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A Concise Approach to a Gelsemine Core Structure using an Oxygen to Carbon Bridge Swapping Strategy

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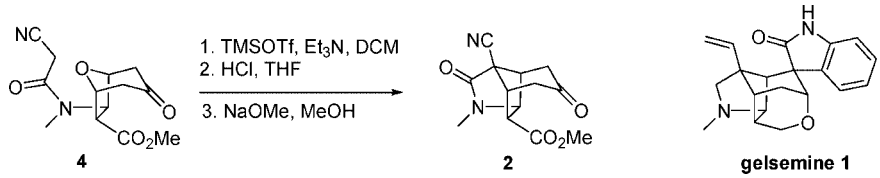
ABSTRACT



4 **2** **gelsemine 1**

A tricyclic core structure 2 related to gelsemine 1 was synthesized from an oxabicyclo[3.2.1]octanone 4 by a three-step bridge swapping strategy involving elimination of the bridging ether oxygen and intramolecular Michael addition of a tethered cyanoacetamide unit.

Although studies of alkaloids isolated from *Gelsemium sempervirens* (yellow jasmine) stretch back into the 1870s, it was not until 1959 that the structure of the major alkaloid from this plant, gelsemine (**1**), was established contemporaneously by two groups through the use of X-ray and NMR spectroscopy.[1,2]

The complex structure of gelsemine has provided a formidable challenge for generations of synthetic chemists,[3] with the first successful total syntheses reported by the research groups of Johnson and Speckamp in 1994.[4] Further syntheses of racemic gelsemine by the groups of Hart, Fukuyama, Overman, and Danishefsky followed,[5] and an asymmetric synthesis was subsequently reported by Fukuyama in 2000.[6]

Most recently, Grecian and Aubé described a new access to an advanced intermediate in the Fukuyama synthesis of gelsemine, which involved a double-conjugate addition to a quinone monoketal.[7] This report has prompted us to describe our own studies in this area, in which an alternative double conjugate addition approach has enabled the preparation of a core structure related gelsemine.

Our analysis of gelsemine focused on the rapid construction of a functionalized bicyclo[3.2.1]octane system, and we identified tricyclic ketolactam **2** as an attractive target and a potential intermediate for gelsemine synthesis (Scheme 1). The key concept that we wanted to establish was assembly of the core bicyclooctane by means of a double-conjugate addition of a one-carbon unit to an appropriately function-

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(1) Wormley; T. G., *Am. J. Pharm.* **1870**, *42*, 1–16.
(2) Lovell, F. M.; Pepinsky, R.; Wilson, A. J. C *Tetrahedron Lett.* **1959**, *1*, 1–5. Conroy, H.; Chakrabarti, J. K. *Tetrahedron Lett.* **1959**, *1*, 6–13.
(3) Lin, H.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 36–51.
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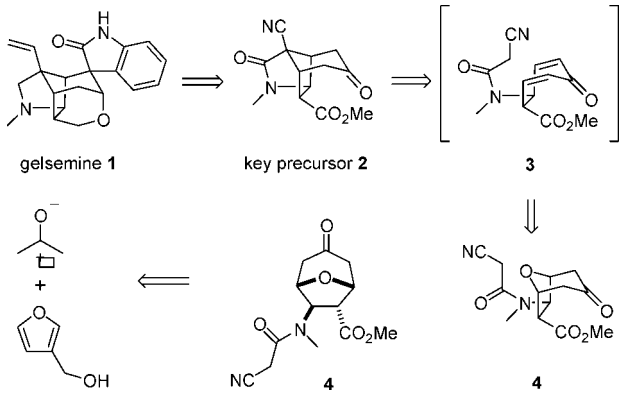
Scheme 1. Bridge Swap Strategy to Gelsemine **1**

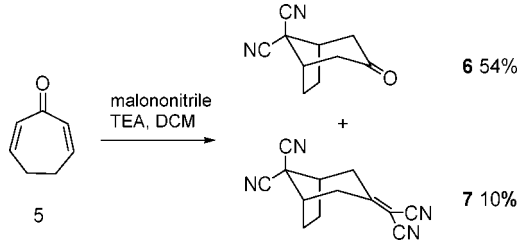


alized cycloheptadienone. Further consideration of stereochemical control led to the idea of using an *intramolecular* double addition of a tethered system, such as the cyanoacetamide **3**, which could furnish tricycle **2** directly. We considered the most straightforward access to cycloheptadienone **3** to be via a double β-elimination of the ether bridge present in *oxa*bicycle **4**. Most appealing was the possibility that treatment of **4** with appropriate base/Lewis acid combinations might effect both the ether elimination steps and the conjugate addition reactions. Such an oxygen to carbon one-atom "bridge-swapping" tactic promised conciseness, and the required oxabicyclooctanone **4** was expected to be available via well established [4 + 3] cycloaddition chemistry of commercial 3-hydroxymethylfuran.[8]

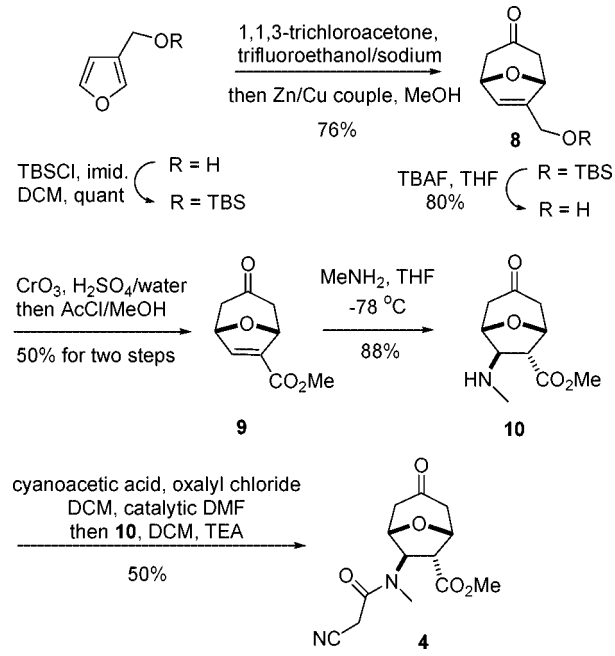
Considering the ubiquitous nature of bicyclo[3.2.1]octanes, we were surprised to find only a single precedent for double addition of a one *carbon* unit, such as malonate (or equivalent) to a cyclohepta-2,6-dienone.[9] We therefore chose to validate this central idea with a simple model before proceeding further.

The parent cycloheptadienone **5** was readily available by oxidation of cycloheptanone with IBX.[10] When a solution of **5** in dichloromethane was treated with a solution of malononitrile and triethylamine in dichloromethane at room temperature, rapid formation of two new products was observed by TLC (Scheme 2). Both products **6** and **7** were products of malononitrile additions to form the [3.2.1] skeleton, as anticipated, with the minor product **7** arising from subsequent 1,2-addition to ketone **6**.

Scheme 2. Model Malononitrile Double Addition



Scheme 3. Synthesis of **4**



Encouraged by these results we embarked on the synthesis of the cyclization precursor **4**. TBS-protected furan-3-methanol was reacted with trichloroacetone under Föhlisch conditions to give ketone **8**,[11] which was deprotected,[12] oxidized with Jones' reagent, and esterified in methanol/acetyl chloride to give the ester **9**. Conjugate addition of methylamine proceeded cleanly with complete facial selectivity giving secondary amine **10**, which was converted into the cyclization precursor **4** on treatment with excess of freshly prepared 2-cyanoacetyl chloride in dichloromethane.

This short, largely unoptimized sequence allowed very rapid access to multigram quantities of ketone **4** for further synthesis.

Whereas β-elimination of the bridging ether oxygen in 8-oxabicyclo[3.2.1]octan-3-one systems, related to **4**, has been described by several research groups, using various Lewis or Brönsted acids,[13] we encountered serious difficulties in attempts to effect the required double-elimination−double-addition process. We tested around 30 sets of conditions for elimination of the bridging ether oxygen in **4**. Use of strong

(8) Harmata, M.; Rashatasakhon, P. *Tetrahedron* **2003**, *59*, 2371–2373.

(9) Only a few examples of malonate additions to benzocycloheptadienone dicarboxylate were reported by Föhlisch's group: Föhlisch, B.; Schupp, E.; Dukek, U.; Graessle, I. *Liebigs Ann. Chem.* **1973**, 1851. Föhlisch, B.; Schupp, E.; Dukek, U.; Shwaiger, G. *Liebigs Ann. Chem.* **1973**, 1861.

(10) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S. *J. Am. Chem. Soc.* **2000**, *122*, 7596–7597.

(11) Föhlisch, B.; Franz, T.; Kreiselmeier, G. *Eur. J. Org. Chem.* **2005**, *21*, 4687.

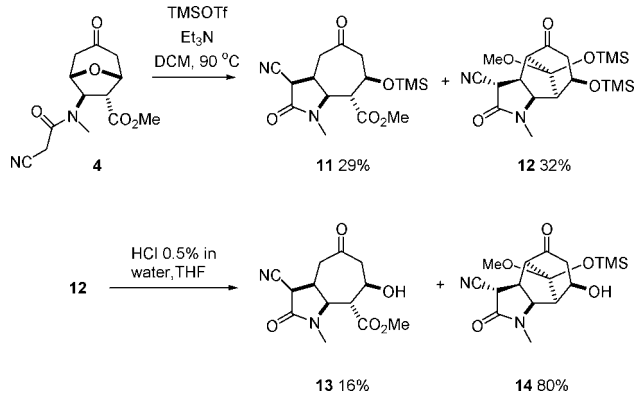
(12) Temporary TBS protection was required to avoid major loss of material due to the high water solubility of the deprotected form of **8**.

(13) Takaya, H.; Hayakawa, Y.; Mikano, S.; Noyori, R. *J. Am. Chem. Soc.* **1978**, *100*, 1778–1785. Föhlisch, B.; Sendelbach, S.; Bauer, H. *Liebig Ann. Chem.* **1987**, 1–5. (c) Bunn, B. J.; Cox, P. J.; Simpkins, N. S. *Tetrahedron* **1993**, *49*, 207–218.

Lewis acids ($TiCl_4$, $SnCl_4$) led to recovery of starting material on basic workup. Use of strong protic acid (FSO_3H) led to complete decomposition. Combination of either strong bases (LDA, LTMP) or mild ones (DBU, Et_3N) with electrophiles (TMSOTf, TMSCl) at room temperature led to the formation of mixtures of ketone enol silanes.

At this point, we speculated that the desired elimination required elevated temperatures, and so a mixture of **4** with 4.5 equiv of TMSOTf and 5.5 equiv of Et_3N in dichloromethane was heated to 90 °C in a sealed tube.[14] TLC analysis showed formation of two new compounds, and the reaction was quenched after 1 h at around 90% conversion. As shown in Scheme 4, the minor product **11**

Scheme 4. First Elimination−conjugate Addition



was found to be the result of a monoelimination and conjugate addition.[15] To our surprise, the major adduct **12** was a tricyclic mixed *O*-silyl acetal due to an unwanted intramolecular Claisen condensation involving the ketone and methyl ester groups.

The mixed *O*-silylacetal **12** proved to be unusually stable allowing column chromatography and even further acid-catalyzed secondary alcohol deprotection to give **14**, accompanied by only small quantities of bicyclic retro-Claisen product **13**.

Pleasingly, this compound proved to be crystalline, and the structure, including the stereochemistry at the acetal center and the nitrile-bearing center, was revealed by X-ray crystallography, Figure 1.

The transformation of **4** into **11** and **12** shows an apparently high tendency for elimination proximal to the ring amide function, since we could not isolate regioisomeric products. We soon discovered that if the reaction was performed with a larger excess of TMSOTf and Et_3N (5.5 equiv and 6.5 equiv, respectively) and over a longer time (4 h) only **12** was formed, in 52% yield.

(14) No reaction was observed at 80 °C.

(15) Most of the bicyclic adducts existed as mixtures of two epimers due to the easily epimerizable center α to the nitrile, but this was of no consequence for later chemistry. Tricycles **12** and **14** were single isomers, as shown in Figure 1 for **12**.

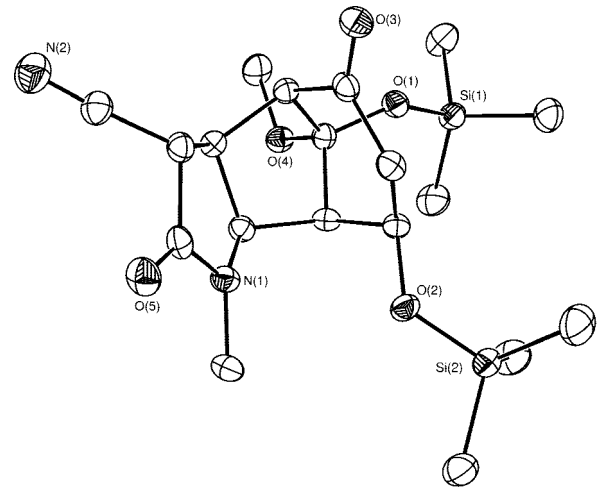


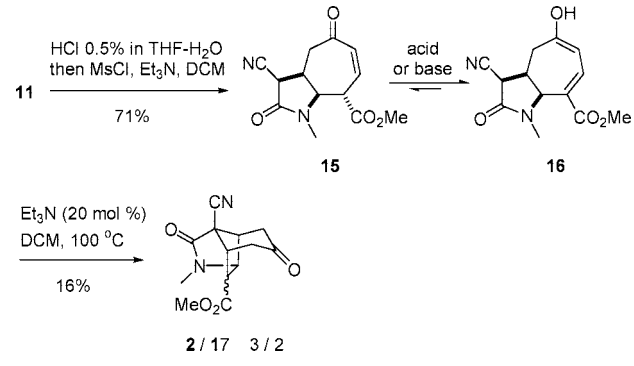
Figure 1. X-ray structure of tricyclic intermediate **12**.

Initially undecided how to proceed with **12**, we concentrated our efforts on bicyclic adduct **11**, which was desilylated and the free hydroxyl was eliminated via the corresponding mesylate to give the enone **15** (Scheme 5).

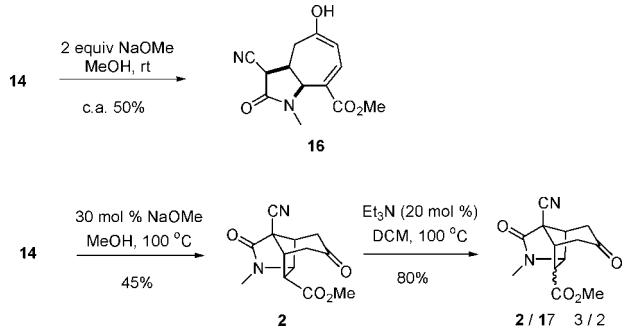
This compound proved to easily tautomerise on standing in chloroform overnight to enol form **16**. The same isomerization was observed by TLC on treatment of **15** with triethylamine in dichloromethane. The second conjugate addition required elevated temperature once again, and the reaction was carried out in a sealed tube at 100 °C, unexpectedly producing the tricyclic adducts **2** and **17** as a 3:2 mixture of diastereoisomers, in low yield (Scheme 5). Epimerization at the ester-bearing center in **2** was later identified as the cause of this result (see below).

Now we were left with the task of optimizing the reaction conditions to improve the low yield and hopefully facilitate formation of **2** as a single diastereomer. Thus, we reinvestigated the retro-Claisen conversion of tricyclic ketal **14** into bicyclic ester **13**. Initially, we treated **14** with sources of fluoride anion (TBAF, HF/pyridine) but both reactions provided multiple products besides **13** as judged by TLC Next, we attempted treatment of **14** with sodium methoxide

Scheme 5. Second Elimination−Conjugate Addition



Scheme 6. Direct Conversion of **14** into **2**



in methanol. To our surprise, treatment of **14** with two equivalents of sodium methoxide at room temperature led to direct formation of the enol form **16** as judged by ^{1}H NMR analysis of the crude reaction mixture (Scheme 6).

Our next task was to combine the basic conditions needed for the retro-Claisen and elimination of the free hydroxyl in **13** with the high temperature required for the Michael addition. After considerable experimentation, we found that less than 1 equiv of sodium methoxide completes the overall transformation with the least decomposition. Finally, the reaction was performed with 30 mol % of base resulting in a gratifying yield of 45% of the tricyclic adduct as a single diastereoisomer **2**.

As mentioned above, we were then able to equilibrate the ester **2** by treatment with 20 mol % of triethylamine in dichloromethane giving a 3/2 mixture of diastereoisomers **2** and **17**, as seen before (Scheme 5). This allowed separation of quantities of both epimeric esters, which then allowed stereochemical assignment based on NOE experiments.[16]

In conclusion, we have achieved a rapid construction of the gelsemine core structure **2** following the proposed one-atom bridge swap strategy. The crucial transformation was achieved in three synthetic steps from an easily available starting material **4**. We anticipate that further streamlining of this route will be possible and that selective manipulation of the groups present in **2** will enable further progress toward gelsemine.

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Supporting Information Available: Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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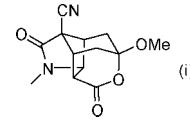
(16) The epimerization of **2** with Et_3N is puzzling, bearing in mind that **2** is obtained from **14** as a single epimer from much more strongly basic conditions. We have no convincing rationale for this result but consider it possible that under the conditions used in Scheme 6 the configuration of the ester could be temporarily locked by formation of a lactone acetal (i), which is then opened by MeOH on work-up (addition of solid NH_4Cl).



(i)