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Thermal and palladium catalyzed pericyclic rearrangements of a pentaene ester

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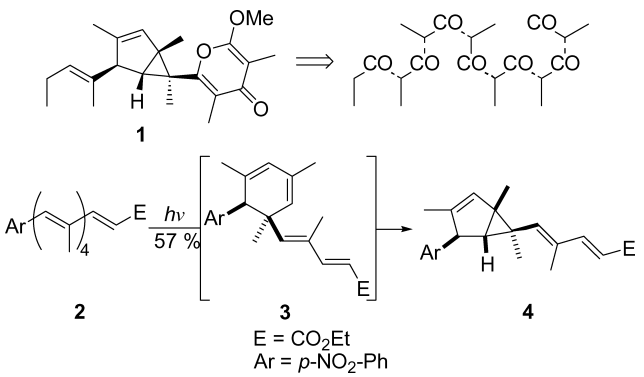
Abstract—This paper describes thermal and/or palladium promoted pericyclic rearrangements of a pentaene ester. These transformations involve selective double bond isomerizations followed by electrocyclizations, affording a cyclohexadiene and a bicyclic[4.2.0] core resulting from a cyclic triene.

1. Introduction

During continuing efforts towards the biomimetic synthesis of the propionate derived natural photodeoxytridachione **1**,[1] we have become interested in the development of pentaene **2** as a flexible synthon (Scheme 1).[2]

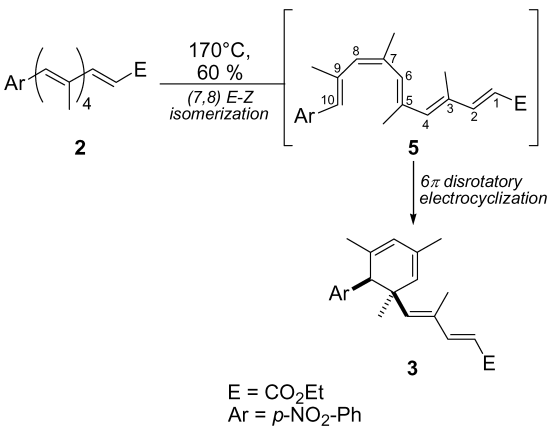


Scheme 1.

As previously reported,[2] polyene ester **2** gives, under photochemical conditions, bicyclo[3.1.0] derivative **4** via cyclohexadiene **3** (Scheme 1). This prompted us to investigate further rearrangements of ester **2**.

2. Results and discussion

Heating **2** to 170 °C[3] afforded cyclohexadiene **3** in 60% yield via a selective (7,8) *E*–*Z* isomerization to give **5**, followed by a 6π disrotatory electrocyclization, thermally allowed by the Woodward–Hoffman rules[4] (Scheme 2).



Scheme 2.

Attempts to increase the yield of **3** by heating at lower temperature failed.[5] Palladium(II) salts are well known to induce double bond isomerization under milder conditions.[6,7a] Thus compound **2** was treated with dichlorobis(acetonitrile)palladium(II) at room temperature (RT).[3] This gave the same cyclization as described above, but generating the diene **3** in only up to 20% yield.[2b] The only other isolated product was cyclooctatriene **7** in up to 20% yield (Scheme 3). The structure of **7** was determined by a

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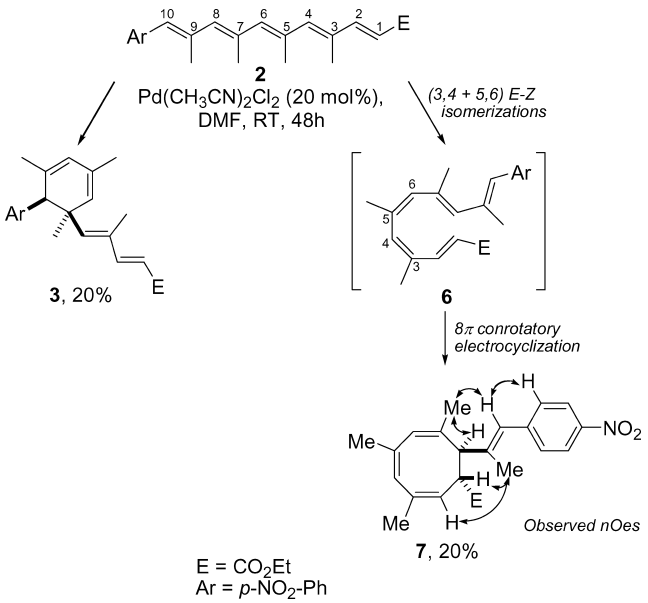
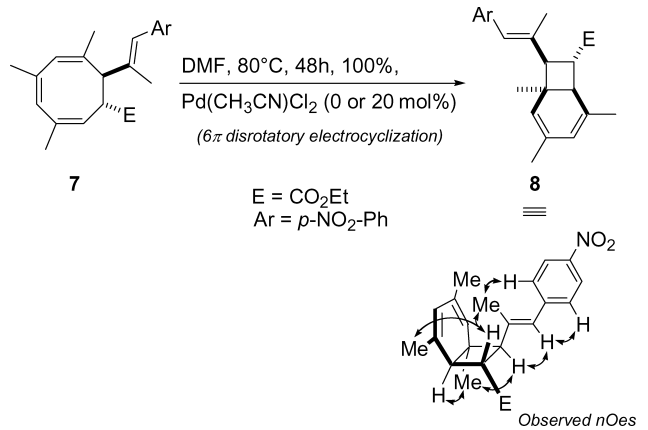


Scheme 3.

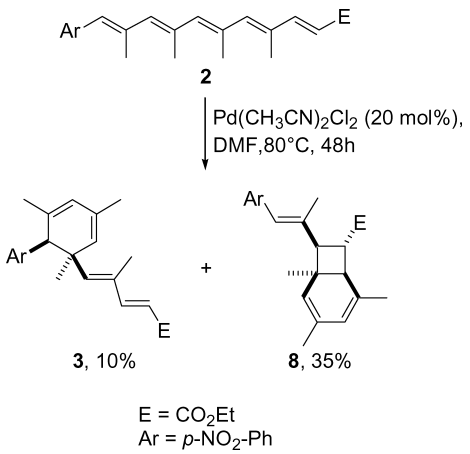
combination of NMR methods, including nOe and 2-D NMR analyses. Mechanistically, we propose that the metal induces selective (3,4+5,6) *E*–*Z* isomerizations to give intermediate **6**. The (*E*,*E*,*Z*,*Z*,*E*)-pentaene **6** then undergoes a thermally allowed 8π conrotatory electrocyclization[4] to generate the cyclic triene **7**. This process might be promoted by a chelation of the electrophilic palladium nucleus to the ester function.

As **7** is, potentially, able to undergo an intramolecular 6π disrotatory electrocyclization,[4,7] it was heated (Scheme 4).



Scheme 4.

Contrary to analogous cyclic trienes which spontaneously cyclize at or below 25 °C,[7] a minimum temperature of 80 °C was required to obtain the expected bicyclic[4.2.0] compound **8** in quantitative yield. The same transformation occurred in the presence of palladium(II) at 80 °C. Efforts to obtain the bicyclic core **8** at a lower temperature by treating **7** with neutral palladium complexes were unsuccessful. This indicates that the 6π disrotatory electrocyclization seems to be a purely thermal reaction.[8] Indeed, as expected, when the palladium catalyzed reaction of **2** was directly carried out at 80 °C,[3] dienes **3** and **8**[9] are obtained in 10 and 35% yield, respectively (Scheme 5).



Scheme 5.

3. Conclusion

In conclusion, we have demonstrated that cyclohexadienes **3** and **8** can be obtained by treating pentaene ester **2** under thermal or palladium promoted conditions. Heating to 170 °C allowed a selective single *E*–*Z* isomerization of pentaene **2** giving intermediate **5**, which then cyclized to form diene **3**, whereas palladium induced a selective double *E*–*Z* isomerization of **2**. This generated intermediate **6**, allowing the formation of cyclooctatriene **7** via an 8π conrotatory electrocyclization. Moreover, compound **7** can be converted quantitatively into the bicyclic[4.2.0] core **8** through a thermally allowed 6π disrotatory electrocyclization. Finally, dienes **3** and **8** can be obtained in a one-pot reaction by heating pentaene **2** in the presence of a catalytic amount of palladium(II) salt. This work demonstrates the feasibility of selective double bond isomerizations of pentaene ester **2** and the efficiency of the subsequent electrocyclizations.

4. Experimental

4.1. General procedure

All solvents and reagents were purified by standard techniques reported in Perrin, D. D.; Amarego, W. L. F., Purification of Laboratory Chemicals, 3rd edition, Pergamon Press, Oxford, 1988 or used as supplied from commercial sources as appropriate. Solvents were removed under reduced pressure using a Buchi R110 or R114 Rotavapor fitted with a water or dry ice condenser as necessary. Final traces of solvent were removed from samples using an Edwards E2M5 high vacuum pump with pressures below 2 mm Hg. All experiments were carried out under a positive atmosphere of argon and in glassware protected from sunlight. ^{1}H NMR spectra were recorded at 400 MHz using Bruker DPX400 instrument or at 500 MHz using Bruker DRX500 instrument. For ^{1}H spectra recorded in C_6D_6, chemical shifts are quoted in parts per million

(ppm) and are referenced to the residual solvent peak. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quadruplet; b, broad. Data are reported in the following manner: chemical shift (integration, multiplicity, coupling constant if appropriate). Coupling constants (*J*) are reported in Hertz to the nearest 0.5 Hz. ^{13}C NMR spectra were recorded at 100 MHz using Bruker DPX400 instrument or at 125 MHz using Bruker DRX500 instrument. Carbon spectra assignments are supported by DEPT-135 spectra, $^{13}C-^{1}H$ (HMQC and HMBC) correlations where necessary. Chemical shifts are quoted in ppm and are referenced to the appropriate residual solvent peak. Flash column chromatography was carried out using Sorbsil™ C60 (40–63 mm, 230–40 mesh) silica gel. Thin-layer chromatography was carried out on pre-coated aluminium plates (silica gel 60 F_{254} from Merck), visualized with UV light, stained with a solution of *p*-anisaldehyde (9.2 mL), H_2SO_4 (12.5 mL), CH_3CO_2H (3.75 mL) in C_2H_5OH (338 mL) followed by charring. Infrared spectra were recorded as a thin film between NaCl plates on a Perkin–Elmer Paragon 1000 Fourier Transform spectrometer with internal referencing. Absorption maxima are reported in wavenumbers (cm^{-1}). High resolution mass spectrometry was measured on a Waters 2790-Micromass LCT electrospray ionization mass spectrometer and on a VG autospec chemical ionization mass spectrometer.

4.2. Ethyl (2*E*,4*E*)-4-methyl-5-[(1*R* *,6*R* *)-1,3,5-trimethyl-6-(4-nitrophenyl)cyclohexa-2,4-dien-1-yl]penta-2,4-dienoate (3)

In a sealed tube purged with argon, a solution of pentaene ester **2** (100 mg, 262 μmol) in xylene (15 mL) was heated at 170 °C during 2 days. The solution was allowed to cool to RT and the solvent evaporated under reduced pressure. Purification by flash silica gel chromatography (99.5:0.5 30–40 P.E./EtOAc) gave title compound **3** as a yellow oil (60 mg, 60%).

4.2.1. Data for 3. R_F 0.5 (3:1 30–40 P.E./EtOAc); ν_{max}/cm^{-1} ($CHCl_3$) 2964, 2927, 2858, 1713, 1618, 1521, 1453, 1330, 1165; δ_H (400 MHz, C_6D_6) 0.85 (3H, s), 0.99 (3H, t, *J*=8.0 Hz), 1.18 (3H, s), 1.42 (3H, s), 1.64 (3H, s), 2.63 (1H, s), 4.06 (2H, q, *J*=8.0 Hz), 5.12 (1H, s), 5.37 (1H, s), 5.58 (1H, s), 5.68 (1H, d, *J*=16.0 Hz), 6.71 (2H, d, *J*=8.0 Hz), 7.42 (1H, d, *J*=16.0 Hz), 7.72 (2H, d, *J*=8.0 Hz); δ_C (100 MHz, C_6D_6) 13.6, 14.8, 21.6, 22.9, 29.7, 44.4, 56.5, 60.5, 117.4, 123.0, 124.3, 127.8, 129.6, 131.1, 135.5, 136.3, 146.5, 146.8, 147.6, 150.3, 167.3; *m*/*z*(CI) 399 (MNH_4^+, 8%), 382 (MH^+, 100), 352 (11), 336 (43), 308 (40); HRMS (CI) calculated for $C_{23}H_{28}NO_4$ (MH^+): 382.2018. Found: 382.2026.

4.3. Ethyl (2*E*,4*E*)-4-methyl-5-[(1*R* *,6*R* *)-1,3,5-trimethyl-6-(4-nitrophenyl)cyclohexa-2,4-dien-1-yl]penta-2,4-dienoate (3) and ethyl (1*R* *,8*S* *)-3,5,7-trimethyl-8-[(*E*)-1-methyl-2-(4-nitrophenyl)ethenyl]cycloocta-2,4,6-triene-1-carboxylate (7)

Ester **2** (300 mg, 786 μmol) and $Pd(MeCN)_2Cl_2$ (41 mg, 157 μmol) were placed in a dry flask, which was purged with argon. DMF (8 mL) was added, and the solution was stirred for 2 days at RT, and then water (8 mL) was added. The mixture was extracted with DCM (3×3 mL) and the combined organic fractions were washed with water (3×2 mL), brine (3 mL) and dried over anhydrous $MgSO_4$. The drying agent was removed by filtration and the mixture concentrated under reduced pressure. The crude yellow residue was purified by flash silica gel chromatography (99.5:0.5 30–40 P.E./EtOAc) to give tetraene **3** as a yellow oil (60 mg, 20%) and cyclooctatriene **7** as a yellow oil (60 mg, 20%).

4.3.1. Data for 7. R_F 0.5 (3:1 30–40 P.E./EtOAc); ν_{max}/cm^{-1} ($CHCl_3$) 3020, 2933, 2855, 1718, 1595, 1517, 1477, 1425, 1345, 1215, 1015, 929, 759; δ_H (500 MHz, C_6D_6) 0.93 (3H, t, *J*=7.0 Hz), 1.62 (3H, s), 1.75 (3H, s), 1.77 (3H, s), 1.77 (3H, s), 3.89 (1H, bs), 3.94 (2H, q, *J*=7.0 Hz), 4.25 (1H, bd, *J*=7.5 Hz), 5.46 (1H, bs), 5.68 (1H, bs), 6.08 (1H, bd, *J*=7.5 Hz), 6.23 (1H, bs), 6.87 (2H, d, *J*=10.0 Hz), 7.87 (2H, d, *J*=10.0 Hz); δ_C (125 MHz, C_6D_6) 14.7, 23.1, 23.1, 27.0, 27.1, 46.4, 56.6, 60.9, 123.9, 126.5, 126.7, 128.9, 129.2, 129.6, 129.7, 129.8, 136.5, 137.6, 144.6, 146.9, 173.2; *m*/*z*(CI) 382 (MH^+, 48%), 352 (18), 325 (95), 279 (100), 262 (77), 232 (83), 212 (64); HRMS (CI) calculated for $C_{23}H_{28}NO_4$ (MH^+): 382.2018. Found: 382.2007.

4.4. Ethyl (1*R* *,6*S* *,7*R* *,8*R* *)-1,3,5-trimethyl-8-[(*E*)-1-methyl-2-(4-nitrophenyl)ethenyl]bicyclo[4.2.0]octa-2,4-diene-7-carboxylate (8)

4.4.1. Thermal conditions. In a sealed tube purged with argon, a solution of cyclooctatriene **7** (50 mg, 131 μmol) in DMF (15 mL) was heated at 80 °C during 2 days. The solution was allowed to cool to RT and the solvent evaporated under reduced pressure to afford title compound **8** as a yellow oil (50 mg, 100%).

4.4.2. Palladium conditions. Same procedure as described above for compounds **3** and **7** but by heating the reaction mixture at 80 °C during 2 days. A purification by flash silica gel chromatography (99.5:0.5 30–40 P.E./EtOAc) gave title compound **8** as a yellow oil (105 mg, 35%) and cyclodiene **3** as a yellow oil (29 mg, 10%).

4.4.3. Data for 8. R_F 0.4 (3:1 30–40 P.E./EtOAc); ν_{max}/cm^{-1} ($CHCl_3$) 3019, 2924, 2855, 1718, 1594, 1517, 1444, 1344, 1216, 1110, 1027, 858, 757; δ_H (500 MHz, C_6D_6) 0.98 (3H, t, *J*=7.0 Hz), 1.18 (3H, s), 1.60 (3H, s), 1.79 (3H, s), 1.86 (3H, s), 2.69 (1H, d, *J*=10.0 Hz), 3.27 (1H, d, *J*=10.0 Hz), 3.40 (1H, t, *J*=10.0 Hz), 3.96 (2H, q, *J*=7.0 Hz), 4.90 (1H, bs), 5.39 (1H, bs), 6.19 (1H, bs), 6.79 (2H, d, *J*=10.0 Hz), 7.85 (2H, d, *J*=10.0 Hz); δ_C (125 MHz, C_6D_6) 14.7, 18.5, 22.0, 22.5, 29.1, 44.0, 45.7, 46.2, 60.4, 60.6, 121.9, 122.6, 123.4, 123.7, 129.7, 131.3, 134.5, 140.2, 144.4, 146.3, 173.6; *m*/*z*(CI) 382 (MH^+, 45%), 352 (45), 340 (24), 310 (23), 279 (15), 262 (18), 232 (100), 205 (29); HRMS (CI) calculated for $C_{23}H_{28}NO_4$ (MH^+): 382.2018. Found: 382.2031.

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References and notes

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3. The reaction was conducted for a 2 day period.
4. Woodward, R. B.; Hoffmann, R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 781.
5. The reaction has been run at 6 different temperatures from 20 to 170 °C, with 30 °C increments.
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8. In order to elucidate this mechanism further modifications will be studied and reported.
9. Compound **8** results from the thermal cyclization of **7**, since the formation and disappearance of **7** is observed during the reaction.