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

Géraldine Grangier[1], William J. Trigg[1], Terence Lewis[2], Michael G. Rowan[1], Barry V. L. Potter[1] and Ian S. Blagbrough[1*]

[1]Department of Medicinal Chemistry, School of Pharmacy and Pharmacology, University of Bath, Bath BA2 7AY,

[2]Zeneca Agrochemicals, Jealott's Hill Research Station, Bracknell RG12 6EY, U.K.

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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.

Methyllycaconitine (MLA) **1** is a hexacyclic norditerpenoid alkaloid which occurs in many *Delphinium* species as well as in *Consolida ambigua* and *Inula royaleana*.[1] MLA **1** is the 2-(*S*)-methylsuccinimido-benzoate ester of neopentyl-like alcohol lycoctonine **2**.[2] These plants, especially the *Delphinium* species, are known to be toxic to mammals[3,4] and to a wide variety of insect species.[5,6] 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.[7,8] MLA has use as a potent, selective ligand for molecular studies of neuronal nAChR implicated in neurodegeneration,[9] and potential as a lead compound for the rational design of insecticides acting at nicotine binding sites.[6,10] 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[11,12] and co-workers, an AEBD-tetracycle by Kraus *et al.*[13] and the synthesis of the BCD- and ABCD-carbocycles of the C_{19} norditerpenoid alkaloid skeleton by van der Baan and co-workers.[14,15]

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[16,17] linking a monocyclic ketone (**13** or **14**) to bicyclic ketone **6**.[18] We chose substituted bicyclic triol **4** as our target. Ketone **6** is formed via a double Mannich[19] 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. β-Ketoester **6** reacts regioselectively with reactive Wittig reagents to produce compounds such as enol ether **7**.[18,20] 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.

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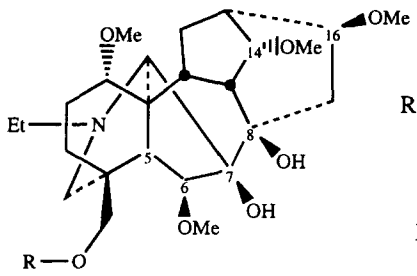
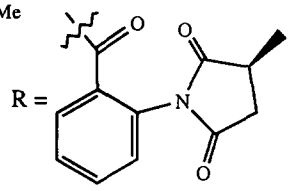
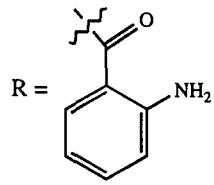


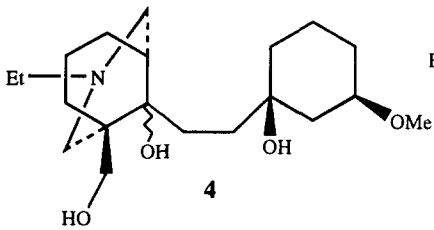


Methyllycaconitine **1**

Lycoctonine **2**



Inuline **3**



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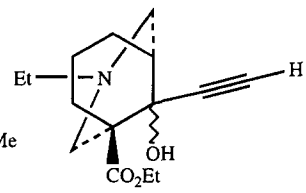

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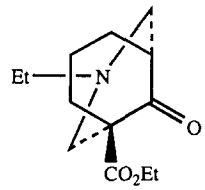
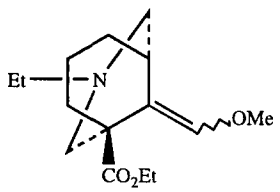


6

β-Ketoester **6** could also be regioselectively attacked with a variety of organometallic nucleophiles. We investigated a series of Grignard[21] and alkyllithium[22] 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[23-29] 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.[30,31]



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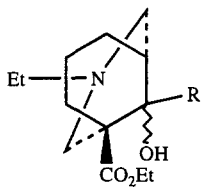
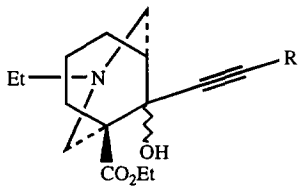
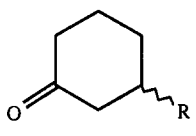


8 R = Me
9 R = Et
10 R = *n*Bu

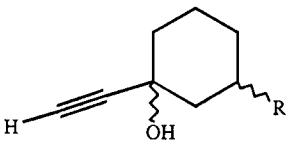


11 R = *n*Pr
12 R = $SiMe_3$

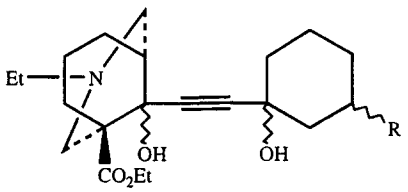
The acetylide anion was prepared from TMS-acetylene, using n-BuLi in THF at -78 °C, and this reacted smoothly with cyclohexanones **13** and **14**. The diastereoisomeric mixture of propargylic alcohols formed was not purified, but was efficiently deprotected under basic conditions (aq. methanolic NaOH) 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 nOe 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.



13 R = H
14 R = OMe

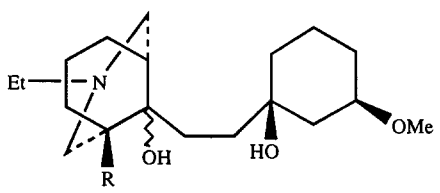


15 R = H
16 R = OMe

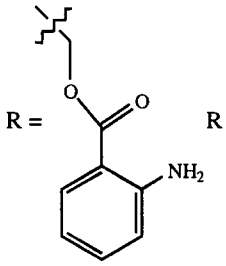


17 R = H
18 R = OMe

Treatment of propargylic alcohols **15** and **16** with 2.4 equivalents of n-BuLi gave the corresponding dianions which were reacted (THF, 0 °C) with bicyclic β-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 diastereo-isomers were separated into two fractions.[16,17] Reduction of ester **19** with LAH yielded triol **4** (Et_2O, 20 °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 °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.[32]



19, 20, 21



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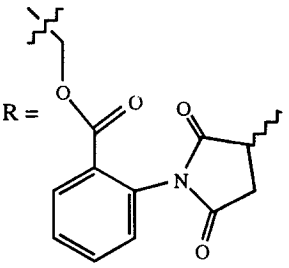
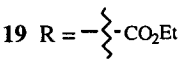


21

19 R = 

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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.