Cascade Carbocyclizations

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Tandem Enyneacetal-Nazarov Brønsted-Acid-Promoted Carbocyclizations Affording Hydroazulenones

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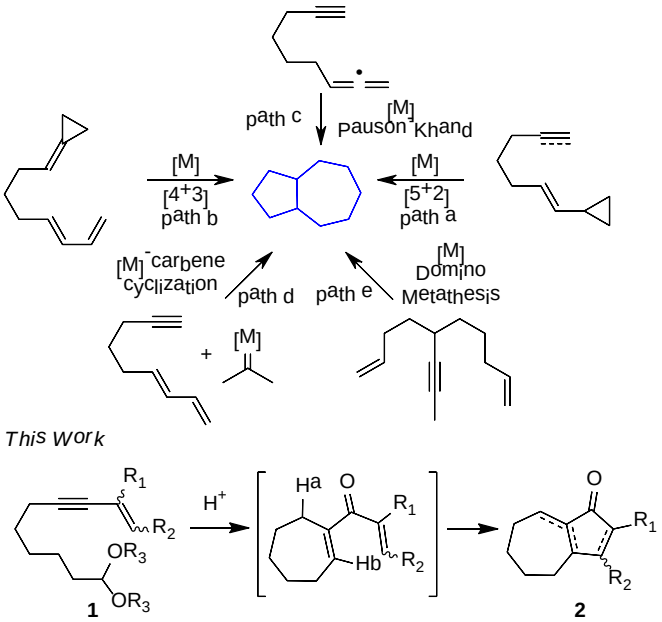
((Dedication----optional))

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, 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] Alternatives for constructing the five-membered ring on the seven-membered ring 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 involving metal-catalyzed cycloaddition reactions (Scheme 1).[7-14] Thus Wender and coworkers 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 and coworkers have explored [5+2] cyclization protocols using Ru catalysts;[8] Mascareñas and coworkers 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 via allenic reactions of 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] Here we report its use in tandem with Nazarov cyclization[7b, 18] to construct hydroazulenone skeletons **2** from enyneacetals **1**[19] (Scheme 1).[20]



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

Our initial starting compound was enyneacetal **1a** (Table 1), which was subjected to the conditions identified as optimal 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). Similar yield but a higher proportion of **2a** was obtained when the reaction was carried out at rt (entry 2). The major regioisomer was the single-bond-fused bicycle **2a**, the thermodynamically less stable isomer.[21] This offers more opportunities for functionalizing the seven-membered ring for future applications;[6f,22] therefore we proceeded to seek conditions to optimize this regioselectivity.

The use of HBF_4 instead of TFA as acid increased the **2a**:**3a** ratio to 3:1 (Table 1, entries 3 and 4). Lowering the reaction temperature to -15ºC increased regioselectivity to 4.5:1, but reduced yield (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 $BF_3.OEt_2$ or H_2SO_4 as acid, yields were low to moderate and **3a** was slightly favoured over **2a** (Table 1, entries 7 and 8). Enone **3a** was also favoured by triflimide, and 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 yield and the **2a**:**3a** ratio fell (*cf.* entries 4 and 11 of Table 1),

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undoubtedly because the reaction intermediate was less electrophilic.[24]

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

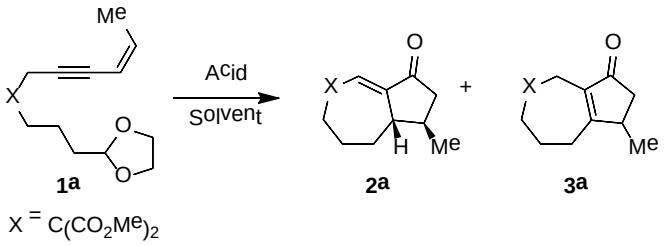


Table 1. Brønsted-acid-promoted carbocyclization of enyneacetal **1a** to hydroazulenones **2a** and **3a**.[a]

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

[a] C*onditions*: **1a** (0.3 mmol), DCM (3 mL). [b] Regioisomers **2a** and **3a** are easily separated by chromatography. [c] Combined isolated yields. [d] DCE as solvent. [e] With the aldehyde corresponding to acetal **1a** as starting compound (0.3 mmol). DCM = dichloromethane. DCE = 1,2-dichloroethane.

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 enyneacetals **1b**-**e** (see Table 2 for atom denominations), 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 *trans* enyne **1b** under optimized conditions A gave a lower yield and **2a**:**3a** ratio (1.5:1, Table 2, entry 2) indicating that a more complex equilibrium of intermediates could affect the regioselectivity of the reaction.[26] Not unexpectedly, the styrene-like enyneacetal **1c** was among the least reactive (66%; Table 2, entry 3) as compared to the *β*,*β*–disubstituted **1e** (84%, Table 2, entry 5). By contrast, the behaviour of **1d** exceeded expectations, its bulky *tert*-butyl *β*–substituent increasing the **2**:**3** ratio to 1:0 (Table 2, entry 4).

We next investigated the effect of modifying the tether. Very satisfyingly, moderate-to-good yields were achieved with complete regioselectivity by appropriate placement of substituents, geminal methyls adjacent to the alkyne fragment giving only **3f** (Table 2, entry 6) and methyl ketal **1g** giving only **2g** (Table 2, entry 7). Interestingly, elimination of the Thorpe-Ingold effect [27] by removal of both $-CO_2Me$ groups also allowed the cyclization, but with slightly reduced yield as well as eliminated all regioselectivity (Table 2, entry 8).[28] Regioselectivity was also inverted by moving the $-C(CO_2Me)_2$ unit closer to the acetal fragment, probably due to the change of the original conformation of the seven-membered ring (*cf.* entries 1 and 9 of Table 2). Gratifyingly, the possibility of using the tandem reaction to prepare azabicycles was confirmed by its success with the tertiary amines *Z*-**1j** or *E*-**1j**, which afforded cyclopenta[*c*]-azepinones[29] with good yields and **2**:**3** ratio up to 4.5:1 in the case of *E*-**1j** (Table 2, entries 10 and 11).

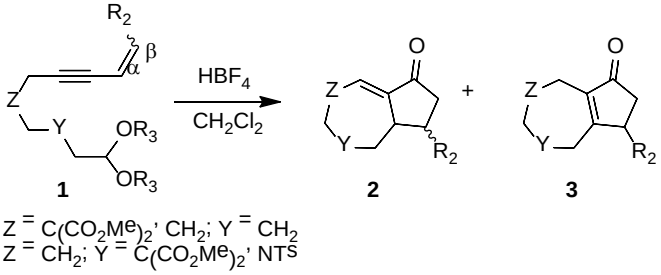
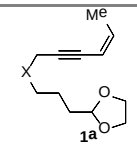
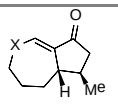
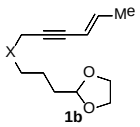
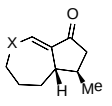
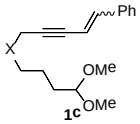
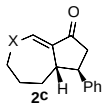
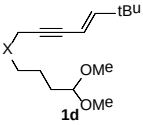
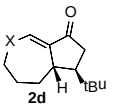
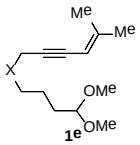
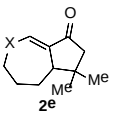
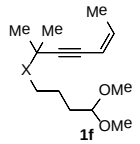
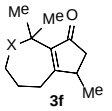
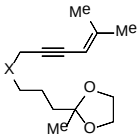
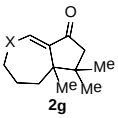
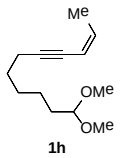
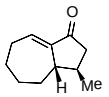
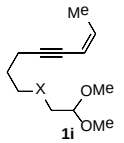
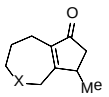
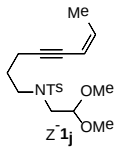
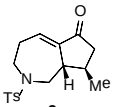
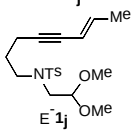
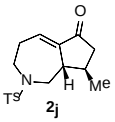


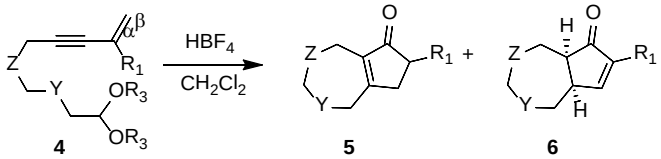
Table 2. Hydroazulenones and azahydroazulenones prepared by tandem carbocyclizations of *β*-substituted enyneacetals **1a**-**j**. [a,b]

Entry	Enyneacetal	Hydroazulenone[c]	**2**:**3** ratio	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
11	 E^{-}**1j**	 **2j**	4.5:1	72

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

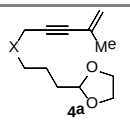
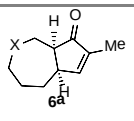
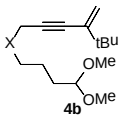
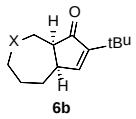
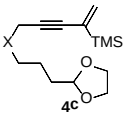
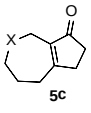
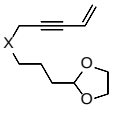
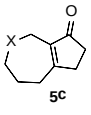
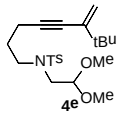
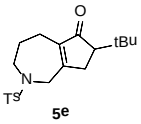
The tandem reaction was equally successful when applied to α-substituted substrates **4** (Table 3), though to our initial surprise the major product afforded by enyneacetal **4a** was hydroazulenone **6a**, a bicyclic enone with both bridgeheads saturated and *cis* stereochemistry (Table 3, entry 1). When the α-substituent was *t*-Bu the reaction was totally regioselective (Table 3, entry 2). By contrast, high regioselectivity in the opposite direction was afforded by the α-substituent TMS, which was lost during the reaction (Table 3, entry 3). For the sake of comparison, cyclization of the α,β-unsubstituted enyneacetal **4d** gave a similar result but following a longer reaction time (14h *vs* 5h, Table 3, entry 4) suggesting that desilylation most likely occurred after the Nazarov cyclization [30, 31] Finally, the toluenesulfonamide **4e** afforded cyclopenta[*c*]azepinones **5e** and **6e** with moderate combined yield (Table 3, entry 5).



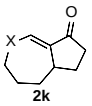
4 **5** **6**

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

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

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

[a] *Optimized conditions A*: **4** (0.3 mmol), HBF_4 (0.9 mmol), CH_2Cl_2 (3 mL), 0ºC, 20-60 min. [b] X = $C(CO_2Me)_2$. [c] Only the major regioisomer is shown. [d] Combined isolated yields. [e] *Optimized conditions B*: **4** (0.3 mmol), TFA (6.0 mmol), DCE (3 mL), r.t., 1h. [f] *Optimized conditions B* but at 90ºC. [g] A low yield of the cyclic enone **2k** (15%, 24%) was also isolated in the tandem carbocyclization of **4**c and **4d**, respectively.

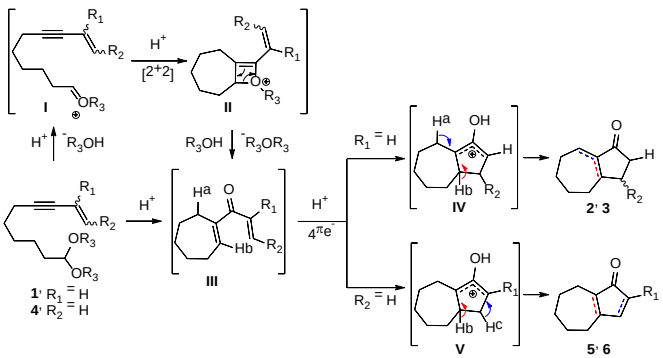


2k

X = $C(CO_2Me)_2$

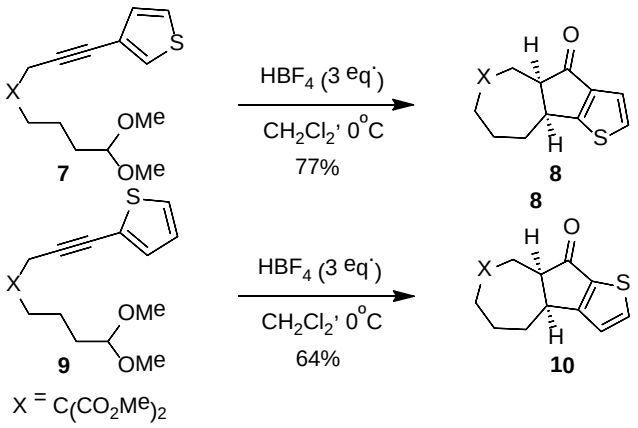
The mechanism of the tandem carbocyclizations undergone by enyneacetals **1** and **4** seems likely to start with the initial Brønsted-acid-induced formation of the electrophilic oxonium species **I** (Scheme 2).[32] This cationic species would evolve by standard heteroalkyne metathesis to the oxete intermediate **II** (through [2+2] cycloaddition)[17a] and then to the divinyl ketone **III** (by ring opening). Subsequently, the Brønsted acid would induce a stereospecific Nazarov reaction ($4\pi e^{-}$ electrocyclization)[18] of this unpolarized[25d] dienone **III** giving one of two possible oxyallyl cations, **IV** and **V,** depending whether the starting compound had been β- or α-substituted. Proton elimination and enol to ketone tautomerization 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.



Scheme 2. Mechanistic rationale of tandem Brønsted-acid-promoted carbocyclizations from enyneacetals to hydroazulenones.

Finally, we investigated the effect of simultaneous 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**.



Scheme 3. Preparation of hydroazulenothiophenones **8** and **10** by tandem carbocyclization of enyneacetals **7** and **9**.

To sum up, we have developed a new, simple and versatile methodology for the synthesis of hydroazulenones from linear enyneacetals. 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] followed by a stereospecific Nazarov cyclization. The new approach nicely 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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[26] a) In fact, when the reaction was performed under optimized conditions B (TFA 20 eq, 20 ºC), in reverse regiosomeric ratio was found (**2a**:**3a**, 1:1.5, 62% combined yield). b) Careful ^{1}H-NMR monitorization (controlled amounts of HBF_4 added in CD_2Cl_2) showed a faster but complex reaction of *trans*-**1b** than *cis*-**1a** indicating, most probably, a less controlled reaction evolution.

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Cascade Carbocyclizations

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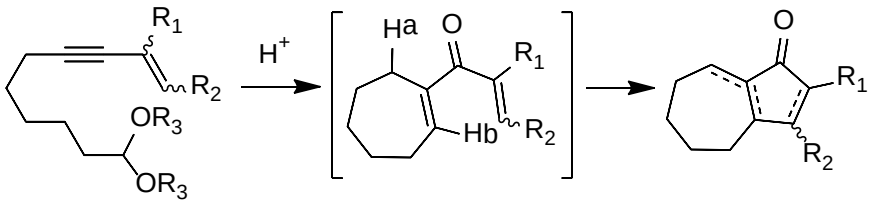
Tandem Enyneacetal-Nazarov Brønsted-Acid-Promoted Carbocyclizations Affording Hydroazulenones



A new and efficient metal-free entry to hydroazulenones is reported. Enyneacetals were easily converted into hydroazulene skeletons by tandem Brønsted-acid-promoted carbocyclizations followed by stereospecific Nazarov cyclizations. The versatility of this transformation also allowed assembly of interesting heteroaromatic tricyclic systems.