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Stereoselective Total Synthesis of Hetisine-Type C_{20}-Diterpenoid Alkaloids: Spirasine IV and XI

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Abstract: *The first total synthesis of the architecturally complex hetisine-type heptacyclic C_{20}-diterpenoid alkaloids (±)-spirasine IV and XI is reported. The A/F/G/C tetracyclic skeleton with the challenging N−C6 and C14−C20 linkages was efficiently constructed by an intramolecular azomethine-ylide-based 1,3-dipolar cycloaddition with unusual regioselectivity. SmI_2-mediated free-radical addition to the arene moiety without prior dearomatization and a stereoselective intramolecular aldol reaction further enabled rapid access to the hetisine core, providing a bicyclo[2.2.2]octane ring with a new oxygen substitution pattern.*

To date, over 1200 diterpenoid alkaloids, mainly from the *Aconitum*, *Consolidum*, *Delphinium*, and *Spiraea* genera of plants, have been isolated and characterized. Extracts from these plants have been used in traditional Chinese medicine for the treatment of pain and cardiovascular diseases for centuries.[1] With guan-fu base A (**2**; Figure 1), an antiarrhythmia agent approved in 2005 in China, as one of its distinguished members, the family of diterpenoid alkaloids exhibits a broad spectrum of biological activities, including acetylcholinesterase inhibition, de-addiction, antiepileptiform, anti-inflammatory, and anticancer effects.[2] Enzymatic C−C and C−N bond formation/cleavage during the biosynthetic process lead to diverse skeletal types in the diterpenoid alkaloids. On the basis of the number of constituent carbon atoms, these alkaloids can be categorized into C_{18}, C_{19}, and C_{20} classes. Among them, the C_{20}-diterpenoid alkaloids can be further classified into several types, with atisine, hetidine, denudatine, and hetisine the most common, depending on the characteristic bond linkages of the skeletons.[2] The hetisine-type C_{20}-diterpenoid alkaloids (a few representative members are shown in Figure 1) feature a heptacyclic skeleton with distinctive N−C6 and C14−C20 linkages.[2] The different degrees of oxygen substitution at various positions of the skeleton differentiate the members of this family from one another and provide a structural basis for the diverse bioactivities.

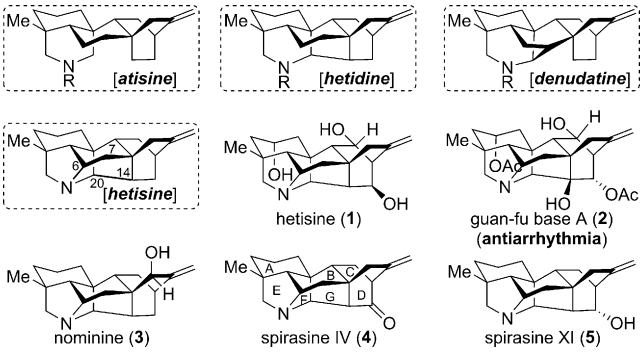

Figure 1. Selected skeleton types of C_{20}-diterpenoid alkaloids and representative members of the hetisine-type alkaloids.

The architectural complexity and notable biological profiles of the C_{20}-diterpenoid alkaloids have made them and their biogenetically relevant diterpenes highly pursued synthetic targets for decades.[3–10] Early synthetic efforts focusing on structurally simpler alkaloids led to the successful synthesis of atisine-,[4] veatchine-,[5] and napelline-type[6] alkaloids. The past decade has witnessed the blossoming of this research field,[7] with many elegant strategies culminating in the synthesis of two more types of C_{20}-diterpenoid alkaloids: hetisine[7a–c] and denudatine alkaloids.[7g,j–l] The Baran group applied a two-phase synthetic strategy to enable unified access to various types of diterpenes,[10b] the biogenetically related atisine alkaloids, and the hetidine skeleton.[7f] Fukuyama and co-workers reported the first total synthesis of lepenine, a denudatine-type alkaloid.[7g] Xu and co-workers described a collective synthesis of atisine-type alkaloids on the basis of an enyne cycloisomerization approach for construction of the atisane skeleton.[7i] Qin, Liu, and co-workers described a biomimetic approach to access the atisine- and denudatine-type alkaloids, as well as the hetidine skeleton.[7k] The Sarpong group demonstrated a unified synthesis of all three classes of C_{18}-, C_{19}-, and C_{20}-diterpenoid alkaloids from a common, advanced intermediate as guided by network analysis,[7j,l,9e] and reported a gallium-catalyzed cycloisomerization approach for the synthesis of dihydronavirine.[7e,h]

Despite these advances, nominine (**3**) was the only hetisine-type alkaloid to have been synthesized prior to this study. In 2004, Natsume and Muratake completed the first total synthesis of nominine in 36 steps.[7a] Soon after, Gin and Peese developed an elegant synthesis of the same molecule by using a dipolar cycloaddition/Diels–Alder cycloaddition strategy, although their key step required harsh reaction

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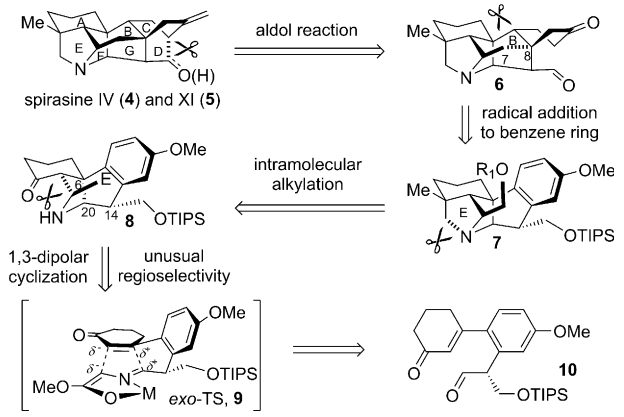
conditions and suffered from low regioselectivity.[7b,c] The difficulties associated with the construction of the N–C6 and C14–C20 linkages, which are not present in simpler congeners (e.g., atisine, hetidine), have probably impeded synthetic progress toward the more complex hetisine-type alkaloids.[3] With the objective of developing a general synthetic strategy with new disconnections, by which rapid construction of the core system and incorporation of functionalities at unusual positions would be possible, we embarked on a synthetic program toward the synthesis of spirasine IV and XI, two hetisine-type C_{20}-diterpenoid alkaloids with characteristic oxygen substituents at C13, which were isolated from *Spiraea japonica* L. f. var. *fortunei* (planchon) Rehd. by Sun and Yu.[11] Herein we report our synthetic endeavors that led to the first total synthesis of (±)-spirasine IV and XI.

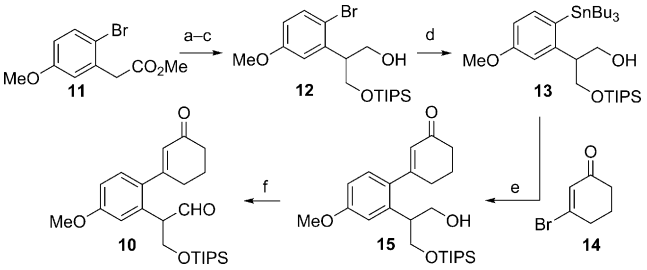
Retrosynthetically, we envisioned that the bicyclo-[2.2.2]octane motif of spirasines could be constructed by a stereoselective aldol reaction, by which a different substitution pattern in terms of the oxygen atoms could be realized in comparison with the commonly used Diels–Alder cycloaddition strategy (Scheme 1).[3e] The B ring of **6** could be



Scheme 1. Retrosynthetic analysis of spirasine IV and XI. TIPS = triisopropylsilyl.

accessed from **7** by radical addition to the arene moiety, with or without prior dearomatization.[3d,e] In turn, the E ring of **7** could be established from **8** by intramolecular alkylation of the nitrogen atom. The tetracyclic intermediate **8**, with the N–C6 and C14–C20 linkages already in place, was the key intermediate in our proposed synthesis of hetisine-type alkaloids. We envisioned that **8** could be accessed by the *exo*-selective intramolecular 1,3-dipolar cycloaddition of an azamethine ylide derived from enolizable aldehyde **10**, with regioselectivity opposite to the intrinsic selectivity observed in the intermolecular reactions.[12] The feasibility of this transformation was foreshadowed by a study by Grigg and coworkers[13] wherein *endo* selectivity was observed with less challenging, non-enolizable aldehydes.[12a]

Our synthetic efforts commenced with the preparation of aldehyde **10** from the known ester **11**. A sequence involving an aldol reaction with paraformaldehyde, protection of the resulting hydroxy group as a silyl ether, and reduction of the ester to an alcohol afforded **12** in good yield (Scheme 2).



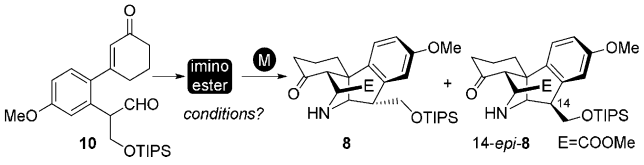
Scheme 2. Decagram-scale preparation of aldehyde **10**. Reagents and conditions: a) $(HCHO)_n$, K_2CO_3, DMF, 0 °C→RT, 97%; b) TIPSOTf, 2,6-lutidine, CH_2Cl_2, room temperature, 99%; c) DIBAL-H, CH_2Cl_2, 0 °C→RT, 91%; d) *n*BuLi, Bu_3SnCl, THF, −78 °C, 65%; e) $Pd(PPh_3)_4$, CuBr, dioxane, 85 °C, 77%; f) Dess–Martin periodinane, CH_2Cl_2, room temperature, 91%. DIBAL-H = diisobutylaluminum hydride, DMF = *N*,*N*-dimethylformamide, Tf = trifluoromethanesulfonyl.

Stannylation proceeded well in the presence of a free hydroxy group by treatment of **12** with nBu_3SnCl after Br–Li exchange, thus providing **13** in 65% yield. Stille coupling of **13** and **14** under Pd–Cu dual catalysis occurred smoothly to provide **15** in 77% yield. Dess–Martin oxidation of the hydroxy group in **15** gave aldehyde **10**, which set the stage for the pivotal 1,3-dipolar cycloaddition. Through this six-step sequence, decagram quantities of **10** were conveniently prepared.

Next, we proceeded to evaluate the efficiency of a variety of metal salts as catalysts and the convenience of amino acetate ester sources for the preparation of the imino ester, the purity of which is critical for the subsequent 1,3-dipolar cycloaddition.[12] As the enolizable aldehyde is a challenging substrate for the azamethine-ylide-based 1,3-dipolar cycloaddition,[12a] we were pleased to find that a phosphinimine, formed by premixing methyl 2-azidoacetate with PPh_3, delivered the ylide precursor imino ester in good purity. This crude imino ester was advanced to the expected cycloaddition product under the catalysis of Ag or Cu, whereas commonly used methyl glycinate led to lower and inconsistent yields (Table 1, entry 8 vs. 9). Among the metal salts screened, AgOAc gave the best result in terms of yield and stereoselectivity. The desired cycloaddition adduct **8** was produced presumably via the favored transition state *exo*-TS **9** shown in Scheme 1, along with the undesired yet separable diastereomer 14-*epi*-**8** in a ratio of 7:1. We did not observe any other isomers in this 1,3-dipolar cycloaddition, presumably because of the intramolecular tethering that forces the regioselectivity to be opposite to the intrinsic selectivity observed in the intermolecular reaction. Besides the high diastereo- and regioselectivity, this key cycloaddition reaction boasts mild conditions (0 °C) and good scalability (> 25 g scale). The structure of this A/F/G/C tetracyclic skeleton and the configuration of the five contiguous stereogenic centers, including a quaternary stereogenic center, were confirmed by X-ray crystallographic analysis of the corresponding 4-nitrobenzenesulfonamide derivatives of **8** and 14-*epi*-**8**.[14]

With decagram quantities of the tetracyclic compound **8** in hand, we proceeded to construct the E ring. The amine group of **8** was protected with a benzyl group, followed by Wittig olefination and hydrolysis of the resulting enol ether to

Table 1: Optimization of the 1,3-dipolar cycloaddition.[a]

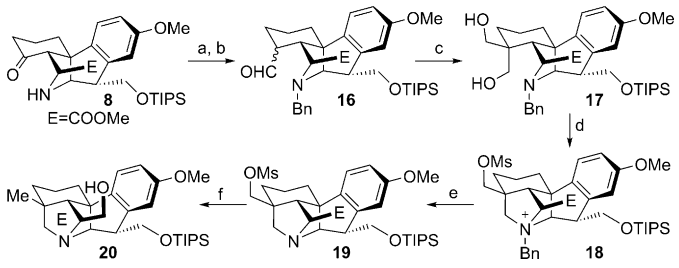


Entry	[M]	Amino ester source	Yield [%][b]	d.r.[c]
1	$CuBF_4$	$Ph_3P{=}NCH_2CO_2Me$	21	2.1:1
2	$CuPF_6$	$Ph_3P{=}NCH_2CO_2Me$	20	2.7:1
3	AgOTf	$Ph_3P{=}NCH_2CO_2Me$	59	5.3:1
4	AgTFA	$Ph_3P{=}NCH_2CO_2Me$	56	5:1
5	$AgBF_4$	$Ph_3P{=}NCH_2CO_2Me$	60	3.5:1
6	$AgClO_4$	$Ph_3P{=}NCH_2CO_2Me$	53	2.5:1
7	Ag_3PO_4	$Ph_3P{=}NCH_2CO_2Me$	50	2.3:1
8	AgOAc	$Ph_3P{=}NCH_2CO_2Me$	68	7:1
9	AgOAc	$NH_2CH_2CO_2Me$	45	5:1
10[d]	AgOAc	$Ph_3P{=}NCH_2CO_2Me$	63	7:1

[a] Conditions unless otherwise stated: **10** (0.12 mmol, 1 equiv), N_3CH_2COOMe/PPh_3 (1.1 equiv) or NH_2CH_2COOMe (1.1 equiv), metal salt (0.1 equiv), DBU (2 equiv), toluene (2 mL), 0 °C, 1 h. [b] Yield of the isolated major isomer **8**. [c] Ratio of the yields of **8** and 14-*epi*-**8** (isolated products). [d] The reaction was conducted on a 27 g scale. DBU = 1,5-diaza[5.4.0]undec-5-ene.

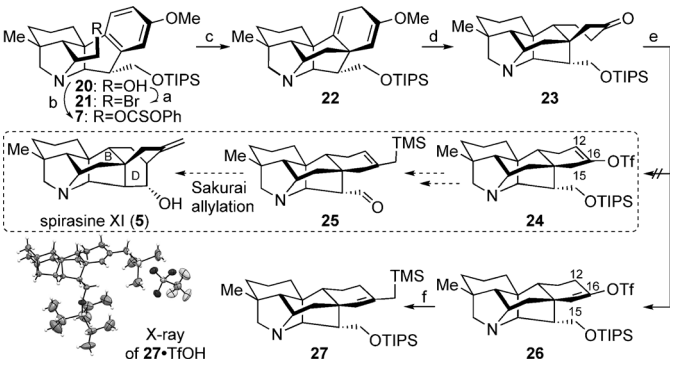
furnish aldehyde **16** in 86% yield as an inconsequential 15:1 mixture of diastereomers (Scheme 3). An aldol reaction with paraformaldehyde and reduction of the aldehyde group with $NaBH_4$ provided diol **17** in 80% yield. As expected, mesylation of both hydroxy groups of **17** resulted in spontaneous construction of the E ring, and the resulting quaternary ammonium salt **18** was then subjected to Pd/C-catalyzed hydrogenation, which furnished **19** in 91% yield. After screening various reducing agents, we were pleased to find that treatment of **19** with Super-Hydride in refluxing dioxane provided alcohol **20** in excellent yield with both the mesylate and ester moieties reduced.

Having the pentacyclic intermediate **20** in hand set the stage for exploring various strategies to construct the final B and D rings. Inspired by the large number of reports on the use of arene dearomatization strategies in natural product



Scheme 3. Construction of the E ring. Reagents and conditions: a) BnBr, K_2CO_3, CH_3CN, 80 °C, 99%; b) $PPh_3CH_2OMe{\cdot}Cl$, *n*BuLi, THF, −78 → −20 °C; then $TiCl_4$, H_2O, CH_2Cl_2, 0 °C, 86%, d.r. 15:1; c) $(HCHO)_n$, K_2CO_3, THF, room temperature; then $NaBH_4$, 0 °C, 80%; d) MsCl, DMAP, pyridine, CH_2Cl_2, room temperature, 72%; e) Pd/C, H_2 (1 atm), MeOH, room temperature, 91%; f) $LiBHEt_3$, 1,4-dioxane, reflux, 96%. Bn = benzyl, DMAP = 4-*N*,*N*-dimethylaminopyridine, Ms = methanesulfonyl.

synthesis,[3e,15] we initially envisioned that formation of the B ring could involve an arene dearomatization step and a subsequent intramolecular free-radical addition reaction. However, our early attempts involving a Birch reduction were unfruitful. We were ultimately drawn to a direct free-radical addition to the benzene ring. As indicated in Scheme 4,



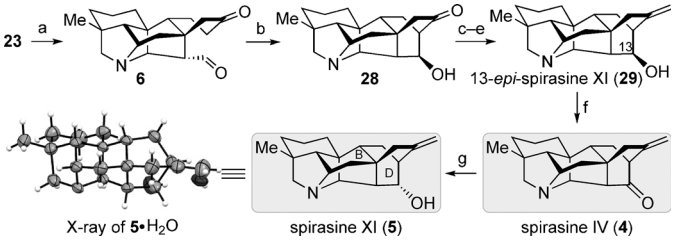
Scheme 4. Study toward the construction of the B and D rings. Reagents and conditions: a) MsCl, pyridine, CH_2Cl_2, room temperature; then LiBr, CH_3CN, reflux, 30%; b) PhOCSCl, DMAP, CH_2Cl_2, −40 °C, 87%; c) SmI_2, *t*BuOH, HMPA, THF, 0 °C, 67% from **21**, 61% from **7**; d) *p*-TsOH, H_2O, THF, room temperature; then Pd/C, H_2 (1 atm), MeOH, 66%; e) $PhNTf_2$, LiHMDS, THF, −78 °C, 70% for **26**; f) $TMSCH_2MgCl$, $Pd(PPh_3)_4$, THF, room temperature, 83%. HMDS = hexamethyldisilazane, HMPA = hexamethylphosphoramide, TMS = trimethylsilyl, Ts = toluenesulfonyl.

mesylation of the hydroxy group and subsequent bromination produced **21** in 30% yield, which was converted into the desired cycloaddition product **22** with the B ring formed in good yield upon treatment with SmI_2.[16] The low yield for the preparation of **21** impelled us to find an alternative precursor. After much experimentation, we were delighted to find that **7**, with a thiocarbonate group rarely used in SmI_2-mediated reactions, could fulfil this goal by enabling the transformation of **20** into **22** in good chemical yield, presumably through reduction of the thiocarbonate group to a primary radical and then radical addition to the benzene ring.[17]

Following the successful construction of the B ring, we focused our attention on constructing the final D ring to access the hetisine skeleton (Scheme 4). Hydrolysis of the enol ether and hydrogenation of the resulting alkene provided **23** in good yield. Our initial attempts to construct the D ring through the preparation of enol triflate **24** from ketone **23** and further elaboration to **25**, which might provide direct access to spirasine XI (**5**) by a well-established intramolecular Sakurai allylation, proved to be problematic. Surprisingly, ketone **23** was transformed predominantly into $\Delta^{15,16}$ enol triflate **26** upon treatment with $PhNTf_2$/LiHMDS, thus disfavoring formation of the desired $\Delta^{12,16}$ enol triflate **24**. This unexpected regioselectivity might be attributed to chelation of the oxygen atom of the silyl ether with Li so as to override the preference for the removal of the less sterically hindered hydrogen atom on C12 by deprotonation. Further screening of less chelating bases (e.g., NaHMDS, KHMDS) only afforded an inseparable mixture of **24** and **26** in a 1:1 ratio.

The structure of **26** was verified by X-ray crystallographic analysis of the corresponding Kumada coupling product **27**.[14]

Owing to the difficulties associated with regioselective enolate formation, we turned our attention to an intramolecular aldol reaction strategy. We anticipated that this strategy might circumvent the above regioselectivity problem, as the expected $\Delta^{12,16}$ enol should be formed in an equilibrium with the $\Delta^{15,16}$ enol. The desired enol could then be trapped selectively by the aldehyde group in an intramolecular reaction. Compound **23** was elaborated to keto aldehyde **6** by a sequence of desilylation with HF and oxidation with TEMPO/NaClO. As expected, exposure of **6** to alkaline methanol effected the cycloaddition to form **28** as a single diastereomer (Scheme 5). With the core system of hetisine in



Scheme 5. Access to the core structure and completion of the total synthesis of spirasine IV and XI. Reagents and conditions: a) aqueous HF, THF, room temperature; then TEMPO, KBr, aqueous NaClO, CH_2Cl_2/H_2O, room temperature; b) K_2CO_3, MeOH, room temperature, 56% from **23**, d.r. > 20:1; c) TESOTf, 2,6-lutidine, CH_2Cl_2, room temperature, 96%; d) dimethyltitanocene, toluene, 110 °C, 82%; e) aqueous HF, THF, room temperature, 63% from **28**; f) Dess–Martin periodinane, CH_2Cl_2, room temperature, 84%; g) L-selectride, THF, −78 °C, 83%, d.r. > 20:1. TEMPO = 2,2,6,6-tetramethylpiperidinooxy, TES = triethylsilyl, L-selectride = lithium tri-*sec*-butylborohydride.

place, the remaining tasks were to install the exomethylene group and adjust the oxidation state as well as the stereochemistry of the C13. Direct olefination of ketone **28** with $Ph_3P{=}CH_2$, the Tebbe reagent, or the Petasis reagent was not successful. A stepwise route including silylation, Petasis olefination, and desilylation enabled access to **29**, an epimer of spirasine XI at C13. Finally, oxidation with Dess–Martin periodinane and diastereoselective reduction of the resulting ketone group furnished spirasine IV (**4**) and spirasine XI (**5**) in 22 and 23 steps from **11**, respectively. The structure of our synthetic spirasine XI (**5**) was unambiguously confirmed by X-ray crystallographic analysis.[14]

In summary, we have developed an expedient synthetic approach to the core structure of hetisine-type C_{20}-diterpenoid alkaloids and completed the total synthesis of (±)-spirasine IV (**4**) and (±)-spirasine XI (**5**). A diastereoselective 1,3-dipolar cycloaddition of an azomethine ylide to an enone with unusual regioselectivity was employed as the key reaction for the assembly of the A/F/G/C tetracycle with the challenging N–C6 and C14–C20 linkages. SmI_2-mediated free-radical addition to the arene moiety without prior dearomatization and a diastereoselective aldol reaction enabled rapid access to the hetisine core. Not only does the aldol reaction approach provide a different oxygen substitution pattern on the bicyclo[2.2.2]octane ring as compared to previous studies,[3e] and the degree and pattern of substitution may have a big impact on the biological activity of the diterpenoid alkaloids,[2] but the functional groups of the resulting hydroxy ketone would also provide handles for the synthesis of other, more highly oxygenated congeners.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alkaloids · dipolar cycloaddition · radical reactions · terpenoids · total synthesis

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Naturstoffsynthese

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Stereoselective Total Synthesis of Hetisine-Type C_{20}-Diterpenoid Alkaloids: Spirasine IV and XI

Sieben Ringe: In der Totalsynthese der Hetisin-artigen heptacyclischen C_{20}-Diterpenoidalkaloide wurde das A/F/G/C-Gerüst durch eine intramolekulare 1,3-dipolare Cycloaddition mit ungewöhnlicher Regioselektivität aufgebaut (siehe Schema). Eine SmI_2-vermittelte radikalische Addition an die Areneinheit ohne vorherige Dearomatisierung und eine Aldolreaktion ermöglichten den schnellen Zugang zum Hesitin-Kern.