



## Synthesis of C5-Substituted AE-Bicyclic Analogues of Lycoctonine, Inuline and Methyllycaconitine

G eralaine Grangier<sup>1</sup>, William J. Trigg<sup>1</sup>, Terence Lewis<sup>2</sup>, Michael G. Rowan<sup>1</sup>, Barry V. L. Potter<sup>1</sup> and Ian S. Blagbrough<sup>1\*</sup>

<sup>1</sup>Department of Medicinal Chemistry, School of Pharmacy and Pharmacology, University of Bath, Bath BA2 7AY,

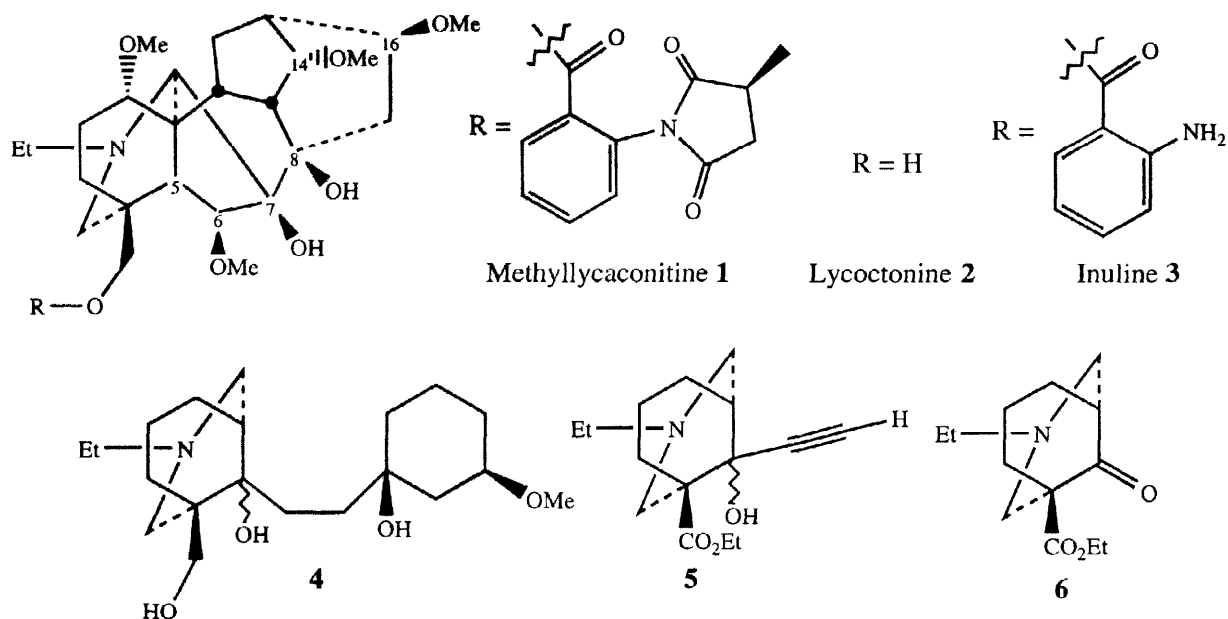
<sup>2</sup>Zeneca Agrochemicals, Jealott's Hill Research Station, Bracknell RG12 6EY, U.K.

Received 27 October 1997; accepted 14 November 1997

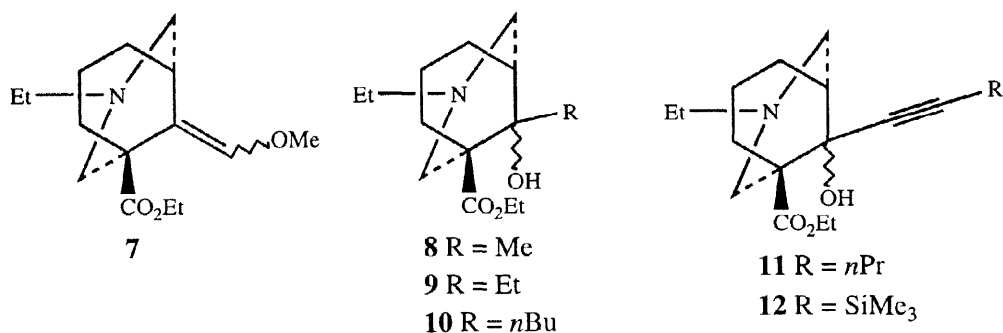
**Abstract:** We have prepared C5-substituted AE-bicyclic analogues of norditerpenoid alkaloids lycoctonine, inuline and methyllycaconitine via an acetylide anion addition strategy. Using two acetylide anions, we have regioselectively linked two cyclic ketones to acetylene.  
  1998 Elsevier Science Ltd. All rights reserved.

Methyllycaconitine (MLA) **1** is a hexacyclic norditerpenoid alkaloid which occurs in many *Delphinium* species as well as in *Consolida ambigua* and *Inula royaleana*.<sup>1</sup> MLA **1** is the 2-(*S*)-methylsuccinimido-benzoate ester of neopentyl-like alcohol lycoctonine **2**.<sup>2</sup> These plants, especially the *Delphinium* species, are known to be toxic to mammals<sup>3,4</sup> and to a wide variety of insect species.<sup>5,6</sup> The insecticidal property of MLA (and of *D. staphisagria* extracts which contain related norditerpenoids, but possibly not MLA) has long been exploited as a herbal treatment for head lice infestations, first reported by Pliny the Elder.<sup>7,8</sup> MLA has use as a potent, selective ligand for molecular studies of neuronal nAChR implicated in neurodegeneration,<sup>9</sup> and potential as a lead compound for the rational design of insecticides acting at nicotine binding sites.<sup>6,10</sup> Previous work on the synthesis of the carbon skeleton of these hexacyclic alkaloids of the lycoctonine family includes the synthesis of an AEF-tricycle by Whiting<sup>11,12</sup> and co-workers, an AEBD-tetracycle by Kraus *et al.*<sup>13</sup> and the synthesis of the BCD- and ABCD-carbocycles of the C<sub>19</sub> norditerpenoid alkaloid skeleton by van der Baan and co-workers.<sup>14,15</sup>

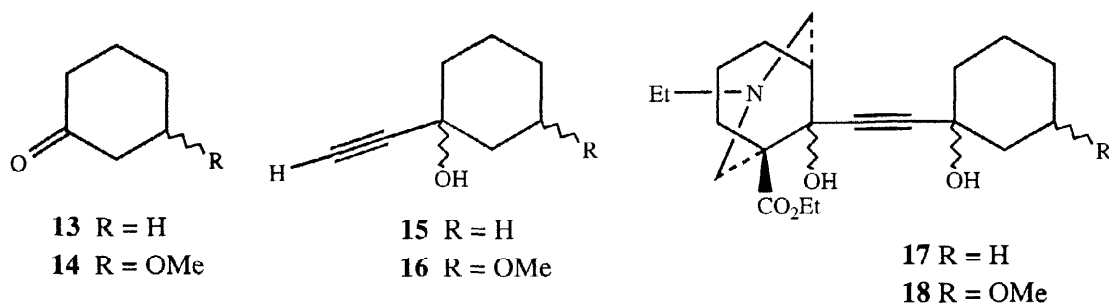
In this *Letter*, we report the syntheses of substituted AE-bicyclic analogues of lycoctonine **2**, inuline **3** and MLA **1** involving a double acetylide addition<sup>16,17</sup> linking a monocyclic ketone (**13** or **14**) to bicyclic ketone **6**.<sup>18</sup> We chose substituted bicyclic triol **4** as our target. Ketone **6** is formed via a double Mannich<sup>19</sup> reaction which yields an enantiomeric mixture of products as both new chiral centres must have new C-C bonds generated with axial stereochemistry (relative to the cyclohexanone) in order to close the piperidine ring. On addition of a nucleophile to ketone **6**, a new chiral centre is generated yielding a mixture of diastereoisomers.  $\beta$ -Ketoester **6** reacts regioselectively with reactive Wittig reagents to produce compounds such as enol ether **7**.<sup>18,20</sup> However, attempts to react this ketone with larger and less reactive phosphorus ylids failed, due either to steric hinderance around the ketone or lack of sufficient nucleophilicity in the ylid.



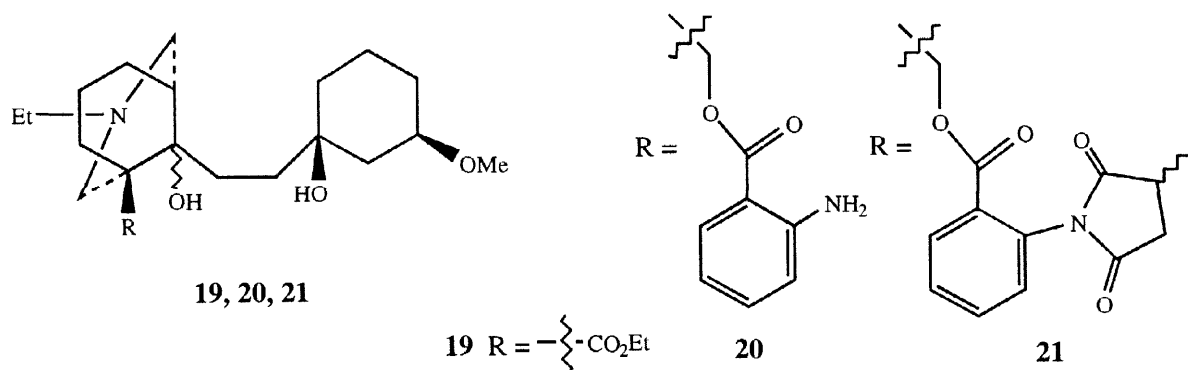
$\beta$ -Ketoester **6** could also be regioselectively attacked with a variety of organometallic nucleophiles. We investigated a series of Grignard<sup>21</sup> and alkyllithium<sup>22</sup> reagents which readily added across this ketone to form tertiary alcohols **8**, **9** and **10** in good yields. The use of alkyllithium and to a lesser extent Grignard reagents, however, did not allow the flexibility of substitution required to synthesise our target molecule **4** mimicking three of the six rings found in MLA **1**. By contrast, the use of lithium acetylide<sup>23-29</sup> as the nucleophile allows us to incorporate C6 and C7 (norditerpenoid numbering) as in propargylic alcohols **5**, **11** and **12** (~60%). However, a dianion derived from **5** (via **12**) reacted with cyclic ketones **13** and **14** to give the desired products **17** and **18** respectively, only in poor yields (<5%). This strategy allows us to incorporate a methoxy group which is in the correct regiochemical orientation to represent the methoxy at either C14 or C16 of MLA **1** and the tertiary alcohol at C8 is also incorporated in **4**. Hence, an alternative route to alkyne **17** was devised, forming C5-C6 after C7-C8, which allowed efficient synthesis of practical quantities of **17**. Cyclohex-2-enone was reacted with methanol under acid catalysis to afford an enantiomeric pair of methyl ethers **14** where the 3-methoxy functional group was presumed to add with an axial orientation and then equilibrate to an axial-equatorial mixture which Djerassi and co-workers have measured (NMR) as 51:49 respectively.<sup>30,31</sup>



The acetylide anion was prepared from TMS-acetylene, using *n*-BuLi in THF at  $-78\text{ }^{\circ}\text{C}$ , and this reacted smoothly with cyclohexanones **13** and **14**. The diastereoisomeric mixture of propargylic alcohols formed was not purified, but was efficiently deprotected under basic conditions (aq. methanolic NaOH) to afford key acetylenic tertiary alcohols **15** and **16** respectively (95 % overall). Purification of **16** gave a 12:1 ratio of diastereoisomers with the favoured isomer having an equatorial 3-methoxy and an equatorial 1-hydroxy substitution pattern (shown by *n*Oe experiments and analysis of coupling constants to be *RS/SR* stereochemistry). The major diastereoisomer **16** (with di-equatorial C-O bonds and axial C-alkyne as required in MLA **1**) was then used for the rest of the synthesis.



Treatment of propargylic alcohols **15** and **16** with 2.4 equivalents of *n*-BuLi gave the corresponding dianions which were reacted (THF,  $0\text{ }^{\circ}\text{C}$ ) with bicyclic  $\beta$ -ketoester **6** at the more electrophilic cyclic ketone functional group, in preference to the ethyl ester. After silica gel chromatography (30% EtOAc-hexane), bis-tertiary alcohols **17** and **18** were isolated as colourless oils (~60 %), co-eluting mixtures of diastereoisomers. Bishydroxy acetylene **18** was then reduced to afford alkane **19** (Pd/C, EtOH, 72 h, 80 %) where the diastereoisomers were separated into two fractions.<sup>16,17</sup> Reduction of ester **19** with LAH yielded triol **4** (Et<sub>2</sub>O,  $20\text{ }^{\circ}\text{C}$ , 16 h, 70 %), the desired target, as a colourless viscous oil. Triol **4** was converted into inuline analogue **20** by reaction with isatoic anhydride with base catalysis (DMF, DMAP,  $70\text{ }^{\circ}\text{C}$ , 16 h, 65 %). The resulting anthranilate ester **20** was converted into MLA analogue **21** by reaction with methylsuccinic anhydride. Initially this reaction afforded a mixture of half acid amides which was cyclised *in situ* to yield the desired methylsuccinimide **21** by the addition of 1,1'-carbonyldiimidazole as a dehydrating agent.<sup>32</sup>



**Acknowledgements:** We thank EPSRC and Zeneca Agrochemicals (CASE award to WJT) and Fondation pour Recherche Médicale (GG) for financial support. We thank Dr. Martin R. Kipps (Zeneca Agrochemicals) for the detailed NMR spectroscopy and for his interest in these studies.

## REFERENCES

1. Manske, R. H. *Can. J. Research* **1938**, *16B*, 57-60.
2. Goodson, J. A. *J. Chem. Soc.* **1943**, 139-141.
3. Keeler, R. F. *Lloydia* **1975**, *38*, 56-61.
4. Manners, G. D.; Panter, K. P.; Pelletier, S. W. *J. Nat. Prod.* **1995**, *58*, 863-869.
5. Nambi Aiyar, V.; Benn, M. H.; Hanna, T.; Jacyno, J.; Roth, S. H.; Wilkens, J. L. *Experientia* **1979**, *35*, 1367-1368.
6. Jennings, K. R.; Brown, D. G.; Wright, D. P. *Experientia* **1986**, *42*, 611-613.
7. Plinius, G. *Naturalis Historia AD77*, Book 23, Chapter 13.
8. 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.
9. Wonnacott, S.; Albuquerque, E. X.; Bertrand D. In *Methods in Neurosciences*; Conn, M., Ed.; Academic Press: New York, 1993, *12*, pp. 263-275.
10. Jennings, K. R.; Brown, D. G.; Wright, D. P.; Chalmers, A. E. *ACS Symposium Series* **1987**, *356*, 316-325.
11. Baillie, L. C.; Bearder, J. R.; Whiting, D. A. *J. Chem. Soc., Chem. Commun.* **1994**, 2487-2488.
12. Baillie, L. C.; Bearder, J. R.; Sherringham, J. A.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2687-2688.
13. Kraus, G. A.; Andersh, B.; Su, Q.; Shi, J. *Tetrahedron Lett.* **1993**, *34*, 1741-1744.
14. van Beek, G.; van der Baan, J. L.; Klumpp, G. W.; Bickelhaupt, F. *Tetrahedron* **1986**, *42*, 5111-5122.
15. van der Baan, J. L.; Barnick, J. W. F. K.; van Beek, G.; Bickelhaupt, F.; Spek, A. L. *Tetrahedron* **1992**, *48*, 2773-2784.
16. Labriola, R.; Ourisson, G. *Tetrahedron* **1973**, *29*, 2105-2114.
17. Montalbetti, C.; Savignac, M.; Bonnefis, F.; Genêt, J. P. *Tetrahedron Lett.* **1995**, *36*, 5891-5894.
18. 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.
19. Shimizu, B.; Ogiso, A.; Iwai, I. *Chem. Pharm. Bull.* **1963**, *11*, 333-336.
20. Ihara, M.; Suzuki, M.; Fukumoto, K.; Kametani, T.; Kabuto, C. *J. Am. Chem. Soc.* **1988**, *110*, 1963-1964.
21. Marshall, J. A.; Karas, L. J.; Royce Jr., R. D. *J. Org. Chem.* **1979**, *44*, 2994-2999.
22. Buhler, J. D. *J. Org. Chem.* **1973**, *38*, 904-906.
23. Milas, N. A.; Macdonald, N. S.; Black, D. M. *J. Am. Chem. Soc.* **1948**, *70*, 1829-1834.
24. Attenburrow, J.; Cameron, A. F. B.; Chapman, J. H.; Evans, R. M.; Hems, B. A.; Jansen, A. B. A.; Walker, T. *J. Chem. Soc.* **1952**, 1094-1111.
25. Olson, G. L.; Cheung, H.-C.; Morgan, K. D.; Borer, R.; Saucy, G. *Helv. Chim. Acta* **1976**, *59*, 567-585.
26. Shimizu, B.; Ogiso, A.; Iwai, I. *Chem. Pharm. Bull.* **1963**, *11*, 760-769.
27. Hollinshead, D. M.; Howell, S. C.; Ley, S. V.; Mahon, M.; Ratcliffe, N. M.; Worthington, P. A. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1579-1589.
28. Weyerstahl, P.; Buchmann, B.; Marschall-Weyerstahl, H. *Liebigs Ann. Chem.* **1988**, 507-523.
29. Weyerstahl, P.; Meisel T. *Liebigs Ann. Chem.* **1994**, 415-427.
30. Gorthey, L. A.; Vairamani, M.; Djerassi, C. *J. Org. Chem.* **1985**, *50*, 4173-4187.
31. Bowen, J. P.; Allinger N. L. *J. Org. Chem.* **1987**, *52*, 1830-1834.
32. 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.