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NEW SYNTHETIC APPROACHES TO ASPIDOSPERMA ALKALOIDS WITH FUNCTIONALISED C(20) SUBSTITUENTS: SOME KEY INTERMEDIATES *via* DIENE-$Fe(CO)_3$ COMPLEXES[1]

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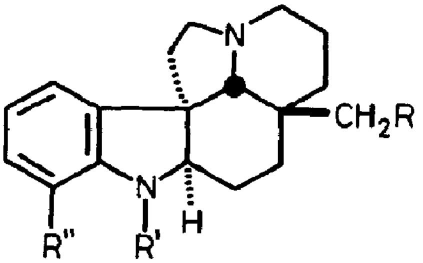
Abstract: A method of constructing the quaternary carbon, corresponding to C-20 of Aspidosperma alkaloids, via tricarbonylcyclohexadienyliumiron salts is described.

Interest in the title compounds bearing C-20 functionalised substituents, e.g. limaspermine (1), N-acetylaspidoalbidine (2), cylindrocarpidine (3), cylindrocarpinol (4) and many others, has recently culminated in a number of synthetic approaches.[2] The most useful approaches employ a strategy similar to Stork's original synthesis of aspidospermine (5), involving construction of a 4,4-disubstituted cyclohexenone with an amino group suitably disposed for intramolecular Michael reaction.[3]

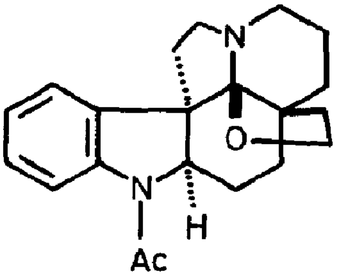


(1) $R=CH_2OH$, $R'=CO.Et$, $R''=OH$

(3) $R=CO_2Me$, $R'=Ac$, $R''=OMe$

(4) $R=CH_2OH$, $R'=H$, $R''=OMe$

(5) $R=Me$, $R'=Ac$, $R''=OMe$



(2)

Work currently in progress in our laboratory is based upon the facile conversion of a wide variety of *para*-substituted anisoles into 4,4-disubstituted cyclohexenones *via* cyclohexadiene-$Fe(CO)_3$ complexes.[4] This communication describes the results of our preliminary investigations towards synthesis of the title compounds, in which we have elaborated cyclohexadienyliumiron complexes with appropriately functionalised lateral chains and have established the regioselectivity of carbanion addition, resulting in good yields of compounds containing the desired quaternary centre, thus indicating the synthetic utility of these complexes.

The crystalline ester complex (6), prepared from p-methoxycinnamic acid by an improvement over our previously reported method[5] (50% overall yield), was reduced to the oily alcohol (7)[6] without decomposition of the complex using diisobutylaluminium hydride (2.4 equiv., THF, -78° → 25°C overnight, 97%). This was converted to the acetate (8a) (Ac_2O, C_5H_5N, 25°C, 20 h) which was then converted regiospecifically to the hexafluorophosphate (9a) (Ph_3CBF_4, CH_2Cl_2, reflux; NH_4PF_6, H_2O; 86% from 7).

Treatment of (7) with p-toluenesulphonyl chloride (C_5H_5N, 0°C, 11 h) gave the tosylate (8b) which was similarly converted to the hexafluorophosphate (9b) (90% from 7).

Reaction of the oily tosylate (8b) with potassium phthalimide (DMF, 20°, 18 h; 40°, 6 h) produced the crystalline phthalimide derivative (8c), m.p. 113-114°C, which was converted to the hexafluorophosphate (9c) (79% from 7).

Thus were available three salts (9a), (9b) and (9c) whose reactivity toward an appropriate carbanion could be assessed in relation to the proposed objective. Treatment with sodiodimethylmalonate (1.2-2.0 equiv., THF, 25°C) gave in each case a mixture of regioisomers containing predominantly (65-80%) the desired compound. The acetate salt (9a) gave (10a) together with a smaller amount of (11a), inseparable on t.l.c. (ratio estimated by ^1H n.m.r., 2:1, yield 94%). Tosylate (9b) gave (10b) and (11b), inseparable (2:1, 90%), and the phthalimide salt (9c) gave (10c) and (11c) which could be separated chromatographically or by fractional crystallisation (3.5:1, 90%). Thus, pure regioisomer (10c) could be readily obtained.

To further test the usefulness of this methodology, the $Fe(CO)_3$ group was removed from (10c) (Me_3NO, benzene, 50°C, 1.5 h, 87%) giving the hydrolytically unstable dienol ether (12) which was converted directly to the stable cyclohexenone (13) (oxalic acid, MeOH, H_2O, 25°C, 40 min, 88%), m.p. 128.5-131.5°C, ν_{max} ($CHCl_3$) 1 772 and 1 714 (C=O imide), 1 733 and 1 757 (C=O esters), 1 675 (C=O, enone); δ($CDCl_3$) 7.85 (4H, m, aromatic-H), 7.13 (1H, d, $\underline{J}$ 10 H_z, 3-H), 5.98 (1H, d, $\underline{J}$ 10 H_z, 2-H), 3.40-3.90 (9H, 2 x COOMe, $C\underline{H}(COOMe)_2$ and $C\underline{H}_2N$), 1.7-2.6 (8H, methylene envelope).

Whilst it is possible that enone (13) could be converted to the desired alkaloids by standard procedures, the amine deprotection requires reprotection of the ketone, which we hoped to avoid using dienol ether (12). Consequently, a superior strategy might involve amine release at the intermediate (10c). These aspects, together with the further elaboration of (13), are currently under scrutiny.

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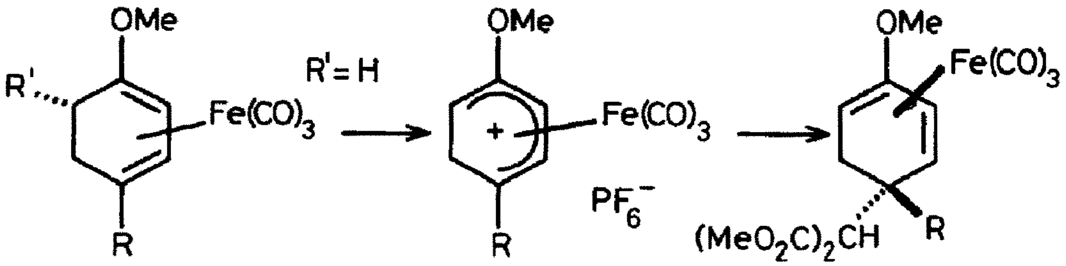


(9) (10)

(6) $R = (CH_2)_2CO_2Me, R' = H$

(7) $R = (CH_2)_2CH_2OH, R' = H$

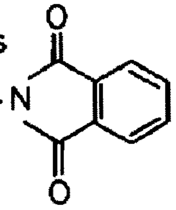
(8) $R' = H$

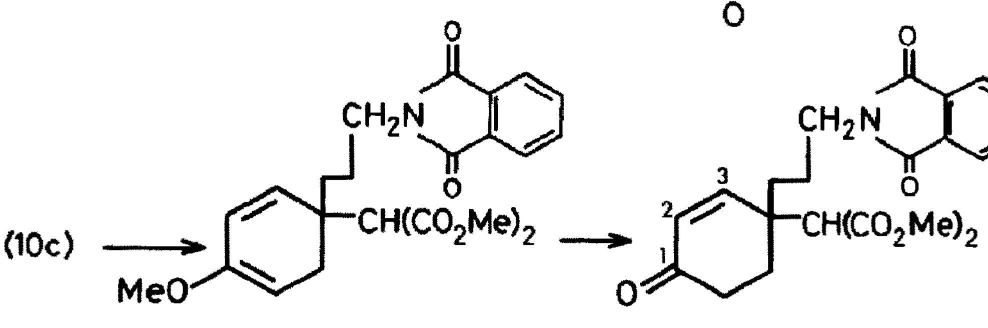
(11) $R' = CH(CO_2Me)_2$

(a) $R = (CH_2)_2CH_2OAc$

(b) $R = (CH_2)_2CH_2OTs$

(c) $R = (CH_2)_2CH_2$—N





(12) (13)

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4. A.J. Pearson, J.C.S. Chem. Comm., 1977, 339; J.C.S. Perkin I, 1977, 2069; ibid., 1978, 495; ibid., 1980, 400; A.J. Pearson and P.R. Raithby, ibid., 1980, 395.
5. A.J. Pearson, J.C.S. Perkin I, 1979, 1255.
6. All new compounds were obtained as racemic mixtures and gave satisfactory analytical and spectroscopic data. Formulae depict relative stereochemistry. We append here the spectral data for phthalimide complex derivatives: (8c) ν_{max} (CHCl$_3$) 2140, 1965, 1772, 1712 cm^{-1}; δ(CDCl$_3$) 7.28 (4H, m), 5.15 (1H, d, J = 5 Hz), 4.96 (1H, d, J = 5 Hz), 3.69 (2H, m), 3.43 (3H, s), 2.6-1.5 (8H). Found: C, 57.6; H, 4.56; N, 3.31%. Calculated for $C_{21}H_{19}FeNO_6$: C, 57.7; H, 4.38; N, 3.20%. (9c) ν_{max} (Nujol) 2115, 2070, 1769, 1724, 845, 564 cm^{-1}; δ(CD$_3$CN) 7.78 (4H), 6.77 (1H, d, J = 6 Hz), 5.62 (1H, d, J = 6 Hz), 3.8 (1H, m), 3.74 (3H, s), 3.59 (2H, t, J = 6 Hz), 2.99 (1H, dd, J = 15, 6 Hz), 2,29 (1H, d, J = 15 Hz), 1.5-1.1 (4H). Found: C, 43.1; H, 3.23; N, 2.42%. Calculated for $C_{21}H_{18}F_6FeNO_6P$: C, 43.4; H, 3.12; N, 2.41%. (10c) m.p. 155.5-156.5^{o}C. ν_{max} (CHCl$_3$) 2055, 1950, 1771, 1755, 1732, 1713, 1490 cm^{-1}; δ(CDCl$_3$) 7.80 (4H, m), 4.98 (1H, dd, J = 6, 2 Hz), 3.71-3.6 (11H, 2 x CO$_2$Me, 4-OMe, C$\underline{H}_2$N), 3.47 (1H, s, C$\underline{H}$(CO$_2$Me)$_2$, 3.27 (1H, m), 2.72 (1H, d, J = 6 Hz), 2.50 (1H, dd, J = 15, 2 Hz), 1.8-1.3 (5H). Found: C, 54.8; H, 4.66; H, 2.48%. Calculated for $C_{26}H_{25}FeNO_{10}$: C, 55.0, H, 4.44; N, 2.47%.

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