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Unexpected epimerization and stereochemistry revision of IMDA adducts from sorbate-related 1,3,8-nonatrienes

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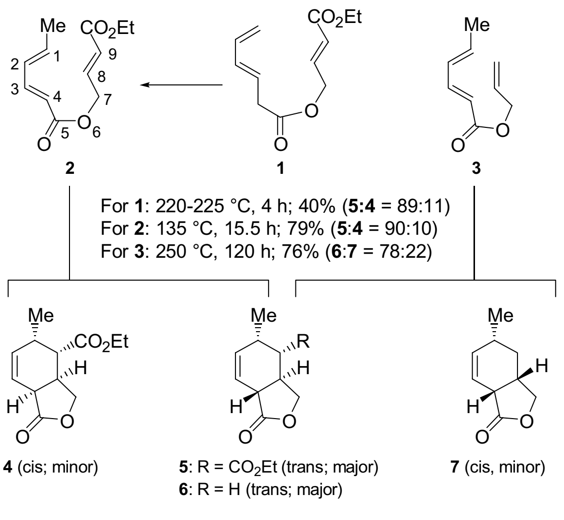
Abstract—Intramolecular Diels–Alder (IMDA) reaction of two sorbate-related 1,3,8-nonatrienes has been investigated in MeCN at 180 °C for 1.5 h under controlled microwave heating. On checking the crude product mixture before purification, partial epimerization of the major adduct was found during the reaction. After column chromatographic purification over silica gel, only two cis adducts were obtained and their structures have been thoroughly established by X-ray crystallographic analysis. It is concluded that the putative major trans adduct predicted by the IMDA reaction mechanism undergoes facile epimerization at high temperature or in the presence of silica gel. Structural revision on the adducts has been made.

Intramolecular Diels–Alder (IMDA) cycloaddition has enjoyed numerous applications in assembling polycyclic molecular architectures, many of which are associated with natural products.[1] During a study on synthesis of cis bicyclic δ-lactones related to vernolepin, Boeckman and Demko reported formation of the bicyclic γ-butyrolactones **4** and **5** in ca. 40% combined yield when the (*E*)-3,5-hexadienate-derived triene **1** was heated at 220–250 °C for 4 h (Scheme 1).[2a] The same adducts were produced from the sorbate-derived 1,3,8-nonatriene **2** at 135 °C for 15.5 h in 79% combined yield. The major adduct was reported to have a melting point of 62–64 °C. From a related IMDA reaction of allyl sorbate **3**, Martin and co-workers prepared the γ-butyrolactones **6** and **7** in 76% combined yield by heating at 250 °C for 120 h.[2b] In both studies, the major adducts **5** and **6** were assigned the same trans bicyclic skeleton but the proposed stereochemistry for the minor cis adducts is different.[2] Paddon-Row and Sherburn[3] used DFT calculations in studies on stereoselectivity of IMDA reactions of penta-1,3-dienyl acrylates and found that trans adducts were generally favored for pentadienyl maleates and fumarates (structurally similar to **2** by relocating the ester carbonyl from C5 to C7).[4] The ester tether is found to orient toward exo direction in trans transition state (*trans*-TS) leading to trans adduct while in *cis*-TS is found to point toward endo position leading to cis adduct.[3] One cause in favor of *trans*-TS is the reduction



Scheme 1. The known IMDA reactions of sorbate-derived 1,3,8-nonatrienes **2** and **3** and originally assigned adducts **4**–**7**. Structures **4** and **5** are incorrectly assigned according to this work.

Keywords: Intramolecular Diels–Alder reaction; Isomerization; Lactone; Microwave; Sorbate; Stereochemistry.

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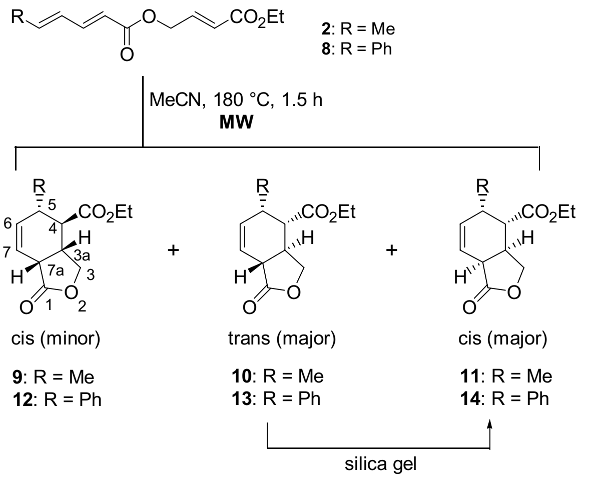
of strain developed in the tether-containing ring as the consequence of twist-mode asynchronicity associated with bond formation in TS.[4,5] If one assumes that a similar factor is playing in the IMDA reaction of sorbate-derived 1,3,8-nonatrienes such as **2** and **3**, the trans adducts **5** and **6** are predicted as the major stereoisomers according to the *trans*-TS and the cis adduct **7** is the minor adduct formed from less favored *cis*-TS. However, structure **4** seems not consistent with the common 'concert' IMDA reaction TS. As a continuation of our studies on microwave-assisted Wittig reaction,[6] tandem Wittig–IMDA reaction,[4] and other heterocycle synthesis,[7] we had an opportunity to examine microwave-assisted IMDA reaction of sorbate-related 1,3,8-nonatrienes. This class of substrates, except for **2**[2a] and **3**,[2b] has not been described in the literature. We report here on an unexpected epimerization of the major adduct and revision of stereochemistry of the isolated adducts on the basis of X-ray crystal structural analysis.

First we repeated the IMDA reaction of the known sorbate **2**[2a] as shown in Scheme 2. The reaction was carried out in a closed pressurized process vial in MeCN at 180 °C for 1.5 h under controlled microwave heating.[8,9] In our previous study on IMDA reaction of pentadienyl fumarates, nearly the same results were obtained for the reaction in MeCN and PhMe.[4] The crude reaction products were checked for diastereomer ratio by ^{1}H NMR spectroscopy. Three sets of doublet signals were found for C5–Me and they are assigned for the bicyclic γ-butyrolactones **9**, **10**, and **11** (Fig. 1a) on the basis of the finding described below. The crude products, a 14:64:22 mixture of **9**:**10**:**11**, upon treating with silica gel in EtOAc–petroleum ether at room temperature for over night, were converted into a 13:87 mixture of **9** and **11** (Fig. 1b). The results clearly indicate that epimerization of **10** into **11** occurred during the IMDA reaction albeit to a limited degree. The process was facilitated by silica gel so that **10** was completely converted into **11** even at room temperature. It was confirmed again when the crude product mixture of **2** was subjected to column chromatographic purification, only **9**[10] and **11**[11] were isolated in 12% and 67% yields, respectively.



Scheme 2. Microwave-assisted IMDA of **2** and **8** and epimerization of trans adducts **10** and **13** into cis isomers **11** and **14** with silica gel.

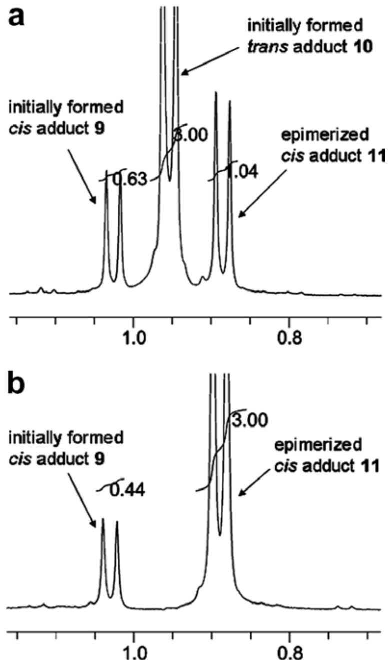


Figure 1. Partial ^{1}H NMR spectra of crude reaction mixture of **2** before (a) and after (b) treating with silica gel.

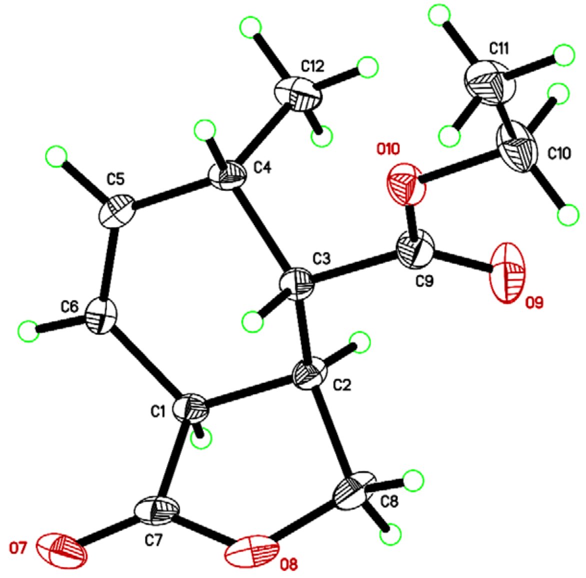


Figure 2. X-ray crystal structure of **11**.

The melting point (60–62 °C) and ^{1}H NMR data of **11** are consistent with those reported for **5**. In order to resolve the discrepancy on the structure of **11**, an X-ray crystal structural analysis was performed. As depicted in Figure 2, **11** is a cis-fused bicyclic γ-butyrolactone.[12] Interestingly, **11** is the structure proposed for the minor adduct **4** in Boeckman and Demko's work.[2a] We found that the ^{1}H NMR data of **4** are consistent with those of **9**. Because the melting point of **9** is 38–40 °C, it's not easy to get suitable quality of single crystals for X-ray

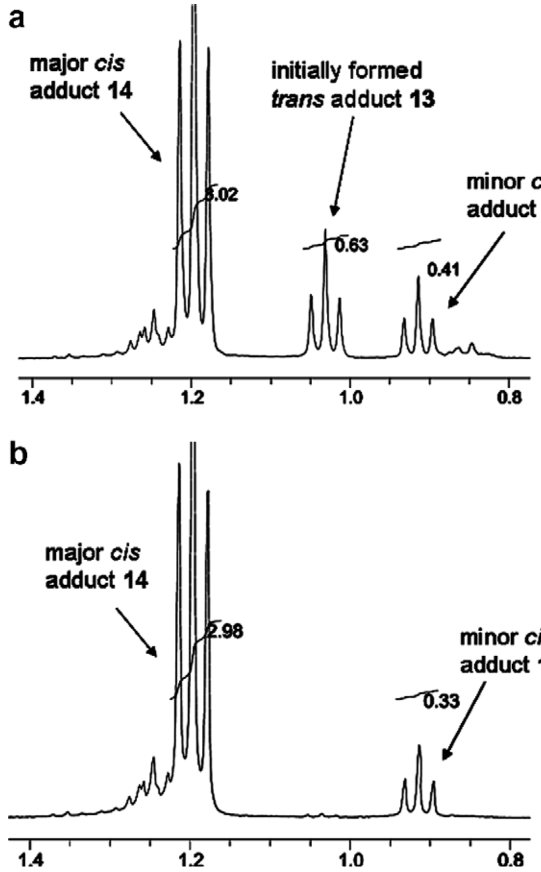


Figure 3. Partial ^{1}H NMR spectra of crude reaction mixture of **8** before (a) and after (b) treating with silica gel.

crystallographic study. We turned our attention to the C5–Ph-substituted analogs **12** and **14** (Scheme 2).

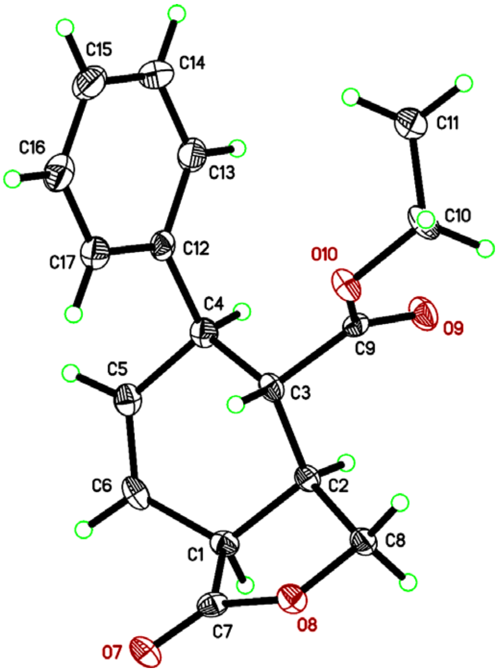


Figure 4. X-ray crystal structure of **12**.

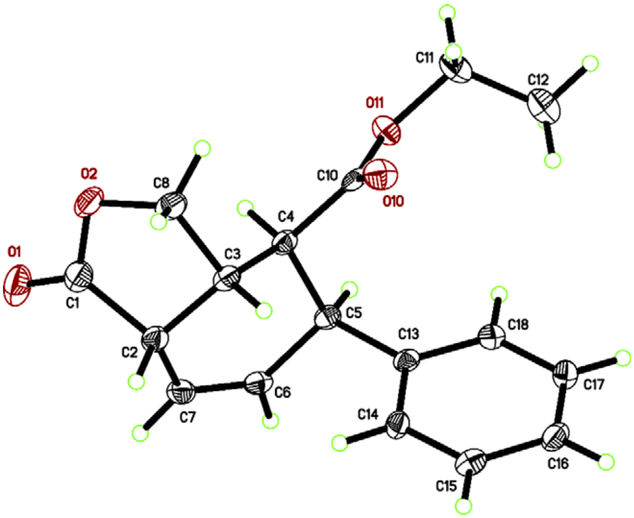


Figure 5. X-ray crystal structure of **14**.

The IMDA reaction of **8** was carried out in a similar manner as described for **2** and the ^{1}H NMR spectra of the crude product mixture before and after treatment with silica gel are shown in Figure 3. In Figure 3a, three sets of triplet signals are identified for the methyl group in the ethyl ester moiety of **12**, **13**, and **14** in a ratio of 10:16:74. It is indicated that the initially formed **13** largely epimerized to **14** during the reaction. After treatment with silica gel, **13** was completely converted into **14**, resulting in a mixture of **12** and **14** in a ratio of 10:90 (Fig. 3b). Pure compounds **12**[13] and **14**[14] were isolated in 10% and 81% yields, respectively. Fortunately, we obtained single crystals for both compounds and determined their structures by X-ray crystal structural analysis.[12] The structures **12** and **14** as depicted in Figures 4 and 5 are all cis-fused bicyclic skeletons. According to the similarity that both **9** and **12** did not undergo epimerization, we suggest that **9** should have the cis-bicyclic structure shown in Scheme 2. According to the TS proposed for the IMDA reaction of the closely related pentadienyl fumatates,[3a] the major adducts formed from **2** and **8** should be the *trans*-**10** and *trans*-**13**, which epimerized to the thermodynamically more stable cis isomers presumably through the enol form of the lactone. Presence of the double bond at C6–C7 is a prerequisite for epimerization because the related γ-butyrolactones generated from pentadienyl fumarates do not undergo epimerization at α-position of the carbonyl group.[4]

In summary, we have observed unexpected epimerization of the major adduct formed from IMDA reaction of the sorbate-related 1,3,8-nonatrienes and determined the structures of both major and minor adducts by X-ray crystal structural analysis. The isolated adducts after column chromatographic separation are all cis-bicyclic γ-butyrolactones, which are complementary to the trans-selective IMDA reaction of pentadienyl-derived 1,3,8-nonatrienes[4] and offer different stereochemical diversity. Our results revise the wrong structures reported in literature.[2a] Further study on the scope and application of the IMDA reaction of sorbate-related 1,3,8-nonatrienes is in progress.

Acknowledgments

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9. All microwave-assisted reactions were carried out on an Emrys creator from Personal Chemistry AB (now under Biotage AB, Uppsala, Sweden) with temperature measured by an IR sensor. The microwave-assisted reaction time is the hold time at the final temperature. Representative procedure: To a 10-mL pressurized process vial was added 1,3,8-nonatriene **2** or **8** (0.40 mmol) in CH_3CN (4 mL). The loaded vial was then sealed with a cap containing a silicon septum, and put into the microwave cavity and heated at 180 °C for 1.5 h. The reaction mixture was evaporated under reduced pressure and the crude residue was analyzed by ^1H NMR spectroscopy (see partial spectra in Figs. 1a and 3a). The above crude residue was dissolved in EtOAc–petroleum ether and, after adding small amount of silica gel, the suspension was stirred at room temperature for overnight. The mixture was filtered with rinsing with EtOAc. The filtrate was evaporated under reduced pressure and the residue was analyzed again by ^1H NMR spectroscopy (see partial spectra in Figs. 1b and 3b). In separate parallel experiments, the crude reaction mixture was directly purified by flash column chromatography (silica gel, 10% EtOAc in petroleum ether) to give products **9** (12%) and **11** (67%) (**11**:**9** = 85:15), or **12** (10%) and **14** (81%) (**14**:**12** = 89:11). The diastereomer ratios of **11**:**9** for IMDA reaction of **2** are 90:10 (PhMe, 135 °C)[2a] and 85:15 (MeCN, 180 °C), indicating that solvent and temperature do not have significant influence on diastereoselectivity. The finding is consistent with the results of IMDA reaction of pentadienyl fumarates.[4]
10. Physical and spectroscopic data for **9** (12% from **2**): colorless needles; mp 38–40 °C (EtOAc–hexane); $R_f = 0.24$ (20% EtOAc in hexane); IR (KBr) 2968, 1778, 1729, 1179, 1160 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.88 (ddd, $J = 10.0, 3.6, 3.6$ Hz, 1H), 5.72 (br d, $J = 9.6$ Hz, 1H), 4.31 (dd, $J = 9.6, 6.0$ Hz, 1H), 4.22 (q, $J = 7.2$ Hz, 2H), 4.10 (d, $J = 9.6$ Hz, 1H), 3.26–3.18 (m, 1H), 2.95–2.86 (m, 1H), 2.49–2.38 (m, 1H), 2.09 (dd, $J = 12.0, 12.0$ Hz, 1H), 1.29 (t, $J = 7.2$ Hz, 3H), 1.03 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 174.2, 135.1, 119.7, 69.6, 61.0, 49.0, 39.8, 37.1, 32.2, 19.3, 14.3; MS (+ESI) *m*/*z* 471 ($2M+Na^+$, 100), 247 ($M+Na^+$, 44); HRMS (+ESI) calcd for $C_{12}H_{16}O_4$ ($M+Na^+$), 247.0941; found, 247.0936.
11. Physical and spectroscopic data for **11** (67% from **2**): colorless needles; mp 60–62 °C (EtOAc–hexane); $R_f = 0.29$ (20% EtOAc in hexane); IR (KBr) 2982, 1765, 1723, 1218, 1281 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.97 (ddd, $J = 8.4, 5.6, 2.4$ Hz, 1H), 5.83 (dd, $J = 10.0, 4.4$ Hz, 1H), 4.45 (dd, $J = 10.0, 6.0$ Hz, 1H), 4.25–4.12 (m, 2H), 4.08 (d, $J = 10.0$ Hz, 1H), 3.22 (ddd, $J = 6.8, 4.4, 2.0$ Hz, 1H), 3.04–2.96 (m, 1H), 2.75–2.65 (m, 1H), 2.62 (dd, $J = 12.4, 5.2$ Hz, 1H), 1.27 (t, $J = 7.2$ Hz, 3H), 0.88 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 172.9, 134.1, 119.5, 71.0, 60.8, 44.3, 39.6, 30.9, 30.6, 15.5, 14.2; MS (+ESI) *m*/*z* 471 ($2M+Na^+$, 100), 247 ($M+Na^+$, 44). Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.22; H, 7.19.
12. The crystallographic data (excluding structure factors) of **11**, **12**, and **14** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 648332, CCDC 648333, and CCDC 648334, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

13. Physical and spectroscopic data for **12** (10% from **8**): as colorless needles; mp 116–118 °C (EtOAc–hexane); $R_f = 0.28$ (20% EtOAc in hexane); IR (KBr) 2984, 1763, 1721, 1180 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32–7.22 (m, 3H), 7.11 (d, $J = 7.2$ Hz, 2H), 6.07 (ddd, $J = 9.6$, 3.6, 3.6 Hz, 1H), 5.94 (br d, $J = 10.0$ Hz, 1H), 4.35 (dd, $J = 9.6$, 6.0 Hz, 1H), 4.12 (d, $J = 10.0$ Hz, 1H), 3.97–3.90 (m, 2H), 3.57 (br d, $J = 10.8$ Hz, 1H), 3.37–3.31 (m, 1H), 3.13–3.05 (m, 1H), 2.51 (dd, $J = 11.6$, 11.6 Hz, 1H), 0.92 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 173.5, 141.6, 133.4, 128.7 (×2), 127.9 (×2), 127.3, 121.0, 69.5, 60.8, 50.0, 44.3, 39.8, 37.3, 13.9; MS (+ESI) *m/z* 309 ($M+Na^+$, 45), 287 ($M+H^+$, 100). Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.29; H, 6.34.
14. Physical and spectroscopic data for **14** (81% from **8**): colorless needles; mp 117–119 °C (EtOAc–hexane); $R_f = 0.42$ (25% EtOAc in hexane); IR (KBr) 2988, 2907, 1774, 1728, 1176, 1148 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32–7.22 (m, 3H), 7.11–7.07 (m, 2H), 6.20 (dd, $J = 10.0$, 4.4 Hz, 1H), 6.08 (ddd, $J = 7.6$, 6.0, 2.4 Hz, 1H), 4.42 (dd, $J = 10.4$ Hz, 6.4, 1H), 4.10–3.98 (m, 3H), 3.97 (dd, $J = 6.0$, 6.0 Hz, 1H), 3.43 (ddd, $J = 7.6$, 4.4, 2.4 Hz, 1H), 3.01 (ddd, $J = 12.4$, 6.0, 6.0 Hz, 1H), 2.90 (dd, $J = 12.4$, 6.0 Hz, 1H), 1.19 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 171.7, 137.3, 130.8, 128.9 (×2), 128.4 (×2), 127.7, 121.9, 70.9, 60.8, 45.8, 42.3, 39.9, 31.2, 14.1; MS (+ESI) *m/z* 309 ($M+Na^+$, 100), 287 ($M+H^+$, 33). Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.31; H, 6.33.