Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 46 (2005) 1111–1113
Tetrahedron Letters

Preparation of advanced intermediates for the synthesis of both methyllycaconitine and racemulsonine via a common intermediate

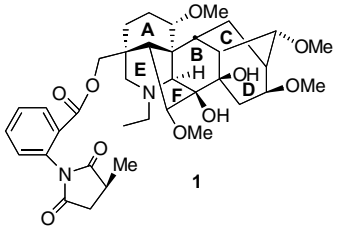
George A. Kraus* and Sarathy Kesavan

Department of Chemistry, Iowa State University, Ames, IA 50011, USA

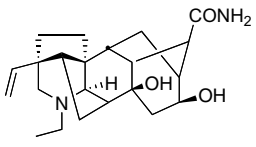
Received 29 November 2004; revised 15 December 2004; accepted 17 December 2004
Available online 11 January 2005

Abstract—Polycyclic precursors to **1** and **2** have been prepared via a common intermediate. The key steps include the intramolecular alkylation of a phenol and a selective metal–ammonia reduction.

Methyllycaconitine (**1**) is a novel hexacyclic alkaloid isolated from tall larkspur.[1] It has been shown to be a potent nicotinic acetylcholine receptor antagonist.[2] Researchers have proposed that methyllycaconitine or analogs thereof could be useful for the treatment of diseases affecting memory or for antiepileptic drug development.[3] Racemulsonine (**2**), a novel C_{20} diterpene alkaloid containing an azabicyclo[3.2.1]octane subunit, was recently isolated by Wang et al.[4]



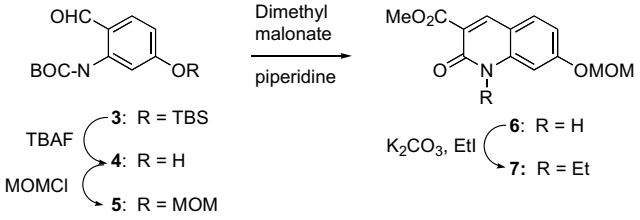
1



2

As a consequence of the biological activity and its novel structure, **1** has been the synthetic objective of several research groups. Brimble and co-workers,[5] Kraus et al.,[6] and Whiting and co-workers[7] have reported the preparation of tricyclic analogs of **1**. Analogs bearing the AE bicyclic unit and the E ring subunit have also been reported.[8] Additionally, Kraus and Dneprovskaia[9] and Blagbrough et al.[10] have reported procedures for attaching the methylsuccinimidobenzoate unit to methyllycaconitine analogs. We report herein the synthesis of a tetracyclic ABEF ring analog, the most complex subunit generated to date, by a route that is distinctly different from all previous approaches.

Our synthesis began with aldehyde **3**, readily available in three steps from 3-aminophenol.[11] Although the TBS protecting group was crucial for the regioselective installation of the carboxaldehyde, the condensation of **3** with dimethyl malonate led to a mixture of products. Therefore, the TBS group was replaced with a methoxymethyl protecting group (TBAF; $MeOCH_2Cl$, $i\text{-}Pr_2NEt$). Condensation of aldehyde **5** with dimethyl malonate and piperidine in boiling ethanol provided a lactam, presumably via a diester that cyclized to form the lactam before BOC deprotection. Selective N-alkylation using anhydrous potassium carbonate and ethyl iodide produced lactam **7** in 73% overall yield from **5**.

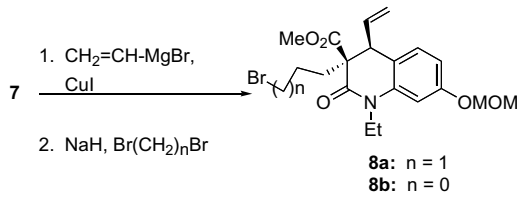


Conjugate addition with vinyl magnesium bromide and copper iodide/dimethyl sulfide and alkylation with 1,3-dibromopropane furnished **8a** in 51% yield.[12] The *cis*-relationship of the vinyl and ester groups were determined by 2D NOESY NMR. Reaction of **7** with vinyl

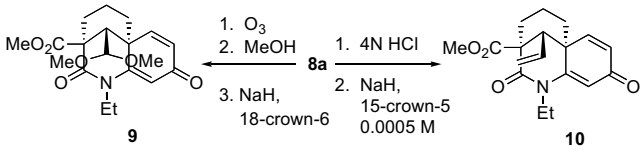
* Corresponding author. Tel.: +1 5152947794; fax: +1 5152940105; e-mail: gakraus@iastate.edu

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.12.092

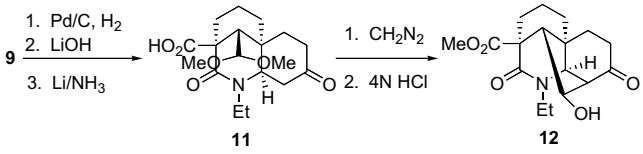
magnesium bromide/copper iodide followed by alkylation with 1,2-dibromoethane provided **8b** in 68% yield.



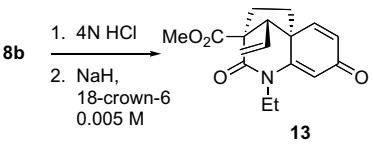
Oxidative cleavage of the alkene in **8a** and subsequent acetal formation/removal of the MOM protecting group (PTSA, MeOH, 25 °C) gave a phenol that underwent intramolecular cyclization with sodium hydride and 18-crown-6 in THF at 75 °C to generate dienone **9** in 72% isolated yield.[13] Interestingly, the phenol produced from **8a** by removing the MOM protecting group underwent cyclization to **10** in only 43% yield and required high dilution conditions (NaH, 15-crown-5, 0.0005 M in THF).



Hydrogenation of **9** followed by hydrolysis of the ester with lithium hydroxide in THF–methanol and metal–ammonia reduction (5 equiv Li, 2 equiv *t*-BuOH in NH_3/THF) of the dienone gave diketo acid **11** as a 3:1 mixture of diastereomers with the isomer shown predominating in 47% yield. Esterification and acid catalyzed (4 N HCl) acetal hydrolysis/aldol condensation afforded ketol **12** in 58% yield. The structure of the methyl ester of **11** was determined by X-ray crystallography.[14]



The key intermediate for the synthesis of **2** was generated from **8b** by hydrolysis of the phenol protecting group with 4 N HCl followed by cyclization to **13** with sodium hydride in 82% yield. In this case, the cyclization could be conducted in boiling THF at lower dilution than for the phenol derived from **8a**.

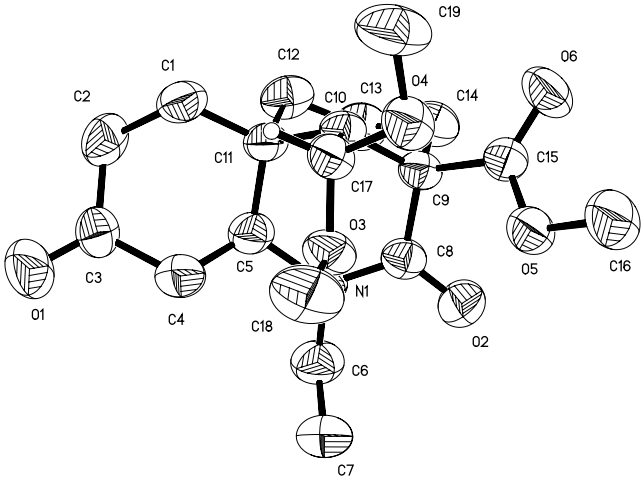


82%

Our B-BE-ABE ring building strategy allows for considerable flexibility in the introduction of the A ring. Compound **7** is a common intermediate for the preparation of both **12**[15] and **13**. The stereochemistry of compound **12** should facilitate the stereoselective appendage of the remaining two rings.

References and notes

1. Manske, R. H. F. *Can. J. Res.* **1938**, *16B*, 57–60; Schramm, L. C. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; J. Wiley and Sons: New York, 1984; Vol. 2, pp 205–462; Yunusov, M. S. *Nat. Prod. Rep.* **1993**, *10*, 471–486.
2. Alkondon, M.; Pereira, E.; Wonnacott, S. *Mol. Pharmacol.* **1992**, *41*, 802–808.
3. Loscher, W.; Potschka, H.; Wlaz, P.; Danysz, W.; Parsons, C. G. *Eur. J. Pharmacol.* **2003**, *466*, 99–111.
4. Wang, F. P.; Peng, C. S.; Yu, K.-B. *Tetrahedron* **2000**, *56*, 7443–7446.
5. Barker, D.; Brimble, M. A.; McLeod, M. D.; Savage, G. P. *Org. Biomol. Chem.* **2004**, *2*, 1659–1669; Barker, D.; McLeod, M. D.; Brimble, M. A.; Savage, G. P. *Tetrahedron Lett.* **2002**, *43*, 6019–6022.
6. Kraus, G. A.; Andersh, B.; Su, Q.; Shi, J. *Tetrahedron Lett.* **1993**, *34*, 1741–1744.
7. Baillie, L. C.; Bearder, J. R.; Li, W.-S.; Sherringham, J. A.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 4047–4056, and references therein.
8. Ismail, K. A.; Bergmeier, S. C. *Eur. J. Med. Chem.* **2002**, *37*, 469–474; Bergmeier, S. C.; Lapinsky, D. J.; Free, R. B.; McKay, D. B. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2263–2266; Grangier, G.; Trigg, W. J.; Lewis, T.; Rowan, M. G.; Potter, B. V. L.; Blagbrough, I. S. *Tetrahedron Lett.* **1998**, *39*, 889–892; Davies, A. R. L.; Hardick, D. J.; Blagbrough, I. S.; Potter, B. V. L.; Wolstenholme, A. J.; Wonnacott, S. *Biochem. Soc. Trans.* **1997**, *25*, 545S; Callis, D. J.; Thomas, N. F.; Pearson, D. P. J.; Potter, B. V. L. *J. Org. Chem.* **1996**, *61*, 4634–4640; Coates, P. A.; Blagbrough, I. S.; Rowan, M. G.; Pearson, D. P. J.; Lewis, T.; Potter, B. V. L. *J. Pharm. Pharmacol.* **1996**, *48*, 210–213.
9. Kraus, G. A.; Dneprovskaia, E. *Tetrahedron Lett.* **1998**, *39*, 2451–2454.
10. Blagbrough, I. S.; Coates, P. A.; Hardick, D. J.; Lewis, T.; Rowan, M. G.; Wonacott, S.; Potter, B. V. L. *Tetrahedron Lett.* **1994**, *35*, 8705–8708.
11. Kondo, Y.; Kojima, S.; Sakamoto, T. *J. Org. Chem.* **1997**, *62*, 6507–6511.
12. Dowd, P.; Choi, S. C. *Tetrahedron* **1989**, *45*, 77–90.
13. Murphy, W. S.; Wattanasin, S. *Chem. Soc. Rev.* **1983**, *12*, 213–250.
14. X-ray structure of the methyl ester of **11**:



15. *Spectral data for* **12**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.83 (1H, dd, J = 7.2 Hz, 4.0 Hz), 3.90–4.00 (1H, m), 3.80 (3H, s), 3.39 (1H, d, J = 2.8 Hz), 3.08 (1H, d, J = 7.6 Hz), 2.70–2.84 (2H, m), 2.42 (1H, d, J = 4 Hz), 2.27–2.33 (2H, m), 2.17 (1H, d, J = 2.8 Hz), 1.90–2.04 (2H, m), 1.7–1.9 (4H, m), 1.2 (3H, t, J = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.6, 172.7, 166.6, 75.2, 68.7, 62.2, 57.4, 55.6, 53.0, 41.7, 41.4, 35.9, 34.9, 33.8, 33.4, 20.1, 12.8; HRMS *m/z* for $C_{17}H_{23}O_5N$ calcd 321.1576, found 321.1581.