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An Expeditious Nazarov Cyclization Strategy toward the Hydroazulene Core of Guanacastepene A

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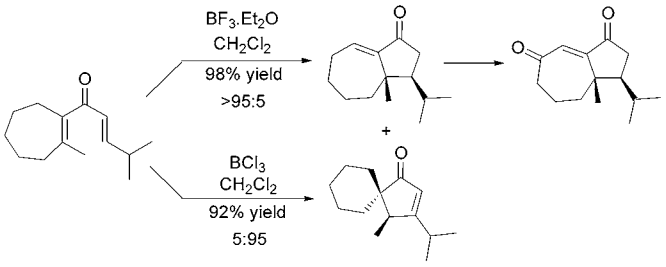
ABSTRACT



The hydroazulene core of guanacastepene A has been synthesized in five steps from commercially available starting materials using a classical Nazarov cyclization to install the stereochemistry in the cyclopentanone diastereoselectively. In the presence or absence of Lewis bases, a hydroazulenone or a spirocyclic ketone generated via a novel Wagner–Meerwein rearrangement is obtained with excellent selectivity and yield.

Guanacastepene A (**1**) has generated immense interest in the scientific community since its isolation and the discovery of its potency against methicillin-resistant and vancomycin-resistant pathogens.[1] The family of guanacastepene diterpenoids is exciting also because they represent a structurally unique carboskeleton never before found in nature. The synthetic organic community responded enthusiastically in efforts toward the total synthesis of these compounds. The first racemic total synthesis of **1** was completed by Danishefsky,[2] followed by a formal total synthesis by Snider.[3] The synthesis of the guanacastepenes has been the subject of many distinct research efforts within the span of three years,[4] all representing unique entries to this interesting system and fully demonstrating the diversity of strategies originating from creative disconnections in total synthesis.

We are also engaged in a study of the total synthesis of the guanacastepenes in which we envisioned a tandem carbene cyclization−cycloaddition cascade reaction to furnish the BC-ring system;[5] the assembly of the cyclopentanone

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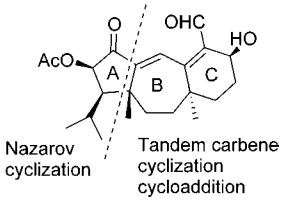
Scheme 1. Retrosynthesis of Guanacastepene A **1**

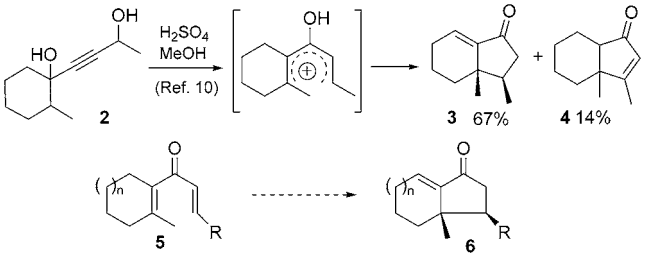


ring A with concomitant functionalization of ring B would both be achieved by a classical Nazarov cyclization.[6] Related efforts reported recently in the synthetic studies of this compound prompted us to disclose our results thus far following this strategy, through which hydroazulenic ketones **6a** and **10** resembling the AB rings of guanacastepene A **1** have been synthesized (Scheme 1).

The Nazarov reaction is an electrocyclic conrotatory ring closure under thermal conditions.[7] Deprotonation typically favors the formation of the product bearing the most substituted double bond; however, unless they are directed by silicon or tin substituents, mixtures of isomeric olefinic products are common.[8] Due to the carbocationic nature of the intermediates, Wagner−Meerwein rearrangements sometimes further complicate the product mixture.[9] However, it is clear that the facility of this reaction for the efficient and stereospecific construction of cyclopentenones has tremendous application in total synthesis.

Previous studies of the cyclopentannulation reaction by Hiyama on systems such as **2** demonstrated the thermal conrotatory electrocyclic ring closure, resulting in cyclopentanones **3** with both methyl groups on the same face, although other products such as **4** are also obtained (Scheme 2).[10] We used dienone substrates **5** to examine the Nazarov reaction, to separate the dehydration and electrocyclization events and better appreciate the effects of acid on the induction of the cyclization. Although many divinyl ketones and dienone substrates have been studied in the context of the Nazarov cyclization, there are few examples where monocyclic β,β,β'-

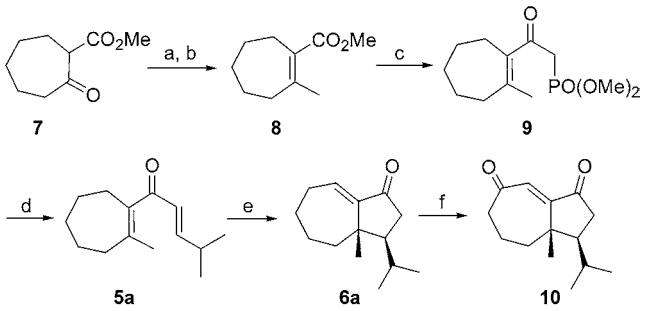
Scheme 2. Synthetic Plan



substituted precursors such as **5** have been examined. In particular, the hydroazulenone core of guanacastepene A implied retrosynthetically a Nazarov cyclization of dienone substrate **5a** ($n = 2$, R = *i*-Pr**)**.

The assembly of dienone **5a** began with commercially available ketoester **7**, which was converted sequentially to the enol phosphate and then to the β-methylated ester to give **8** by Weiler's protocol (Scheme 3).[11] The Horner−Emmons reagent, **9**, synthesized by treatment of **8** with lithio dimethylmethylphosphonate, was poised to react with an aldehyde to install a *trans*-olefin. In the event, reaction of **9** with isobutyraldehyde gave dienone **5a** exclusively in good yield.

Scheme 3. Synthesis of Hydroazulenedione **10**[a]



[a] Reaction conditions: (a) NaH, $(MeO)_2P(O)Cl$, THF; (b) Me_2CuLi, 91% over two steps. (c) $LiCH_2P(O)(OMe)_2$, 96%. (d) Me_2CHCHO, LiCl, *i*-Pr_2NEt, MeCN, 88%. (e) $BF_3{\cdot}Et_2O$, CH_2Cl_2, 98%. (f) $Pd(OH)_2/C$, *t*-BuOOH, CH_2Cl_2, 48 h, 65%.

Treatment of dienone **5a** with various acids to induce electrocyclic ring closure was examined next (Table 1). Substrate **5a**, with a 1:1 mixture of concentrated sulfuric acid and methanol, underwent a remarkably clean Nazarov cyclization to give hydroazulenone **6a** in 91% yield (entry 1). NOESY spectra of **6a** confirmed the syn relative stereochemistry of the methyl and isopropyl groups. To further demonstrate that the cycloheptene nucleus destined to be ring B could be functionalized for appending ring C, allylic oxidation of **6a** using Corey's conditions furnished enedione **10** (Scheme 3).[12] Compound **10** is an intermediate prepared previously by Snider in his synthetic studies of **1**.[3]

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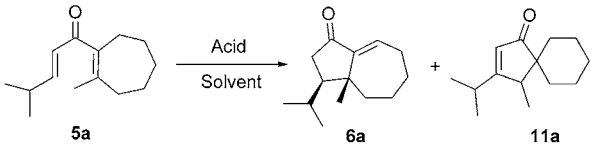
Table 1. Nazarov Cyclization of Divinyl Ketone **5a**



entry	acid[a]	solvent	*T*/*t* (h)	ratio of **6a**:**11a**[b]	yield[c]
1	H_2SO_4/MeOH (1:1)		0°C /1	>95:5	91%
2	H_2SO_4		0°C/1	17:83	90%
3	CF_3SO_3H		0°C/1	7:93	90%
4	CF_3SO_3H	CH_2Cl_2	0°C/1	7:93	96%
5	CF_3SO_3H/DMSO (2:3)	CH_2Cl_2	rt/4	91:9	86%
6	$BF_3{\cdot}Et_2O$	CH_2Cl_2	0°C/1	>95:5	98%
7	BCl_3	CH_2Cl_2	0°C/1	5:95	92%
8	$SnCl_4$	CH_2Cl_2	0°C/1	39:61	87%
9	70% $HClO_4$		rt/2	87:13	90%
10	70% $HClO_4$/H_2O (1:1)		rt/2	>95:5	95%

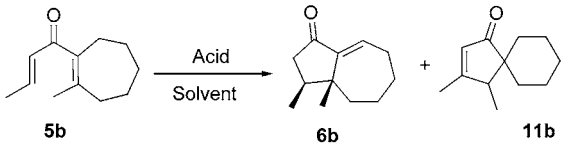
[a] Performed with 3.0 equiv of acid. [b] Ratio determined by integration of proton signals of the crude product mixture. [c] Combined isolated yield of products after silica gel column chromatography.

Surprisingly, the treatment of **5a** with sulfuric acid in the absence of methanol selectively afforded another bicyclic product (Table 1, entry 2). Examination of this new compound revealed that it was not the precedented secondary hydroazulenone product related to **4**, but that it was spiro-[4.5]decenone **11a**. The use of triflic acid generated **11a** almost exclusively, irrespective of the concentration of acid in the reaction (entries 3, 4). Spirocyclic ketone **11a** did not arise from a subsequent transformation of **6a** under the reaction conditions, because resubjecting **6a** to treatment with triflic acid failed to convert it to **11a**. Thus, **11a** was generated in the course of the electrocyclic ring closure by a ring contraction via a Wagner−Meerwein shift. Although carbocationic shifts in the course of the Nazarov cyclization are known, the generation of such spirocyclic products under these reaction conditions has never been reported.

We examined the reaction in greater detail and found conditions that could selectively produce either cyclization product **6a** or **11a** in excellent yield. It was found that the use of boron trifluoride etherate generated **6a** as the sole product in quantitative yield (entry 6), while the use of boron trichloride in dichloromethane favored the formation of **11a** with a selectivity of >95:5, also in nearly quantitative yield (entry 4). The overall trend appears to be that both Brønsted and Lewis acids in noncoordinating solvents favored carbocationic rearrangement leading to **11a,** while acids in the presence of Lewis basic solvents such as ether and methanol induced deprotonation rapidly before rearrangement, generating **6a**. The effect of Lewis basic solvents was particularly apparent in the experiments using sulfuric acid (entries 1, 2), triflic acid (entries 4, 5), $BF_3{\cdot}Et_2O$ vs BCl_3 (entries 6, 7), and perchloric acid (entries 9, 10).

We examined the Nazarov reaction of other dienone substrates to see if reaction conditions could be manipulated to selectively generate either cyclization product **6** or **11**.

Table 2. Nazarov Cyclization of Divinyl Ketone **5b**



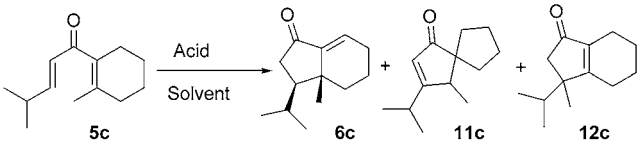
entry	acid[a]	solvent	*T*/*t* (h)	ratio of **6b**:**11b**[b]	yield[c]
1	H_2SO_4	MeOH	0°C/1	>95:5	86%
2	H_2SO_4		0°C/1	84:16	83%
3	$BF_3{\cdot}Et_2O$	CH_2Cl_2	rt/1	>95:5	95%
4	CF_3SO_3H	CH_2Cl_2	rt/1	>95:5	86%
5	CF_3SO_3H		60°C/1	87:13	74%

[a] Performed with 3.0 equiv of acid. [b] Ratio determined by integration of proton signals of the crude product mixture. [c] Combined isolated yield of products after silica gel column chromatography.

The reaction of divinyl ketone substrate **5b**, which differed from **5a** only in that both vinyl substituents were methyl groups, generated fused bicyclic **6b** without ring contraction as the major product under all conditions examined, even those that previously favored the formation of the rearranged product (Table 2). Only in the case of sulfuric acid was some of **11b** generated (entry 2). Heating to encourage rearrangements also generated more of **11b**, although **6b** remained the major product (entry 5).

Cyclohexadienone substrate **5c** had the same vinyl substituents as **5a**. Treatment of **5c** with various acids in Lewis basic solvents was highly selective for **6c** (Table 3, entries

Table 3. Nazarov Cyclization of Divinyl Ketone **5c**



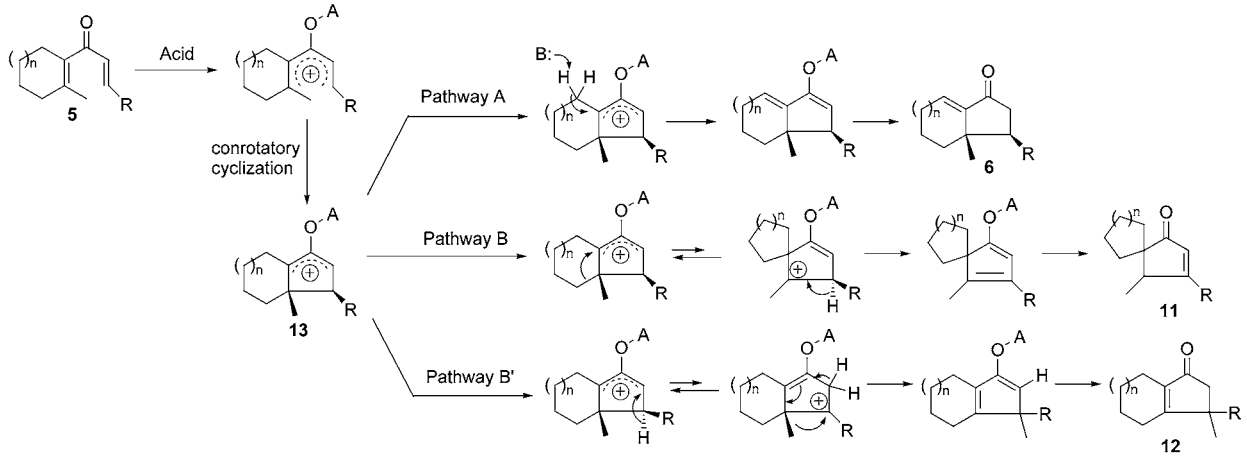
entry	acid[a]	solvent	*T*/*t* (h)	ratio of **6c**:**11c**:**12c**[b]	yield[c]
1	H_2SO_4	MeOH	0°C/1	>90:5:5	86%
2	H_2SO_4		0°C/1	1:13:86	85%
3	$BF_3{\cdot}Et_2O$	CH_2Cl_2	rt/2	>90:5:5	93%
4	CF_3SO_3H	CH_2Cl_2	rt/1	0:58:42	86%
5	70% $HClO_4$		rt/2	11:30:59	81%

[a] Performed with 3.0 equiv of acid. [b] Ratio determined by integration of proton signals of the crude product mixture. [c] Combined isolated yield of products after silica gel column chromatography.

1, 3). Otherwise, carbocationic rearrangements predominated, generating products **11c** and **12c**. Wagner−Meerwein shifts in the Nazarov intermediate leading to products such as **12c** have been previously observed.[10]

Scheme 4 summarizes the mechanistic pathways that account for the formation of cyclization products **6**, **11**, and **12**. Treatment of divinyl ketone **5** with acid induced a

Scheme 4. Mechanistic Pathways Leading to **6**, **11**, and **12**



conrotatory electrocyclization, leading to the carbocationic intermediate **13**. In the presence of proton acceptors (e.g., methanol, ether), fused bicyclic products with structure **6** are favored (Pathway A). In the absence of Lewis bases, Wagner−Meerwein shifts predominate. These experiments showed that ring contraction to give **11** is a favored carbocationic rearrangement for certain ring sizes, for example, $n = 2$, leading to [4.5]spirocyclic compounds (Pathway B). Otherwise, the strain in spirocyclic compound **11** (e.g., $n = 1$) would give way to other kinds of rearrangements, generating products like **12** (Pathway B′).[13] Besides the unavailability of bases, the steric strain of the cis substituents in **13** may also result in a propensity toward rearrangement. This may explain the divergent fates of intermediates **13a** and **13b** derived from **5a** and **5b**, which differ only in R being an isopropyl or a methyl group. Whereas the less-congested **13b** underwent deprotonation both in the presence or absence of Lewis bases (Pathway A), **13a** preferred ring contraction, as steric strain is relieved by rearrangement but not by deprotonation (Pathway B).[13]

We have shown herein that hydroazulenones **6a** and **10** have been synthesized in good yield and selectivity to demonstrate a Nazarov cyclization strategy for the construction of ring A in **1**. The success of this reaction as applied to the final synthesis of guanacastepene A will depend on the sense and degree of torquoselectivity of the Nazarov reaction with respect to the stereochemistry defined by the proposed tandem carbene cyclization−cycloaddition cascade to generate the BC nucleus, an aspect that is currently under investigation. Furthermore, it has been demonstrated that post-cyclization carbocationic rearrangement to afford spirocyclic [4.5]decenones can be high yielding and selective, and this tandem cyclization−ring contraction reaction could potentially also be exploited for natural product synthesis.

Acknowledgment. Financial support from the University of Hong Kong is gratefully acknowledged.

Supporting Information Available: Experimental procedures for all reactions; full characterization and ^{1}H and ^{13}C NMR spectra for compounds **5a**−**c**, **6a**−**c**, **9**, **10**, **11a**−**c**, and **12c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Contrathermodynamic carbocationic rearrangements in Pathways B and B′ could be driven by the ultimate formation of stable products **11** and **12**. We thank the referee for input concerning aspects of the mechanism.