Synthesis and Stereochemistry of (E,E)-1,4-Diacetoxy-2-methyl-1,3-butadiene and Related Compounds

John F. W. Keana*[1] and Paul E. Eckler

Department of Chemistry, University of Oregon, Eugene, Oregon 97403

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Enol acetylation of aldehyde **2**, prepared from **1** by SeO_2 oxidation, has led to crystalline (*E,E*)-1,4-diacetoxy-2-methyl-1,3-butadiene (**6**) together with lesser amounts of the *Z,E* isomer **7** and the *E,Z* isomer **8**. The overall yield of **6** + **7** + **8** from isoprene was about 20%. Stereochemical assignments followed from the uv and NMR spectra of the dienes and constituted a revision of an earlier assignment.[2] Unlike dienes **7** and **8**, diene **6** was at least as reactive in a Diels–Alder reaction toward benzoquinone as the known *E,E* diene **10**. The *E,E* stereochemistry of **6** was confirmed by conversion of **6** into diacetate **14** and diol **20**. These latter two substances were prepared from diene **16** via photooxygenation followed by reduction and acetylation.

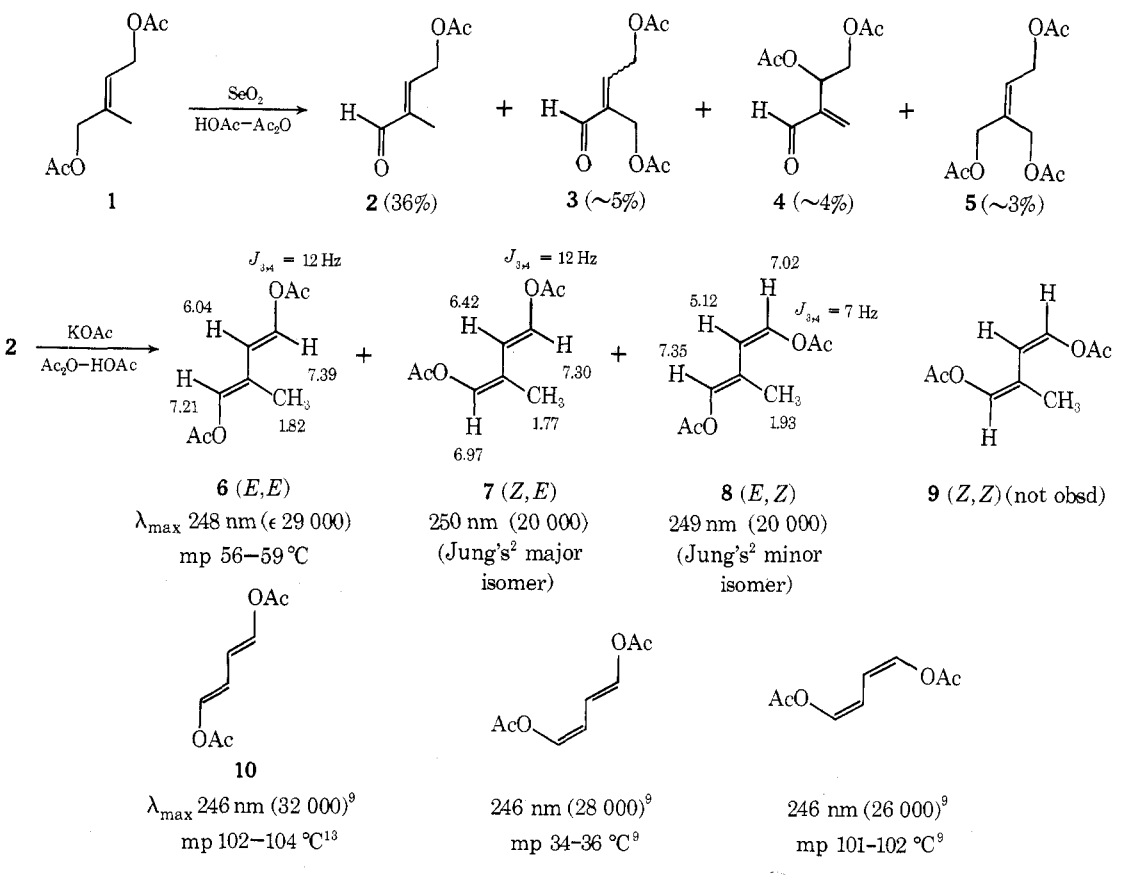
Recently, Jung[2] described a stereoselective synthesis of two oily isomers of 1,4-diacetoxy-2-methyl-1,3-butadiene. The *E,E* stereochemistry **6** and the *Z,Z* stereochemistry **7** were assigned to these substances based primarily on the NMR spectra of the substances and their tricyclic precursors. In connection with our synthetic program related to tetrodotoxin,[3] we have prepared (*E,E*)-1,4-diacetoxy-2-methyl-1,3-butadiene (**6**), mp 56–59 °C, by a different route and find the substance to be neither of those isomers previously described.[2] Herein, we describe our synthesis of **6** together with chemical and spectroscopic evidence which permits stereochemical assignment of all three presently known isomers of 1,4-diacetoxy-2-methyl-1,3-butadiene.

In our approach diacetate **1**[4] (predominantly the *E*[5] isomer) (Chart I), readily prepared by bromination[6] (84% yield) of isoprene followed by reaction (95% yield) of the dibromide mixture with KOAc–HOAc,[4] was oxidized with SeO_2 in $HOAc–Ac_2O$, producing the known[7] aldehyde **2** as the predominant product together with small quantities of aldehydes **3** and **4** and triacetate **5**. The structures of the latter three compounds followed from the analytical and spectral data given in the Experimental Section. Conversion of aldehyde **2** into a mixture of diacetoxydienes **6**, **7**, and **8** (67:16:17) was accomplished in 81% yield (after distillation) (20% overall from isoprene) by reaction of **2** with $KOAc–Ac_2O–HOAc$.[8] Upon cooling the isomeric mixture to −4 °C, the *E,E* isomer separated out as white crystals, obtained in 10% yield, mp 56–59 °C, after sublimation.

The stereochemical assignments shown in Chart I were deduced from the uv and NMR spectra as follows. Of the three isomers, crystalline **6** has the largest molar extinction coefficient in its uv spectrum. In the normethyl isomer series, crystalline (*E,E*)-1,4-diacetoxy-1,3-butadiene (**10**) also shows the largest ϵ value.[9]

With NMR spectra of three of the four possible *E,Z* isomers of 1,4-diacetoxy-2-methyl-1,3-butadiene in hand, one can

Chart I

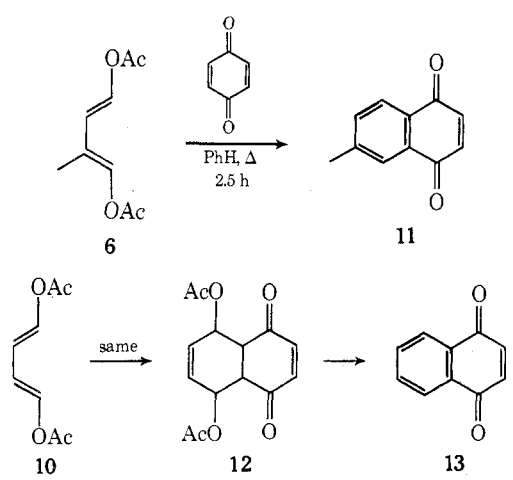


complete the stereochemical assignments by noting that in a conjugated diene, a vinyl proton cis to the other carbon–carbon double bond should be more deshielded than a proton in the trans position.[10] Secondly, a vinyl proton cis to an acetoxy group attached to the same double bond should be more deshielded than a corresponding trans proton.[11]

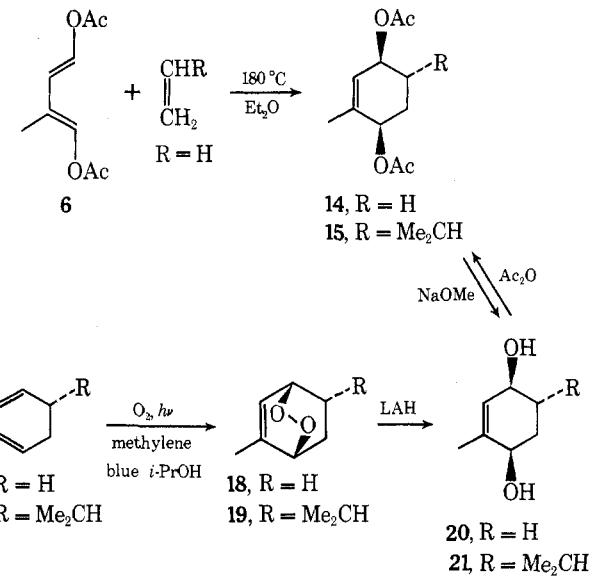
An inspection of the NMR data included with structures **6**, **7**, and **8** in Chart I shows the stereochemical assignments to be completely consistent with these earlier observations. It is clear from the magnitudes of $J_{3,4}$ that the *E* configuration about the $\Delta^{3,4}$ double bond obtains in isomers **6** and **7**. One would therefore predict that since H-3 is cis to the C-4 acetoxy group in **6** and **7**, the resonance (6.04 and 6.42 ppm, respectively) for this proton should appear at lower field than that of H-3 (5.12 ppm) in isomer **8**. Also, since H-4 is cis to the other carbon–carbon double bond in **6** and **7**, the resonance (7.39 and 7.30 ppm, respectively) for this proton should appear at lower field than that of H-4 (7.02 ppm) in isomer **8**. Both predictions are correct.

In order to assign the configuration about the $\Delta^{1,2}$ double bond in these isomers, one observes that H-1 appears at 7.21 and 7.35 ppm in compounds **6** and **8**, consistent with H-1 being cis to the other carbon–carbon double bond in these isomers. However, a value of 6.97 ppm for H-1 in isomer **7** requires that this isomer have the *Z* configuration about the $\Delta^{1,2}$ double bond. Based on these assignments, the major isomer of Jung[2] is the *Z,E* isomer **7**. Jung's minor isomer is the *E,Z* isomer **8** and our crystalline isomer is the *E,E* isomer **6**.

The following chemical evidence also corroborates the stereochemical assignments above. While Jung's major isomer **7** was unreactive toward benzoquinone in boiling benzene (no reaction after 18 h),[2] our *E,E* isomer **6** was at least as reactive as (*E,E*)-1,4-diacetoxy-1,3-butadiene (**10**).[13] Reaction was complete after 2.5 h, **6** affording naphthoquinone **11** in good yield and **10** affording the rather unstable, crystalline adduct **12** which slowly aromatized in solution to **13**. Hill and Carlson[12] have also described this latter reaction, obtaining directly naphthoquinone **13** together with small amounts of anthroquinone.



An independent confirmation of the *E,E* stereochemistry of **6** was obtained as follows. Reaction of **6** with ethylene at 180 °C afforded Diels–Alder adduct **14** in good yield. Methanolysis (NaOMe, MeOH) of **14** produced diol **20**. These latter two substances were synthesized by a stereospecific route which paralleled the known photooxygenation and subsequent transformations of α-phellandrene (**17** → **19** → **21** → **15**).[14] Thus, photooxygenation of 2-methyl-1,3-cyclohexadiene (**16**)[15] followed by reduction of the resulting epidioxide **18** with $LiAlH_4$ led to diol **20**. Both diol **20** and its diacetate **14** obtained in this way were identical with those substances obtained by the Diels–Alder reaction.



Crystalline **6** shows evidence of decomposition after exposure to air for 1 h. Samples stored in sealed vials at −20 °C show discoloration after several days. Crude samples are best sublimed and then stored at −20 °C under frozen cyclohexane. However, in view of the superior reactivity of *E,E* isomer **6** in the Diels–Alder reaction, the distilled mixture of isomers (see above) is probably suitable for many synthetic purposes.

Experimental Section[16]

Oxidation of Diacetate 1 with SeO_2. A. (*E*)-4-Acetoxy-2-methyl-2-butenal (2). A mixture of 64.4 g (0.345 mol) of freshly distilled 1,4-diacetoxy-2-methyl-2-butene[4] (**1**) (~4:1 *E:Z* by NMR), 32.7 g (0.294 mol) of SeO_2, 16 ml of Ac_2O, and 160 ml of HOAc was heated with stirring under N_2 at 115 °C for 3 h. The precipitated black Se (14.96 g, 65% based on SeO_2) was removed by filtration. Distillation of the filtrate through a heated column afforded crude **2** in two fractions, 16.57 g [bp 90–95 °C (12 mm)] and 2.80 g [bp to 70 °C (0.05 mm)]. A high-boiling fraction [bp 70–120 °C (0.05 mm)] was collected (20.63 g) and retained for further separation (see below). Redistillation of crude **2** afforded 17.8 g (36%) of **2**, bp 88–96 °C (12 mm) [lit.[7] bp 66–72 °C (2 mm)]; 2,4-DNP mp 164–166 °C (lit.[7] mp 166 °C).

The high-boiling fractions from two similar preparations of **2** were combined, amounting to 41.3 g. This mixture came from a total of 119 g of **1** and by NMR was about 1:1:1 **3:4:5**. Repeated distillation (see below) afforded fractions enriched in one or the other of the components.

B. 2-(Acetoxymethyl)-4-acetoxy-2-butenal (3). A 6.03-g fraction (5%), bp 82–90 °C (0.025 mm), was obtained by spinning band distillation and was shown to be essentially pure **3** by VPC on column B at 185 °C (t_R 4.0 min). Preparative VPC produced an analytical specimen as a colorless oil: NMR δ 2.06 (s, 3, Ac), 2.13 (s, 3, Ac), 4.86 (s, 2, CH_2), 5.05 (d, J = 6 Hz, 2, CH_2), 6.72 (t, J = 6 Hz, 1, vinyl), 9.50 (s, 1, CHO); ir 2815, 1745, 1695 cm^{-1}; uv max 218 nm (ε 11 500).

Anal. Calcd for $C_9H_{12}O_5$: C, 54.00; H, 6.04. Found: C, 53.82; H, 6.05.

A 2,4-DNP derivative was prepared by the method of Pattenden,[7] mp 151–153 °C (orange plates from MeOH).

Anal. Calcd for $C_{15}H_{16}N_4O_8$: C, 47.37; H, 4.24. Found: C, 47.42; H, 3.93.

C. 3,4-Diacetoxy-2-methylenebutanal (4). A 5.30-g fraction (4%), bp 62–73 °C (0.025 mm), was obtained by spinning band distillation and was shown to be essentially pure **4** by VPC on column B at 185 °C (t_R 2.0 min). A pure sample of **4** was obtained as a colorless oil by preparative VPC: NMR δ 2.05 (s, 3, Ac), 2.12 (s, 3, Ac), 4.29 (d, J = 5 Hz, 2, CH_2), 5.87 (t, J = 5 Hz, 1, H-3), 6.24 (bs, 1, vinyl), 6.52 (bs, 1, vinyl), 9.58 (s, 1, CHO); ir (film) 2830, 1750, 1690 cm^{-1}; uv max 212 nm (ε 8100).

A 2,4-DNP derivative was prepared by the method of Pattenden,[7] mp 170.5–171.5 °C (yellow needles from MeOH).

Anal. Calcd for $C_{15}H_{16}N_4O_8$: C, 47.37; H, 4.24. Found: C, 47.29; H, 4.20.

D. 1,4-Diacetoxy-2-(acetoxymethyl)-2-butene (5). A 3.9-g fraction (3%), bp 100–110 °C (0.025 mm), was obtained by spinning band distillation and was shown to be essentially pure **5** by VPC analysis on column B at 185 °C (t_R 5.8 min). Preparative VPC pro-

duced the analytical specimen of **5** as a colorless oil: NMR δ 2.06–2.08 (s, 9, Ac), 4.63 (s, 2, CH_2), 4.71 (s, 2, CH_2), 4.75 (d, J = 6 Hz, 2, CH_2), 5.87 (bt, J = 6 Hz, 1, vinyl); ir 1740, 1230 cm^{-1}; no uv max; MS m/e 244.092 (calcd for $C_{11}H_{16}O_6$, 244.095), 184, 171, 129.

(Z)-1,4-Diacetoxy-2-methyl-2-butene. A 1.51-g sample of (Z)-2-methyl-2-butene-1,4-diol[6] was treated with 1.50 g of KOAc (fused) in 3.0 ml of Ac_2O at 100 °C for 1 h. The mixture was diluted with Et_2O and $CHCl_3$ and the salt was removed by filtration. Distillation afforded 1.66 g (60%) of the title compound, bp 60–63 °C (0.10 mm). Preparative VPC afforded the analytical sample as a colorless oil: NMR δ 1.82 (s, 3, Me), 2.04 (s, 3, Ac), 2.07 (s, 3, Ac), 4.65 (s, 2, CH_2), 4.67 (d, J = 7 Hz, 2, CH_2), 5.59 (t, J = 7 Hz, 1, vinyl).

Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 57.72; H, 7.75.

(E,E)-1,4-Diacetoxy-2-methyl-1,3-butadiene (6). A solution of 3.91 g (27.6 mmol) of freshly distilled aldehyde **2** and 4.5 g (46 mmol) of KOAc (fused) in 5 ml of HOAc and 40 ml of Ac_2O was heated at 100–115 °C under N_2 for 19 h. Dilution with $CHCl_3$, removal of the salts by filtration, and distillation of the filtrate through a heated column produced 4.11 g (81%) of a mixture of **6, 7,** and **8,** bp 63–65 °C (0.03 mm). An average of five integrations of the C-3 protons in the NMR spectrum indicated the isomeric composition of the mixture to be 67% (E,E)-**6,** 16% (Z,E)-**7** and 17% (E,Z)-**8.** Upon standing overnight at −4 °C the mixture crystallized. The mass was warmed to 25 °C, slurried, and then filtered, washing with cyclohexane. The crystals were immediately sublimed (bath 50 °C, 0.005 mm), producing 532 mg (10%) of pure **6:** mp 53–58 °C; NMR δ 1.82 (s, 3, Me), 2.15 (s, 3, Ac), 2.18 (s, 3, Ac), 6.04 (d, J = 12 Hz, 1, H-3), 7.21 (s, 1, H-1), 7.39 (d, J = 12 Hz, 1, H-4); ir ($CHBr_3$) 1745, 1633, 1370, 1220, 930 cm^{-1}; uv max 248 nm (29 000); MS m/e 184.075 (calcd for $C_9H_{12}O_4$, 184.074), 142, 100. Our best sample of **6** showed mp 56–59 °C.

Relative Reactivities of Diene 6 and Diene 10 toward Benzoquinone. The reactions were run in NMR tubes following the procedure of Jung.[2] Tube I contained 17 mg (0.10 mmol) of diene **10** and 11 mg (0.10 mmol) of benzoquinone in 0.30 ml of CCl_4 (containing 3 drops of $CHCl_3$ per milliliter); tube II contained 17 mg (0.10 mmol) of diene **10** and 11 mg (0.10 mmol) of benzoquinone in 0.30 ml of benzene; tube III contained 23 mg (0.13 mmol) of diene **6,** mp 56–59 °C, and 14 mg (0.13 mmol) of benzoquinone in 0.38 ml of benzene; tube IV contained 22 mg (0.12 mmol) of diene **6** and 13 mg (0.12 mmol) of benzoquinone in 0.36 ml of CCl_4 (containing 3 drops of $CHCl_3$ per milliliter). All tubes were placed in an oil bath maintained at 86 ± 1 °C. The crystalline dienes dissolved on heating. After 2.5 h the tubes were cooled to 25 °C.

A. 5ξ,8ξ-Diacetoxy-5,8,9β,10β-tetrahydro-1,4-naphthoquinone (12). The solvent was removed from the crystalline mass obtained upon cooling tube I. THe 28-mg residue was essentially pure **12** by NMR. Crystallization from EtOAc–hexane afforded 13 mg, mp 90–94 °C. Recrystallization from $CHCl_3$–hexane afforded the analytical sample of **12:** mp 99–101 °C; NMR δ 2.02 (s, 6, OAc), 3.72 (dd, J = 2 and 4 Hz, 2, H-9, 10), 5.42 (dd, J = 2 and 4 Hz, 2, H-5, 8), 6.02 (bs, 2, H-6, 7), and 6.76 (s, 2, H-2, 3); uv max 233 nm (ε 8350) and 330 (570); MS m/e 278.078 (calcd for $C_{14}H_{14}O_6$, 278.079), 236, 219, 176, 136.

The NMR spectrum observed directly on tube II indicated that only quinone **12** was present. The solution darkened upon standing and the formation of quinone **13** was shown by the NMR spectrum. Chromatography over silica gel afforded 9 mg (50%) of yellow, crystalline quinone **13.** Sublimation afforded a sample of mp 116–120 °C (lit.[17] mp 125–126 °C).

B. 6-Methyl-1,4-naphthoquinone (11). The solvent was removed from tube III. An NMR spectrum of the residue showed that quinone **11** was the major product. The sample was combined with tube IV and chromatographed, affording 25 mg (73%) of quinone **11.** Sublimation afforded yellow crystals, mp 88–90 °C (lit.[18] mp 90–91 °C).

***cis*-3,6-Diacetoxy-1-methylcyclohexene (14).** A 1-l. high-pressure hydrogenation reactor was charged with 90 ml of ether and 1.426 g (7.75 mmol) of diene **6,** mp 50–57 °C. The reactor was sealed and pressurized with ethylene (cylinder pressure, 80 atm) (ca. 3 mol of ethylene added). The reactor was heated at 180–190 °C for 53 h (occasional agitation). After cooling, the reactor was vented and the contents were filtered. The filtrate was concentrated and distilled, affording 1.168 g (71%) of adduct **14** as a colorless oil, bp 65–69 °C (0.03 mm). A portion was chromatographed over silica gel and then purified by preparative VPC on column B at 180 °C (t_R 2.5 min): NMR δ 1.72 (s, 3, Me), 1.88 (m, 4, CH_2), 2.06 (s, 3, Ac), 2.10 (s, 3, Ac), 5.22 (m, 2, H-3, 6), 5.79 (m, 1, vinyl).

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.55. Found: C, 62.34; H, 7.50.

***cis*-1-Methylcyclohexene-3,6-diol (20).** A solution of 982 mg (4.56 mmol) of diacetate **14** in 10 ml (9.2 mmol) of 0.92 M NaOMe in MeOH was stirred at 0 °C for 1 h and then neutralized with HOAc and evaporated. The oily residue was chromatographed over silica gel. Elution with EtOAc afforded 495 mg (97%) of pure diol **20** as a colorless oil: NMR δ 1.82 (m, 7), 3.9–4.2 (m, 2, H-3, 6), 5.60 (m, 1, vinyl); MS m/e 128.085 (calcd for $C_7H_{12}O_2$, 128.084), 118, 95.

Diol 20 and Diacetate 14 from Photooxygenation of Diene 16. The procedure of Stolow[14] was followed. An ice-cooled solution of 100 mg of diene **16,** obtained[15] by preparative VPC, and 1 mg of methylene blue in 50 ml of isopropyl alcohol was irradiated with a 275-W GE sun lamp in the presence of excess O_2. When the chromophore at 259 nm reached a minimum (75 min), the solution was evaporated, giving 64 mg of a blue oil. Preparative TLC produced 28 mg (21%) of pure epidioxide **18** as a colorless, sharp-odored oil: NMR δ 1.45 (d, J = 8 Hz, 2, H-7, 8), 1.95 (d, J = 2 Hz, 3, Me), 2.25 (d, J = 8 Hz, 2, H-7, 8), 4.44 (bs, 1, H-1), 4.59 (bd, J = 6 Hz, 1, H-4), 6.30 (bd of q, J = 2 and 6 Hz, 1, H-3).

The entire sample was dissolved in 5 ml of ether and treated with 10 mg of $LiAlH_4$. After 1 h at 25 °C the usual workup afforded 25 mg (88%) of diol **20,** identical with the hydrolyzed Diels-Alder product (see above) by NMR, ir, and TLC behavior. Acetylation of diol **20** (prepared from epidioxide **18**) afforded 38 mg (90%) of diacetate **14,** identical with the Diels-Alder product by NMR, ir, TLC, and VPC behavior.

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Registry No.—*E*-**1,** 59054-99-8; *Z*-**1,** 59055-00-4; **2,** 26586-02-7; **3,** 59055-01-5; **3** 2,4-DNP, 59055-02-6; **4,** 59055-03-7; **4** 2,4-DNP, 59055-04-8; **5,** 59055-05-9; **6,** 52884-86-3; **10,** 15910-11-9; **12,** 59055-06-0; **14,** 59055-07-1; **16,** 1489-57-2; **18,** 59055-08-2; **20,** 59055-09-3; (Z)-2-methyl-2-butene-1,4-diol, 40560-13-2.

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