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Mechanism leading to the observed product of intramolecular aryl Diels–Alder reaction

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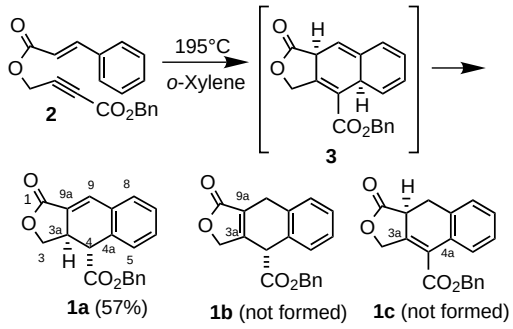
Abstract—A mechanistic investigation into the recently reported intramolecular aryl Diels–Alder reaction was carried out using deuterium labeling. These studies led to the conclusion that the initial Diels–Alder adduct is isomerized to a highly conjugated tetra-ene intermediate which undergoes a stereospecific suprafacial 1,5-dienyl hydrogen shift to give the observed product.

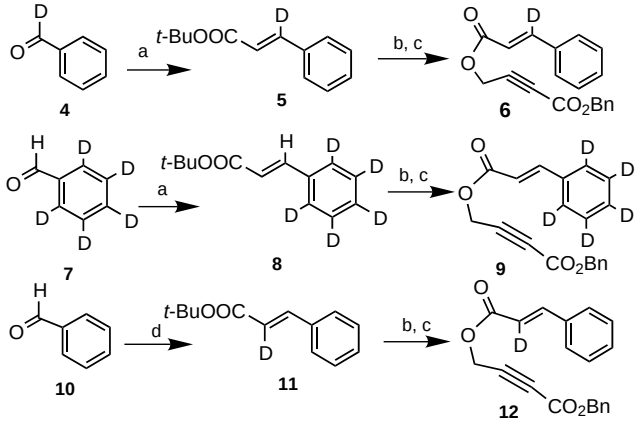
We have recently reported[1] a novel intramolecular aryl Diels–Alder reaction (IMDA) that leads to the stereospecific formation of $\Delta^{9,9a}$ dihydronaphthofuranone **1a** (Scheme 1).[2] The reaction is general to a variety of substrates, proceeds in good yields, and can be performed on a 100 g scale. In all cases, a single diastereomer of the product was isolated with exclusive presence of the double bond at the C_9–C_{9a} position. This remarkable diastereoselectivity evoked our curiosity into the mechanism of this reaction. Particularly noticeable was the absence of any of the isomeric products corresponding to structures **1b** or **1c**, although ab initio calculations[3] suggested an order of stability **1b**>**1c**>**1a**.

In this communication, we wish to report the results of mechanistic studies conducted on the intramolecular Diels–Alder reactions of propargyl cinnamates employing deuterium labeled precursors. These studies convincingly prove that the initial intramolecular Diels–Alder adduct **3** undergoes a double bond isomerization to give the intermediate **18** followed by a stereospecific 1,5-dienyl proton transfer to give the observed product **1a** (Scheme 4).



Scheme 1. Intramolecular aryl Diels–Alder reaction.

The deuterium labeled IMDA precursors were synthesized as shown in Scheme 2 in an overall yield ranging from 50 to 60%. Reaction of commercially available benzaldehyde-α-d_1 (**4**) with *tert*-butyl dimethylphosphonoacetate under basic conditions yielded the *tert*-butyl



Scheme 2. *Reagents and conditions*: (a) $(MeO)_2P(O)CH_2CO_2Bu$-*tert*, *n*-BuLi–hexane, THF, 0°C; (b) (i) TFA, CH_2Cl_2; (ii) $(COCl)_2$, DMF (cat.), CH_2Cl_2, rt; (c) Et_3N, $HOCH_2CCCO_2Bn$ (**13**), CH_2Cl_2, 0°C; (d) $(MeO)_2P(O)CD_2CO_2Bu$-*tert* (**14**),[5] *n*-BuLi–hexane, THF, 0°C.

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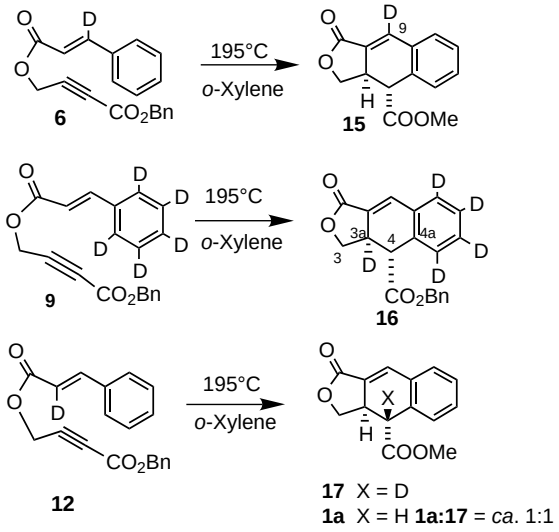
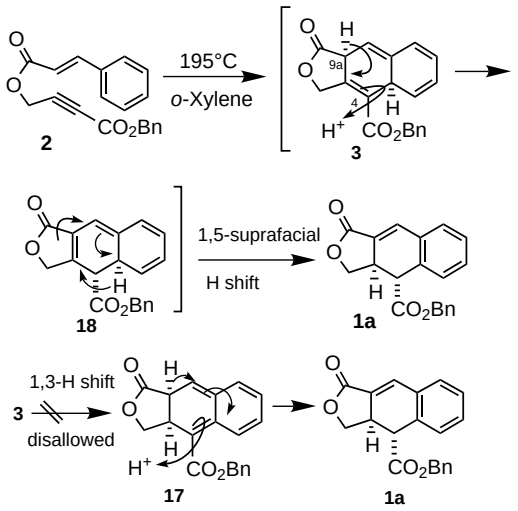
cinnamate **5** which was transformed to the Diels–Alder precursor **6** by acid mediated hydrolysis followed by esterification with propargylic alcohol **13**.[1] Similarly, the precursor **9**, labeled with deuterium in the benzene ring, was prepared from benzaldehyde-2,3,4,5,6-d_5 (**7**).[4] Using a similar sequence, the α-deuterated cinnamate precursor **12** was synthesized from benzaldehyde and deuterated phosphonate **14**.[5]

The results of the intramolecular aryl Diels–Alder reaction studies are shown in Scheme 3. Thermal cyclization of deuterium-labeled precursor **6** in *o*-xylene at 195°C gave tricyclic derivative **15** in 48% yield with complete retention of deuterium at C_9 as indicated by the proton NMR and mass spectral data. Cyclization of the d_5-labeled precursor **9** under similar conditions gave a single dihydronaphthofuranone **16** which retained all five deuterium atoms according to mass spectroscopic data and showed a remarkably simple ^{1}H NMR spectrum in the aliphatic region with a pair of doublets at 4.04 and 4.64 ppm corresponding to the C_3 protons and a singlet at 3.86 ppm corresponding to the C_4 benzylic methine proton (Scheme 3).[6] The multiplet corresponding to the C_{3a} methine proton at 3.60–3.70 ppm, present in the dihydronaphthofuranone **1a** (Scheme 1), was totally absent in the ^{1}H NMR spectrum[7] of tricyclic derivative **16**. Under identical conditions, cyclization of α-deutero-cinnamate **12** gave approximately a 1:1 mixture of tricyclic compounds **1a** and **17**, indicating partial incorporation of deuterium at C_4.

The following conclusions can be made based on the above observations. First, the total lack of deuterium exchange or scrambling for the cyclization of precursor **6** to the tricyclic product **15** (Scheme 3) rules out a sequential double bond isomerization of the initial Diels–Alder adduct **3** to **1a**, via the intermediates **1c** and **1b** (Scheme 1), that necessarily involves at least partial loss of deuterium label at C_9. The outcome of the cyclization of the d_5-labeled precursor **9** is more revealing. Only a single dihydronaphthofuranone



Scheme 3.

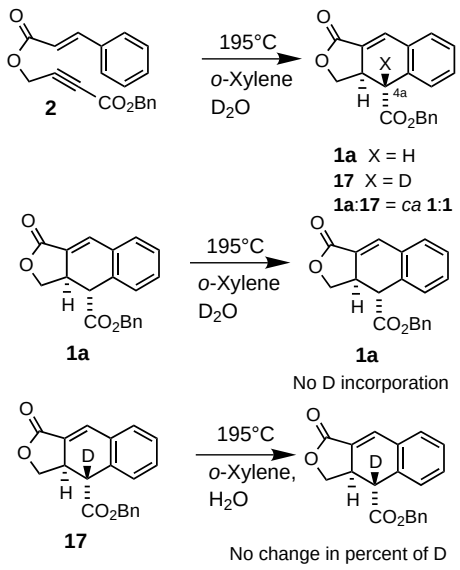


Scheme 4. Mechanism of intramolecular aryl Diels–Alder reaction.

product (**16**) was isolated and it contained complete incorporation of deuterium at C_{3a} which suggests a highly efficient intramolecular transfer of deuterium from C_{4a} to C_{3a}.

Based on the above observations, we propose the following mechanism outlined in Scheme 4 for the intramolecular aryl Diels–Alder reaction. The initial intramolecular Diels–Alder adduct **3** undergoes a double bond isomerization[7] to give the highly conjugated tetra-ene derivative **18** which subsequently undergoes a stereospecific 1,5-dienyl suprafacial proton shift[8] to give the observed product **1a**. Under these circumstances, one would expect a deuterium label at C_{9a} of intermediate **3** to be completely lost into the reaction medium and be partially incorporated at C_4. In fact, the intramolecular Diels–Alder cyclization of the α-deuterated cinnamate **12** further lends credence to this mechanism (Scheme 3). When the reaction is carried out in *o*-xylene, about 50% of the deuterium that was present α-to the carbonyl group of cinnamate **12** was incorporated at C_4. An alternative mechanism involving C_{4a}–C_{3a} suprafacial 1,3-hydrogen shift of intermediate **3** (Scheme 4) is ruled out since it is a symmetry-forbidden thermal process.[9] The highly stereospecific nature of deuterium transfer from C_{4a} to C_{3a} of intermediate **3** also rules out a diradical mechanism.

Although it is likely that the relative stereochemistry at C_4 of the final product **1a** is under thermodynamic control, C_4 axial protonation of the enolate of **3** (Scheme 4) should also yield the thermodynamically stable, equatorially substituted carboxylic ester. Cyclization of the unlabeled precursor **2** in the presence of trace amounts of deuterium oxide in xylene gave about 50% incorporation of deuterium at C_4 suggesting proton exchange between this center and the solvent during the reaction (Scheme 5). However, when cyclized product **1a** was subjected to identical reaction conditions in the presence of deuterium oxide, it did not undergo any deuterium exchange suggesting the thermodynamic stability of the equatorial carboxylic ester.



Scheme 5. External deuterium incorporation studies.

Additionally, when the C_4 deuterated tricyclic derivative **17** was subjected to the intramolecular Diels–Alder reaction conditions in the presence of trace amounts of water (Scheme 5), no change in the percentage of deuterium at C_4 was noted, which further corroborated the stability of the equatorially oriented carboxylic ester at C_4.

In summary, we have established a plausible mechanism of the intramolecular aryl Diels–Alder reaction that accounts for the observed product, using deuterium labeling. The initial cycloadduct **3** undergoes a double bond isomerization to give the tetra-ene intermediate **18** which undergoes a stereospecific 1,5-suprafacial dienyl hydrogen shift to give dihydronaphthofuranone **1a** (Scheme 4).

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3. Ab initio calculations using full DF(B3LYP) optimization were carried out on the *tert*-butyl esters corresponding to compounds **1a**, **1b** and **1c**, giving heats of formation of −601741.55403, −601743.25662 and −601741.66614 kcal/mol, respectively. According to this calculation, the *tert*-butyl ester corresponding to **1b** is 1.70259 kcal/mol more stable than *tert*-butyl ester corresponding to **1a**, and the *tert*-butyl ester corresponding to **1c** is 0.11211 kcal/mol more stable than the *tert*-butyl ester corresponding to **1a**. The choice of *tert*-butyl ester was made to reduce calculation time. Similar calculations performed on the corresponding ethyl esters also showed the same trend of relative stability.
4. Although only the *ortho* protons of cinnamate **2** (Scheme 1) are of interest from a mechanistic standpoint, we used 2,3,4,5,6-d_5 labeled benzaldehyde **7** due to its commercial availability.
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6. Physical data **1a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.60–3.70 (m, 1H), 3.86 (d, J=15.0 Hz, 1H), 4.04 (t, J=9.0 Hz, 1H), 4.64 (t, J=9.0 Hz, 1H), 5.28 (d, J=12.0 Hz, 1H), 5.38 (d, J=12.0 Hz, 1H), 7.16–7.21 (m, 2H), 7.29–7.45 (m, 8H); IR (neat) 1785, 1735 cm^{-1}; MS (ESI) m/e 321 (M+H)$^+$. **9**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.93 (s, 2H), 5.22 (s, 2H), 6.44 (d, J=16.0 Hz, 1H), 7.38 (m, 5H), 7.75 (d, J=16.0 Hz, 1H); HRMS (FAB) calcd for $C_{20}H_{12}D_5O_4$ (M+H)$^+$ m/e 326.1441, found m/e 326.1442. **16**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86 (s, 1H), 4.04 (d, J=9.0 Hz, 1H), 4.64 (d, J=9.0 Hz, 1H), 5.37 (d, J=12.1 Hz, 1H), 5.43 (d, J=12.1 Hz, 1H), 7.49 (m, 6H). HRMS (FAB) calcd for $C_{20}H_{12}D_5O_4$ (M+H)$^+$ m/e 326.1441, found m/e 326.1440.
7. The double bond isomerization which occurs prior to aromatization is likely to be facilitated by the high acidity of C_{9a} proton and the highly conjugated nature of the resultant tetra-ene intermediate **18**.
8. (a) Jiao, H.; Schleyer, P. v. R. *J. Chem. Soc., Faraday Trans*. **1994**, *90*, 1559; (b) Doering, W. v. E.; Roth, W. R.; Breuckmann, R.; Figge, L.; Lennartz, H.-W.; Fessner, W. D.; Prinzbach, H. *Chem. Ber.-Recueil* **1998**, *121*, 1; (c) Jensen, F.; Houk, K. N. *J. Am. Chem. Soc*. **1987**, *109*, 3139.
9. (a) Berson, J. A. *Acc. Chem. Res*. **1972**, *5*, 406; (b) Woodward, R. B.; Hoffman, R. *The Conservation of Orbital Symmetry*; Academic Press: New York, NY, 1970.