# Palladium Hydride Promoted Stereoselective Isomerization of Unactivated Di(exo)methylenes to Endocyclic Dienes

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Ⓢ Supporting Information

ABSTRACT: The exomethylenes of 2,6-disubstituted bicyclo[3.3.1]nonan-9-ones **2** are readily isomerized over a palladium catalyst under an atmosphere of hydrogen to predominantly form the isomer **3** with C_2 symmetry with very little formation of the analogous product with C_s symmetry. A hydrogen source is essential to effect the rearrangement.
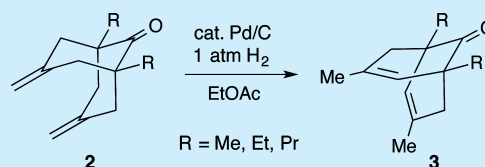
The isomerization of alkenes using catalytic amounts of transition metals and their complexes has been widely studied.[1] For example, allyl units bearing heteroatoms, e.g., allylic amines, alcohols, and ethers, can be easily converted to their propenyl isomers.[2] Allyl arenes can likewise be transformed into the alkylstyrene isomers.[3] One can also effect an equilibration between E and Z alkene isomers.[4] However, there has been little research on the isomerization of unfunctionalized alkenes. Of the few accounts reported, many use large transition-metal complexes, numerous additives, high temperatures, and long reaction times.[5] For the synthesis of rugulosone, **1** (Figure 1),[6] we required a simple protocol to
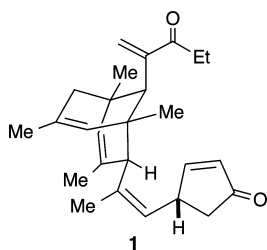

Figure 1. Structure of rugulosone.

prepare the bicyclo[3.3.1]nonadiene core and investigated the isomerization of a symmetric di(exo)methylene to the endocyclic diene. We tested this process on the simple analogue, 1,5-dimethyl-3,7-dimethylenebicyclo[3.3.1]nonan-9-one **2a**. The required dienone **2a** was prepared in one step by the tetraalkylation of 3-pentanone with 1-chloro-2-(chloromethyl)-2-propene. We report here the successful isomerization of this diene **2a** to the desired C_2-symmetric bicyclo[3.3.1]nonadienone **3a** and the isomerization of related analogues.

The double rearrangement of this substrate **2a** to the C_2 isomer **3a** rather than the C_s isomer **4a** (Scheme 1) would be required to give the natural product. We believed that **3a** would be more stable than **4a** due to the steric nonbonded interaction of the indicated hydrogens in **4a** (Figure 2). Initial attempts to directly isomerize diene **2a** with transition-metal catalysts such

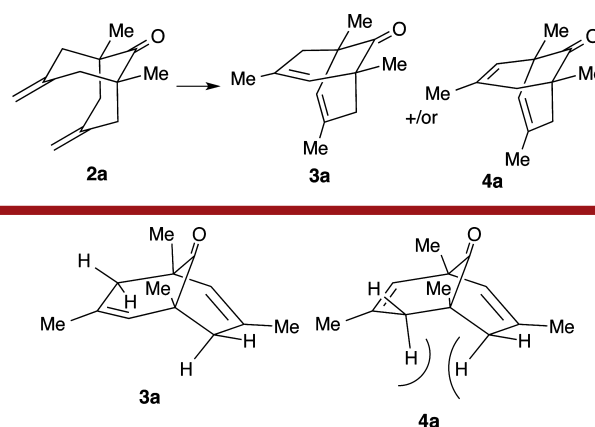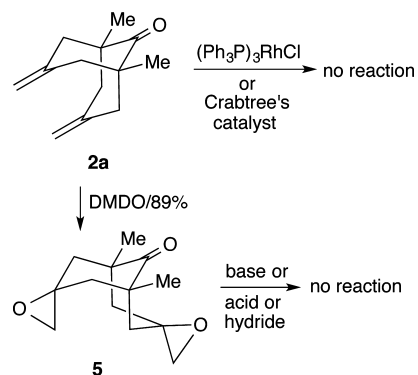**Scheme 1. Isomerization of 2a To Give 3a and/or 4a**

Figure 2. Structures of the C_2 and C_s dienes.

as Wilkinson's or Crabtree's catalyst failed to yield either **3a** or **4a**; only starting material was recovered (Scheme 2). The uniquely strained and/or hindered structure of the bicyclono-

**Scheme 2. Attempts To Isomerize 2a**

nane core may cause this lack of reactivity. Unable to directly isomerize the olefins, we examined a longer, more complicated process. Epoxidation of **2a** (DMDO, 23 °C, 3 h) afforded the diepoxide **5** in 89% yield. All attempts at acid- or base-promoted ring-opening of these epoxides to give allylic alcohols failed, as did attempts to prepare the tertiary alcohols through various hydride reductions.

The desired isomerization was, however, effected by the use of an activated palladium catalyst mixed with hydrogen gas. Thus, treatment of **2a** in methanol with 4 mol % of Pd/C under a balloon of hydrogen afforded the desired C_2 isomer **3a** along with the monoreduced isomerized product **6a** and the fully reduced material **7a** in a 68:28:4 ratio (by GCMS) (Scheme 3).

Scheme 3. Isomerization of 2a To Give 3a
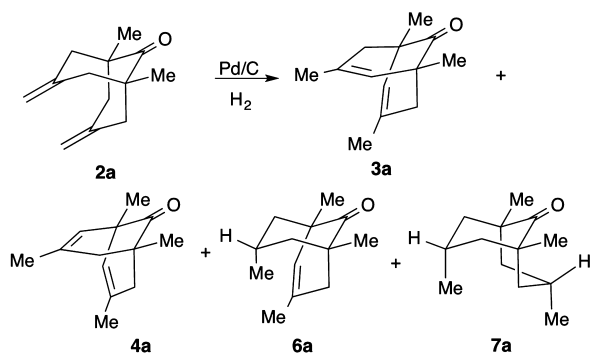
A number of control experiments were conducted to demonstrate that hydrogen was required for this isomerization. The use of an argon atmosphere instead of hydrogen afforded no isomerization. Pretreating the catalyst with hydrogen gas to activate the palladium and then purging the flask with argon gave no isomerization. The addition of excess cyclohexene (to remove all the H_2 gas) before the addition of **2a** was also unsuccessful. The use of ammonium formate (transfer hydrogenation) also produced the expected isomerization. Thus, it seems that the reaction requires a small amount of hydrogen to initiate the isomerization.[7]

We postulated that alkene isomerization might be favored over reduction if the hydrogenation pathway could be slowed down, perhaps by a change in the solvent, since solvent effects on hydrogenation rates have been well studied.[8] For that reason, various solvent systems were examined to see if solvent effects could improve the yield of isomerization (Table 1). Polar, protic solvents, such as methanol and 2-propanol, gave large amounts of the monoreduced product **6a** and some of the fully reduced material **7a**. Reaction in ethyl acetate gave the desired C_2 product **3a** along with the first observation of the formation of the C_s isomer **4a** and the monoreduced product

Table 1. Effect of Solvents on Conversion of 2a to 3a, 4a, 6a, and 7a

entry	solvent	time (h)	3a	4a	6a	7a	2a
1	MeOH	1	68	0	28	4	0
2	iPrOH	1	68	0	26	6	0
3	EtOAc	1	87	9	4	0	0
4	hexane	1	81	7	12	0	0
5	acetone	1	79	6	14	0	0
6	dioxane	1	64	6	11	0	19
7	THF	1	77	9	13	0	1

6a. Isomerization in other nonpolar solvents, e.g., hexane, gave similar results. Other aprotic polar solvents, e.g., acetone, dioxane and THF, also largely produced the desired C_2 product **3a** along with small amounts of the C_s isomer **4a** and the monoreduced compound **6a**.

We explored whether the isomerization to the C_2 isomer in great preference to the C_s isomer was general. The additional di(exo)methylene compounds, **2b–d**, were prepared from the corresponding substituted ketones and the bis(chloromethyl)-ethylene. Treatment of both **2b** and **2c** under the conditions described above, namely Pd/C under an atmosphere of hydrogen gas, afforded predominately the C_2 products **3b** and **3c** in preference to the possible C_s product (Scheme 4).

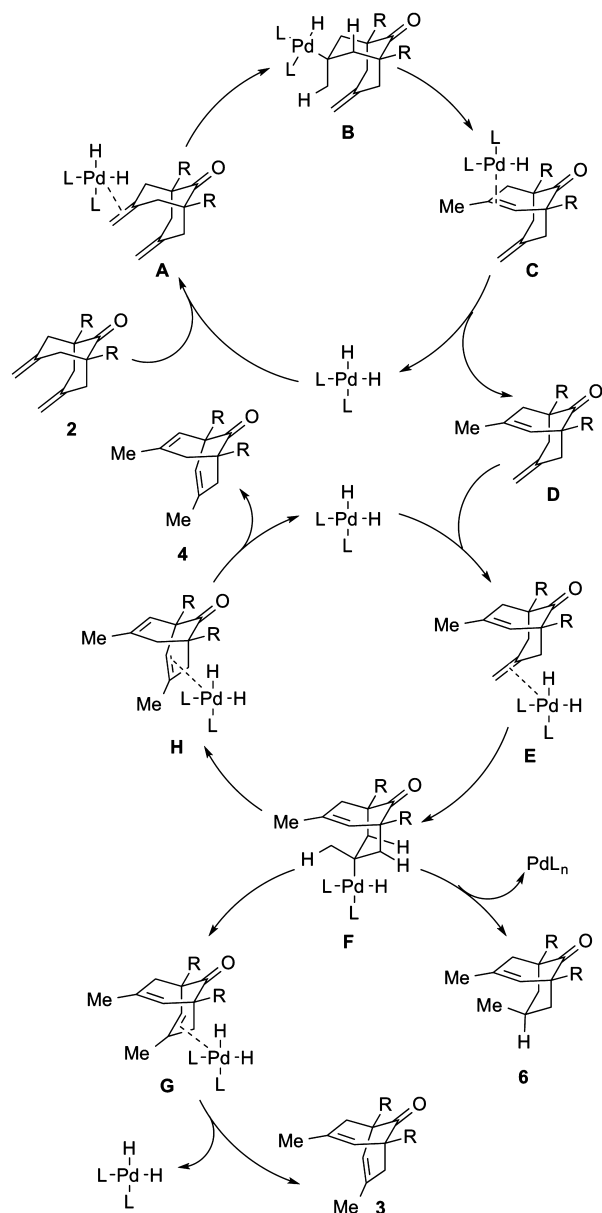**Scheme 4. Isomerization of Alkenes 2bc**
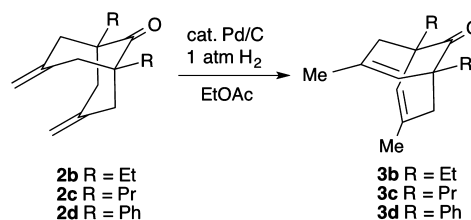
However, the diphenyl-substituted analogue **2d** gave only starting material under these conditions with no production of any isomeric or reduction products. Thus, this preference for the C_2 product **3** rather than the C_s product **4** occurs for all alkyl substituents at the bridgehead carbons.

The proposed mechanism is shown in Scheme 5. Coordination of the di(exo)methylene **2** with palladium to give **A**, hydride addition to form **B**, β-hydride elimination to afford **C**, and then decomplexation converts **2** to the monoisomerized product **D**, which has never been observed. The same type of process can convert **D**, via the intermediates **E–H**, to either the C_2 isomer **3** or the C_s isomer **4** and can interconvert these isomers as well. All processes are reversible, and the product ratio is most likely determined by thermodynamic stabilities.[9]

In order to establish the energies of each of the isomers, we calculated the structures and energies of reactants, the monoisomerized species, and the isomeric di-isomerized species with density functional theory. Using Gaussian 09,[10] optimizations were performed using B3LYP/6-31G(d),[11] followed by M06-2X/6-311+G(d,p) single-point calculations to account properly for dispersion effects.[12] The results are shown in Table 2. The parent unsubstituted system **2** (R = H) shows a 2.9 kcal/mol preference for the C_2 isomer over the C_s diene. All the trisubstituted alkenes were significantly more stable than the disubstituted alkene starting materials. Methyl and larger alkyl substituents at the bridgehead carbons led to a greater preference for the C_2 isomer. This is in good agreement with the fact that under all conditions the C_2 diene **3** is the predominant product.

We set out to investigate the source of the preference for the C_2 isomer. As mentioned before, the examination of molecular models revealed a possible unfavorable steric interaction involving the two allylic hydrogen atoms in **4a** as shown in Figure 2. Inspection of the optimized geometries reveals that, although the decrease in H---H distance correlates well with an increase in stability across the isomers (Figure 3), a 2.28 Å distance is not sufficient to conclude that the 3−4 kcal/mol thermodynamic preference is dominated by steric repulsion.

Scheme 5. Proposed Mechanism for the Isomerization of 2

Figure 3. Monoisomerized and C_2 and C_s bis-isomerized optimized structures. Free energies calculated using M06-2X/6-311+G(d,p)// B3LYP/6-31G(d) are relative to **2a**.

ring strain induced by nonbonding interactions as being another component of the energy difference. This slight rotation relieves some of the unfavorable eclipsing interactions and translates to an increase in the endo hydrogen distance.

In summary, the facile isomerization of the di(exo)methylene bicyclo[3.3.1]nonanone systems gives rise predominantly to the C_2 products rather than the possible C_s products. Theoretical calculations reveal that the origin of this preference stems from thermodynamics effects, involving transannular hydrogen–hydrogen interactions and ring strain induced by these interactions. Further calculations and the use of this procedure in the synthesis of rugulosone **1** are currently underway and will be reported in due course.

◼ ASSOCIATED CONTENT

ⓢ Supporting Information

Experimental procedures and proton and carbon NMR for all new compounds, plus the gas-phase geometries and total energies of the structures calculated using the Gaussian program. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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Table 2. Free Energy Calculations for Isomers[a]

R	exo (SM)	C_2	C_s	difference
H	0.0	−8.0	−5.1	2.9
Me	0.0	−7.1	−3.8	3.3
Et	0.0	−9.0	−5.2	3.8
Pr	0.0	−8.7	−4.6	4.1
Ph	0.0	−9.2	−6.4	2.8

[a]Gas-phase calculations were carried out using M06-2X/6-311+G-(d,p)//B3LYP/6-31G(d) and are quoted in kcal/mol.

Interestingly, a twisting of the bicyclo[3.3.1]nonadienone core in **3a**, which is not observed in the less stable **4a**, points toward
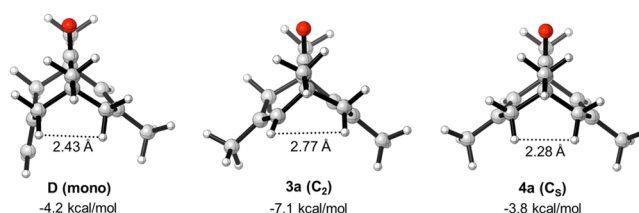
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