Pure & Appl. Chem., Vol. 66, Nos 10/11, pp. 2163–2166, 1994.
Printed in Great Britain.

N-acyliminium ion cyclisations in natural product chemistry: Synthesis of gelsemine

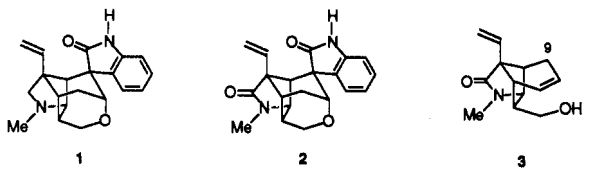
W. Nico Speckamp*, Nicholas J. Newcombe, Henk Hiemstra, Fang Ya, Robert J. Vijn and Wim-Jan Koot

Laboratory of Organic Chemistry, University of Amsterdam
Nieuwe Achtergracht 129, 1018 WS Amsterdam, The Netherlands

Abstract - The oxindole alkaloids gelsemine and 21-oxogelsemine have been synthesised using a stereospecific *N*-acyliminium ion cyclisation to prepare a key intermediate.

Gelsemium sempervirens (the Carolina or yellow jasmine) has a long history of medicinal use and for this reason the isolation and characterisation of the active constituents of this plant continues to receive much attention.[1] Gelsemine (1) is the principal alkaloid component and the elucidation of its unusual structure in 1959[2] has prompted many groups to attempt a total synthesis.[3] Our efforts towards assembling this complex molecule have focused on the early construction of the tricyclic core portion, represented by alcohol (3) (Fig. 1).[4] The synthesis of this key intermediate and the subsequent elaboration to gelsemine (1) and 21-oxogelsemine (2), a related constituent of *Gelsemium sempervirens*[5] will be described in this paper.

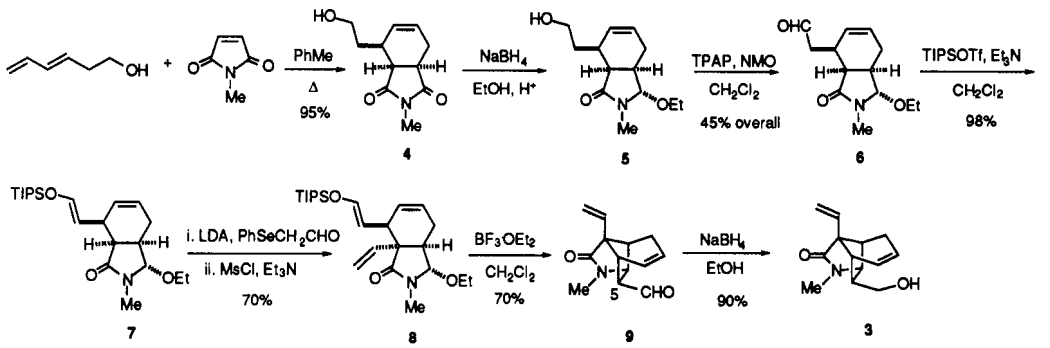
Figure 1



1 2 3

Tricyclic alcohol (3) can be conveniently prepared as shown below (Scheme 1). The Diels Alder reaction of (*E*)-3,5-hexadien-1-ol (available in 3 steps[6] from sorbic acid) with *N*-methylmaleimide afforded the pure *endo*-adduct, imide (4) in excellent yield.[7]

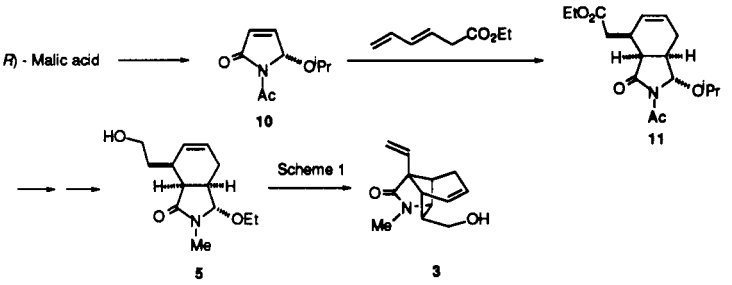
Scheme 1



4 5 6 7 8 9 3

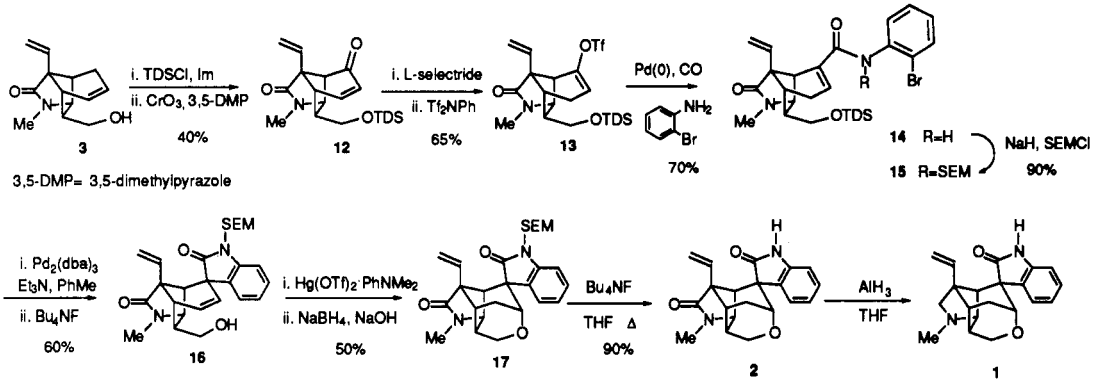
Acid-assisted partial reduction of (4) followed by ethanolysis gave ethoxylactam (5).[4] Subsequent oxidation[8] of (5) gave aldehyde (6) which was treated with triisopropylsilyl triflate in the presence of triethylamine to give enol ether (7) (*E*:*Z*, 3:1).[4] Vinylation of (7) afforded enol ether (8) (*E*:*Z*, 3:1), the precursor for the *N*-acyliminium ion cyclisation. Exposure of (8) to boron trifluoride etherate resulted in a highly stereospecific *N*-acyliminium ion cyclisation to give aldehyde (9) as a separable 3:1 mixture of isomers (at C-5). After chromatographic purification, aldehyde (9) was reduced with sodium borohydride to give tricyclic alcohol (3), the key intermediate in our synthesis, as a crystalline solid.

Scheme 2



Tricyclic alcohol (3) was also accessible in enantiopure form using (*R*)-malic acid as a chiral pool precursor (Scheme 2). Transformation of (*R*)-malic acid into pyrrolinone (10) and subsequent Diels-Alder reaction of this compound with (*E*)-ethyl-3,5-hexadienoate furnished adduct (11) in good overall yield.[9] Lactam (11) could then be converted into ethoxylactam (5), an intermediate in our synthesis of alcohol (3) (Scheme 1).

Scheme 3



The next step in our synthesis was to build on the spiro-oxindole moiety present in gelsemine (1), and for this we required a suitable functional handle at C-9 of alcohol (3). Thus alcohol (3) was first protected as a thexyldimethylsilyl ether and then subjected to an allylic oxidation with the complex derived from chromium trioxide and 3,5-dimethylpyrazole.[10] This afforded enone (12) in moderate yield along with a minor byproduct, the isomeric enone resulting from an allylic rearrangement. We now planned to introduce the spiro-oxindole moiety *via* the intramolecular palladium-catalysed alkene arylation (Heck reaction) of a suitably protected anilide.[11] Enone (12) was therefore reduced in a 1,4-selective manner with L-selectride and a subsequent *in situ* trapping of the resultant enolate species with *N*-phenyltrifluoromethanesulfonimide furnished enol triflate (13).[12,13] This enol triflate was then exposed to standard palladium-catalysed carbonylation conditions in the presence of 2-bromoaniline to afford anilide

(14) in good yield.[14] Since it is known that the Heck cyclisation of unprotected amides gives poor results,[11] anilide (14) was protected as its trimethylsilylethoxymethyl (SEM) derivative by treatment with sodium hydride and SEM chloride to give our cyclisation precursor (15). Surprisingly, we found that cyclisation of (15) 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 (15) under the modified Heck cyclisation conditions recently disclosed by Overman,[13] gave spiro-oxindole (16) in 60% overall yield after removal of the thexyldimethylsilyl protecting group. We also obtained the epimeric spiro-oxindole from this reaction in 30% yield after deprotection, the stereochemistry of the spiro-oxindole products being assigned on the basis of NOE difference spectroscopy.

With oxindole (16) in hand we investigated the remaining tetrahydropyran ring-forming reaction. Our preliminary studies on the cyclisation of tricyclic alcohol (3) suggested that an iodine-mediated etherification might be a suitable method for this transformation.[4] However, attempts at iodoetherification (I_2, $NaHCO_3$, MeCN) or bromoetherification (NBS, MeCN)[16] of (16) 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-oxindole (16) to the complex formed from mercury(II) triflate and *N,N*-dimethylaniline.[17] Reduction of the resultant organomercurial compound with alkaline sodium borohydride afforded SEM-protected 21-oxogelsemine (17) in moderate overall yield. Treatment of (17) with tetrabutylammonium fluoride in THF at reflux in the presence of powdered 4 Å 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 accomplished by reaction of (2) with freshly prepared aluminium hydride in THF[18,19] to give (±)-gelsemine (1) in moderate yield. This synthetic sample exhibited spectral data consistent with that observed for the natural product.

In conclusion, the synthesis of (±)-gelsemine and (±)-21-oxogelsemine has been achieved. The availability of enantiopure alcohol (3) from (*R*)-malic acid[9] should allow a synthesis of the natural alkaloids.

Acknowledgements

We thank M. T. Verhaar and M. J. Moolenar for technical assistance. The Royal Society are gratefully acknowledged for a postdoctoral fellowship (N. J. N.). This investigation was partly supported by the Netherlands' Foundation for Chemical Research (SON) with financial aid from the Netherlands' Organisation for the Advancement of Pure Research (NWO).

References

1 (a) Z.-J. Liu and R.-R. Lu, in *The Alkaloids*, ed. A. Brossi, vol. 33, p. 83, Academic Press, New York, (1988) and references cited therein; (b) L.-Z. Lin, S. Yeh, G. A. Cordell, C.-Z. Ni and J. Clardy, *Phytochemistry*, **30**, 679, (1991)

2 (a) F. M. Lovell, R. Pepinsky and A. J. C. Wilson, *Tetrahedron Lett.*, 1, (1959); (b) H. Conroy and J. K. Chakrabarti, *Tetrahedron Lett.*, 6, (1959).

3 For recent studies in this area, see: (a) D. J. Hart and S. C. Wu, *Tetrahedron Lett.*, **32**, 4099, (1991); *Heterocycles*, **35**, 1351, (1993); (b) I. Fleming, R. C. Moses, M. Tercel and J. Ziv, *J. Chem. Soc., Perkin Trans. 1*, 617, (1991); (c) W. G. Earley, T. Oh and L. E. Overman, *Tetrahedron Lett.*, **29**, 3785, (1988); L. E. Overman and M. J. Sharp, *J. Org. Chem.*, **57**, 1035, (1992); (d) G. Stork, M. E. Krafft and S. A. Biller, *Tetrahedron Lett.*, **28**, 1035, (1987); (e) J. E. Saxton, *Nat. Prod. Rep.*, 393, (1992).

4 H. Hiemstra, R. J. Vijn and W. N. Speckamp, *J. Org. Chem.*, **52**, 3882, (1987).

5 (a) A. Nikiforov, J. Latzel, K. Vasmuzan and M. Wichtl, *Monatsh. Chem.*, **105**, 1292, (1974); (b) S. Yeh, G. A. Cordell and M. Garland, *J. Nat. Prod.*, **49**, 483, (1986).

6 T. R. Hoye, A. S. Magee and W. S. Trumper, *Synth. Commun.*, **12**, 183, (1982).

7 R. J. Vijn, H. Hiemstra, J. J. Kok, M. Knotter and W. N. Speckamp, *Tetrahedron*, **43**, 5019, (1987).

8 W. P. Griffith, S. V. Ley, G. P. Whitcombe and A. D. White, *J. Chem. Soc., Chem. Commun.*, 1625, (1987).

9 W.-J. Koot, H. Hiemstra and W. N. Speckamp, *J. Org. Chem.*, **57**, 1059, (1992).

10 W. G. Salmond, M. A. Barta and J. L. Havens, *J. Org. Chem.*, **43**, 2057, (1978).

11 M. M. Abelman, T. Oh and L. E. Overman, *J. Org. Chem.*, **52**, 4130, (1987).

12 J. M. Fortunato and B. Ganem, *J. Org. Chem.*, **41**, 2194, (1976).

13 D. S. Fullerton and C. M. Chen, *Synth. Commun.*, **6**, 217, (1976).

14 S. Cacchi, E. Morera and G. Ortar, *Tetrahedron Lett.*, **26**, 1109, (1985).

15 A. Madin and L. E. Overman, *Tetrahedron Lett.*, **33**, 4859, (1992).

16 A. B. Reitz, S. O. Ortey and B. E. Maryanoff, *J. Org. Chem.*, **52**, 4191, (1987).

17 M. Nishizawa, H. Takenaka and Y. Hayashi, *J. Org. Chem.*, **51**, 806, (1986).

18 H. C. Brown and N. M. Yoon, *J. Am. Chem. Soc.*, **88**, 1464, (1966).

19 S. F. Martin, B. Benage, L. S. Geraci, J. E. Hunter and M. Mortimer, *J. Am. Chem. Soc.*, **113**, 6161, (1991).