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Acid-induced transannular cyclization of 2-methyl- and 10-methyl-5-cyclodecenone

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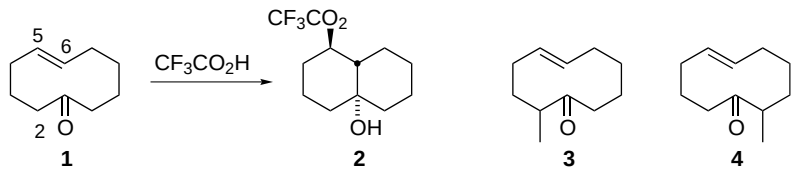
Abstract—2-Methyl- and 10-methyl-5-cyclodecenone were made by anionic oxy-Cope rearrangement of the corresponding 1,2-divinylcyclohexanols, and their transannular cyclizations were induced using trifluoroacetic acid. In each case, a single diastereomer of a *trans* fused bicyclo[4.4.0]decan-1-ol with an equatorial methyl group was isolated. The methyl substituent at C2 or C10 of the 5-cyclodecenone did not alter the regio- and stereochemistry previously observed for the parent ring system, (*E*)-5-cyclodecenone. The relative stereochemistry of the products was determined spectroscopically from *J*-value analysis and NOE.

In previous work we have shown that (*E*)- and (*Z*)-5-cyclcodecenone undergo ring closure to give products from either transannular 1,5-cyclization or 1,6-cyclization, depending on the reaction conditions.[1] 1,6-Cyclization of this ring system under acidic conditions is particularly interesting, as it stereospecifically converts the three prochiral sp^2-hybridized centers at C1, C5 and C6 of (*E*)-5-cyclodecenone (**1**) into the three asymmetric centers in the product **2**. Such cyclizations lead to products that are far more complex structurally than their starting materials. Indeed, among one-bond disconnections of the bicyclo[4.4.0]decane system, transannular cyclization of a ten-membered ring leads to the greatest increase in complexity.[2]

The stereospecificity of the 1,6-cyclization of 5-cyclodecenone **1** can be understood to arise from two phenomena given that the alkene is *trans*. One is that the reaction takes place from a parallel conformation, i.e. one in which the C5–C6 and C1–10 bonds of 5-cyclodecenone **1** are parallel, which leads to a *trans* ring fusion. The other phenomenon is that the reaction takes place with net *anti* addition of the carbonyl carbon and conjugate base of the acid to the alkene. These two phenomena lead to the relative stereochemistry among the three stereocenters of bicyclo[4.4.0]decanol **2**, i.e. with a *trans* ring fusion at C1 and C6, and the substituent at C5 in an equatorial position.

In our syntheses of africanol and isoafricanol,[3] we examined the affect of a methyl group at C2 on the transannular cyclization of a 5-cyclodecenone that underwent 1,5-cyclization, but we have not previously investigated such an affect in a system that would be expected to undergo 1,6-cyclization based on its structure and the reaction conditions. Herein we report on the preparation and acid-induced transannular cyclization of (*E*)-2-methyl- and (*E*)-10-methyl-5-cyclodecenones (**3** and **4**).

*Synthesis of (E)-2-methyl-5-cyclodecenone (**3**) and (E)-10-methyl-5-cyclodecenone (**4**).* (*E*)-2-Methyl-5-cyclodecenone (**3**) was prepared from commercially available 2-chlorocyclohexanone. Addition to this chloroketone of one equivalent of vinylmagnesium bromide followed



1 **2** **3** **4**

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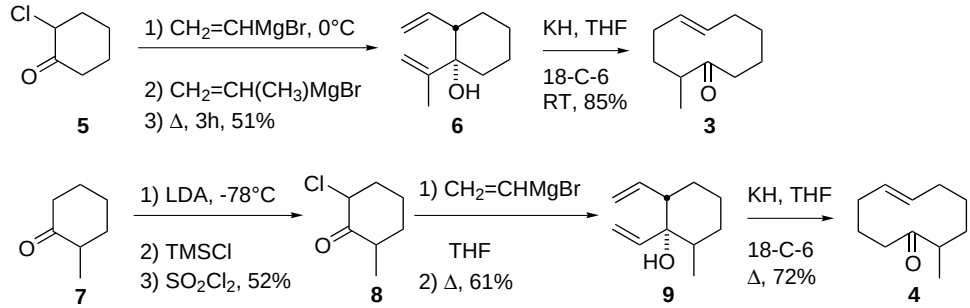


Scheme 1.

by one equivalent of isopropenylmagnesium bromide gave the known divinylcyclohexanol **6**,[4] which in turn underwent anionic oxy-Cope rearrangement to give (*E*)-2-methyl-5-cyclodecenone (**3**).

The synthesis of (*E*)-10-methyl-5-cyclodecenone (**4**) began with 2-methylcyclohexanone (**7**). The kinetic enolate of 2-methylcyclohexanone was first converted into the corresponding enolsilane, which was then treated with sulfuryl chloride to give 2-chloro-6-methylcyclohexanone (**8**) as a single diastereomer. Addition of an excess of vinylmagnesium bromide to the chloroketone gave the divinylcyclohexanol **9**. Anionic oxy-Cope rearrangement of the alcohol led to 5-cyclodecenenone **4** (Scheme 1).

5-Cyclodecenone **4** is also available from 1,2-divinylcyclohexanol itself, as previously reported.[5] Diastereomers **10** and **12** were each independently subjected to oxy-Cope rearrangement under basic conditions, and both gave (*E*)-10-methyl-5-cyclodecenone (**4**) upon quenching with methyl iodide. In these reactions, either before or during the alkylation step, both 1,5-dienolates **11** and **13** undergo rearrangement to a 1,6-dienolate that is trapped by methyl iodide (Scheme 2).

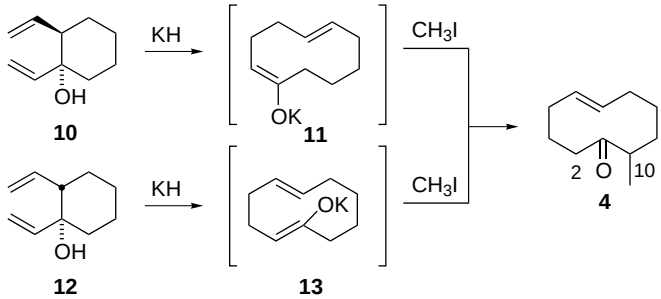
*Acid-induced transannular cyclization of (E)-2-methyl- and (E)-10-methyl-5-cyclcodecenone (**3** and **4**) and determination of the relative stereochemistry of the products.* Cyclization of cyclodecenones **3** and **4** in methylene chloride with trifluoroacetic acid was highly selective, leading to bicyclo[4.4.0]decanols **14** and **15**, respectively.

The relative stereochemistry of bicyclo[4.4.0]decanols **14** and **15** was determined spectroscopically. It is apparent from the splitting patterns and coupling constants for the hydrogen alpha to the trifluoroacetoxy group at C5 (td, $J=10.2$ and 4.5 Hz for **14** and td, $J=10.7$ and 4.6 Hz for **15**) that the hydrogens at C5 and C6 are both axial in both products. This data is consistent with the hydrogen at C5 being axial and vicinal to two axial hydrogens (one on C4 and one on C6) with approximately equal coupling constants (J_{ax-ax} between 10 and 11 Hz), and vicinal to one equatorial hydrogen on C4 ($J_{ax-eq}=4.5$–4.6 Hz).

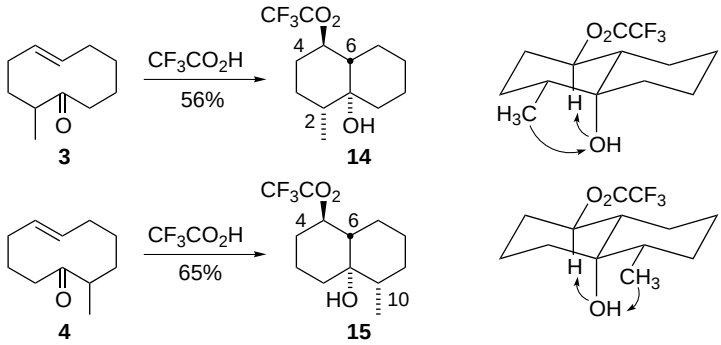
The alcohol proton of bicyclo[4.4.0]decanols **14** and **15** appears as a sharp singlet at 4 ppm in DMSO-d_6, which makes it possible to relate relative stereochemistry at C1, C5, and either C2 (for **14**) or C10 (for **15**). Irradiation of the methyl group signal at around 0.8 ppm leads to a clean enhancement of hydroxyl proton at 4 ppm. Likewise, irradiation of the hydroxyl proton leads to an enhancement not only of the methyl group but also of the hydrogen on C5. Given that the hydrogens at C5 (and C6) are both axial from their *J* values, it follows that the hydroxyl group at C1 must also be axial in order to observe an NOE with the axial hydrogen at C5. Likewise, the methyl group on C2 of **14** and C10 of **15** must be equatorial in order to observe an NOE with the axial hydroxyl group at C1 (Scheme 3).

The stereochemical outcome for the 1,6-cyclizations of 5-cyclodecenones **3** and **4** is akin to that observed for the unsubstituted cyclodecenone **1**, i.e. they all take place from a parallel conformation with net *anti* addition to the alkene. The additional factor in the cyclizations of 5-cyclodecenones **3** and **4** is the orientation of the methyl group at C2 or C10 during the cyclization, as some parallel conformations would lead to an equatorial orientation, and others to an axial orientation.

The observed preference for the equatorial position in the cyclizations of both 5-cyclodecenones **3** and **4** can be understood in terms of steric effects that destabilize the transition states leading to an axial methyl group. For 5-cyclodecenone **3**, transition states leading to the methyl group in an axial position would experience *gauche* interactions between the methyl group and the axial hydrogens at C4, C6 and C10 in bicyclo[4.4.0]decanol **14**. Such interactions are absent in the competing transition states that lead to the methyl group in an equatorial position. For 5-cyclodecenone **4**,



Scheme 2.



Scheme 3.

a similar argument holds, except that the steric interactions would be between the methyl group and the axial hydrogens at C2, C6 and C8 in bicyclo[4.4.0]decanol **15**.

It should be noted, however, that it does not follow from this limited study that any non-hydrogen substituent at C2 or C10 of an (*E*)-5-cyclodecenone will end up equatorial upon 1,6-cyclization, *syn* to an axial bridgehead hydroxyl group. Substituents that are smaller than a methyl group would experience less of a steric effect, and other factors besides steric effects could play a role in the diastereoselectivity of the reaction. For example, we have previously studied the 1,5-cyclization of a 5-cyclodecenone substituted at C2 with an ethoxy group.[6] Although not entirely analogous, the trifluoroacetic acid-induced cyclization led to the ethoxy group being *anti* to the bridgehead hydroxyl group at C1 of the bicyclo[5.3.0]decan-1-ol. We attributed the diastereoselectivity of the reaction to an electronic effect, i.e. a minimization of the net dipole moment in the transition state that led to the product. However, in the acid-induced cyclizations of 5-cyclodecenones, absent a silyl or stannyl group to alter the regiochemistry of the cyclization, there appears to be a clear preference in a 1,6-cyclization for an alkyl substituent at C2 or C10 to end-up equatorial in the product.

In conclusion, the diastereoselectivity in the 1,6-cyclization of substituted 5-cyclodecenones was tested via the acid-induced transannular cyclizations of 2-methyl- and 10-methyl-5-cyclodecenones. The alkyl substituent at C2 or C10 did not alter the regio- and stereoselectivity of the parent ring system under the reaction conditions, and the methyl group ends-up equatorial in the product. These cyclizations are most notable for the three asymmetric centers created in the reaction with predictable relative stereochemistry, which bodes well for its application in the synthesis of more highly substituted hydronaphthanol derivatives.

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