CHEMISTRY
A EUROPEAN JOURNAL

COMMUNICATION

DOI: 10.1002/chem.201302669

Total Synthesis of Stemaphylline *N*-Oxide and Related C9a-Epimeric Analogues

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The *Stemona* alkaloids represent a class of more than eighty structurally diverse alkaloids isolated from plants belonging to the Stemonaceae family.[1] Structurally these alkaloids are characterized by the conserved pyrrolo[1,2-*a*]azepine core usually linked to a terminal lactone. These plants have been used in folk medicine in East Asia for thousands of years to treat the symptoms of bronchitis, pertussis, and tuberculosis and have been used as antiparasitics in humans and animals.

Recently, Lie and co-workers disclosed the structures of two new *Stemona* alkaloids from the root extracts of *Stemona aphylla*: stemaphylline (**1**) and stemaphylline *N*-oxide (**2**), featuring the central pyrrolo[1,2-*a*]azepine core linked to a 3,5-disubstituted γ-lactone moiety (Figure 1).[2] Stemaphylline was found to have low acetylcholinesterase (AChE) inhibitory activity, pronounced insecticidal activity, weak antimicrobial activity against *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas auruginosa* and weak antifungal activity against *Candida albicans*.

Due to the unique properties of azabicyclic containing natural products, our group has developed general methods for their asymmetric synthesis and applied these methods towards the total synthesis of azabicycle containing natural products (Scheme 1).[3] This method utilizes nucleophilic addition of a Grignard reagent containing a protected aldehyde to an Ellman chiral aldimine (**3**),[4] acid-mediated deprotection and acetal cleavage, and subsequent reductive amination to form the pyrrolidine ring (**4**).[4b] Ring-closing metathesis (RCM) gives the azabicyclic ring system (**5**).

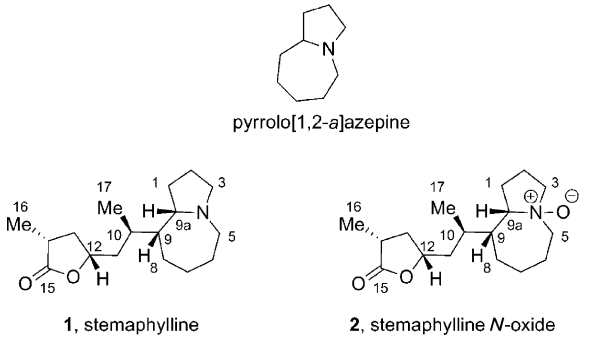
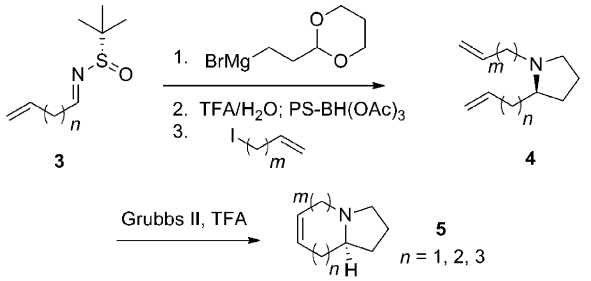


Figure 1. Pyrrolo[1,2-*a*]azepine core and stemaphylline (**1**) and stemaphylline *N*-oxide (**2**).



Scheme 1. Approach for the enantioselective synthesis of azabicyclic ring systems.[3]

Based on this approach, we planned an enantioselective total synthesis of stemaphylline, which would allow further evaluation of its biological activity and the preparation of unnatural analogues. In addition to construction of the azepine ring through RCM, our retrosynthetic analysis included concomitant cyclization of the γ-lactone from tetraene **7** to form **6**, which would give stemaphylline (**1**) upon olefin reduction. Chiral tetraene **7** would be formed from chiral *N*-sulfinyl imine **8**, as outlined in Scheme 2. Intermediate **8** represented an attractive point of entry into the preparation of unnatural analogues, because the nitrogen stereocenter can be inverted by preparation of the opposite chiral Ellman *N*-sulfinyl imine. Preparation of both diastereomers of aldimine **8** would also provide an opportunity to study the ability of the chiral Ellman auxiliary to control the asymmetric Grignard addition to a substrate possessing a significant Felkin–Anh substrate bias. The C10 and C9 stereogenic centers in intermediate **8** could be installed by oxa-

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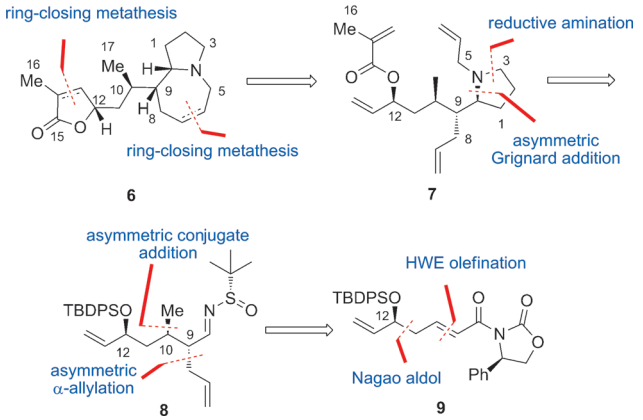
Supporting information for this article contains full experimental details and is available on the WWW under http://dx.doi.org/10.1002/chem.201302669.

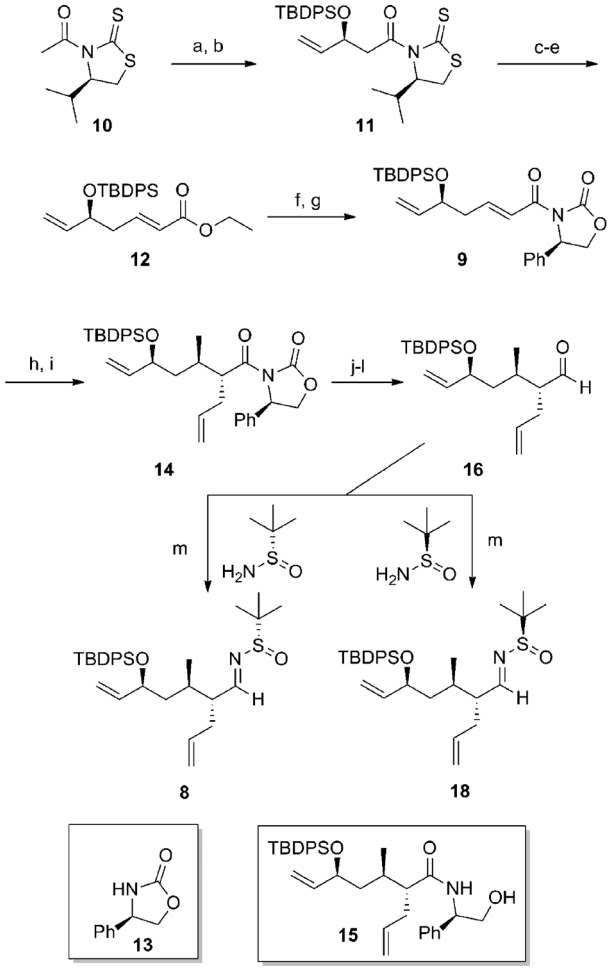


Scheme 2. Retrosynthetic analysis of stemaphylline (**1**). TBDPS = *tert*-butyldiphenylsilyl.

zolidine-mediated asymmetric conjugate addition followed by asymmetric α-allylation of α,β-unsaturated ester **9**. A Nagao aldol reaction would be used to install the allylic alcohol stereogenic center at C12.[5]

Our synthesis began with the precedented Nagao aldol reaction of thiazolidine thione **10** with acrolein (90% yield and 5:1 diastereomeric ratio (d.r.)),[5] and was followed by silyl protection of the allylic alcohol to afford **11**. Removal of the chiral auxiliary with $LiBH_4$, Swern oxidation, and Horner–Wadsworth Emmons olefination with triethyl phosphonoacetate by using the conditions of Masamune and Roush[6] led to the rapid construction of α,β-unsaturated ester **12** in 82% yield over three steps. Ester hydrolysis and coupling of the resultant carboxylic acid with Evans auxiliary **13** led to oxazolidinone **9**. After some experimentation, conjugate addition of mono-organocuprate species Li[MeCuI] in the presence of TMSI, as was developed by Bergdahl,[7] was found to provide better stereocontrol than the addition of higher-order cuprates, and successfully installed the C10 methyl stereocenter in 90% yield and 17:1 d.r. Subsequent enolate formation with LiHMDS in the presence of HMPA and allylation with allyl iodide gave intermediate **14** in 87% yield and 15:1 d.r. (Scheme 3).

Removal of the oxazolidine chiral auxiliary and reduction to the primary alcohol in the presence of $LiBH_4$ or LAH proved to be problematic. Poor yields were obtained (ca. 30%), and degradation of starting material was observed, presumably due to the steric congestion adjacent to the oxazolidinone. A similar observation was made by Wee and coworkers with a sterically encumbered substrate, and circumvented through adoption of a two-step protocol involving saponification to the carboxylic acid in the presence of $LiOH/H_2O_2$ and LAH reduction to the desired alcohol.[8] Employing this procedure proved to be effective for substrate **14**, affording the desired primary alcohol in 81% yield over two steps. Serendipitously, in our efforts to modify oxazolidine **14**, we isolated ring-opened intermediate **15**, which could be crystallized to give X-ray suitable crystals. This crystal structure confirmed the correct configuration of the C9, C10, and C12 stereocenters (Figure 2).



Scheme 3. Synthesis of aldimines **8** and **18**. a) $TiCl_4$, DIEA, CH_2Cl_2, −45°C; then acrolein, −78°C, 90%, d.r. 5:1; b) TBDPSCl, imidazole, CH_2Cl_2, 0°C to RT, 92%; c) $LiBH_4$, THF/MeOH, 0°C, 93%; d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78°C to RT, 98%; e) DBU, LiCl, triethyl phosphonate, MeCN, RT, 90%; f) LiOH, THF/H_2O (3:1), 55°C, 89%; g) Et_3N, PivCl, THF, −78°C to 0°C; then **13**, *n*BuLi, THF, 78°C to 0°C, 95%; h) CuI–DMS, MeLi, TMSI, THF, −78°C, 90%, d.r. 17:1; i) LiHMDS, HMPA, THF, −78°C; then allyl iodide, −45°C, 87%, d.r. 15:1; j) H_2O_2, LiOH, THF/H_2O (3:1), 0°C to RT, 96%; k) LAH, THF/Et_2O (4:1), 0°C, 84%; l) TPAP, NMO, 4 Å molecular sieves, CH_2Cl_2, 85%; m) (*S*)- or (*R*)-*tert*-butanesulfinamide, $Ti(OEt)_4$, THF, 40°C, 81%. TBDPS = *tert*-butyldiphenylsilyl; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; Piv = pivaloyl; DMS = dimethyl sulfide; LiHMDS = lithium bis(trimethylsilyl)amide; HMPA = hexamethylphosphoramide; LAH = lithium aluminum hydride; TPAP = tetrapropylammonium perruthenate; NMO = *N*-methylmorpholine oxide.

Ley oxidation and condensation with (*S*)- and (*R*)-*tert*-butanesulfinamides provided access to chiral *N*-sulfinyl imines **8** and **18** (Scheme 3). With these substrates in hand, we next studied the effect of Felkin–Anh substrate control in the Ellman asymmetric Grignard addition. Initial efforts revealed the large degree of Felkin control for this substrate, because formation of (2-(1,3-dioxan-2-yl)ethyl)magnesium bromide (**19**) in THF and addition to *N*-sulfinyl imine **8** gave poor selectivity (d.r. 1:1, Scheme 4). In contrast, addition to *N*-sulfinyl imine **18**, proceeded with much improved selectivity (d.r. 10:1). These observations are consistent with

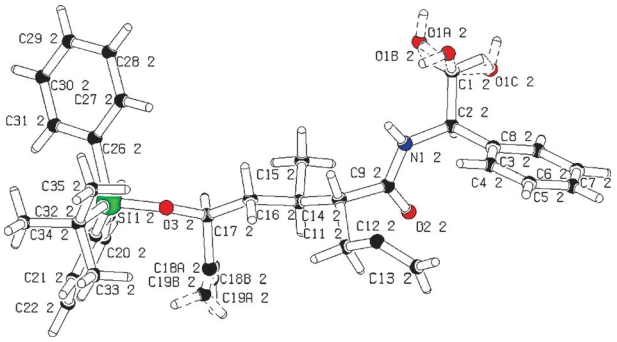
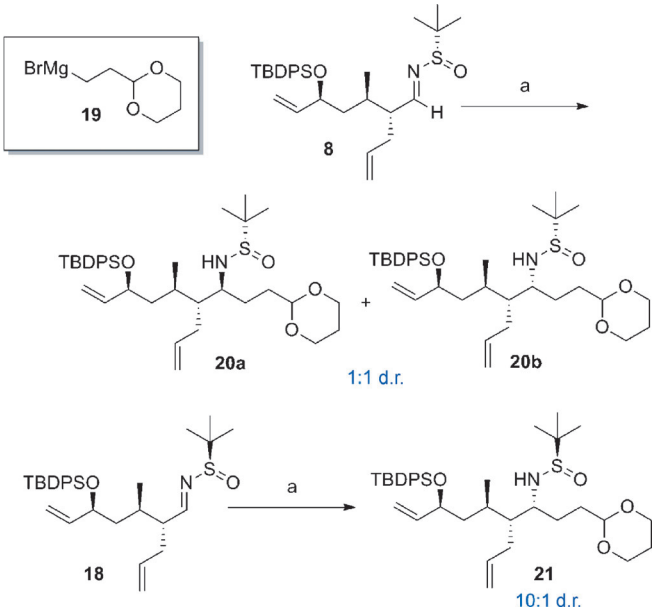


Figure 2. Crystal structure of **15** and confirmation of C9, C10, and C12 stereocenters. CCDC-949920 (**15**) contains the supplementary crystallographic data (excluding structure factors) for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.



Scheme 4. Asymmetric Grignard addition to aldimines **8** and **18**. a) **19** (1.0 M solution in THF), THF, −45 °C to RT, 86 %. TBDPS = *tert*-butyldiphenylsilyl.

the known sense of stereoinduction observed when employing (2-(1,3-dioxan-2-yl)ethyl)magnesium bromide **19**[3b,4b] and the Felkin control dictated by the C9 stereocenter in aldimines **8** and **18**. In an attempt to improve the selectivity with aldimine **8** to obtain increased quantities of desired stereoisomer **20a**, we further investigated the asymmetric Grignard reaction (Table 1). Hypothesizing that the chelating ability of the solvent could play a role in stereocontrol, we attempted to form Grignard reagent **19** in less-coordinating Et_2O,[4b] but were unsuccessful. Minimizing the amount of THF present by increasing the concentration of the Grignard reagent to 3.0 M and performing the reaction in CH_2Cl_2 led to a slight increase in selectivity (1:1.5); however, in favor of the undesired stereoisomer. Switching to formation of Grignard **19** in 2-MeTHF further increased selectivity for the undesired stereoisomer **20b** (Table 1, entry 4), and increased dilution of aldimine **8** in CH_2Cl_2 exacerbated this effect (Table 1, entry 5). These results suggest that non-coordinating solvents may deteriorate or reverse the selectivity of the Ellman chiral auxiliary in substrates such as **8**.

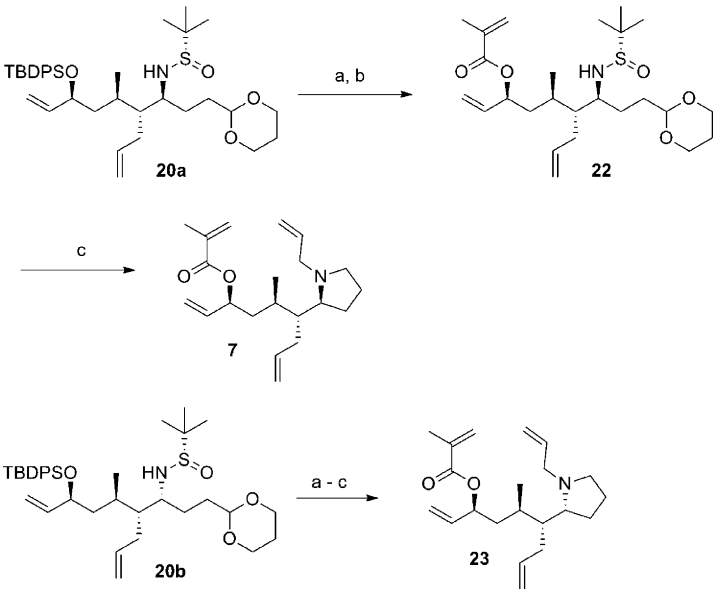
Table 1. Conditions for Grignard addition of **19** to aldimine **8**.[a]

Entry	Aldimine **8** [M]	RMgX solvent	RMgX [M]	Yield [%]	d.r. (**20a**/**20b**)
1	0.2	THF	1.0	90	1:1
2	0.2	Et_2O	1.0	n.r.	–
3	0.2	THF	3.0	61	1:1.5
4	0.2	2-MeTHF	3.0	83	1:2.7
5	0.1	2-MeTHF	3.0	86	1:4

[a] In all cases, to a solution of aldimine **8** in CH_2Cl_2 at −45 °C was added Grignard reagent **19** followed by warming to RT and stirring for 18 h. n.r. = no reaction.

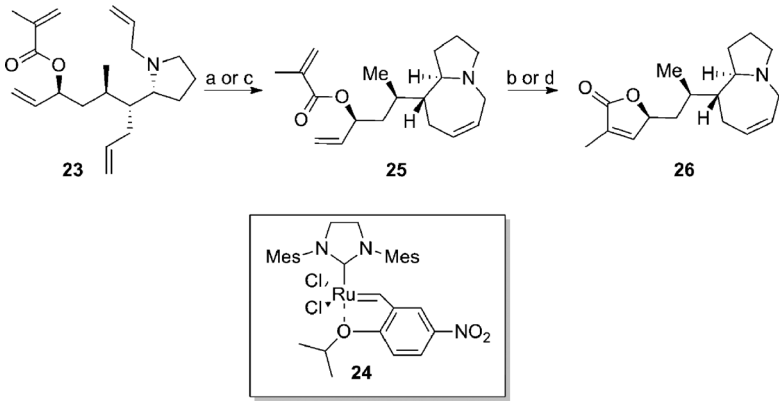
Unable to improve the selectivity for desired Grignard addition product **20a**, we moved forward with our effort toward the total synthesis of stemaphylline, as shown in Scheme 5. Silyl deprotection with TBAF, followed by ester formation with methacrylic anhydride gave intermediate **22**. Nitrogen deprotection and concomitant acetal cleavage with TFA/H_2O, followed by reductive amination in the presence of PS-BH(OAc)$_3$[3a,4b] and pyrrolidine allylation with allyl iodide gave tetraene **7** in 47 % yield for the three-step sequence. The corresponding stereoisomer **23** containing the opposite amine stereocenter was also synthesized in analogous fashion with similar yield.

With tetraene pyrrolidines **7** and **23** in hand, we began exploring conditions for the tandem RCM to construct the azepine ring and γ-lactone. Having larger quantities of tet-



Scheme 5. Synthesis of pyrrolidines **7** and **23**. a) TBAF, THF, 0 °C to RT, 97 %; b) methacrylic anhydride, Et_3N, DMAP, CH_2Cl_2 RT, 82 %; c) i) TFA/H_2O, (95:5); ii) PS-BH(OAc)$_3$, DCE, RT; iii) allyl iodide, K_2CO_3, DMF, RT, 47 % over three steps. DMAP = 4-dimethylaminopyridine; DCE = dichloroethane; PS = polymer supported.

raene **23** from our studies on the asymmetric Grignard addition, we chose to first explore the tandem RCM with this substrate. RCM of amine containing substrates are known to be difficult and require the use of acid additives to prevent coordination of the amine to the ruthenium, which can result in catalyst poisoning. Previously, we have successfully employed Grubbs II catalyst in the presence of TFA and heating to close azabicylic ring systems.[3c]



Scheme 6. Tandem RCM of **23**. a) TFA (1 equiv), toluene; then **24** (15 mol%), RT; b) **24** (25 mol%), toluene, 90°C, 26% yield over two steps; c) CSA (2 equiv), toluene; then **24** (10 mol%), RT, 65%; d) **24** (2×10 mol%), 90°C, 52% yield over two steps. TFA = trifluoroacetic acid; CSA = camphorsulfonic acid; Mes = mesityl.

Unfortunately, these conditions were unsuccessful. Although consumption of starting material and formation of a product corresponding to the mass of a single ring closure was observed by LC/MS, no progression toward the desired bis-ring closure product was observed, and significant decomposition of starting material occurred.

Grela and co-workers have reported Ru catalyst **24** with improved reactivity and mild reaction conditions for challenging RCM reactions including a protected nitrogen-containing azepane ring, as well as a trisubstituted α,β-unsaturated δ-lactone.[9] Based on these reports, we hoped to selectively form the azepine ring system by reaction at room temperature, and then to close the γ-lactone under elevated temperatures. Excitingly, this proved to be successful, because reaction with Grela catalyst **24** in the presence of TFA (1 equiv) stirring first at room temperature and then at 90°C gave the desired bis-ring closure product in 26% yield (Scheme 6). With this result, we next studied the effect of the acid on the closure of the azepine ring, examining acids with a range of pK_a values (Table 2). Without an acid additive, the reaction did not progress, and CSA with a pK_a value in the middle of the acids surveyed was found to provide the greatest degree of conversion, as was measured by LC/MS (Table 2, entry 5). Doubling the amount of CSA to two equivalents was found to greatly improve the efficiency of the reaction, resulting in complete consumption of tetraene **23** within 6 h, and affording 65% isolated yield of pyrroloazepine **25**.

With optimized conditions for closure of the azepine ring, we applied these conditions (Table 2, entry 6) to the tandem ring closure of tetraene **23**, heating the reaction to 90°C after complete conversion to **25**. Although conversion to bis-ring closure product was observed by LC/MS (ca. 20% conversion), the use of additional catalyst (2×10 mol%) and extended heating was required for full conversion of **25** to **26**. A small selection of metathesis catalysts were screened with these optimized conditions (Hoveyda–Grubbs II, Zhan 1B, Grubbs II, Schrock catalysts). Grela and Hoveyda–Grubbs II catalysts were found to be optimal and exhibited comparable activity. Thus, reaction of tetraene **23** in the presence of CSA (2 equiv) and Grela catalyst **24** (3×10 mol%) gave **26** in 52% isolated yield (Scheme 6).

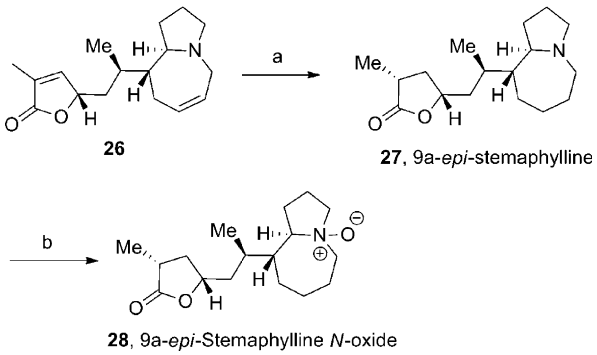
Table 2. Acid screen for tandem ring-closing reaction.

Entry	Acid [pK_a]	[equiv]	Ratio **25**/**23**
1	–	–	no conv.
2	TFA (−0.25)	1	1:4.5
3	PTSA (−2.8)	1	1:2.2
4	AcOH (4.76)	1	>1:20
5	CSA (1.2)	1	1:1.3
6	CSA (1.2)	2	>20:1

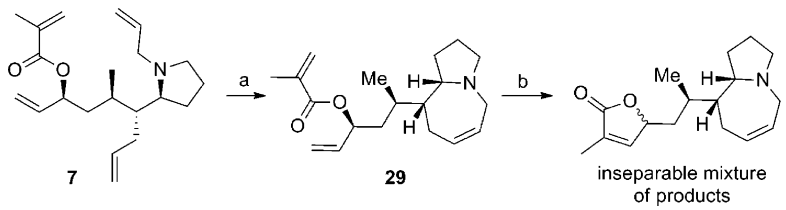
[a] To as solution of tetraene **23** in toluene, acid was added. After stirring for 10 min, Grela catalyst (10%) was added, and stirring was continued at RT for 7 h.

As shown in Scheme 7, intermediate **26** was carried forward to unnatural analogue 9a-*epi*-stemaphylline **27** through olefin reduction employing Pearlman's catalyst,[10] which also set the final C14 stereocenter in 95% yield and 7:1 d.r. Reaction of **27** in the presence of O_3 led to the corresponding *N*-oxide **28** (53% yield).[11]

With successful conditions for the tandem RCM reaction, we turned our attention toward the synthesis of stemaphylline, subjecting pyrrolidine tetraene **7** to the optimized



Scheme 7. Synthesis of 9a-*epi*-stemaphylline and 9a-*epi*-stemaphylline *N*-oxide. a) $Pd(OH)_2/C$, H_2, THF, RT, 95%; b) O_3, CH_2Cl_2, −78°C, 54%.



Scheme 8. Tandem RCM of **7**. a) CSA (2 equiv), 1,4-benzoquinone (50 mol%) toluene; then Hoveyda–Grubbs II (3×10 mol%), RT, 48%; b) Hoveyda–Grubbs II (2×10 mol%), 90°C. CSA = camphorsulfonic acid.

tandem RCM reaction conditions with the Grela catalyst (Scheme 8). Surprisingly, the ring closure proceeded more slowly, and upon isolation an inseparable mixture of products was obtained. In consideration that olefin migration could be leading to epimerization, we tested the addition of 1,4-benzoquinone reported to suppress undesirable olefin migration;[12] however, a mixture of bis-ring closure products, in which the C12 carbon of the lactone was epimerized, was still observed.

To elucidate when the suspected epimerization was occurring, the reaction was stopped after closure of the azepine ring in the presence of Hoveyda–Grubbs II, CSA, and 1,4-benzoquinone at room temperature. Isolation of mono-ring closure product **29** demonstrated that a single product was formed and that closure of the γ-lactone was the problematic step (Scheme 8). Unfortunately, subjection of **29** to a variety of acid additives and RCM catalysts were ineffective in suppressing the formation of the mixture of products.

In an attempt to gain insight into the differences in reactivity between tetraene **7** and **23** and azepeines **29** and **25**, the four compounds were sketched and minimized using the MMFF force field to an energy gradient of <0.01 while preserving the stereochemistry. These calculations were performed by using MOE (v2012.10; Chemical Computing Group; www.chemcomp.com). The resulting global minima 3D structures revealed that tetraene **23** possesses an intramolecular hydrogen bond, which could preorganize the substrate for RCM. In contrast, tetraene **7** possesses a more disordered conformation with the olefins splayed apart providing a possible rationale for the lower reactivity of tetraene **7** in the RCM reaction. Examination of azepines **25** and **29** revealed a striking difference in the orientation of the α,β-unsaturated ester and its proximity to the olefin RCM partner. Although the two olefins in intermediate **25** are in close proximity, the reacting olefins in **29** are pointed away from one another. This disfavorable orientation of the γ-lactone in **29** then allows competing reaction pathways or epimerization of the C12 stereocenter during the course of the reaction (Figure 3). These data suggest a conformational bias that supports the observed experimental outcomes; however, there are many freely rotatable bonds, and solvation is not accounted for, thus, this ground-state analysis is laden with caveats, yet provides a partial explanation for the differential substrate reactivity.

From this analysis, we began investigation of methods to expedite the closure of the γ-lactone to prevent the suspected epimerization. Recently, Hoye and co-workers have developed a relay ring-closing-metathesis (RRCM) strategy[13] to accelerate reactivity for difficult substrates, and as a means to preload the ruthenium-metathesis catalyst at a desired olefin to improve selectivity. By incorporating dienes

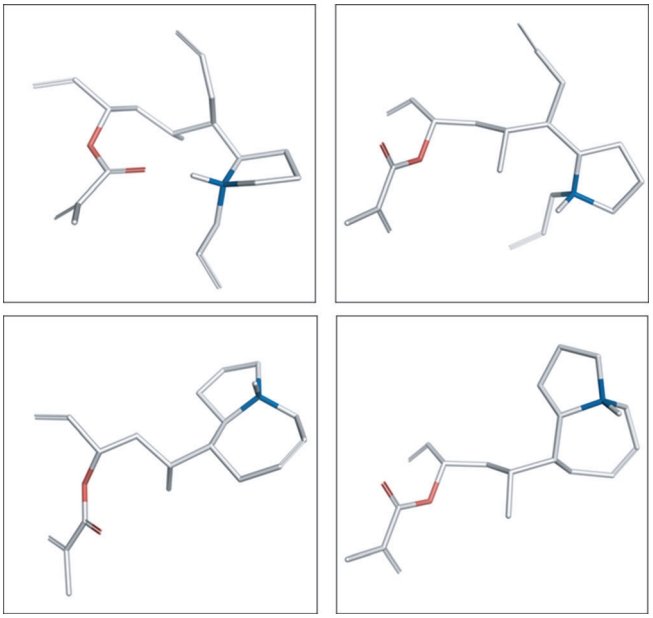
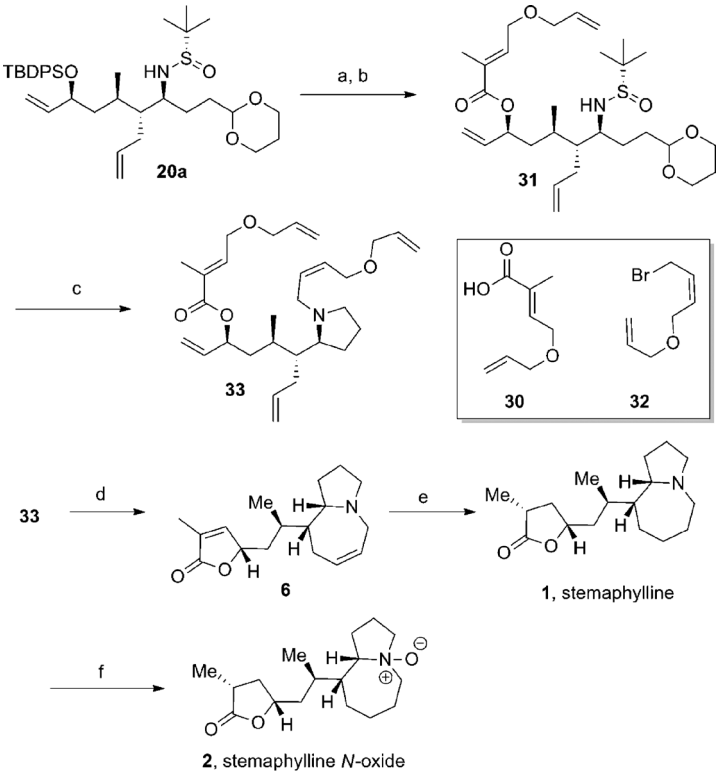


Figure 3. Energy-minimized 3D structures of **23** (top left), **7** (top right), **25** (bottom left), and **29** (bottom right).

30[14] and **32**[15] into intermediate **20a** (Scheme 9), we formed RRCM substrate **33** to determine if directing the formation of the ruthenium alkylidene would prove beneficial. Reaction at room temperature revealed significant amounts of truncation products, presumably intermediates **7** and **29**. However, vigorous reflux and argon spurge led to rapid formation of the desired RCM product **6**, and excitingly with only minor epimerization (10:1). Reduction with Pearlman's catalyst[10] gave stemaphylline in 62% yield and with 4:1 selectivity at the C12 stereocenter. Spectral and rotation data of the synthetic material was generally in agreement with that reported for the natural product **1**, though complicated by the presence of 4:1 ratio of inseparable diastereomeric products.[2] Further confirmation was achieved by conversion to stemaphylline *N*-oxide **2**. Attempts to form the *N*-oxide in the presence of O_3 was ineffective; however, formation with *m*CPBA in CH_2Cl_2 at 0°C gave stemaphylline *N*-oxide **2** in 74% yield, isolated as a single isomer by reverse-phase chromatography. The synthetic **2** was in complete agreement with the spectral and rotation data reported, thus completing the first total synthesis of **3** and, by inference, **2**.[2]



Scheme 9. Synthesis of RRCM substrate **33** and synthesis of stemaphylline **1** and stemaphylline *N*-oxide **2**. a) TBAF, THF, 0 °C to RT, 97 %; b) **30**, MNBA, Et_3N, DMAP, CH_2Cl_2, reflux, 98 %; c) i) TFA/H_2O, (95:5); ii) PS-BH(OAc)$_3$, DCE, RT; iii) **32**, K_2CO_3, DMF, RT, 40 % over three steps; d) CSA (2 equiv), toluene, RT; then Hoveyda–Grubbs II (20 mol %) reflux, argon spurge, 37 %; e) Pd(OH)$_2$/C, H_2, THF, RT, 62 %; f) *m*CPBA, CH_2Cl_2, 0 °C, 74 %. MNBA = 2-methyl-6-nitrobenzoic acid.

In conclusion, we have completed the first total synthesis of both stemaphylline **1** (19 steps) and stemaphylline *N*-oxide **2** (20 steps) through a tandem bis-RCM strategy, as well as unnatural 9a-*epi*-stemaphylline **27** and 9a-*epi*-stemaphylline *N*-oxide **28**. The linear tetraene substrate leading to **27** and **28** was suggested by modeling to be preorganized for the bis-tandem RCM and smoothly gave the desired unnatural products; however, the tetraene corresponding to natural **1** and **2** was disorganized, leading to lower reactivity and ruthenium alkylidene-mediated epimerization. Thus, adopting a RRCM strategy enabled access to **1** and **2**. Biological evaluation of both natural and unnatural analogues is underway and will be reported in due course.

Acknowledgements

The authors acknowledge the Vanderbilt Department of Pharmacology, VUMC, and the NIH for funding our research, and in particular the MLPCN (U54MH084659) for the Vanderbilt Specialized Chemistry Center. The financial support from the Warren Foundation in the form of the William K. Warren, Jr. Endowed Chair is gratefully acknowledged.

Keywords: alkaloids · metathesis · stemaphylline · stemaphylline *N*-oxide · total synthesis

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Received: July 9, 2013
Published online: August 16, 2013

