Conversion of a 2,5,7-Nonatrien-4-one to a Bicyclo[4.2.0]octenone by a Series of Electrocyclic Reactions

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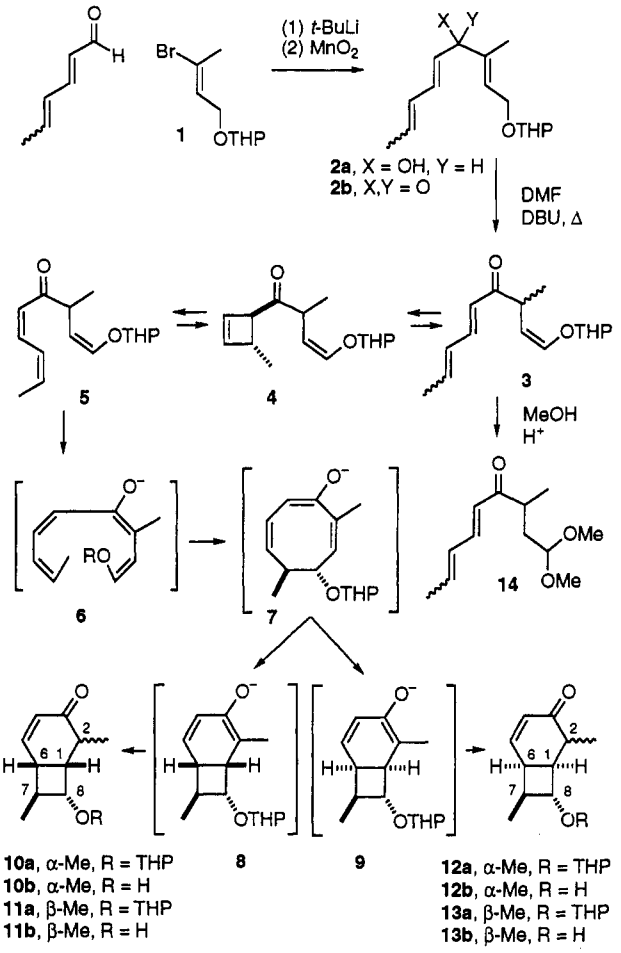
During the attempted base-catalyzed addition of nucleophiles to trienone **2b**, we found, to our surprise, that **2b** underwent base-catalyzed isomerization to give three bicyclo[4.2.0]octenones **11a–13a**. We report here experiments that establish the structures of the products and suggest the mechanism for this unexpected, deep-seated rearrangement.



Trienone **2b** was prepared by addition of the lithium reagent prepared from **1**[1] to the commercially available 4.5:1 mixture[2] of (2*E*,4*E*)- and (2*E*,4*Z*)-2,4-hexadienal to give **2a** in quantitative yield. Oxidation of **2a** with activated MnO_2 provided 78% of **2b**. A 0.1 M solution of trienone **2b** in DMF was heated with 10 equiv of DBU for 2 h at 125 °C to provide a mixture of **11a–13a**. Since the THP chiral center complicated the structure assignment, this mixture was hydrolyzed in MeOH (*p*-TsOH, 30 min, 25 °C) to give 10% of **11b**, 10% of **12b**, and 9% of **13b**.

The ^1H NMR spectra of each of these compounds were similar suggesting that they were stereoisomers. The chemical shifts and coupling constants of the alkene protons suggested the presence of a 4-monosubstituted 2-cyclohexenone. The spectra also indicated the presence of a secondary alcohol and two secondary methyl groups. Decoupling experiments established the connectivity pattern indicating that the compounds were three of the eight possible stereoisomeric bicyclo[4.2.0]octenones: the four stereoisomers **10b–13b** and four additional isomers with the substituents on C_7 and C_8 cis rather than trans.

The stereochemistry of the three diastereomers was unambiguously assigned as **11b–13b** based on the coupling constants and the NOE's observed in ROESY experiments. The observed coupling constants for **11b–13b** agreed very well with those calculated by MM2 for the most stable conformers shown in Figure 1.[3] In the least-polar isomer **11b**, there was a strong NOE between H_1 and both methyl groups, indicating that H_1 and both methyl groups are on the convex face. This was confirmed by the coupling constant, J = 10.6 Hz, between H_1 and H_2, which verified that these hydrogens are trans and diaxial on the cyclohexenone. A moderate NOE between H_6 and H_8 across the cyclobutane ring indicated that these hydrogens are on the same face. The absence of an NOE between H_1 and H_7 suggested that these hydrogens are not on the same face.

In the middle isomer **13b**, there was a strong NOE between H_8 and both methyl groups that established that H_8 and both methyl groups are on the concave face. A moderate NOE between H_1 and H_7 across the cyclobutane ring indicated that these hydrogens are on the convex face. The stereochemistry at C_2 was confirmed by a moderate NOE between H_2 and H_6.

In the most-polar isomer **12b**, there was a strong NOE between H_1 and C_2-Me and between H_2 and C_7-Me and no NOE between H_6 and H_8. The stereochemistry was confirmed by the coupling constant, $J \approx 0$ Hz, between H_1 and H_2, which established that these hydrogens are trans with a dihedral angle of 90° on the cyclohexenone.

The stereochemical assignments of **12b** and **13b** were confirmed by equilibration of each stereoisomer with DBU in DMF at 90 °C for 1 h to give the same 58:42 mixture of **13b** and **12b**. The third stereoisomer **11b** was stable to these conditions.

TLC analysis of the reaction of **2b** with DBU in DMF at 125 °C indicated the presence of a transient intermediate. At lower temperatures this intermediate did not react further. Treatment of **2b** with DBU in DMF for 2 h at 55 °C gave 18% of **3** as a 1:1 mixture of diastereomers. The stereochemistry of the enol ether double bond was established by the coupling constant, J = 6.2 Hz, which is consistent only with a cis double bond.[4] Hydrolysis of the enol ether double bond with *p*-TsOH in MeOH gave dimethyl acetal **14**, confirming the structure assignment of **3**.

The most likely mechanism for the formation of bicyclo[4.2.0]octenones **11a–13a** involves the conrotatory electrocyclic ring closure[5] of tetraenolate **6** to give cyclooc-

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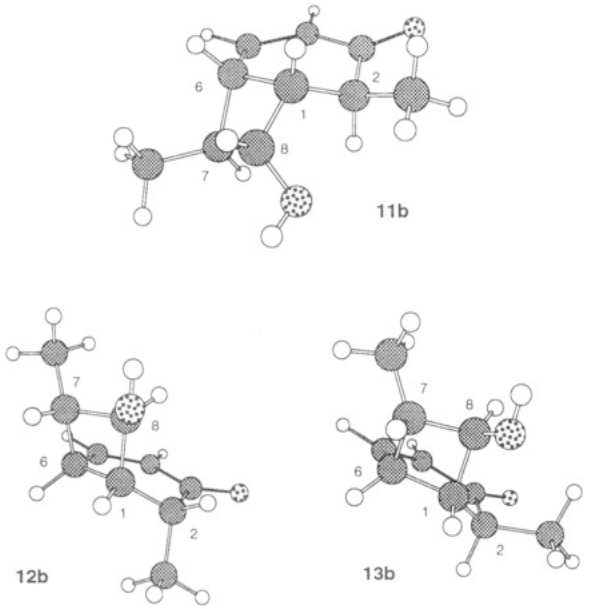

Figure 1. Calculated conformations of **11b–13b**.

tatrienolate **7**, followed by the disrotatory electrocyclic ring closure[5b,6] of **7** to give cyclohexadienolates **8** and **9** and protonation to give **10a–13a**. The equilibration studies discussed above indicate that **12a** and **13a** will equilibrate under these reaction conditions as will **10a** and **11a** so that thermodynamic mixtures at C_2 are probably obtained.

Cyclooctatrienolate **7** with the methyl and OTHP substituents trans would be obtained from conrotatory cyclization of a tetraene with the two terminal double bonds either both cis or both trans. The isolation of **3** with a cis 1,2-double bond suggests that tetraenolate **6** with both terminal double bonds cis is the more likely intermediate. The conversion of **3** to **6** requires the inversion of stereochemistry of both double bonds of the major 7*E* isomer of dienone **3**. The most likely mechanism for this process is the conrotatory closure of dienone **3** to give trans 3,4-disubstituted cyclobutene **4** that can undergo an allowed conrotatory opening to regenerate *trans,trans*-dienone **3** or generate *cis,cis*-dienone **5**. This isomerization is well-precedented in the work of Marvel, who established that (1*E*,3*Z*,5*Z*,7*E*)-1,8-diphenyloctatetraene isomerized at 175 °C to the all *E* isomer by a process compatible with conrotatory ring closure to a 3,4-trans-disubstituted cyclobutene followed by conrotatory ring opening to give the all trans isomer.[7] Enolization of all *cis*-trienone **5** will give tetraenolate **6** that will cyclize to give **7**.

The enolate of **6** and **7** may facilitate the electrocyclic ring closure reaction analogous to the acceleration of the oxy-Cope reaction by conversion of the alcohol to the alkoxide. Although the cyclization of trienols and trienyl silyl ethers to give cyclohexenones have been described,[8] we are unaware of any studies indicating the effect of the oxygen on the rate of the cyclization.

Conrotatory electrocyclic ring closures of (1,3*Z*,5*Z*,7)-octatetraenes to give 1,3,5-cyclooctatrienes that undergo a second, disrotatory electrocyclic ring closure to give a bicyclo[4.2.0]octadiene have been extensively studied.[5,6] To the best of our knowledge, both the electrocyclization of tetraenolates and the generation of the required *Z* geometry of the central double bonds of the octatetraene by thermal isomerization of *E* double bonds is unprecedented.

The base-catalyzed conversion of **2b** to **11a–13a** provides a very simple route to highly substituted bicyclo[4.2.0]-octenones that may be of value for the synthesis of the antibiotic MK4588.[9]

Experimental Section

General Procedures. NMR spectra were recorded at 300 MHz in $CDCl_3$. Chemical shifts are reported in δ using TMS as an internal standard and coupling constants in hertz. DQF-COSY and ROESY experiments were recorded at 500 MHz on a Bruker AM1 spectrometer. All reactions were carried out under N_2. DMF was purified by concentration under reduced pressure until one-third of its volume had evaporated; the remaining DMF was stored over 4-Å molecular sieves.

(2*E*,5*E*,7*E*)-3-Methyl-1-[(tetrahydro-2*H*-pyran-2-yl)oxy]-nona-2,5,7-trien-4-ol (2). *t*-BuLi (16.24 mL, 1.65 M in pentane, 26.8 mmol) was added dropwise to a solution of **1**[1] (3.500 g, 14.8 mmol) in 40 mL of THF at −78 °C. The solution was stirred for 5 min, and 2,4-hexadienal (95%, 4.5:1 *4E*- and 4*Z*-isomers,[2] 1.48 mL, 12.8 mmol) was added dropwise. The reaction mixture was stirred for 30 min at −78 °C and quenched by the addition of 40 mL of saturated aqueous $NaHCO_3$ solution and 20 mL of EtOAc. The layers were separated, and the organic layer was washed with saturated aqueous $NaHCO_3$ (2 × 40 mL). The combined aqueous layers were extracted with EtOAc (2 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to give 3.756 g (100%) of crude **2a** as a 4:1 7E–7*Z* mixture that was used without purification: ^{1}H NMR (7*E*) 6.23 (dd, 1, J = 10.4, 14.7), 6.05 (ddd, 1, J = 1.5, 10.6, 15.0), 5.65–5.80 (m, 2), 5.55 (dd, 1, J = 6.6, 15.8), 4.63 (br, 1), 4.57 (br d, 1, J = 6.6), 4.30 (m, 1), 4.07 (m, 1), 3.88 (ddd, 1, J = 3.8, 7.6, 11.4), 3.53 (m, 1), 1.5–1.9 (m, 12); (7*Z*) 6.59 (dddd, 1, J = 1.1, 1.1, 11.2, 15.2).

(2*E*,5*E*,7*E*)-3-Methyl-1-[(tetrahydro-2*H*-pyran-2-yl)oxy-nona-2,5,7-trien-4-one (2b). Activated MnO_2 (1.4 g, 16 mmol) was added to a solution of **2a** (389 mg, 1.54 mmol, 4:1 7*E*–7*Z*) in 15 mL of CH_2Cl_2 at rt. The mixture was stirred for 2 h and filtered through a plug of Celite 521. The residue was washed with CH_2Cl_2 and 85:15 hexanes–EtOAc. The combined filtrates were concentrated under reduced pressure to yield 329 mg of crude **2b**. Flash chromatography (85:15 hexanes–EtOAc) provided 270 mg (78% based on recovered **2a**) of trienone **2b** as a 5:1 mixture of 7*E*:7*Z* isomers, followed by 41 mg of recovered **2a**: ^{1}H NMR (7*E*) 7.22 (dd, 1, J = 9.5, 15.0), 6.66 (m, 2), 6.22 (m, 2), 4.68 (dd, 1, J = 2.9, 3.9), 4.50 (dd, 1, J = 5.3, 14.7), 4.28 (dd, 1, J = 6.0, 14.7), 3.89 (ddd, 1, J = 3.7, 7.4, 11.1), 3.55 (ddd, 1, J = 4.2, 4.9, 11.1), 1.7–1.9 (m, 8), 1.5–1.7 (m, 4); (7*Z*) 7.62 (ddd, 1, J = 1.0, 11.8, 15.1); ^{13}C NMR (7*E*) 191.9, 143.7, 140.0, 138.5, 137.5, 130.5, 122.6, 98.6, 64.5, 62.4, 30.6, 25.4, 19.4, 18.8, 12.2; IR (neat) 1659, 1629, 1590, 1135, 1121, 1067, 1030, 1000 cm^{-1}.

(1*Z*,5*E*,7*E*)-3-Methyl-1-[(tetrahydro-2*H*-pyran-2-yl)oxy]-nona-1,5,7-trien-4-one (3). A solution of **2b** (41 mg, 0.16 mmol, 6:1 7*E*–7Z) and DBU (0.24 mL, 1.6 mmol) in 1.5 mL of DMF was warmed at 55 °C for 2 h. Workup as described below afforded 78 mg of a dark, orange-brown oil. Flash chromatography (85:15 hexanes–EtOAc) provided 7.3 mg (18%) of **3** as a 4:1 7*E*–7Z mixture and ≈1:1 mixture of diastereomers: ^{1}H NMR (7*E*) 7.25 (ddd, 1, J = 1.6, 8.7, 15.2), 6.31 (dd, 0.5 × 1, J = 0.9, 6.2, H_1), 6.28 (dd, 0.5 × 1, J = 0.9, 6.2, H_1), 6.15–6.30 (m, 3), 4.97 (dd, 0.5 × 1, J = 2.9, 2.9), 4.95 (dd, 0.5 × 1, J = 3.1, 3.1), 4.43 (br dd, 1, J = 6.2, 9.5, H_2), 3.92 (br dq, 1, J = 9.5, 6.8), 3.83 (m, 1), 3.60 (m,

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1), 1.86 (br d, 3, J = 5.1), 1.56–1.91 (m, 6), 1.19 (d, 0.5 × 3, J = 6.8), 1.18 (d, 0.5 × 3, J = 6.8); (7*Z*) 7.63 (ddd, 0.5 × 1, J = 0.9, 10.4, 11.4), 7.62 (ddd, 0.5 × 1, J = 0.9, 10.4, 11.4); ^{13}C NMR (7*E*) (142.9, 142.8), (142.6, 142.4), (139.8, 139.7), (130.5, 130.5), 126.5, (107.6, 107.3), (98.6, 98.6), (62.0, 61.9), (40.9, 40.8), (29.7, 29.7), (25.1, 25.1), 18.8, (18.7, 18.6), (16.4, 16.4), the C=O was not observed; IR (neat) 1688, 1667, 1636, 1595, 1124, 1027 cm^{-1}.

Preparation of (1α,2α,6α,7α,8β)-, (1α,2α,6α,7β,8α),- and (1α,2β,6α,7β,8α)-8-Hydroxy-2,7-dimethylbicyclo[4.2.0]oct-4-en-3-one (11b, 12b, and 13b). A solution of **2b** (267 mg, 1.1 mmol, 5:1 7*E*–7*Z*) and DBU (1.60 mL, 10.7 mmol) in 10 mL of DMF was slowly heated to 125 °C over 1 h. The solution was heated for an additional 1 h, cooled to 25 °C, quenched with 20 mL of saturated aqueous $NaHCO_3$ solution, and then diluted with 10 mL of EtOAc. The layers were separated, and the organic layer was washed with saturated aqueous $NaHCO_3$ solution (2 × 20 mL). The aqueous layers were combined and extracted with EtOAc (2 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered through silica gel, and concentrated under reduced pressure to give 220 mg of crude **11a–13a** that still contained some residual DMF. This orange oil was dissolved in 10 mL of MeOH, and *p*-TsOH (20 mg) was added. The solution was stirred for 30 min at 25 °C, quenched with 10 mL of saturated aqueous $NaHCO_3$ solution, and then diluted with 10 mL of EtOAc. The layers were separated, and the organic layer was washed with saturated $NaHCO_3$ solution (2 × 10 mL). The aqueous layers were combined and extracted with EtOAc (2 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to give 102 mg of crude **11b–13b**. Flash chromatography (7:3 hexanes–EtOAc) provided 14.3 mg (10%) of cyclohexenone **11b**, followed by 14.0 mg (9%) of cyclohexenone **13b** and 14.5 mg (10%) of cyclohexenone **12b**, as colorless oils.

The data for **11b**: ^{1}H NMR 6.78 (ddd, 1, J = 1.0, 4.6, 10.0, H_5), 5.95 (dd, 1, J = 1.2, 10.0, H_4), 4.00 (ddd, 1, J = 5.6, 7.1, 7.3, H_8), 2.80 (dq, 1, J = 10.6, 6.5, H_2), 2.60 (dddd, 1, J = 1.0, 7.0, 7.6, 10.6, H_1), 2.35 (ddq, 1, J = 7.3, 9.4, 6.7, H_7), 2.15 (dddd, 1, J = 1.2, 4.6, 7.6, 9.4, H_6), 1.7 (d, 1, J = 5.7, OH), 1.25 (d, 3, J = 6.7, C_7-CH_3), 1.15 (d, 3, J = 6.5, C_2-CH_3); ^{13}C NMR 146.8, 128.4, 71.0, 46.4, 44.2, 38.0, 33.9, 17.7, 15.2, the C=O was not observed; IR (neat) 3420, 1665 cm^{-1}.

The data for **12b**: ^{1}H NMR 6.84 (ddd, 1, J = 1.0, 3.8, 10.3, H_5), 6.04 (dd, 1, J = 1.7, 10.3, H_4), 3.64 (ddd, J = 6.3, 7, 8, H_8), 2.92 (dddd, 1, J = 1.7, 3.8, 7.6, 7.8, H_6), 2.60 (br q, 1, J = 7.4, H_2), 2.42 (m, 2, H_1 and H_7), 1.82 (d, 1, J = 6.3, OH), 1.15 (d, 3, J = 7.4, C_2-CH_3), 1.08 (d, 3, J = 8.0, C_7-CH_3); ^{13}C NMR 149.1, 128.8, 75.6, 47.2, 42.3, 41.5, 28.4, 18.8, 13.3, the C=O was not observed; IR (neat) 3415, 1665 cm^{-1}.

The data for **13b**: ^{1}H NMR 6.78 (ddd, 1, J = 1.2, 3.9, 10.2, H_5), 6.12 (dd, 1, J = 1.8, 10.2, H_4), 3.64 (ddd, 1, J = 6.3, 7, 8, H_8), 2.96 (dddd, 1, J = 1.8, 3.9, 7, 9, H_6), 2.68 (dddd, 1, J = 1.2, 6.8, 7, 8, H_1), 2.58 (dq, 1, J = 6.8, 6.8, H_2), 2.43 (ddq, 1, J = 6.9, 9, 6.9, H_7), 1.74 (d, 1, J = 6.3, OH), 1.20 (d, 3, J = 6.8, C_2-CH_3), 1.06 (d, 3, J = 6.9, C_7-CH_3); ^{13}C NMR 148.5, 130.4, 75.0, 46.1, 42.6, 40.3, 30.5, 13.0, 11.5, the C=O was not observed; IR (neat) 3415, 1665 cm^{-1}.

Equilibration of 11b–13b. A solution of **11b** (3.9 mg, 0.024 mmol) and 40 mg of DBU in 0.75 mL of DMF was heated at 90 °C for 1 h. Workup as described above gave 3.2 mg of pure recovered **11b**. A similar reaction starting with either 3.6 mg of **13b** or 3.2 mg of **12b** gave 3.0 mg of a 58:42 mixture of **13b** and **12b** as determined by ^{1}H NMR analysis.

(5*E*,7*E*)-1,1-Dimethoxy-3-methylnona-5,7-dien-4-one (14). A solution of **3** (8.6 mg, 0.034 mmol, 4:1 7*E*–7*Z*) and 2 mg of *p*-TsOH in 2 mL of MeOH was stirred for 1 h at 25 °C. Normal workup provided 8.6 mg of a colorless oil. Flash chromatography (85:15 hexanes–EtOAc) provided 2.9 mg (40%) of dimethyl acetal **14** as a 5:1 7*E*–7*Z* mixture: ^{1}H NMR ($CDCl_3$) (7*E*) 7.20 (br dd, 1, J = 10.0, 15.4), 6.21 (m, 2), 6.12 (d, 1, J = 15.4), 4.33 (dd, 1, J = 5.7, 5.8, H_1), 3.31 (s, 3), 3.29 (s, 3), 2.92 (ddq, 1, J = 7.2, 7.2, 7.0, H_3), 2.07 (ddd, 1, J = 5.7, 7.2, 14, H_2), 1.87 (d, 3, J = 4.8, H_9), 1.60 (ddd, 1, J = 5.8, 7.2, 14, H_2), 1.12 (d, 3, J = 7.0, C_3-CH_3); (7*Z*) 7.60 (ddd, 0.7, 11.3, 14.8); IR (neat) 1685, 1660, 1636, 1595, 1125, 1069, 1049 cm^{-1}.

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Supplementary Material Available: ^{1}H and ^{13}C NMR spectra for **2a**, **2b**, **3**, **11b**, **12b**, **13b**, and **14** (12 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.