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 tazettine4 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 (→ lactams 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”6,7c as an intramolecular crossed-Cannizzaro rearrangement (during isolation); (f) lactol oxidation.

Scheme 1. Outline Biosynthesis of Tazettine and Lycorenine-Type Alkaloids from Norbelladine (1) via “Ring-Switching”.

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.

Wildman subsequently corroborated these hypotheses by tritium feeding experiments in Sprekelia formosissima for...
tazettine (5) and in Narcissus ‘King Alfred’ for lycorine. Moreover, Wildman developed a biomimetic protocol for the synthesis of pretazettine (4) from haemannthidine (3) which has been employed in all but two subsequent total syntheses of tazettine and pretazettine. However, Wildman was unable to develop a corresponding protocol for biomimetic conversion of lycorine to lycorine-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 haemannthidine/pretazettine series (3 → 4). Consequently, although Mizukami and Koteru have developed a multistep, nonbiomimetic synthetic sequence for this type of interconversion based on the von Braun reaction, Barton’s original hypothesis remains synthetically unverified. Herein we describe a concise, fully diastereoselective total synthesis of the lycorine-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 miniflora Regel in 1956 by Wildman, and its relative and absolute stereochemistry was established by Jeffs et al. in 1971. To date, the only synthesis of (±)-clivonine has been reported by Irie in 1973 (17 steps, 0.43% overall yield from piperonal). Nevertheless, the synthesis of clivonine progenitor 15 parallels our previous synthesis of (+)-trianthine (16), employing a retro-Cope elimination (11 → 12) as the key step (Scheme 2).

Although trianthine (16) and clivonine progenitor 15 both have trans B–ClCt C–D ring-junctions, they are diastereomic 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 and trapping as acetate (79% yield), the diastereomers were separable by flash column chromatography and characterized as follows:

- Clivonine progenitor 15 (79% yield), a one-pot Ireland–Claisen rearrangement/CH2N2 esterification was employed to relay the stereochemistry at C11b to C3a with retention of configuration (~85% yield; cf. the vinyl cuprate S,2′ displacement with inversion of configuration employed for trianthine). Ester to aldehyde reduction (DIBAL-H) and then oxime reduction (NaCNBH3) to afford 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.
- Hydrogenolysis of the NO–O bond (Raney-Ni, 94% yield), and formation (HCO2O-Me3, 93% yield), and then Bischler–Napieralski ring closure catalyzed by concomitant acetamide protection (POC1) gave water-soluble iminium salt 15 after purification by ion-exchange and then C18 reverse-phase solid-phase extraction (SPE) (42% yield).

Prior studies in which we had been unable to obtain lactamol 17 cleanly, via lactam half-reduction (LiEtBH3) or via Polonovski reactions from the amine-N-oxide (Ac2O 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, and into lactamol 17 according to procedures developed by Dostáš for sanguinarine using NaOD in d5-MeCN/D2O or Na2CO3/D2O, also induced substantial disproportionation. However, treatment of a solution of iminium salt 15 in d5-DMSO/D2O (5:1 v/v) with

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a solution of Cs₂CO₃ in D₂O (0.77 M, 1.3 equiv) reproducibly gave clean conversion to a single, unassigned epimer of lactamol 17 in ~5 min, as evidenced by ¹H NMR spectroscopy (iminium methine, s at δ ~9.07 ppm; lactamol methine, s at δ ~4.92 ppm) (Scheme 3).

Next, we explored N-methylation. Wildman⁶ 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 K₂CO₃ and extraction into CHCl₃ was the method adopted (with modifications)⁷,¹¹ in subsequent syntheses, but Eschweiler–Clarke reductive methylation (HCO₂H/H₂CO) 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 ¹H NMR spectroscopy. Extensive experimentation established that addition of just 1 equiv of a dilute solution of MeI in d₆-DMSO to freshly prepared solution of lactamol 17/Cs₂CO₃ (in d₆-DMSO/D₂O) afforded a mixture of species, of which the major component was tentatively assigned as N-methyl aldehyde 18 by ¹H 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., Me₂SO₄, 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 lycoserine-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 lycorine⁷ 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

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**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).