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Synthesis of Novel Unsaturated AE-Bicyclic Analogues of Lycoctonine, Inuline and Methyllycaconitine: with olefinic J = 13.5 Hz, but still *cis*

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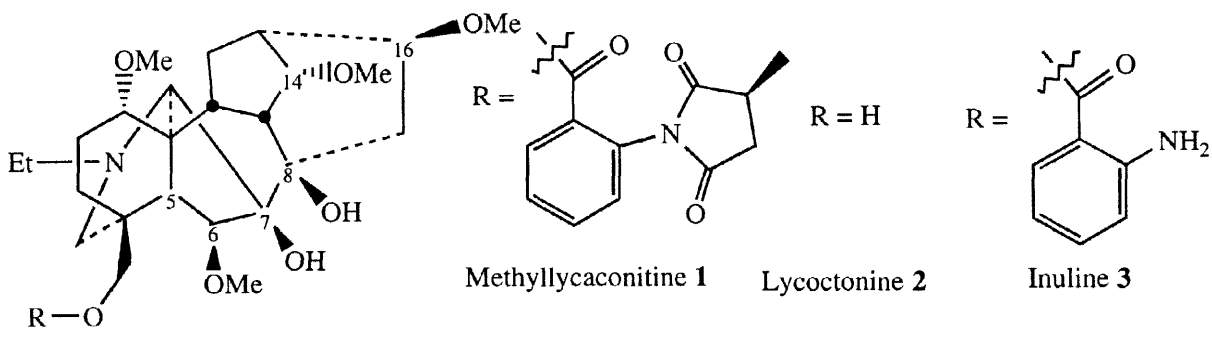
Abstract: We have synthesised unsaturated AE-bicyclic analogues of lycoctonine class norditerpenoid alkaloids by acetylide addition and regiochemically controlled reductions. Reduction of a substituted propargylic alcohol with hydrogen gas (poisoned Pd catalyst) gave an alkene with vicinal J = 13.5 Hz. This was shown to be of Z-geometry by unambiguously preparing the corresponding E-alkene (J = 15.4 Hz).

Methyllycaconitine (MLA) **1** is a hexacyclic norditerpenoid alkaloid of the lycoctonine class.[1-3] MLA **1** is the 2-(*S*)-methylsuccinimidobenzoate ester of neopentyl-like alcohol lycoctonine **2**.[4-6] MLA **1** and closely related alkaloids occur in many *Delphinium* species as well as in *Consolida ambigua* and *Inula royaleana*.[6,7] *Delphinium* species are toxic to mammals causing many (economically significant) cattle deaths each year across North American ranges.[8] Furthermore, these norditerpenoid alkaloids are toxic to a wide variety of insect species, and this potentially important insecticidal property of MLA **1** has been investigated by Jennings and co-workers.[9,10] We have used MLA **1** as a selective ligand for molecular studies of neuronal nAChR and for the rational design of insecticides acting at nicotine binding sites.[1-3] We are continuing our structure-activity relationship (SAR) studies of these norditerpenoid alkaloids by synthesising novel C5-substituted unsaturated AE-bicyclic analogues of MLA **1**.[3] Other workers have recently contributed significantly to this research area, achieving controlled syntheses of several of the carbocycles found in the alkaloid skeleton.[11-15]



Methyllycaconitine **1** Lycoctonine **2** Inuline **3**

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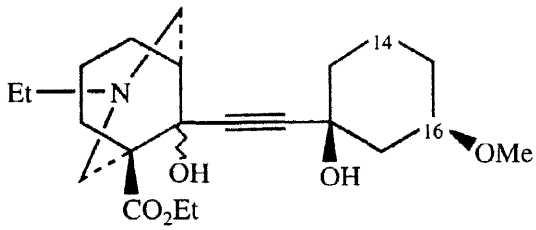
In the preceding *Letter*,[3] we reported a route to C5-substituted AE-bicyclic analogues of lycoctonine **2**, inuline **3**, and MLA **1**. Herein, we describe regio- and stereochemically selective reductions of alkyne **4**[3] to unsaturated analogues of lycoctonine **2**, and their subsequent conversion into the corresponding analogues of inuline **3** and MLA **1**. To synthesise *Z*-alkene **5**, alkyne **4** (as a co-eluting mixture of four diastereoisomers with methoxy at C14*R* or C16*R*, both are required in MLA **1**, but only one pair has been shown for clarity)[3] was reduced with hydrogen gas in the presence of a poisoned palladium catalyst. Initially, we employed Lindlar's catalyst (Pd on $CaCO_3$ poisoned with lead, EtOH), but this gave a relatively poor yield (25 %).[16,17] When we used 10 % Pd/C poisoned with 10 % pyridine in EtOH, a higher yield was obtained (50 %).[18] Both reactions were stirred at 20 °C for 72 h (little reaction was detected after 24 h) under an atmosphere of hydrogen. The resulting colourless viscous oil was purified over flash silica gel (1:19 MeOH-DCM) and yielded two homogeneous fractions **5a** and **5b** (each a mixture of two co-eluting diastereoisomers).



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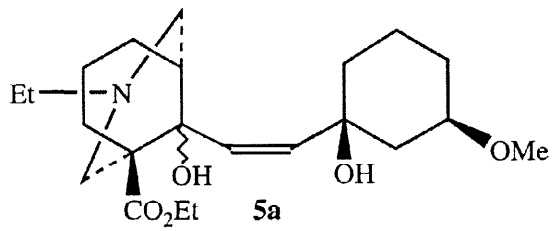
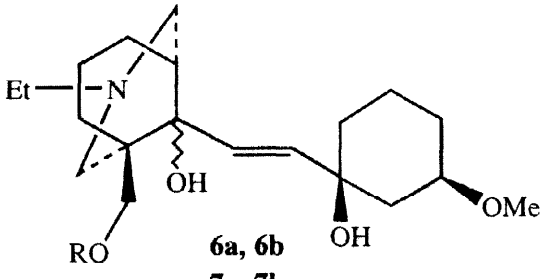


5a

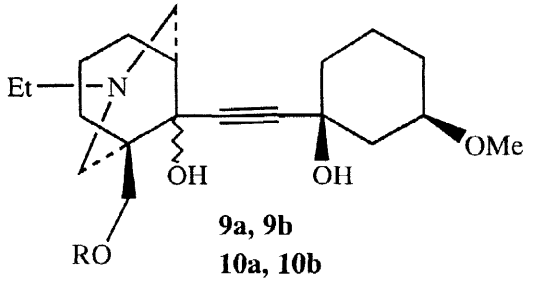
5b

Spectroscopic analysis (^{1}H NMR) of each fraction showed that alkene formation had occurred, but the vicinal (alkenyl) coupling constant was higher (J = 13.5 and 13.6 Hz) than is normally predicted for a *Z*-alkene (0-12 Hz, typically 6-8 Hz).[19-22] As 13.5 Hz is above the typical higher limit for a *Z*-alkene and within the limits (12-18 Hz, typically 14-16 Hz) for an *E*-alkene, there was some doubt about the geometry of this carbon-carbon double bond. Furthermore, the long reaction time (with the alkene in contact with the catalyst) could have allowed isomerism to the *E*-alkene, and there is literature precedent for Lindlar's catalyst mediating the formation of an *E*-alkene.[23] Thus, there was some ambiguity with respect to our assignment of the geometry of this double bond. Therefore, in order to assign this geometry and to prepare (unambiguously) *E*-alkenes for our SAR programme, we took advantage of the ready reduction of propargylic alcohols with $LiAlH_4$ (Et_2O, 18 h, 20 °C) to afford the desired *E*-alkenes,[17,24] allylic alcohols **6a** and **6b** which were purified over flash silica gel (3:17 MeOH-DCM). The key vicinal coupling constants (J = 15.4 and 15.6 Hz) are indicative of *trans*-geometry. That the ester functional group was reduced before the alkyne was also confirmed by the isolation of alkyntriols **12a** and **12b** (combined yield 82 %, ~1:1:1:1). We then converted separated diastereoisomeric esters **5a** and **5b** into the corresponding neopentyl-like alcohols, triols **12a** and **12b** ($LiAlH_4$, THF, 16 h, 20 °C) which were purified over flash silica gel (1:19 MeOH-DCM, ~80 % each diastereoisomeric pair).

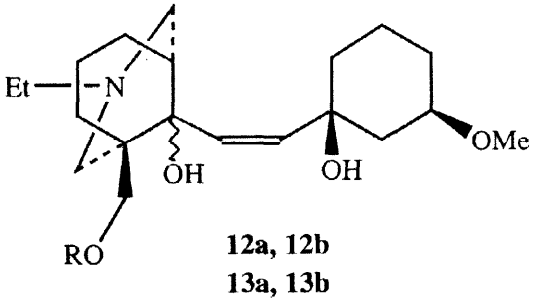
Triols **12a and 12b** are directly comparable with triols **6a** and **6b**. For the former, vicinal coupling constants, although high (J = 13.5 and 13.6 Hz, comparable with **5a** and **5b**), are indicative of *cis*-geometry with respect to those displayed by the latter (J = 15.4 and 15.6 Hz) and indicative of *trans*-geometry when taken together with the respective synthetic routes. As J depends strongly upon the electronegativity of substituents (decreasing with increasing electronegativity)[19-22] and upon the C.C.H angles of coupled nuclei, and given that J_{trans} is always greater than J_{cis},[19-22] then there must be significant angle strain in **5a** and **5b** and in **12a** and **12b** in comparison with typical *cis*-alkenes. We conclude that J = 13.0-13.6 Hz is within the acceptable range for vicinal coupling across a *cis*-alkene when substituted with two quaternary carbons (tertiary alcohol functional groups). Weyerstahl and co-workers have reported J = 12.5 Hz for certain *cis*-alkenes derived from C_{13}-degraded carotenoids (alkynol-isophorones) in their studies on fragrances.[25,26]



6a, 6b
7a, 7b
8a, 8b



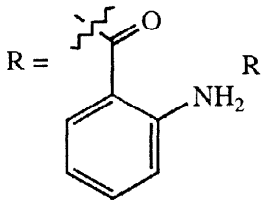
9a, 9b
10a, 10b
11a, 11b



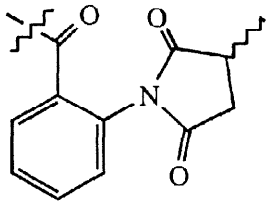
12a, 12b
13a, 13b
14a, 14b

R = H

6, 9, 12



7, 10, 13



8, 11, 14

All six of the above purified neopentyl-like alcohols (**6a**, **6b**, **9a**, **9b**, **12a** and **12b**), analogues of lycoctonine **2**, were converted into anthranilate esters (**7a**, **7b**, **10a**, **10b**, **13a** and **13b** respectively), analogues of inuline **3**, by reaction with isatoic anhydride using 4-dimethylaminopyridine as catalyst (DMF, 16 h, 70 °C, ~50-85 %).[27] Reaction of anthranilate esters (**7a**, **7b**, **10a**, **10b**, **13a** and **13b**) with methylsuccinic anhydride initially yielded half acid amides which were then cyclised to form 2-methylsuccinimidobenzoate esters (**8a**, **8b**, **11a**, **11b**, **14a** and **14b** respectively) *in situ* with 1,1'-carbonyldiimidazole as a dehydrating agent (DCM, 48 h, 20 °C), analogues of MLA **1**.[27] These compounds were purified by flash chromatography over silica gel (1:19 MeOH-DCM) and isolated as colourless viscous oils (~80 %).

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REFERENCES

1. Coates, P. A.; Blagbrough, I. S.; Rowan, M. G.; Potter, B. V. L.; Pearson, D. P. J.; Lewis, T. *Tetrahedron Lett.* **1994**, *35*, 8709-8712.
2. Hardick, D. J.; Blagbrough, I. S.; Cooper, G.; Potter, B. V. L.; Critchley, T.; Wonnacott, S. *J. Med. Chem.* **1996**, *39*, 4860-4866.
3. Grangier, G.; Trigg, W. J.; Lewis, T.; Rowan, M. G.; Potter, B. V. L.; Blagbrough, I. S. *Tetrahedron Lett.* **1998**, *39*, 889-892.
4. Manske, R. H. *Can. J. Research* **1938**, *16B*, 57-60.
5. Goodson, J. A. *J. Chem. Soc.* **1943**, 139-141.
6. Coates, P. A.; Blagbrough, I. S.; Hardick, D. J.; Rowan, M. G.; Wonnacott, S.; Potter, B. V. L. *Tetrahedron Lett.* **1994**, *35*, 8701-8704.
7. Benn, M. H.; Jacyno, J. M. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; John Wiley and Sons: New York, 1983, *1*, pp. 153-210.
8. Keeler, R. F. *Lloydia* **1975**, *38*, 56-61.
9. Jennings, K. R.; Brown, D. G.; Wright, D. P. *Experientia* **1986**, *42*, 611-613.
10. Jennings, K. R.; Brown, D. G.; Wright, D. P.; Chalmers, A. E. *ACS Symposium Series* **1987**, *356*, 274-282.
11. van Beek, G.; van der Baan, J. L.; Klumpp, G. W.; Bickelhaupt, F. *Tetrahedron* **1986**, *42*, 5111-5122.
12. van der Baan, J. L.; Barnick, J. W. F. K.; van Beek, G.; Bickelhaupt, F.; Spek, A. L. *Tetrahedron* **1992**, *48*, 2773-2784.
13. Kraus, G. A.; Andersh, B.; Su, Q.; Shi, J. *Tetrahedron Lett.* **1993**, *34*, 1741-1744.
14. Baillie, L. C.; Bearder, J. R.; Whiting, D. A. *J. Chem. Soc., Chem. Commun.* **1994**, 2487-2488; Baillie, L. C.; Bearder, J. R.; Sherringham, J. A.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2687-2688.
15. Ihara, M.; Suzuki, M.; Hirabayashi, A.; Tokunaga, Y.; Fukumoto, K. *Tetrahedron Asymmetry* **1995**, *6*, 2053-2058.
16. Labriola, R.; Ourrison, G. *Tetrahedron* **1973**, *29*, 2105-2114.
17. Walborsky, H. M.; Wüst, H. H. *J. Am. Chem. Soc.* **1982**, *104*, 5807-5808.
18. Montalbetti, C.; Savignac, M.; Bonnefis, F.; Genêt, J. P. *Tetrahedron Lett.* **1995**, *36*, 5891-5894.
19. Jackman, L. M.; Sternhell, S. *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*; Pergamon Press: Oxford, 2nd edn., 1969, pp. 300-304.
20. Abraham, R. J.; Loftus, P. *Proton and Carbon-13 NMR Spectroscopy*; Heyden: London, 1978, pp. 40-43.
21. Kemp, W. *NMR in Chemistry: A Multinuclear Introduction*; Macmillan: Basingstoke, 1986, pp. 62-64.
22. Williams, D. H.; Fleming, I. *Spectroscopic Methods in Organic Chemistry*; McGraw-Hill: Maidenhead, 4th edn., 1989, pp. 91-99.
23. Heublin, G.; Stadermann, D. *J. Prakt. Chem.* **1970**, *312*, 1121-1129.
24. Koczka, K.; Agocs, P.; Megyeri, T. *Acta Phys. Chem.* **1967**, *13*, 73-76.
25. Weyerstahl, P.; Buchmann, B.; Marschall-Weyerstahl, H. *Liebigs Ann. Chem.* **1988**, 507-523.
26. Weyerstahl, P.; Meisel T. *Liebigs Ann. Chem.* **1994**, 415-427.
27. Blagbrough, I. S.; Coates, P. A.; Hardick, D. J.; Lewis, T.; Rowan, M. G.; Wonnacott, S.; Potter, B. V. L. *Tetrahedron Lett.* **1994**, *35*, 8705-8708.