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Tandem Brønsted Acid Promoted and Nazarov Carbocyclizations of Enyne Acetals to Hydroazulenones**

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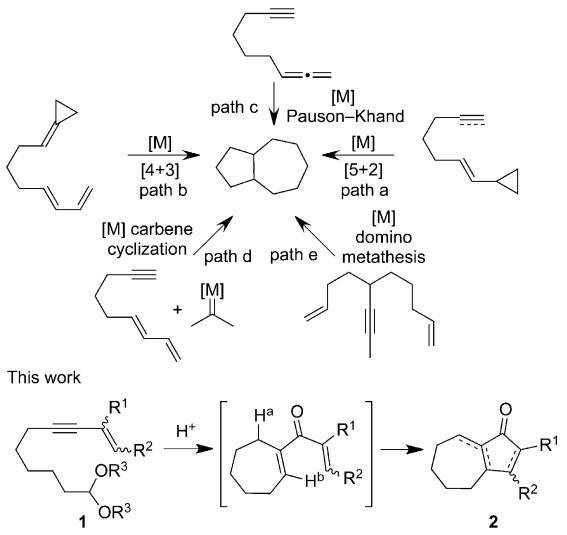
The presence of hydroazulen(on)e skeletons in many bioactive natural products, such as guanacastepene[1] or pleocarpenone,[2] has resulted in sustained interest in their synthesis. A wide variety of approaches have been described.[3] The most common approaches, other than the use of rearrangement reactions,[3,4] have started from the five-membered ring, on which the seven-membered ring has been assembled by ring enlargement, reductive cyclization, metathesis, or aldol condensation.[3,5] Alternative methods have involved the construction of the five-membered ring on the seven-membered ring and have employed metathesis, aldol condensation, ring expansion, or Nazarov cyclization.[3,6]

Highly efficient approaches in which both rings are created in one pot have also been developed, most of them involve metal-catalyzed cycloaddition reactions (Scheme 1).[7–14] Thus Wender et al. have used both intramolecular Rh-catalyzed [5+2] cycloaddition (Scheme 1, path a)[7a] and intermolecular tandem Rh-catalyzed [5+2]/Nazarov cyclization;[7b] Trost et al. have explored [5+2] cyclization protocols using Ru catalysts;[8] Mascareñas and co-workers have employed Pd- and Pt-catalyzed [4+3] cycloaddition[9] (Scheme 1, path b);[10] and Ahmar et al.,[11a] Brummond et al.[11b] and Mukai et al.[11c] have reported various approaches employing allenic reactions of the Pauson–Khand type (Scheme 1, path c).[12] Strategies based on the cyclization of acyclic dienynes, mediated[13a] or catalyzed[13b] by metal carbenes, have also been reported (Scheme 1, paths d and e).[14]

As a contribution to the development of metal-free, environmentally less hazardous synthetic methods,[15] we recently described an efficient intramolecular cyclization of alkynals promoted by Brønsted acids.[16,17] Herein we report its use in tandem with a Nazarov cyclization[7b,18] to construct hydroazulenone skeletons **2** from enyne acetals **1**[19] (Scheme 1).[20]



Scheme 1. Metal-catalyzed and tandem enyne acetal-Nazarov Brønsted acid promoted carbocyclizations to hydroazulen(on)es.

Initially, we subjected enyne acetal **1a** (Table 1), to the optimized reaction conditions identified in our previous work (heating in DCE in the presence of excess trifluoroacetic acid).[16] Cyclization proceeded smoothly to give an almost equimolar mixture of enones **2a** and **3a** in excellent combined yield (Table 1, entry 1). When the reaction was carried out at room temperature a similar yield was obtained but there was a higher proportion of **2a** (Table 1, entry 2). The major regioisomer was the single-bond-fused bicycle **2a**, which is the thermodynamically less-stable isomer.[21] This bicycle can potentially be further functionalized in the seven-membered ring for future applications;[6f,22] therefore we proceeded to seek reaction conditions to optimize this regioselectivity.

The use of HBF_4 instead of TFA as acid resulted in an increase in the **2a**/**3a** ratio to 3:1 (Table 1, entries 3 and 4). When the reaction temperature was lowered to −15 °C the regioselectivity increased to 4.5:1, but a lower yield was obtained (Table 1, entry 5). No reaction occurred if the amount of HBF_4 was reduced from 3 to 1 equivalents (Table 1, entry 6). With $BF_3{\cdot}OEt_2$ or H_2SO_4 as acid, yields were low to moderate and **3a** was slightly favored over **2a** (Table 1, entries 7 and 8). Formation of enone **3a** was also favored when triflimide was employed, and it was the exclusive product when triflic acid was used,[20c] although in both cases yields were low (Table 1, entries 9 and 10).[23] When the aldehyde corresponding to acetal **1a** was used as the starting compound and HBF_4 as the acid, both the yield and the **2a**/**3a** ratio decreased (compare Table 1, entries 4 and 11), undoubtedly because the reaction intermediate was less

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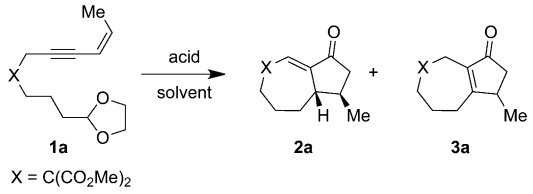
Table 1: Brønsted acid promoted carbocyclization of enyne acetal **1a** to hydroazulenones **2a** and **3a**.[a]



X = $C(CO_2Me)_2$

Entry	Brønsted acid	*T* [°C]	*t* [h]	**2a**/**3a**[b]	Yield [%][c]
1	TFA (20 equiv)	90[d]	0.5	1.2:1	93
2	TFA (20 equiv)	20[d]	3	1.8:1	96
3	HBF_4 (3 equiv)	20	0.5	2.5:1	84
4	HBF_4 (3 equiv)	0	1	3:1	89
5	HBF_4 (3 equiv)	−15	1.3	4.5:1	63
6	HBF_4 (1 equiv)	20	72	–	–
7	$BF_3{\cdot}OEt_2$ (3 equiv)	20	1.5	1:1.6	39
8	H_2SO_4 (3 equiv)	20	0.7	1:1.6	60
9	TfOH (3 equiv)	20	0.4	0:1	39
10	Tf_2NH (3 equiv)	0	0.4	1:2.6	47
11[e]	HBF_4 (3 equiv)	0	0.6	2.3:1	52

[a] Reaction conditions: **1a** (0.3 mmol), CH_2Cl_2 (3 mL). [b] Regioisomers **2a** and **3a** are easily separated by chromatography. [c] Combined yields of the isolated products. [d] DCE as solvent. [e] With the aldehyde corresponding to acetal **1a** as starting compound (0.3 mmol). DCE = 1,2-dichloroethane, Tf = trifluoromethanesulfonyl, TFA = trifluoroacetic acid.

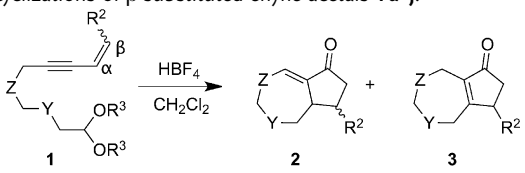
electrophilic.[24] In view of these results, in most subsequent experiments we used the reaction conditions of entry 4 (referred to below as optimized conditions A) or entry 2 (optimized conditions B).

The relative configuration of **2a** corresponds to the conrotatory ring closure of an *E* olefin, thus indicating that, under the reaction conditions, the divinyl ketone intermediate might undergo a *Z*-to-*E* isomerization prior to the Nazarov cyclization (Scheme 1).[25]

Once the viability of the tandem diastereoselective process had been established we explored its scope, initially by applying it to the β-substituted enyne acetals **1b–e** (see Table 2), in which, as in **1a**, the tether between the acetal and the triple bond includes a quaternary carbon with two COOMe substituents. Surprisingly, cyclization of **1b**, the *trans* isomer of **1a**, under optimized conditions A gave a lower yield and **2a**/**3a** ratio than that of **1a** (1.5:1; Table 2, entry 2); this result indicates that a more complex equilibrium of intermediates could affect the regioselectivity of the reaction.[26] Not unexpectedly, the styrene-containing enyne acetal **1c** was one of the least reactive substrates (66%; Table 2, entry 3), whereas the reaction of the β,β-disubstituted **1e** was one of the more higher yielding reactions (84%, Table 2, entry 5). The results of the reaction of **1d** were better than we expected; the presence of the bulky *tert*-butyl β substituent resulted in an increased **2**/**3** ratio of 1:0 (Table 2, entry 4).

We next investigated the effect of modifying the tether. Satisfyingly, moderate to good yields and complete regioselectivity were achieved with the appropriate substituents; the reaction of the substrate containing geminal methyl groups adjacent to the alkyne fragment gave only **3f** (Table 2,

Table 2: Hydroazulenones and azahydroazulenones prepared by tandem carbocyclizations of β-substituted enyne acetals **1a–j**.[a,b]



Z = $C(CO_2Me)_2$, CH_2; Y = CH_2
Z = CH_2; Y = $C(CO_2Me)_2$, NTs

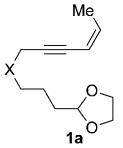
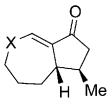
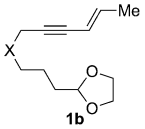
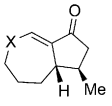
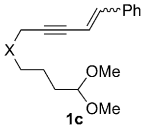
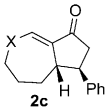
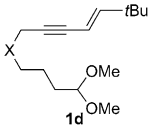
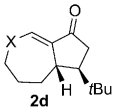
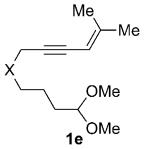
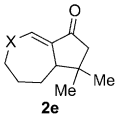
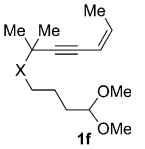
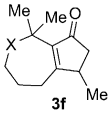
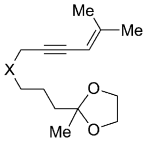
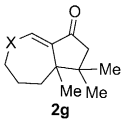
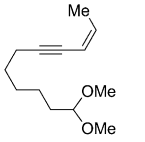
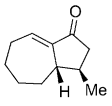
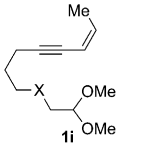
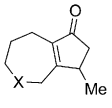
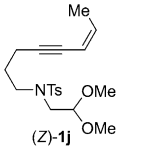
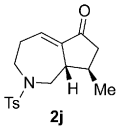
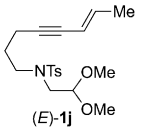
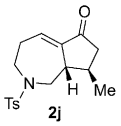
Entry	Enyne acetal	Hydroazulenone[c]	**2**/**3**	Yield[d] [%]
1	 **1a**	 **2a**	3:1	89
2	 **1b**	 **2a**	1.5:1 (1:1.5)	45 (62)[e]
3	 **1c**	 **2c**	2:1	66
4	 **1d**	 **2d**	1:0	62
5	 **1e**	 **2e**	2:1	84
6	 **1f**	 **3f**	0:1	77
7	 **1g**	 **2g**	1:0	63
8	 **1h**	 **2h**	1[f]:1	73
9	 **1i**	 **3i**	1:3	76
10	 (*Z*)-**1j**	 **2j**	2:1	80

Table 2: (Continued)

Entry	Enyne acetal	Hydroazulenone[c]	2/3	Yield[d] [%]
11	 (*E*)-**1j**	 **2j**	4.5:1	72

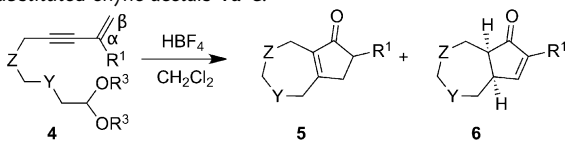
[a] Conditions A: **1** (0.3 mmol), HBF_4 (0.9 mmol), CH_2Cl_2 (3 mL), 0 °C, 20–60 min. [b] X = $C(CO_2Me)_2$. [c] Only the major regioisomer is shown. [d] Combined yields of the isolated products. [e] Conditions B: **4** (0.3 mmol), TFA (6.0 mmol), DCE (3 mL), RT, 30 min. [f] Compound **2h** was obtained as a 2:1 mixture of *trans* and *cis* diastereomers as a result of the partial isomerization of the divinylketone intermediate (only the major diastereomer is shown).[25] Ts = *p*-toluenesulfonyl.

entry 6) and that of methyl ketal **1g** gave only **2g** (Table 2, entry 7). Interestingly, when the substrate not containing the CO_2Me groups was used, thus eliminating the Thorpe–Ingold effect,[27] the cyclization still occurred, but with slightly reduced yield and no regioselectivity (Table 2, entry 8).[28] The opposite regioselectivity was obtained (that is **3** was favored) when the substrate with the $C(CO_2Me)_2$ unit placed closer to the acetal fragment (Table 2 entry 9); this result probably due to the change of the original conformation of the seven-membered ring. Gratifyingly, this tandem reaction could be used to prepare azabicycles, as confirmed by the successful reactions of the tertiary amines (*Z*)-**1j** and (*E*)-**1j**, which afforded cyclopenta[*c*]azepinones[29] with good yields and a **2**/**3** ratio of up to 4.5:1 in the case of (*E*)-**1j** (Table 2, entries 10 and 11).

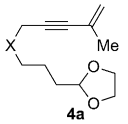
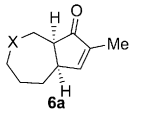
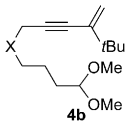
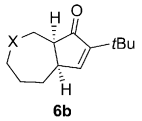
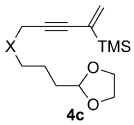
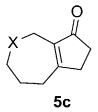
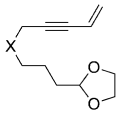
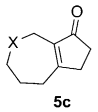
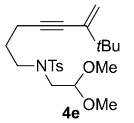
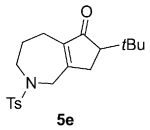
The tandem reaction was equally successful when applied to α-substituted substrates **4** (Table 3), although to our initial surprise the major product afforded by enyne acetal **4a** was hydroazulenone **6a**, a bicyclic enone with both bridgeheads saturated and *cis* stereochemistry (Table 3, entry 1). When the α substituent was *tert*-butyl the reaction was totally regioselective (Table 3, entry 2). In contrast, when the α substituent was TMS, which was lost during the reaction, the other regioisomer was formed with high selectivity (Table 3, entry 3). Cyclization of the α,β-unsubstituted enyne acetal **4d** gave a similar result but required a longer reaction time (14 h vs. 5 h, Table 3, entry 4), thus suggesting that desilylation most likely occurred after the Nazarov cyclization[30,31] Finally, the toluenesulfonamide **4e** afforded cyclopenta[*c*]-azepinones **5e** and **6e** with a moderate combined yield (Table 3, entry 5).

We believe the mechanism of the tandem carbocyclizations of enyne acetals **1** and **4** most likely starts with the Brønsted acid induced formation of the electrophilic oxonium species **A** (Scheme 2).[32] This cationic species would undergo standard heteroalkyne metathesis to the oxete intermediate **B** (through [2+2] cycloaddition),[17a] which upon ring opening would give the divinyl ketone **C**. Subsequently, the Brønsted acid would induce a stereospecific Nazarov reaction ($4\pi e^-$ electrocyclization)[18] of this unpolarized[25d] dienone **C** to give one of two possible oxyallyl cations, **D** and **E**, depending whether the starting compound had been β or α substituted. Proton elimination and enol-to-ketone tautomerization

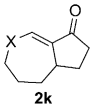
Table 3: Hydroazulenones prepared by tandem carbocyclization of α-substituted enyne acetals **4a**–**e**.[a,b]



Z = $C(CO_2Me)_2$; Y = CH_2
Z = CH_2; Y = NTs

Entry	Enyne acetal	Hydroazulenone[c]	5/6	Yield[d] [%]
1[e]	 **4a**	 **6a**	1:2	72
2	 **4b**	 **6b**	0:1	58
3[f]	 **4c**	 **5c**	1:0	85[g] (5 h)
4[f]	 **4d**	 **5c**	1:0	79[g] (14 h)
5	 **4e**	 **5e**	2:1	52

[a] Conditions A: **4** (0.3 mmol), HBF_4 (0.9 mmol), CH_2Cl_2 (3 mL), 0 °C, 20–60 min. [b] X = $C(CO_2Me)_2$. [c] Only the major regioisomer is shown. [d] Combined yields of the isolated products. [e] Conditions B: **4** (0.3 mmol), TFA (6.0 mmol), DCE (3 mL), RT, 30 min. [f] Conditions B but at 90 °C. [g] A low yield of the cyclic enone **2k** (15%, 24%) was also obtained in the tandem carbocyclization of **4c** and **4d**, respectively. TMS = trimethylsilyl.


2k

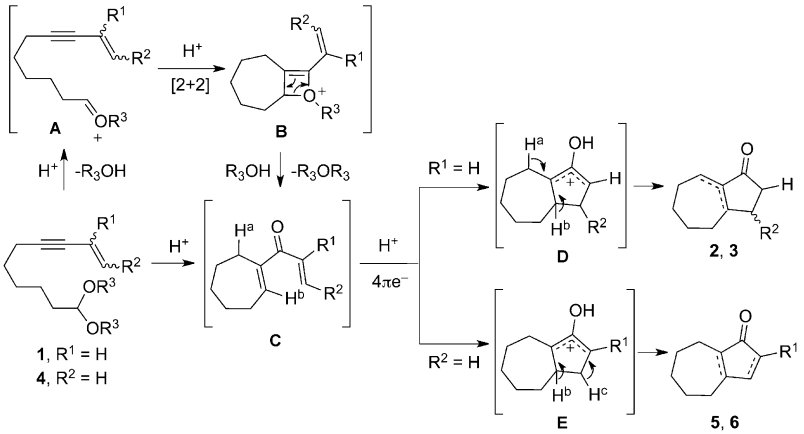
X = $C(CO_2Me)_2$

would finally afford the observed bicyclo[5,3,0]decenones **2**, **3**, **5**, and **6**.

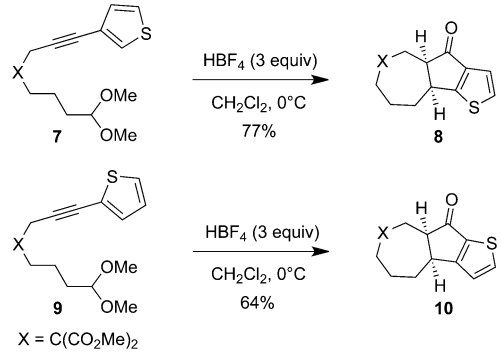
As expected, the regioselectivity of the reaction seems to depend to a large extent on the position of the alkene substituent, α or β, and on the nature of the tether, through its influence on the conformation of the oxyallyl cation intermediate.[6f,18b–e,33] In most cases, it is the single-bond-fused product that is favored.

Finally, we investigated the effect of linked α and β substituents by replacing the terminal alkene group with thiophene systems (Scheme 3).[34] To our delight, the attractive tricyclic systems **8** and **10** were obtained in good yields from the 2- and 3-thiophenyl species **7** and **9**, respectively.

In summary, we have developed a new, simple, and versatile method for the synthesis of hydroazulenones from



Scheme 2. Mechanistic rationale for tandem Brønsted acid promoted carbocyclizations from enyne acetals to hydroazulenones.



Scheme 3. Preparation of hydroazulenothiophenones **8** and **10** by tandem carbocyclization of enyne acetals **7** and **9**, respectively.

linear enyne acetals. This metal-free procedure may be described as taking place through tandem Brønsted acid promoted carbocyclizations, a regioselective *exo*-carbocyclization previously applied to alkynals,[16] and a stereospecific Nazarov cyclization. The new approach complements previously described methods based on metal-catalyzed cyclizations. Its full scope is currently being further investigated by application to a number of challenging cyclizations.

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