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Synthesis of Polysubstituted *Meta*-Halophenols by Anion-Accelerated 2π-Electrocyclic Ring Opening

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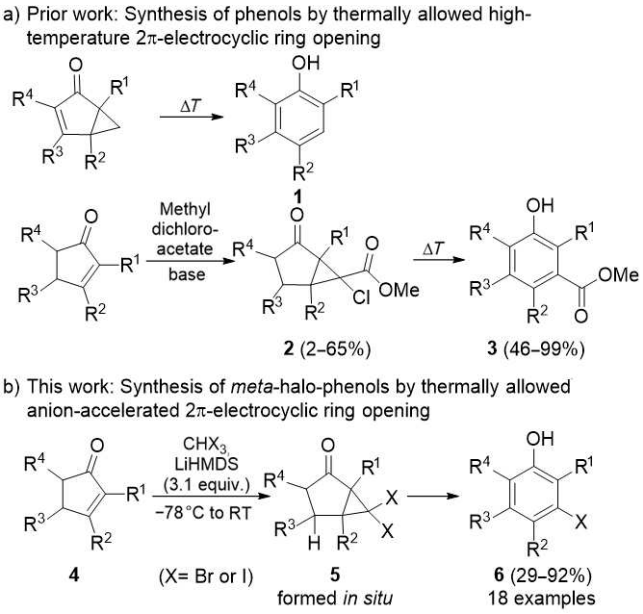
Abstract: Disrotatory – thermally allowed – 2π-electrocyclic ring-opening reactions require high temperatures to proceed. Herein, we report the first anion-accelerated 2π-electrocyclic ring opening of 6,6-dihalobicyclo[3.1.0]hexan-2-ones at low temperature to give the corresponding *meta*-halophenols in good to high yields (18 examples, 29–92% yield, average: 65%). Many of the phenols have unconventional substitution patterns and are reported here for the first time. Furthermore, the strength of the methodology was shown by the total synthesis of the densely functionalized phenolic natural product caramboxin (isolated as the lactam dehydrate). The reaction mechanism underlying the anion-acceleration was investigated in an ab initio study, which concluded that base-mediated proton abstraction *anti* to the concurrently departing *endo*-bromine was the initiating step in an overall concerted reaction mechanism leading directly to the *meta*-halophenol.

Introduction

Phenols are frequent motifs in pharmaceutical agents as well as in agrochemicals,[1] thus, their halo-functionalized analogues are highly valuable building blocks in the synthesis thereof. For electron-rich aromatic rings, such as phenols, the electronic distribution directs electrophiles to the *ortho*/*para* positions when undergoing electrophilic aromatic substitution reactions. However, only few methods have been reported for direct synthesis of *meta*-halophenols from their aromatic precursors, all of which require harsh conditions or expensive transition-metal catalysts.[2]

As an alternative strategy for the synthesis of phenols, electrocyclic ring opening of bicyclo[3.1.0]hex-3-en-2-ones under thermal conditions to give the corresponding phenols **1** has been studied (Scheme 1a).[3] However, the difficult access to these bicyclic systems limits the practical use of this overall strategy. Recently, Magauer and co-workers reported the synthesis of a series of *meta*-(methoxycarbonyl)phenols by the 1,4-addition of methyl dichloroacetate to cyclopent-2-en-1-ones to isolate the corresponding 6-halo-6-methoxycarbonyl-bicyclo[3.1.0]hexan-2-ones **2** in 2–65% yield (Scheme 1a). Subsequent heating to high-temperature (190 °C) facilitated electrocyclic ring opening to the corresponding phenols **3**.[4]



Scheme 1. a) High-temperature thermal electrocyclic ring opening of bicyclo[3.1.0]hex-3-en-2-ones **1** to the corresponding phenols. b) Synthesis of *meta*-halo-phenols **6** from the corresponding cyclopentenones **3** by anion-accelerated electrocyclic ring opening.

Results and Discussion

We envisaged that synthetically versatile *meta*-halophenols **6** could be derived from 6,6-dihalobicyclo[3.1.0]hexan-2-ones **5**. However, the synthesis of dibromocyclopropane **5** has only been reported as an intermediate in the total synthesis of (±)-γ-

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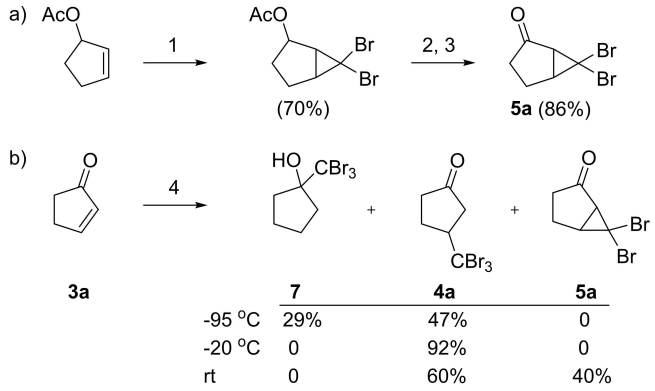
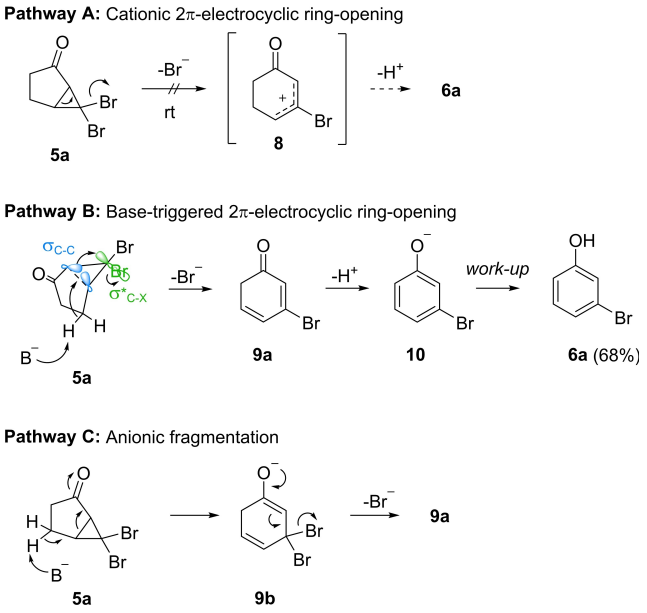
lycorane (Scheme 2a).[5] Thus, an efficient method to access dibromocyclopropanes **5** was required, which ideally would also allow a direct in situ transformation to their corresponding phenols.

The findings by Krebs et al. that bromoform undergoes 1,2- and 1,4-addition to 2-cyclopentenone **3a** at −95 °C in a 2:3 ratio (Scheme 2b),[7] served as the starting point for us to further explore if 1,4-adduct **4a** could undergo in situ ring-closure to form the corresponding 6,6-dibromobicyclo[3.1.0]hexan-2-one **5a** upon temperature increase (Scheme 2). In fact, warming the reaction to −20 °C resulted in full conversion to the thermodynamically more stable 1,4-adduct **4a** in 92% yield (Scheme 2b), demonstrating that the 1,2- and 1,4-adducts (**7** and **4a**, respectively) were at equilibrium. Most satisfying, further warming of the reaction mixture to room temperature led to partial formation of the desired dibromocyclopropane product **5a** (3:2 ratio of **4a**:**5a** determined by ^{1}H NMR) after 30 minutes (Scheme 2b). However, continued stirring at room temperature did not lead to the identification of phenol **6a** (Scheme 3).



Scheme 2. a) Synthesis of 6,6-dibromobicyclo[3.1.0]hexan-2-one in a three-step carbene/hydrolysis/oxidation procedure. 1) $CHBr_3$, NaOH, nBu_4NCl; 2) KOH, MeOH; 3) pyridinium chlorochromate.[6] b) Bromoform undergoes 1,2- and 1,4-addition to cyclopent-2-eneone **3a** at −95 °C in a 2:3 ratio. 4) $CHBr_3$ (1.0 equiv.), BuLi (1.0 equiv), −95 °C[7] or LiHMDS (1.0 equiv.), −20 °C and RT, THF.

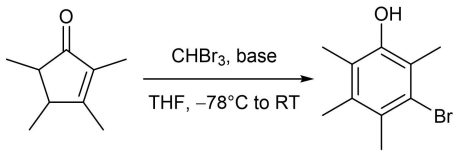


Scheme 3. Ring opening of intermediate **5a** to afford *meta*-bromophenol **6a** is only observed upon addition of a total of 3.1 equiv. of LiHMDS to **3a** at −78 °C to RT (pathway B).

Anion-assisted rate acceleration are an often-observed effect in many sigmatropic reactions like the anionic oxy-Cope or the Ireland-Claisen rearrangements.[8] On the other hand, reports on utilizing this effect in electrocyclic reactions are less common.[9] We hypothesized that running the reaction with three equivalents of LiHMDS could promote the departure of the bromide in an *electron-push* mechanistic way. As the developing cation would be energetically counterbalanced by the already present anion, this would open up an anion-accelerated pathway towards neutral ketone **9a** and eventually phenoxide **10** after proton abstraction (Scheme 3, pathway B). This strategy also alleviates the stability problem with cation **8** being in conjugation with the electron-withdrawing carbonyl group. As an alternative mechanism (pathway C), anionic fragmentation of **5a** could lead to enolate **9b**, which upon elimination of bromide also gives rise to neutral ketone **9a**.

To our delight, performing the reaction with 3.1 equivalents of LiHMDS at −78 °C to room temperature led to clean conversion to give the corresponding *meta*-bromophenol **6a**, in 68% isolated yield. With this breakthrough secured, we turned to investigate and determine the optimal reaction conditions for this new transformation. Due to observed issues with the volatility of *meta*-bromophenol **6a**, we decided to use the tetramethylated analog **6d** for the further detailed investigation of reaction conditions. First, we decided to explore the influence of the metal counter ion by employing NaHMDS and KHMDS (Table 1, entries 2 and 3). In both cases several side products were formed, along with a clear decline in product formation (57 and 11%, respectively). It remains unclear how the Lewis acid character of the metal counter ion plays such a decisive role in this transformation. To our surprise, the use of the stronger base LDA (Table 1, entry 4) led to several side products with only a trace amount of product **6d** (<1%). This demonstrates that also the pK_a value of the base is important for the reaction to proceed.

Table 1. Screening of bases.



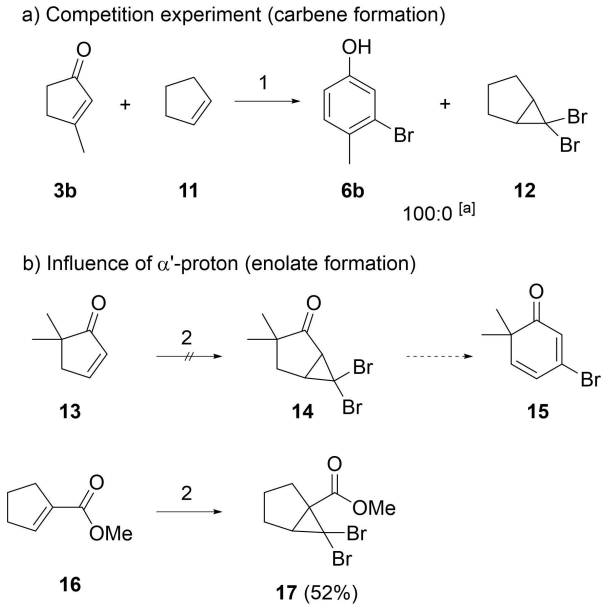
	Base	Equivalents	Isolated yield [%]	qNMR yield [%][a]
1	LiHMDS	3.1	89	92
2	NaHMDS	3.1	–	57
3	KHMDS	3.1	–	11
4	LDA	3.1	–	traces

[a] Yield determined by quantitative ^{1}H NMR of the crude product using 1,3,5-trimethoxybenzene as internal standard.

Next, we ran a reaction with a 1:1 mixture of 3-methyl cyclopentenone **3b** and cyclopentene **11** to address if dibromocarbene formation (through the reaction of bromoform with strong base) is involved in the reaction mechanism (Scheme 4a). From this experiment, only the corresponding *meta*-bromophenol **6b** was observed, which rules out dibromocarbene formation being involved in the reaction mechanism.

To further address *endo*-cyclic enolate formation playing a key part in the mechanism, we employed non-α′-enolizable substrate 5,5-dimethylcyclopent-2-en-1-one **13** and non-α-enolizable substrate methyl 1-cyclopentene-1-carboxylate **15** (Scheme 4b). The reactions were carried out with only 2.1 equivalents of base as aromatization cannot take place in these two transformations. For dimethyl analog **13**, the outcome was a complex reaction mixture with no indication of the desired product **15**, presumably due to the instability of the *gem*-dibromocyclopropane intermediate **14** as previously seen for the unsubstituted analog. The *exo*-cyclic ester **16** led to formation of dibromocyclopropane **17** in 52% yield as the only product, underlining the necessity for *endo*-cyclic carbonyl functionality and its interplay on generation of an anionic state prior to electrocyclic ring opening at low to room temperature.

With the optimized reaction conditions in place, we set out to investigate the scope and limitations of this transformation (Table 2). Firstly, iodoform was substituted for bromoform and gave access to attractive *meta*-iodo phenols **6c**, **e** in average to good yields (47 and 73%). Unfortunately, using chloroform and dibromofluoromethane to introduce *meta*-chloro and *meta*-fluoro substituents was not successful. The former led to sole formation of the 1,2-adduct, whereas the latter resulted in formation of a complex reaction mixture. Next, the option of quenching the phenoxide product in situ was intriguing to us.



Scheme 4. Investigation of the mechanism. 1) $CHBr_3$ (1.0 equiv), LiHMDS (3.1 equiv.), THF, 0 °C to RT, 30 min; 2) $CHBr_3$ (1.0 equiv), LiHMDS (2.1 equiv.), THF, −78 °C to RT, 18 h. [a] Ratio determined by ^1H NMR of the crude product.

Addition of 1.5 equiv. of TsCl to the reaction mixture at room temperature, gave the corresponding tosylate **6f** in excellent yield (78%), opening up for efficient onward functionalization of the 1-position. Finally, we turned to investigate the compatibility with substituents in the 2, 3, 4 and 5 positions of the cyclopentenone core.

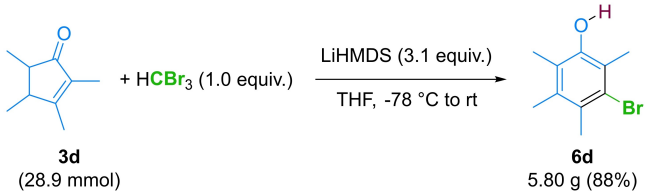
At this stage, we had already demonstrated that methyl groups in all four positions of cyclopentenone was well-tolerated (**6d**, 89%) and a methyl group in the 4-position (**6b**, 75%). Alkyl substituents in the 2-position were extended to the 2-*n*-pentyl analog **6g** in high yield (83%) and also the *cis*-2-(pent-2′-enyl), 4-methyl analog **6h** derived from natural product *cis*-jasmone was obtained in excellent yield (92%) with full retention of regio- and stereochemistry of the alkene. A 2-hydroxy group was also compatible with the reaction conditions, allowing the synthesis of 1,2-catechols **6i** in 40% yield, while the catechol-2-ethers **6j**, **k** were obtained in 55 and 68%, respectively, showing the strength of this transformation for selective synthesis of mono-O-alkylated catechols.

The two heterobicyclic systems **6l** and **6m** were obtained in modest to average yield, and serve to demonstrates the expedite synthesis of complex scaffolds using starting materials readily accessible by Pauson-Khand reaction. The 2,3-dibromo- and 2-iodo-3-bromo phenols **6n** and **6o** were obtained in 83 and 45%, respectively. Free benzylic alcohol **6p** was obtained in 57% and finally we showed that biaryls 2-phenyl **6q** and 4-phenyl **6r** could be obtained in 29 and 65% yields, respectively.

The strength of the methodology was further underlined by conducting a gram-scale synthesis of fully substituted *meta*-bromophenol **6d**. We were pleased to see that we could isolate **6d** in 5.80 g corresponding to 88% yield (Scheme 5).

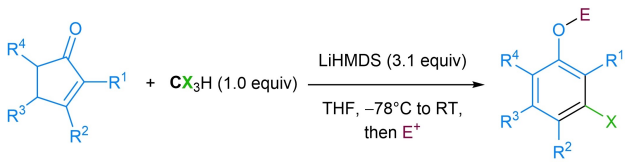
The mechanism for this base-triggered transformation was investigated in a detailed ab initio study. A rationale for the distinctively different reactivity in basic and neutral medium, can be rationalized based on calculated geometries and relative energies of reactants, products and the transition states that are involved. At the computational level, the problem was reduced to first calculating the geometries of the parental system dibromocyclopropane **5a** and its 5,5-dimethyl analog **14** (Figure 1).

For the reaction to proceed under neutral conditions the initial step is a heterolytic cleavage of either of the two carbon-bromine bonds to form a cyclopropane cation which then undergoes 2π-disrotatory electrocyclic ring opening to give **15**. However, all attempts to locate and calculate the geometry of the resulting carbocation after heterolytic cleavage of the either of the carbon-bromine, were not successful as the structure



Scheme 5. Gram-scale synthesis of tetramethylated *meta*-bromophenol **6d**.

Table 2. Scope and limitations of employed haloform, in situ quenching with TsCl and substituents on the cyclopentenone.



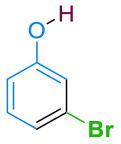
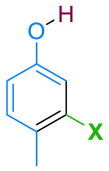
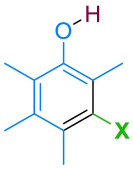
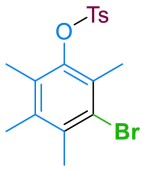
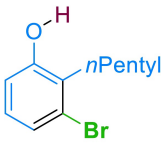
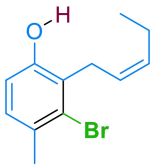
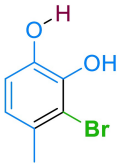
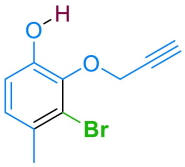
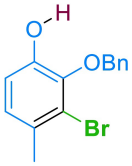
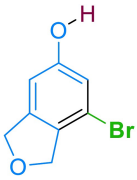
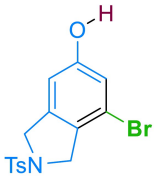
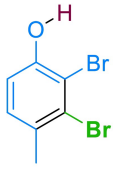
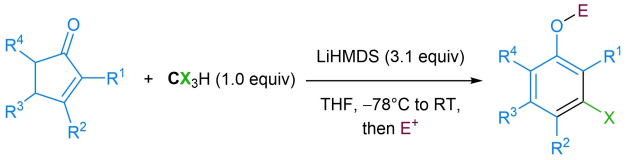
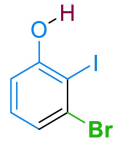
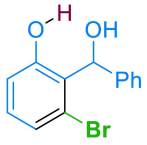
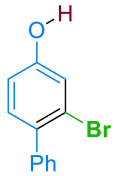
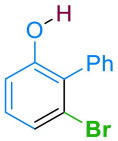
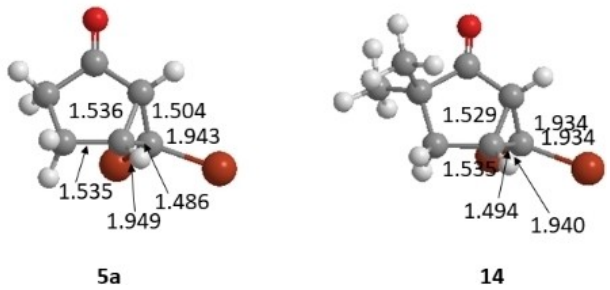
1	 **6a** (68%)	2	 **6b**: X = Br (75%) **6c**: X = I (47%)
3	 **6d**: X = Br (89%) **6e**: X = I (73%)	4	 **6f** (78%)
5	 **6g** (83%)	6	 **6h** (92%) (1:9 *E*:*Z*)
7	 **6i** (40%)[a]	8	 **6j** (55%)
9	 **6k** (68%)	10	 **6l** (70%)[b]
11	 **6m** (54%)	12	 **6n** (83%)

Table 2. continued



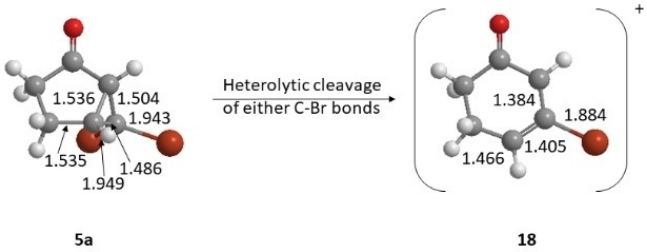
13	 **6o** (45%)	14	 **6p** (57%)[a]
15	 **6q** (29%)	16	 **6r** (65%)

[a] 4.1 equiv. LiHMDS were used. [b] 1.0 equiv. LiHMDS, −78 °C to 0 °C, 1 h, 2.1 equiv. LiHMDS, 0 °C to RT.



5a **14**

Figure 1. Calculated geometries (the G4MP2 composite method) of parental system **5a** and 5,5-dimethylated analog **14** with selected bond lengths in ångström.



5a **18**

Figure 2. The calculated geometry (the G4MP2 composite method) from heterolytic cleavage of either of the two carbon-bromine bonds in **5a** to give directly ring-opened carbocation **18**. Selected bond lengths are given in ångström.

immediately collapsed to the ring-opened product **15** (Figure 2).

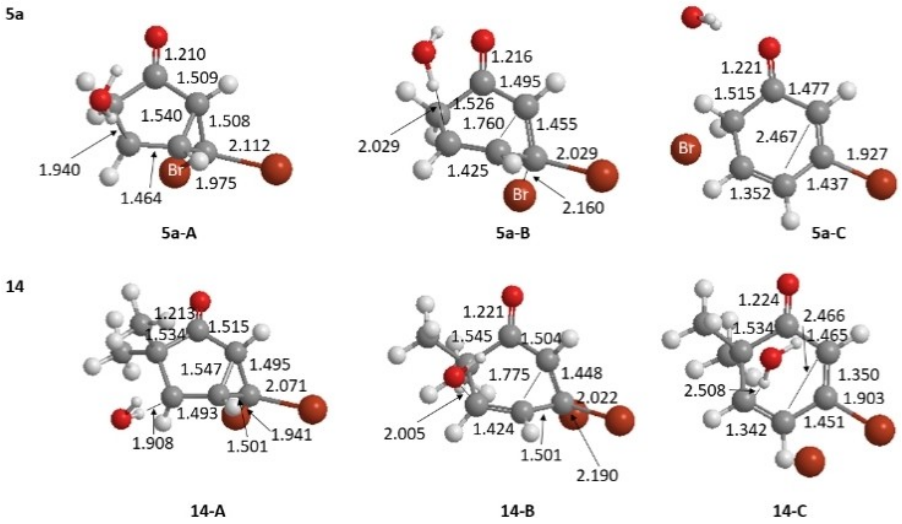


Figure 3. Calculated geometries (the G4MP2 composite method) with selected bond lengths in ångström.

This result shows that as soon at the energy barrier for carbocation formation has been overcome the thermally allowed 2π-electrocyclic ring opening proceeds without additional energy demand. There is no reason to believe that heterolytic cleavage of the carbon-bromine bond is particularly fast. It takes place from a secondary carbon with an electronegative substituent and the sp^3 to sp^2 rehybridization will induce additional strain in the three membered ring. Thus, the requirement for high temperatures to proceed.

We next turned to investigate the reaction under basic conditions with the aim to explain the differences in reactivity between the parental system **5a** and its 5,5-dimethylated analog **14**. For this part, we selected the hydroxide anion as the prototypical base. The calculated geometries of the reactants, transition states and products are shown in Figure 3.

The study shows that for **5a**, the hydroxide base attacks the hydrogen *anti* to the cyclopropane unit (ring carbon number four) and in a concerted fashion expels the *endo*-bromine atom (**5a-A** to **5a-C**, Figure 3). This is in agreement with the Woodward-Hoffmann rules for thermally allowed 2π-disrotatory electrocyclic ring openings, as expulsion of the *exo*-bromine would lead to a highly strained intermediate (Figure S1 in the Supporting Information).[10] A *syn* attack by the base leads to a slightly more complex reaction pathway with an energy barrier about five times higher (not shown). The study did not identify enolate **9b** (Scheme 3, pathway C) as a potential energy minimum in the sense that any attempt at optimization led to ring opening. This finding further strengthens a concerted base-triggered 2π-electrocyclic ring opening as the reaction mechanism (Scheme 3, pathway B).

The explanation for the stereoselective proton abstraction is found in the combination of stereo-electronic- and steric effects. Finally, it is noteworthy that the study does not suggest enolate formation (abstraction of a proton from the 5-carbon) to be the initial step and driver for subsequent cleavage of the carbon-bromine bond. For dimethylated analogs **14** the reaction pathway follows the same *anti* pathway as identified for **5a** (**14-A** to **14-C**, Figure 3). The energy barriers and reaction

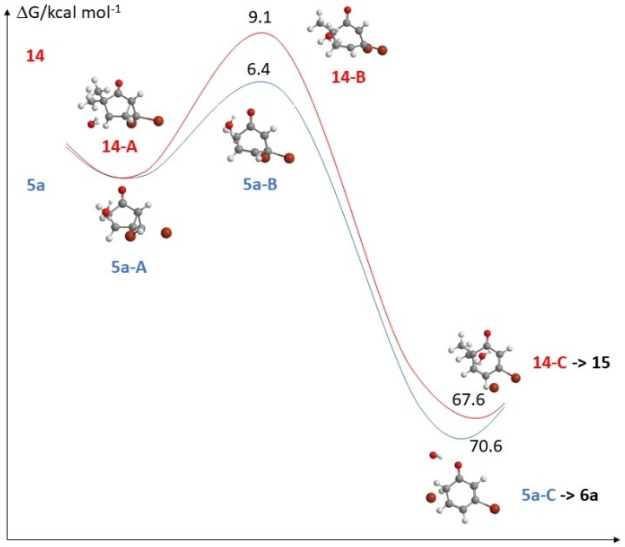
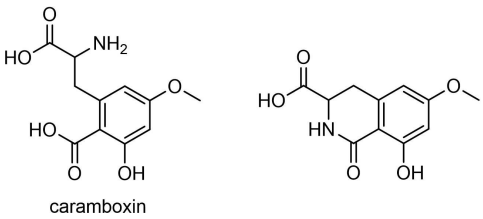
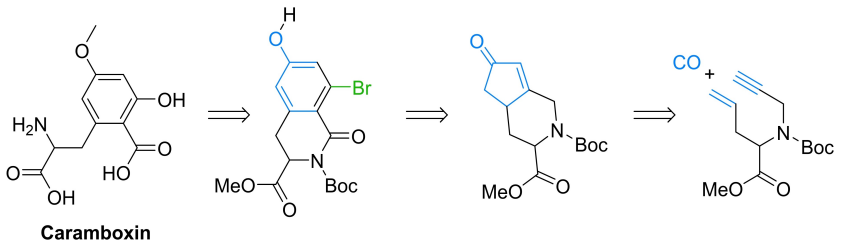


Figure 4. Schematic energy profile showing the competition between the base-assisted concerted ring opening of the parental system **5a** and dimethylated analog **14**. The free energies at 298.18 K are calculated at the G4MP2 level of theory.



Scheme 6. Chemical structure of the natural product and neurotoxin caramboxin and its corresponding inactive lactam.



Scheme 7. Retrosynthetic analysis of natural product caramboxin.

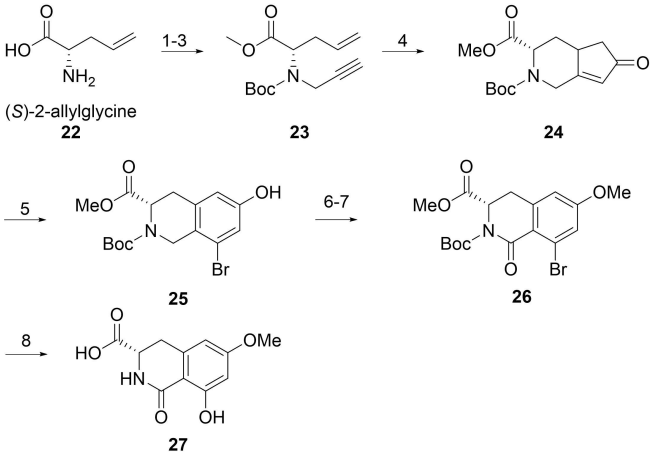
energies for both **5a** and **14** are summarized in a schematic energy profile (Figure 4). It shows that the reaction barrier is in the order of 3 kcal/mol higher for the dimethylated analog **14** compared to **5a**. This, however, cannot alone explain the fact that no product formation is observed for **14**, and we speculate if steric hindrance may play a key role.

In summary, the ab initio study shows that base-mediated abstraction of the proton *anti* to the cyclopropane ring is the initiation stage. This promotes a concerted reaction pathway in which the concave carbon-bromine bond is cleaved in a heterolytic fashion, and the electrocyclic ring-opening of dihalocyclopropanes **5** proceeds to their corresponding *meta*-halophenols **6**. The possibility of enolate formation seems to be of little importance to the mechanism.

The natural product caramboxin (Scheme 6) is a constituent of starfruit and shown to be a neurotoxin acting on the glutamatergic neurotransmitter system. Upon its isolation it has been reported to readily cyclize in water even under neutral conditions to form its inactive corresponding tetrahydroisoquinolinic derivative (Scheme 6).[11] The absolute stereochemistry of caramboxin remains unknown, however, due to its structural similarity with phenylalanine, it is assumed to be *S*, based on the fact that caramboxin has identical optical rotation phase with (*S*)-phenylalanine (negative).[11]

Considering the fact that caramboxin comprises a trisubstituted phenol, we decided to conduct a retrosynthetic analysis to explore the application of the methodology reported here (Scheme 7). Our strategy builds on the 4-methoxy group to originate from methylation of a phenol formed at a late stage in our methodology, with the starting material being a structural motif readily recognized as the product of a Pauson-Khand reaction.

The synthesis of caramboxin (Scheme 8) commenced with esterification of (*S*)-2-allyl glycine to give the corresponding ester in quantitative yield. N-Alkylation with propargyl bromide in 61% yield, followed by Boc-protection gave corresponding alkyne **23** in 57% yield. The following Pauson-Khand reaction to give **24** proceeded in excellent yield of 80%. Applying the standard procedure, the corresponding phenol **25** was obtained in 30% yield, being acceptable considering the high functional group density of the product. After methylation of the phenoxide under basic conditions with methyl iodide, the resulting product **26** was oxidized to the lactam using a variant of ruthenium catalysis previously reported for transformation of a structurally related compound with excellent



Scheme 8. Total synthesis of the lactam analog of caramboxin. 1) $SOCl_2$, MeOH, RT, quant.; 2) $LiOH{\cdot}H_2O$, propargyl bromide, 3 Å molecular sieve, DMF, RT, 61%; 3) Boc_2O, NEt_3, CH_2Cl_2, RT, 86%; 4) $Co_2(CO)_8$, DMSO, THF, 50 °C, 80%; 5) 3.1 equiv. LiHMDS (1.0 M in THF), 1.0 equiv. $CHBr_3$, THF, −78 °C to RT, 30%; 6) MeI, K_2CO_3, acetone, 60 °C, 64%; 7) $RuCl_3$, $NaIO_4$, EtOAc, H_2O, RT, 55%; 8) Cu_2O, $n$$Bu_4NBr$, pyridine-2-aldoxime, $CsOH{\cdot}H_2O$, H_2O, 100 °C.

chemoselectivity.[12] The last step comprising the hydroxylation of the arylbromide was expected to deliver globally deprotected caramboxin due to the elevated temperatures being employed, leading to hydrolysis of the ester, amide and carbamate. Unfortunately, even careful neutralization was found to promote ring closure to the inactive lactam analogue **27**. Although further attempts to isolate uncyclized caramboxin failed, this synthesis highlights the applicability of the herein reported methodology towards diversely substituted phenol derivatives.

Conclusion

In conclusion, we have reported a methodology for the expedited synthesis of substituted *meta*-halophenols **6** from their corresponding cyclopentenones **3** in good to high yields (18 examples, 29–92% yield, average 65%, and on an up to 5.8 g scale). Several of the phenols reported herein are new chemical entities and difficult to synthesize by means of conventional strategies. Furthermore, the methodology was applied to the synthesis of the lactam form of the natural

product caramboxin, which contains a densely functionalized phenol.

The base-triggered ring-opening reaction of 6,6-dibromobicyclo[3.1.0]hexan-2-ones **5** was investigated in an ab initio study that suggested that proton abstraction *anti* to the cyclopropane ring proceeds in a concerted fashion with heterolytic cleavage of the *endo* carbon-bromine bond. To the best of our knowledge, the methodology reported herein represents the first example of an anion-accelerated 2π-electrocyclic ring opening of a dihalocyclopropane.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: 2pi-electrocyclic ring opening · ab initio study · anion-assisted · *meta*-halophenols · natural product synthesis

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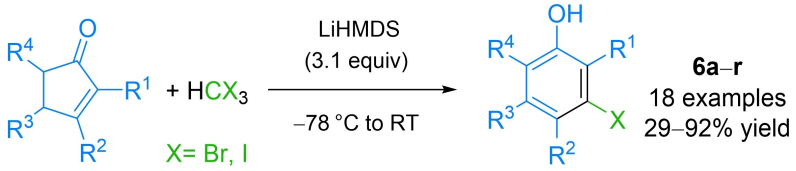

Opening the way to densely functionalized natural products: We report the first anion-accelerated, thermally allowed, 2π-electrocyclic ring opening as a novel route to substituted phenols **6a–r** and prove its efficacy in the total synthesis of the densely functionalized phenolic natural product caramboxin (isolated as the lactam dehydrate).

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Synthesis of Polysubstituted *Meta*-Halophenols by Anion-Accelerated 2π-Electrocyclic Ring Opening