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# Acid-catalyzed conversion of caryolan-1-ol to isoclovene: A computational investigation of the multi-step carbocation rearrangement

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ABSTRACT

Acid-catalyzed conversion of caryolan-1-ol to isoclovene involves a multi-step carbocation rearrangement. Electronic structure calculations show that the pathway proceeds through an initial 3° carbocation, as well as a series of three other 3° carbocations. The key stage in which the ring structure is rearranged occurs not as might initially be imagined, in two separate steps with the intermediacy of a 2° carbocation, but rather in a single, concerted but highly asynchronous dyotropic rearrangement. The transition structure for this dyotropic rearrangement strongly resembles the 2° carbocation that would be involved in a stepwise mechanism. However, the dyotropic rearrangement is stereochemically unusual. While one of the bond migrations is suprafacial, as expected, the other is effectively antarafacial. This unusual stereochemical outcome is enforced by the geometric constraints of the polycyclic structure.



## 1. Introduction

Acid hydrolysis of the sesquiterpenol caryolan-1-ol (**1**) has long been known to yield a variety of products with rearranged carbon skeletons, among them isoclovene (**2**) (Scheme 1).[1,2] The structure of isoclovene in fact took some time to establish with confidence, but was ultimately confirmed both by X-ray crystallography[3,4] and by total synthesis.[5–7] However, almost nothing has been said about the mechanism by which this structural rearrangement takes place. In 1961 Clunie and Robertson proposed a highly abbreviated mechanistic outline that includes a carbocation, the formation of which is difficult to understand, and that subsequently undergoes a seemingly unlikely 1,3 shift.[4] Other publications from the era say essentially nothing about the mechanism of this particular transformation. On the other hand, in a 1972 paper primarily concerned with a different structure (pseudoclovene-B), Crane et al. proposed a mechanism that proceeds via an acid-catalyzed fragmentation reaction to a diene, which subsequently undergoes acid-catalyzed dimerization, and then two hydride shifts and one methyl shift. However, no evidence is presented to support the conjectured mechanism.[8]

The reaction does, however, make an appealing mechanistic problem for introductory organic chemistry students, and in fact the author first encountered the reaction in this context, as a problem he inherited from a predecessor for use in teaching introductory organic chemistry. The mechanism a sophomore organic chemistry student would likely write, and which the author has always presumed to be correct, is depicted in Scheme 2. The last three steps of this mechanism are in fact the same as for the proposal Crane et al. made in 1972.

However, is this mechanism correct? While they of course cannot prove the mechanism, electronic structure calculations can nonetheless help establish whether a mechanism is plausible. This approach has been used previously to good effect for the study of carbocation rearrangements in caryolene systems.[9] Density functional and CBS-QB3 Computations were carried out with this intention.

## 2. Results and discussion

Potential energy minima for carbocations **3**, **5**, **6**, and **7** in Scheme 2 were located without difficulty. Similarly, it was straightforward to find and verify the transition structures leading from **5** to **6**, and from **6** to **7**. Both are ordinary suprafacial 1,2-shifts,

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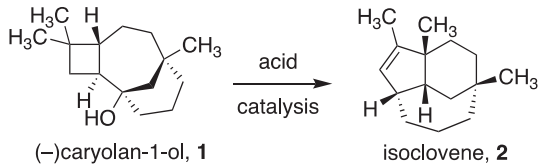
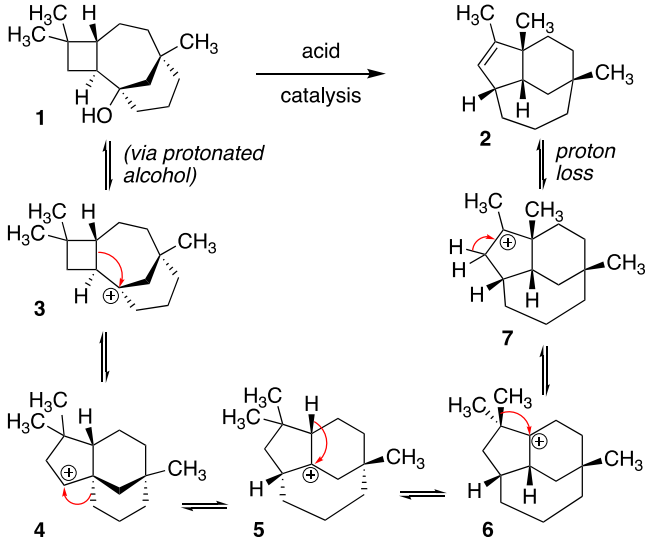



**Scheme 1.** Acid-catalyzed conversion of caryolan-1-ol to isoclovene.

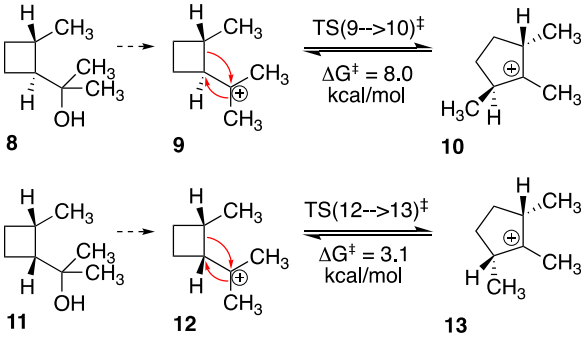



**Scheme 2.** Proposed mechanistic pathway for conversion of caryolan-1-ol to isoclovene.

of a hydride in the first case and a methyl group in the second, having low barriers.

However, perhaps not surprisingly, the 2° carbocation **4** proved elusive. The pathway from **3** to **5** thus turned out not to be entirely straightforward to find. In fact, many attempts to do so ended up linking carbocation **5** not to the *trans*-fused carbocation **3**, but rather its *cis*-fused epimer. A detour was therefore taken to examine the model systems shown in Scheme 3. The *trans* structure **8** is of course similar to caryolan-1-ol, while the *cis* structure **11** is similar to the structure from which carbocation **5** seemed more easily derived.

The rearrangement of **9** to **10** occurs not in two steps, with an intermediate 2° carbocation, but rather in a single step. The same is true for the rearrangement of **12** to **13**. Carbocation rearrangements of this sort, in which two σ-bonds migrate simultaneously, have been termed dyotropic, a term first coined by Reetz and Hoffmann and Williams.[10] More recently, dyotropic rearrangements in terpenoids have been studied computationally by Guitierrez and Tantillo.[11–14] The examples here follow the "type I" designation, in which two σ-bonds trade places.




**Scheme 3.** Simple model system for first stage(s) of rearrangement.

As Guitierrez and Tantillo observed, the reaction occurs in such a way that one of the σ-bonds migrates across one face, and the other σ-bond across the opposite face, of the bond that links the two centers between which migration occurs.[11] Formally speaking, each center undergoes inversion, because each migrating group remains on the same "face" as where it began, just as in an ordinary 1,2-hydride or alkyl shift. In this case, that means the bridgehead hydrogens retain their original orientations: *trans* for **8** → **9** → **10**, and *cis* for **11** → **12** → **13**.

The transition structures TS(**9** → **10**)‡ and TS(**12** → **13**)‡ are shown in Fig. 1. They are similar in structure to the 2° carbocations that one might classically have envisioned as intermediates in these transformations. It appears that the 2° carbocations are too unstable to correspond to minima on the potential energy surface. Such avoidance of a true 2° carbocation intermediate is common in terpenoid biosynthesis.[12] However, the reaction pathway nonetheless proceeds through structures that strongly resemble these 2° carbocations, even if they are not strictly speaking intermediates. The dyotropic rearrangements, at least in these two cases, involve concerted but highly asynchronous migration of the two σ-bonds. The migration that causes expansion of the ring is essentially complete by the time the migration of the methyl group begins. It is also interesting to note that in the two different transition structures, the two oppositely positioned methyl groups migrate. That is, in TS(**9** → **10**)‡, the methyl group on the proximal face of the structure undergoes migration, whereas in TS(**12** → **13**)‡, the methyl group on the distal face of the structure undergoes migration.

The *trans* alcohol **8** is lower in energy than isomer **11** by 2.8 kcal/mol. However, *trans* carbocation **9** has a significantly higher barrier to rearrangement than the corresponding *cis* structure **12**: 8.0 kcal/mol for **9**, compared to 3.1 kcal/mol for **12**. Nonetheless, both barriers are low enough that rearrangement would likely be possible at reaction temperatures within the lifetime of the carbocation.

Using the transition structure TS(**9** → **10**)‡ in the model system

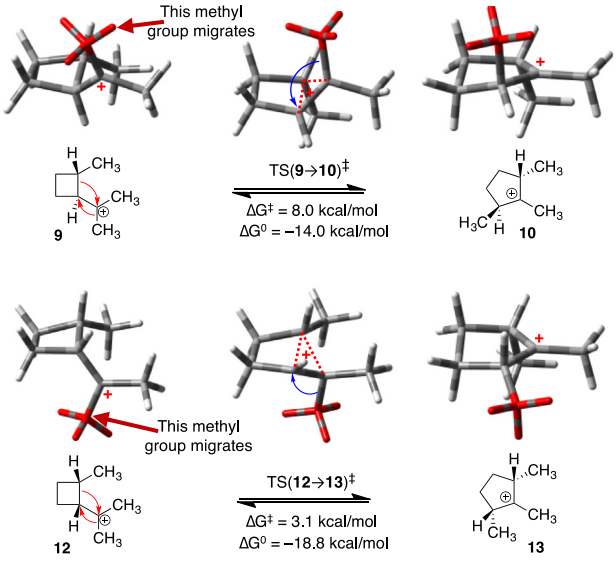



**Fig. 1.** Rearrangements of model systems. The migrating methyl is shown in red in each case.