H, s, CH_3), 2.38 (1H, m, $C_{3b}HH$), 3.98 (2H, m, CH_2), 4.29 (1H, td, *J* 10.5, 5.0, C_5H), 4.79 (1H, d, *J* 5.0, C_6H), 5.96 (2H, s, OCH_2O), 6.12 (1H, d, *J* 2.0, C_2H), 6.79 (1H, dd, *J* 8.5, 1.0, $C_{ar}H$), 7.05 (1H, d, 8.5, $C_{ar}H$), 7.07 (1H, d, 1.0, $C_{ar}H$); δ_C ($CDCl_3$, 100 MHz) 19.96 (q), 20.37 (q), 26.08 (q), 28.53 (q), 32.08 (t), 32.51 (d), 32.63 (t), 56.38 (t), 72.36 (d), 74.02 (d), 100.97 (t), 106.51 (d), 108.18 (d), 108.78 (s), 119.53 (d), 131.25 (d), 133.24 (s), 134.30 (s), 143.38 (s), 147.05 (s), 147.75 (s); *m*/*z* (CI$^+$) 374 (MH^+, 100); Found: *m*/*z* MH^+, 374.1969, $C_{21}H_{28}NO_5$, requires 374.1967 (Δ = +0.5 ppm); Calculated for $C_{21}H_{27}NO_5$ C, 67.54%; H, 7.29%; N 3.75%; O, 21.42%, found C, 67.58%; H, 7.31%; N, 3.70; O, 21.41%.%. For a single crystal X-ray structure determination on this compound see ESI.†

Crystal data for **16**: $C_{21}H_{27}NO_5 \cdot H_2O$, *M* = 391.45, monoclinic, $P2_1/n$ (no. 14), *a* = 7.2818(1), *b* = 33.8728(3), *c* = 8.3252(1) Å, *β* = 104.148(1)°, *V* = 1991.17(4) Å^3, *Z* = 4, D_c = 1.306 g cm^{-3}, *μ*(Cu-Kα) = 0.784 mm^{-1}, *T* = 173 K, colourless blocks, Oxford Diffraction Xcalibur PX Ultra diffractometer; 3808 independent measured reflections (R_{int} = 0.0259), F^2 refinement, R_1(obs) = 0.0424, wR_2(all) = 0.1248, 3426 independent observed absorption-corrected reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta_{max}$ = 143°], 263 parameters. CCDC 792817.

(3a*R*,5*S*,6*R*,7*S*,7a*R*)-5,6-Di-*O*-isopropylidene-1-carbomethoxy-7-[3,4-(methylenedioxy)phenyl]-2,3,3a,4,5,6,7,7a-octahydroindole 18. To a stirred solution of amine (+)-**6** (13 mg, 0.041 mmol) and a crystal of 4-DMAP in CH_2Cl_2 (2 mL) at 0 °C were added sequentially and dropwise triethylamine (17 μL, 12.5 mg, 0.12 mmol) and then a solution of methylchloroformate in CH_2Cl_2 (100 μL, 1 M, 0.1 mmol). The solution was stirred for 2 h at 0 °C and for 16 h at RT. The reaction mixture was partitioned between CH_2Cl_2 and sat. aq. $NaHCO_3$, the aqueous phase extracted with CH_2Cl_2 (3 × 10 mL), the combined organic phases washed with sat. aq. NH_4Cl (10 mL), the aqueous phase extracted with CH_2Cl_2 (3 × 20 mL), the combined organic phases dried over Na_2SO_4 and the solvent evaporated *in vacuo*. The residue was purified by FC (SiO_2; Et_2O/pentane, 1 : 1) to give methyl carbamate (+)-**18** as a white solid (15.0 mg, 98%): Mp 49 °C (Et_2O/pentane); $[\alpha]_D$ +17.7 (*c.* 0.88, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 3007, 2952, 1683, 1604, 1504, 1491, 1451, 1383, 1234, 1206, 1120, 1074, 1043, 938, 864, 779, 745; δ_H ($CDCl_3$, 400 MHz) 1.31 (3H, s), 1.45 (3H, s), 1.83 (2H, m), 2.12 (2H, m), 2.38 (1H, sextet, *J* 8), 2.64 (1H, dd, *J* 10.5, 11.5), 3.21 (3H, broad s), 3.34 (1H, m), 3.63 (1H, m), 3.97 (1H, t, *J* 8.5), 4.30 (1H, m), 4.40 (1H, dd, *J* 10.5, 6.5), 5.91 (2H, AB_q, *J* 1.5), 6.67 (1H, dd, *J* 6.5, 1), 6.74 (1H, d, *J* 8), 6.78 (1H, d, *J* 1.5); δ_C ($CDCl_3$, 100 MHz) 24.90 (q), 27.80 (q), 30.20 (t), 31.00 (t), 35.06 (d), 44.70 (t), 47.60 (d), 51.86 (d), 59.90 (q), 73.10 (d), 77.82 (d), 100.76 (t), 107.91 (d), 108.64 (d), 108.82 (s), 122.29 (d), 133.51 (s), 146.30 (s), 147.40 (s), 155.46 (s); *m*/*z* (EI) 375 (15), 360 (10), 317 (100), 299 (50), 242 (10), 215 (15), 190 (10), 177 (15), 140 (100), 126 (10), 88 (10); Found: *m*/*z* M^+, 375.1682, $C_{20}H_{25}NO_6$, requires 375.1675 (Δ = +1.9 ppm).

(3a*R*,5*S*,5a*R*,11b*S*,11c*R*)–5,5a–Dihydroxyisopropylidene–1,2,3b,3a,4,5,11b,11c-octahydro-[1,3]dioxolo[4,5–f]pyrrolo-[3,2,1–*de*]-phenantridin-7-one 19. (*Using the Banwell modification of Bischler–Napieralski*[49,50]): To a stirred solution of methyl carbamate (+)-**18** (100 mg, 0.266 mmol) and 4-DMAP (98 mg, 0.80 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added dropwise trifluoromethylsulfonic anhydride (251 μL, 376 mg. 1.33 mmol). The resulting dark suspension was allowed to warm to RT and stir for a further 14 h. The reaction mixture was then diluted with CH_2Cl_2 (40 mL), washed with sat. aq. $NaHCO_3$ (20 mL), the aqueous phase extracted with CH_2Cl_2 (3 × 30 mL), the combined organic phases washed with sat. aq. NH_4Cl (20 mL), the aqueous phase extracted with CH_2Cl_2 (30 mL), the combined organic phases dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by FC [SiO_2, Et_2O/pentane/MeOH (NH_3 sat.), 60 : 35 : 5] to give lactam (–)-**19** as a white solid (76 mg, 82%): Mp 224 °C (Et_2O/pentane); $[\alpha]_D$ −75.4 (*c.* 0.92, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 2928, 1642, 1609, 1504, 1461. 1415, 1384, 1352, 1270, 1241, 1211, 1163, 1127, 1043, 937, 874, 832; δ_H ($CDCl_3$, 400 MHz) 1.44 (3H, s), 1.53 (3H, s), 1.67 (2H, m), 2.24 (2H, m), 2.43 (1H, m), 2.96

(1H, dd, *J* 14.5, 8), 3.23 (1H, dt, *J* 12, 5.5), 3.52 (1H, dd, *J* 14, 10.5), 4.22 (1H, dd, *J* 12, 5.5), 4.30 (2H, m), 6.01 (2H, AB_q, *J* 1.5), 7.19 (1H,d, *J* 1), 7.49 (1H, s); δ_C ($CDCl_3$, 100 MHz) 24.44 (q), 27.25 (q), 32.20 (t), 32.41 (t), 34.95 (d), 40.59 (d), 45.16 (t), 57.32 (d), 74.89 (d), 75.69 (d), 101.48 (t), 106.29 (d), 108.25 (d), 109.52 (s), 124.76 (s), 135.33 (s), 146.88 (s), 150.61 (s), 161.91 (s); *m/z* (EI) 344 (7), 343 (10), 268 (6), 121 (26), 111 (18), 97 (29), 85 (27), 69 (56), 57 (100); Found: *m/z* M^+, 343.1415, $C_{19}H_{21}NO_5$, requires 343.1419 (Δ = –1.2 ppm).

(3a*R*,5*S*,5a*R*,11b*S*,11c*R*)–5,5a–Dihydroxyisopropylidene–1,2,3b,3a,4,5,11b,11c-octahydro-[1,3]dioxolo[4,5–f]pyrrolo-[3,2,1–*de*]-phenantridine 20. *Method 1* [*$LiAlH_4$ reduction of lactam* (-)-**19**]: To a solution of lactam (–)-**19** (12 mg, 0.03 mmol) in THF (3 mL) at RT was added $LiAlH_4$ (4 mg, 0.11 mmol). After stirring for 2 h, the reaction mixture was quenched with brine (3 mL) and concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (5 mL) and H_2O (3 mL) and the organic phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were dried over Na_2CO_3 and concentrated *in vacuo* to give amine (–)-**20** as white solid (11 mg, 95%): Mp 162–164 °C (Et_2O/pentane) [*NB*. sublimes 155 °C]; R_f 0.35 (EtOAc/MeOH, 4 : 1); $[\alpha]_D$ –14.0 (*c*. 0.50, $CHCl_3$); ν_{max}/cm^{-1} (KBr) 3440, 2988, 2905, 2775, 1485, 1380, 1252, 1237, 1050, 1036, 933; δ_H ($CDCl_3$, 400 MHz) 1.40 (3H, s), 1.53 (3H, s), 1.55–1.68 (2H), 2.11 (3H, m), 2.27 (1H t, *J* 10), 2.47 (1H, td, *J* 9, 5), 2.84 (1H, t, *J* 10), 3.07 (1H, ddd, *J* 10, 6, 2), 3.70 (1H, dd, *J* 14.5, 1), 4.01 (1H, d, *J* 14.5), 4.14 (1H, dd, *J* 10, 7.5), 4.24 (1H, ddd, *J* 11, 7.5, 5), 5.91 (2H, s), 6.55 (1H, s), 7.31 (1H, s); δ_C ($CDCl_3$, 100 MHz) 24.2 (q), 27.2 (q), 31.8 (t), 32.2 (t), 33.2 (d), 41.4 (d), 53.6 (t), 55.7 (t), 62.1 (d), 75.5 (d), 76.6 (d), 100.7 (t), 106.5 (d), 107.8 (d), 108.7 (s), 129.1 (s), 132.2 (s), 145.9 (s), 146.1 (s); *m/z* (CI^+) 330 (MH^+, 100); *m/z* (EI^+) 329 (M^+, 44), 328 (100), 314 (7), 270 (4), 254 (6), 214 (2), 187 (3); Found: *m/z* M^+, 329.1619, $C_{19}H_{23}NO_4$, requires 329.1627 (Δ = –2.4 ppm). For a single crystal X-ray structure determination on this compound see ESI.†

Crystal data for **20**: $C_{19}H_{23}NO_4$, *M* = 329.38, hexagonal, $P6_1$ (no. 169), *a* = *b* = 10.695(1), *c* = 25.134(4) Å, *V* = 2489.7(5) Å^3, *Z* = 6, D_c = 1.318 g cm^{-3}, μ(Mo-Kα) = 0.092 mm^{-1}, *T* = 298 K, colourless prisms, Stoe Stadi-4 diffractometer; 2331 independent measured reflections (R_{int} = 0.0), F^2 refinement, R_1(obs) = 0.0446, wR_2(all) = 0.0846, 1415 independent observed absorption-corrected reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta_{max} = 46°$], 218 parameters. The absolute structure of **20** could not be determined by either an *R*-factor test [$R_1^+ = 0.0446$, $R_1^- = 0.0446$] or by use of the Flack parameter [$x^+ = 0.0(17)$, $x^- = 2.6(17)$], and so was assigned by internal reference on C(7), C(8), C(12), C(14) and C(22). CCDC 792818.

Method 2 [*Pictet–Spengler reaction*[46,47] *using Eschenmoser's salt on hydrindane* (+)-**6**]: To a solution of amine (+)-**6** (173 mg, 0.54 mmol) in THF (20 mL) was added Eschenmoser's salt[66] (151 mg, 0.82 mmol, 1.5 equiv) and the suspension stirred at 40 °C. After 40 h the solution was quenched with NH_4OH (10% aq. 10 mL) and the resulting biphasic solution concentrated *in vacuo*. The residue was suspended in CH_2Cl_2 (30 mL), washed with water (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by FC (Et_2O/pentane, 1 : 1 → Et_2O; column presaturated with Et_3N/Et_2O, 1 : 9) to give amine (–)-**20** as a white solid (95.2 mg, 53%) and recovered amine (+)-**6** (12.0 mg, 7%). Spectroscopic data as above.

(3a*R*,5*S*,6*R*,7*S*,7a*R*)-5,6-Di-*O*·isopropylidene-1-phenoxycarbonyl-7-[3,4-(methylenedioxy)-6-chloromethylphenyl]-2,3,3a,4,5,6,7,7a-octahydroindole 21. To a stirred suspension of amine (–)-**20** (3.2 mg, 0.040 mmol) and $NaHCO_3$ (50 mg) in CH_2Cl_2 (5 mL) at 0 °C was added a solution of phenylchloroformate in CH_2Cl_2 (70 μL, 1 M) dropwise. The suspension was stirred for 2 h at 0 °C and then refluxed for 13 h. The reaction mixture was then diluted with CH_2Cl_2 (30 mL), washed with aq. sat. $NaHCO_3$, the aqueous phase extracted CH_2Cl_2 (4 × 10 mL), the combined organic phases dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by FC (SiO_2; Et_2O/pentane, 1 : 1) to give phenyl carbamate (–)-**21** as a yellow waxy solid (17.4 mg, 89%): Mp 64 °C (Et_2O/pentane); $[\alpha]_D$ –24.3 (*c*. 0.42, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 3020, 1709, 1507, 1488, 1406, 1220, 1073, 1043, 929, 792; δ_H ($CDCl_3$, 400 MHz, 328 K) 1.30 (3H, s), 1.49 (3H, s), 1.93 (2H, m), 2.20 (2H, m), 2.54 (1H, m), 3.31 (1H, t, *J* 10.5), 3.53 (1H, m), 3.82 (1H, ddd, *J* 8, 8, 5.5), 4.33 (3H, m), 4.62 (2H, AB_q, *J* 11.5), 5.54 (1H, broad s), 5.81 (1H, broad s), 6.74 (2H, d, *J* 7), 6.75 (1H, s), 6.94 (1H, s), 7.07 (1H, t, *J* 7.5), 7.22 (2H, t, *J* 7.5); δ_C ($CDCl_3$, 100 MHz, 328 K, 1 carbon absent) 24.69 (q), 27.65 (q), 30.77 (t), 35.47 (d), 42.63 (d), 44.58 (t), 45.51 (t), 60.23 (d), 73.19 (d), 79.37 (d), 101.17 (t), 108.81 (s), 108.81 (d), 109.87 (d), 121.10 (2 × d), 124.59 (d), 128.83 (2 × d), 130.35 (s), 133.46 (s), 146.38 (s), 148.44 (s), 151.44 (s), 153.05 (s); *m/z* (EI) 487 (35),485 (100), 450 (80), 427 (90), 392 (30), 334 (100), 298 (90), 202 (75), 97 (50), 71 (60); Found: *m/z* M^+, 485.1614, $C_{26}H_{28}NO_6{}^{35}Cl$, requires 485.1598 (Δ = +3.3 ppm).

(3a*R*,5*S*,6*R*,7*S*,7a*R*)-5,6-Di-*O*-isopropylidene-1-phenoxycarbonyl-7-[3,4-(methylenedioxy)-6-oxomethylphenyl]-2,3,3a,4,5,6,7,7a-octahydroindole 22. To a stirred solution of benzylchloride (–)-**21** (10 mg, 0.0206 mmol) in DMSO (2 mL) was added trimethylamine-*N*-oxide (50 mg, 0.533 mmol) and the resulting solution stirred at RT for 24 h. The reaction mixture was then diluted with Et_2O (20 mL) and partitioned with sat. aq. NH_4Cl (20 mL). The phases were separated, the aqueous phase was extracted with Et_2O (3 × 20 mL) and the combined organic phases dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by FC (SiO_2; Et_2O/pentane, 9 : 1) to give aldehyde (+)-**22** as a white solid (7.8 mg, 81%): Mp 74 °C (Et_2O/pentane); $[\alpha]_D$ +20.4 (*c*. 0.35, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 3022, 2926, 1712, 1612, 1505, 1486, 1384, 1252, 1199, 1043, 937, 867, 770, 730; δ_H ($CDCl_3$, 400 MHz, 331 K) 1.32 (3H, s), 1.46 (3H, s), 2.23 (4H, m), 2.51 (1H, d, *J* 7.5), 3.50 (1H, m), 3.73 (1H, td, *J* 11.5, 7.5), 4.16 (1H, m), 4.30 (1H, m), 4.40 (1H, m), 4.48 (1H, m), 5.69 (1H, broad s), 5.92 (1H, s), 6.69 (2H, m), 7.08 (2H, m), 7.22 (3H, m), 10.10 (1H, s); δ_C ($CDCl_3$, 100 MHz, 331 K, 1 carbon absent) 25.09 (q), 27.71 (q), 29.69 (t), 30.04 (t), 31.18 (t), 35.69 (d), 39.96 (d), 45.82 (t), 61.00 (d), 73.34 (d), 78.00 (d), 101.85 (t), 108.48 (2 × d), 109.13 (2 × d), 120.95 (d), 124.71 (d), 128.91 (s), 130.80 (s), 139.69 (s), 147.22 (s), 151.31 (s), 152.90 (s), 189.66 (d); *m/z* (EI) 465 (20), 450 (10), 407 (25), 344 (100), 268 (30), 205 (25),175 (100), 77 (20). Found: *m/z* M^+, 465.1788, $C_{26}H_{27}NO_7$, requires 465.1780 (Δ = +1.7 ppm).

(3a*R*,5*S*,6*R*,7*S*,7a*R*)-5,6-Di-*O*-isopropyfidene-1-methyl-7-[3,4-(methylendioxy)-6-hydroxymethylphenyl]-2,3,3a,4,5,6,7,7a-octahydroindole 23. To a solution of aldehyde (+)-**22** (55 mg, 0.118 mmol) in THF (8 mL) was added a solution of $LiAlH_4$ (64 mg, 1.88 mmol) in Et_2O (12 mL) and the reaction mixture heated at reflux for 4.5 h. The reaction mixture was cooled to RT

and MeOH (1 mL) added dropwise. The reaction mixture was then partitioned between CH_2Cl_2 (25 mL) and sat. brine (25 mL). The phases were separated, the aqueous phase extracted with CH_2Cl_2 (5 × 20 mL), the combined organic phases dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by FC (SiO_2; Et_2O/pentane/MeOH (NH_3 sat.), 58 : 40 : 2] to give benzyl alcohol (+)-**23** as a colourless oil (38 mg, 89%): $[\alpha]_D$ +15.4 (*c.* 1.14, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 3521, 2987, 2889, 1616, 1502, 1480, 1458, 1382, 1262, 1229, 1077, 1044, 930, 870, 793, 750; δ_H ($CDCl_3$, 400 MHz) 1.31 (3H, s), 1.42 (3H, s), 1.64 (5H, broad s), 2.06 (1H, m), 2.17 (1H, td, J 13, 5.5), 2.32 (3H, m), 3.08 (1H, m), 3.21 (1H, t, *J* 10.5), 4.23 (1H, d, *J* 12), 4.31 (1H, m), 4.43 (1H, dd, *J* 10, 7.5), 4.82 (1H, d, *J* 11.5), 5.95 (2H, AB_q, *J* 1), 6.85 (1H, s), 6.89 (1H, s); δ_C ($CDCl_3$, 100 MHz) 24.35 (q), 27.29 (q), 32.07 (t), 32.53 (t), 36.28 (d), 43.16 (d), 43.74 (d), 56.98 (t), 63.18 (t), 68.47 (q), 74.23 (d), 77.86 (d), 101.11 (t), 106.05 (2 × d), 108.85 (2 × d), 111.02 (d), 132.89 (s), 135.46 (s), 146.15 (s), 147.97 (s).

(3a*R*,5*S*,6*R*,7*S*,7a*R*)-5,6-Di-*O*-isopropylidene-l-methyl-7-[3,4-(methylenedioxy)-6-oxomethylphenyl]-2,3,3a,4.5,6,7,7a-octahydroindole 24. To a stirred solution of benzyl alcohol (+)-**23** (24 mg, 0.066 mmol) in CH_2Cl_2 (8 mL) at RT was added a solution of Dess–Martin periodinane (35 mg, 0.083 mmol) in CH_2Cl_2 (7 mL) dropwise. After 75 min a further portion of periodinane (20 mg, 0.047 mmol) was added and the reaction mixture was stirred for further 2.5 h at RT. The reaction mixture was then diluted with CH_2Cl_2 (30 mL), washed with sat. aq. $NaHCO_3$ (20 mL), the phases separated, the aqueous phase re-extracted with CH_2Cl_2 (3 × 10 mL), the combined organic phases dried over Na_2SO_4 and the solvent evaporated *in vacuo*. The residue was purified by (SiO_2; Et_2O/pentane/MeOH (NH_3 sat.), 60 : 37 : 3] to give aldehyde (+)-**24** as a pale yellow solid (8.8 mg, 37%): ν_{max}/cm^{-1} ($CHCl_3$) 2921, 2780, 1671, 1616, 1480, 1458, 1382, 1365, 1284, 1251, 1158, 1044, 935, 864, 641; δ_H ($CDCl_3$, 200 MHz) 1.29 (3H, s), 1.40 (3H, s), 1.57 (1H, m), 1.72 (3H, s), 2.11 (1H, m), 2.97 (1H, dd, *J* 8, 7.5), 3.71 (1H, t, *J* 9), 4.28 (2H, m), 6.01 (2H, AB_q, *J* 1), 6.94 (1H, s), 7.40 (1H, s), 10.26 (1H, s); δ_C ($CDCl_3$, 50 MHz, diagnostic peaks only) 24.21 (q), 27.12 (q), 31.15 (d), 32.74 (t), 35.78 (t), 41.29 (d), 42.32 (d), 57.11 (t), 67.89 (q), 74.16 (d), 78.25 (d), 101.82 (t), 106.12 (d), 107.30 (d).

(3a*R,5*S**,6*R**,7*S**,7a*R**)-5,6-Di-*O*-isopropylidene-1-phenylcarbamate-7-[3,4-(methylenedioxy)phenyl]-2,3,3a,4,5,6,7,7a-octahydroindole 25.** To a solution of pyrrolidine (±)-**6** (620 mg, 1.96 mmol), Et_3N (1 mL, 7.82 mmol) and DMAP (17 mg, 0.02 mmol) in CH_2Cl_2 (10 mL) at RT was added phenyl chloroformate (736 µL, 5.87 mmol). After stirring for 10 min, the reaction mixture was quenched with $NaHCO_3$ (sat. aq., 5 mL) and the organic phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by FC (SiO_2; petrol/Et_2O, 1 : 1) to give carbamate (±)-**25** as a white solid (670 mg, 78%): Mp 231.5–234.7 °C. R_f 0.30 (SiO_2; petrol/Et_2O, 1 : 1); ν_{max} (neat)/cm^{-1} 987, 1043, 1178 (C–O), 1504, 1689 (C═O), 2861, 2942; δ_H ($CDCl_3$, 500 MHz, 328 K) 1.35 (3H, s, CH_3), 1.50 (3H, s, CH_3), 1.89 (1H, m, C_4HH), 1.99 (1H, m, C_3HH), 2.18–2.24 (2H, C_4HH & C_3HH), 2.54 (1H, *app* sext, *J* 7, $C_{3a}H$), 2.78 (1H, dd, *J* 11.5, 10.5, $C_{11b}H$), 3.48 (1H, m, C_2HH), 3.81 (1H, m, C_2HH), 4.19 (1H, m, $C_{11c}H$), 4.35 (1H, td, *J* 8.5, 6.0, C_5H), 4.48 (1H, m, $C_{5a}H$), 5.71 (1H, br s, OC*H*HO), 5.85 (1H, br s, OCH*H*O), 6.65–6.75 (3H, 3 × $C_{ar}H$), 6.81 (1H, d, *J* 1.5, $C_{ar}H$), 7.09 (1H, t, *J* 7.0, $C_{ar}H$), 7.23 (2H, t, *J* 7.0, $C_{ar}H$), 7.28 (1H, $C_{ar}H$); δ_C ($CDCl_3$, 125 MHz, 328 K) 24.95 (q), 27.85 (q), 29.85 (t), 30.63 (t), 34.63 (d), 45.01 (t), 47.52 (d), 60.42 (d), 73.74 (d), 78.68 (d), 100.82 (t), 108.13 (d), 108.49 (d), 108.75 (s), 120.99 (2 × d), 122.75 (d), 124.74 (d), 129.28 (2 × d), 133.09 (s), 146.65 (s), 147.79 (s), 151.02 (s), 153.07 (s); *m*/*z* (CI^+) 438 (MNH^+, 90), 455 (MNH_4^+, 100); Found: *m*/*z* MH^+, 438.1920, $C_{25}H_{28}NO_6$, requires 438.1917 (Δ = +0.8); Calculated for $C_{25}H_{27}NO_6$ C, 68.63%; H, 6.22%; N, 3.20%; O, 21.94%, found C, 68.60%; H, 6.21%; N, 3.18%; O, 22.01%.

(3a*R,5*S**,6*R**,7*S**,7a*R**)-5,6-Di-*O*-isopropylidene-1-methyl-7-[3,4-(methylenedioxy)phenyl]-2,3,3a,4,5,6,7,7a-octahydroindole 26.** To a solution of phenyl carbamate (±)-**25** (199 mg, 0.45 mmol) in THF (20 mL) at RT was added $LiAlH_4$ (258 mg, 0.68 mmol). The resulting suspension was refluxed in the dark for 3 h and then allowed to cool to RT. The reaction mixture was then partitioned between brine (10 mL) and EtOAc (15 mL) and the organic phase was extracted with EtOAc (3 × 15 mL). The combined organic phases were dried over Na_2CO_3, filtered and concentrated *in vacuo* to afford *N*-methylindoline (±)-**26** as a colourless oil (130 mg, 88%). R_f 0.35 (SiO_2; petrol/Et_2O, 1 : 4); ν_{max} (neat)/cm^{-1} 983, 1050, 1187, 1504, 2875, 2942; δ_H ($CDCl_3$, 400 MHz) 1.30 (3H, s, CH_3), 1.46 (3H, s, CH_3), 1.53 (1H, ddd, *J* 12.0, 10.0, 6.0, C_4HH), 1.68 (1H, dt, *J* 13.0, 10.5, C_3HH), 1.82 (3H, s, NCH_3), 2.03 (1H, ddd, *J* 12.0, 8.5, 6.0, C_4HH), 2.13–2.25 (2H, $C_{11b}H$, C_3HH), 2.25 (1H, m, $C_{3a}H$), 2.32 (1H, t, *J* 10.0, C_2HH), 2.72 (1H, t, *J* 10.0, C_2HH), 2.99 (1H, dd, *J* 10.5, 7.5, $C_{11c}H$), 4.15 (1H, dd, *J* 11.0, 7.0, $C_{5a}H$), 4.33 (1H, dt, *J* 10.5, 7.0, C_5H), 5.97 (2H, *AB*, *J* 1.5, OCH_2O), 6.70 (3H, m, 3 × $C_{ar}H$); δ_C ($CDCl_3$, 100 MHz) 24.63 (q), 27.54 (q), 30.70 (t), 32.98 (t), 35.40 (q), 42.77 (d), 49.95 (d), 57.84 (t), 68.59 (d), 74.31 (d), 79.61 (d), 100.92 (t), 108.31 (d), 108.44 (s), 108.72 (d), 121.89 (d), 135.88 (s), 146.34 (s), 147.75 (s); *m*/*z* (CI^+) 332 (MH^+, 100); Found: *m*/*z* MH^+, 332.1867, $C_{19}H_{26}NO_4$, requires 332.1862 (Δ = +1.6).

(3a*R,5*S**,6*R**,7*S**,7a*R**)-5,6-Di-*O*-isopropylidene-1-*N*-methyl-7-[3,4-(methylenedioxy)-6-bromophenyl]-2,3,3a,4,5,6,7,7a-octahydroindole 27.** To a solution of carbamate (±)-**25** (200 mg, 0.46 mmol) and K_2CO_3 (69 mg, 0.50 mmol) in CH_2Cl_2 (15 mL) at −78 °C was added Br_2 dropwise. After stirring for 6 h at −78 °C, the reaction mixture was allowed to warm-up to RT over 14 h. ^{1}H-NMR of the crude suggested a partial deprotection of the acetonide. Hence, DMP (61 µL, 0.50 mmol) and *p*-TSA (5 mg, 0.03 mmol) were added at RT. After stirring for 40 min, the reaction mixture was partitioned between $NaHCO_3$ (sat. aq., 10 mL) and CH_2Cl_2 (10 mL) and the organic phase was extracted with CH_2Cl_2 (10 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was dissolved in degassed THF (5 mL) and $LiAlH_4$ (52 mg, 1.38 mmol) was added. The suspension was refluxed in the dark at 80 °C for 5 h and quenched with MeOH (2 mL). The reaction mixture was partitioned between brine (15 mL) and Et_2O (15 mL) and the organic phase was extracted with Et_2O (3 × 15 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by FC (SiO_2; Et_2O/petrol, 5 : 1 → Et_2O 100%) to give bromo-*N*-methyl indoline (±)-**27** as a yellow oil (38 mg, 21%). R_f 0.70 (Et_2O/MeOH, 4 : 1); ν_{max} (neat)/cm^{-1} 983, 1078 (C_{ar}–Br), 1187, 1504, 2875, 2942; δ_H ($CDCl_3$, 400 MHz) 1.29 (3H, s, CH_3), 1.52 (3H, s, CH_3), 1.71 (1H,

m, C_4HH), 1.82 (1H, m, C_3HH), 1.90 (3H, s, NCH_3), 1.96–2.14 (3H, C_2HH, C_3HH, C_4HH), 2.15–2.22 (2H, C_2HH & $C_{3a}H$), 2.99 (1H, t, *J* 11.0, $C_{11b}H$), 3.54 (1H, m, $C_{11c}H$), 4.08 (1H, dd, *J* 11.0, 7.0, $C_{5a}H$), 4.38 (1H, dt, *J* 10.0, 7.0, C_5H), 5.96 (1H, d, *J* 1.5, $OCHHO$), 6.00 (1H, d, *J* 1.5, $OCHHO$), 6.80 (1H, s, $C_{ar}H$), 7.04 (1H, s, $C_{ar}H$); δ_C ($CDCl_3$, 100 MHz) 24.80 (q), 27.33 (q), 29.98 (t), 33.03 (t), 35.10 (q), 41.87 (d), 47.26 (d), 57.61 (t), 70.03 (d), 74.21 (d), 79.99 (d), 101.72 (t), 107.56 (d), 109.10 (s), 112.85 (d), 116.78 (s), 135.10 (s), 146.73 (s), 147.59 (s); *m/z* (CI^+) 410 [MH^+(^{79}Br), 100], 412 [MH^+(^{81}Br), 97]; Found: *m/z* [MH^+(^{79}Br)], 410.0973, $C_{19}H_{25}{}^{79}BrNO_4$, requires 410.0967 (Δ = +1.5).

(3a*R,5*S**,6*R**,7*S**,7a*R**)-5,6-Di-*O*-isopropylidene-1-(4-chlorobenzoyl)methyl-7-[3,4-(methylenedioxy)phenyl]-2,3,3a,4,5,6,7,7a-octahydroindole 28.** To a solution of hydrindane (±)-**6** (620 mg, 1.96 mmol), Et_3N (1 mL, 7.82 mmol) and 4-DMAP (12 mg, 0.1 mmol) in CH_2Cl_2 (15 mL) at RT was added 4-chlorobenzoyl chloride (441 mg, 2.52 mmol) dropwise. After stirring for 18 h, the reaction mixture was partitioned between $NaHCO_3$ (sat. aq., 10 mL) and CH_2Cl_2 (5 mL) and the aqueous phase extracted with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by FC (SiO_2; Et_2O) to give amide (±)-**28** as a white solid (545 mg, 61%): Mp 186.4–188.3 °C. R_f 0.45 (Et_2O); ν_{max}/cm^{-1} (neat) 987, 1081, 1192, 1516, 1648 (C═O), 2878, 2939; δ_H ($CDCl_3$, 400 MHz) 1.30 (3H, s, CH_3), 1.41 (3H, s, CH_3), 1.55 (1H, m, C_4HH), 1.86–1.97 (2H, C_4HH & C_3HH), 2.03–2.18 (2H, C_3HH & C_2HH), 2.48 (1H, m, $C_{3a}H$), 2.74 (1H, m, C_2HH), 3.54 (2H, m, $C_{11b}H$ & $C_{11c}H$), 4.30 (2H, m, C_5H & $C_{5a}H$), 5.85 (1H, d, *J* 1.5, $OCHHO$), 5.90 (1H, d, *J* 1.5, $OCHHO$), 6.65 (2.3 H, m, $C_{ar}Hs$), 7.07 (1.7 H, m, $C_{ar}Hs$), 7.26 (3H, m, 3 × $C_{ar}H$); δ_C ($CDCl_3$, 100 MHz) 24.91 (q), 27.84 (q), 29.70 (t), 30.02 (t), 31.32 (d), 34.36 (t), 47.24 (2 × d), 73.08 (d), 78.21 (d), 100.92 (t), 108.47 (2 × d), 108.70 (s), 122.34 (d), 128.22 (2 × d), 128.73 (2 × d), 132.74 (s), 134.98 (s), 135.81 (s), 146.84 (s), 147.81 (s), 168.90 (s); *m/z* (CI^+) 456 [MH^+(^{35}Cl), 100], 458 [MH^+(^{37}Cl), 35]; Found: *m/z* [MH^+(^{35}Cl)], 456.1567, $C_{25}H_{26}{}^{35}ClNO_5$, requires 456.1578 (Δ = +1.1 ppm); Calculated for $C_{25}H_{26}ClNO_5$: C, 65.86%; H, 5.75%; Cl, 7.78%; N, 3.07%; O 17.55%, found C, 65.90%; H, 5.72%; Cl, 7.79%; N, 3.05%; O 17.54%. For a single crystal X-ray structure determination on this compound see ESI.†

Crystal data for **28**: $C_{25}H_{26}ClNO_5$, *M* = 455.92, triclinic, $P\bar{1}$ (no. 2), *a* = 6.0988(2), *b* = 11.8551(4), *c* = 16.3205(5) Å, α = 102.804(3), β = 98.740(3), γ = 102.130(3)°, *V* = 1100.31(6) Å^3, *Z* = 2, D_c = 1.376 g cm^{-3}, μ(Cu-Kα) = 1.854 mm^{-1}, *T* = 298 K, colourless plates, Oxford Diffraction Xcalibur PX Ultra diffractometer; 4218 independent measured reflections (R_{int} = 0.0256), F^2 refinement, R_1(obs) = 0.0368, wR_2(all) = 0.1087, 3060 independent observed absorption-corrected reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta_{max}$ = 143°], 290 parameters. CCDC 792819.

(3a*R,5*S**,6*R**,7*S**,7a*R**)-5,6-Di-*O*-isopropylidene-1-(4-chlorobenzyl)-7-[3,4-(methylenedioxy)-6-oxomethylphenyl]-2,3,3a,4,5,6,7,7a-octahydroindole 29 and (3a*R**,5*S**,6*R**,7*S**,7a*R**)-5,6-di-*O*-isopropylidene-1-(4-chlorobenzyl)-7-[3,4-(methylenedioxy)phenyl]-2,3,3a,4,5,6,7,7a-octahydroindole 30.** To a solution of amide (±)-**28** (164 mg, 0.36 mmol) and K_2CO_3 (102 mg, 0.74 mmol) in CH_2Cl_2 (15 mL) at −78 °C was added Br_2 dropwise. After stirring for 6 h at −78 °C, the reaction mixture was allowed to warm to RT over 14 h. ^{1}H-NMR of the crude suggested a partial deprotection of the acetonide so 2,2-dimethoxypropane (54 μL, 0.44 mmol) and *p*-TSA (5 mg, 0.03 mmol) were added at RT. After stirring for 40 min, the reaction mixture was partitioned between $NaHCO_3$ (sat. aq., 10 mL) and CH_2Cl_2 (10 mL) and the organic phase was extracted with CH_2Cl_2 (10 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue (150 mg, 0.28 mmol) was dissolved in degassed THF (5 mL) and $LiAlH_4$ (55 mg, 1.43 mmol) was added. The suspension was refluxed in the dark at 80 °C for 5 h and quenched with MeOH (2 mL). The reaction mixture was partitioned between brine (15 mL) and Et_2O (15 mL) and the organic phase was extracted with Et_2O (3 × 15 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by FC (SiO_2; petrol/Et_2O, 3 : 1) to give the intermediate aryl bromide as a white solid (154 mg, 0.29 mmol, 80%): R_f 0.55 (Et_2O/petrol, 1 : 2); δ_H ($CDCl_3$, 400 MHz) 1.27 (3H, s, CH_3), 1.49 (1H, m, C_4HH), 1.49 (3H, s, CH_3), 1.80 (1H, *app* td, *J* 13.6, 10.2, C_4HH), 1.92 (2H, m, C_3H_2), 2.09 (1H, ddd, *J* 11.1, 6.4, 4.4, C_2HH), 2.21 (1H, m, $C_{3a}H$), 2.52 (1H, *app* t, *J* 11.1, C_2HH), 2.61 (1H, d, *J* 12.6 $C_{ar}CHHN$), 2.75 (1H, m, $C_{11c}H$), 3.35 (1H, d, *J* 12.6, $C_{ar}CHHN$), 3.64 (1H, t, *J* 10.7, $C_{11b}H$), 4.12 (1H, dd, *J* 10.7, 7.1, $C_{5a}H$), 4.34 (1H, *app* dt, *J* 10.2, 7.1, C_5H), 5.91 (1H, *AB*, J 1.3, $OCHHO$), 5.95 (1H, AB_q, 1.3, $OCHHO$), 6.76 (1H, s, $C_{ar}H$), 6.97 (1H, s, $C_{ar}H$), 7.11 (2H, d, *J* 8.4, 2 × $C_{ar}H$), 7.17 (2H, d, *J* 8.4, 2 × $C_{ar}H$); δ_C ($CDCl_3$, 100 MHz) 24.72 (q), 27.35 (q), 30.36 (t), 32.88 (t), 34.97 (d), 47.70 (d), 53.79 (t), 59.56 (t), 67.94 (d), 74.11 (d), 79.73 (d), 101.77 (t), 107.37 (d), 108.96 (s), 112.91 (d), 116.92 (s), 128.11 (2 × d), 130.21 (2 × d), 132.23 (s), 134.87 (s), 138.55 (s), 146.80 (s), 147.77 (s); *m/z* (CI^+) 520 [MH^+ (^{79}Br, ^{35}Cl), 75], 522 [MH^+ (^{79}Br, ^{37}Cl), (^{81}Br, ^{35}Cl), 100], 524 [MH^+ (^{81}Br, ^{35}Cl), 25]; Found: *m/z* [MH^+ (^{79}Br, ^{35}Cl)], 520.0884, $C_{25}H_{28}NO_4{}^{35}Cl{}^{79}Br$, requires 520.0890 (Δ = −1.2 ppm). The bromide was immediately dissolved in THF (4 mL) and cooled to −78 °C. To this solution was added *tert*-BuLi (367 μL, 1.5 M in hexanes, 0.55 mmol) dropwise. After stirring for 1 h at −78 °C, DMF (341 μL, 4.43 mmol) was added dropwise and the reaction mixture was allowed to warm to RT over 14 h. The resulting suspension was then partitioned between $NaHCO_3$ (sat. aq., 10 mL) and CH_2Cl_2 (10 mL) and the organic phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by FC (SiO_2; petrol/Et_2O, 2 : 1) to give:

Aldehyde (±)-**29** as a white solid [86 mg, 51% from amide (±)-**28**]: Mp 43.4-46.1 °C (Et_2O/petrol); R_f 0.45 (petrol/Et_2O, 2 : 1); ν_{max}/cm^{-1} (neat) 983, 1078, 1187, 1206, 1697 (C═O), 2875, 2930; δ_H ($CDCl_3$, 400 MHz) 1.33 (3H, s, CH_3), 1.44 (3H, s, CH_3), 1.55–1.71 (2H, C_4HH & C_3HH), 2.00–2.38 (3H, C_3HH, C_2HH & C_4HH), 2.34 (1H, m, $C_{3a}H$), 2.69 (1H, *app* t, *J* 10.0, C_2HH), 2.80 (2H, m, $C_{ar}CHHN$ & $C_{11c}H$), 3.11 (1H, d, *J* 13.0, $C_{ar}CHHN$), 3.90 (1H, t, *J* 10.0, $C_{11b}H$), 4.37 (2H, m, C_5H & $C_{5a}H$), 6.03 (1H, *AB*, J 1.0, $OCHHO$), 6.07 (1H, AB_q, 1.0, $OCHHO$), 6.91 (2H, d, *J* 8.5, 2 × $C_{ar}H$), 6.94 (1H, s, $C_{ar}H$) 7.16 (2H, d, *J* 8.5, 2 × $C_{ar}H$), 7.40 (1H, s, $C_{ar}H$), 10.41 (1H, s, CHO); δ_C ($CDCl_3$, 100 MHz) 24.29 (q), 27.18 (q), 31.24 (t), 32.59 (t), 35.47 (d), 41.39 (d), 53.66 (t), 59.87 (t), 66.68 (d), 74.02 (d), 78.27 (d), 101.97 (t), 106.13 (d), 107.44 (d), 108.87 (s), 128.19 (2 × d), 129.89 (2 × d), 130.96 (s), 132.44 (s), 137.65 (s), 141.60 (s), 146.98 (s), 152.72 (s), 188.95 (d); *m/z* (CI^+) 470 [MH^+(^{35}Cl), 100], 472 [MH^+(^{37}Cl), 40]; Found: *m/z* [MH^+(^{37}Cl)], 470.1749, $C_{26}H_{29}NO_5{}^{37}Cl$, requires

470.1734 (Δ = +3.2 ppm); Calculated for $C_{26}H_{28}ClNO_5$: C, 66.45%; H, 6.01%; Cl, 7.54%; N, 2.98%; O, 17.02%, found C, 66.47%; H, 6.03%; Cl, 7.52%; N, 2.97%; O, 17.01%.

Reduced product (±)-**30** as a white solid [41 mg, 26% from amide (±)-**28**]: Mp 34.2–38.6 °C (Et_2O/petrol); R_f 0.35 (petrol/Et_2O, 2 : 1); ν_{max}/cm^{-1} (neat) 983, 1078, 1187, 1206, 1505, 2875, 2930; δ_H ($CDCl_3$, 400 MHz) 1.33 (3H, s, CH_3), 1.48 (4H, s, CH_3 & C_4HH), 1.68 (1H, m, C_3HH), 1.95–2.16 (3H, C_3HH, C_2HH & C_4HH), 2.26 (1H, m, $C_{3a}H$), 2.64 (1H, t, *J* 10.0, C_2HH), 2.71 (1H, d, *J* 13.0, $C_{ar}CHHN$), 2.82 (2H, m, $C_{11b}H$,$C_{11c}H$), 3.25 (1H, d, *J* 13.0, $C_{ar}CHHN$), 4.26 (1H, dd, *J* 10.5, 7.5, $C_{5a}H$), 4.34 (1H, m, C_5H), 5.92 (1H, d, *J* 1.5, $OCHHO$), 5.95 (1H, d, *J* 1.5, $OCHHO$), 6.77–6.85 (3H, 3 × $C_{ar}H$), 7.03 (2H, d, *J* 8.5, $C_{ar}H$), 7.20 (2H, d, *J* 8.5, $C_{ar}H$); δ_C ($CDCl_3$, 100 MHz) 24.53 (q), 27.49 (q), 30.91 (t), 32.83 (t), 35.38 (d), 50.15 (d), 54.06 (t), 59.77 (t), 66.62 (d), 74.25 (d), 79.25 (d), 100.95 (t), 108.38 (s), 108.49 (d), 108.62 (d), 121.98 (d), 128.25 (2 × d), 129.56 (2 × d), 132.21 (s), 135.67 (s), 138.60 (s), 146.41 (s), 147.88 (s); *m*/*z* (CI^+) 442 [MH^+(^{35}Cl), 100], 444 [MH^+(^{37}Cl), 40]; Found: *m*/*z* [MH^+(^{35}Cl)], 442.1786, $C_{25}H_{29}NO_4{}^{35}Cl$, requires 442.1786 (Δ = +0.2 ppm); Calculated for $C_{25}H_{28}ClNO_4$: C, 67.94%; H, 6.39%; Cl, 8.02%; N, 3.17%; O, 14.48%, found C, 67.89%; H, 6.41%; Cl, 8.01%; N, 3.15%; O, 14.54%.

(±)-*1*-(4-Chlorobenzyl)-1-desmethylclivonine 31. To a solution of aldehyde (±)-**29** (20 mg, 0.04 mmol) in THF (3 mL) at RT was added aq. HCl (0.5 mL, 2 M). After stirring for 3 h at RT, the reaction mixture was freeze-dried and the residue was dissolved in toluene (2 mL). Fetizon's reagent (*i.e.* Ag_2CO_3–Celite®)[61] (327 mg, 0.57 mmol, 0.57 g/mol) was added and the reaction mixture heated for 1 h at 90 °C. The resulting black suspension was cooled to RT and filtered through Celite® eluting with EtOAc (20 mL). The filtrate and combined washings were concentrated *in vacuo* to yield a brown solid. This residue was purified by FC (SiO_2; Et_2O) and triturated with ice-cold Et_2O (2 mL) to give 1-(4-chlorobenzyl)-1-desmethylclivonine (±)-**31** as a white solid (15 mg, 82%): Mp 247.8–250.2 °C; R_f 0.55 (Et_2O); ν_{max}/cm^{-1} (neat) 984, 1078, 1187, 1206, 1505, 1735 (C═O), 2875, 2930, 3205 (OH); δ_H ($CDCl_3$, 400 MHz) 1.87 (1H, ddd, *J* 15.0, 6.5, 4.0, C_4HH), 2.13 (1H, m, C_3HH), 2.37 (3H, m, OH, C_4HH & C_3HH), 2.61 (2H, m, $C_{3a}H$ & C_2HH), 3.17 (2H, m, C_2HH & $C_{11c}H$), 3.39 (1H, dd, *J* 12.0, 10.0, $C_{11b}H$), 3.76 (1H, d, *J* 14.0, $C_{ar}CHHN$), 4.03 (1H, d, *J* 14.0, $C_{ar}CHHN$), 4.18 (1H, dd, *J* 12.0, 2.5, $C_{5a}H$), 4.31 (1H, dd, *J* 6.5, 2.5, C_5H), 6.05 (2H, AB_q, *J* 1.5, OCH_2O), 7.29 (2H, s, 2 × $C_{ar}H$), 7.36 (2H, s, 2 × $C_{ar}H$), 7.51 (1H, s, $C_{ar}H$), 7.90 (1H, s, $C_{ar}H$); δ_C ($CDCl_3$, 100 MHz) 28.59 (t), 30.20 (t), 33.32 (d), 34.18 (d), 49.94 (t), 60.81 (t), 67.38 (d), 68.90 (d), 81.82 (d), 101.95 (t), 107.12 (s), 109.36 (d), 118.67 (s), 128.25 (2 × d), 129.68 (2 × d), 132.21 (s), 137.93 (s), 140.63 (s), 146.77 (s), 152.67 (s), 164.63 (s); *m*/*z* (CI^+) 428 [M H^+(^{35}Cl), 100], 430 [MH^+(^{37}Cl), 35]; Found: *m*/*z* [MH^+(^{35}Cl)], 428.1256, $C_{23}H_{22}NO_5{}^{35}Cl$, requires 428.1265 (Δ = −2.0 ppm); Calculated for $C_{23}H_{22}ClNO_5$: C, 64.56%; H, 5.18%; Cl, 8.29%; N, 3.27%; O, 18.70%, found C, 64.60%; H, 5.19%; Cl, 8.27%; N, 3.26%; O, 18.68%.

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Notes and references

1 Z. Jin, *Nat. Prod. Rep.*, 2009, **26**, 363–381 and previous reviews in this series.
2 O. Hoshino, *The Alkaloids*, 1998, **51**, 323–424.
3 S. F. Martin, *The Alkaloids*, 1987, **30**, 251–376.
4 B. Weniger, L. Italiano, J.-P. Beck, J. Bastida, S. Bergoñon, C. Codina, A. Lobstein and R. Anton, *Planta Med.*, 1995, **61**, 77–89.
5 A. Evidente, *Phytochem. Rev.*, 2009, **8**, 449–459.
6 A. Evidente, A. S. Kireev, A. R. Jenkins, A. E. Romero, W. F. A. Steelant, S. V. Slambrouck and A. Kornienko, *Planta Med.*, 2009, **75**, 501–507.
7 G. Schmeda-Hirschmann, L. Astudillo, J. Bastida, F. Viladomat and C. Codina, *Bol. Soc. Chil. Quim.*, 2000, **45**, 1119.
8 L. Szlávik, Á. Gyuris, J. Minárovits, P. Forgo, J. Molnár and J. Hohmann, *Planta Med.*, 2004, **70**, 871–873.
9 J. Renard-Nozaki, T. Kim, Y. Imakura, M. Kihara and S. Kobayashi, *Research in Virology*, 1989, **140**, 115–128.
10 A. Evidente, A. Andolfi, A. H. Abou-Donia, S. M. Touema, H. M. Hammoda, E. Shawky and A. Motta, *Phytochemistry*, 2004, **65**, 2113–2118.
11 A. Numata, T. Takemura, H. Ohbayashi, T. Katsuno, K. Yamamoto, K. Sato and S. Kobayashi, *Chem. Pharm. Bull.*, 1983, **31**, 2146.
12 J. Bastida, R. Lavilla and F. Viladomat, *The Alkaloids*, 2006, **63**, 87–179.
13 C. K. Briggs, P. F. Highet, R. J. Highet and W. C. Wildman, *J. Am. Chem. Soc.*, 1956, **78**, 2899–2904.
14 B. Mehlis, *Naturwissenschaften*, 1965, **52**, 33–34.
15 W. Dopke, M. Bienert, A. L. Burlingame, P. W. Jeffs and D. S. Farrier, *Tetrahedron Lett.*, 1967, 451–457.
16 T. Kitagawa, S. Uyeo and N. Yokoyama, *J. Chem. Soc.*, 1959, 3741–3751.
17 M. Shiro, T. Sato and H. Koyama, *Chem. Ind.*, 1966, 1229.
18 P. W. Jeffs, J. F. Hansen, W. Dopke and M. Bienert, *Tetrahedron*, 1971, **27**, 5065–5079.
19 H. K. Schnoes, D. H. Smith, A. L. Burlingame, P. W. Jeffs and W. Döpke, *Tetrahedron*, 1968, **24**, 2825–2837.
20 H. Irie, Y. Nagai, K. Tamoto and H. Tanaka, *J. Chem. Soc., Chem. Commun.*, 1973, 302–303.
21 H. Tanaka, H. Irie, S. Babu, S. Uyeo, A. Kuno and Y. Ishiguro, *J. Chem. Soc., Perkin Trans. 1*, 1979, 535–538.
22 H. Tanaka, Y. Nagai, H. Irie, S. Uyeo and A. Kuno, *J. Chem. Soc., Perkin Trans. 1*, 1979, 874–878.
23 C. Giro-Manas, V. L. Paddock, C. G. Bochet, A. C. Spivey, A. J. P. White, I. Mann and W. Oppolzer, *J. Am. Chem. Soc.*, 2010, **132**, 5176–5178.
24 N. J. Cooper and D. W. Knight, *Tetrahedron*, 2004, **60**, 243–269.
25 A. C. Spivey, *Chimia*, 2009, **63**, 864–866.
26 C. R. Johnson, P. A. Ple and J. P. Adams, *J. Chem. Soc., Chem. Commun.*, 1991, 1006–1007.
27 Y. Sutbeyaz, H. Secen and M. Balci, *J. Chem. Soc., Chem. Commun.*, 1988, 1330–1331.
28 N. C. Yang, M.-J. Chen and P. Chen, *J. Am. Chem. Soc.*, 1984, **106**, 7310–7315.
29 F. Fabris, E. Rosso, A. Paulon and O. De Lucchi, *Tetrahedron Lett.*, 2006, **47**, 4835–4837.
30 T. Hudlicky, R. L. Fan, T. Tsunoda, H. Luna, C. Andersen and J. D. Price, *Isr. J. Chem.*, 1991, **31**, 229–238.
31 K. Ramesh, M. S. Wolfe, Y. Lee, D. V. Velde and R. T. Borchardt, *J. Org. Chem.*, 1992, **57**, 5861–5868.
32 N. Kornblum and H. E. De, La Mare, *J. Am. Chem. Soc.*, 1951, **73**, 880–881.
33 A. G. Griesbeck, T. Deufel, K. Peters, E.-M. Peters and H. G. von Schnering, *J. Org. Chem.*, 1995, **60**, 1952–1958.
34 A. C. Spivey, C. Giro-Manas and I. Mann, *Chem. Commun.*, 2005, 4426–4428.
35 W. Oppolzer, A. C. Spivey and C. G. Bochet, *J. Am. Chem. Soc.*, 1994, **116**, 3139–3140.
36 E. Pretsch, P. Buhlmann, and C. Affolter, *Structure Determination of Organic Compounds - Tables of Spectral Data*, Springer, Berlin, 3rd edn, 2000.

37 L. O. Jeroncic, M. P. Cabal and S. J. Danishefsky, *J. Org. Chem.*, 1991, **56**, 387–395.
38 A. S. Cieplak, *Chem. Rev.*, 1999, **99**, 1265–1336.
39 For an excellent summary of potential stereoelectronic factors in this type of situation see: Fleming, I.*'Molecular Orbitals and Organic Chemical Reactions - Reference Edition'*, Wiley, Chichester, 2010, pp2246–2250.
40 D. W. Knight and R. Salter, *Tetrahedron Lett.*, 1999, **40**, 5915–5918.
41 I. Komaromi and J. M. J. Tronchet, *J. Phys. Chem. A*, 1997, **101**, 3554–3560.
42 S. Mizukami, *Tetrahedron*, 1960, **11**, 89–95.
43 K. Kotera, Y. Hamada and R. Nakane, *Tetrahedron*, 1968, **24**, 759–770 and references therein.
44 R. D. Harken, C. P. Christensen and W. C. Wildman, *J. Org. Chem.*, 1976, **41**, 2450–2454.
45 H. A. Hageman, *Org. React.*, 1953, **7**, 198–262.
46 G. E. Keck and R. R. Webb, *J. Am. Chem. Soc.*, 1981, **103**, 3173–3177.
47 O. Hoshino, M. Ishizaki, K. Kamei, M. Taguchi, T. Nagao, K. Iwaoka, S. Sawaki, B. Umezawa and Y. Iitaka, *Chem. Lett.*, 1991, 1365–1368.
48 H. U. Reissig and H. Lorey, *Liebigs Ann. Chem.*, 1986, 1914.
49 M. G. Banwell, C. J. M. Cowden and R. W. Gable, *J. Chem. Soc., Perkin Trans. 1*, 1994, 3515.
50 M. G. Banwell, B. D. Bissett, S. Busato, C. J. Cowden, D. C. R. Hockless, J. W. Holman, R. W. Read and A. W. Wu, *J. Chem. Soc., Chem. Commun.*, 1995, 2551–2553.
51 J. D. Hobson and J. G. McCluskey, *J. Chem. Soc. C*, 1967, 2015–2017.
52 J. Campbell, *J. Org. Chem.*, 1957, **22**, 1259–1260.
53 R. A. Olofson, J. T. Martz, J. P. Senet, M. Piteau and T. Malfroot, *J. Org. Chem.*, 1984, **49**, 2081–2082.
54 H. Normant, T. Cuvigny and P. Savignac, *Synthesis*, 1975, 805.
55 G. Gardillo, M. Orena, G. Porzi and S. Sandri, *Synthesis*, 1981, 793.
56 G. Gardillo, M. Orena and S. Sandri , *Tetrahedron Lett.*, 1976, 3985.
57 V. Franzen and S. Otto, *Chem. Ber.*, 1961, **94**, 1360.
58 T. T. Tidwell, *Synthesis*, 1990, **1990**, 857–870.
59 R. K. Boeckman, P. Shao and J. J. Mullins, *Org. Synth.*, 2004, **Coll. Vol. 10**, 696.
60 H. Pinnick, W. E. Childers and B. Bal, *Tetrahedron*, 1981, **37**, 2091.
61 M. Fetizon, *J. Org. Chem.*, 1971, **36**, 1339–1341.
62 L. E. Overman, C. Y. Hong and N. Kado, *J. Am. Chem. Soc.*, 1993, **115**, 11028–11029.
63 W. L. E. Armarego, and C. L. L. Chai, *Purification of Laboratory Chemicals*, Butterworth-Heinmann, New York, 5th Edition edn, 2003.
64 L. Zetta, G. Gatti and C. Fuganti, *J. Chem. Soc., Perkin Trans. 2*, 1973, 1180–1184.
65 S. Kobayashi, H. Ishikawa, E. Sasakawa, M. Kihara, T. Shingu and A. Kato, *Chem. Pharm. Bull.*, 1980, **28**, 1827–1831.
66 J. Schreiber, H. Maag, N. Hashimoto and A. Eschenmoser, *Angew. Chem., Int. Ed. Engl.*, 1971, **10**, 330–331.

