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Total Synthesis of the Lycorenine-Type Amaryllidaceae Alkaloid (±)-Clivonine via a Biomimetic Ring-Switch from a Lycorine-Type Progenitor

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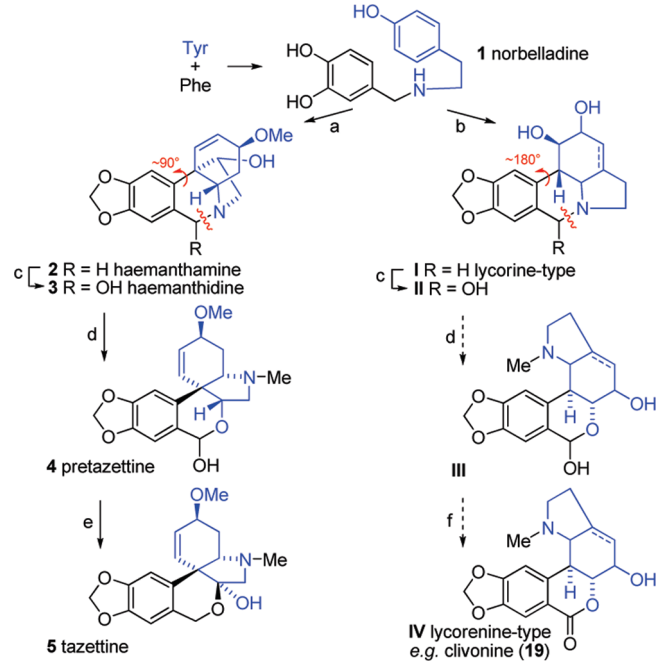
Abstract: A fully diastereoselective total synthesis of the lycorenine-type Amaryllidaceae alkaloid (±)-clivonine (**19**) is reported via a route that employs for the first time a biomimetic ring-switch from a lycorine-type progenitor, thereby corroborating experimentally the biogenetic hypothesis first expounded for these compounds by Barton in 1960.

Introduction

The Amaryllidaceae alkaloids are a large class of naturally occurring bases isolated from herbaceous perennials such as daffodils that can mostly be classified as belonging to one of eight skeletally distinct subclasses.[1] All these alkaloids derive from a common bisphenol biosynthetic precursor, norbelladine (**1**, itself derived from Phe and Tyr).[2] This biogenetic scheme was first enunciated by Barton in 1957.[3] He used the Amaryllidaceae alkaloids to illustrate his thesis that intramolecular phenolic oxidative coupling constituted a critical diversifying step in alkaloid biosynthesis, an idea that proved correct and revolutionized our understanding of alkaloid biogenesis.[2] Initially, Barton was unable to account for the tazettine[4] and lycorenine subclasses within this regime, proposing that these compounds were possibly derived from intermolecular phenolic coupling,[3] but in 1960 he revised his proposal to encompass their formation by rearrangement of haemeanthamine (**2**) and lycorine-type (**I**) progenitors, respectively.[5] Interconversion was proposed to involve benzylic oxidation (→ lactamols **3** and **II**) and then ring-opening/bond rotation/ring closure/*N*-methylation (→ lactols **4** and **III**), a process we will refer to as "ring-switching". An intramolecular crossed-Cannizzaro rearrangement (during isolation)[6,7c] accounts for the conversion of pretazettine (**4**) to tazettine (**5**), whereas lactol **III** to lactone **IV** oxidation occurs in the lycorenine series (Scheme 1).

Wildman subsequently corroborated these hypotheses by tritium feeding experiments in *Sprekelia formosissima* for

Scheme 1. Outline Biosynthesis of Tazettine and Lycorenine-Type Alkaloids from Norbelladine (**1**) via "Ring-Switching" [a]



[a] Precise structures and non-essential stereochemistry are omitted from **I**–**IV**. (a) *p,p*-Phenolic coupling; (b) *o,p*-phenolic coupling; (c) benzylic oxidation; (d) ring-switching (including *N*-methylation); (e) Cannizzaro redox process (during isolation); (f) lactol oxidation.

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[†] Deceased March 15, 1996.

(1) (a) Jin, Z. *Nat. Prod. Rep.* **2009**, *26*, 363–381, and previous reviews in this series. (b) Hoshino, O. *The Alkaloids* **1998**, *51*, 323–424. (c) Martin, S. F. *The Alkaloids* **1987**, *30*, 251–376.
(2) Herbert, R. B. *The Biosynthesis of Secondary Metabolites*, 2nd ed.; Springer: Berlin, 1989.
(3) Barton, D. R. H. *Festshrift Arthur Stoll*; Birkhauser: Basel, Switzerland, 1957; pp126−129.
(4) In 1957, tazettine was thought to be a natural product. Later, Wildman showed it to be an artifact of isolation during which an intramolecular crossed-Cannizzaro rearrangement takes place; pretazettine is the natural product[6,7c]
(5) (a) Barton, D. R. H. *Welch Foundation J.* **1960**, 165–180. (b) Barton, D. R. H. *Proc. Chem. Soc.* **1963**, 293–298. (c) Battersby, A. R. *Proc. Chem. Soc.* **1963**, 189–200.

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tazettine (**5**)[8] and in *Narcissus* 'King Alfred' for lycorenine.[9] Moreover, Wildman developed a biomimetic protocol for the synthesis of pretazettine (**4**) from haemeanthidine (**3**)[6] which has been employed in all but two[10] subsequent total syntheses of tazettine[7] and pretazettine.[11] However, Wildman was unable to develop a corresponding protocol for biomimetic conversion of lycorine to lycorenine-type ring systems (**I** → **IV**), noting that this conversion requires a ~180° rotation and minimal relief of strain, as compared to a ~90° rotation accompanied by significant relief of strain in the haemeanthidine/pretazettine series (**3** → **4**).[6,7c,9] Consequently, although Mizukami and Kotera have developed a multistep, nonbiomimetic synthetic sequence for this type of interconversion based on the von Braun reaction,[12] Barton's original hypothesis remains synthetically unverified. Herein we describe a concise, fully diastereoselective total synthesis of the lycorenine-type Amaryllidaceae alkaloid (±)-clivonine (**19**) from a lycorine-type progenitor **17** in which this key transformation has finally been accomplished.

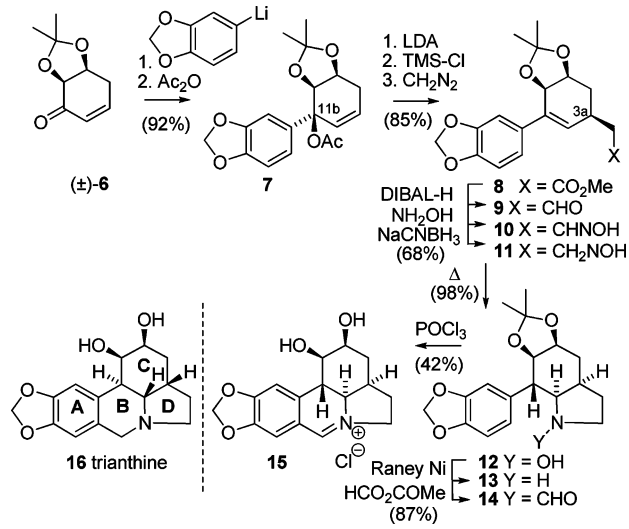
Results and Discussion

Clivonine (**19**) was isolated and characterized from *Clivia miniata* Regel in 1956 by Wildman,[13] and its relative and absolute stereochemistry was established by Jeffs et al. in 1971.[14,15] To date, the only synthesis of (±)-clivonine has been that reported by Irie in 1973 (17 steps, 0.43% overall yield from piperonal).[16]

The synthesis of (±)-clivonine progenitor **15** parallels our previous synthesis of (+)-trianthine (**16**), employing a *retro*-Cope elimination[17] (**11** → **12**) as the key step (Scheme 2).[18]

Although trianthine (**16**) and clivonine progenitor **15** both have *trans* B−C/*cis* C−D ring-junctions, they are diastereomeric with respect to the ring C *cis*-diol motif. Consequently, following 1,2-addition of aryllithium reagent to the convex face of bicyclic enone (±)-**6**[19,20] and trapping as acetate **7** (92% yield), a one-pot Ireland−Claisen rearrangement/CH_2N_2 esterification was employed to relay the stereochemistry at C11b to C3a with *retention* of configuration (→ **8**, 85% yield; cf. the vinyl cuprate S_N2' displacement with *inversion* of configuration employed for trianthine).[18a] Ester to aldehyde reduction (DIBAL-H) and then oximation ($NH_2OH \cdot HCl$, 82% yield, 2 steps) and oxime reduction ($NaCNBH_3$) then afforded retro-Cope elimination substrate **11** (83% yield). Hydroxylamine **11** cyclized smoothly upon heating as a 0.014 M solution in degassed toluene at 80 °C for 17 h to provide *N*-hydroxyhydrindole **12** as a single stereoisomer in 98% yield.[18a] Hydrogenolysis of the N−O bond (Raney-Ni, 94% yield), *N*-formylation (HCO_2COMe, 93% yield), and then Bischler−Napieralski ring B closure with concomitant acetonide deprotection ($POCl_3$) gave water-soluble iminium salt **15** after purification by ion-exchange and then C18 reverse-phase solid-phase extraction (SPE) (42% yield).

Scheme 2. Synthesis of Clivonine Progenitor **15**



Prior studies in which we had been unable to obtain lactamol **17** cleanly, via lactam half-reduction ($LiEtBH_3$) or via Polonovski reactions from the amine-*N*-oxide (Ac_2O or TFAA), had taught us that lactamol **17** was extremely sensitive to Cannizzaro disproportionation to give a 1:1 mixture of the corresponding amine and lactam, particularly under basic conditions. Attempts to transform iminium salt **15** into the corresponding *N*-methyl aldehyde according to a procedure developed by Rozwadowska for hydrastinine using MeI in MeOH,[21,22] and into lactamol **17** according to procedures developed by Dostál for sanguinarine using NaOD in d_3-MeCN/D_2O)[23] or Na_2CO_3/D_2O,[24] also induced substantial disproportionation. However, treatment of a solution of iminium salt **15** in d_6-DMSO/D_2O (5:1 v/v) with

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(19) Prepared by a telescoped variant of the method described by Hudlicky, T.; Fan, R. L.; Tsunoda, T.; Luna, H.; Andersen, C.; Price, J. D. *Isr. J. Chem.* **1991**, *31*, 229–238. Ramesh, K.; Wolfe, M. S.; Lee, Y.; Velde, D. V.; Borchardt, R. T. *J. Org. Chem.* **1992**, *57*, 5861–5868. See Supporting Information.
(20) Enone **6** can also be prepared in enantiomerically pure form [(5*S*, 6*S*)-(+)-**6**] via *Pseudomonas putida* microbial oxidation of chlorobenzene, see: (a) Spivey, A. C.; Giró Mañas, C.; Mann, I. *Chem. Commun.* **2005**, 4426–4428. (b) Reference 18a.
(21) Rozwadowska, M. D. *Bull. Acad. Pol. Sci., Sci. Chim.* **1971**, *19*, 673–679.
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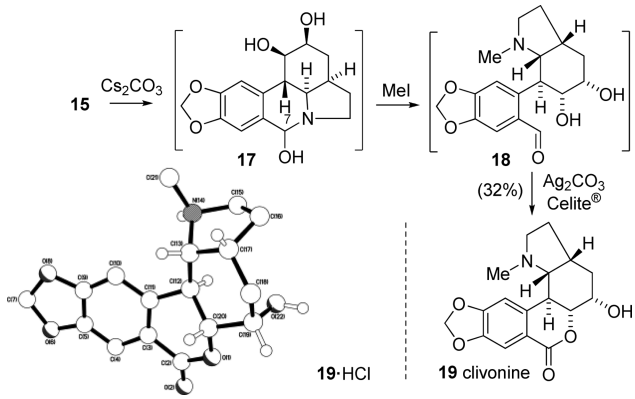
Scheme 3. Biomimetic Ring-Switch of Lycorine-Type Progenitor **17** into Clivonine (**19**) and the Molecular Structure of **19**·HCl (X-ray)



a solution of Cs_2CO_3 in D_2O (0.77 M, 1.3 equiv) reproducibly gave clean conversion to a single, unassigned epimer of lactamol **17** in ~5 min, as evidenced by ^{1}H NMR spectroscopy (**15** iminium methine, s at δ ~9.07 ppm → **17** lactamol methine, s at δ ~4.92 ppm) (Scheme 3).

Next, we explored *N*-methylation. Wildman[6] described two protocols for conversion of haemeanthidine (**3**) to pretazettine (**4**): *N*-methiodide salt formation (MeI in MeOH) and then careful basification of an aqueous acidic solution of this salt with K_2CO_3 and extraction into $CHCl_3$ was the method adopted (with modifications)[7,11] in subsequent syntheses, but Eschweiler−Clarke reductive methylation (HCO_2H/H_2CO) and then basification and extraction was reportedly equally efficient. In our hands, the Eschweiler−Clarke method returned only the corresponding amine when applied to lactamol **17**, whereas treatment with methanolic MeI gave a complex mixture of products containing methyl ether/acetal signals by ^{1}H NMR spectroscopy. Extensive experimentation established that addition of just 1 equiv of a dilute solution of MeI in d_6-DMSO to freshly prepared solution of lactamol **17**/Cs_2CO_3 (in d_6-DMSO/D_2O) afforded a mixture of species, of which the major component was tentatively assigned as *N*-methyl aldehyde **18** by ^{1}H NMR spectroscopy (aldehyde proton, s at δ ~9.67 ppm; *N*-Me, s at δ ~2.35 ppm). Further optimization was confounded by the formation of what appeared to be quaternized salts, which were also formed to a greater extent when employing alternative methylating agents (e.g., Me_2SO_4, MeOTf). However, freeze-drying of this mixture, suspension of the residue in toluene, and treatment with Fetizon's reagent reproducibly afforded (±)-clivonine (**19**) in 32% yield after chromatography from iminium salt **15** (12 steps, 6.1% overall yield from enone **6**). All spectroscopic data matched those reported for the natural material,[14,25] and its molecular structure was confirmed by a single-crystal X-ray structure determination on its hydrochloride (Scheme 3).

Conclusion

In conclusion, we have reported the total synthesis of the lycorenine-type Amaryllidaceae alkaloid (±)-clivonine (**19**) via a route that employs, for the first time, a biomimetic ring-switch from a lycorine-type progenitor, thereby finally corroborating experimentally the biogenetic hypothesis first expounded for these compounds by Barton 50 years ago.

We are currently exploring this approach for the synthesis of hippeastrine from lycorine[1] and investigating whether there is a causal relationship between ring-switching and the life-cycle of the herbaceous perennials in which these alkaloids are found.[26]

Acknowledgment. We gratefully acknowledge the Swiss National Science Foundation, the EPSRC, and GSK for financial support for this work.

Supporting Information Available: Full experimental details, NMR spectra, and details of the crystallographic analysis, including CIF file, of structure **19**·HCl. This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) The isolated yields of these alkaloid constituents show strong seasonal dependence (e.g., ref 8).