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A mechanistic study on the intramolecular ionic Diels–Alder reaction of 2-methyl-3,9,11-tridecatriene-2-ol and 2,11-dimethyl-1,3,9,11-dodecatetraene

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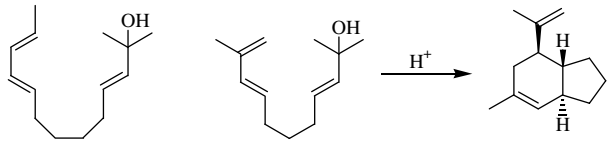
Abstract—Intramolecular ionic Diels–Alder reaction of 2-methyl-3,9,11-tridecatriene-2-ol (**1**) was studied under acidic conditions. Treatment of 2-methyl-3,9,11-tridecatriene-2-ol (**1**) with trifluoromethanesulfonic acid yielded 7-methyl-8-isopropenyl-1,2,3,4,4a*R**,7*R**,8*R**,8a*S**-octahydronaphthalene (**4**) and (1*Z*)-1-((*E*)-but-2-enylidene)-2-(2-methylpropenyl)cyclohexane (**5**) through regioselective intramolecular ionic Diels–Alder reaction. The reaction appeared to proceed partly through a stepwise mechanism involving a carbocation intermediate. However, a concerted pathway rather than a stepwise one is suggested to be involved in the acid-catalyzed intramolecular Diels–Alder reaction of 2,11-dimethyl-1,3,9,11-dodecatetraene (**13**).

The intramolecular Diels–Alder reaction is one of the most powerful methods for the synthesis of polycyclic compounds including natural products.[1] Particularly, ionic Diels–Alder reactions are shown to be synthetically useful reactions due to their increased reactivity and excellent stereoselectivity.[2] A comprehensive mechanistic study on the reactions of allyl cations with 1,3-dienes was carried out by Woodward and Hoffmann.[3] Gassman investigated extensively the scope of the intramolecular ionic Diels–Alder reaction[4] and discussed briefly whether the additions of dienes to allyl cations are concerted or stepwise. They synthesized 15 tetraenes[4d] as precursors of allyl cations and treated them with an acid to study the mechanistic pathway of the intramolecular ionic Diels–Alder reactions.[5] In most cases, cycloadducts were produced apparently stemming from concerted processes, while stepwise processes might have been favored in some cases. A similar treatment of a dilute solution of triene-2-ol **2** with 5 mol % of trifluoromethanesulfonic acid at −25 °C for 20 min gave only product **3** stereoselectively in a high yield via the concerted process (Fig. 1).[4b]



1 **2** **3**

Figure 1.

Based upon these observations, we were interested in the mechanism of the intramolecular ionic Diels–Alder reaction of trienol **1**, which was different from **2** in the chain length of the tethering group and the position of methyl group at the diene unit. A bicyclo[4.4.0]decane system, instead of a bicyclo[4.3.0]nonane system, was expected from trienol **1**. Herein we report on the mechanistic studies based upon the intramolecular Diels–Alder reaction of trienol **1** using trifluoromethanesulfonic acid at various temperatures.

Trienol **1** was synthesized according to a literature procedure.[6] Treatment of trienol **1** with trifluoromethanesulfonic acid at various reaction temperatures gave a mixture of bicyclo[4.4.0]decyl ring product **4** and monocyclic triene **5** (Table 1).[7] The distribution of the products was significantly sensitive to the reaction temperature. The reaction of trienol **1** with 20 mol % of trifluoromethanesulfonic acid at 12 °C for 5 min afforded **4** and

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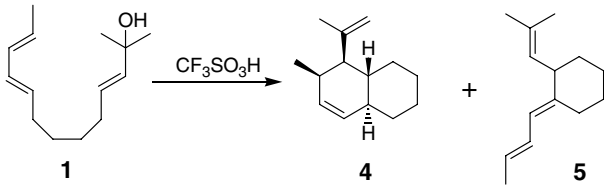
Table 1. Intramolecular ionic Diels–Alder reaction of trienol **1**



Entry	CF_3SO_3H[a] (mol %)	Temperature (°C)	Time (min)	Yields[b] (%)	
				4	**5**
1	20	12	5	38	21
2	20	0	5	35	45
3	20	−30	5	20	49
4	20	−78	5	13	36

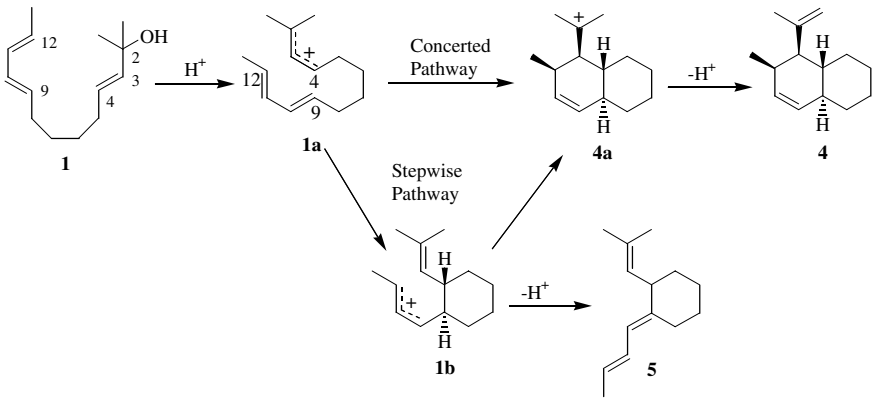
[a] 0.05 M of CF_3SO_3H in dry CH_2Cl_2 was used.
[b] Isolated yields after chromatography based on starting trienol **1**.

5 in 38% and 21% yields, respectively (Table 1, entry 1). The structure of compound **4** was assigned to the expected trans-fused cycloadducts by using NOESY experiments.[8] A similar treatment of trienol **1** with the same amount of trifluoromethanesulfonic acid at 0 °C for 5 min afforded **4** and **5** in 35% and 45% yields, respectively (Table 1, entry 2). Under these conditions, the combined yield of **4** and **5** was 80%. At −30 °C, **4** and **5** were produced in a 69% combined yield with a 20:49 ratio after 5 min (Table 1, entry 3). However, the yields of both **4** and **5** were noticeably decreased at −78 °C (Table 1, entries 4 and 5).

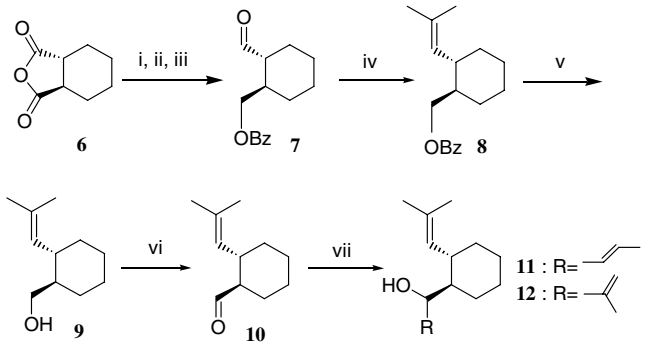
On the basis of these results, we proposed a plausible mechanistic pathway (Scheme 1). Formation of allyl cation **1a** through protonation at the hydroxyl group followed by the exclusive formal cycloaddition involving the C3–C4 portion of the allyl cation and the diene would give a cation **4a** via a concerted process. Deprotonation of **4a** affords Diels–Alder product **4**. According to Roush's hypothesis,[9] this reaction would proceed through an endo transition state and produce the trans-fused product **4**. Alternatively, allyl cation **1a** is delocalized between the tertiary and secondary sites and is cyclized across the C4–C9 to form allyl cation **1b**, which upon deprotonation would give a monocyclic triene **5**. On the other hand, allyl cation **1b** would also cyclize across the C3–C12 bond to give **4a**.

Thus, the formation of **4** from **1**, which was the formal intramolecular ionic Diels–Alder product, appears to have resulted from a stepwise process. However, the possibility of a concerted process could not be eliminated. On the assumption that the reaction proceeds through a stepwise pathway, intermediate **1b** was of particular interest to us. In order to establish that allyl cation **1b** was an intermediate in the formation of cycloadducts **4** and **5**, we prepared 1-(2-(2-methyl-1-propenyl)cyclohexyl)-2-buten-1-ol (**11**) (Scheme 2) as a precursor for intermediate **1b**. The synthesis of **11** began with the reduction of *trans*-1,2-cyclohexanedicarboxylic anhydride (±)-**6**. Synthesis of alcohol **9** was accomplished through a series of reactions including Wittig reaction of aldehyde **7**[10] and removal of the benzoyl group from **8**. Swern oxidation of **9** led to aldehyde **10**, which was treated with 1- or 2-propenyl Grignard reagents to yield precursors **11** and **12**, respectively.[11]

Treatment of **11** with 10 mol % of trifluoromethanesulfonic acid at 0 °C for 5 min gave **4** and **5** in 32% and 46% yields, respectively. Thus, the same products as those obtained from the reaction with trienol **1** (Table 1) were obtained in a similar ratio. When the amount of trifluoromethanesulfonic acid was increased to 20 mol % under otherwise the same reaction conditions, the yields of **4** and **5** were in 30% and 35%, respectively. When **11** was treated with 50 mol % of trifluoromethanesulfonic

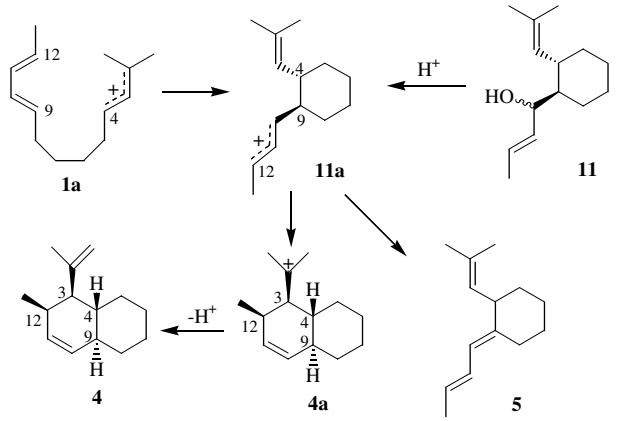


Scheme 1.



Scheme 2. Reagents and conditions: (i) LAH, THF, reflux, 2 h, 93%; (ii) NaH, benzoyl chloride, THF, 0 °C, 30 min, 66%; (iii) DMSO, oxalyl choride, CH_2Cl_2, −60 °C, 30 min, 76%; (iv) *n*-BuLi, isopropylidenetriphenylphosphorane, C_6H_6, 0 °C, 1.5 h, 80%; (v) NaOH, MeOH, H_2O, 20 h, 81%; (vi) DMSO, oxalyl choride, CH_2Cl_2, −60 °C, 30 min, 90%; (vii) 1-propenylmagnesium bromide, THF, −20 °C, 30 min.

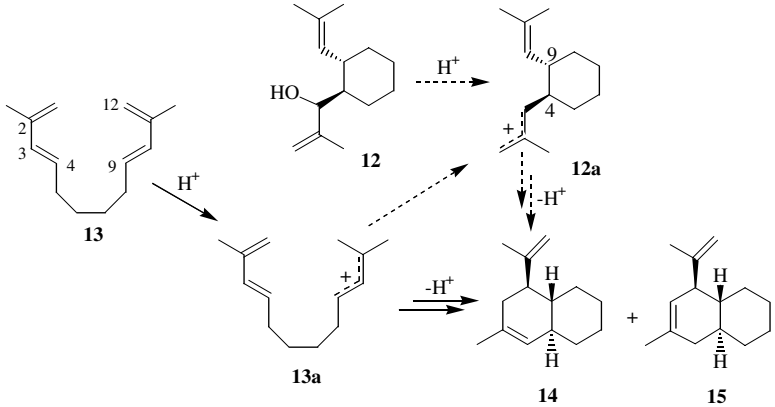
acid at −30 °C for 5 min, **5** was obtained in 12% yield and unreacted starting compound **11** was recovered in an 82% yield. An attempt of the reaction at −78 °C did not promote any reaction and **11** was recovered in a 95% yield. These results suggest that allyl cation **11a** (**1b**, Scheme 1) may serve as a precursor of cycloadduct **4** outlined in Scheme 3. Thus, it is assumed that the trans-fused Diels–Alder product **4** arises at least in part from a stepwise cyclization mechanism that involves an intermediate **1b**. However, the yields and ratios of the products depend strongly on the concentration of the acid and reaction temperature.



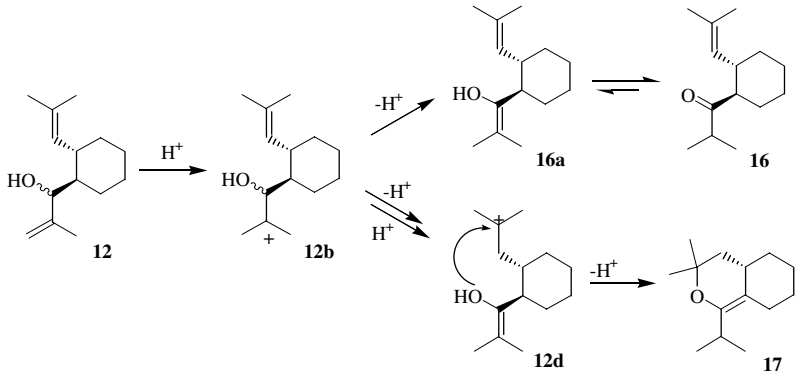
Scheme 3.

Gassman reported that the reaction of dodecatetraene **13**[4d] with trifluoromethanesulfonic acid afforded two major trans-fused bicyclo[4.4.0] products **14** and **15** (Scheme 4). Protonation at the C1 of **13** gives an allyl cation **13a**, which is quite similar to the allyl cation generated from the deprotonation of trienol **1** (Scheme 1). They differ from each other in the position of the methyl group on the diene unit. Accordingly, we became interested in exploring the detailed mechanistic pathway in the intramolecular ionic Diels–Alder reactions of tetraene **13**.

In order to establish whether a cationic intermediate **12a** (Scheme 4) is involved in the intramolecular ionic Diels–Alder reaction of tetraene **13**, we prepared 2-methyl-1-(2-(2-methyl-1-propenyl)cyclohexyl)-2-propen-1-ol (**12**) (Scheme 2) as a precursor of an allyl cation **12a**. Treatment of **12** with trifluoromethanesulfonic acid gave only two major products, **16** and **17** (Scheme 5).[12] Surprisingly, the formation of Diels–Alder products **14** and **15** was not observed. This result indicates that the formation of allyl cation **12a**,[13] which would be cyclized to **14** and **15**, is energetically more unfavorable than the protonation at the olefin of allylic alcohol **12** to form a tertiary cation **12b** (Scheme 5). This tertiary cation might be readily transformed to an enol and be rearranged to ketone **16** through tautomerism[14] or cyclization[15] to bicycle **17** (Scheme 5). Thus, it is highly plausible that the reaction of tetraene **13** has no intermediate and it may prefer to proceed through a concerted pathway rather than a stepwise one. The ratio of **16** and **17** strongly depended on the reaction conditions. When **12** was treated with 10 mol % trifluoromethanesulfonic acid at 0 °C for 10 min, only **16** was obtained in a 37% yield. Under strong acidic conditions, the enol system undergoes a cyclization and affords bicycle product **17**. Treatment with 50 mol % trifluoromethanesulfonic acid at 0 °C for 10 min afforded **16** and **17**[16] in 3% and 30% yields, respectively, and polymer as major products.



Scheme 4.



Scheme 5.

In conclusion, we have demonstrated that intramolecular ionic Diels–Alder reaction of trienol **1** proceeds, at least in part, via a stepwise mechanism through intermediate **1a** to give Diels–Alder adducts **4** and **5**. The yields and distribution of products in the Diels–Alder reactions of **1** were strongly dependent upon the reaction conditions. In contrast, we have not been able to obtain experimental evidence leading to the stepwise mechanism for the cyclization of tetraene **13**. Moreover, allyl cation precursor **12** did not produce the same products as tetraene **13** did. Instead, it produced new products **16** and **17** under the same acidic conditions. Thus, we have characterized the mechanism of these intramolecular ionic Diels–Alder reactions as a concerted process where the asynchronicity in the C–C bond-formation depends on the position of electron-releasing methyl group on the diene unit.

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.11.144.

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7. *Analytical data for compound* **4**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.60 (d, $J = 9.84$ Hz, 1H), 5.36 (d, $J = 9.84$ Hz, 1H), 4.93 (s, 1H), 4.58 (s, 1H), 2.35–2.25 (m, 1H), 2.18 (dd, $J = 11.48$, 5.85 Hz, 1H), 2.05–1.95 (d, $J = 12.9$ Hz, 1H), 1.80–1.65 (m, 4H), 1.70 (dd, $J = 1.32$, 0.85 Hz, 3H), 1.35–1.20 (m, 3H), 1.15–1.05 (m, 1H), 0.85 (d, $J = 7.15$ Hz, 3H), 0.80–0.70 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.0, 132.5, 130.7, 112.3, 50.5, 43.7, 37.5, 33.6, 33.4, 30.2, 27.0, 26.9, 23.2, 17.8; HRMS calcd for $C_{14}H_{22}$ (M^+): 190.1721, found: 190.1718. *Analytical data for compound* **5**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.33 (ddt, $J = 1.66$, 10.86, 14.67 Hz, 1H), 5.75 (d, $J = 8.83$ Hz, 1H), 5.62 (dq, $J = 14.78$, 6.8 Hz, 1H), 5.17 (d, $J = 8.83$ Hz, 1H), 2.88 (s, 1H), 2.66 (dt, $J = 13.75$, 4.92 Hz, 1H), 1.97 (t, 1H), 1.76 (d, $J = 6.95$ Hz, 3H), 1.75 (s, 3H), 1.85–1.65 (m, 2H), 1.58 (s, 3H), 1.60–1.20 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.4, 131.6, 127.4, 127.1, 126.8, 120.7, 43.4, 35.2, 28.6, 27.7, 25.9, 25.4, 18.3, 17.9; HRMS calcd for $C_{14}H_{22}$ (M^+): 190.1721, found: 190.1726.
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11. *Analytical data for compound* **11**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.60 (d, $J = 9.84$ Hz, 1H), 5.36 (d, $J = 9.84$ Hz, 1H), 4.93 (s, 1H), 4.58 (s, 1H), 2.35–2.25 (m, 1H), 2.18 (dd, $J = 11.48$, 5.85 Hz, 1H), 2.05–1.95 (d, $J = 12.9$ Hz, 1H), 1.80–1.65 (m, 4H), 1.70 (dd, $J = 1.32$, 0.85 Hz, 3H), 1.35–1.20 (m, 3H), 1.15–1.05 (m, 1H), 0.85 (d, $J = 7.15$ Hz, 3H),

0.80–0.70 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.0, 132.5, 130.7, 112.3, 50.5, 43.7, 37.5, 33.6, 33.4, 30.2, 27.0, 26.9, 23.2, 17.8; HRMS calcd for $C_{14}H_{24}O$ (M^+): 208.1827, found: 208.1819.

Analytical data for compound **12**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.96 (s, 1H), 4.89 (d, $J = 9.74$ Hz, 1H), 4.87 (d, $J = 1.44$ Hz, 1H), 4.12 (d, $J = 2.17$ Hz, 1H), 2.33 (qd, $J = 10.56$, 3.62 Hz, 1H), 1.78–1.73 (m, 1H), 1.70 (s, 3H), 1.67 (s, 3H), 1.64 (s, 3H), 1.69–1.61 (m, 2H), 1.49–1.46 (m, 1H), 1.42 (d, $J = 4.97$ Hz, 1H), 1.29–1.03 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 147, 131.4, 129.5, 108.9, 74.5, 44.4, 38.5, 33.8, 26.2, 26.0, 25.9, 23.1, 20.1, 18; HRMS calcd for $C_{14}H_{24}O$ (M^+): 208.1827, found: 208.1840.

12. On the basis of 1D- and 2D NMR spectra and mass spectra, it was assigned to **16** and **17**. *Analytical data for compound* **16**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.73 (dd, $J = 8.54$, 0.96 Hz, 1H), 2.50 (sep, $J = 6.91$ Hz, 1H), 2.37 (qd, $J = 10.6$, 3.24 Hz, 1H), 2.32 (qd, $J = 11.06$, 3.06 Hz, 1H), 1.73–1.50 (m, 2H), 1.54 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 218.1, 131.5, 128.7, 54.8, 41.7, 39.4, 32.9, 29.6, 26.0, 25.7, 25.6, 18.2, 18.1, 17.7; HRMS calcd for $C_{14}H_{24}O$ (M^+): 208.1827, found: 208.1841.

Analytical data for compound **17**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.76 (sep, $J = 7$ Hz, 1H), 2.51 (d, $J = 13.8$ Hz, 1H), 1.90 (m, 1H), 1.78–1.61 (m, 4H), 1.31–1.26 (m, 2H), 1.21 (s, 3H), 1.19–1.06 (m, 2H), 1.05 (s, 3H), 1.00 (d, $J = 6.85$ Hz, 3H), 0.94 (qd, $J = 12.4$, 2.62 Hz, 1H) 0.91 (d, $J = 6.78$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 147.9, 105.8, 71.3, 42.7, 34.5, 32.1, 29.7, 27.5, 27.4, 26.3, 23.3, 20.2, 20.1, 17.8; HRMS calcd for $C_{14}H_{24}O$ (M^+): 208.1827, found: 208.1840.

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16. Treatment of ketone **16** with 50 mol % trifluoromethanesulfonic acid at 0 °C gave also **17** in a 35% yield and it was characterized by ^{1}H, ^{13}C, 2D COSY, HSQC, and HMBC NMR spectra.