Pergamon

Tetrahedron Letters 41 (2000) 127–129

TETRAHEDRON LETTERS

A biomimetic synthesis of the pyrrolizidine ring by sequential intramolecular cyclizations

Charles M. Marson,[a,*,†] Jennifer H. Pink,[a] Christopher Smith,[b] Michael B. Hursthouse [c] and K. M. Abdul Malik [c]

[a]*Department of Chemistry, University of Sheffield, Sheffield, S3 7HF, UK*
[b]*Rhône-Poulenc Rorer Ltd., Rainham Road South, Dagenham, Essex, RM10 7XS, UK*
[c]*Department of Chemistry, The University of Southampton, Highfield, Southampton, SO17 1BJ, UK*

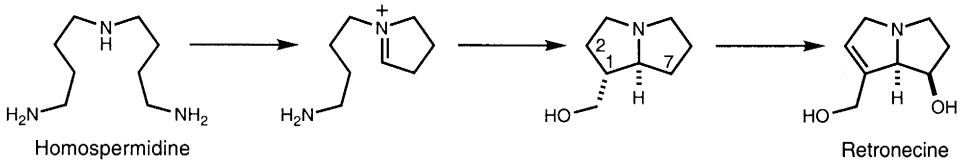
Received 10 September 1999; accepted 26 October 1999

Abstract

The pyrrolizidine ring system is generated from an acyclic amide in an acid-catalyzed cyclization in one laboratory operation.

The possibility of the direct formation of a five-membered ring via an acyliminium species[1] has been considered for some time, but seldom realized beyond a few cases.[2,3] Given the natural abundance and medicinal significance of pyrrolidine and pyrrolizidine rings,[4,5] their construction under biomimetic conditions[6] is a fundamental issue. The pyrrolizidine alkaloids are a class of compounds of central pharmacological interest, e.g. australine, a potent inhibitor of amyloglucosidase.[4b] The aza-Cope rearrangement provides an indirect route to the pyrrolizidine ring,[7] but places a substituent at C-2, normally inappropriate to the synthesis of a pyrrolizidine alkaloid.

In the biosynthetic pathway to the pyrrolizidine alkaloids such as retronecine (Scheme 1),[6] an iminium intermediate is considered crucial to the formation of both rings. The action of pea seedling oxidase and catalase upon homospermidine has been shown to effect cyclization to a substituted pyrrolizidine which

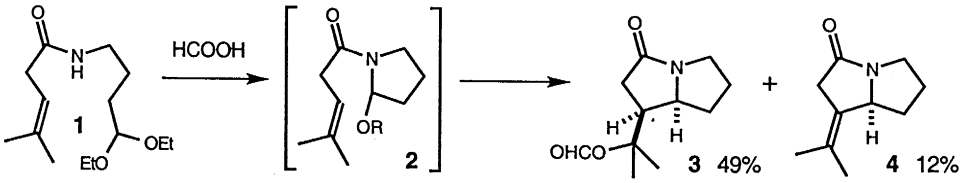


Scheme 1. Biosynthesis of retronecine

* Corresponding author.
† Current address: Department of Chemistry, University College London, Christopher Ingold Laboratories, 20 Gordon Street, London WC1H 0AJ, UK.

0040-4039/00/$ - see front matter
PII: S0040-4039(99)02031-6

after borohydride reduction afforded trachelanthamidine.[8] We sought to contrive a cationic cyclization related to those biosynthetic transformations, and here report what we believe to be the first example (Scheme 2) of a nonenzymic one-pot synthesis of the pyrrolizidine ring from an acyclic precursor, proceeding directly (i.e. without skeletal rearrangement) and with the biomimetic formalism of Scheme 1. Condensation of the acid chloride prepared from 4-methyl-3-pentenoic acid and $(COCl)_2$ (20°C, 6 h) with 4-aminobutanal diethylacetal (1.3 equiv.) under Schotten–Baumann conditions (1.3 equiv. NaOH in 7:3 water:THF) afforded the amidic acetal **1** (71%) which with 97% HCOOH (25°C, 6 h) gave **3** (49%) as prisms, mp 82–83°C and **4** (12%) as an oil, after isolation by column chromatography. Alternatively, treatment of **1** with 3.5% aq. hydrochloric acid in diethyl ether afforded a 1:1 mixture of **2** (R=H and OEt); this mixture was cyclized with 97% HCOOH (25°C, 48 h) to give **3** (45%), and **4** (11%). The pattern of reactivity is ascribed to an acyliminium species, analogous to the iminium intermediate in Scheme 1. The relative configuration of **3**, the only diastereoisomer isolated, was confirmed by X-ray crystallography on a single crystal (Fig. 1). MM2 calculations indicate that **3** is less thermodynamically stable (nonbonding interactions with 1β-substituent) by some 4 kcal mol^{-1} than its *exo*-epimer. This is of synthetic utility, since: (i) the route provides a means of access to the kinetic isomer of a substituted pyrrolizidine ring, and without having to separate diastereoisomers; and (ii) both *endo*- and *exo*-C-1 substituents are commonly encountered in pyrrolizidine alkaloids.[4] Nonbonding interactions developing between the pyrroleninium ring and the methyl group nearer to it would disfavour formation of the 1-*exo*-epimer.



Scheme 2. Sequential intramolecular cyclization affording the pyrrolizidine ring

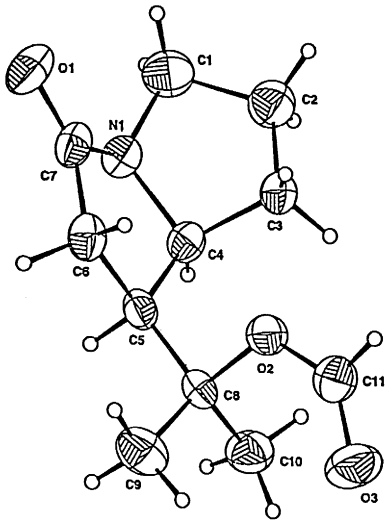


Fig. 1. ORTEP representation of **3**

Radical cyclizations to pyrrolizidine rings are known,[9] but those examples involved a preformed lactam and proceeded with moderate stereocontrol. In previous studies, the amidic carbonyl group has commonly been part of a lactam ring.[7,9] The present work shows that placement of a carbonyl group in

the chain of the second ring to be formed is consistent with both sequential cyclization and isolation of a single diastereoisomeric pyrrolizidine, also the kinetic product. Such direct cyclizations could provide succinct routes to the synthesis of a variety of pyrrolizidine alkaloids as well as mechanistic insight into conformational and stereoelectronic requirements for in vivo enzyme-mediated cyclizations.

Acknowledgements

Financial support from Rhône–Poulenc Rorer and the Engineering and Physical Sciences Research Council (CASE award to J.H.P.) is gratefully acknowledged, as is use of the EPSRC National Crystallography Service.

References

1. Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367.
2. Schoemaker, H. E.; Kruk, C.; Speckamp, W. N. *Tetrahedron Lett.* **1979**, *26*, 2437.
3. Marson, C. M.; Grabowska, U. G.; Walsgrove, T.; Eggleston, D. S.; Baures, P. W. *J. Org. Chem.* **1994**, *59*, 284.
4. (a) Robins, D. J. *Nat. Prod. Rep.* **1989**, *6*, 221; (b) Robins, D. J. *Nat. Prod. Rep.* **1990**, *7*, 377.
5. Robins, D. J. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, **1995**, *46*, pp. 1–61.
6. Herbert, R. B. *Nat. Prod. Rep.* **1993**, *10*, 576.
7. Hart, D. J.; Yang, T.-K. *J. Org. Chem.* **1985**, *50*, 235.
8. Robins, D. J. *J. Chem. Soc., Chem. Commun*. **1982**, 1289.
9. Burnett, D. A.; Choi, J.-K.; Hart, D. J.; Tsai, Y.-M. *J. Am. Chem.* Soc. **1984**, *106*, 8201.