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Total Synthesis of Gelsemoxonine through a Spirocyclopropane Isoxazolidine Ring Contraction

Stefan Diethelm, Erick M. Carreira*

Eidgenössische Technische Hochschule Zürich, Vladimir-Prelog-Weg 3, HCI H335, 8093 Zürich, Switzerland

ABSTRACT: Plants of the species *Gelsemium* have found application in traditional Asian medicine for over a thousand years. Gelsemoxonine represents a novel constituent of this plant incorporating a highly functionalized azetidine at its core. We herein report a full account of our studies directed towards the total synthesis of gelsemoxonine that relies on a conceptually new approach for the construction of the central azacyclobutane. A spirocyclopropane isoxazolidine ring contraction was employed to access a key β-lactam intermediate, which could be further elaborated to the azetidine of the natural product. In the course of our studies, we have gained detailed insight into this intriguing transformation. Furthermore, we report on previously unnoticed oligomerization chemistry of gelsemoxonine. We also document an enantioselective synthesis of a key precursor en route to gelsemoxonine.

Introduction

The use of plant extracts to treat human diseases has a long history in traditional folk medicine all around the globe. This knowledge, accumulated over thousands of years, harbors a still largely unexplored potential for modern pharmaceutical chemistry. In this context, exploration of the constituents of medicinally relevant plants is of great interest for the discovery of novel bioactive natural products with potential application in pharmacy.[1] Plants from the species *Gelsemium*, endemic to China and Japan, have been used as an analgesic and antispasmodic agent as well as for the treatment of skin ulcers over a thousand years in traditional Asian medicine.[2] Detailed chemical studies on *Gelsemium* plants led to the identification of an intriguing class of alkaloids, characterized by a range of biological activities.[3] Several members of the *Gelsemium* alkaloid class have been shown to exhibit potent antitumor activity or are capable of attenuating inflammatory and neuropathic pain in mouse models.[4] Moreover, these natural products comprise unusual structural features such as a densely functionalized and compact core as exemplified by the two prominent members gelsedine (**1**) and gelsemine (**2**) (Figure 1, top). In 1991, Clardy and co-workers isolated the novel alkaloid gelsemoxonine (**3**) from *Gelsemium* elegans bentham.[5] More than a decade later, Aimi and co-workers corrected the originally proposed structure based on X-ray crystallographic analysis and 2D NMR studies.[6] The authors reported that gelsemoxonine (**3**) incorporates an unusual azetidine as a key structural element, which distinguishes it from all other members of the *Gelsemium* family. The four-membered heterocycle is completely embedded in a polycyclic framework, which severely aggravates the strain associated with the core of gelsemoxonine. Furthermore, a spiro-fused *N*-methoxy oxindole ring, an ethyl ketone appendage as well as a fully substituted stereocenter as part of the azetidine add to the complexity of the natural product.

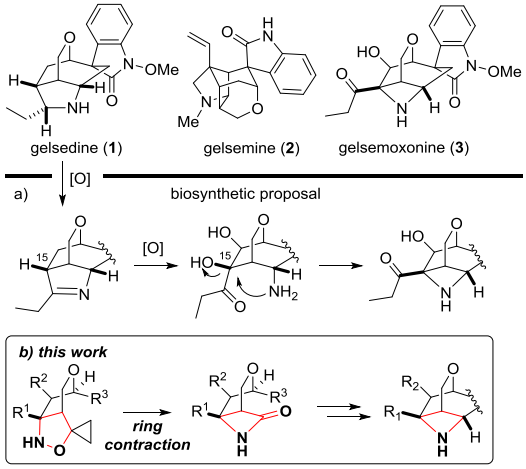


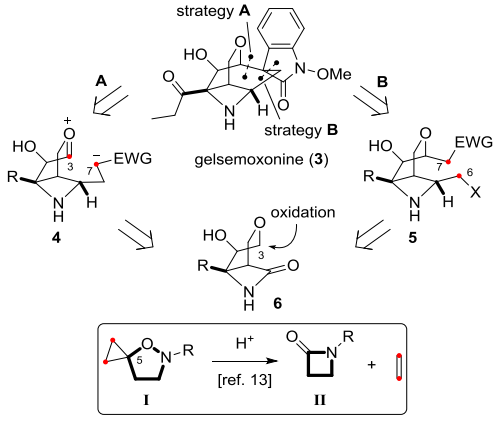
Figure 1. *Gelsemium* alkaloids and azetidine synthesis.

The biosynthesis of gelsemoxonine (**3**) has been suggested to start from gelsedine (**1**).[6] After initial oxidation steps, nucleophilic displacement of the resulting C(15) tertiary alcohol by an amine was invoked to explain formation of the azacyclobutane (Figure 1, a). Similarly, in their pioneering total synthesis of gelsemoxonine, Fukuyama and co-workers employed a biomimetic strategy for the construction of the central azetidine.[7] Our group has been interested for some time in the preparation and characterization of small saturated heterocycles as building blocks for drug discovery.[8] In the context of this research program, we decided to embark on studies directed towards the total synthesis of gelsemoxonine employing a conceptually new approach to the construction of its unusual azetidine ring (Figure 1, b).

We herein report a full account of efforts leading to the total synthesis of gelsemoxonine.[9] The synthesis relies on a strategic spirocyclopropane isoxazolidine ring contraction providing a β-lactam intermediate, which is further elaborated into the azetidine of the natural product (Figure 1, b). The studies reported here have led to a more detailed understanding of this intriguing transformation. In the course of this work, we have observed previously unnoticed oligomerization chemistry of gelsemoxonine. Furthermore, we present an enantioselective approach to a key intermediate en route to the natural product.

As outlined in Scheme 1, the synthetic strategy focused on a late-stage construction of the central seven-membered carbocycle of gelsemoxonine (**3**). To implement this plan, two general strategies were considered as indicated in Scheme 1 (strategy A vs. B). Retrosynthetic cleavage of the C(3)-C(7) bond would lead back to oxonium intermediate **4**, which would be susceptible to attack by a suitable C(7) nucleophile (strategy A).[10] Alternatively, formation of the C(6)–C(7) bond could be achieved by exploiting the nucleophilic character at C(7) through displacement of a leaving group at the C(6)-methylene leading back to intermediate **5** (strategy B). Most conveniently, introduction of the oxindole ring system could in either case be carried out before or after construction of the gelsemoxonine core fragment. Additionally, we opted for a unified approach that would allow access to both intermediates **4** and **5** through a common precursor. β-lactam **6** was thereby identified as a versatile platform, which would enable access to both these intermediates through manipulations including introduction of the C(6)-methylene by extension at the amide carbonyl along with oxidation of the C(3) position. The latter transformation could possibly be carried out relying on a C–H oxidation approach, whereby the inherent tendency of etheral methylene groups to undergo C–H bond cleavage would be exploited.[11] Furthermore, the ethyl ketone appendage of the natural product was planned to be introduced as an inert surrogate (-R in Scheme 1), which could later be elaborated to the required ketone functionality.

Scheme 1. Alternative synthetic strategies towards gelsemoxonine.

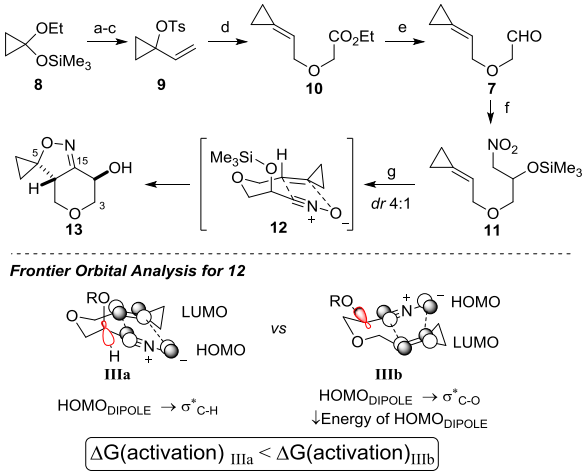


Focusing on the preparation of projected key intermediate **6**, we realized that this unusually substituted β-lactam would not be amenable to traditional construction strategies, relying on established protocols for β-lactam synthesis.[12] However, a report by Cordero and Brandi describing the acid mediated ring contraction of spirocyclopropane isoxazolidines **I** to form β-lactam products **II** caught our attention (Scheme 1, box).[13] Although this transformation is unexplored in the service of complex molecule synthesis, it offered an intriguing opportunity for the construction of the projected key intermediate **6**. Accordingly, a cyclization substrate would first have to be prepared incorporating various functional groups, which could potentially interfere with the desired reaction. Nonetheless, we set out to prepare a collection of precursors for the ring contraction.

Results and Discussion

Synthesis of β-lactam 17: Our synthetic efforts commenced with the preparation of a suitable ring contraction precursor, enabling late-stage oxidative functionalization of C(3). The required isoxazolidine, incorporating a spiro-fused cyclopropane at C(5), could be conveniently prepared by intramolecular [3+2] dipolar cycloaddition of a corresponding alkylidenecyclopropane derivative. As outlined in Scheme 2, known alkylidenecyclopropane substituted aldehyde **7** was chosen as a starting point.[14] Preparation of **7** was carried out using a slightly modified literature protocol that allowed for the synthesis of multigram quantities of this volatile aldehyde. Commercial cyclopropanone hemiacetal **8**[15] was first subjected to reaction with vinyl Grignard followed by transformation of the resulting

Scheme 2. Synthesis of oxazoline 13.[a]



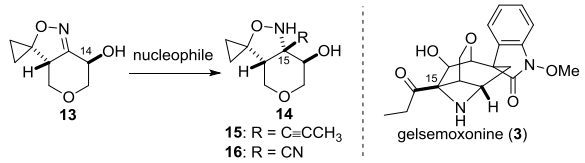
[a]Reagents and conditions: (a) HCl, MeOH, rt, 10 min, 80-90%. (b) CH_2=CHMgCl, THF, 80 °C, 30 min, 75%. (c) TsCl, NEt_3, CH_2Cl_2, rt, 12 h, 67%. (d) ethyl glycolate, NaH, THF, 0 °C, 30 min; then **9**, $Pd(dba)_2$ (1 mol%), dppe (2 mol%), THF, rt, 12 h, 83%. (e) DIBAL-H, CH_2Cl_2, –78 °C, 2 h. (f) $MeNO_2$, LDA, THF, –78 °C, 30 min; then **7**, –78 °C, 1 h; then TMSCl, –78 °C to rt, 1 h, 78% (2 steps). (g) PhNCO, NEt_3, C_6H_6, rt, 12 h; then HCl, rt, 5 min, 75%, dr 4:1.

tertiary alcohol into tosylate **9**. Tsuji-Trost reaction using ethyl glycolate as the nucleophilic component delivered ester **10** in 83% yield. Finally, DIBAL-H mediated reduction of the ester group cleanly furnished aldehyde **7**. Generation of a reactive dipole for the cycloaddition was planned to be carried out from a respective nitroalkene precursor.[16]

Henry addition of lithiated nitromethane provided, after quenching with Me_3SiCl, silyl ether **11** in 78% yield (2 steps). When **11** was exposed to phenyl isocyanate, dehydrative formation of putative nitrile oxide intermediate **12** occurred, followed by dipolar cycloaddition to provide isoxazoline **13** as a 4:1 mixture of diastereomers. The relative configuration of this intermediate could be confirmed by nOe analysis (see Supporting Information). Interestingly, the major product observed is consistent with a pseudo-axial arrangement of the silyl ether substituent, as indicated in transition state **12**. We speculate that when the reactions proceeds through transition state **IIIa** the rate is faster, or accordingly the activation energy is lowest. Structure **IIIa** is preferred because it avoids positioning the ether C-O bond in the equatorial arrangement as shown for **IIIb**, wherein its interaction with the dipole HOMO would lead to lowering of its energy and thus an increase of the activation energy for the dipolar cycloaddition.

We next turned to the introduction of a suitable ethyl ketone surrogate at C(15) to access *cis*-fused isoxazolidine **14**. As outlined in table 1, **13** was subjected to various nucleophiles to effect diastereoface selective addition to the dihydroisoxazole. We thereby chose coupling partners that would enable elaboration of a ketone functionality at C(20) at a late stage of the synthesis. It has been previously noted that isoxazolines are generally poorly reactive towards nucleophilic reagents. We were therefore not surprised to find that treatment of **13** with buten-2-yl lithium at -78 °C did not yield any coupled product (data not shown). Lewis acid activation has been previously reported to enhance the nucleophilicity of isoxazolidine.[17] However, addition of BF_3 etherate or $ZnCl_2$[18] as Lewis acid promoter did not change the reaction outcome (entry 1). We reasoned that attack of any nucleophile from the convex face of **13** might be sterically hampered by the adjacent hydroxyl or alkoxy substituent. Accordingly, smaller nucleophiles such as propen-2-yl lithium or vinylmagnesium bromide were tested under similar conditions (entries 2 and 3). Indeed, addition of propen-2-yl lithium successfully provided the desired product albeit with very low conversion (entry 2). We next tested addition of propyn-1-yl lithium to isoxazoline **13**, whereby the triple bond could later serve as a handle for ketone introduction through regioselective hydration (entries 4-7). Direct treatment of **13** with this reagent again led to complete recovery of unreacted starting material (entry 4). Reports on solution studies of lithium acetylides have indicated that addition of amine bases to these reagents can alter their aggregation behavior and attendant reactivity.[19] In our case however, the addition of either triethylamine or TMEDA to the reaction mixture did not result in any product formation (entry 5). We next tested the use of different Lewis acid activators in the reaction. Although $TiCl_4$ was ineffective (entry 6),[20] addition of BF_3 etherate provided the desired product **15** in low yield of 22% (entry 7). Seebach and co-workers have investigated the use of preformed titanium acetylides as mild nucleophiles in the addition to ketones.[21] Following these reports, we tested triisopropoxy(propyn-1-yl) titanium as a potential nucleophile (entry 8). Again however, no product was obtained under these conditions. A frequently encountered problem for the addition of organometallic nucleophiles to carbonyl compounds is competing enolization due the dual role of the organometal species as a nucleophile as well as a strong base. Various strategies have been studied to alleviate the problem.[22] In particular, addition of lanthanide salts to these reactions was found to decrease the basicity of the organometallic reagent, thus disfavoring the competing deprotonation pathway.[23] Indeed, when anhydrous $CeCl_3$[24] was added to propyn-1-yl lithium prior to exposure to the electrophile **13**, we were able to isolate the desired product in good yield (68%) and with complete diastereoselectivity for the desired isomer. We next tested addition of cyanide to oxime ether **13**. Various standard protocols known for the conversion of ketones to cyanohydrins were tested to this effect. However, only treatment of **13** with Et_2AlCN at 60 °C afforded the desired nitrile **16** in 63% yield.[25]

Table 1. Addition of nucleophiles to isoxazoline 13.[a]



Entry	Nucleophile	Additives	Conditions	Yield
1		$BF_3{\cdot}OEt_2/ZnCl_2$	–78 °C, THF	-
2		$BF_3{\cdot}OEt_2$	–78 °C, THF	19%
3		$BF_3{\cdot}OEt_2$	rt, THF	-
4		-	–78 °C, THF	-
5		NEt_3 or TMEDA[b]	–78 °C, Et_2O	-
6		$TiCl_4$	–78 °C, THF	-
7		$BF_3{\cdot}OEt_2$	–78 °C, THF	22%
8		$TiCl_4$	–78 °C, THF	-
9		$BF_3{\cdot}OEt_2$[c]	–78 °C, THF	**68%**[d]
10	Et_2AlCN	-	60 °C, THF	**63%**

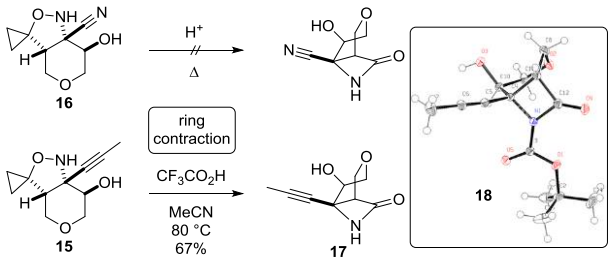
[a]Conditions: substrate (0.3 mmol), nucleophile (4.0 equiv.), additive (1.0 equiv.), 2 h. [b]used as co-solvent (1:1).

[c]2.0 equiv. BF_3·OEt_2 used. [d]49% yield (65% brsm) with 24 mmol substrate.

Interestingly, attempts to add any nucleophiles to *O*-protected analogues of **13** (such as the *O*-trimethylsilyl or *O*-benzyl derivative of **13**) failed and unreacted starting material was recovered. Moreover, using a starting material with the opposite configuration at the C(14) hydroxyl stereocenter failed to give the expected product (data not shown). These observations, along with the data presented above, led us to suggest that the hydroxyl group in **13** plays a key role in the reaction, probably by acting as a directing group for the incoming organometalic reagent.

Having a short, efficient route to oxazolidines **15** and **16** in hand, we set out to test the key ring contraction. As outlined in Scheme 3, nitrile **16** was subjected to reported reaction conditions.[13] To our surprise, no product formation could be observed using various different protic acid additives. We reasoned that the electron withdrawing effect of the nitrile might be responsible for the impaired reactivity of the system. We next treated alkyne **15** with trifluoroacetic acid (TFA) at 80 °C.[26] To our delight, after 6 hours of reaction time β-lactam **17** was isolated as the only product in good yield (67%). The structure of **17** was confirmed by X-ray crystallographic analysis of Boc-protected derivative **18** (Scheme 3, box). Notably, in contrast to the original report, no nitrogen protecting group was needed for the ring contraction to proceed. Moreover, an unprotected alcohol as well as an electron rich alkyne were well tolerated under the reaction conditions.

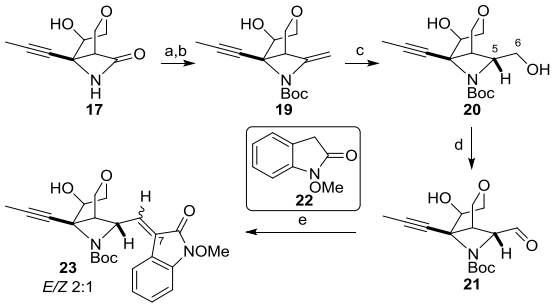
Scheme 3. Ring contraction of isoxazolidines 16 and 15.



Directed C–H oxidation at C(3): To gain access to the full carbon framework of gelsemoxonine starting from **17**, installation of the C(6) methylene group by manipulation of the β-lactam carbonyl was required. However, any manipulation of the azacyclobutanone would be accompanied by the risk of undesired ring opening.[27] We sought conditions which would avoid such side reactions leaving the four-membered heterocycle intact. Initial experiments involving Corey-Chaykovsky-type epoxide formation on the amide carbonyl[28] or addition of carbenes to the respective β-thiolactam,[29] failed to give any of the desired products. Relying on the well-known chemistry of amides to participate in olefination reactions, we were hoping to access a respective enamine intermediate by methylenation of β-lactam **17**.[30] Following this plan, **17** was first converted into the corresponding acylcarbamate by treatment with Boc_2O. Subjecting this intermediate to Petasis' reagent (Cp_2TiMe_2) in the presence of pyridine indeed afforded the strained enecarbamate **19** in good yield (74%).[31] Notably, this intermediate proved stable to chromatography on silica gel and could be handled without significant hydrolysis of the sensitive methyleneazacyclobutane. Next, the C(5) stereocenter was installed by hydroboration of the olefin using 9-BBN dimer followed by oxidative workup (H_2O_2/NaOH). Diol **20** was obtained as a single diastereomer at C(5), indicating exclusive attack of the hydroborating agent from the convex face of the molecule.

Installation of the oxindole moiety was first attempted by nucleophilic displacement at C(6) starting from various derivatives of primary alcohol **20** (tosylate, mesylate, iodide). Surprisingly however, all of these compounds proved inert towards nucleophiles, reflecting the dense steric environment around C(6). Successful introduction of the C(7) oxindole fragment was finally achieved by conversion of alcohol **20** to aldehyde **21** (TEMPO, $PhI(OAc)_2$)[32] and subsequent aldol condensation with *N*-methoxy oxindole **22**[33] using conditions previously reported by Evans.[34] Olefin **23** was obtained as an *E*/*Z* mixture of 2:1 favoring the *E* isomer as confirmed by nOe analysis (see Supporting Information for further details).

Scheme 4. Synthesis of oxindole derivative 23.[a]



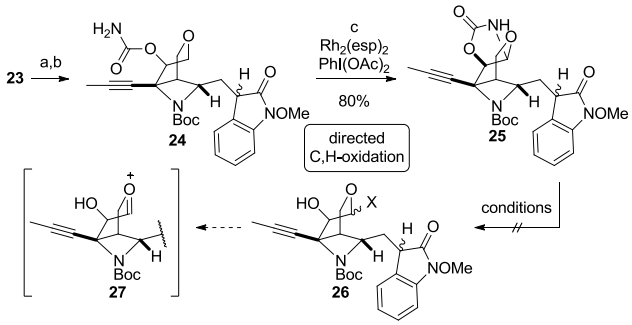
[a]Reagents and conditions: (a)Boc_2O, NEt_3, DMAP, CH_2Cl_2, rt, 30 min, 58%. (b) Cp_2TiMe_2, pyridine, toluene, 70 °C, 5 h, 74%. (c) 9-BBN dimer, THF, rt, 1 h; then H_2O_2/NaOH, rt, 4 h, 79%. (d) TEMPO (30 mol%), $PhI(OAc)_2$, CH_2Cl_2, rt, 2 h, 80%. (e) **22**, $MgBr_2$ (15 mol%), TMSCl, NEt_3, THF, rt, 20 min; then **21**, rt, 15 min, 82% (*E*/*Z* 2:1).

For the closure of the seven-membered carbocycle of gelsemoxonine by construction of the C(3)–C(7) bond, we initially opted for the generation of an oxonium ion at C(3), which would eventually be trapped by an oxindole enolate (Scheme 1, strategy A). To implement this plan, adjustment of the oxidation state at the C(3) ether of intermediate **23** was required. Etheral C–H bonds are known to be susceptible to direct oxidation due to their reduced C–H bond strength. Numerous protocols have been developed in the past to achieve C–H oxidations in highly complex settings.[35] However, model studies with our system revealed that targeting of the C(3)–H bond using such protocols was unsuccessful, instead resulting in the preferential oxidation of other C–H bonds or the

complete decomposition of the respective substrates (see Supporting Information for further details). Moreover, attempted elimination of the secondary alcohol in **23** resulted in rapid decomposition of the starting material.

We next set out to evaluate directed oxidation of the C(3) methylene relying on the adjacent C(14) hydroxyl group as a handle to achieve selectivity.[36] In this context, Du Bois and co-workers have reported an elegant approach for the functionalization of unbiased C–H bonds in the vicinity of hydroxyl groups.[37] Their strategy is based on the generation of a reactive nitrene species covalently linked to an OH through a sulfonamide or carbamate group. Accordingly, we prepared carbamate **24** as described in Scheme 5. Subsequent treatment of this intermediate with $Rh_2(esp)_2$[38] in the presence of $PhI(OAc)_2$ as the stoichiometric oxidant cleanly afforded oxazolidinone **25** in excellent yield (80%). It is noteworthy that the electron rich alkyne adjacent to the reactive nitrene is not touched and selective insertion into the C(3) methylene C–H occurs as the exclusive reaction. Although we had achieved the desired oxidation of C(3), we were unable to generate precursors such as **26** suitable for the generation of putative oxonium ion **27** as the oxazolidinone in **25** resisted any attempts directed towards its cleavage (see Supporting Information for further details).

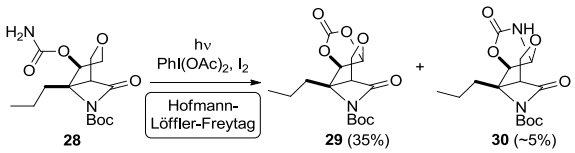
Scheme 5. Directed C–H oxdiation of carbamate 24.[a]



[a]Reagents and conditions: (a)$NaBH_4$, THF/MeOH (1:1), 0 °C, 20 min, 63%. (b) trichloroacetyl isocyanate, CH_2Cl_2, rt, 15 min; then $NaHCO_3$, MeOH, rt, 1 h, 80%. (c) $Rh_2(esp)_2$ (4 mol%), $PhI(OAc)_2$, MgO, CH_2Cl_2, 60 °C (sealed tube), 4 h, 81%.

As outlined in Scheme 6, an alternative C(3) oxidation approach involving a Hofmann-Löffler-Freytag reaction was investigated next. This transformation relies on the generation of a highly reactive nitrogen-centered radical species, which engages in an intramolecular 1,5-hydrogen abstraction.[39] In a modification of the original protocol, Barton and co-workers have reported the transformation of primary amides to yield lactone products.[40] Following this strategy, we evaluated primary carbamate **28** as precursor for C(3) oxidation. Irradiation of this model system under UV light and in the presence of $PhI(OAc)_2$ and I_2 delivered cyclic carbonate **29** in 35% yield along with a minor amount of oxazolidinone **30**. Unfortunately however, application of this protocol to substrates harboring a more complex substitution pattern failed. In particular, the electron rich alkyne in substrates such as **24** was not tolerated under the reaction conditions. Various other procedures for the generation of a nitrogen-centered radical from carbamate derivatives were evaluated but remained without success (see Supporting Information for further detail).[41]

Scheme 6. Hofmann-Löffler-Freytag reaction on model system 28.[a]

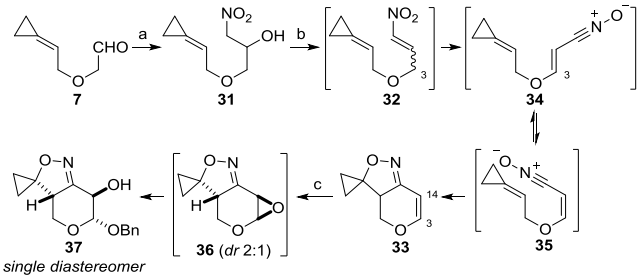


[a]Reagents and conditions: hν (UV), $PhI(OAc)_2$, I_2, MeCN, rt, 45 min, 35% (**29**).

Early oxidation of C(3): Based on the previously described results, it became apparent that C(3) functionalization at a late stage of the synthesis would be met with major hurdles due to the high functionalization of any substrate. Accordingly, we turned our attention to adjustment of the C(3) oxdiation state early in the synthesis. Scheme 7 describes our strategy to realize this notion. The revised strategy entailed initial formation of secondary alcohol **31** through a Henry reaction starting with previously employed aldehyde **7** (70%). When this intermediate was treated with Boc_2O in the presence of DMAP, rapid formation of an *E*/*Z* mixture of nitroolefin **32** was observed (15 min). However, when the reaction was run for a prolonged period of time (12 h), intermediate **32** reacted further to ultimately form enol ether **33**. We hypothesize that dehydration of the nitro group in **32** mediated by Boc_2O leads to the production of nitrile oxide **34**, whereby the double bond transposes by one carbon unit thus functionalizing C(3). However, only the thermodynamically less favored *Z*-isomer **35** can undergo subsequent intramolecular cycloaddition to form the final product. We surmise that an equilibrium between isomers **34** and **35** exists, which most likely results from an addition/elimination sequence of the DMAP additive to the unsaturated nitrile oxide. In fact, it proved crucial to add 2 equivalents of DMAP to the reaction mixture in order to achieve a good yield of **33** (79%).[42] With enol ether **33** in hand, we next turned to further functionalization of C(14) and C(3). As outlined in Scheme 7, this goal was achieved by initial epoxidation of the olefin in **33** followed by nucleophilic opening of the highly unstable oxirane. Among the various reagent systems tested for oxidation, only dimethyldioxirane (DMDO) provided the desired intermediate **36** in quantitative yield.[43,44] The unstable product was obtained as a 2:1 mixture of diastereomers favoring the desired isomer as shown in Scheme 7. The stereochemistry could be confirmed later in the synthesis by X-ray crystallographic analysis. Epoxide **36** proved highly sensitive to water or chromatographic purification (SiO_2) and was therefore directly treated with benzyl alcohol to give acetal **37** in 73% yield, again as

a 2:1 mixture of diastereomers (major isomer shown). The newly installed benzyl ether functionality could later serve to conveniently access the projected oxonium intermediate.

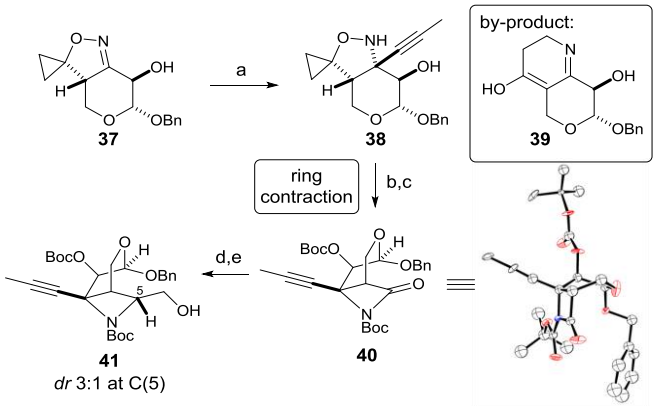
Scheme 7. Synthesis and oxidation of enol ether 33.[a]



[a]Reagents and conditions: (a) $MeNO_2$, LDA, THF, –78 °C, 30 min; then **7**, –78 °C to rt, 2 h, 70%. (b) Boc_2O, DMAP, toluene, rt, 12 h, 79%. (c) DMDO, 4Å MS, CH_2Cl_2/acetone (1:1), 0 °C, 2 h; then BnOH, $CHCl_3$, rt to 60 °C, 12 h, 73%, dr 2:1.

Having achieved efficient oxidation of C(3), we next focused on the elaboration of a suitable substrate for the projected C(7)–C(3) ring closure to assemble the gelsemoxonine core. As presented in Scheme 8, application of the previously developed chemistry was successfully applied to benzyl acetal **37**. Addition of the propynyl appendage to **37** delivered oxazolidine **38** in 35% yield (77% brsm). Notably, we did not observe any by-products resulting from the reaction of the acid-labile acetal group in **37**. Interestingly, when the reaction was performed in the presence of more than 2 equivalents of BF_3 etherate, a significant amount (10-20%) of ring expanded dihydropyridine **39** was isolated along with the desired product (Scheme 8, box). Brandi and Salaün had previously described the ring expansion of spirocyclopropane isoxazolines.[45] However, the conditions originally employed involved high temperature (130-200 °C), whereas formation of by-product **39** was observed at –78 °C. This circumstance suggests a polar mechanism for the formation of **39**, opposed to the radical pathway proposed for the high temperature ring expansion.

Scheme 8. Synthesis of alcohol 41.[a]

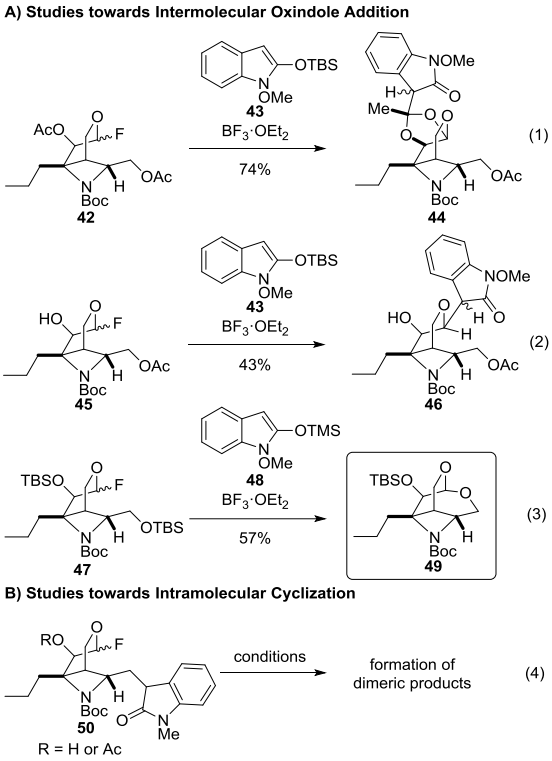


[a]Reagents and conditions: (a) 1-bromo-1-propene, *n*-BuLi, THF/hexanes (1:1), –78 °C, 1.5 h; then $CeCl_3$, –78 °C, 30 min; then **37**, $BF_3{\cdot}OEt_2$, –78 °C, 2.5 h, 35% (77% brsm). (b) CF_3CO_2H, MeCN, 80 °C, 2 h, 78%. (c) Boc_2O, NEt_3, DMAP, CH_2Cl_2, rt, 30 min, 77%. (d) Cp_2TiMe_2, pyridine, toluene, 70 °C, 6 h, 80%. (e) 9-BBN dimer, THF, rt, 3 h; then H_2O_2/NaOH, rt, 1 h, 88% (3:1 mixture of diastereomers at C(5)).

Isoxazolidine **38** was subjected to the conditions employed previously for acid-mediated ring-contraction (CF_3CO_2H, 80 °C). The desired β-lactam was thereby obtained in 78% yield. It is important to note, that the acid-sensitive acetal in substrate **38** was not affected by the reaction conditions. The structure of the β-lactam product was confirmed by X-ray crystallographic analysis of carbamate **40**. Access to primary alcohol **41** was gained through the previously established sequence of Petasis olefination followed by enecarbamate hydroboration. Interestingly, alcohol **41** was obtained as a 3:1 mixture of diastereomers at C(5) as confirmed by derivatization and subsequent nOe analysis (see Supporting Information).[46]

With compound **41** in hand, we embarked on studies aimed towards the addition of an oxindole nucleophile to C(3) *via* the generation of an oxonium intermediate accessible from the benzyl acetal. Preliminary experiments revealed that α-fluoroacetal intermediates served optimally for the generation of an oxonium ion at C(3). α-Fluoroacetals have been successfully employed as donors in glycosylation chemistry based on their stability and the straightforward mode of activation.[47] Accordingly, various glycosyl donor-type substrates were prepared starting from alcohol **41** and evaluated for their ability to undergo intermolecular reaction with oxindole nucleophiles (Scheme 9).[48]

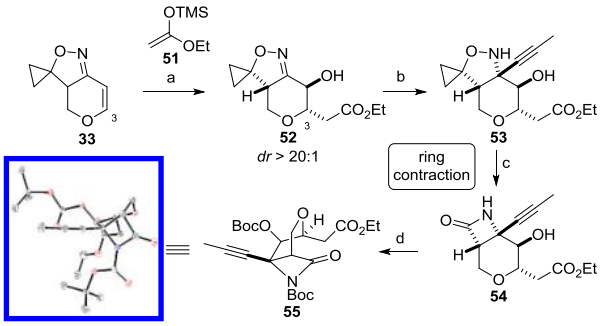
Scheme 9. Investigations towards C(7) functionalization.



As shown in Scheme 9, our efforts started with acetate protected diol **42**. We reasoned that the C(14) acetate could be engaged as a participating group in parallel with its ability to undergo anchiomeric assistance as observed in glycosylation reactions. In such a scenario, the incoming nucleophile would be posed to attack opposite the acetate group. In the event, treatment of **42** with *N*-methoxy oxindole derived silyl enol ether **43** in the presence of BF_3 etherate[49] as an activator delivered acetal **44** as the only product (equation 1). This outcome closely parallels the chemistry of glycosyl donors incorporating a sterically hindered anomeric center, whereby the acetate participating group is attacked by the nucleophile rather than the anomeric carbon.[50] In order to circumvent such issues, we next tested substrate **45**, devoid of a protecting group on the C(14) hydroxyl (equation 2). Indeed, we observed the exclusive formation of C(3)-coupled oxindole **46** under the conditions used before. However, closer spectroscopic analysis as well as follow-up transformations of this product indicated that the newly formed stereocenter at C(3) had the wrong configuration as indicated in Scheme 9. We reasoned that installation of a bulky protecting group on the C(14) alcohol could shield the outer face of the putative oxonium intermediate and thereby allow attack only from the opposite face. Following this hypothesis, silyl ether **47** was prepared and treated with silyl enol ether **48** in the presence of BF_3 etherate. To our surprise, cyclic acetal **49** was obtained as the only product in moderate yield (57%) indicating intramolecular trapping of the highly hindered oxonium by the C(6) oxygen. Although we ultimately opted for the addition of carbon nucleophile to C(3), this transformation represented a proof of concept that formation the gelsemoxonine core might indeed be possible through an oxonium addition strategy. Motivated by this result, we set out to prepare various substrates suited for intramolecular ring closure by attack of a carbon nucleophile to C(3). Unfortunately, subjecting α-fluoroacetals such as **50**, incorporating an oxindole nuclephile at C(6), to various cyclization conditions, produced a complex mixture of dimeric products (equation 4). Substrates incorporating smaller nucleophiles at C(6) were not able to undergo ring closure.[51] We hypothesized that the congested environment around C(3) did not allow for carbon nucleophiles to attack from the concave face of the molecule.

The failure of the cyclization reactions detailed above demanded drastic changes to the synthetic strategy. An alternative approach for the construction of the central ring of gelsemoxonine would entail early introduction of C(7) and subsequent ring closure between a C(7) nucleophile and a leaving group at C(6) (Scheme 1, strategy B). According to this plan, we investigated functionalization of the C(3) position in enol ether **33** by a carbon appendage (Scheme 10). Again relying on the chemistry developed earlier, DMDO mediated epoxidation of enol ether **33** delivered a highly reactive oxirane, which was then subjected to various carbon nucleophiles to effect epoxide opening. We found that the use of ketene silyl acetal **51** was most successful providing ethyl ester **52** in 56% yield. It is thereby noteworthy that careful tuning of the reaction conditions and Lewis acid additive ($InBr_3$) allowed for the differential reaction of only the major epoxide diastereomer, whereas the minor undesired isomer remained unreactive and decomposed during workup. We were therefore able to isolate **52** cleanly without the need for tedious chromatographic separation of diastereomers. Addition of the propynyl side chain proceeded readily to produce isoxazolidine **53** in 78%. Notably, the ethyl ester in **52** was not affected under these conditions and only addition to the dihydroisoxazole was observed. Ring contraction of **53** proceeded in 45% yield

Scheme 10. Synthesis of ester 55.[a]

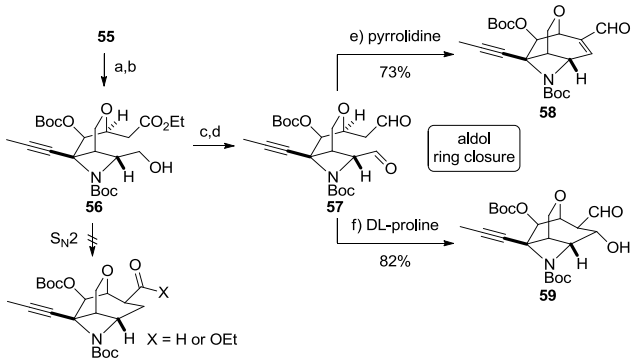


[a]Reagents and Conditions: (a) DMDO, 4Å MS, CH_2Cl_2/acetone (1:1), 0 °C, 2 h; then **51**, $InBr_3$ (5 mol%), CH_2Cl_2, –60 °C to rt, 2 h, 56% (dr > 20:1). (b) 1-bromo-1-propene, *n*-BuLi, THF/hexanes (1:1), –78°C, 1.5 h; then $CeCl_3$, –78 °C, 30 min; then **52**, BF_3·OEt_2, –78 °C, 2 h, 78%. (c) CF_3CO_2H, MeCN, 80 °C, 6 h, 40-45%; or CF_3CO_2H, MeCN, 80 °C, 2 h; then NEt_3, 35% (70% brsm). (d) Boc_2O, NEt_3, DMAP, CH_2Cl_2, rt, 30 min, 85%.

under the previously used conditions to produce **54**. However, careful quenching of the reaction with NEt_3 proved essential to achieve acceptable product yield. Subsequent protection of the amide and the alcohol using Boc_2O delivered acylcarbamate **55**. X-ray crystallographic analysis confirmed the structure of **55**.

As outlined in Scheme 11, introduction of the C(6) methylene could again be achieved using the Petasis olefination/hydroboration[52] sequence employed previously delivering alcohol **56**. No reaction of the ester was observed during the olefination step. We next attempted closure of the cycloheptane ring of gelsemoxonine through conversion of the C(6) hydroxyl group into a potent leaving group (e.g. OMs or OTs) followed by S_N2 displacement by a C(7) nucleophile. However, all the reactions tested towards this end involving enolate or enol chemistry, proved unsuccessful. We next prepared dialdehyde **57**, which would be amenable to an intramolecular aldol cyclization. Intramolecular aldol reactions of dialdehydes are often hampered by regioselectivity issues.[53] However, we surmised that the C(7) aldehyde in **57** might preferentially act as a nucleophile due to favorable steric factors. Indeed, when **57** was exposed to 20 mol% of pyrrolidine at –40 °C, condensation product **58** was obtained in 73% yield as the sole product. Interestingly, when DL-proline (20 mol%) was used as the promoter, we selectively obtained secondary alcohol **59** (82%) as a single diastereomer as confirmed by nOe and *J*-coupling analysis. The ability to control the outcome of the aldol cyclization step later proved essential in the synthesis as detailed below.

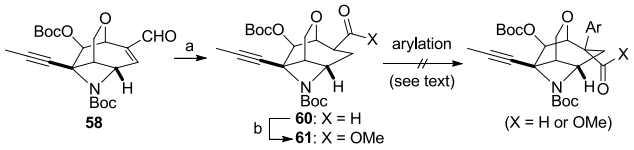
Scheme 11. Closure of the gelsemoxonine core.[a]



[a]Reagents and conditions: (a) Cp_2TiMe_2, pyridine, toluene, 70 °C, 8 h, 77% (85% brsm). (b) 9-BBN dimer, THF, rt, 45 min; then $NaBO_3{\cdot}4H_2O$, THF/H_2O (1:1), rt, 1 h, 92%. (c) DIBAL-H, THF/CH_2Cl_2 (2:1), –78 °C, 75 min, 81%. (d) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, 15 min; then diol substrate, –78 °C, 45 min; then NEt_3, –78 °C to rt, 1 h, 73%. (e) pyrrolidine (20 mol%), toluene, –40 °C, 2 h, 73%. (f) DL-proline (20 mol%), DMSO, rt, 12 h, 82%.

Oxindole formation: With the carbocyclic framework of gelsemoxonine established, we next turned to the installation of the oxindole of the natural product including the quaternary stereocenter at C(7). We initially envisioned the use of enolate arylation chemistry to achieve this goal. For this purpose, saturated aldehyde **60** was prepared by reduction of enal **58** using Stryker's reagent. Remarkably, we found that this reaction best proceeds at –78 °C to give the product as a 2:1 mixture of diastereomers after only 20 min of reaction time. Generally, elevated temperatures and reaction times up to 24 h are required to achieve the reduction of unsaturated aldehydes using Stryker's reagent.[54] The unusually high reactivity of substrate **58** can be attributed to a highly strained double bond as a result of the tricyclic scaffold.

Scheme 12. Attempts for enolate arylation.[a]



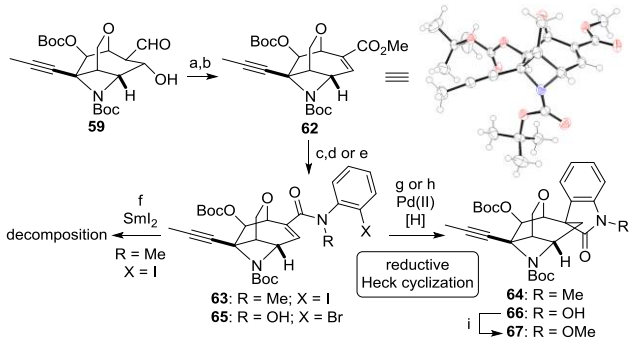
[a]Reagents and conditions: (a) $[(PPh_3)CuH]_6$, toluene, –78 °C, 20 min, 68% (dr 2:1). (b) $NaClO_2$, $NaH_2PO_4{\cdot}2H_2O$, 2-methyl-2-butene, *t*-BuOH/H_2O (4:1), rt, 1 h; then $TMSCHN_2$, CH_2Cl_2/MeOH (9:1), rt, 15 min, 65%.

With saturated aldehyde **60** and its ester derivative **61** in hand, various approaches for the introduction of an aryl group at C(7) were tested. Very efficient protocols for enolate arylation have recently been developed by Buchwald, Hartwig and Miura[55] relying on addition of arylpalladium reagents to esters,[56] amides[57] or aldehydes.[58] However, all protocols tested on either aldehyde **60**, ester **61** or amide derivatives thereof, failed to give the desired products. Moreover, more traditional approaches such as Fischer indolization[59] or addition of electrophiles to enolates of **60** or **61** similarly failed. We attribute the difficulties for functionalization of C(7) to the steric hindrance around this center as well as on difficulties of generating the respective enolate of **61**.[60]

An alternative strategy for the installation of the C(7) oxindole group would entail arylation of the olefin in unsaturated aldehyde **58** or its derivatives. In this respect, intramolecular enolate arylation of an anilide would provide the requisite regioselectivity. Unfortunately, all the conditions we evaluated for the oxidation of aldehyde **58** to its corresponding unsaturated carboxylic acid were unsuccessful due to complications with the highly reactive double bond in **58**. Luckily, as depicted in Scheme 13, we were able to perform Pinnick oxidation/esterification of saturated aldehyde **59** obtained from the proline-mediated aldol condensation shown in Scheme 11. Subsequent elimination of the secondary alcohol in the intermediate methyl ester was achieved employing TFAA to produce unsaturated ester **62**. The structure of **62** could be confirmed by X-ray crystallographic analysis. Ester hydrolysis proved difficult as nucleophilic reagents such as LiOH or KOTMS[61] reacted with the strained double bond through conjugate addition. Only the use of Me_3SnOH at 80 °C provided the desired unsaturated carboxylic acid in excellent yield.[62] Transformation into the

corresponding acid chloride followed by amide bond formation using 2-iodo-*N*-methylaniline as coupling partner delivered *N*-methylamide **63** in 70% yield over 2 steps.

Scheme 13. Construction of the oxindole.[a]



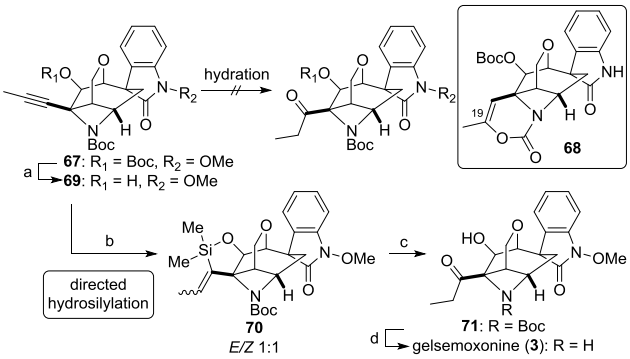
[a]Reagents and conditions: (a) $NaClO_2$, $NaH_2PO_4{\cdot}2H_2O$, 2-methyl-2-butene, *t*-BuOH/H_2O (4:1), rt, 20 min; then $TMSCHN_2$, CH_2Cl_2/MeOH (9:1), rt, 10 min, 91%. (b) TFAA, DBU, THF, rt, 30 min, 94%. (c) Me_3SnOH, 1,2-dichloroethane, 80 °C, 24 h. (d) $(COCl)_2$, DMF (cat.), CH_2Cl_2, rt, 1.5 h; then 2-iodo-*N*-methylaniline, NEt_3, CH_2Cl_2, rt, 45 min, 70% (2 steps) (for **63**). (e) $(COCl)_2$, DMF (cat.), CH_2Cl_2, rt, 1 h; then *N*-(2-bromophenyl)hydroxylamine, $NaHCO_3$, Et_2O/CH_2Cl_2 (3:1), 0 °C, 45 min, 58% (85% brsm, 2 steps) (for **65**). (f) SmI_2, *N*,*N*,*N*',*N*'-tetramethylguanidine, H_2O (3.0 euqiv.), THF, –20 °C. (g) **63**, $Pd(OAc)_2$ (10 mol%), $KHCO_2$, *n*-Bu_4NBr, DMF, rt, 12 h, 68% (dr 10:1) (**64**). (h) **65**, $PdCl_2(MeCN)_2$ (10 mol%), 1,2,2,6,6-pentamethylpiperidine, HCO_2H, DMF, 60 °C, 1.5 h, 72% (dr > 20:1) (**66**). (i) NaH, MeI, DMF, 0 °C to rt, 45 min, 92%.

Several reports have appeared documenting radical mediated cyclization of unsaturated *N*-arylamides to form oxindole products.[63] Following these procedures, we exposed iodoarene **63** to various conditions for generation of the corresponding radical. Whereas the use of AIBN/Bu_3SnH only resulted in protodeiodination, employing SmI_2 as radical generator in the presence of various different additives led to decomposition of the starting material.

Overman and coworkers have extensively studied the Heck reaction for the synthesis of oxindole rings harboring quaternary stereocenters, starting from haloarenes such as **63**.[64] However, the transiently formed alkyl palladium intermediate generally undergoes β-hydride elimination to deliver an olefin as the final product, as dictated by the Heck mechanism. In contrast, engaging amide **63** in a Heck cyclization would need to be followed by *in situ* reductive quenching of a respective alkyl palladium intermediate to directly deliver a saturated product such as **64**.[65] Moreover, a few delicate obstacles would have to be overcome to access **64** *via* a reductive palladium mediated cyclization. An initially formed aryl palladium species would have to attack the electron deficient olefin in **63** selectively at the highly congested C(7) with an approach from the top face of the double bond. Such a diastereoselective olefin functionalization would not be expected on steric grounds.[66] Furthermore, following any successful cyclization, the resulting alkyl palladium intermediate could undergo various side reactions competing with the desired reductive quenching step, including β-hydride elimination,[67] opening of the adjacent azetidine or oxindole ring opening leading back to the starting aryl palladium species. Regardless of these expected difficulties, **63** was treated with $Pd(OAc)_2$ in the presence of potassium formate as hydride donor. To our delight, oxindole **64** was isolated in 68% yield in a diastereomeric ratio of 10:1 favoring the desired isomer as confirmed by nOe analysis. We suspect that the face selectivity results from coordination of the palladium species to the adjacent oxygen of the ether bridge in **63**.[68] We next focused on the introduction of the methoxy group found on the amide nitrogen of glesemoxonine (**3**). After initial attempts for oxidation of an amide NH in either uncyclized aryl amides or oxindole derivatives had failed, we turned our attention to the synthesis of hydroxamic acid **65**.[69] However, *N*-selective coupling of the gelsemoxonine core fragment with various *N*-hydroxyaniline derivatives proved unexpectedly difficult.[70] We finally succeeded in synthesizing **65** through the combination of an etheral solution[71] of the acid chloride derived from **62** with 2-bromo-*N*-hydroxyaniline in the presence of solid $NaHCO_3$.[72] Reductive Heck cyclization of **65** was achieved under slightly modified conditions using $PdCl_2(MeCN)_2$ (10 mol%) and formic acid as reductant.[65b] Oxindole **66** was thereby obtained in 72% yield and as a single diastereomer. After methylation (MeI, K_2CO_3) the relative stereochemistry at C(7) of oxindole **67** was again confirmed by nOe analysis.

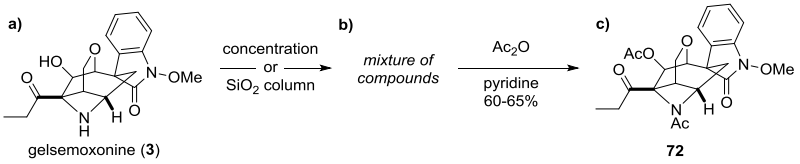
The final remaining task to elaborate the natural product gelsemoxonine involved conversion of the alkyne in **67** to an ethyl ketone moiety. To this end, various protocols for triple bond hydration were evaluated on **67** and derivatives thereof (Scheme 14).[73] However, all of the tested conditions failed to deliver the desired product. Instead, exposure of substrates incorporating a Boc protecting group on the azetidine to carbophilic reagents such as $(Ph_3P)AuNTf_2$[74] or $[Cl_2Pt(C_2H_4)]$ (Zeise's dimer)[75] resulted in the formation of products such as **68** through attack of the carbamate carbonyl group to C(19) (see Supporting Information for further details). We therefore opted for an alternative strategy involving a directed hydrosilylation of the alkyne.[76] As outlined in Scheme 14, selective deprotection of the C(14) hydroxyl was carried out using K_2CO_3/MeOH (87%). Subsequent treatment of the resulting alcohol **69** with $(Me_2SiH)_2NH$ (neat, 50 °C) delivered an unstable siloxane, which was directly subjected to $\{[RuCl_2(C_6H_6)]_2\}$ (20 mol%) providing vinylsilane **70** as the only product in 58% yield. Interestingly, **70** was obtained as a mixture of *E*/*Z* double bond isomers. This observation is in agreement with previous reports on alkyne hydrosilylation reactions using $\{[RuCl_2(C_6H_6)]_2\}$ as catalyst.[77] Ethyl ketone **71** could be accessed in 65% yield from vinylsilane **70** by Tamao-Flemming oxidation using $KHF_2/H_2O_2/Ac_2O$.[78,79]

Scheme 14. Synthesis of ketone 71.[a]



[a]Reagents and conditions: (a) K_2CO_3, MeOH, 50 °C, 30 min, 87%. (b) $(Me_2SiH)_2NH$, 50 °C, 2.5 h; then $\{[RuCl_2(C_6H_6)]_2\}$ (20 mol%), CH_2Cl_2, rt, 17 h, 58%, *E*/*Z* 1:1. (c) KHF_2, Ac_2O, H_2O_2, DMF, rt, 12 h, 65%. (d) 3 M HCl, EtOAc, 0 °C, 10 min, 97%.

Various Brønsted and Lewis acids were tested to effect final removal of the Boc carbamate. After some experimentation we found that treatment of **71** with 3 M HCl in EtOAc delivered the natural product gelsemoxonine (**3**) in 97% after aqueous workup of the reaction mixture. NMR spectroscopic data (Figure 2, a) as well as IR and MS characterization of the synthetic material were in complete agreement with the reported data of the natural product. Interestingly though, attempted chromatographic purification[8o] of synthetic gelsemoxonine (**3**) or repeated concentration of the material from solution ($CHCl_3$ or EtOAc) resulted in the formation of a complex mixture of compounds, as indicated by the ^{1}H NMR spectrum obtained after these attempts (Figure 2, b). The same result was obtained when using d_6-pyridine as the NMR solvent, excluding the possibility that residual acid promotes the observed chemistry.[8i] The original report documenting the isolation and characterization of gelsemoxonine did not mention any difficulties associated with the handling of the natural product



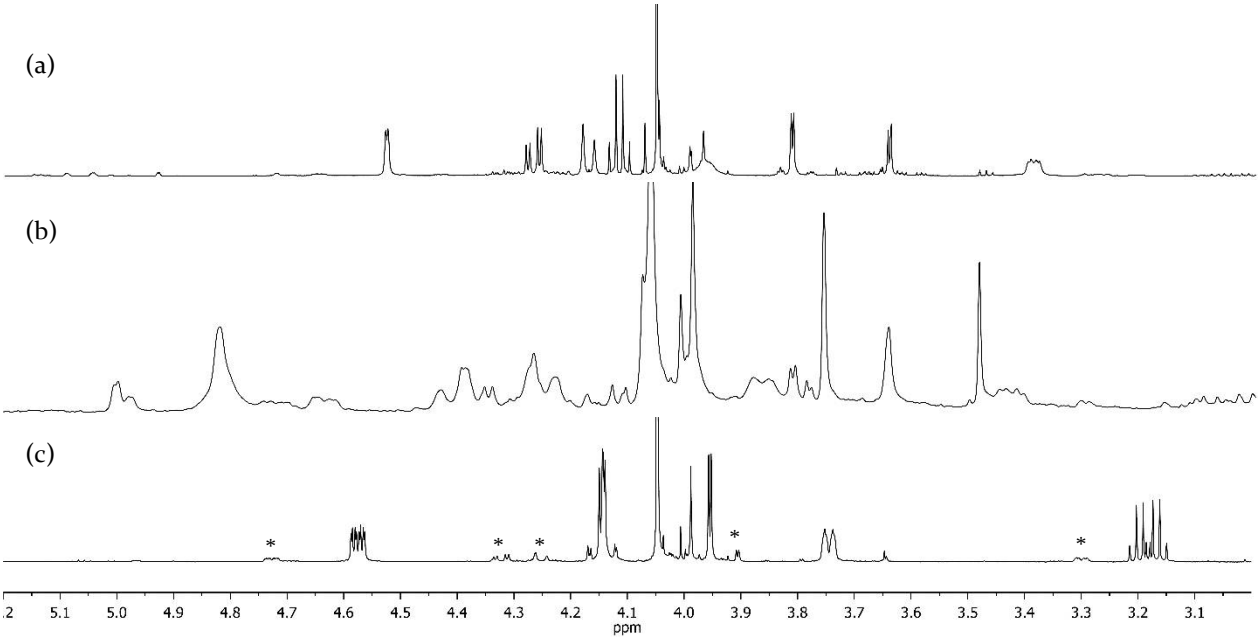
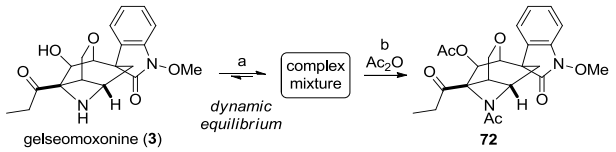


Figure 2. Comparision of ^{1}H NMR spectra in $CDCl_3$ (5.2-3.0 ppm range) of (a) crude gelsemoxonine (**3**); (b) compound mixture obtained after column chromatography (CH_2Cl_2/MeOH) or concentration of **3** from solution ($CHCl_3$ or EtOAc); (c) product of acetylation of the mixture shown in (b) corresponding to bisacetoxy gelsemoxonine **72** (after chromatography). *peaks from rotamers (see also 2D NMR spectra of **72** in the Supporting Information).

under similar conditions.[6] However, the authors reported a bisacetylated derivative of gelsemoxonine obtained after treatment of the isolated alkaloid with Ac_2O/pyridine. Accordingly, we subjected the complex product mixture obtained after concentration of synthetic gelsemoxonine to the acetylation conditions. To our surprise, we obtained a single product **72** from this reaction. Spectroscopic analysis indicated that this compound was identical to the bisacetylated gelsemoxonine derivative reported by the isolation group (Figure 2, c). Based on these results along with a closer spectroscopic analysis of the compound mixture obtained from synthetic gelsemoxonine (see Supporting information for further details) we propose that the natural product is prone to the formation of

oligomeric species upon concentration or chromatographic purification.[82] As indicated in Scheme 15, we hypothesize that a dynamic equilibrium of various aggregated species exists, likely

Scheme 15. Proposed chemistry of gelsemoxonine.[a]

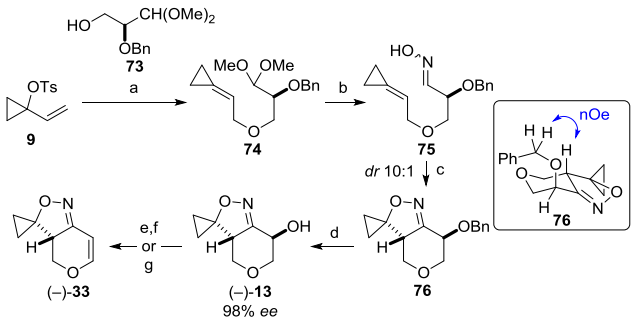


[a]Reagents and conditions: (a) repeated concentration from solution. (b) Ac_2O, pyridine, rt, 12 h, 60-65%.

resulting from the addition of the nucleophilic azeditine nitrogen to the electrophilic ketone.[83] This analysis is further supported by the observation that the presence of either the ketone or a free azetidine functionality alone is not sufficient to produce the observed chemistry of the natural product. We surmise that treatment of this complex mixture of oligomers with Ac_2O results in the exclusive reaction of the monomeric species, delivering **72** as the sole product.

Enantioselective synthesis of enol ether 33: With an efficient synthesis to (±)-gelsemoxonine (**3**) established, we envisioned the development of an enantioselective strategy to a key intermediate en route to the natural product. Enol ether **33** thereby offered various opportunities for enantioselective preparation. As outlined in Scheme 16, we implemented this plan by addition of enantioenriched alcohol **73**, obtained in three steps from (+)-diethyl tartrate,[84] to allylic tosylate **9**. Subsequent conversion of the resulting methylene cyclopropane derivative **74** to oxime **75** could be carried out in one step (86%) without any erosion of the stereochemistry at C(14) as confirmed by SFC analysis later in the synthesis. Dipolar cycloaddition was effected by the generation of a reactive nitrile oxide from **75** using $(n\text{-}Bu_3Sn)_2O/t\text{-}BuOCl$.[85] Oxazolidine **76** was obtained in 88% and as a 10:1 mixture of diastereomers favoring the isomer depicted in Scheme 16 as confirmed by nOe analysis (Scheme 16, box). Removal of the benzyl group was not possible by hydrogenolysis, as the N–O bond underwent reductive cleavage under these conditions. However,

Scheme 16. Enantioselective synthesis of (–)-33.[a]



[a]Reagents and conditions: (a) **73**, NaH, THF, 0 °C, 30 min; then **9**, $Pd(dba)_2$ (5 mol%), dppe (7 mol%), THF, rt, 12 h, 52% (62% brsm). (b) $H_2NOH{\cdot}HCl$, MeCN/H_2O (1:1), 80 °C, 12 h, 86%. (c) $(n\text{-}Bu_3Sn)_2O$, CH_2Cl_2, rt, 1 h; then *t*-BuOCl, –30 °C to rt, 30 min, 88% (dr 10:1). (d) $FeCl_3$, CH_2Cl_2, 0 °C to rt, 1 h, 87%. (e) PPh_3, I_2, imidazole, toluene/MeCN (5:1), rt, 12 h. (f) DBU, toluene/MeCN (4:1), 100 °C, 6 h, 82% (2 steps). (g) PPh_3, I_2, imidazole, toluene/MeCN (5:1), rt, 12 h; then DBU, 100 °C, 12 h, 62%.

treatment of **76** with $FeCl_3$ delivered enantioenriched alcohol (–)-**13** in 87% yield. Elimination of the secondary alcohol using standard protocols resulted in very low product yield or complete decomposition of the starting material. Fortunately, we found that conversion into the corresponding alkyl iodide (PPh_3, I_2) followed by DBU mediated elimination delivered enol ether (–)-**33** in 82% yield (2 steps). Alternatively, the substitution/elimination sequence could be performed in one single step delivering the product in slightly lower yield (62%).

Conclusion

In summary, we have achieved the total synthesis of gelsemoxonine (**3**) in 21 steps starting from known aldehyde **7**. Construction of the central azetidine of the natural product was possible through the use of an unusual spirocyclopropane isoxazolidine ring contraction. In the course of our synthetic studies, we have gained insight into the electronic requirement as well as the functional group tolerance of this transformation. Our group has also recently reported a mechanistic study of this reaction revealing a concerted nature of the reaction mechanism.[86] Furthermore, we have discovered previously unnoticed chemistry of gelsemoxonine. The experimental data suggests that the natural product can form oligomers through condensation of its ketone functionality with the nucleophilic azetidine nitrogen. Finally, we documented an enantioselective approach to a key intermediate of the presented synthesis.

ASSOCIATED CONTENT

Experimental procedures and characterization data for all reactions and products, including ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

erickm.carreira@org.chem.ethz.ch

Notes

The authors declare no competing financial interests.

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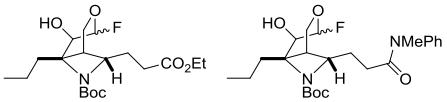

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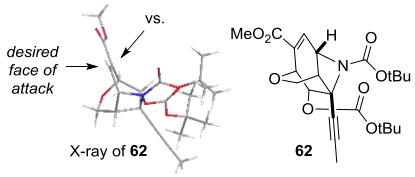

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(80) Column chromatography was tried with several different solvent systems but the oligomerization chemistry was observed under any of these conditions (see Supporting Information for further details).

(81) Upon dissolving the crude material in d_6-pyridine, gelsemoxonine slowly (within about 10-20 min) underwent the described oligomerization chemistry as observed for other solvents.

(82) We believe that residual acid (either from $CHCl_3$ or from the workup) as the promotor of the observed oligomerization chemistry can be excluded, as already concentration of clean gelsemoxonine from EtOAc or measuring the NMR spectra in pyridine produces the observed chemistry. Again, these oligomers could be resolved by acetylation.

(83) Retro-aldol reactions involving the ketone, hydroxyl, ether or oxindole moieties can be ruled out based on experiments with various derivatives of **3**, the observed clean acetylation of the compound mixture presented in Figure 2 as well as spectroscopic analysis of this mixture (see Supporting Information).

(84) **73** has been previously prepared using a slightly different procedure: Suami, T.; Tadano, K.-I.; Suga, A.; Ueno, Y. J. Carbohydr. Chem. **1984**, *3*, 429. For further details see Supporting Information.

(85) Moriya, O.; Takenaka, H.; Iyoda, M.; Urata, Y.; Endo, T. J. Chem. Soc., Perkin Trans. 1 **1994**, 413.

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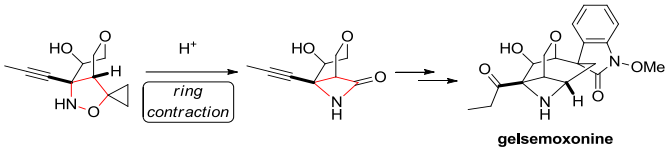

gelsemoxonine