Stereochemical Relay Through a Cationic Intermediate: Helical Preorganization Dictates Direction of Conrotation in the halo-Nazarov Cyclization

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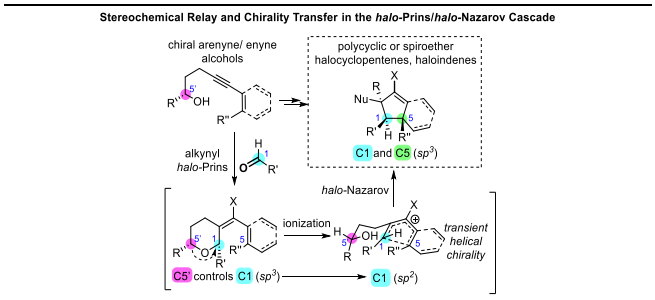
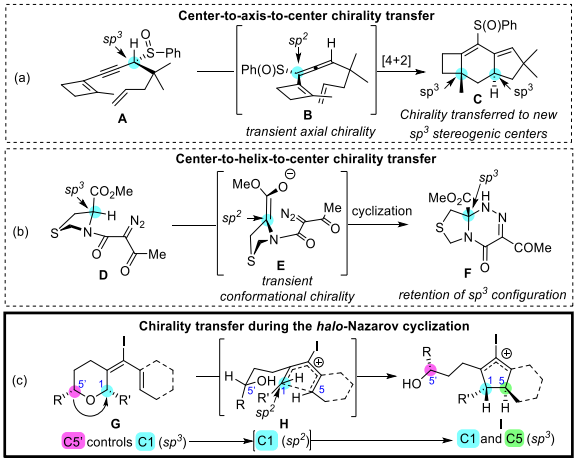
Supporting Information Placeholder



ABSTRACT: A stereocontrolled *halo*-Prins/*halo*-Nazarov cyclization protocol is reported, where chiral information from a secondary alcohol is relayed through several intermediates yielding halocyclopentene products diastereoselectively. An enantiopure product is obtained when a nonracemic secondary alcohol is used. Experimental and computational studies are described, enabling the design and synthesis of systems that ionize and cyclize with >95% chirality transfer through a mechanism involving the creation and preservation of transient helical chirality in a pentadienyl cation intermediate. First, a diastereoselective alkynyl Prins cyclization is executed to synthesize a conformationally distorted dihydropyran intermediate with a curved backbone and high reactivity. This chiral precursor adopts a specific helical alignment early in the subsequent cationic ionization/*halo*-Nazarov cyclization process, dictating the direction of conrotation in the electrocyclization. Notably, despite the ablation of an sp^3 stereogenic center during ionization, the low *halo*-Nazarov barrier enables efficient capture of a cationic intermediate with dynamic conformational chirality. The ionization and electrocyclization thus occur with "memory of chirality".

In most cyclizations that create sp^3 stereogenic centers *de novo*, the ring-forming step is also the stereodetermining step. Chirality transfer strategies can also induce stereocontrolled cyclizations, although this approach is less obvious and therefore uncommon. In these transformations, preexisting chirality in the reactant is transferred during the cyclization to generate a new sp^3 stereogenic center.[1] Numerous cyclizations using axis-to-center chirality transfer to install sp^3 stereogenic centers have been disclosed.[1–4] Center-to-axis-to-center transfer from reactant **A** to product **C** via axially chiral intermediate **B** has also been demonstrated, as shown in *Scheme 1a*.[5]

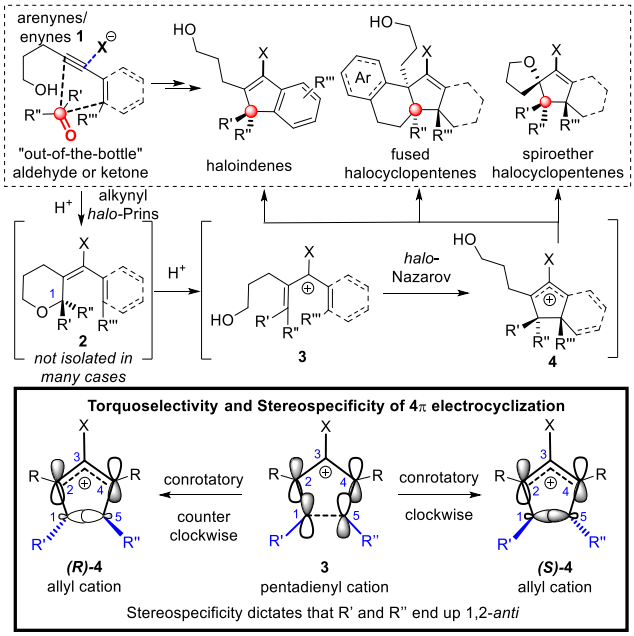
Scheme 1. Transfer of Chirality in Cyclization Reactions



Chirality transfer from an origin sp^3 carbon to a destination sp^3 carbon can also proceed through a hypothetically stereodynamic intermediate with no fixed central or axial chirality but with a conformation retained from the reactant. This phenomenon has been described as "memory of chirality". [6–8] For example, in *Scheme 1b*, reactant **D** (with point chirality) enolizes to chiral conformer **E**. When **E** cyclizes, its conformational chirality is captured as an sp^3 stereogenic center in product **F**.[9–11] In this early example, the authors ascribed the selectivity to "hidden axial chirality." Notably, in these examples, the stereogenic center in the reactant preorganizes the system such that as the intermediate evolves, one atropisomer is generated preferentially. In this study, we describe how a reactant with fixed chirality and a rigid, curved backbone (**G**, *Scheme 1c*) evolves into a reactive intermediate with transient helical chirality (**H**), enabling efficient chirality transfer in the *halo*-Nazarov cyclization.

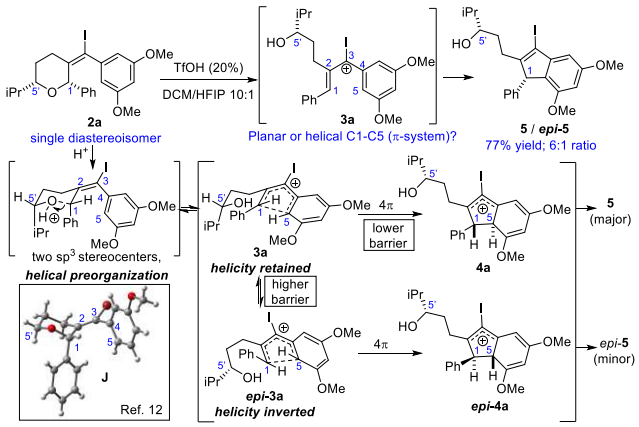
We have previously described cationic cascades that join alkynyl alcohols **1** with aldehydes and ketones to generate different types of halocyclopentenes (*Scheme 2*).[12–14] These cascades occur under acidic conditions, beginning with an alkynyl *halo*-Prins reaction and then ionization of the Prins adduct **2** to generate cation **3**. The 4π cationic *halo*-Nazarov electrocyclization of **3** to **4** creates two sp^3 stereogenic centers simultaneously and stereospecifically.[15,16] Capture of haloallyl cation **4** yields haloindenes, fused halocyclopentenes, or spiroether halocyclopentenes, depending on the termination step. If no asymmetric feature is present in the molecule or promoter then both clockwise and counterclockwise conrotation occurs, producing racemic **4** (bottom of *Scheme 2*).

Scheme 2. The *halo*-Prins/*halo*-Nazarov Sequence



Until recently, we assumed that the C1 sp3 stereogenic center of **2** is lost upon ionization and that the 3-halopentadienyl cation **3** would be equally likely to undergo either clockwise or counter-clockwise conrotation. However, the result shown in *Scheme 3* led us to question that assumption. In this experiment, dihydropyran **2a** (isolated as a single diastereoisomer)[17] was ionized and cyclized to afford haloindenes **5**/***epi-5*** (6:1 ratio) in 77% yield. This result was unexpected: if the C1 stereocenter is ablated, one would expect a ratio close to 1:1, given the distance between C5' and the emerging C1/C5 bond. How could the remote C5' stereogenic center exert such strong stereochemical influence on the cyclization?

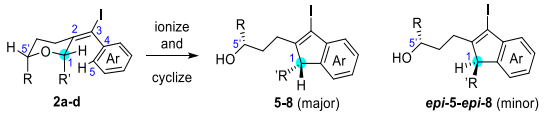
Scheme 3. Initial Observation and Hypothesis

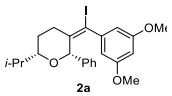
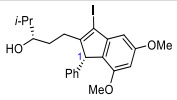
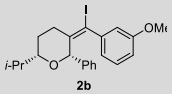
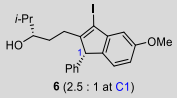
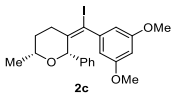
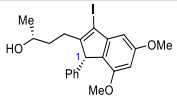
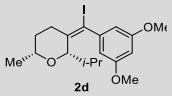
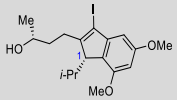


The distorted conformation seen in the X-ray structure of a similar dihydropyran **J** (*Scheme 3*, inset) provides a clue.[18] The phenyl group at C1 is oriented in an axial position, avoiding allylic strain, and the arene moiety is twisted out of plane with the C2-C3 double bond. It appears that C1-C4 is arrayed in a relatively rigid curve, with only the arene ring free to rotate about C3-C4. If the system aligns during ionization as shown in **J**, with the C5 carbon opposite the C1 oxygen, the generated helically chiral pentadienyl cation (see **3a**)[19] can only rotate in one direction.[20–26] As such, the chirality of reactant **2a** is largely retained throughout the ionization / cyclization process, even though the point chirality at C1 of **2a** is lost. These findings suggest that the kinetic barrier for cyclization of **3a** to **4a** is slightly lower than the barrier for conformational inversion of **3a** to *epi*-**3a**, with the minor isomer *epi*-**5** resulting from cyclization and rearomatization of *epi*-**3a**. Thus, ionization and cyclization of **2a** occurs with 86% chirality transfer and 14% inversion.

We continued investigating chirality transfer in ionization/ cyclization of other reactants **2** derived from arenyne alochols **1** and found the results illuminating (*Table 1*). For example, **2b**, which has only one electron-donating group and consequently a higher 4π electrocyclization barrier than **2a**, ionizes to furnish **6** with only 71% chirality transfer (*Entry 2*). Similar degree of chirality transfer is obtained for **2c** (R = Me) when compared to **2a** (R = i-Pr) (*Entries 1* vs. *3*), indicating that the C5' substituent does not impact chirality transfer efficiency. These observations suggest that the C1 sp^3 center in **2** *alone* controls the direction of conrotation by enforcing a rigid conformation in both reactant and cyclization intermediates. Ionization of **2d** (R'=*i*-Pr) affords **8** in 61% yield with 86% chirality transfer (*Entry 4*), a comparable result to *Entry 3*, demonstrating that reactants **2** with both aliphatic and aromatic groups at C1 still adopt the conformation that dictates direction of conrotation.

Table 1. Chirality Transfer in the Ionization/Cyclization of Dihydropyrans 2a-2e Derived from Arenyne Alcohols 1[a]

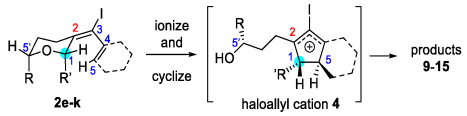


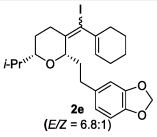
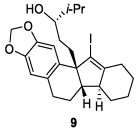
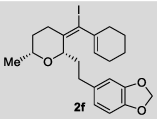
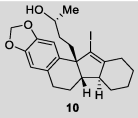
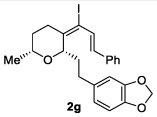
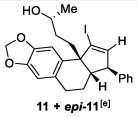
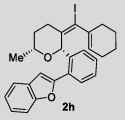
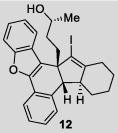
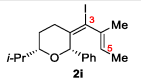
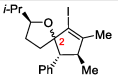
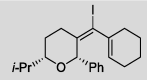
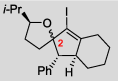
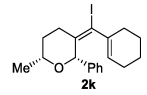
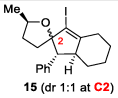
entry	reactant 2	product	chirality transfer[b]	yield
1	 **2a**	 **5** (6 : 1 at C1)	86%	77%
2	 **2b**	 **6** (2.5 : 1 at C1)	71%	92%
3	 **2c**	 **7** (6 : 1 at C1)	86%	72%
4	 **2d**	 **8** (6 : 1 at C1)	86%	61%

[a] *Reagents and Conditions*: TfOH (20 mol%) CH_2Cl_2/ HFIP (10:1), 0 ºC. [b] Chirality transfer from C1 of **2a-d** to C1 of **5-8** from diastereomeric ratios determined by ^{1}H NMR.

According to the hypothesis from *Scheme 3*, lower electrocyclization barriers correlate with higher chirality transfer. In earlier experimental and computational studies, we found that the simple pentadienyl cations **3** prepared from enynes **1** (*Scheme 2*) have cyclization barriers calculated to be 4-6 kcal/mol lower than those for aryl allyl cations like **3a**.[12] Based on these computational data, we opted to test reactants **2e**-**2k**, expecting efficient chirality transfer. It was exciting to find that ionization of **2e** produces **9** as a single diastereomer in 78% yield (*Entry 1, Table 2*). This result indicates that ionization / electrocyclization occurs with >95% chirality transfer from C1 of reactant **2e** to C1 and C5 of cation **4**, followed by diastereoselective arylation at C2. Similarly, ionization of **2f** (R = Me) yields **10** in quantitative yield as a single diastereoisomer (*Entry 2, Table 2*) and ionization of **2g** (C4 substituent = H) occurs with 86% chirality transfer (6:1 ratio of **11**/*epi*-**11**) in high yield (*Entry 3, Table 2*). Reactant **2h**, containing a heteroaromatic nucleophile in conjugation with the pentadienyl cation, also undergoes >95% chirality transfer upon cyclization, yielding a single diastereomer **12** in 79% yield.

Table 2. Chirality Transfer in the Ionization/Cyclization of Dihydropyrans 2e-2k Derived from Enyne Alcohols 1[a]



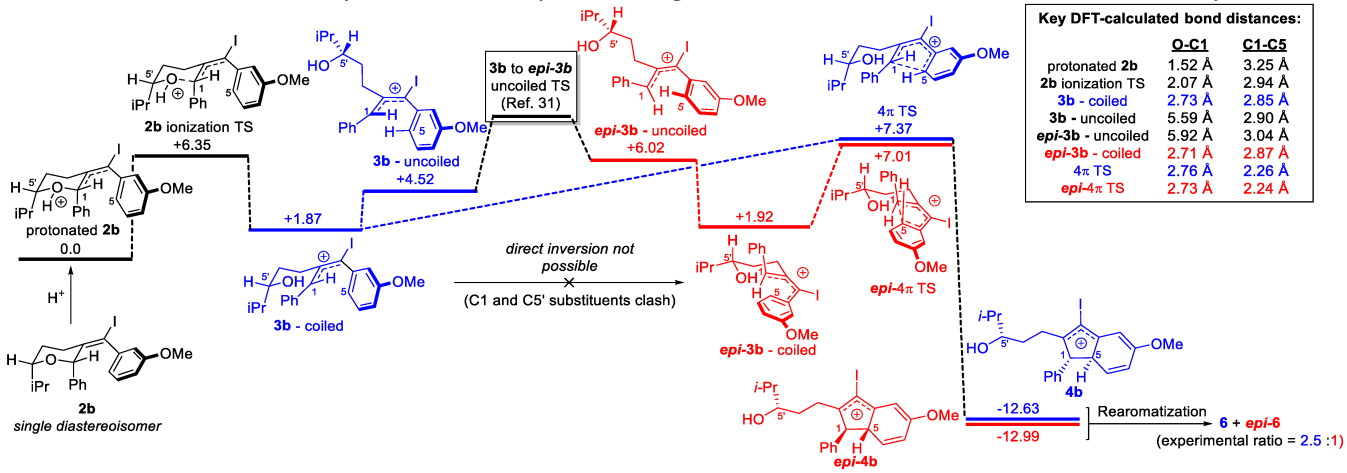
entry	reactant 2	product	chirality transfer[b]	yield
1[c]	 2e (*E*/*Z* = 6.8:1)	 9	>95%	78%
2	 2f	 10	>95%	99%
3	 2g	 11 + *epi*-11[e]	86%	93%
4	 2h	 12	>95%	79%
5[d,f]	 2i (*E*/*Z* at C1, C3 = 9.5:2.5:1)	 13 (dr 1.3:1 at C2)	>95%	91%
6[f]	 2j	 14 (dr 1.3:1 at C2)	>95%	77%
7[f]	 2k	 15 (dr 1:1 at C2)	>95%	73%

[a] *Reagents and Conditions*: TfOH (20 mol%) CH_2Cl_2/ HFIP (10:1), -50 °C to 0 °C. [b] Chirality transfer from C1 of 2 to C1/C5 of **9-15** (via **4**) from diastereomeric ratios determined by ^{1}H NMR. [c] Only the E isomer reacted. [d] Ratio of *E*/*Z* double bond isomers ratios determined by ^{1}H NMR. Only the *E,E* isomer (C3 and C5) reacted. [e] 6:1 ratio of **11** to ***epi*-11** (see SI). (f) Experiment was performed with 2 equiv. HFIP.

We then explored the ionization of *halo*-Prins adducts **2i-2k**, which generate spiroether products **13-15** when the pendent alcohol traps haloallyl cation **4** at C2.[13] Ionization and cyclization of **2i** (*E,E* isomer)[27] furnishes **13** as a 1.3:1 ratio of diastereoisomers at C2 (*Entry 5*).[28] Similarly, reaction of **2j** produces **14** (1.3:1), and **2k** provides a 1:1 ratio of spiroether epimers **15**. Overall, the findings indicate that the cyclization of reactants **2i-2k** (*Entries 5-7*) occurs with >95% chirality transfer, but the product spiroethers ionize rapidly under the acidic reaction conditions to deliver a thermodynamic mixture of spiroether diastereoisomers, epimeric at C2.

Next, we used DFT methods to analyze the conversion of **2b** to **6**/**epi-6** (*Table 1*, *Entry 2*). This case was chosen for in-depth analysis because the reduced efficiency of chirality transfer (71%) suggests that both retention and inversion pathways are accessible. In *Scheme 4,* the intermediates along the reaction coordinate starting with ionization of **2b** (optimized at the M06-2x/Def2TZVP level)[29,30] and leading to the major product **6** are shown in blue.[31] Shown in red is the cyclization pathway involving C1-C5 helical inversion, leading to the minor product ***epi*-6**. The computational modeling (*Scheme 4)* provides three valuable insights into the process: i) the pentadienyl cations **3b**/***epi*-3b** are more stable in a coiled conformation than in an uncoiled one; ii) these lower-energy coiled cationic intermediates electrocyclize just as readily as their uncoiled counterparts ($\Delta G^{\ddagger}$=5.49 for **3b**-coiled and $\Delta G^{\ddagger}$=5.72 for **3b**-uncoiled; $\Delta G^{\ddagger}$=5.10 kcal/mol for ***epi*-3b**-coiled and $\Delta G^{\ddagger}$=5.64 kcal/mol for ***epi*-3b**-uncoiled);[31] iii) C1-C5 helical inversion is a complex process. This third finding emerged when we analyzed the DFT-optimized structure of **3b**-coiled and found that clockwise rotation along the C1-C2 bond is disfavored due to steric clash between the phenyl group and the bulky substituents on C5'. In other words, there is no direct pathway from the **3b**-coiled cation to the ***epi*-3b**-coiled cation. The system must uncoil before it can epimerize (**3b**-coiled to **3b**-uncoiled to ***epi*-3b**-uncoiled to ***epi*-3b**-coiled). The chirality transfer observed can thus be rationalized as follows: ionization of **2b** generates only one helical conformer (**3b**-coiled), which is more likely to electrocyclize to **4b** ($\Delta G^{\ddagger}$=5.49 kcal/mol) than to traverse the inversion pathway that leads to uncoiled cation ***epi*-3b** (+6.02 kcal/mol) en route to *epi*-**4b**. This effect should be magnified if the electrocyclization barrier is lowered, which is in line with our experimental findings.

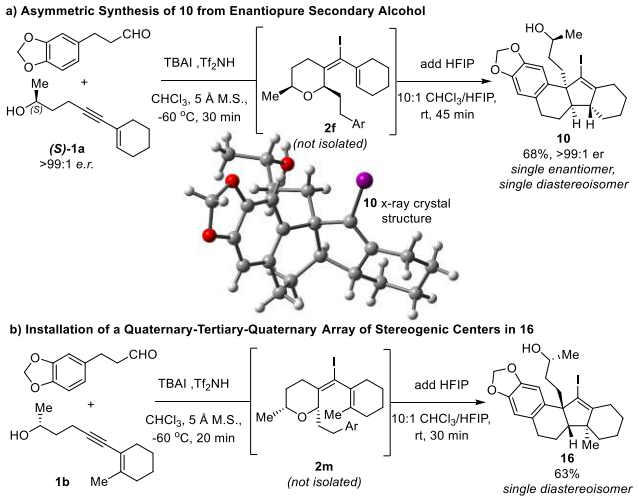
Scheme 4. DFT Analysis of the Pathways Governing Retention or Inversion of C1-C5 Helical Chirality



All structures and transition states optimized at the M06-2x/Def2TZVP level; PCM = dichloromethane (all values are in kcal/mol).

With the results and mechanistic hypothesis in hand, we sought to demonstrate the utility of this chirality transfer method for the asymmetric synthesis of *halo*-Nazarov products from enantiopure enynes **1**. When enantiopure enyne ***(S)*-1a** (>99:1 *e.r.*) is subjected to *halo*-Prins/*halo*-Nazarov cascade conditions,[14] **10** is isolated as a single enantiomer and diastereoisomer, in 68% yield in a single synthetic operation (*Scheme 5*). This example showcases how the C5' chiral information in the secondary alcohol enyne reactant **1** can be propagated through a series of intermediates with static and transient chirality,[32] to finally install the C1, C2 and C5 *sp3* stereogenic centers in **10** with complete stereochemical fidelity.

Scheme 5. Stereochemical Relay in a One-Pot *halo*-Prins/ *halo*-Nazarov Cascade



In addition to enantioenriched products, the same one-pot method can be executed with tetrasubstituted enyne **1b**, delivering **16** in 63% yield (*Scheme 5*). Fused halocyclopentene **16** contains a quaternary-tertiary-quaternary array of contiguous stereocenters, and is forged with complete stereocontrol, again derived from a preexisting, remote secondary alcohol stereocenter in the reactant.

In conclusion, the *halo*-Prins/ *halo*-Nazarov sequence consists of a stereochemical relay (C5' to C1 during diastereoselective dihydropyran formation),[32] followed by ionization/ cyclization with transfer of chirality (C1 to C1/C5). All stereochemistry in the complex products **5-16** can therefore be traced back to C5' of the secondary alcohols **1**. The rigid, curved C1-C4 backbone of dihydropyrans **2** mandates a specific helical orientation during ionization as positive charge develops and the carbon-oxygen bond at C1 lengthens. Because conrotation cannot occur in a direction that interferes with the trajectory of the departing alcohol during ionization, the helicity of the reactive intermediate is actually preordained by the C1 stereogenic center of the reactant. Thus, the stereodetermining step of the sequence is not electrocyclization, as one might expect, but formation of a dihydropyran with a relatively rigid three-dimensional conformation imposed by allylic strain.

These findings may reveal an underappreciated feature of cyclization reactions and a potential liability for synthetic planning. We note that in *Scheme 1*, unanticipated conformational restrictions (upon loss of a sp^3 stereogenic center) have a strong influence upon the stereochemical outcome of each cyclization.[33,34] In any anionic or cationic cyclization that is predicated upon planarization, transient conformational chirality could be inherited from a precursor in this way. Thus, a synthetic operation prior to the ring-closing step may be partially or completely stereodetermining. To achieve stereocontrolled cyclizations under these circumstances, it is critical to understand how conformational chirality evolves over the course of the reaction and focus optimization efforts accordingly. Further investigation of this phenomenon and its relevance to the development of asymmetric cyclizations is warranted. In our lab we are continuing to study stereoselectivity in the *halo*-Prins/*halo*-Nazarov sequence using experimental and computational techniques.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. (SI, Spectral Data, CIF files)

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Notes

The authors declare no competing financial interests.

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(18) See Ref. 12-14 for x-ray crystal structures of dihydropyrans **2**. The R' group at C1 (see *Scheme 3*) is in a pseudoaxial position, avoiding allylic strain due to the substituent on the vinyl halide.

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(31) See SI for all DFT-optimized structures. No transition state was found for the conformational inversion between **3b-**uncoiled and ***epi*-3b-**uncoiled. However similar studies report values of 7.8 – 11.2 kcal/mol for pentadienyl cation isomerizations (see Ref. 25 and a similar study by the same authors: Faza, O. N.; López, C. S.; Álvarez, R.; de Lera, Á. R. Regio-, Peri-, and Torquoselectivity in Hydroxy Heptatrienyl Cation Electrocyclizations: The Iso/Homo-Nazarov Reaction. *Chem. Eur. J.,* **2010,** *15* (32) 9818-9828). While we cannot rule out an SN2 cyclization mechanism, no transition state was found connecting protonated **2b** directly to **4b**. Mechanistic studies are ongoing in our lab to probe this question experimentally.

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SYNOPSIS TOC: Same text as abstract.