The Total Synthesis of (±)-Gelsemine

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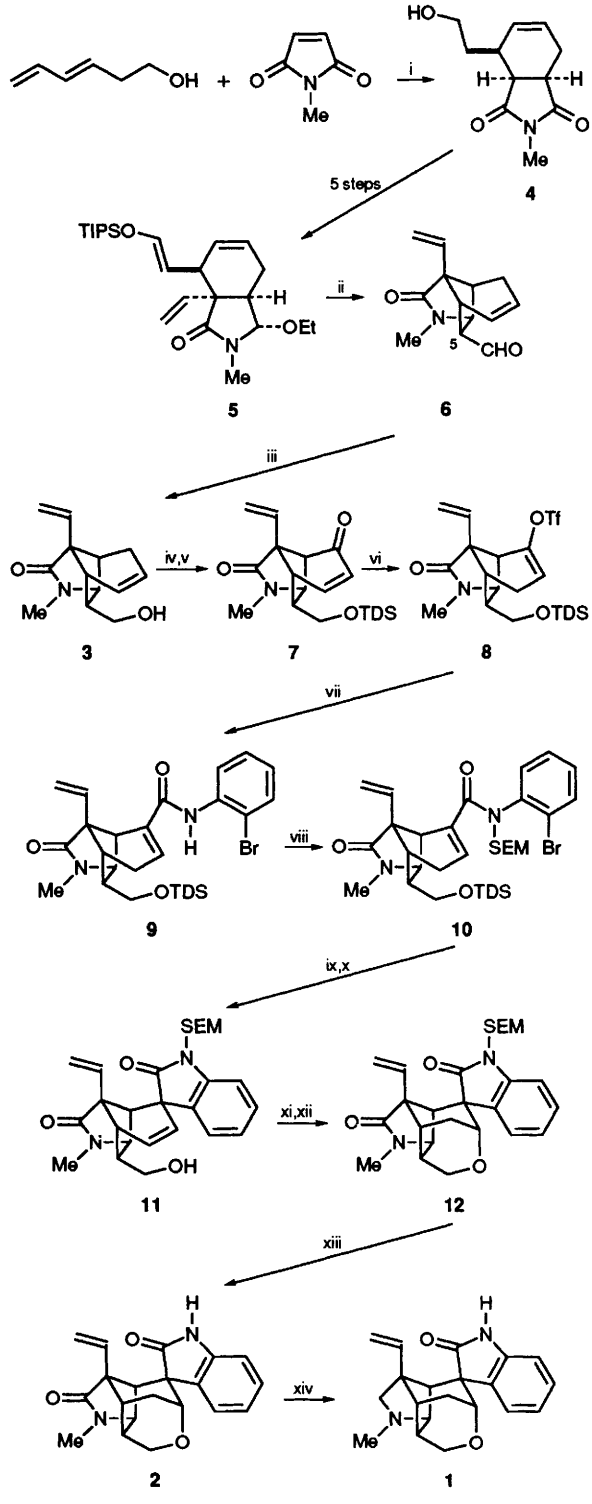
Oxindole alkaloids gelsemine and 21-oxogelsemine in racemic form are synthesised from sorbic acid.

For over a century the isolation and characterisation of novel alkaloids from *Gelsemium sempervirens*, have been described.[1] Gelsemine **1** is the principal alkaloid component and, since the full elucidation of its structure in 1959,[2] has attracted numerous synthetic studies.[3] Our approach to this intriguing alkaloid is based upon the use of tricyclic alcohol **3** as a key building block.[4] In this communication we describe the total synthesis of gelsemine **1** and 21-oxogelsemine **2**, a related constituent of *G. sempervirens*.[5]

The Diels–Alder reaction of (*E*)-hex-3,5-dien-1-ol[6] with *N*-methylmaleimide afforded the pure *endo*-adduct, imide **4**, in excellent yield (Scheme 1).[7] Imide **4** was converted in five steps into ethoxylactam **5** [(*E*):(*Z*), 3:1].[4] Subsequent exposure of **5** to $BF_3{\cdot}Et_2O$ resulted in a highly stereospecific *N*-acyliminium ion cyclisation to give aldehyde **6** as a separable 3:1 mixture of isomers (at C-5). After chromatography aldehyde **6** was reduced with sodium borohydride to give tricyclic alcohol **3**† as a crystalline solid.

To build on the spiro-oxindole moiety present in gelsemine **1** we required a suitable functional handle at C-9 of alcohol **3**. Thus **3** was first protected as a thexyldimethylsilyl (TDS) ether and then subjected to an allylic oxidation with the complex derived from chromium trioxide and 3,5-dimethylpyrazole.[8] This afforded enone **7** in moderate yield along with a minor byproduct, the isomeric enone resulting from an allylic rearrangement. To introduce the spiro-oxindole moiety *via* the intramolecular palladium-catalysed alkene arylation (Heck reaction) of a suitably protected anilide,[9] enone **7** was reduced in a 1,4-selective manner with L-selectride and a subsequent *in situ* trapping of the resultant lithium enolate with *N*-phenyltrifluoromethanesulfonimide and furnished enol triflate **8**[10,11] which was then exposed to standard palladium-catalysed carbonylation conditions in the presence of 2-bromoaniline to give anilide **9**.[12] Since it is known that the Heck cyclisation of such unprotected amides gives poor results,[9] **9** was protected as its trimethylsilylethoxymethyl derivative to give **10**. We found that cyclisation of **10** under standard Heck arylation conditions [$Pd(OAc)_2$, PPh_3, Et_3N, MeCN, reflux, 3 d] gave a single spiro-oxindole product possessing the opposite spiro stereochemistry to that required. However, reaction of **10** under the modified Heck cyclisation conditions recently disclosed by Madin and Overman,[13] gave spiro-oxindole **11** in 60% overall yield after removal of the thexyldimethylsilyl protecting group.‡ In addition we also obtained the epimeric spiro-oxindole in 30% yield.§

With oxindole **11** in hand we investigated the remaining tetrahydropyran ring-forming reaction. Attempts at iodoetherification (I_2, $NaHCO_3$, MeCN) or bromoetherification (NBS, MeCN)[14] of **11** failed to give the required tetrahydropyran. In both cases it was found that the cyclohexene double bond was unreactive, presumably due to steric crowding, and that reaction occurred at the vinyl group to give complex product mixtures. Formation of the tetrahydropyran ring was finally achieved by exposure of spiro-



Scheme 1 *Reagents and conditions*: i, PhMe, reflux, 95%; ii, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 10 °C, 10 min, 70%; iii, $NaBH_4$, EtOH, 90%; iv, TDSCl, imidazole, DMF; v, CrO_3, 3,5-dimethylpyrazole, CH_2Cl_2, −30 °C, 45%; vi, L-selectride, THF, −78 °C then Tf_2NPh, room temp., 18 h, 65% overall; vii, $Pd(OAc)_2$, PPh_3, Et_3N, CO, 2-bromoaniline, DMF, room temp., 24 h, 70%; viii, NAH, SEMCl, THF; ix, $Pd_2(dba)_3$ (dba = benzylidene acetone), Et_3N, PhMe, reflux, 4 h; x, Bu_4NF, THF, room temp., 2 h; xi, HgO, Tf_2O (Tf = trifluoromethanesulfonyl), *N,N*-dimethylaniline, $MeNO_2$, room temp., 3 d, 60%; xii, $NaBH_4$, NaOH, CH_2Cl_2, EtOH, 80%; xiii, Bu_4NF, THF, 4 Å mol. sieves, reflux, 4 h, 90%; xiv, AlH_3, THF, −65–0 °C, 4 h, 50%

oxindole **11** to the complex formed from mercury(II) triflate and *N,N*-dimethylaniline.[15] Reduction of the resultant organomercurial compound with alkaline sodium borohydride afforded SEM-protected 21-oxogelsemine **12**. Treatment of **12** with tetrabutylammonium fluoride in THF at reflux in the presence of powdered molecular sieves gave 21-oxogelsemine **2** which displayed identical spectral data to that reported in the literature.[5b] Finally, selective reduction of the lactam moiety was achieved by reaction of **2** with aluminium hydride in THF[16] to give (±)-gelsemine **1** in moderate yield which exhibited spectral data consistent with that observed for the natural product.

In conclusion the synthesis of (±)-gelsemine and (±)-21-oxogelsamine has been achieved. The availability of enantiopure alcohol **3** from (*R*)-malic acid[17] should allow the synthesis of the natural alkaloids.

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Footnotes

† New compounds displayed ^{1}H NMR, ^{13}C NMR, IR and mass spectra in accord with their assigned structures. Elemental composition was established by combustion or high-resolution mass spectral analysis.

‡ The change in selectivity for the $Pd_2(dba)_3$ catalysed Heck cyclisation was in accordance with the mechanism proposed by Madin and Overman.[13]

§ The stereochemistry of the spiro-oxindoles was proven by NOE difference spectroscopy.

References

1 Z.-J. Liu and R.-R. Lu, in *The Alkaloids*, ed. A. Brossi, Academic Press, NY, 1988, vol. 33, p. 83 and references cited therein; L.-Z. Lin, S. Yeh, G. A. Cordell, C.-Z. Ni and J. Clardy, *Phytochemistry*, 1991, **30**, 679.
2 F. M. Lovell, R. Pepinsky and A. J. C. Wilson, *Tetrahedron Lett.*, 1959, 1; H. Conroy and J. K. Chakrabarti, *Tetrahedron Lett.*, 1959, 6.
3 For recent studies in this area, see *e.g.* D. J. Hart and S. C. Wu, *Tetrahedron Lett.*, 1991, **32**, 4099; *Heterocycles*, 1993, **35**, 135; I. Fleming, R. C. Moses, M. Tercel and J. Ziv, *J. Chem. Soc., Perkin Trans 1*, 1991, 617; W. G. Earley, T. Oh and L. E. Overman, *Tetrahedron Lett.*, 1988, **29**, 3785; L. E. Overman and M. J. Sharp, *J. Org. Chem.*, 1992, **57**, 1035; G. Stark, M. E. Krafft and S. A. Biller, *Tetrahedron Lett.*, 1987, **28**, 1035; J. E. Saxton, *Nat. Prod. Rep.*, 1992, 393.
4 H. Hiemstra, R. J. Vijn and W. N. Speckamp, *J. Org. Chem.*, 1987, **52**, 3882.
5 (*a*) A. Nikiforov, J. Latzel, K. Vasmuzan and M. Wichtl, *Monatsh. Chem.*, 1974, **105**, 1292; (*b*) S. Yeh, G. A. Cordell and M. Garland, *J. Nat. Prod.*, 1986, **49**, 483.
6 T. R. Hoye, A. S. Magee and W. S. Trumper, *Synth. Commun.*, 1982, **12**, 183.
7 R. J. Vijn, H. Hiemstra, J. J. Kok, M. Knotter and W. N. Speckamp, *Tetrahedron*, 1987, **43**, 5019.
8 W. G. Salmond, M. A. Barta and J. L. Havens, *J. Org. Chem.*, 1978, **43**, 2057.
9 M. M. Abelman, T. Oh and L. E. Overman, *J. Org. Chem.*, 1987, **52**, 4130.
10 J. M. Fortunato and B. Ganem, *J. Org. Chem.*, 1976, **41**, 2194.
11 D. S. Fullerton and C. M. Chen, *Synth. Commun.*, 1976, **6**, 217.
12 S. Cacchi, E. Morera and G. Ortar, *Tetrahedron Lett.*, 1985, **26**, 1109.
13 A. Madin and L. E. Overman, *Tetrahedron Lett.*, 1992, **33**, 4859.
14 A. B. Reitz, S. O. Ortey and B. E. Maryanoff, *J. Org. Chem.*, 1987, **52**, 4191.
15 M. Nishizawa, H. Takenaka and Y. Hayashi, *J. Org. Chem.*, 1986, **51**, 806.
16 S. F. Martin, B. Benage, L. S. Geraci, J. R. Hunter and M. Mortimer, *J. Am. Chem. Soc.*, 1991, **113**, 6161.
17 W.-J. Koot, H. Hiemstra and W. N. Speckamp, *J. Org. Chem.*, 1992, **57**, 1059.