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The synthesis of (±)-gelsemine

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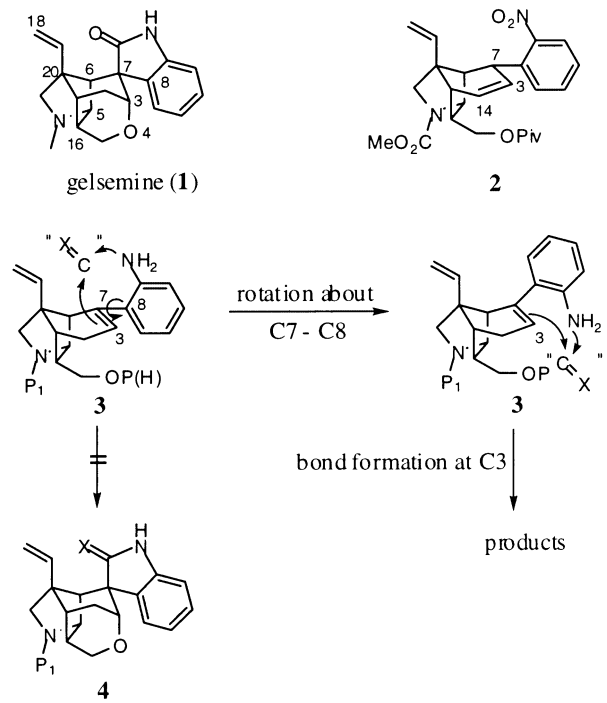
Abstract—The synthesis of (±)-gelsemine has been completed from tetracyclic intermediate **2** via a stereospecific [3,3]-rearrangement followed by a one carbon excision to convert a δ-lactam (**13**) to a γ-lactam (**19**). © 2002 Published by Elsevier Science Ltd.

In the preceding paper[1] we reported on a synthesis of compound **2** in furtherence of a proposed total synthesis of gelsemine (**1**).[2] Before describing how gelsemine was reached via **2**, we must place our study in context. It was possible in several settings to accomplish overall isomerization of the non conjugated $\Delta 3^{(14)}$ double bond to the conjugated $\Delta 3^{(7)}$ series, in which the aromatic amino function is also presented (see Scheme 1, structure type **3**). With this capability, a number of possibilities for introduction of a one carbon residue between C7 and the anilino nitrogen group were surveyed (cf. **3**→**4**, with or without concurrent participation from the primary hydroxy function). These attempts were uniformly unsuccessful. Instead, those reactions that could be achieved, were initiated by attack of a one carbon moiety at C3 (in a Markovnikov sense) rather at C7 as would be required for spirocyclization to a 5-membered anilide.[3]

A key element in the overall isomerization (ie. conjugation) of the double bond to the $\Delta 3^{(7)}$ series was allylic bromination of a $\Delta 3^{(14)}$ double bond isomer to introduce a β-bromine at C14 with reappearance of the double bond at the $\Delta 3^{(7)}$ position.[4] This reaction was now conducted on pivaloate **2**, thereby affording **5** (Scheme 2).[5] Debromination of **5** (tri-*n*-butyltin hydride) in the presence of O_2, followed by the reduction of the resulting hydroperoxide with sodium borohydride afforded **6** with high stereoselectivity.[6] Alternatively, acetolysis of **5** was accomplished, with silver acetate in acetic acid, to provide **7**.[7] The overall stereochemical retention result in this reaction attests to the highly hindered nature of the α-face of the 'ball-like' surface of **5**, and species derived therefrom. Reduction of the nitro group afforded the amine, which was protected with CbzCl to provide **8**. Deprotection of the acetate afforded **9**.

Major efforts were directed to the goal of using the C14 β-OH group to introduce a β-one carbon fragment at C7 by suprafacial allylic transposition (cf. **10**→**11**, Scheme 3). Such attempts were uniformly unsuccessful. A particularly disappointing case is seen in the high



Scheme 1.

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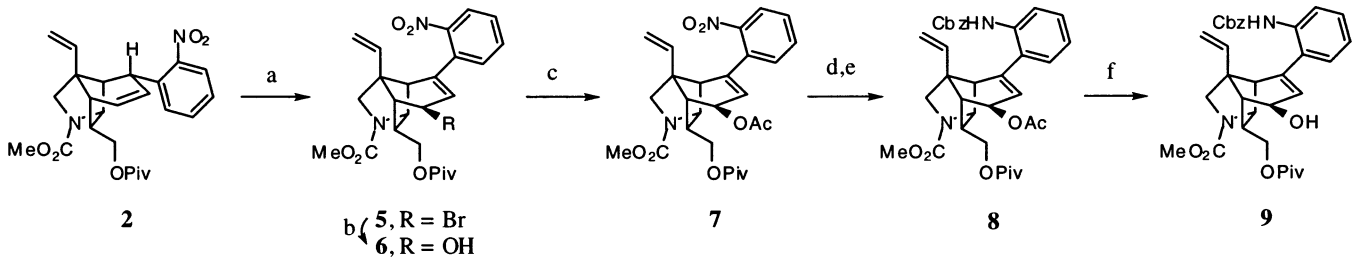
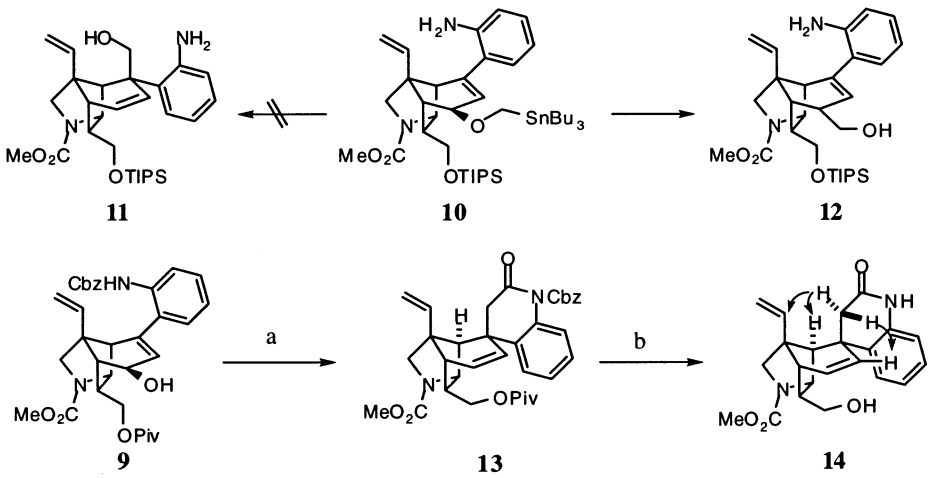


Scheme 2. *Reagents and conditions*: (a) NBS, AIBN, hν, CCl_4/CH_2Cl_2, reflux, 60% based on recovered starting material; (b) AIBN, Bu_3SnH, dry air, hν, toluene, 60°C; $NaBH_4$, 0°C; 55% based on recovered starting material; (c) AgOAc, HOAc, 52%; (d) zinc dust, THF/HOAc; (e) CbzCl, $NaHCO_3$ (aq.), CH_2Cl_2, 94% for two steps; (f) K_2CO_3, MeOH, 90%. NBS = *N*-bromosuccinimide, AIBN = 2,2′-azobisisobutyronitrile, CbzCl = benzyl chloroformate.



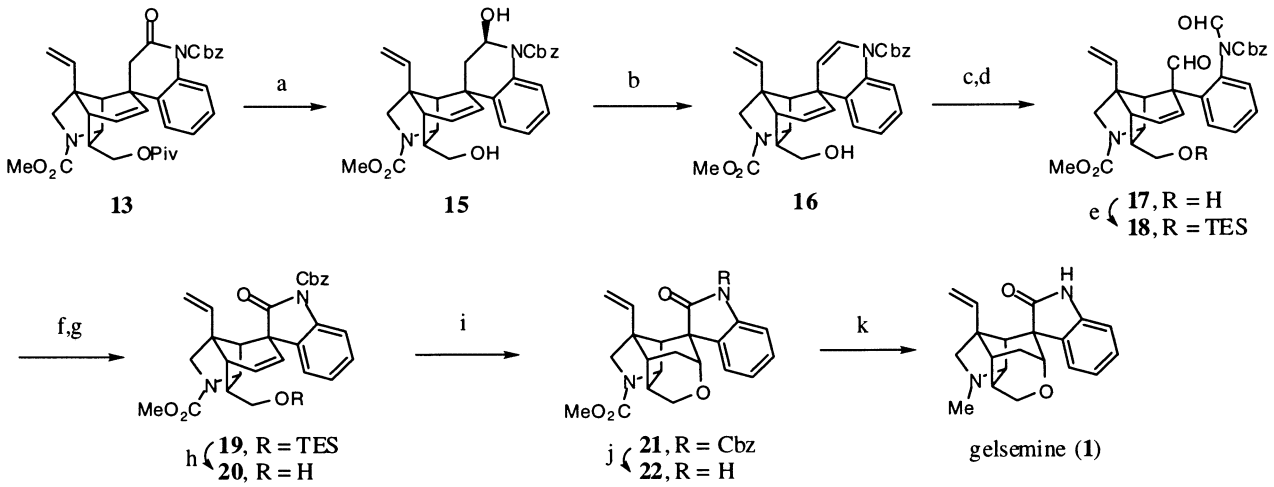
Scheme 3. *Reagents and conditions*: (a) $CH_3C(OMe)_2NMe_2$, *m*-xylene, silica gel purification, 30–40%; (b) NaOMe, MeOH, 74%.

yielding transformation of **10**→**12**[8] by apparent [1,2] transposition,[9] in the context of a projected Still–Wittig rearrangement.[10] Apparently, formidable steric forces are arrayed against carbon–carbon bond formation even on the β-face of C7, and even by intramolecular means. Fortunately, it was found that the Eschenmoser amide acetal version of the Claisen rearrangement took place in the desired [3,3] sense.[11] Subjection of **9** to the conditions shown, led to **13** and, following deprotection of the pivaloate group, **14**.[12]

We now faced the challenging prospect of shrinking the 6-membered lactam to a 5-membered spiroanilide for purposes of reaching gelsemine (**1**). The sequence to accomplish this goal began with reduction of the imide-like functionality of **13** to afford aminal **15** (Scheme 4). Dehydration of this aminal, as shown, furnished enamide **16** (50% yield over two steps). Dihydroxylation of **16**, across the more electron-rich enamide double bond, provided a trihydroxy intermediate, which was subjected to oxidative cleavage, as shown. This degradation provided a 45% yield of **17**, containing an all-important β-face aldehyde at C7. Protection of the hydroxy group of **17** led to silyl ether **18**. Methanolysis of this compound served to accomplish *N*-deformylation and, concurrently, ring closure to a cyclic hemiaminal. The latter, following oxidation, gave rise to oxindole **19**. Desilylation of **19**, as shown, led to **20** in which the extremely hindered free hydoxymethyl group on α-face (initially derived by intramolecular oxetane opening)[1] was now poised to close the tetrahydropyran ring.

Oxymercruation of **20** with $Hg(OTf)_2$ *N*,*N*-dimethylaniline complex in CH_3NO_2[13,14] afforded the desired mercuric cyclization product which, following reductive demercuration (using Fukuyama's protocol),[15] furnished hydropyran **21** in 60% yield. Hydrolysis of the Cbz protected oxindole in **21**,[16] with 10% of NaOH in THF afforded a 90% yield of **22**. Finally, the methyl carbamate of **22** was reduced to an *N*-methyl group with $LiAlH_4$,[17] thereby affording **1** whose spectroscopic and chromatographic properties matched those of naturally derived gelsemine.

In summary, we had set out to explore some novel synthetic constructions using the synthesis of gelsemine (**1**) as an orienting, clearly defined, goal. Many interesting issues of selectivity, both at regiochemical and stereochemical levels, were resolved in favorable ways.[1,18] Our findings as to reaction specificities in subtle cases merit continuing study. While confident application of these findings to new cases would require broadening of our database as to scope and limitations, the finding reported here as part of the synthesis, already invite potentially important interpretations.



Scheme 4. *Reagents and conditions*: (a) DIBAL, CH_2Cl_2, −78°C; (b) $TsOH{\cdot}H_2O$, CH_2Cl_2, reflux, 50% for two steps; (c) OsO_4, THF, −25°C; Na_2SO_3 (aq.); (d) $NaIO_4$, THF/H_2O, 45%; (e) TESOTf, Et_3N, CH_2Cl_2, 0°C, 80%; (f) NaOMe, MeOH; (g) TPAP, NMO, CH_2Cl_2, 4 Å MS, 50% for two steps; (h) TBAF/HOAc 1:1, THF, 80%; (i) $Hg(OTf)_2{\cdot}C_6H_5NMe_2$, CH_3NO_2; $NaBH_4$, 10% NaOH, Et_3BnNCl, CH_2Cl_2, 60%; (j) 10% NaOH, THF, 90%; (k) $LiAlH_4$, THF, 0–25°C, 81%. DIBAL = diisobutylaluminum hydride, TESOTf = triethylsilyltrifluoromethanesulfonate, TPAP = tetrapropylammonium perruthenate, NMO = *N*-methylmorpholine *N*-oxide.

Unfortunately, the focused gelsemine target goal became quite complicated in that its solution required excision of a one carbon unit from a six-membered lactam to a five-membered spiroanilide (see **13→19**). In the end, this ring contraction was accomplished. A full account of these experiments and other interesting excursions directed to gelsemine (**1**) is planned.

Acknowledgements

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