A Formal Intermolecular 4+4 Approach to Cyclooctanoids: 4+3 Capture of the Nazarov Oxyallyl Intermediate with Simple 1,3-Dienes

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General information. All air or moisture sensitive reactions were carried out in oven dried (120 °C) or flame dried glassware under nitrogen atmosphere. Reactive liquids were transferred by syringe or cannula and were added into the reaction flask through rubber septa. Ether and tetrahydrofuran (THF) were freshly distilled from sodium-benzophenone ketyl, and methylene chloride was distilled from CaH₂. Thin layer chromatography (TLC) was performed on glass plates coated with 0.25 mm Kieselgel 60 F₂₅₄ (Merck). Flash columns were packed with 230-400 mesh silica gel (Merck or Baxter). All solvents were distilled before use. Commercial reagents were used without further purification unless otherwise noted. Compound **1a** was prepared from 3-pentanone and benzaldehyde by the literature procedure.¹

¹H NMR spectra and ¹³C NMR spectra were recorded on a Varian Unity-300, Varian XL-300 (¹H, 300 MHz; ¹³C, 75 MHz) or Varian VXR-500 (¹H, 500 MHz; ¹³C, 126 MHz) spectrometer. The chemical shifts are reported on the δ scale (ppm) and the spectra are referenced to tetramethylsilane (δ = 0 ppm, ¹H; ¹³C) or to deuteriochloroform (δ = 7.26 ppm, ¹H; δ = 77.23 ppm, ¹³C) as internal standard. Coupling constants (*J*) are reported in Hertz (Hz). Assignment in the ¹H spectra were achieved based on the corresponding ¹H-¹H COSY and NOESY NMR. Infrared (IR) spectra were measured with a Mattson FTIR 3000 infrared spectrometer. Mass spectra were determined on a Finnigan Mat 95 high resolution gas chromatography/mass spectrometer with Finnigan Mat ICIS II operating system.

(E)-2,4-Dimethylhepta-1,4-dien-3-ol. The Grignard reagent prepared from 2-bromopropene (1.53 g, 12.8 mmol) and Mg powder (123 mg, 14.3 mmol) in THF (50 mL) was cooled to 0 °C. 2-Methyl-2-pentenal (1.05 g, 10.7 mmol) was added dropwise as a solution in THF (5 mL). After stirring at 0 °C for 30 min, the reaction was quenched with water. The layers were separated and the aqueous layer was extracted with ether (2 x 50 mL). The organic phases were combined, washed with brine (50 mL), dried over MgSO₄ and concentrated. Purification by flash chromatography (1:10 EtOAc/hexanes, 60 g of silica gel, 20 x 3 cm column) provided 1.02 g (68%) of the dienol product as a clear, colorless oil: *R*_f 0.20 (1:9 EtOAc/hexanes); IR (film) 3393, 3083, 2961, 1649, 1450, 1375, 1054,

991, 899, 839 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.50 (t, 1 H, $J = 7.1$ Hz), 5.07 (br s, 1 H), 4.92 (br s, 1 H), 4.40 (s, 1 H), 2.08 (br p, 2 H, $J = 7.5$ Hz), 1.63 (br s, 1 H), 1.61 (s, 3 H), 1.51 (s, 3 H), 0.98 (t, 3 H, $J = 7.6$ Hz); ^{13}C NMR (126 MHz, CDCl_3) δ 145.66, 134.28, 129.79, 110.71, 80.90, 21.21, 18.96, 14.23, 11.38; Anal. Calcd for $\text{C}_9\text{H}_{16}\text{O}$: C, 77.09; H, 11.50. Found: C, 76.96; H, 11.37.

(*E*)-2,4-Dimethyl-1-phenylpenta-1,4-dien-3-ol. This dienol was prepared by following the procedure above. The product was obtained as a colorless oil in 86% yield: R_f 0.23 (1:9 EtOAc/hexanes); IR (film) 3337, 3077, 2988, 1647, 1490, 1446, 1373, 1057, 902, 753, 698 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.38-7.18 (m, 5 H), 6.61 (br s, 1 H), 5.15 (br s, 1 H), 4.99 (br s, 1 H), 4.59 (br s, 1 H), 1.91 (br s, 1 H), 1.78 (d, 3 H, $J = 1.5$ Hz), 1.69 (s, 3 H); ^{13}C NMR (126 MHz, CDCl_3) δ 145.27, 137.99, 137.74, 129.14, 128.31, 126.87, 126.69, 111.80, 81.15, 18.68, 13.59; Anal. Calcd for $\text{C}_{13}\text{H}_{16}\text{O}$: C, 82.94; H, 8.57. Found: C, 82.78; H, 8.52.

1-(3-hydroxy-2-methylpropen-3-yl)cyclopentene. The desired dienol was prepared from cyclopentenecarboxaldehyde[ref] following the procedure above. The product was obtained as a colorless oil in 67% yield: R_f 0.23 (1:9 EtOAc/hexanes); IR (thin film) 3374, 3069, 2950, 1652, 1444, 1372, 1044, 897, 802, 759 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.70-5.66 (m, 1 H), 5.02 (br s, 1 H), 4.89 (br s, 1 H), 4.68 (br s, 1 H), 2.40-2.31 (m, 2 H), 2.26-2.16 (m, 2 H), 1.93-1.85 (m, 2 H), 1.66 (br s, 3 H); ^{13}C NMR (126 MHz, CDCl_3) δ 145.84, 144.88, 126.53, 111.29, 75.51, 32.56, 31.63, 23.51, 18.14; Anal. Calcd for $\text{C}_9\text{H}_{14}\text{O}$: C, 78.21; H, 10.21. Found: C, 77.92; H, 10.20.

1-(3-hydroxy-2-methylpropen-3-yl)cyclohexene. To a solution of cyclohexanone triisopropylsulfonylhydrazone (1.89 g, 5.0 mmol) in THF (15 mL) at -78°C was added *sec*-BuLi (8.4 mL, 11 mmol, 1.3 M in cyclohexane). After 15 min the red-orange solution was warmed to 0°C with an ice bath, and nitrogen evolution was observed. When the evolution of nitrogen stopped (10 min), methacrolein (350 mg, 5.0 mmol) was added as a solution in THF (3 mL). The reaction mixture was stirred at 0°C for another 10 min and water (20 mL) was added. The aqueous phase was washed with ether (2 x 30 mL), and the combined ether phases were washed with water (20 mL), brine (20 mL), dried over MgSO_4 , and concentrated. Further purification by flash chromatography (1:15 EtOAc/hexanes, 30 g of silica gel, 20 x 2 cm column) provided 532 mg (71%) of the dienol product as a clear, colorless oil: R_f 0.42 (2:8 EtOAc/hexanes); IR (film) 3352, 3071, 2942, 1650, 1440, 1138, 1036, 991, 898 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.76 (br s, 1 H), 5.04 (br s, 1 H), 4.91 (br s, 1 H), 4.38 (br s, 1 H), 2.08-2.02 (m, 2 H), 1.98-1.89 (m, 1 H), 1.84-1.76 (m, 1 H), 1.72 (s, 1 H), 1.63 (s, 3 H), 1.64-1.50 (m, 4 H); ^{13}C NMR (126 MHz, CDCl_3) δ 145.73, 137.75, 124.23, 110.87, 79.85, 25.26, 23.80, 22.82, 22.74, 18.73; HRMS calcd for $\text{C}_{10}\text{H}_{16}\text{O}$ (M^+) 152.1201; found 152.1198.

(*E*)-2,4-Dimethylhepta-1,4-dien-3-one 1c. To a solution of the Dess-Martin periodinane (1.13 g, 2.67 mmol) in CH_2Cl_2 (10 mL) was added pyridine (1.05 g, 13.3 mmol). The resulting mixture was stirred for 5 min, then a solution of (*E*)-2,4-dimethylhepta-1,4-dien-3-ol (374 mg, 2.67 mmol) in CH_2Cl_2 (10 mL) was added dropwise. Stirring was continued for another 15 min and the reaction mixture was poured onto a silica gel plug (20 g), which was washed with CH_2Cl_2 (200 mL). The filtrate was concentrated and further purification by flash chromatography (1:30 ether/pentane, 30 g of silica gel, 20 x 2 cm column) provided 302 mg (82%) of **1c** as a clear, colorless oil: R_f 0.48 (1:9 EtOAc/hexanes); IR (thin film) 3031, 2957, 2927, 1648, 1456, 1321, 1209, 1057, 931, 786 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.41 (br t, 1 H, $J = 7.4$ Hz), 5.59 (br s, 1 H), 5.42 (br s, 1 H), 2.26 (dq, 2 H, $J = 7.5, 7.5$ Hz), 1.96 (br s, 3 H), 1.85 (br s, 3 H), 1.07 (t, 3 H, $J = 7.5$ Hz); ^{13}C NMR (126 MHz, CDCl_3) δ 201.02, 146.35, 144.09, 135.48, 122.81, 22.43, 19.53, 13.33, 12.27; HRMS calcd for $\text{C}_9\text{H}_{14}\text{O}$ (M^+) 138.1045; found 138.1046.

(E)-2,4-Dimethyl-1-phenylpenta-1,4-dien-3-one 1b. Dienone **1b** was prepared from (E)-2,4-Dimethyl-1-phenylpenta-1,4-dien-3-ol by following the procedure for the preparation of **1c**. Compound **1b** was obtained as a colorless oil in 84% yield: R_f 0.52 (1:9 EtOAc/hexanes); IR (thin film) 3079, 2940, 2917, 1642, 1621, 1448, 1327, 1181, 1052, 772, 695 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.43-7.27 (m, 6 H), 5.69 (dq, 1 H, $J = 1.5, 1.5$ Hz), 5.58 (dq, 1 H, $J = 1.5, 1.0$ Hz), 2.13 (d, 3 H, $J = 1.4$ Hz), 2.03 (dd, 3 H, $J = 1.5, 0.9$ Hz); ^{13}C NMR (126 MHz, CDCl_3) δ 201.26, 144.08, 140.46, 136.64, 136.10, 129.85, 128.64, 128.60, 123.83, 19.51, 14.37; Anal. Calcd for $\text{C}_{13}\text{H}_{14}\text{O}$: C, 83.83; H, 7.58. Found: C, 83.57; H, 7.60.

Cyclohexen-1-yl Propen-2-yl Ketone 1d. Dienone **1d** was prepared from 1-(3-hydroxy-2-methylpropen-3-yl)cyclohexene by following the procedure for the preparation of **1c**. Compound **1e** was obtained as a colorless oil in 87% yield: R_f 0.53 (1:9 EtOAc/hexanes); IR (thin film) 3024, 2974, 2925, 1647, 1559, 1456, 1313, 1711, 925 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.68 (tt, 1 H, $J = 3.8, 1.5$ Hz), 5.57 (dq, 1 H, $J = 1.4, 1.4$ Hz), 5.42 (dd, 1 H, $J = 1.5, 0.9$ Hz), 2.31-2.21 (m, 4 H), 1.94 (dd, 3 H, $J = 1.5, 1.1$ Hz), 1.70-1.61 (m, 4 H); ^{13}C NMR (126 MHz, CDCl_3) δ 200.19, 143.91, 142.00, 138.27, 122.58, 26.17, 23.94, 22.19, 21.88, 19.46; HRMS calcd for $\text{C}_{10}\text{H}_{14}\text{O}$ (M^+) 150.1045; found 150.1049.

Cyclopenten-1-yl Propen-2-yl Ketone 1e. Dienone **1e** was prepared from 1-(3-hydroxy-2-methylpropen-3-yl)cyclopentene by following the procedure for the preparation for **1c**. The product was obtained as a colorless oil in 86% yield: R_f 0.55 (1:9 EtOAc/hexanes); IR (thin film) 3082, 3061, 2950, 2917, 1641, 1623, 1435, 1373, 1357, 1161, 949, 935, 779 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.55 (tt, 1 H, $J = 2.6, 1.8$ Hz), 5.65-5.63 (m, 2 H), 2.65-2.54 (m, 4 H), 1.95 (br s, 3 H), 1.94 (br p, 2 H, $J = 7.4$ Hz); ^{13}C NMR (126 MHz, CDCl_3) δ 196.02, 144.94, 144.69, 144.02, 123.41, 34.14, 31.78, 22.83, 18.73.

Cyclooctene 2a. To a solution of dienone **1a** (50 mg, 0.19 mmol) and furan (26 mg, 0.38 mmol) in CH_2Cl_2 (20 ml) at -78°C was added $\text{BF}_3\cdot\text{OEt}_2$ (26 μL , 0.24 mmol). After 30 min., the reaction was quenched at -78°C by addition sat. NaHCO_3 (5 mL) and the mixture was allowed to warm to r.t. The organic layer was separated and dried (MgSO_4). Solvent was removed under reduced pressure, and the residue preadsorbed on silica gel and purified by chromatography on silica gel (EtOAc/hexanes 1:10) yielding **2a** as a white solid (44 mg, 70%): mp $174\text{--}177^\circ\text{C}$; R_f 0.22 (1:10 EtOAc/hexanes); IR (thin film) 3108, 3006, 2880, 1736, 1451 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz) δ 7.56-7.00, (m, 10H), 6.41 (dd, 1H, $J = 5.9, 1.6$ Hz), 6.37 (dd, 1H, $J = 5.9, 1.6$), 4.73, (m, 1H), 4.30, (br s, 1H), 4.04, (d, 1H, $J = 7.4$ Hz), 4.01, (d, 1H, $J = 7.4$ Hz), 1.10 (s, 3H), 0.71 (s, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 212.5, 142.3, 137.4, 135.6, 134.5, 130.2, 128.7, 128.6, 128.4, 127.1, 126.9, 88.5, 84.8, 60.0, 59.7, 58.0, 54.0, 13.7, 12.7.

Cyclooctene 3a. To a solution of dienone **1a** (50 mg, 0.19 mmol) and 2,3-dimethyl-1,4-butadiene (156 mg, 1.90 mmol) in CH_2Cl_2 (20 ml) at -78°C was added $\text{BF}_3\cdot\text{OEt}_2$ (26 μL , 0.24 mmol). After 3 h, the reaction was quenched at -50°C with sat. NaHCO_3 (5 mL). The organic layer was separated and dried (MgSO_4). The solvent was removed under reduced pressure, and the residue preadsorbed on silica gel and purified by chromatography on silica gel (EtOAc/hexanes 1:20) yielding **3a** as a white solid (35 mg, 50%): mp $144\text{--}147^\circ\text{C}$; R_f 0.47 (1:10 EtOAc/hexanes); IR (thin film) 3151, 2992, 1736, 1651, 1558, 1493, 1452 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz) δ 7.27-7.08 (m, 10H), 4.17 (d, 1H, $J = 12.5$ Hz), 3.37 (d, 1H, $J = 12.5$ Hz), 2.39 (d, 1H, $J = 16.8$ Hz), 2.34 (d, 1H, $J = 17.3$ Hz), 1.92 (d, 1H,

$J=17.3$ Hz), 1.84 (d, 1H, $J=16.8$ Hz), 1.80 (s, 3H), 1.67 (s, 3H), 1.11 (s, 3H), 0.67 (s, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 222.9, 140.5, 138.0, 129.4, 128.9, 128.4, 128.3, 127.1, 127.5, 126.7, 125.3, 55.0, 53.6, 51.3, 50.5, 50.5, 42.8, 23.1, 23.0, 22.4, 20.6; Anal. Calcd $\text{C}_{25}\text{H}_{28}\text{O}$: C, 87.16; H, 8.19. Found: C, 87.16; H, 8.16.

Cyclooctene 4a. To a solution of dienone **1a** (50 mg, 0.19 mmol) and isoprene (130 mg, 1.90 mmol) in CH_2Cl_2 (20 mL) at -78°C was added $\text{BF}_3\cdot\text{OEt}_2$ (26 μL , 0.24 mmol). The reaction was allowed to warm to -25°C over a period of 2.5 h, at which time it was quenched with sat. NaHCO_3 (5 mL). The organic layer was separated and dried (MgSO_4). Solvent was removed under reduced pressure, and the residue preadsorbed on silica gel and purified by chromatography on silica gel (EtOAc/hexanes 1:20) yielding **4a** as a white solid (0.021 g, 20%): mp $122\text{--}124^\circ\text{C}$; R_f 0.41 (1:10 EtOAc/hexanes); IR (film) ν_{max} 3063, 3031, 2974, 2933, 1736, 1650, 1451 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 7.42–7.11 (m, 10H), 5.45 (m, 1H), 4.17 (d, 1H, $J = 12.5$ Hz), 3.39 (d, 1H, $J = 12.5$ Hz), 2.39 (dd, 1H, $J = 17.5, 5.9$ Hz), 2.25 (dd, 1H, $J = 18.2, 1.3$ Hz), 1.84 (d, 1H, $J = 17.9$ Hz), 1.73 (s, 3H), 1.66 (d, 1H, $J = 17.9$ Hz), 1.17 (s, 3H), 0.72 (s, 3H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 222.4, 140.4, 138.0, 134.9, 129.3, 128.8, 128.4, 128.3, 127.1, 126.6, 121.3, 54.9, 53.3, 51.3, 50.3, 43.7, 39.1, 28.1, 22.7, 20.4.

Cyclooctene 2b. To a solution of dienone **1b** (76 mg, 0.41 mmol) and furan (55 mg, 0.82 mmol) in CH_2Cl_2 (20 mL) at -78°C was added $\text{BF}_3\cdot\text{OEt}_2$ (52 μL , 0.41 mmol). The solution was then warmed to -50°C and stirring was continued for 3 h at that temperature. Sat. aqueous NaHCO_3 (5 mL) was added and the mixture was allowed to warm to r.t. The aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic phases were washed with brine (10 mL), dried over MgSO_4 , and concentrated. Purification by flash chromatography (1:10 EtOAc/hexanes, 30 g of silica gel, 20 x 2 cm column) gave 78 mg (74%) of **1b** as a white solid: mp $124\text{--}125^\circ\text{C}$; R_f 0.26 (1:9 EtOAc/hexanes); IR (thin film) 3028, 2994, 2937, 1739, 1503, 1452, 1041, 896, 771, 746, 712 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.26–7.15 (m, 3 H, Ar-H), 6.96–6.94 (m, 2 H, Ar-H), 6.43 (dd, 1 H, $J = 6.0, 1.5$ Hz), 6.33 (dd, 1 H, $J = 6.0, 1.5$ Hz), 4.51 (br s, 1 H), 4.45 (br s, 1 H), 3.44 (dd, 1 H, $J = 10.4, 4.7$ Hz), 2.76 (dd, 1 H, $J = 13.2, 10.5$ Hz), 1.63 (dd, 1 H, $J = 13.1, 4.6$ Hz), 1.14 (s, 3 H), 0.58 (s, 3 H); ^{13}C NMR (126 MHz, CDCl_3) δ 213.09, 143.74, 134.82, 134.01, 128.68, 128.50, 126.71, 88.04, 87.52, 58.84, 54.82, 47.28, 41.69, 14.18, 12.50; Anal. Calcd for $\text{C}_{17}\text{H}_{18}\text{O}$: C, 80.28; H, 7.13. Found: C, 80.19; H, 7.24.

Cyclooctene 8b. To a solution of the dienone **1b** (54 mg, 0.29 mmol) and cyclopentadiene² (0.11 mL, 0.58 mmol, 5.0 M in CH_2Cl_2) in CH_2Cl_2 (15 mL) at -20°C was added $\text{BF}_3\cdot\text{OEt}_2$ (0.58 mL, 0.29 mmol, 0.50 M in CH_2Cl_2). The stirring was continued for 2 h at that temperature. Sat. aqueous NaHCO_3 (5 mL) was added and the mixture was allowed to warm to rt. The aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic phases were washed with brine (10 mL), dried over MgSO_4 , and concentrated. Purification by flash chromatography (1:40 EtOAc/hexanes, 30 g of silica gel, 20 x 2 cm column) gave 45 mg (62%) of **8b** as a white solid: mp $68\text{--}69^\circ\text{C}$; R_f 0.56 (1:9 EtOAc/hexanes); IR (thin film) 3046, 2964, 1740, 1651, 1495, 1453, 1375, 761, 701 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.25–7.15 (m, 3 H, Ar-H), 6.96–6.94 (m, 2 H, Ar-H), 6.24 (dd, 1 H, $J = 5.7, 2.6$ Hz, HC(7)), 6.14 (dd, 1 H, $J = 5.7, 2.2$ Hz, HC(6)), 3.16 (dd, 1 H, $J = 10.5, 5.0$ Hz, HC(2)), 2.57 (dddd, 1 H, $J = 3.5, 2.2, 2.2, 1.0$ Hz), 2.53 (dd, 1 H, $J = 14.3, 10.4$ Hz, HC(3)), 2.49 (dddd, 1 H, $J = 3.3, 2.4, 2.4, 0.9$ Hz), 2.37 (d, 1 H, $J = 11.2$ Hz), 1.67 (dd, 1 H, $J = 14.1, 4.8$ Hz, HC(3)), 1.66 (ddd, 1 H, $J = 11.3, 3.5, 3.5$ Hz), 1.17 (s, 3 H), 0.59 (s, 3 H); ^{13}C NMR (126 MHz, CDCl_3) δ 215.78, 144.33, 137.88, 136.99, 128.59, 128.50, 126.60, 56.11, 53.75, 52.02, 51.78, 48.53, 42.89, 39.55, 18.41, 16.41; HRMS calcd for $\text{C}_{18}\text{H}_{20}\text{O}$ (M^+) 252.1514; found 252.1514.

Cyclooctene 3b. To a solution of dienone **1b** (44 mg, 0.25 mmol) and 2,3-dimethylbutadiene (41 mg, 0.50 mmol) in CH₂Cl₂ (13 mL) at –20 °C was added BF₃•OEt₂ (31 μL, 0.25 mmol). Stirring was continued for 2 h at that temperature. Sat. aqueous NaHCO₃ (5 mL) was added and the mixture was allowed to warm to rt. The aqueous phase was extracted with CH₂Cl₂ (2 x 10 mL). The combined organic phases were washed with brine (10 mL), dried over MgSO₄, and concentrated. Purification by flash chromatography (1:20 EtOAc/hexanes, 30 g of silica gel, 20 x 2 cm column) gave 58 mg (90%) of **3b** as a white solid: mp 86–87 °C; R_f 0.54 (1:9 EtOAc/hexanes); IR (thin film) 3029, 2941, 1733, 1456, 1377, 764, 702 cm^{–1}; ¹H NMR (500 MHz, CDCl₃) δ 7.26–7.15 (m, 3 H, Ar-H), 6.96–6.93 (m, 2 H, Ar-H), 3.09 (dd, 1 H, *J* = 10.1, 5.7 Hz), 2.33 (dd, 1 H, *J* = 13.9, 10.1 Hz), 2.21 (d, 1 H, *J*_{AB} = 15.2 Hz), 2.20 (d, 1 H, *J*_{A'B'} = 15.1 Hz), 2.09 (d, 1 H, *J*_{A'B'} = 15.1 Hz), 2.01 (d, 1 H, *J*_{AB} = 15.2 Hz), 1.85–1.80 (m, 1 H), 1.83 (br s, 3 H), 1.79 (br s, 3 H), 1.26 (s, 3 H), 0.62 (s, 3 H); ¹³C NMR (126 MHz, CDCl₃) δ 225.00, 145.65, 128.64, 128.58, 128.48, 126.96, 126.37, 53.34, 50.61, 48.92, 48.52, 47.72, 41.55, 24.13, 24.03, 23.71, 20.93; HRMS calcd for C₁₉H₂₄O (M⁺) 268.1827; found 268.1827.

Cyclooctenes 4b and 5b. Cycloadducts **4b** and **5b** were prepared by following the procedure for the preparation of **3b** using isoprene in place of dimethylbutadiene. A colorless oil was obtained as an inseparable 5:1 mixture (determined by integration of the methyl ¹H NMR signals at 1.31 and 1.27 ppm) of two regioisomers in 84% combined yield. For the major product **5b**: R_f 0.54 (1:9 EtOAc/hexanes); IR (thin film) 3055, 2946, 2899, 1733, 1456, 1377, 1215, 1076, 763, 702 cm^{–1}; ¹H NMR (500 MHz, CDCl₃) δ 7.30–7.16 (m, 3 H, Ar-H), 6.97–7.01 (m, 2 H, Ar-H), 5.51–5.47 (m, 1 H), 3.25 (dd, 1 H, *J* = 9.7, 6.6 Hz), 2.31 (dd, 1 H, *J* = 13.9, 9.7 Hz), 2.21 (br dd, 1 H, *J* = 16.4, 7.1 Hz), 2.12–2.02 (m, 2 H), 1.97 (br d, 1 H, *J* = 16.2 Hz), 1.93 (dd, 1 H, *J* = 13.8, 6.6 Hz), 1.79 (br s, 3 H), 1.31 (s, 3 H), 0.64 (s, 3 H, H); ¹³C NMR (126 MHz, CDCl₃) δ 224.44, 145.25, 135.40, 128.60, 128.49, 126.45, 121.34, 53.59, 48.39, 48.17, 45.82, 43.55, 41.86, 28.46, 24.24, 20.81; Anal. Calcd for C₁₈H₂₂O: C, 84.99; H, 8.72. Found: C, 84.72; H, 8.70.

Cycloaddition of Dienone 1c with Furan: Endo- and Exo-Ethyl Epimers of 2c. To a solution of dienone **1c** (23 mg, 0.17 mmol) and furan (23 mg, 0.34 mmol) in CH₂Cl₂ (10 mL) at –78 °C was added BF₃•OEt₂ (20 μL, 0.17 mmol). The solution was then warmed to –50 °C and stirring was continued for 3 h at that temperature. Sat. aqueous NaHCO₃ (3 mL) was added and the mixture was allowed to warm to rt. The aqueous phase was extracted with CH₂Cl₂ (2 x 10 mL). The combined organic phases were washed with brine (10 mL), dried over MgSO₄, and concentrated. Purification by flash chromatography (1:10 EtOAc/hexanes, 30 g of silica gel, 20 x 2 cm column) provided 14 mg of **2c** (*exo* ethyl epimer) as a white solid and 11 mg of **2c** (*endo* ethyl epimer) as a clear, colorless oil (combined yield 72%).

2c (exo Et): R_f 0.22 (1:9 EtOAc/hexanes); IR (thin film) 3062, 2942, 1743, 1450, 1378, 1045, 943, 900 cm^{–1}; ¹H NMR (500 MHz, CDCl₃) δ 6.35 (br dd, 1 H, *J* = 6.1, 1.4 Hz), 6.29 (br dd, 1 H, *J* = 6.1, 1.4 Hz), 4.36–4.34 (m, 2 H), 2.38 (dd, 1 H, *J* = 12.4, 9.8 Hz, HC(3)), 2.09–2.16 (m, 1 H, HC(2)), 1.41–1.49 (m, 1 H), 1.04–0.95 (m, 1 H, HC(3)), 1.00 (s, 3 H), 0.92 (s, 3 H), 0.89 (t, 3 H, *J* = 7.3 Hz), 0.82–0.72 (m, 1 H); ¹³C NMR (126 MHz, CDCl₃) δ 212.78, 134.44, 133.77, 87.70, 87.20, 57.52, 53.81, 41.52, 38.90, 25.39, 14.46, 11.94, 11.52; Anal. Calcd for C₁₃H₁₈O: C, 75.69; H, 8.80. Found: C, 75.78; H, 8.88.

2c (endo Et): R_f 0.21 (1:9 EtOAc/hexanes); mp 54–55 °C; IR (thin film) 3082, 2989, 1745, 1454, 1377, 1044, 937, 903 cm^{–1}; ¹H NMR (500 MHz, CDCl₃) δ 6.33–6.30 (m, 2 H), 4.49 (br s, 1 H), 4.37 (br s, 1 H), 1.88 (dd, 1 H, *J* = 12.2, 5.8 Hz, HC(3)), 1.83–1.76 (m, 1 H), 1.65–1.71 (m, 1 H), 1.62 (dd, 1 H, *J* = 12.1, 10.3 Hz, HC(3)), 1.51 (dddd, 1 H, *J* = 10.2, 10.2, 5.8, 3.9 Hz, HC(2)), 1.04 (s, 3 H), 0.98 (s, 3 H), 0.97 (t, 3 H, *J* = 7.3 Hz); ¹³C NMR (126 MHz, CDCl₃) δ 212.52, 134.26, 133.99, 87.11,

85.01, 57.35, 54.38, 44.86, 37.65, 21.35, 14.15, 13.14, 12.56; Anal. Calcd for C₁₃H₁₈O: C, 75.69; H, 8.80. Found: C, 75.87; H, 8.98.

Cyclooctene 8c. Cycloadduct **8c** was prepared by following the procedure for the preparation of **8b**. The product was obtained as a colorless oil in 64% yield: *R_f* 0.48 (1:9 EtOAc/hexanes); IR (thin film) 3035, 2947, 1743, 1456, 1376, 1008, 947, 902 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.17 (dd, 1 H, *J* = 5.6, 2.7 Hz), 6.11 (dd, 1 H, *J* = 5.6, 2.7 Hz), 2.42 (br s, 1 H), 2.38 (br s, 1 H), 2.21 (br d, 1 H, *J* = 11.1 Hz), 2.14 (dd, 1 H, *J* = 13.3, 9.5 Hz), 1.86-1.85 (m, 1 H), 1.52 (ddd, 1 H, *J* = 11.2, 3.7, 3.4 Hz), 1.45 (m, 1 H), 1.03 (s, 3 H), 0.99 (dd, 1 H, *J* = 13.5, 4.4 Hz), 0.95 (s, 3 H), 0.87 (t, 3 H, *J* = 7.1 Hz), 0.78-0.68 (m, 1 H); ¹³C NMR (126 MHz, CDCl₃) δ 215.39, 137.51, 136.71, 54.69, 53.33, 51.69, 50.80, 42.77, 40.38, 39.18, 26.23, 18.78, 15.28, 12.16; Anal. Calcd for C₁₄H₂₀O: C, 82.30; H, 9.87. Found: C, 82.05; H, 9.95.

Cyclooctene 3c. Cycloadduct **3c** was prepared by following the procedure for the preparation of **3b**. The product was obtained as a colorless oil in 93% yield: *R_f* 0.56; IR (thin film) 2989, 2961, 1735, 1557, 1455, 1377 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 2.13-2.06 (m, 2 H), 2.04 (dd, 1 H, *J* = 13.3, 9.3 Hz), 1.99-1.91 (m, 2 H), 1.80-1.72 (m, 1 H), 1.71 (br s, 3 H), 1.70 (br s, 3 H), 1.55-1.48 (m, 1 H), 1.18 (br dd, 1 H, *J* = 12.6, 6.4 Hz), 1.08 (s, 3 H), 0.99 (s, 3 H), 0.95-0.90 (m, 1 H), 0.87 (t, 3 H, 6.4 Hz); ¹³C NMR (126 MHz, CDCl₃) δ 225.58, 127.60, 126.51, 51.62, 50.76, 48.94, 47.98, 41.80, 40.41, 26.85, 24.02, 23.82, 23.81, 18.80, 12.15; Anal. Calcd for C₁₅H₂₄O: C, 81.76; H, 10.98. Found: C, 81.85; H, 11.05.

Cyclooctenes 4c and 5c. Cycloadducts **4c** and **5c** were prepared by following the procedure for the preparation of **3b** using isoprene in place of dimethylbutadiene. A colorless oil was obtained as an inseparable 4.2:1 mixture (determined by integration of the methyl ¹H NMR signals at 1.13 and 1.10 ppm) of two regioisomers in 84% combined yield. For the major product **5c**: *R_f* 0.54 (1:9 EtOAc/hexanes); IR (thin film) 3070, 2965, 1735, 1454, 1377 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.31 (br d, 1 H, *J* = 5.3 Hz), 2.07 (dd, 1 H, *J* = 13.2, 9.0 Hz), 2.00-1.85 (m, 5 H), 1.71 (br s, 3 H), 1.57-1.51 (m, 1 H), 1.29 (dd, 1 H, *J* = 13.2, 7.0 Hz), 1.13 (s, 3 H), 1.02 (s, 3 H), 1.00-0.93 (m, 1 H), 0.89 (t, 3 H, *J* = 6.9 Hz); ¹³C NMR (126 MHz, CDCl₃) δ 225.03, 134.26, 121.28, 52.04, 47.82, 45.69, 43.57, 42.60, 41.04, 28.33, 26.63, 24.48, 18.58, 12.32; Anal. Calcd for C₁₄H₂₂O: C, 81.50; H, 10.75. Found: C, 81.33; H, 10.88.

Cyclooctene 3d. Cycloadduct **3d** was prepared by following the procedure for the preparation of **3b**. The product was obtained as a colorless oil in 92% yield: *R_f* 0.57 (1:9 EtOAc/hexanes); IR (thin film) 2923, 2864, 1735, 1540, 1436, 1378 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 2.32 (dd, 1 H, *J* = 13.1, 8.0 Hz), 2.17 (br d, 1 H, *J* = 17.1 Hz), 2.10-1.89 (m, 4 H), 1.86-1.79 (m, 1 H), 1.77-1.71 (m, 1 H), 1.64 (br s, 3 H), 1.61 (br s, 3 H), 1.57-1.52 (m, 2 H), 1.26 (d, 1 H, *J* = 13.0 Hz), 1.17 (s, 3 H), 1.14-1.04 (m, 3 H), 0.84-0.75 (m, 1 H); ¹³C NMR (126 MHz, CDCl₃) δ 223.86, 126.53, 124.88, 54.21, 50.35, 50.19, 45.83, 41.45, 38.87, 33.97, 32.04, 26.17, 24.74, 23.48, 23.40, 22.58; Anal. Calcd for C₁₆H₂₄O: C, 82.70; H, 10.41. Found: C, 82.72; H, 10.37.

Cyclooctene 3e. To a solution of dienone **1e** (30 mg, 0.22 mmol) and 2,3-dimethylbutadiene (36 mg, 0.44 mmol) in ClCH₂CH₂Cl (12 mL) at rt was added BF₃•OEt₂ (40 μ L, 0.022 mmol, 0.5 M in CH₂Cl₂). The solution was then heated to 40 °C and stirring was continued for 1 h at that temperature. Sat. aqueous NaHCO₃ (5 mL) was added and the mixture was allowed to cool to rt. The aqueous phase was extracted with CH₂Cl₂ (2 x 10 mL). The combined organic phases were washed with brine (10 mL), dried over MgSO₄, and concentrated. Purification by flash chromatography (1:80 EtOAc/hexanes,

30 g of silica gel, 20 x 2 cm column) gave 32 mg (67%) of **3e** as a clear, colorless oil: R_f 0.57 (1:9 EtOAc/hexanes); IR (thin film) 2918, 2985, 1736, 1451, 1375, 1234 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 2.38 (br d, 1 H, $J = 16.5$ Hz), 2.30-2.25 (m, 1 H), 2.22-2.17 (m, 1 H), 2.09 (dd, 1 H, $J = 13.1, 9.8$ Hz), 2.08 (br d, 1 H, $J = 16.8$ Hz), 1.99 (br d, 1 H, $J = 17.1$ Hz), 1.95 (br d, 1 H, $J = 16.7$ Hz), 1.83-1.77 (m, 1 H), 1.69 (br s, 3 H), 1.68 (br s, 3 H), 1.59-1.52 (m, 1 H), 1.36-1.22 (m, 3 H), 1.20 (ddd, 1 H, $J = 13.2, 6.4, 1.5$ Hz), 1.07 (s, 3 H); ^{13}C NMR (126 MHz, CDCl_3) δ 225.80, 127.15, 126.41, 60.72, 51.10, 49.25, 47.28, 41.87, 41.81, 36.59, 35.95, 25.99, 23.96, 23.38, 23.33; Anal. Calcd for $\text{C}_{15}\text{H}_{22}\text{O}$: C, 82.52; H, 10.16. Found: C, 82.60; H, 10.02.

Cyclooctenes 4e and 5e. Cycloadducts **4e** and **5e** were prepared by following the procedure for the preparation of **3e**. A colorless oil was obtained as a 4.3:1 mixture (determined by integration of the methyl ^1H NMR signals at 1.08 and 1.11 ppm) of two regioisomers in 55% combined yield. The major product was determined as **4e**: R_f 0.58 (1:9 EtOAc/hexanes); IR (thin film) 3028, 2964, 1735, 1650, 1453, 1375, 1210 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.35 (br s, 1 H), 2.32-2.20 (m, 3 H), 2.11 (dd, 1 H, $J = 13.3, 9.8$ Hz), 2.10-1.90 (m, 2 H), 1.84 (br d, 1 H, $J = 18.0$ Hz), 1.82-1.75 (m, 1 H), 1.69 (br s, 3 H), 1.60-1.55 (m, 1 H), 1.35-1.26 (m, 3 H), 1.22 (ddd, 1 H, $J = 13.4, 7.4, 1.8$ Hz), 1.08 (s, 3 H); ^{13}C NMR (126 MHz, CDCl_3) δ 225.43, 134.04, 121.82, 60.47, 51.61, 43.48, 42.46, 41.97, 41.84, 37.04, 35.88, 27.95, 25.79, 23.24; Anal. Calcd for $\text{C}_{14}\text{H}_{20}\text{O}$: C, 82.30; H, 9.87. Found: C, 82.45; H, 9.94.

^1H NMR Basis for Stereochemical Assignments

General Trends. In the bicyclo[4.2.1]nonen-9-ones prepared in this study, *endo*-disposed protons on the 2-carbon bridge were consistently found to appear at lower field than their *exo* counterparts. This is consistent with analogous trends observed for intramolecular [4+3]-adducts,³ as well as earlier observations by Lightner for structurally similar bicyclo[2.2.1]heptan-7-ones.⁴ These consistent chemical shift differences, together with diagnostic *cis* and *trans* coupling constants for the protons in the 2-carbon bridge and nOe interactions, allowed for their unequivocal assignment.

Specific Examples from Cycloadducts of **1c**:

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- ¹ Yates, P.; Yoda, N.; Brown, W.; Mann, B. *J. Am. Chem. Soc.* **1958**, *80*, 202-205.
- ² Cyclopentadiene was prepared from its dimeric form by distillation according to the literature procedure: Partridge, J. J.; Chadha, N. K.; Uskokovic, M. R. *Org. Synth.* **1984**, *63*, 44.
- ³ Wang, Y.; Arif, A. M.; West, F. G. *J. Am. Chem. Soc.* **1999**, *121*, 876-877.
- ⁴ Lightner, D. A.; Crist, B. V.; Kalyanam, N.; May, L. M.; Jackman, D. E. *J. Org. Chem.* **1985**, *50*, 3867-3878.

1d

1e

INDEX	FREQUENCY (PPM)	HEIGHT	INDEX	FREQUENCY (PPM)	HEIGHT
1	7.588	2.0	35	4.726	2.8
2	7.583	2.8	36	4.724	2.8
3	7.558	3.2	37	4.721	2.4
4	7.341	1.6	38	4.300	2.7
5	7.317	3.9	39	4.057	2.3
6	7.312	1.7	40	4.032	2.4
7	7.297	1.3	41	3.006	2.1
8	7.292	2.4	42	2.981	2.1
9	7.292	2.5	43	1.551	3.0
10	7.262	11.3	44	1.115	21.7
11	7.258	2.2	45	0.724	19.4
12	7.238	1.7	46	0.001	22.1
13	7.234	2.3			
14	7.215	3.8			
15	7.210	2.4			
16	7.196	1.5			
17	7.192	3.6			
18	7.169	2.3			
19	7.165	1.4			
20	7.146	2.0			
21	7.027	2.8			
22	7.021	3.7			
23	6.999	2.9			
24	6.995	2.1			
25	6.442	1.5			
26	6.437	1.4			
27	6.422	3.1			
28	6.417	3.2			
29	6.392	3.3			
30	6.387	3.1			
31	6.372	1.4			
32	6.367	1.5			
33	5.303	1.3			
34	4.729	2.5