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SHORT COMMUNICATION

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A Model Study toward the Concise Synthesis of Bromotyrosine-Derived Spiroisoxazoline Natural Products and Analogous Core Structures

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Keywords: Natural products / Heterocycles / Spiro compounds / Synthetic methods / Multifunctionalization / Cyclization

A model study of the first nonaromatic ring based approach toward α-hydroxyspiroisoxazolines resembling the bromotyrosine-derived natural product and analogous spiroisoxazoline core structures was implemented. The desired molecular architecture was achieved through the multifunctionalization of a key 1,3-diketo spiroisoxazoline. Our strategy could serve as an efficient alternative to previously developed approaches that involve aromatic ring oxidation as the essential step to synthesize this class of natural products.

Introduction

Over the past 50 years, marine sponges of the order *Verongida* have been distinguished as affluent sources of α-oximinotyrosine-derived marine natural products (Figure 1).[1] Most recently, the Red Sea sponge *Suberea mollis* was also found to be a source of two new bromotyrosine-derived natural products, subereamollines A and B, as secondary metabolites containing the spirocyclohexadienyl isoxazoline moiety.[2] These widespread spiroisoxazoline natural products can easily be distinguished by three major structure categories in which the brominated spiroisoxazoline core contains a cyclohexadiene, a bromo epoxy ketone, or a bromohydrin moiety (Figure 1). The structural diversity arising from the unique spiro linkage between a brominated cyclohexadiene, an ioxazoline, and a wide range of amine and diamine linkages brings about a broad spectrum of pharmacological activities including antiviral,[3] antimicrobial,[4] anti-HIV,[5] antifungal,[6] antifouling,[7]

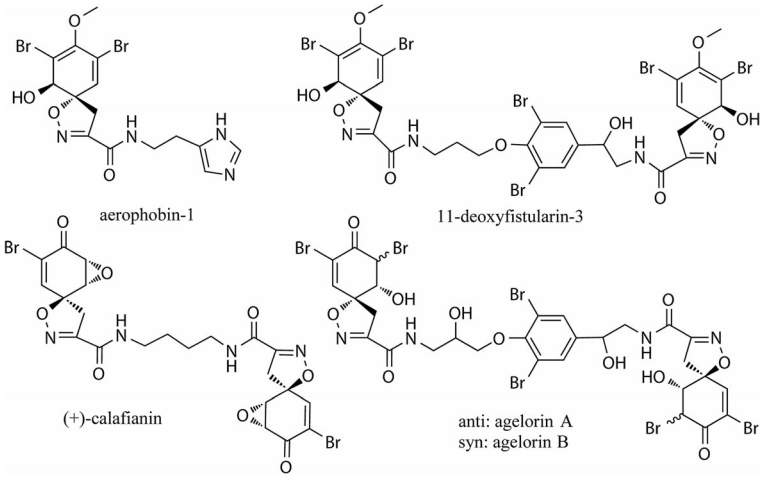

Figure 1. Spiroisoxazoline natural products.

Na^+/K^+ ATPase inhibition,[8] histone deacetylase (HDAC) inhibition,[9] histamine H_3 antagonism,[10] mycothiol *S*-conjugate amidase inhibition,[11] isoprenylcysteine carboxy methyltransferase (Icmt) inhibition,[12] and antineoplastic properties.[13]

Therefore, constructing the unique and synthetically challenging spiro skeleton has been of great interest to

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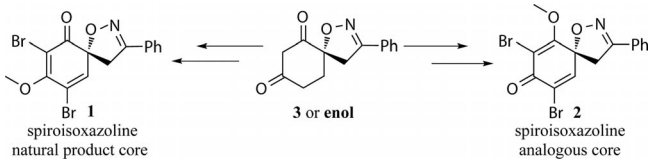
many chemists.[14,15] However, continuing efforts have resulted in only a few synthetic strategies for the syntheses of functionalized carbocyclic spiroisoxazolines.[15] Although significant progress in the oxidation of an aromatic ring with thallium(III) trifluoroacetate,[15a,15b] electroorganic oxidation,[15c,15d] and *N*-bromosuccinimide (NBS)[15f] followed by the intramolecular cyclization of a pendant oxime has been achieved in past decades, oxidative methods for spiroisoxazoline synthesis remain restricted to aromatic systems in which the desired products are sometimes isolated in moderate yields and often require the use of toxic oxidants.[15a–15d] However, the oxidative cyclization of oxime esters by using diacetoxyiodobenzene was proven to be the most suitable reagent to date.[15e,15g–15i]

In this context, our continuing efforts and success in developing new methodology[16] enabled us to generate a novel synthetic strategy toward the bromotyrosine class of natural products (Scheme 1). Herein, we report the multifunctionalization of a 1,3-cyclohexanedione to furnish the desired spiroisoxazoline as a model study for the core structure of bromotyrosine-derived spiroisoxazoline natural products and their analogues (Scheme 1). Furthermore, this methodology could potentially serve as an alternative synthetic strategy toward the targeted natural products and closely related spiroisoxazolines as novel analogues of biological interest.

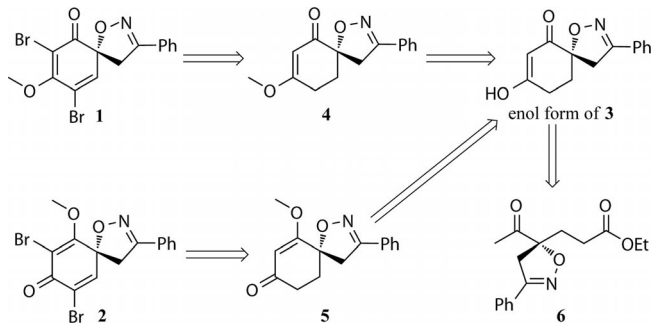


Scheme 1. Our synthetic strategy.

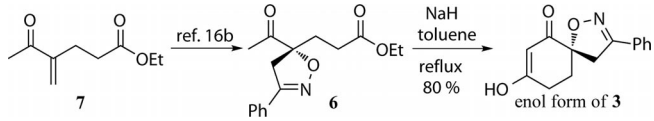
Results and Discussion

Our synthesis basically relied on two approaches, a non-aromatic approach towards the spirodiketone and a multifunctionalization approach to furnish the desired molecular architecture resembling the bromotyrosine-derived natural product core. Retrosynthetic analysis of the aforementioned natural product core model study showed that most synthetically interesting core spiroisoxazolines **1** and **2** could be obtained from corresponding spiromethoxyenone derivatives **4** and **5**, which in turn could be achieved from the same spiro-1,3-diketone moiety **3**. Spirodiketone **3** could be easily prepared from base-mediated intramolecular condensation of corresponding keto ester **6** (Scheme 2).

In our synthesis, acyclic isoxazole derivative **6**[16b,17] was used as a key precursor for this model study. After treating **6** with sodium hydride, diketone spiroisoxazoline **3** was isolated in 80% yield (Scheme 3). Analysis of **3** by ^{1}H NMR spectroscopy showed that it existed as an enol, which results in the fast exchange of one of the protons between the two carbonyl groups. Notably, the ready availability of cyclohexane-1,3-dione and its diverse reactivity often render cyclohexane-1,3-dione and its analogues as suitable starting materials for a number of natural product syntheses.[18] However, for our synthetic strategy we needed to convert the diketone into a conjugated diene system for additional functionalization.



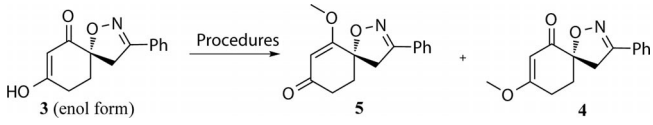
Scheme 2. Retrosynthetic analysis.



Scheme 3. Synthesis of the spirovinylogous acid of **3**.

We subjected **3** to a variety of reported reaction conditions[19] to determine the best reagent that would afford spiroisoxazoline regioisomers **4** and **5** in the highest yields (Table 1). On the basis of the data shown in Table 1, entry 4, which features $TiCl_4$ (5 mol-%) in methanol[19d] with triethylamine, both spiroisoxazolines **5** and **4** were isolated in 97% yield in a 1:2.5 ratio in favor of spiroisoxazoline **4** after 15 min (Table 1). Owing to the fact that both regioisomers were isolated, divergent synthetic pathways were explored in which spiroisoxazoline **4** was utilized as a precursor for the natural product core structure (analogous to 11-deoxyfistularin-3), whereas spiroisoxazoline **5** was developed into a spiroisoxazoline that was more comparable to the agelorin natural products in which the carbonyl and isoxazoline moieties have a 1,4-relationship.[21]

Table 1. Synthesis of methoxyenone.

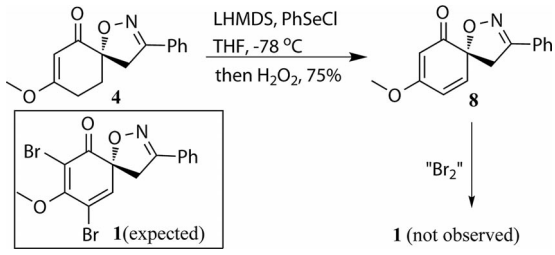


Entry	Procedure	**5**:**4**	Yield [%]
1	10% HCl/MeOH	1:2	50
2	concd. H_2SO_4/MeOH, reflux, 12 h	1:2	70
3	2.5 mol-% *p*TSA[a]/MeOH, reflux, 6 h	1:1.5	60
4	5 mol-% $TiCl_4$/MeOH/Et_3N, reflux, 6 h	1:2.5	97
5	CeC_{13}·7H_2O/MeOH, 6 min	1:2	40
6	NaH/THF, reflux 2 h, then Me_2SO_4	1:2	82
7	*t*BuOK/THF, 10 min, then Me_2SO_4	1:2.5	80

[a] *p*TSA = *p*-toluenesulfonic acid.

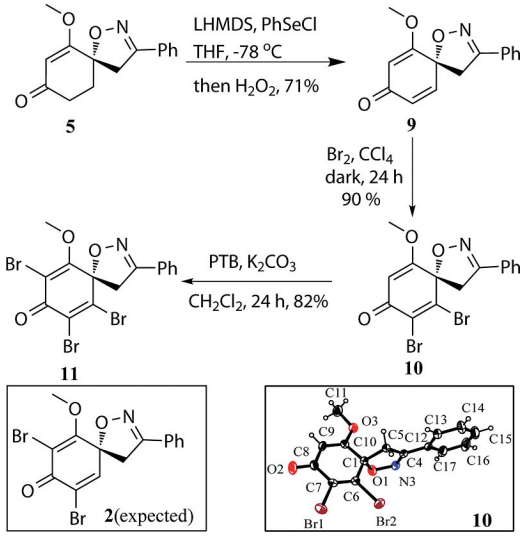
With the anticipation of furnishing a conjugated double bond, we treated predominant isomer **4** with lithium hexa-

methyldisilazane (LHMDS) and PhSeCl followed by H_2O_2.[20,22] As a result, deprotonation of the allylic proton of **4** and subsequent formation and elimination of the selenoxide afforded **8** in 75% yield (Scheme 4). To accomplish the core structure, the spirodiene was then exposed to a number of reaction conditions to bring about dibromination and concomitant dehydrohalogenation. Unfortunately, after a number of attempts to introduce bromine to **8** through a variety of bromine sources [pyridinium tribromide (PTB)/K_2CO_3, Br_2/CCl_4, NBS/CCl_4], none of desired product **1** was isolated; instead, decomposition of the starting material was realized (Scheme 4).



Scheme 4. First-generation synthesis of spirodiene.

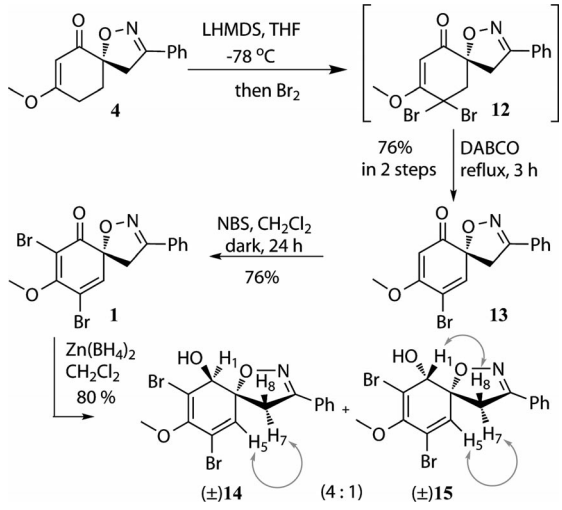
Isomer **5** was also treated under a comparable reaction series, as shown in Scheme 4, to introduce the other double bond to furnish the natural product derivative as a model study for the synthesis of the spiroisoxazoline analogue (Scheme 5). Although isomer **5** was treated with LHMDS and PhSeCl followed by H_2O_2, we isolated spiro derivative **9** in 71% yield (Scheme 5). Bromination of **9** with bromine in the absence of light afforded vicinal dibromo derivative **10**[23] in 90% yield, as result of over bromination followed by dehydrohalogenation. We did not realize any dibromination of the α-carbon with respect to the ketone to afford expected product **2**. The feasibility of introducing the third bromine at the α position of **10** was further attempted under PTB/K_2CO_3 conditions, which afforded **11** in 82% yield



Scheme 5. First-generation synthesis of bromospiroisoxazoline.

(Scheme 5). However, our target was to synthesize 1,3-dibromo derivative **2**.

After this setback, we then decided to switch the electrophile used in the synthesis of **1** from phenylselenium chloride to phenylselenium bromine. We anticipated that after treating **4** with an excess amount (2.5 equiv.) of LHMDS, treatment with an excess amount of bromine would provide allylic geminal dibromo compound **12** through monobromination. Therefore, we followed this reaction pathway, and, without further purification, crude allylic geminal dibromo compound **12** was treated with 1,4-diazabicyclo[2.2.2]-octane (DABCO) in situ to afford **13** in 76% yield over two steps in one reaction vessel (Scheme 6). Bromination of **13** adjacent to the carbonyl was achieved in 76% yield with NBS in the dark. Diastereoselective reduction of **1** with $Zn(BH_4)_2$[24] afforded desired spiroisoxazoline core structures (±)-**14** and (±)-**15** in a 4:1 diastereomeric ratio (Scheme 6).

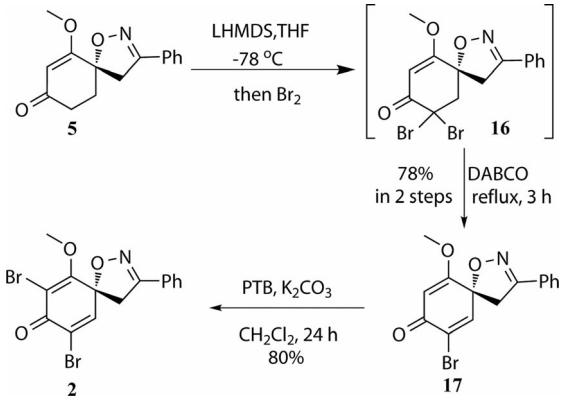


Scheme 6. Second-generation synthesis of the bromospiroisoxazoline core.

Purification of the crude mixture gave (±)-**14** and (±)-**15** in 64 and 16% yield, respectively. The diastereomeric ratio favoring desired *trans* isomer **14** over undesired *cis* isomer **15** was rationalized by intramolecular hydride delivery through a five-membered zinc chelate that avoids the steric demands of the isoxazoline methylene group, and this results in the delivery of the hydride from the *alpha* face of the ketone.[25] Though we synthesized racemic **14** and **15**, the rigid scaffold of the spiroisoxazolines showed signs of distinct NOE interactions between the diagnostic protons that enabled us to establish the relative stereochemical assignment of the hydroxy group on the basis of the NOESY spectrum (Scheme 6). The distinct NOE interactions indicated strong cross-peaks between H^5 and H^7 for **14**, whereas in the case of **15**, strong cross-peaks were observed between H^5 and H^7 and also between H^1 and H^8, which suggested the formation of *trans*-**14** and *cis*-**15**, as a result of diastereoselective reduction (Scheme 6).

Having succeeded in constructing desired spiroisoxazoline **1** through our model studies, we then focused on trans-

forming minor isomer **5** into its corresponding dibromo derivative **2** (Scheme 7). Following a similar protocol that was used in Scheme 6, **5** was treated with an excess amount of LHMDS and Br_2 followed by DABCO under reflux conditions to provide desired monobromo derivative **17** in 78% yield. Further bromination of **17** by using PTB/K_2CO_3 provided desired α-dibromo derivative **2** in 80% yield (Scheme 7).



Scheme 7. Second-generation synthesis of the quinone-spiroisoxazoline core.

Conclusions

In conclusion, we successfully accomplished the synthesis of a core skeleton that is very similar to naturally available spiroisoxazolines, such as 11-deoxyfistularin-3; we also synthesized an isomeric spiroisoxazoline core in which the isoxazoline moiety and the carbonyl group are positioned in a fashion similar to that found in agelorin A and B. The diverse reactivity of the key 1,3-diketospiroisoxazoline precursor enabled us to quickly furnish the desired molecular structures in good to very good yields. Owing to the success of this model study, we are positioned to imminently apply the reported synthetic methodology from this model system toward the syntheses of spiroisoxazoline-containing natural products as well as their synthetic analogues for biological evaluation.

Supporting Information (see footnote on the first page of this article): Characterization data (^{1}H NMR and ^{13}C NMR spectra) for all new compounds, 2D NMR (NOESY and HMBC) spectra for **14** and **15**, and X-ray crystal structure of **10**.

Acknowledgments

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[23] CCDC-967652 (for **10**) contains the supplementary crystallographic data 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.

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