Synthesis of Lysergic Acid Derivatives by Triple Radical Cyclisation

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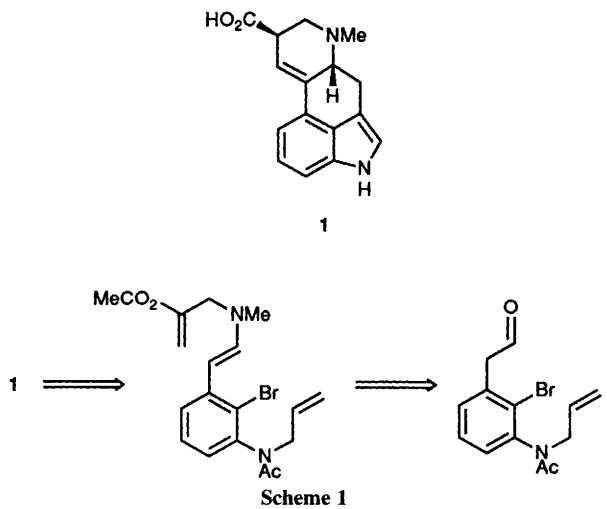
The lysergic acid ring system, characteristic of the ergot alkaloids, is constructed from 2-bromoaniline derivatives by triple radical cyclisation, initiated with tri-n-butyltin hydride; formation of a 6- rather than a 5-membered D ring is controlled by a terminal phenylthio group.

Lysergic acid **1**[1] and its derivatives have been used over the years as psychoactive drugs, and reports as early as 1582 describe the use of ergot extracts to control uterine contractions.[2] The interesting biological profile of the ergot alkaloids coupled with the possibility of deriving new 5-HT bioactive molecules led us to design new ways of constructing lysergic acid and its analogues. Earlier synthetic approaches to **1** have relied on annulation reactions from an indolyl unit;[3] we now report a method for the construction of lysergic acid which utilises the triple radical cyclisation reaction[4] detailed in the analysis shown in Scheme 1.

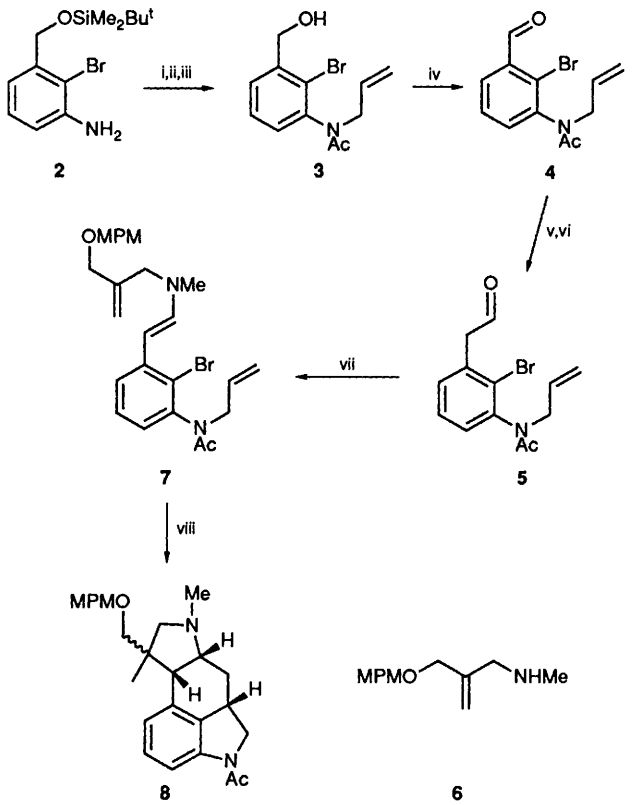
Our synthetic approach to the framework of lysergic acid is shown in Scheme 2 and begins with the readily available amine **2** (Scheme 2a). Treatment of the substituted aniline **2** with one equivalent of lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at −78 °C followed by the sequential addition of allyl bromide and acetyl chloride gave, after work-up with aqueous HF in acetonitrile (2%), the alcohol **3** (83% overall). Conversion of alcohol **3** into aldehyde **4** was achieved in 95% yield using freshly prepared MnO_2 in dry THF. The aldehyde **4** reacted smoothly with methoxymethylenetriphenylphosphorane to give, after work-up with aqueous HCl in THF, the homologated aldehyde **5**† in 85% yield. Exposure of the aldehyde **5** to the allylic amine **6** in dry benzene containing Linde 13X molecular sieves gave the enamine **7** (90%). Addition of Bu_3SnH (1 equiv.) in benzene containing azoisobutyronitrile (AIBN) (10 mol%) to a boiling solution of enamine **7** in benzene (18 h) gave the tetracyclic amine **8** (70%) as a mixture of diastereoisomers at C-8. Formation of the five-membered ring in the D ring of **8** was disappointing, but a ring expansion could be used to create the desired six-membered ring.

A direct approach to the desired six-membered D ring utilises the enamine **10** (Scheme 3) in that the phenylthio group would act as a leaving group in the radical cyclisation.



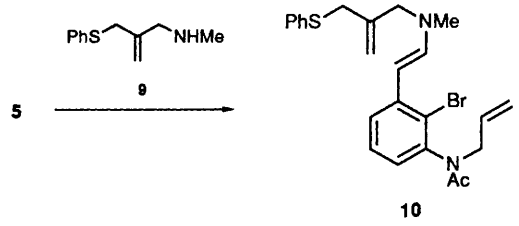
Scheme 1

† *Spectroscopic data*: Compound **5**: ν_{max} (film) 1735 s, and 1660 s br cm^{-1}; δ_H (270 MHz; $CDCl_3$) 1.82 (3 H, s), 3.63–3.71 (1 H, m), 4.00 (2 H, d, *J* 1.35 Hz), 4.78–4.85 (1 H, m), 5.03–5.13 (2 H, m), 5.82–5.97 (1 H, m), 7.03–7.44 (3 H, m) and 9.81 (1 H, t, *J* 1.35 Hz); δ_C (67.9 MHz; $CDCl_3$) 22.4 (q), 50.8 (t), 51.1 (t), 118.6 (t), 126.8 (s), 128.4 (d), 130.2 (d), 131.6 (d), 132.7 (d), 135.4 (s), 142.2 (s), 170.0 (s) and 197.4 (d).



2 3 4 7 5 8 6

Scheme 2 *Reagents*: i, LDA, $BrCH_2CH{=}CH_2$, THF; ii, AcCl, THF; iii, HF, MeCN, H_2O; iv, MnO_2, THF; v, $Ph_3P{=}CH(OMe)$; vi, HCl, THF, H_2O; vii, **6**, PhH, 13X mol. sieves, room temp.; viii, Bu_3SnH, AIBN, PhH, heat



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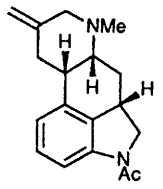
Scheme 3



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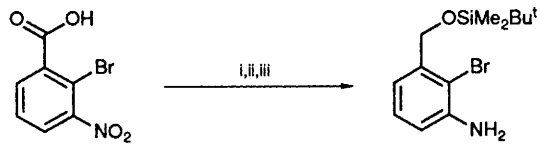

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Scheme 2a *Reagents*: i, BH_3, THF; ii, Fe, HOAc, EtOH; iii, Bu^tMe_2SiCl, DMF, imidazole

Reaction of the secondary amine **9** with **5** as before gave the enamine **10** (90%). Cyclisation of **10** mediated with Bu_3SnH gave the desired tetracyclic indoline **11** (20%) as the only isolable product.

With these results we are working on the ring expansion of the amine **8** and methods to establish the desired 9,10-double bond in lysergic acid using radical chemistry.

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