A Total Synthesis of Gelsemine: Synthesis of a Key Tetracyclic Intermediate

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The synthesis of tetracyclic ketone **21**, a key intermediate in the total synthesis of the alkaloid gelsemine, is described.

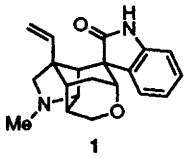
The presence of alkaloids in *Gelsemium sempervirens* more commonly known as yellow jasmine, was first established in 1870.[1] The principal component is gelsemine **1** whose structure was eventually elucidated in 1959 by X-ray analysis[2] and independently by a combination of ^{1}H NMR spectroscopy and biosynthetic considerations.[3] Synthetic studies have been reported since 1967,[4,5] but to date there has only been one total synthesis of gelsemine **1**[6] which relates to our work which we report here.

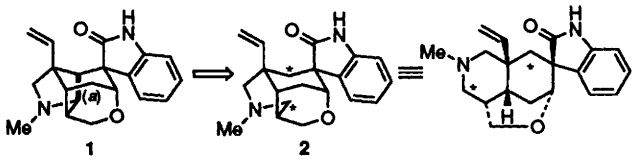
Our approach is based on the application of an extended version of the Corey rules[7] for the strategic bond recognition in bridged polycyclic systems to gelsemine **1**. This led to the identification of one particular bond [bond (*a*) in **1**, Scheme 1], the retrosynthetic disconnection of which yields an intermediate **2** of much greater simplicity.

The functionality present in gelsemine **1** itself did not suggest an obvious method of making this bond. However, if the oxindole unit was removed from gelsemine **1**, in the retrosynthetic sense, to give ketone **3**, this compound should be able to form the required bond by an intramolecular Mannich reaction of the iminium species **4** (Scheme 2) which in turn might be derived by protonation of enamine **5**.

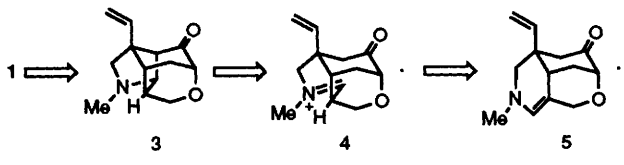
The first key reaction in our successful implementation of this approach involved a photoinduced intramolecular cycloaddition of the triene **6** Scheme 3), which gave the key tricyclic diester intermediate **7** which not only possesses 12 of the 13 carbon atoms present in the target ketone **3**, but also has the masked vinyl group in the required *cis* relationship to the hydrogen substituent at the ring fusion.†

The tricyclic diester **7** was reduced to the corresponding diol, using a sixfold excess of lithium aluminium hydride (a relatively slow reaction because of the steric crowding of the ester groups). The tetrahydropyranyl ring was formed using silver acetate-iodine, which gave the acetoxy alcohol **8**. After **8** had been oxidised to the corresponding acid and esterified, the base labile acetoxy group was exchanged for the TBDMS protecting group, to give the methyl ester **9** (Scheme 3).





Scheme 1

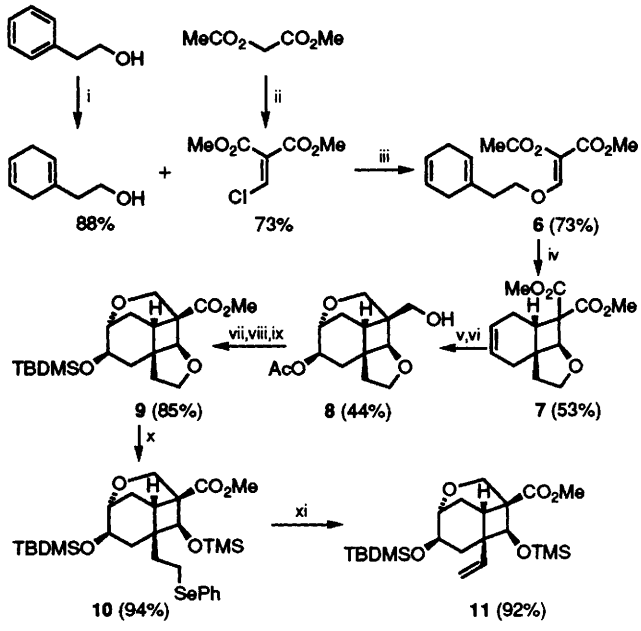


Scheme 2

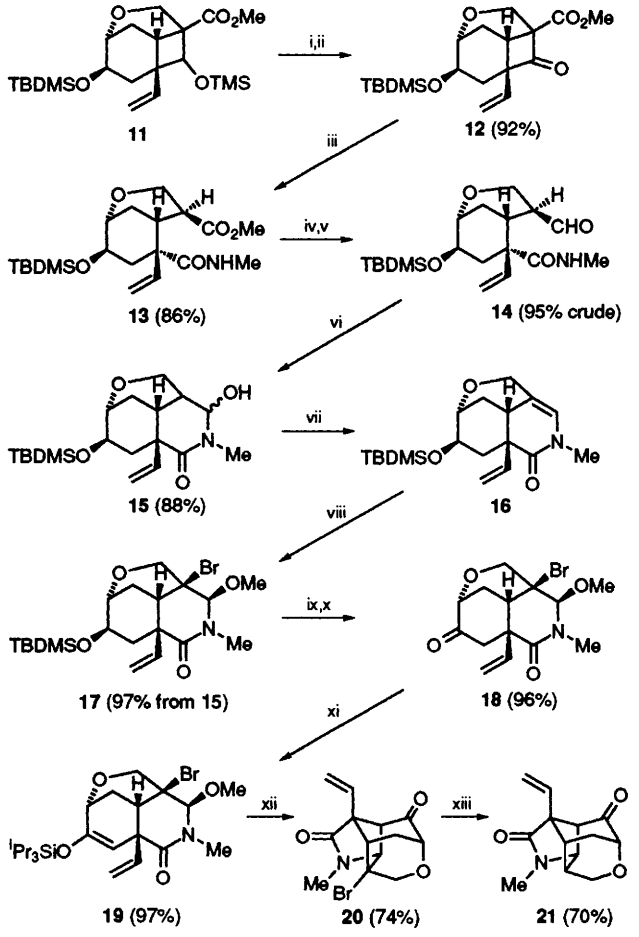
It had initially been intended that the key intramolecular Mannich reaction would be carried out on a compound retaining the tetrahydrofuranyl mask for the vinyl group, but extensive experimentation[8] has provided no example where the desired cyclisation could be achieved in the presence of this tetrahydrofuran ring. Accordingly, phenyl trimethylsilylselenide in the presence of catalytic zinc iodide was used to cleave the tetrahydrofuran ring of **9** to give the tricyclic selenide **10** in almost quantitative yield. Neither ester demethylation nor cleavage of the tetrahydropyranyl ether ring were observed. One possible explanation for this selectivity involves iniitial chelation of the zinc cation by the ester and tetrahydrofuranyl ether groups of **9** followed by attack of a selenide nucleophile. This highly selective ether cleavage using phenyltrimethylsilylselenide appears to be a new use for this reagent which had previously been used to cleave esters and lactones.[9] Oxidative deselenylation of **10** gave the alkene **11**.

11 was desilylated with care to give an unstable cyclobutanol, (under more strongly basic conditions the compound underwent a retroaldol ring opening), which was immediately oxidised to the cyclobutane-β-ketoester **12**. Cleavage of the cyclobutanone ring of **12** in a retro Claisen reaction was accomplished by treatment with methylamine (Scheme 4), which cleanly afforded the amido ester **13** as a single diastereoisomer, whose stereochemistry was confirmed by NOE experiments.

The amido ester **13** was converted into the aldehyde **14** by a two-step process. This involved the chemoselective reduction of the ester function to the alcohol, using lithium methoxyborohydride and reoxidation using the procedure of Ratcliffe and Rodehorst.[10] The aldehyde **14** thus obtained was found not to be stable and was therefore subjected to further



Scheme 3 *Reagents and conditions*: i, K_2CO_3, MeOH, THF; ii, (*a*) Me_2SO, TFAA, −70 °C, (*b*) $POCl_3$, reflux; iii, pyridine; iv, *hν*, MeOH, trace AcOH; v, $LiAlH_4$, THF; vi, AgOAc, I_2, AcOH; vii, (*a*) $RuCl_3$, $NaIO_4$, MeCN, CCl_4, H_2O, (*b*) CH_2N_2, Et_2O; xiii, K_2CO_3, MeOH, THF; ix, Bu^tMe_2SiOTf, 2,6-lutidine, DCM, −5 °C; x, $PhSeSiMe_3$, ZnI_2, PhMe, reflux; xi, (*a*) *m*CPBA, THF, −25 °C, (*b*) Pr_2NH, CCl_4, reflux



Scheme 4 *Reagents and conditions*: i, K_2CO_3, MeOH, THF; ii, (*a*) Me_2SO, TFAA, −70 °C, (*b*) Et_3N; iii, $MeNH_2$, MeOH, THF; iv, $LiBH_4$, MeOH, Et_2O; v, CrO_3, pyridine, DCM; vi, K_2CO_3, MeOH; vii, TsOH, DCM; viii, Br_2, MeOH; ix, Bu_4NF, THF; x, (*a*) Me_2SO, $(COCl)_2$, (*b*) Et_3N; xi, Pr^i_3SiOTf, Et_3N; xii, TFA, reflux, 15 min; xiii, Bu_3SnH, benzene, reflux

transformations in its crude state immediately after preparation. The aldehyde **14** did not, however, spontaneously cyclise to the hydroxy amide **15**, which confirmed the stereochemical assignment of the ester **13**, since in this stereoisomer the reactive centres are too far apart for cyclisation to occur. Epimerisation of the aldehyde **14** with methanolic potassium carbonate brought the carbonyl group of the aldehyde and the amide nitrogen within bonding distance, and allowed cyclisation to occur to give the hydroxy lactam **15** (Scheme 4) which readily dehydrated to the corresponding enamide **16**.

Although enamides are well known *N*-acyliminium ion precursors, compound **16** is also a vinylogous *N*-acylaza-acetal, and as such would be expected to undergo cleavage of the pyran cycle upon treatment with strong acid. Clearly, it is desirable to modify the functionality of the enamide double bond in a way that isolates the pyran ring yet retains the capacity to generate the desired *N*-acyliminium cation. This was achieved by treatment of enamide **16** with methanolic bromine in the presence of suspended calcium carbonate buffer which gave a near quantitative yield of the tertiary methoxy bromide **17**.

Desilylation and oxidation of **17** gave the key intermediate ketolactam **18**, a close relative of the target ketoiminium structure **4**, suggested by retrosynthetic analysis. The ketolactam **18** was then converted into its enol silyl ether **19**, thus setting the stage for the operation of the key reaction in the whole sequence, the acyliminium ion variation of the desired intramolecular Mannich reaction. In practice, the conversion of **19** of the bromoketone **20**‡ proceeded very cleanly in hot trifluoroacetic acid. This cyclisation can be viewed as a 5-*endo-trig* cyclisation and the smooth occurrence of this normally disfavoured reaction might reflect the fact that very few, if any, alternative reaction pathways are available to the acyliminium ion generated from **19**.

Reductive debromination of the ketone **20** with tri-butyltin hydride and AIBN in refluxing benzene gave **21**, the oxo derivative of the intermediate target **3**. The conversion of **3** to 21-oxogelsemine and gelsemine is described in the following paper.

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Footnotes

† Shown by a single crystal X-ray structure determination carried out by Dr E. M. McPartlin, University of North London.

‡ Structure confirmed by a single crystal X-ray structure determination carried out by Dr M. Thornton-Pett, University of Leeds.

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