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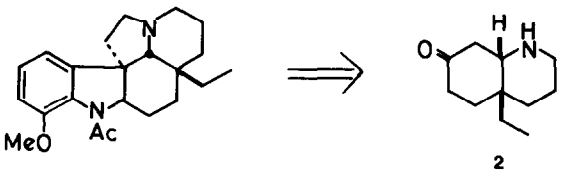
NEW APPROACH TO ASPIDOSPERMINE TOTAL SYNTHESIS USING ORGANOIRON COMPLEXES

Anthony J. Pearson

University Chemical Laboratory,
Lensfield Road,
Cambridge, CB2 1EW.

Abstract: The conversion of p-ethylanisole, via the tricarbonyl(diene)-iron complex (3), to the bicyclic amino ketone (2), which is a known precursor for aspidospermine total synthesis, is described. The synthetic route demonstrates the stability of the diene-$Fe(CO)_3$ unit to a number of useful synthetic transformations.

Since the total synthesis of aspidospermine (1) was achieved by Stork and Dolfini[2], there has been continued synthetic interest in this class of compounds, with the evolution of a number of useful approaches.[3] We are currently exploring the application of tricarbonyl(cyclohexadienylium)iron cation complexes to the total synthesis of a diverse range of natural products, all of these utilising their simple conversion to 4,4-disubstituted cyclohexenones.[4] The intermediate (2) used by Stork can be derived from this type of precursor, and so we decided to investigate its synthesis using organoiron derivatives, with a view to using the methodology for the preparation of more advanced and more highly functionalised intermediates.



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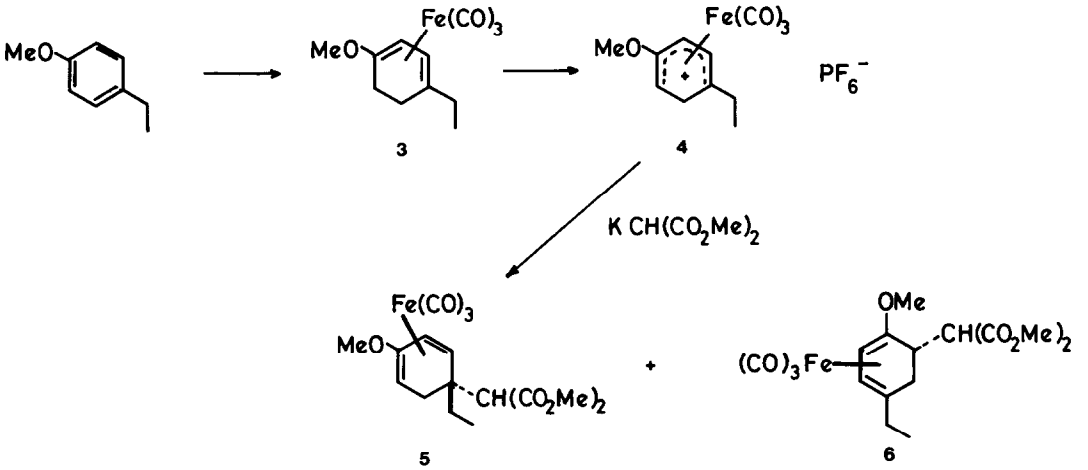
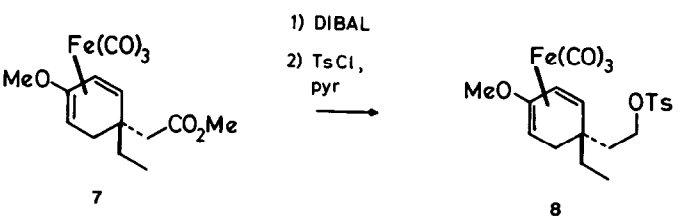
Birch reduction of p-ethylanisole, followed by conjugation of the resulting 1,4-diene (TsOH, 80°C, 1.2h)[5] gave an equilibrium mixture of 1,3- and 1,4-dienes, which was treated in the usual way[6] ($Fe(CO)_5$, Bu_2O, reflux, 48h) to give the complex (3)[7] (36% overall). This was readily converted to the hexafluorophosphate (4) (Ph_3CPF_6, CH_2Cl_2 reflux, 1h; Et_2O, filter; 90%). Reaction of (4) with dimethyl potassiomalonate (from $KOBu^t$ $CH_2(CO_2Me)_2$,

THF, 0°C)proceeded smoothly to give quantitatively a 5.8 :1 mixture of regioisomers (5) and (6), from which was obtained the pure desired complex (5) in 78% yield from (4) by crystallisation from pentane; m.p. 101.5-102°, $\nu_{max}(CHCl_3)$ 2055, 1975. 1756, 1730, 1488 cm^{-1}.

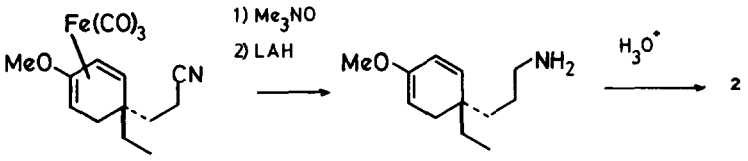


Decarbomethoxylation of (5) (Me_4N OAc, HMPA, 95°, 12h) afforded the monoester (7), ν_{max}, 2050,1970, 1728, 1487 cm^{-1}, but in only 51% yield (not optimised; we are currently examining this transformation further). The monoester (7) was converted to tosylate (8), m.p. 45-46.5°, ν_{max} 2055, 1980, 1490, 1365, 1195, 1180 cm^{-1}, in 88% overall yield ((a) DIBAL, THF, 0-20°C, 12h; (b) TsCl, pyr., 0°C, 13h). Homologation of (8) was readily achieved by displacement of the tosylate with cyanide (NaCN, HMPA, 60°C, 2.5h) to give the crystalline nitrile (9) in 84% yield after chromatographic purification, m.p. 72-73°C, ν_{max} 2262, 2055, 1980, 1490 cm^{-1}.



The next steps were performed on the crude nitrile, obtained in 93-96% yield, and without purification of sensitive dienol ether intermediates. Removal of iron (excess anhydrous Me_3NO, benzene 45-50°, 2h, 83%) followed by lithium aluminium hydride reduction[8] (ether, 20°C, 0.75h) afforded the primary amine

(10) which was converted directly to the required bicyclic amino ketone (2) (oxalic acid, MeOH, H_2O, 20°C, 1 h; basify, extract with $CHCl_3$) which was purified chromatographically, m.p. 46-48° (lit.[2] 47-50°), ν_{max} 1712 cm^{-1}, and which gave a single N-acetyl derivative (t.l.c.) ν_{max} 1712, 1627 cm^{-1}.



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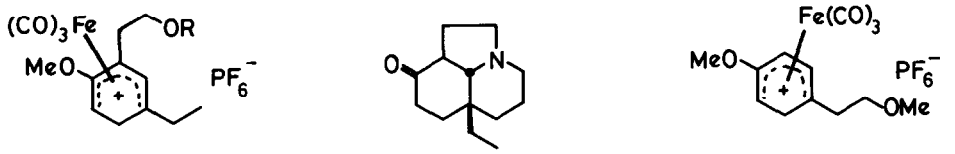
Whilst the above route to the intermediate (2) is longer than that of Stork and Dolfini, it offers a number of advantages for aspidospermine total synthesis. For example, Birch et al[9] have recently demonstrated that complexes similar to (3) can be prepared in optically active form by asymmetric induction, and since nucleophile addition occurs stereospecifically on the uncomplexed face of the dienyl system, the method described above provides access to asymmetric synthesis. Also, it may be possible to apply similar methods using trisubstituted complexes such as (11), which could



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provide a route to the tricyclic intermediate (12), accessible only with difficulty from (2). Furthermore, we have already shown[10] that the complex (13) reacts with dimethyl sodiomalonate mainly at C-1, so that the above methodology might be applied to the synthesis of Aspidosperma alkaloids related to cylindrocarpinol.[11] These aspects of the work are currently under scrutiny.

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References

1. Organoiron Complexes in Organic Synthesis, Part 20. Part 19, A.J. Pearson and C.W. Ong, J. Am. Chem. Soc., in press.
2. G. Stork and J.E. Dolfini, J. Am. Chem. Soc., 1963, 85, 2872.
3. Recent review: G.A. Cordell, The Alkaloids, Ed. R.H.F. Manske and R.G.A. Rodrigo, Vol 17, Academic Press, New York, 1979, p.199. For more recent approaches see: S.F. Martin, S.R. Desai, G.W. Phillips and A.C. Miller, J. Am. Chem. Soc., 1980, 102, 3294; J. Hajicek and J. Trojanek, Tetrahedron Lett., 1981, 22 1823.
4. A.J. Pearson, Acc. Chem. Res., 1980, 13, 463; Transition Met. Chem., 1981, 6, 67.
5. A.J. Birch and K.P. Dastur, J. Chem. Soc. Perkin Trans 1, 1973, 1650.
6. A.J. Pearson, J. Chem. Soc. Perkin Trans 1, 1980, 400.
7. All new compounds, obtained as racemic mixtures, were characterised spectroscopically and gave satisfactory combustion analyses and/or high resolution mass spectra.
8. L.H. Amundsen and L.S. Nelson, J. Am. Chem. Soc., 1951, 73, 242.
9. A.J. Birch, W.D. Raverty and G.R. Stephenson, Tetrahedron Lett., 1980, 21, 197, J. Chem. Soc. Chem. Commun., 1980, 857; A.J. Birch and G.R. Stephenson, Tetrahedron Lett., 1981, 22, 779.
10. A.J. Pearson and M. Chandler, J. Chem. Soc. Perkin Trans 1, 1980, 2238.
11. For a total synthesis of cylindrocarpinol and related alkaloids, see G. Lawton, J.E. Saxton and A.J. Smith, Tetrahedron, 1977, 33, 1641.

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