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Double Conjugate Addition of a Nitropropionate Ester to a Quinone Monoketal: Synthesis of an Advanced Intermediate to (±)-Gelsemine

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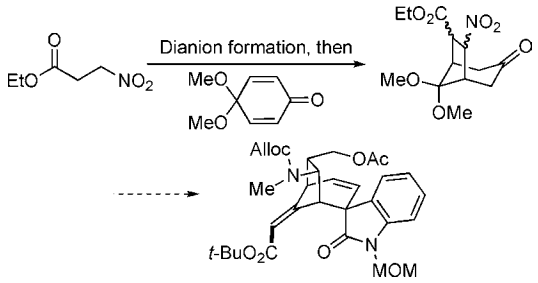
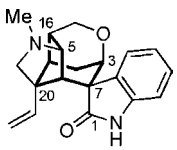
ABSTRACT



A double conjugate addition between the lithium dianion of ethyl 3-nitropropionate and *p*-benzoquinone dimethyl ketal afforded a mixture of diastereomeric [3.2.1]bicyclooctanones. These products were converted into an advanced intermediate previously carried forward to (±)-gelsemine by Fukuyama and Liu.

Gelsemine (**1**) is the principal component of *Gelsemium sempervirens*, also known as yellow jasmine or Carolina jasmine, and was first reported in 1870.[1] More than 70 years of chemical degradation studies established that gelsemine contained the same five functional groups as strychnine but provided little information about its complex skeleton. In 1959, Conroy and Chakrabarti proposed the now accepted structure of gelsemine,[2] which was verified through X-ray crystallographic analysis.[3]



gelsemine (**1**)

Gelsemine's complex structure has attracted considerable attention from the synthetic community.[4] Following initial efforts mounted in the 1960s, the first total syntheses were reported by the research groups of Johnson and Speckamp in 1994. Additional racemic syntheses have been achieved by the Hart, Fukuyama, Overman, and Danishefsky research groups,[5] with one asymmetric synthesis reported by Fukuyama in 2000.[6]

Herein, we report a new approach to gelsemine that involves the one-step synthesis of a functionalized [3.2.1]-bicyclooctanone **2** from the dimethyl quinone ketal of benzoquinone (Scheme 1). We felt that the central location of this bicyclic ring system made it an attractive starting point for gelsemine synthesis. In this paper, we describe the synthesis of **2** via a double conjugate addition reaction and

(1) Wormley, T. G. *Am. J. Pharm.* **1870**, *42*, 1−16.

(2) Conroy, H.; Chakrabarti, J. K. *Tetrahedron Lett.* **1959**, *1*, 6−13.

(3) Lovell, F. M.; Pepinsky, R.; Wilson, A. J. C. *Tetrahedron Lett.* **1959**, *1*, 1−5.

(4) Lin, H.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 36−51.

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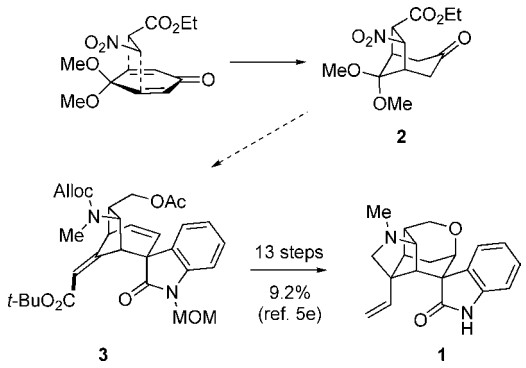
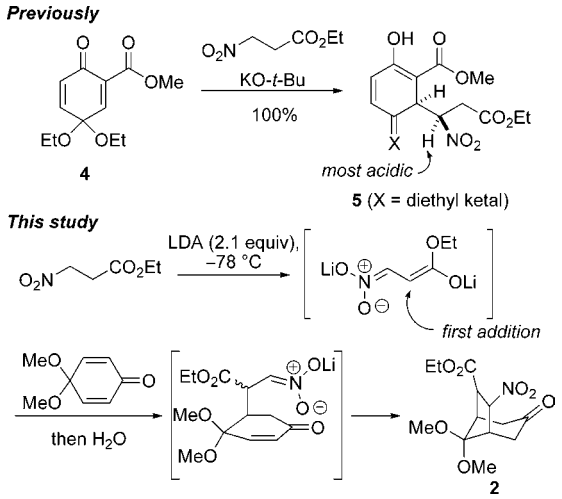
Scheme 1. Strategy for Gelsemine Synthesis



its conversion into a key intermediate to (±)-gelsemine reported by Fukuyama and co-workers.[5e]

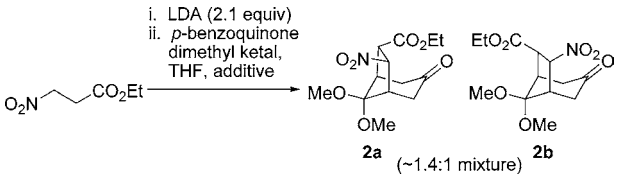
In previous work, we surveyed the regioselective double conjugate additions of a series of bifunctional nucleophiles to quinone ketals.[7] Although 1,3-bisnucleophiles such as ethyl acetoacetate routinely afforded [3.3.1]bicyclooctanone products using KO-*t*-Bu in THF, we could not extend this methodology to 1,2-bisnucleophiles under those conditions. In particular, when 1.0 equiv of quinone monoketal ester **4** was treated with 1.0 equiv of ethyl 3-nitropropionate and KO-*t*-Bu in THF, adduct **5** formed. This material could not be induced to undergo a second, intramolecular addition under any conditions (Scheme 2). It is likely that any subsequent deprotonation only occurs α to the nitro group in **5** due to the large difference in pK_a between the protons α to the ester (pK_a = 25) and the nitro group (pK_a = 10). If so, we surmised that if initial conjugate addition could be effected α to the ester, a second conjugate addition α to the nitro group should be facile.

Scheme 2. Conjugate Addition Reactions



Seebach and co-workers reported direct functionalization of methyl 3-nitropropionate α to the ester by generation of the corresponding dianions and subsequent treatment with electrophiles (Scheme 2).[8] Thus, generation of the lithium dianion of ethyl 3-nitropropionate (2.1 equiv of LDA, THF, HMPA, −78 °C) followed by dropwise addition of *p*-benzoquinone dimethyl ketal afforded conjugate addition adduct as a dienolate. Warming to 0 °C and addition of water presumably quenched the ketone enolate, leaving the nitronate anion intact to undergo intramolecular cyclization. Workup by the addition of 1.0 M HCl provided [3.2.1]-bicyclooctanones **2a** and **2b** as a ca. 1.4:1 inseparable mixture of diastereomers after silica gel chromatography in 51−59% yield (Table 1, entry 1).

Table 1. Survey of Conditions for Double Conjugate Addition Reactions



entry	nitroester (equiv)	quinone (equiv)	additives (equiv)	yield (%)
1	1.0	1.2	HMPA (12)	51−59
2	1.0	1.2	none	<5
3	1.0	1.2	DMPU (12)	8
4	1.0	1.2	TMEDA (12)	50
5	1.0	1.0	HMPA (12)	54
6	1.2	1.0	HMPA (14.4)	44
7	1.0	1.5	HMPA (12)	59
8	1.0	1.2	HMPA (12), TMEDA (2.4)	64−69

When either no additive or DMPU was used in these reactions, the yield dropped precipitously, but TMEDA could be used with only a minimal decrease in yield (cf. entries 2−4). Furthermore, reaction efficiency was increased when an excess of quinone ketal was used relative to ethyl 3-nitropropionate (cf. entries 1, 5−7). Interestingly, a combination of HMPA and TMEDA was superior to either additive alone (cf. entry 1,4, and 8).[9] The reaction could be easily scaled to up to provide ca. 10 g of **2a**,**b**.

(5) (a) Sheikh, Z.; Steel, R.; Tasker, A. S.; Johnson, A. P. *J. Chem. Soc., Chem. Commun.* **1994**, 763−764. (b) Dutton, J. K.; Steel, R. W.; Tasker, A. S.; Popsavin, V.; Johnson, A. P. *J. Chem. Soc., Chem. Commun.* **1994**, 765−766. (c) Newcombe, N. J.; Ya, F.; Vijn, R. J.; Hiemstra, H.; Speckamp, W. N. *J. Chem. Soc., Chem. Commun.* **1994**, 767−768. (d) Atarashi, S.; Choi, J. K.; Ha, D. C.; Hart, D. J.; Kuzmich, D.; Lee, C.-S.; Ramesh, S.; Wu, S. C. *J. Am. Chem. Soc.* **1997**, *119*, 6226−6241. (e) Fukuyama, T.; Liu, G. *J. Am. Chem. Soc.* **1996**, *118*, 7426−7427. (f) Madin, A.; O'Donnell, C. J.; Oh, T.; Old, D. W.; Overman, L. E.; Sharpe, M. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 2934−2936. (g) Ng, F. W.; Lin, H.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 9812−9824.

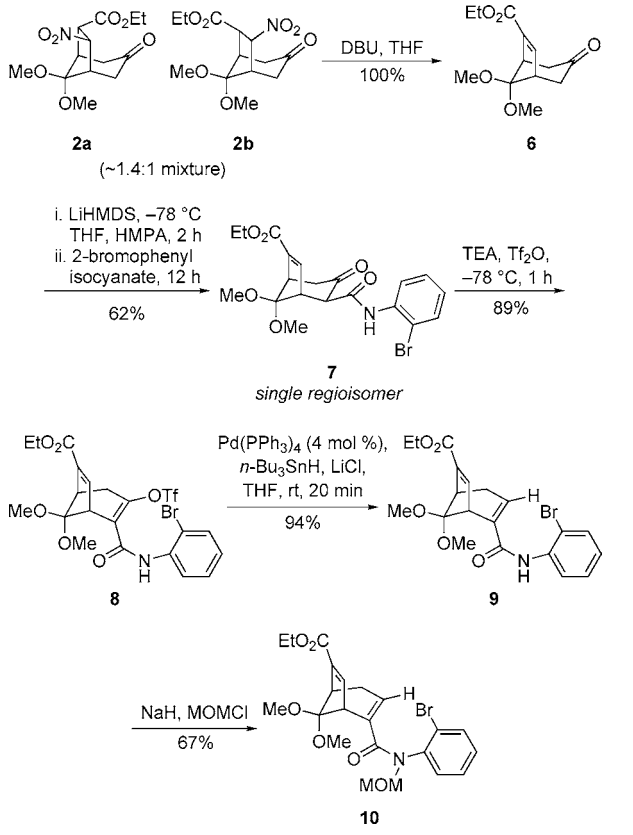
(6) Yokoshima, S.; Tokuyama, H.; Fukuyama, T. *Angew. Chem., Int. Ed.* **2000**, *39*, 4073−4075.

(7) Grecian, S.; Wrobleski, A. D.; Aubé, J. *Org. Lett.* **2005**, *7*, 3167−3170.

(8) Seebach, D.; Henning, R.; Mukhopadhyay, T. *Chem. Ber.* **1982**, *115*, 1705−1720.

(9) Collum, D. B. *Acc. Chem. Res.* **1992**, *25*, 448−454.

Scheme 3. Preparation of Heck Precursor **10**

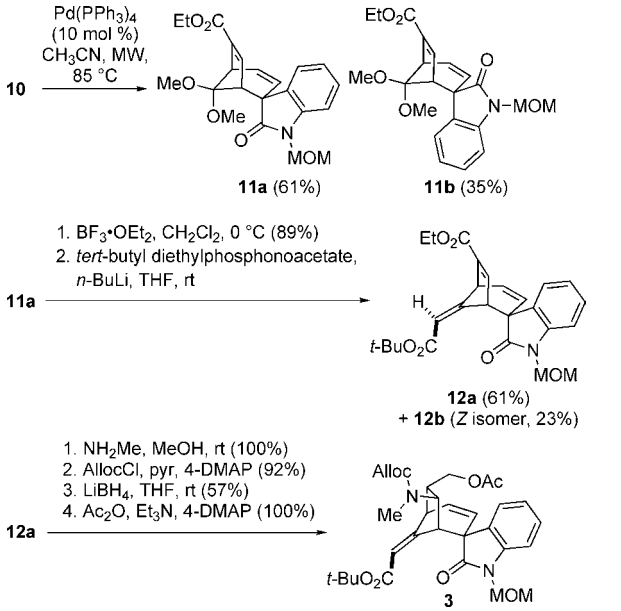


The mixture of diastereomers **2** quantitatively converged onto unsaturated ester **6** by DBU-mediated elimination and filtration through a plug of silica gel (Scheme 3). We then focused on the regio- and stereoselective incorporation of the spirooxindole. After some experimentation, we were gratified—if surprised—to find that treatment with LiHMDS at −78 °C followed by the addition of 2-bromophenyl isocyanate and warming to room temperature provided β-keto anilide **7** as a *single regioisomer* in 62% yield.[5d,10] Apparently, the ethyl ester blocks either deprotonation or electrophilic attack leading to the undesired regioisomer. Initial attempts to carry out a spirocyclization reaction at the oxidation level of keto amide (e.g., by conversion to the OMOM ether and subsequent Heck reaction[5f]) failed. Taking another tack, we found that β-keto anilide **7** could be reduced to the corresponding olefin by conversion to enol triflate **8** (Tf_2O, TEA) followed by Pd-catalyzed reduction (*n*-Bu_3SnH, 4 mol % of $Pd(PPh_3)_4$). This provided unsaturated anilide **9** in excellent yield without disturbing the aryl bromide. *N*-Methoxymethyl protection of this compound gave Heck cyclization precursor **10**.

With **10** in hand, a number of Heck reaction conditions were surveyed.[11] Though none of the conditions we investigated were highly diastereoselective, nearly complete conversion to the desired spirooxindole **11a** and its epimer **11b** was possible when 10 mol % of $Pd(PPh_3)_4$ was used, and the reaction was heated at 85 °C in a microwave reactor.[12] Lower conversions were observed when the reaction was carried out under oil bath conditions, although a rigorous comparison was not made.

To effect elongation at C20, we sought conditions to deprotect the dimethyl ketal while leaving the *N*-methoxymethyl group intact. After some experimentation, it was found that by treating **11a** with 1.5 equiv of $BF_3{\cdot}OEt_2$ at 0 °C for 20 min, clean conversion to the ketone was possible without affecting the MOM group (Scheme 4). Following

Scheme 4. Completion of Fukuyama's Gelsemine Intermediate



the precedent established by Fukuyama's group,[5e,6] one-carbon elongation of this ketone was achieved by Horner−Wadsworth−Emmons reaction with *tert*-butyl diethylphosphonoacetate, which gave olefin isomers **12a** and **12b** in 61% and 23% yield, respectively. 1,4-Addition of methylamine to **12a** proceeded quantitatively and was completely diastereoselective. To complete the synthesis of **3**, Alloc-protection was performed on the resulting amino ester (AllocCl, pyridine, 4-DMAP, 92%), followed by reduction with $LiBH_4$ in THF (57%), and finally acetylation. The spectral data obtained for **3**, which has previously been converted to (±)-gelsemine in 13 steps and 9.2% overall yield, matched those reported by Fukuyama and co-workers (^1H NMR, ^{13}C NMR, IR).[5e]

In summary, we have extended our previous work[7] by showing that it is possible to construct a [3.2.1]bicycooc-

(10) Hendi, S. B.; Hendi, M. S. H.; Wolfe, J. F. *Synth. Commun.* **1987**, *17*, 13−18.

(11) (a) For a review of Heck reactions in total synthesis, see: Link, J. T.; Overman, L. E. Intramolecular Heck reactions in Natural Product Chemistry. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P., Eds.; Wiley-VCH: New York, 1998; pp 231−269. (b) Earley, W. G.; Oh, T.; Overman, L. E. *Tetrahedron Lett.* **1988**, *29*, 3785−3788. (c) Madin, A.; O'Donnell, C. J.; Oh, T.; Old, D. W.; Overman, L. E.; Sharp, M. J. *J. Am. Chem. Soc.* **2005**, *127*, 18054−18065. Also see refs 5c,f.

(12) The stereochemistry of the spirooxindoles was determined by NOE spectroscopy for each diastereomer. See the Supporting Information for details.

tanone via the double conjugate addition of a 1,2-bisnucleophile to a quinone ketal. In addition, we have demonstrated the utility of the product as an intermediate in complex natural product synthesis by converting it into an advanced gelsemine intermediate (and in so doing report a formal synthesis of this popular target). We are currently examining the scope of this approach to complex alkaloids.

Acknowledgment. We thank Angelica Meyer of this laboratory for help with the optimization of the double conjugate additions. We thank the National Institutes of Health for financial support via GM-49093. S.G. gratefully acknowledges receipt of a Madison and Lila Self Graduate Fellowship.

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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