Registry No. (±)-**1**, 80514-49-4; (±)-**2**, 39765-89-4; (±)-**3**, 80502-13-2; (±)-**4**, 80514-50-7; (±)-**5**, 80502-14-3; (±)-**6**, 80502-15-4; (±)-**7**-(α-OH), 80502-16-5; (±)-**7**-(β-OH), 80558-53-8; (±)-**8**, 80502-17-6; (±)-**9**, 80514-55-2; **10**, 80502-18-7; **11**, 80502-19-8; (±)-**12**, 80514-51-8; (±)-**14**, 80514-52-9; (±)-**15**, 80514-53-0; (±)-**16**, 80514-54-1; 1-methoxy-3-trimethylsilyloxy-1,3-butadiene, 80502-20-1; (±)-**13**, 80531-97-1.

Total Synthesis of (±)-Limaspermine Derivatives Using Organoiron Chemistry

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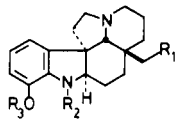
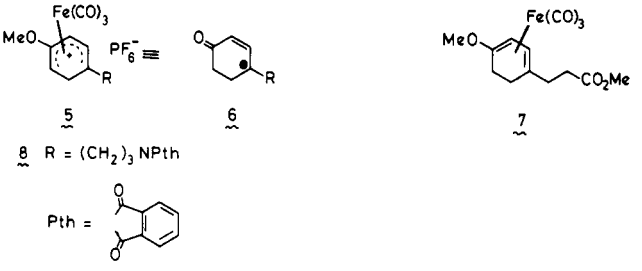
The aspidosperma alkaloids, a group of compounds typified by the simple derivative Aspidospermine (**1**), are now a well-known class of natural products.[1] A number of alkaloids possessing a functionalized C-20 angular grouping have been characterized in recent years,[2] some examples being cylindrocarpinol (**2**), cylindrocarine (**3**), and limaspermine (**4**), among others. Aspi-



1 R_1 = Me, R_2 = Ac, R_3 = Me
2 R_1 = CH_2OH, R_2 = H, R_3 = Me
3 R_1 = CO_2Me, R_2 = H, R_3 = Me
4 R_1 = CH_2OH, R_2 = CO·Et, R_3 = H
19 R_1 = CH_2OMe, R_2 = H, R_3 = Me
20 R_1 = CH_2OMe, R_2 = CO·Et, R_3 = Me
21 R_1 = CH_2OH, R_2 = CO·Et, R_3 = Me

dospermine itself was synthesized by Stork and Dolfini[3] in 1963, while construction of the functionalized derivatives has been reported by Ban et al.[4] and Saxton's group.[5] Our interest in total synthesis of these compounds was stimulated as part of a program aimed at the synthetic utilization of tricarbonylcyclohexadienyliumiron complexes of general structure **5**, which we[6] and others[7] have shown to be synthetic equivalents of the cyclohexenone γ-cation **6**. We were interested in applying suitably functionalized complexes to the synthesis of relatively complex natural products, and in this respect we recently described the conversion of the tricarbonyl(cyclohexadiene)iron complex **7**, readily obtained from *p*-methoxycinnamic acid,[9] to the protected amino derivative **8** in 77% overall yield. We present here the results of our further investigation into the synthetic utility of **8**, culminating in a total synthesis of (±)-limaspermine.

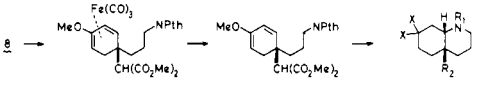


5 **6** **7**

8 R = $(CH_2)_3$NPth

Pth =

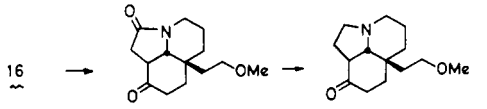
Reaction of **8** with dimethyl potassiomalonate[10] (THF, 20 °C, 15 min), followed by crystallization, afforded the complex **9** in 68% yield; mp 155.5–156.5 °C; ν_{max} 2055, 1950, 1771, 1755, 1732, 1713, 1490 cm^{-1}. We noted that it would be necessary at some



9 **10**

11 X,X = O, R_1 = H, R_2 = $CH(CO_2Me)_2$
12 X,X = OCH_2CH_2O, R_1 = Ac, R_2 = $CH(CO_2Me)_2$
13 X,X = OCH_2CH_2O, R_1 = Ac, R_2 = CH_2CO_2Me
14 X,X = OCH_2CH_2O, R_1 = Ac, R_2 = $(CH_2)_2OMe$
15 X,X = OCH_2CH_2O, R_1 = H, R_2 = $(CH_2)_2OMe$
16 X,X = O, R_1 = $CO·CH_2Cl$, R_2 = $(CH_2)_2OMe$
22 X,X = O, R_1 = H, R_2 = Et

stage to effect decarbomethoxylation of the gem diester, and the following strategy is the one which proved to be least problematical Removal of the metal from **9** (anhydrous Me_3NO, benzene, 50 °C, 1.5 h) gave the hydrolytically unstable dienol ether **10** in 87% yield as an analytically pure white solid which did not give a sharp melting point. Liberation of the primary amine (N_2H_4, MeOH, 40 °C, 1 h) proceeded smoothly, and the resulting dienol ether was hydrolyzed ($[CO_2H]_2$, MeOH, H_2O, 20 °C, 60 min) and cyclized ($NaHCO_3$, MeOH, H_2O, 20 °C, 45 min, 74% overall) to give the *cis*-decahydroquinoline derivative **11**; ν_{max} (CCl_4) 1760, 1740, 1730 cm^{-1}. A number of attempts to decarbomethoxylate **11** resulted in very low yields of the corresponding monoester, and it was necessary to fully protect this compound ((i) Ac_2O, C_5H_5N, 20 °C, 18 h; (ii) $[CH_2OH]_2$, benzene, *p*-TsOH, reflux, 24 h) to give **12** in order to achieve this conversion satisfactorily, at the expense of lengthening the sequence. Decarbomethoxylation of **12** (2 equiv of NaCN, wet Me_2SO, 118 °C, 13 h) afforded the monoester **13** as an analytically pure white solid in 79% overall yield from **11**; mp 71–82 °C (amide resonance shown in 400-MHz NMR spectrum); ν_{max} (CCl_4) 1738, 1650 cm^{-1}. Selective reduction of the ester ($LiBH_4$, THF, 20 °C, 3.5 days, 38 °C, 8 h) followed by protection of the resulting alcohol (NaH, MeI, THF, 20 °C, 15 h) produced the methyl ether **14** (77%); mp 88–93 °C (amide resonance); ν_{max} (CCl_4) 1643 cm^{-1}; 90-MHz NMR ($CDCl_3$) δ 4.6 (1 H, m), 3.97 (4 H, s), 3.43 (2 H, t, J = 7 Hz), 3.33 (3 H, s), 3.65 (2 H, m), 2.09 (3 H, s), 2.3–1.2 (12 H). Deprotection of the amino functionality of **14** proved to be impossible under standard conditions (KOH, aqueous MeOH, reflux) but was readily effected in 96% yield by metal reduction[11] (Ca, liquid NH_3, DME, EtOH, 4 h) to give **15** as a colorless oil, which was converted to the intermediate **16** in the normal way ((i) $ClCH_2COCl$, C_5H_5N, benzene, 10 °C, 4 h, 84%, (ii) ethanolic HCl, 76 °C, 2 h, 95%); ν_{max} ($CHCl_3$) 1720, 1648 cm^{-1}. The remaining steps of the synthesis are unexceptional, following exactly the methodology already used in other syntheses.[3-5] Thus, treatment of **16** with base (1.1 equiv. KOBu-*t*, *t*-BuOH, benzene, 20 °C, 4.5 h) afforded the crystalline tricyclic amido ketone **17** (mp 123–124.5 °C) in 95% yield [ν_{max}($CHCl_3$) 1712, 1687 cm^{-1}] which was converted to the oily tricyclic amino ketone **18** [ν_{max} ($CHCl_3$) 2810, 2735, 2690 (Bohlmann bands), 1705 cm^{-1}] in three steps ((i) $[CH_2OH]_2$, *p*-TsOH, benzene, reflux, 20 h, (ii) $LiAlH_4$, THF, 20 °C, 1 h, (iii) 9% ethanolic HCl, 90 °C, 1 h; 33% overall). This inter-



16 → **17** → **18**

mediate was converted in 39% yield to *O*-methylcylindrocarpinol **19** by Fischer indole cyclization ((i) 2-methoxyphenylhydrazine, HCl, EtOH, reflux, 1 h, (ii) AcOH, 95 °C, 1 h, (iii) $LiAlH_4$, Et_2O); ν_{max} ($CHCl_3$) 3380, 2810, 2735, 1619, 1597 cm^{-1}; 90-MHz

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NMR ($CDCl_3$) δ 6.80–6.50 (3 H, m), 3.77 (3 H, s), 3.60 (1 H, m), 3.14 (3 H, s), 3.40–2.90 (4 H), 2.4–1.0 (15 H, and 1 H exch D_2O). Noteworthy, is the observation that the broad signal at δ 3.60 becomes a sharp doublet of doublets upon D_2O shake. This pattern is typical for H-2 of Aspidosperma alkaloids and is indicative of the correct stereochemistry.[4,5] Treatment of **19** with propionyl chloride–pyridine (4 equiv) in benzene afforded *O,O*-dimethyllimaspermine (**20**), mp 162–163.5 °C, which now showed the characteristic doublet of doublets (J = 9 and 6 Hz) for H-2 at δ 4.56 in the NMR spectrum, again indicative of the correct stereochemistry. We have carried out preliminary studies on the deprotection of the methyl ether group of **20** which are encouraging. Thus, treatment of **20** with iodotrimethylsilane ($CHCl_3$, C_5H_5N, 60 °C, 21 h) afforded a low yield (ca. 25%) of limaspermine (**4**), having IR and mass spectra in agreement with those of the natural product,[2] together with unreacted **20**. Treatment of the dimethyl ether with BBr_3 (4.4 equiv, CH_2Cl_2, −78 °C, then 20 °C, 17 h) gave a low yield of limaspermine monomethyl ether **21**, together with unreacted **20**. No other alkaloid products were evident from these reactions.

Since the above sequence is relatively long, we have not undertaken further deprotection studies of **17**, but instead we have diverted our attention to a more flexible and efficient synthesis of the intermediate **16**, based on methodology we recently developed[12] for a preparation of Stork's aspidospermine intermediate **22**. The work described here establishes a precedent for the application of functionalized tricarbonyldienyliumiron complexes to the total synthesis of nontrivial natural product molecules.

Acknowledgment. We are grateful to the S.E.R.C. and I.C.I. Pharmaceuticals Limited for financial support.

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Silyl Ketone Chemistry.[1] Synthesis and Reactions of Olefinic and Acetylenic Silyl Ketones

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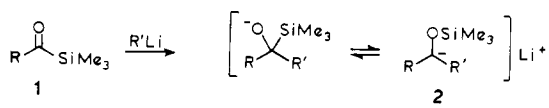
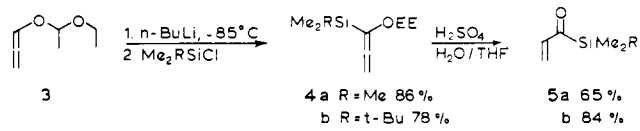
The reaction of organolithium reagents with silyl ketones (**1**) gives siloxy carbanions (**2**), valuable synthetic intermediates for the preparation of enol, dienol, and allenol silyl ethers.[1,2] The

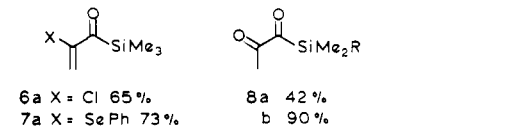


full potential of this methodology cannot be explored without convenient syntheses of silyl ketones with varied substituents R. We report here successful routes to previously unknown or poorly accessible silyl ketones having α,β-olefinic, α,β-acetylenic, and α-keto functions (**1**, R = vinyl, alkynyl, and acyl) and on some of their chemistry.

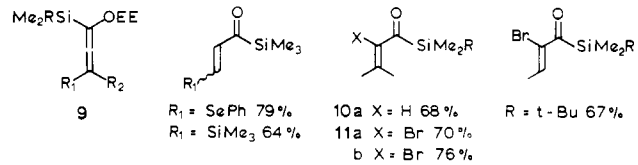
Vinyl silyl ketones have ben prepared by several methods[1b,2d,3] of which the one reported by Leroux and co-workers[3a] seemed to us to be suitable for more general application.[3b] The procedure we have developed uses as starting material the alkoxyallene **3**, readily available from propargyl alcohol.[4] Deprotonation of **3**



and silylation gave silanes **4a** and **4b**[5] (throughout this paper the a series refers to trimethylsilyl and the b to *tert*-butyldimethylsilyl). These compounds are key intermediates for the preparation of a whole family of new silyl ketones. Hydrolysis of **4** (0.2 N H_2SO_4 in 10% aqueous THF) gave the yellow silyl enones **5a**[6a] and **5b**, whereas reaction with other electrophiles such as sulfuryl chloride or benzeneselenenyl chloride (CH_2Cl_2, −78 °C) gave the α-substituted enones **6a** and **7a**.[1a,3b] Oxidation of **4** under carefully controlled conditions[7] gave the deep red α-dicarbonyl compound **8**.[6b]



The silylallenes **4** can be subjected to additional metalations followed by reaction with electrophiles to produce new allenes having one or two γ substituents (**9**).[8] Hydrolysis or bromination



(Br_2, CH_2Cl_2, −78 °C) of these allenes leads to a series of silyl enones, some representative examples of which are shown. Yields in each case are based on compound **4**. Only one of these substances (**10a**) has been prepared previously.[3e]

We have also been successful in using **5** to synthesize the first α,β-acetylenic silyl ketones **12b** and **13b**. The triple bond is formed

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(5) The silylation with *t*-$BuMe_2SiCl$ was carried out in Et_2O, HMPA (1.6 equiv), −85 °C, 15 h.

(6) All new compounds showed IR, NMR, and mass spectra consistent with the structures assigned. Some representative data are as follows. **5a**: NMR δ 0.08 (s, 9 H), 5.76, 5.88 (dd, J = 10, 2 Hz; dd, J = 18, 2 Hz, 2 H), 6.28 (dd, J = 18, 10 Hz, 1 H); ^{13}C NMR δ -2.5 (q), 127.7 (t), 141.0 (d), 236.7 (s); IR 1641, 1604 cm^{-1}; UV (cyclohexane) λ_{max} (ε) 434 (96.4), 213 (8630); MS, M^+ 128.0656 (Calcd 128.06577). (b) **8a**: NMR δ 0.13 (s, 9 H), 2.03 (s, 3 H); IR 1713, 1658 cm^{-1}; ^{13}C NMR δ −2.9, 21.5, 199.2, 235.5; UV (cyclohexane) λ_{max} (ε) 535 (99), 296 (41), 285 (40). (c) **13b**: NMR δ 0.10 (s, 6 H), 0.87 (s, 9 H), 2.05 (s, 3 H); ^{13}C NMR δ −7.5, 4.3, 16.7, 26.3, 85.0, 98.2, 225.7; IR 2200, 1731, 1605 cm^{-1}; UV (cyclohexane) λ_{max} (ε) 420 (170), 227 (7450). (d) **18b**: NMR δ 0.07 (s, 6 H), 0.89 (s, 9 H), 1.21 (t, J = 7.1 Hz, 3 H), 1.72 (s, 6 H), 3.77 (q, J = 7.1 Hz, 2 H), 4.55 (d, J = 6.7 Hz, 1 H), 5.91 (d, J = 6.7 Hz, 1 H); IR 1943 cm^{-1}.

(7) For **8a**: MCPBA (1 equiv), pentane, −10 °C, 15 min; 25 °C, 45 min. For **8b**: MCPBA (1 equiv), CH_2Cl_2, −78 °C, 20 min; 0 °C, 45 min.

(8) The metalations were generally carried out with *n*-BuLi/THF, −78 °C, 30 min. Compound **9** (R_1 = CH_3, R_2 = H) was deprotonated with *sec*-BuLi/THF, −78 °C, 15 min. The derivatizations with Ph_2Se_2, Me_3SiCl, and CH_3I proceeded essentially exclusively at the γ-position.

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