Pergamon

Tetrahedron Letters, Vol. 37, No. 22, pp. 3915-3918, 1996

PII: S0040-4039(96)00688-0

0040-4039/96 $15.00 + 0.00

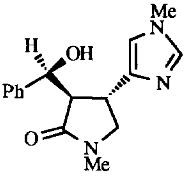
A Short Dipolar Cycloaddition Approach to γ-Lactam Alkaloids from *Cynometra Hankei*

Colin W.G. Fishwick,* Richard J. Foster
School of Chemistry, University of Leeds, Leeds, LS2 9JT, UK.

Robin E. Carr
GlaxoWellcome Research and Development Ltd., Medicines Research Centre, Stevenage, Herts., SG1 2NY, UK.

Abstract: The γ-lactam based alkaloid cynometrine has been synthesised in four steps from 1-methyl-imidazole-4-carboxaldehyde. The key step involves an efficient regio-, stereo-, and chemoselective 1,3-dipolar cycloaddition of a dithiolane-fused azomethine ylide.

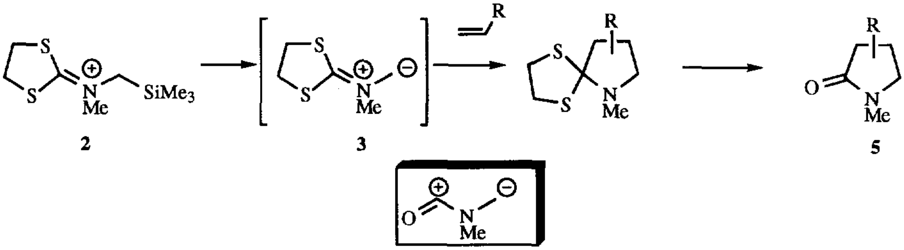
The stem bark and seeds of *Cynometra hankei* have yielded a number of interesting imidazole-based alkaloids whose structures contain a γ-lactam framework[1]. Amongst these, cynometrine **1** appears to posses potential as an analgesic[2] (Figure 1).



1

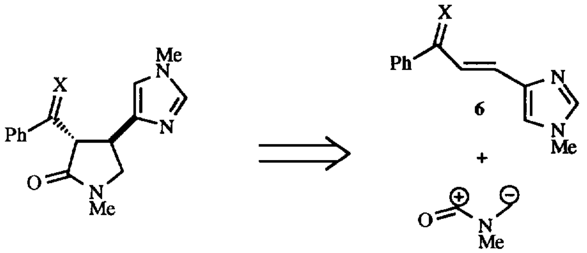
Figure 1

We have recently found[3] that dithiolane-fused azomethine ylide **3**, easily generated via fluoride-induced desilylation of imminium salt **2** undergoes efficient cycloaddition to electron deficient dipolarophiles to yield lactams **5** following deprotection of the initially formed dithiolane-containing adducts. Ylide **3** can thus be regarded as a synthetic equivalent to carbonyl-fused dipole **4** (Scheme 1).



Scheme 1

We were thus intrigued by the possibility of utilising this cycloaddition methodology in a short synthesis[4] of alkaloid **1** as outlined below (Scheme 2).

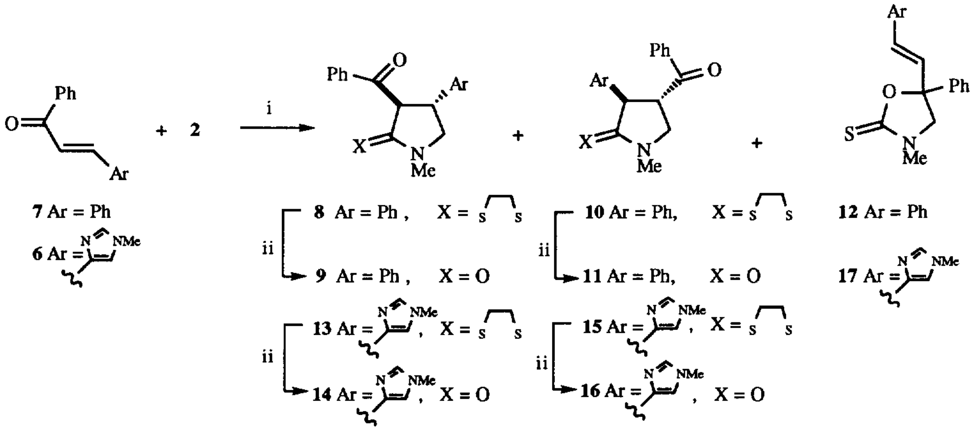


Scheme 2

This approach to alkaloid **1**, involving cycloaddition of dipole **3** to olefin **6** (X = O, Scheme 2) clearly requires the cycloaddition to be regio- and stereoselective. An additional potential problem was the possible participation of the carbonyl group of alkene **6** in the cycloaddition. Indeed, we have recently found[5] that dipole **3** adds efficiently to hetero-dipolarophiles including aryl-linked carbonyl groups.

To test the viability of this approach, the cycloaddition of dipole **3** to chalcone **7** was examined as a model system. We had predicted[6], on the basis of FMO theory, that this cycloaddition should show a regiochemical preference in the direction required for the synthesis of alkaloid **1**.

Indeed, it was found that the cycloaddition produced a 2:1 ratio of regioisomeric adducts **8** and **10** respectively in 62% yield (inseparable by chromatography). In addition, a small amount of thione **12** was isolated (5%) resulting from addition of the carbonyl group to ylide **3** and fragmentation of the resulting dithiolane[5]. Hydrolysis of the mixture of **8** and **10** yielded lactams **9** and **11** in 48% and 23% yields respectively following chromatographic separation (Scheme 3).



Reagents: i CsF, ii SO_2Cl_2, SiO_2, H_2O

Scheme 3

Encouraged by these results, imidazole-based alkene **6** was prepared in good yield *via* aldol condensation of 1-methyl-imidazole-4-carboxaldehyde[7] with acetophenone. Stirring a solution of alkene **6** in the presence of salt **2** and cesium fluoride yielded adducts **13** and **15** as an inseparable mixture in the ratio 4:1 (71%). Deprotection gave lactams **14** (60%) and **16** (17%) after chromatographic separation. A small quantity of carbonyl addition product **17** was also isolated (5%).

The stronger preference for the cycloaddition involving imidazole-alkene **6** to yield the required regioisomer **13** compared to the cycloaddition involving chalcone was fortunate but initially somewhat puzzling. Indeed, calculations concerning both the extent of FMO interactions between dipole **3** and alkene **6**, and of the interaction of electronic dipole moments respectively, predicted a relatively poor degree of regiocontrol and possibly even a reverse of stereochemical preference in favour of the wrong isomer **15**[6].

However, the well-known ability of the imidazole ring to co-ordinate to metals[8] prompted us to consider the possibility of a cesium-assisted cycloaddition in which the lone-pair from N-3 of the imidazole ring in alkene **6** is co-ordinated to a cesium ion originating from cesium fluoride, thus rendering the imidazole electron deficient.

The effects of this on the FMO interactions in the cycloadditions were modelled using **18** which is an N-3 protonated version of alkene **6**. Comparison of the calculated FMO coefficients and energies for the neutral, and protonated alkenes **6** and **18** respectively revealed considerable differences, particularly in terms of the much lower HOMO and LUMO energies, and a reversal in the relative coefficient sizes in the LUMO on the alkene carbons in the protonated system **18** (Figure 2).

Comparison of the calculated interaction energies[6] for the additions of each of these species to dipole **4** now indicates a strong preference for protonated alkene **18** to yield the regioisomer analogous to **13** (Scheme 3), in agreement with the observed stereochemical preference. This is supported by the observation that use of tetra-n-butyl ammonium fluoride (TBAF) as initiator in place of cesium fluoride yields a reduced preference (1.5:1) for regioisomer **13**.

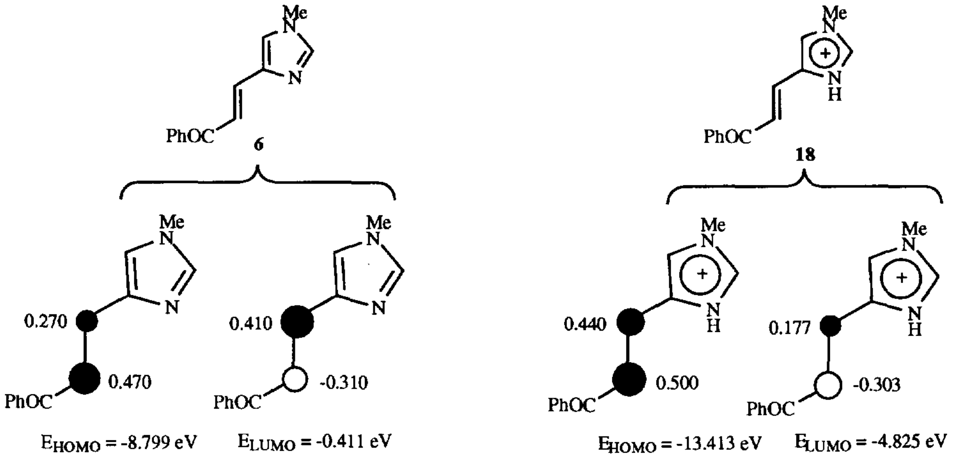
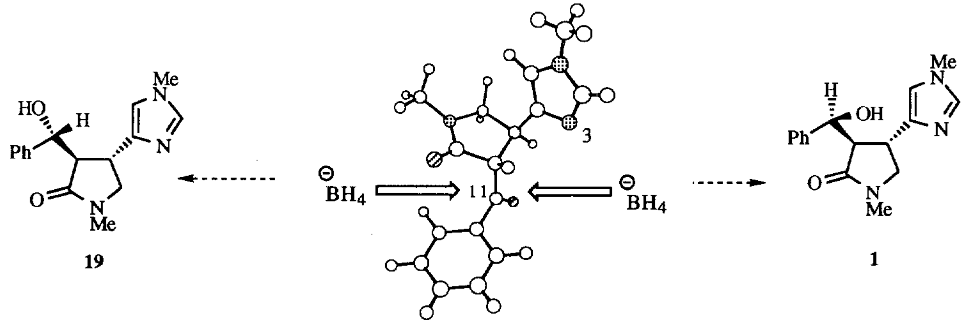


Figure 2

To complete the synthesis of (±)-cynometrine **1**, ketone **14** was reduced with sodium borohydride to yield (±)-cynometrine **1** and the C-11 epimeric alcohol **19** (4:1, 74%)[9], (Scheme 4).

Again, although fortunate, the stereoselectivity of this reduction was surprising in view of the fact that reduction of the phenyl-containing ketone **9** had yielded essentially equal amounts of both possible epimeric alcohol's. Here also, it would appear that the co-ordinating ability of the imidazole ring may be having a considerable effect on reaction selectivity. The calculated[6] lowest-energy conformation of ketone **14** locates the lactam and ketone carbonyls in opposing directions, which presumably is a result of favourable anti-parallel alignment of their respective electronic dipoles. Formation of the predominant epimeric alcohol would then result from hydride delivery from a trajectory close to the imidazole, which would be facilitated by co-ordination of the imidazole N-3 to the attacking borohydride[10] (Scheme 4).

In summary, the use of dithiolane-fused azomethine ylides provides rapid regio- and stereoselective access to lactam-containing natural products. In addition, imidazole-containing dipolarophiles appear to exhibit an intriguing reversal of expected regiochemical preference upon cycloaddition in the presence of a co-ordinating metal.



Scheme 4

Acknowledgements.

We are grateful to the EPSRC and GlaxoWellcome Research and Development Ltd, Stevenage, for their financial support. We also thank Dr. D.W. Jones and Dr. G.R. Sparkes for helpful discussion.

References and Notes.

1. Waterman, P.G.; Faulkner, D.F. *Phytochemistry* **1981**, *20*, 2765. Monseur, X.; Khuong-Huu, F.; Ratle, G.; Lukacs, G.: Goutarel, R. *Tetrahedron Lett.* **1973**, 1757.
2. Hennart, J.A.A. **Ger Offen.** 2,307,867 (*Chem. Abs.* **1974**, *80*, 19535b), Omnium Chimique S.A. **Belg.** 780, 935 (*Chem. Abs.* **1973**, *78*, 133642t).
3. Fishwick, C.W.G.; Foster, R.J: Carr, R.E. *Tetrahedron Lett.* **1995**, *36*, 9409.
4. Khuong-Huu, F.; Benechie, M.; Tchissambou, L. *Tetrahedron*, **1982**, *38*, 2687.
5. Fishwick, C.W.G.; Foster, R.J: Carr, R.E. *Tetrahedron Lett.* **1996**, *37*, 711.
6. Molecular models were constructed on a Silicon Graphics *Indigo* using MacroModel v3.0, developed by Professor W.C. Still. All models were fully optimised using the AM1 Hamiltonian in MOPAC v6.0 running on a Silicon Graphics Challenge eight processor parallel computer. Molecular oribital energies, coefficients, and electronic dipole moments were obtained from the AM1 calculations. Interaction energies were calculated using the expression derived by Salem with a value of 5.0 for the resonance overlap integral for carbon-carbon bond formation, βc-c , at 2.0 Å, see; Salem, L. *J. Am. Chem. Soc.* **1968**, *90*, 543.
7. Buchanan, R.M.; Richardson, J.F. *Inorg. Chem.* **1994**, *33*, 2376.
8. The stereochemical-directing effects of other azoles upon reductions of proximal carbonyl groups has been noted, see: Thieme, P.C.: Sauter, H.: Reissenweber, E. *Chem. Ber.*, **1988**, *121*, 1059.
9. Selected spectroscopic data; (±)-cynometrine **1**, ^{1}H NMR ($CDCl_3$/TMS): δ= 2.87 (3H, s, lactam-NCH_3), 3.08 (2H, m, H-6), 3.42 (2H, m, H-7 and H-10), 3.45 (3H, s, imidazole- NCH_3), 5.08 (1H, d, J = 6.0Hz, H-11), 5.92 (1H, s, H-5), 7.19-7.38 (6H, m, Ar-H).

   Compound **19**, ^{1}H NMR ($CDCl_3$/TMS): δ= 2.85 (3H, s, lactam-NCH_3), 3.22 (1H, m), 3.37 (1H, m), 3.43 (2H, m), 3.49 (3H, s, imidazole- NCH_3), 5.23 (1H, d, J = 3.0Hz, H-11), 6.09 (1H, s, H-5), 7.19-7.38 (6H, m, Ar-H). All new compounds gave satisfactory spectroscopic and analytical data consistent with their proposed structures. Full experimental details will be published elsewhere.
10. Gimmett, M.R. in: *Adv. Het. Chem.*; Eds. Katritzky, A.R.: Boulton, A.J. Academic Press, **1970**, *12*, 103-183.

(*Received in UK* 1 *April* 1996; *accepted* 12 *April* 1996)