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Ensemble of Pinanones from the Permanganate Oxidation of Myrtenal

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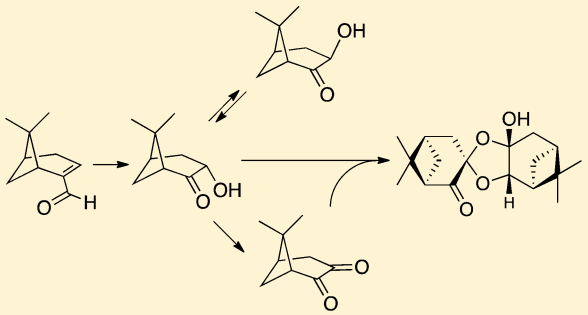
Supporting Information

ABSTRACT: The buffered permanganate oxidation of (−)-myrtenal, a member of the pinene family, provides the α-hydroxyketone (−)-(1*R*,3*S*,5*R*)-3-hydroxy-6,6-dimethylbicyclo[3.1.1]heptan-2-one in preparative yield (65% on a multigram scale). This α-hydroxyketone is oxidized, in a second reaction, to the α,β-diketone (1*R*,5*R*)-6,6-dimethylbicyclo[3.1.1]heptane-2,3-dione ("PinDione"). As both oxidations are fast, simple, safe, inexpensive, good-yielding, and multigram scalable, these transformations are a preparative expansion of the pinane family.



The terpenes have particular value as both starting materials and chiral auxiliaries. Among the terpenes, the pinene family is exceptional, as it offers enantiomers that are commercial (or easily made), affordable, and have excellent enantiomeric purity.[1] (1*R*,3*S*)-(−)-Myrtenal **1** is commercially available, and (1*S*,3*R*)-(+)-myrtenal is made from (+)-α-pinene in a single step (by SeO_2-catalyzed oxygenation).[2] Both enantiomers are versatile starting materials for auxiliary synthesis.[3−6]

In the course of a medicinal chemistry study, (−)-myrtenal (**1**) was subjected to buffered $KMnO_4$ oxidation[7] with the expectation of myrtenoic acid (**2**) as the product (Scheme 1). To our surprise, an ensemble of five products was obtained (Scheme 1), none of which was **2**. While compound **2** was obtained immediately thereafter (by buffered $NaOCl_2$ oxidation of **1**), the assignment of structures to the ensemble from the permanganate oxidation attracted our interest. Each compound in the ensemble had distinctive properties. The most polar product, obtained in low and variable yield, was a diacid. The second product (approximately 25% yield under unoptimized conditions) was a monoacid. The third (approximately 65% yield) was a colorless neutral compound. The fourth and least polar compound (approximately 5−10% yield) was a lemon yellow colored solid. The fifth, also a minor product, was a crystalline compound obtained by letting the washed and concentrated organic extracts from the reaction stand. It was a neutral compound of an unexpected molecular mass (empirical formula of $C_{18}H_{26}O_4$, hence a product of "dimeric" origin). The structures of the five products were assigned by the appropriate combination of elemental analysis, IR and NMR spectroscopy, mass spectrometry, X-ray crystallography, and comparison to literature data.

The diacid product was pinic acid **3**.[8] Optimization of the oxidation (vide infra) reduced the yield of this diacid to an acceptably low value. The data for the monocarboxylic acid gave an empirical formula of $C_{10}H_{14}O_4$. Placement of the carboxylic acid (accounting for two of the four oxygens) on the β-carbon of a ketone (^{13}C NMR δ 209.2) was strongly suggested by the copious release of gas accompanying its sharp melting point. The identity of the fourth oxygen atom as a tertiary alcohol followed from the spectroscopic data (IR 3328 cm^{-1}; ^{13}C NMR δ 82.1). Accordingly, this acid was formulated as a 2-hydroxy-3-oxobicycloheptan-2-oic acid. The uncertainty of the stereochemistry was dispatched by single-crystal X-ray analysis (structure **4**). The relative stereochemistry of **4** coincides with permanganate approach to the sterically more accessible alkene face.[9] Optimization of the myrtenal oxidation procedure reduced the yield of **4** to very small quantities.

The major product of the reaction was a waxy, low-melting colorless solid having an empirical formula of $C_9H_{14}O_2$. On the presumption that the probable mechanism for loss of a single carbon atom was decarboxylation, and recognizing that the two oxygen atoms of the product required separate assignments to a ketone (IR 1718 cm^{-1}; ^{13}C NMR δ 213.8) and to a secondary alcohol (IR 3447 cm^{-1}; ^{13}C NMR δ 71.2), this product was formulated as 1*R*-(1α,3α,5α)-3-hydroxy-6,6-dimethylbicyclo-[3.1.1]heptan-2-one (**5**). The assigned C-3 stereochemistry coincides again with the approach of the permanganate to the less protected alkene face. This relative stereochemistry for **5** was supported by ^1H NOE (Figure S9 of the Supporting Information). The alternative formulation of this ketol as the 2-hydroxybicyclo[3.1.1]heptan-3-one was excluded by the ^1H NMR resonance of the alcohol methine (δ 4.17, dd, J = 9.6, 3.2 Hz, hence showing two ^3J couplings to the diastereotopic

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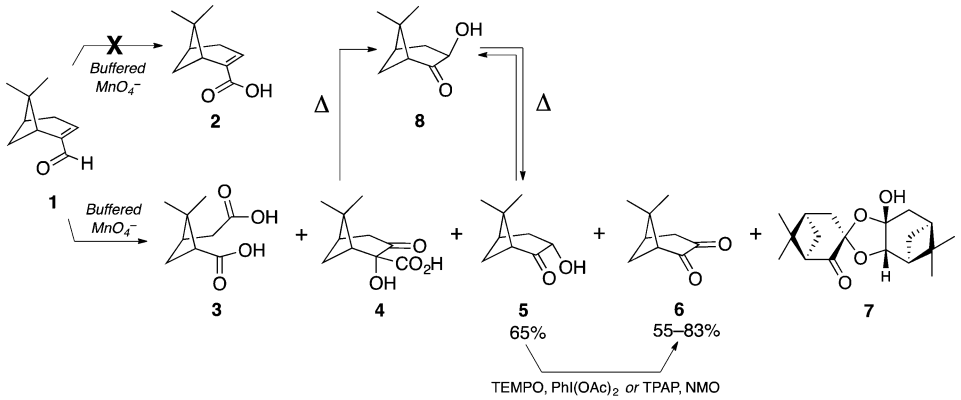
Scheme 1. Preparative Transformations of (−)-Myrtenal to Pinanedione 6 and Pinanones 5, 7, and 8



hydrogens of an adjacent methylene carbon). Although (−)-**5** is known, it is an uncharacterized pinane derivative. In contrast, its enantiomer (+)-**5** was characterized by Lavallée and Bouthillier using a synthetically unambiguous route.[10] The physical and spectroscopic data match. Optimization of the myrtenal oxidation gave (−)-**5** in multigram quantities in an isolated yield of 65%.

Elemental analysis and MS gave an empirical formula for the yellow colored neutral molecule of $C_9H_{12}O_2$. Its assignment as the dehydrogenation product of **5**—that is, the known[11,12] β-diketone "PinDione" **6**—followed from its yellow color[11] and its spectroscopic (IR 1737, 1721 cm^{-1}; ^{13}C NMR δ 197.1 and 195.8) data. Diketone **6** is presumed to arise by adventitious permanganate oxidation of **5**.

The fifth compound was the crystalline compound that set out upon prolonged—months—standing of the washed and concentrated crude reaction organic extract. Analysis of these crystals gave an empirical formula of $C_{18}H_{26}O_4$, hence signifying a new product arising from the combination of two reaction products. Its identity as structure **7** was by crystallographic analysis. Although not evident from the planar structure of Scheme 1, **7** is stabilized by an intramolecular hydrogen bond between the alcohol of its hemiketal and its ketone (Figure 1). The chemistry leading to this structure is the

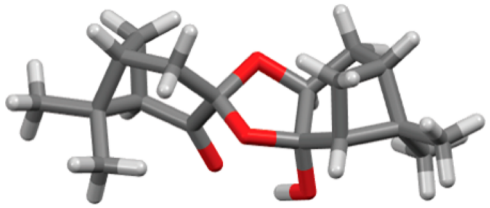


Figure 1. Solid-state structure of **7**.

complementary pairing of the α-hydroxyketone substructure of **5** with the dione substructure of **6**. A separate experiment indicated that at the millimolar concentrations of ^1H NMR analysis in $CDCl_3$ solution, **7** does not form instantaneously (examination of an equimolar mixture of **5** and **6** indicates a slow reaction, occurring over a period of weeks). Formation of **7** occurs much more rapidly when the solvent of this same reaction mixture is allowed to slowly evaporate. Once formed, the compound is stable under the conditions of NMR and melting point analyses.[13]

The value of these structures correlates directly to the enantiomeric purity of the myrtenal. Commercial (−)-myrtenal **1** has a nominal purity of ≥97% and a representative rotation (neat) of $[\alpha]_D^{20} = -14.6 \pm 1$. Previous observation supports enantiomeric purity. The enantiomeric ratio (er) reported by Hayoz and von Zelewsky for commercial (−)-myrtenal was ≥93:7.[3a] Zepeda et al.[4a] reported an er of ≥95:5, while Sala et al.[3f] reported an er value of 98:2. The purified (−)-myrtenal–derived auxiliaries of von Zelewsky et al.[3b] have an er ≥98:2. In our hands, analysis by chiral support chromatography confirmed an er for **5** of ≥97:3 (Figure S10 of the Supporting Information).

The reaction conditions were optimized for the yield and purity of ketol **5**. An important improvement was the use of $NaMnO_4$ as the permanganate oxidant. Although $NaMnO_4$ is more expensive than $KMnO_4$, its cost is still modest and its much greater water solubility significantly improved the reproducibility and experimental ease of the oxidation. Other improvements were the optimization of the $NaMnO_4$ stoichiometry and the use of vigorous mechanical stirring. The full product ensemble is recovered by EtOAc extraction of the quenched (acid and bisulfite) reaction. The carboxylic acid(s) are removed by $NaHCO_3$ extraction. Ketol **5** of ≥85% purity is obtained by removal of the solvent (yield 75%), while ketol **5** of analytical purity is obtained by silica chromatography purification (isolated yield 65%). Dione **6** is made from ketol **5** in ≥55% yield by TEMPO/$PhI(OAc)_2$ oxidation and purification by silica chromatography.

One question remained. The vigorous decarboxylation that occurs at the melting point of **4** suggested that formation of **5** occurred via in situ decarboxylation of **4**. Accordingly, the thermal decarboxylation of **4** was examined. The temperature required for this decarboxylation (12 h reflux in toluene as solvent, compared to the subambient temperature and reaction over minutes for the permanganate oxidation) excluded this possibility. The product was a *single* ketol, distinct from **5**. The ^1H NMR spectrum of the new ketol—notably the alcohol methine (δ 4.40, dd, J = 10.7 and 6.6 Hz, also showing two ^3J couplings to the diastereotopic hydrogens on an adjacent methylene carbon)—supports assignment of the new ketol as the 3β-diastereomer of **5**, 1*R*-(1α,3β,5α)-3-hydroxy-6,6-dimethylbicyclo[3.1.1]heptan-2-one (**8**). Under the same conditions used for the decarboxylation of **4**, compound **5** undergoes partial epimerization (approximately 10% conversion) to **8**. Hence compound **8** arises from **4** by a mechanism not requiring **5** as an intermediate. The identical epimerization was observed in a hot (60 °C) $CDCl_3$ solution (5:1 **5**/**8** after 24 h; 4:3 **5**/**8** after 48 h; 2:1 **5**/**8** after 72 h albeit with the appearance of new and unassigned ^1H resonances). Addition of

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superstoichiometric CD_3CO_2D to the $CDCl_3$ solution (60 °C, 24 h) facilitated the formation of an apparent equilibrium mixture of approximately 5:1 **5**/**8**.[14] This observation is consistent with the observations of Dumas et al.[15] and Kosugi et al.,[16] supporting the greater stability of 3β-substitution compared to 3α-substitution in the 6,6-dimethylbicyclo[3.1.1]-heptan-2-one system. Due to close R_f values, preparative separation of **5** and **8** by silica chromatography (within the confines of the limited number of solvent combinations we examined) was not practical.

The pinene family is an important source of reagents for stereochemical control. The permanganate oxidation of (−)-(1*R*)-myrtenal is a practical synthesis of hydroxypinanone **5**, from which further oxidation easily provides the pinanedione **6**. This two-step sequence to **6** is very competitive compared to existing routes that use nopinone as the immediate precursor.[12] Both oxidations are fast, simple, safe, scalable, and inexpensive. Moreover, as (+)-(1*S*)-myrtenal is prepared trivially (via *t*BuOOH/SeO_2 allylic oxidation of (+)-(1*R*)-α-pinene),[2] there is preparative access to both enantiomers. These reactions expand the functional group array available for preparative transformation within the pinane family.

EXPERIMENTAL SECTION

The NMR chemical shifts were referenced internally to $CDCl_3$ (^{1}H δ 7.26; ^{13}C δ 77.1). Coupling constants are reported as they are observed and are uncorrected for non-first-order behavior. ^{1}H NMR assignments were made (where reported) with reference to the 7-CH_2 Z-bridge (*endo*, *exo*) and 2-keto containing the X-bridge (*syn*, *anti*) made in previous assignments.[17] The compound numbering and stereochemical terminology for the pinanes are given in Figure S7 (representative NOE data for **5**) of the Supporting Information. Due to the difficulty of unambiguous assignment of the diastereotopic 4-CH_2 ^{1}H resonances,[17d] the 4-CH_2 assignments where given are tentative. Several commercial lots of (−)-1*R*,5*S*-myrtenal (**1**, [18486-69-6]) were purchased from Aldrich or Fluka. The "purum" quality of these lots was 97%, with a nominal (neat) rotation at ambient temperature of $[\alpha]_D$ −14.6. In our hands, the observed $[\alpha]_D$ for (+)-myrtenal [23727-16-4], prepared from (+)-α-pinene having a 97:3 er, was +14.95 (neat). Using the presumption that the contribution of the impurities in commercial (−)-myrtenal to the rotation is negligible, the nominal rotation of commercial (−)-myrtenal corresponded to an approximate er value of no less than 95:5. Our chromatographic estimation for the enantiomeric purity of **5** (er of 97:3) was fully consistent with previous observation (as discussed above).

(1*R*,3*R*)-3-Carboxy-2,2-dimethylcyclobutaneacetic acid [106454-26-6] (3, $C_9H_{14}O_4$). Using the optimized reaction conditions, the yield of this diacid from **1** was variable (≤10%). Its structure assignment was made by comparison of the ^{1}H NMR spectrum to an authentic sample:[8] ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.78 (dd, 1H, J = 10.3, 7.8 Hz), 2.44−2.30 (m, 3H), 2.16−2.09 (m, 1H), 1.97−1.89 (m, 1H), 1.25 (s, 3H), 1.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.5, 179.2, 46.1, 43.0, 37.9, 35.1, 29.9, 24.2, 17.5; MS (ESI−) m/z 185.15 (calcd $[M - H]^-$ 185.08).

(−)-(1*R*,3*S*,5*R*)-3-Hydroxy-6,6-dimethylbicyclo[3.1.1]heptan-2-one [477334-65-9] (ref 18) (5, $C_9H_{14}O_2$). This procedure optimized the yield of **5**. To a vigorously (overhead) stirred solution of myrtenal (7.50 g, 50 mmol) in acetone (0.15 L) in a 2 L Morton flask was added a solution of NaH_2PO_4 (20.9 g, 0.12 mol) in water (0.15 L). An emulsion formed, having a meringue-like appearance. The emulsion thinned quickly with stirring to give a clear solution. An ice−water bath was placed under the flask to cool the reaction mixture to an internal temperature of 5−10 °C (approximately 5 min). A solution of $NaMnO_4$ (11.0 g, 77.5 mmol) in water (0.12 L) was added over 20 min (very rapid dropwise pace). The reaction was weakly exothermic. The mixture was stirred for 5 min after the $NaMnO_4$ addition was complete. EtOAc (0.25 L) was added as a single portion, with continued stirring, followed by the rapid dropwise addition of aqueous 6 M HCl (0.12 L). Solid $NaHSO_3$ (5 g) was added to clarify the solution.[19] Stirring was stopped after several minutes. The mixture was decanted into a separatory flask, leaving behind a small quantity of brown MnO_2 precipitate. The pale lemon yellow colored EtOAc solution was separated. The aqueous solution was extracted with four additional 0.25 L EtOAc portions. NMR analysis of the combined EtOAc extracts showed the presence of ketol **5** as the major product (approximately 80%) and ketoacid **4** (<5%) and dione **6** (<10%) as minor products. The combined EtOAc extracts were washed successively with brine (2 × 0.05 L), saturated aq $NaHCO_3$ (2 × 0.1 L), and brine (2 × 0.05 L). EtOAc was evaporated to give a yellow oil. The oil was taken up in Et_2O (0.1 L) and dried (Na_2SO_4). The Et_2O solution was filtered and evaporated to provide 5.96 g (approximately 35 mmol, 75%) of the ketol as a yellow oil containing approximately 5% of dione **6**. The ^{1}H NMR spectrum of this oil is given in the Supporting Information (Figure S1). Ketol of analytical purity was obtained by chromatographic purification. The crude ketol was dissolved in CH_2Cl_2 and applied to a 0.2 kg flash silica column equilibrated in CH_2Cl_2. The column was developed with steps of CH_2Cl_2 (0.4 L) and 9:1 CH_2Cl_2/Et_2O (0.8 L) to afford 0.40 g (2.6 mmol, 5%) of the dione **6** as a soft, lemon yellow colored solid and 5.00 g (32.4 mmol, 65%) of the hydroxyketone **5** as a colorless, waxy crystalline solid: mp 41−43 °C (enantiomer lit.[10] mp 39−42 °C); TLC R_f = 0.37 (4:1 $PhCH_3$/EtOAc), 0.33 (9:1 CH_2Cl_2/Et_2O), 0.58 (20:1 CH_2Cl_2/MeOH), 0.40 (initial development with 3:1 hexanes/Et_2O and final development with 2:1 hexanes/Et_2O); $[\alpha]_D^{25}$ −71 (*c* 1.06, $CHCl_3$) [enantiomer lit.[10] +67 (*c* 10, $CHCl_3$)]; HPLC (*R*,*R*)-Whelk-O column, 98:2 heptane/2-pentanol, 1.0 mL min^{-1}, t_R = 14.8 min (minor), t_R = 17.1 min (major), ≥97:3 er by peak integration; IR (neat) 3427, 2941, 2889, 1716, 1468, 1452, 1389, 1371, 1296, 1247, 1211, 1201, 1145, 1106, 1095, 1056, 1025 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.16 (3-CH, dd, 1H, J = 9.6, 3.3 Hz), 2.74−2.70 (1-CH, non-first-order m), 2.72−2.67 (7-CH_{anti}, obscured m showing partial J = 6.0, 2.4 Hz), 2.55 (4-CH_{endo}, symmetrical 11-line m with ω = 29.0 Hz, assigned as a dddd with J = 14.3, 9.4, 2.5, 2.5 Hz), 2.25 (5-CH, symmetrical seven line m with ω = 17.2 Hz, assigned as a dddd with J = 6, 6, 3, 3 Hz), 1.88 (4-CH_{exo}, ddd, J = 14.3, 3.2, 3.2), 1.60 (7-CH_{2syn}: d, J = 10.0 Hz), 1.35 (6-Me_{anti}, s), 0.87 (6-Me_{syn}, s); spin system assigned as $J_{1,5}$ = 5.6 Hz, $J_{1,7exo}$ = 5.6 Hz, $J_{3,4endo}$ = 9.6 Hz, $J_{3,4exo}$ = 3.2 Hz, $J_{4,4}$ = −14.3 Hz, $J_{4endo,5}$ = 2.5 Hz; $J_{4exo,5}$ = 2.5 Hz, $J_{4endo,7anti}$ = 2.5 Hz; $J_{5,7exo}$ = 6.0 Hz, $J_{7,7}$ = −10.0 Hz; ^{13}C NMR ($CDCl_3$, 100 MHz) δ C 213.8 (2-C), 40.4 (C-6); CH 69.2 (3-CH), 57.6 (1-CH), 40.7 (5-CH); CH_2 32.4 (4-CH_2), 28.0 (7-CH_2); CH_3 26.0 (*anti*), 23.2 (*syn*); MS (EI, 70 eV) m/z (rel intensity) 154 (18), 136 (20), 121 (15), 96 (10), 95 (67), 92 (10), 91 (12), 86 (18), 85 (14), 83 (100), 82 (11), 81 (21), 55 (30), 54 (18), 53 (21); MS (ESI QTOF) m/z 177.0915 (calcd for $[C_9H_{14}O_2 + Na]^+$, 177.0886). Anal. Calcd: C, 69.80; H, 9.28. Found: C, 70.10; H, 9.15).

(+)-(1*R*,2*R*,5*R*)]-2-Hydroxy-6,6-dimethyl-3-oxobicyclo[3.1.1]-heptan-2-oic Acid (4, $C_{10}H_{14}O_4$). Acidification of the aqueous bicarbonate extracts from the preceding protocol, followed by EtOAc extraction, secures only very small quantities of this acid. Using the preceding procedure, but with 7.5 equiv of NaH_2PO_4 and 2.5 equiv of $NaMnO_4$, this acid (2.1 g, 27%) was isolated from the silica column as a colorless amorphous solid. From this reaction were also isolated **5** (3.4 g, 55%) and **6** (0.69 g, 11%). Acid **4** was exceptionally crystalline. Crystallization from EtOAc provided analytically pure material: mp 139.5−140.5 °C (with decarboxylation); TLC R_f = 0.21 (80:20:1 $PhCH_3$/EtOAc/HCO_2H); $[\alpha]_D^{25}$ +77 (*c* 0.83, EtOH); IR (mineral oil mull) 3329, 1743, 1716, 1693, 1408, 1257, 1213, 1123, 1043, 880, 847, 834, 637 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.84 (4−CH_{2a}, ddd, 1H, J = 19.1, 2.7, 2.7 Hz), 2.70 (4-CH_{2b}, dd, 1H, J = 19.1, 3.3 Hz), 2.61 (1-CH, dd, 1H, J = 6.1, 6.1 Hz), 2.57 (7-CH_{exo}, dddd, 1H, J = 11.2, 6.0, 6.0, 2.7 Hz), 2.16 (5-CH, dddd, 1H, J = 6.1, 6.1, 3.1, 3.1 Hz), 1.49 (7-CH_{endo}, d, 1H, J = 11.2 Hz), 1.41 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (CD_3OD, 100 MHz) δ C 209.3, 174.3, 82.1, 40.4; CH 48.9 (5-CH), 39.7 (1-CH); CH_2 43.9, 28.88; CH_3 27.3, 21.6; MS (EI, 70 eV) m/z (rel intensity) 198 (M^+, 1), 180 (2), 156 (12), 138 (7), 113 (9), 112 (8), 111 (27), 110 (18), 109 (6), 97 (13), 95 (28), 96 (12), 85 (11),

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84 (15), 83 (43), 81 (12), 70 (10), 69 (100), 68 (11), 67 (17), 56 (19), 55 (45), 54 (18). The structure of **4** was determined by X-ray analysis of a 0.1 × 0.2 × 4.2 mm clear prism crystal, obtained upon cooling of a hot saturated EtOAc solution. Hydroxyketoacid **4** crystallized from EtOAc in the $P2_12_12_1$ space group (a = 6.968 Å, b = 8.073 Å, c = 17.744 Å).

(1*R*,5*R*)-6,6-Dimethylbicyclo[3.1.1]heptane-2,3-dione [145165-80-6] (6, $C_9H_{12}O_2$). Larger quantities of the dione were made from **5** via TEMPO-catalyzed oxidation. To a solution of 4.00 g (25.9 mmol) of crude **5** (from the EtOAc extractions) in CH_2Cl_2 (0.10 L), in a light-protected flask, were added $PhI(OAc)_2$ (8.40 g, 26.0 mmol) and TEMPO (0.40 g). The reaction mixture was stirred for 15 h. It was concentrated in vacuo to a volume of approximately 40 mL. This solution was diluted with hexanes (60 mL). A very small quantity of *i*PrOH was added to remove a slight cloudiness. The solution was applied to a silica column (0.25 kg, 25 cm × 6.0 cm diameter and protected from light) equilibrated in 1000:200:100:5 hexanes/CH_2Cl_2/EtOAc/*i*PrOH. Careful flash elution provided the pure dione, eluting as a yellow band immediately behind a brown band of TEMPO-derived residue and an additional impurity that contaminates the early dione fractions. Evaporation of the heart-cut fractions provides 2.20 g (14.4 mmol, 55%) of pure **6** as a lemon yellow colored semisolid: mp 85−88 °C; TLC R_f = 0.20 (10:1 hexanes/EtOAc), 0.60 (4:1 toluene/EtOAc); $[\alpha]_D^{25}$ +140 (c 1.0, EtOH); IR (mineral oil mull) 1737, 1721, 1480, 1332, 1294, 1261, 1247, 1218, 1207, 1196, 1099, 1054, 1042, 999, 988, 936, 850, 824 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.02 (1-CH, dd, J = 5.9, 5.9 Hz), 2.94−2.87 (7-CH_{2exo}, overlapping m assigned as a dddd, J = 11.7, 6.0, 6.0, 3.8 Hz), 2.87 (4-CH_{2endo}, overlapping m assigned as a ddd, J = 19.3, 3.8, 3.2 Hz), 2.72 (4-CH_{2exo}, dd, J = 19.5, 3.2 Hz), 2.48 (5-CH, symmetric seven line m assigned as a dddd, J = 6.0, 6.0, 3.2, 3.2 Hz), 1.71 (7-CH_{2endo}, d, J = 11.7 Hz), 1.48 (s, 6-Me_{anti}), 0.96 (s, 6-Me_{syn}); spin system assigned as $J_{1,5}$ = 6.0 Hz, $J_{1,7exo}$ = 6.0 Hz, $J_{4,4}$ = −19.3 Hz, $J_{4endo,5}$ = 3.7 Hz, $J_{4exo,5}$ = 3.2 Hz, $J_{4endo,7exo}$ = 2.7 Hz, $J_{5,7exo}$ = 6.0 Hz, $J_{7,7}$ = −11.4 Hz; ^{13}C NMR ($CDCl_3$, 75 MHz) δ C 197.0 (2-C), 195.7 (1-C), 42.4 (6-C); CH 56.6 (1-CH), 38.1 (5-CH); CH_2 41.3 (4-CH_2), 28.2 (7-CH_2); CH_3 26.4 (*anti*), 22.1 (*syn*), identical to literature values;[12a] MS (EI, 70 eV) m/z (rel intensity) 152 (M^+, 4), 151 (53), 137 (3), 124 (10), 110 (3), 109 (32), 108 (12), 96 (23), 95 (21), 83 (100), 82 (27), 81 (82), 80 (8), 79 (13), 69 (82), 67 (35), 55 (50), 54 (11), 53 (20); MS (ESI QTOF) m/z 153.0905 (calcd for $[C_9H_{13}O_2]^+$, 153.0910. Anal. Calcd: C, 70.57; H, 8.16. Found: C, 71.03; H, 7.95).

On a smaller scale, the diketone may be obtained in a higher yield using catalytic tetra-*N*-propylammonium perruthenate (TPAP) oxidation. To a stirred mixture of **5** (489 mg, 3.15 mmol) and NMO (350 mg, 3.2 mmol) in CH_2Cl_2 (6 mL) at room temperature under N_2 was added TPAP (52 mg, 5 mol %). After 20 min, the entire reaction mixture was transferred to a Sohxlet thimble. The thimble was extracted with pentane to give, upon evaporation of the pentane, 403 mg (2.7 mmol, 83%) of **6** as a yellow solid (mp 86−88 °C).

(1*R*,3*R*,3a′*S*,4′*S*,5*R*,6′*S*,7a′*R*)-7a′-Hydroxy-5′,5′,6,6-tetramethylhexahydrospiro[bicyclo[3.1.1]heptane-3,2′-[4,6]-methanobenzo[*d*][1,3]dioxol]-2-one (7, $C_{18}H_{26}O_4$). Following the bicarbonate, brine, and water washes of the reaction used to prepare **5**, the EtOAc extracts were concentrated to give a light yellow liquid. Upon standing for several months, colorless crystals formed. The crystals were collected and washed carefully with hexanes to remove their surface liquid. One crystal was mounted for the X-ray analysis. A portion of the remaining crystals was dissolved in $CDCl_3$ for NMR analysis. **7**: mp 120−122 °C; ^1H NMR (500 MHz) δ 5.69 (s, 1H), 4.07 (d, J = 7.8 Hz, 1H), 2.67 (dd, J = 5.5, 5.5 Hz, 1H), 2.55 (symm 16-line m, ω = 25.0 Hz including J = 10.6, 5.4, 2.4 Hz; 1H), 2.42 (ddd, J = 14.8, 2.1, 2.1 Hz, 1H), 2.32 (dd, J = 14.8, 4.2 Hz, 1H), 2.29 (broadened 3-line multiplet, assigned as a dd with the large J = 5.7, 5.7 Hz and unresolved small J, 1H), 2.25−2.17 (unsymm 18-line m, ω = 41.2 Hz, 3H), 2.01 (d, J = 10.6 Hz, 1H), 1.95−1.92 (7 line m, ω = 16.8 Hz, 1H), 1.87 (dd, J = 14.6, 4.1 Hz, 1H), 1.41 (d, J = 10.8 Hz, 1H), 1.38 (s, 3H), 1.30 (s, 3H), 0.89 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (125 MHz) δ C 211.6, 107.9, 104.4, 45.3, 38.3; CH 79.5, 55.8, 49.5, 40.3, 38.8; CH_2 37.0, 31.2, 25.9, 25.3; CH_3 26.8, 26.4, 23.3, 22.2; MS (ESI QTOF) m/z 329.1686 (calcd for $[C_{18}H_{26}O_4 + Na]^+$, 329.1723). The space group in the crystal structure of **7** is $P2_12_12_1$ (a = 9.420 Å, b = 9.708 Å, c = 17.113 Å).

(1*R*,3*R*,5*R*)-3-Hydroxy-6,6-dimethylbicyclo[3.1.1]heptan-2-one (8, $C_9H_{14}O_2$). A solution of **4** (396 mg, 2.00 mmol) in toluene (5 mL) was refluxed overnight. The reaction mixture was cooled to rt and diluted with water and extracted with EtOAc (2 × 20 mL). The EtOAc extracts were combined, dried ($MgSO_4$), and evaporated. The residue was purified by silica chromatography (98:2 $CHCl_3$/acetone) to give 397 mg (2.61 mmol, 83%) of **8** as an oil: TLC R_f = 0.38 (98:2 $CHCl_3$/acetone), 0.30 (initial development with 3:1 hexanes/Et_2O and final development with 2:1 hexanes/Et_2O); ^1H NMR ($CDCl_3$, 400 MHz) δ 4.37 (3-CH, dd, 1H, J = 10.6, 6.7 Hz), 2.73 (1-CH, dd, 1H, J = 6.2, 4.5 Hz), 2.69 (4-CH_{2endo}, ddd, 1H, J = 13.5, 10.6, 4.5 Hz), 2.50 (7-CH_{2exo}, ddd, 1H, J = 10.8, 6.2, 5.4 Hz), 2.25 (5-CH, dddd, 1H, J = 5.4, 4.5, 4.5, 1 Hz), 1.76 (4-CH_{2exo}, ddd, 1H, J = 13.5, 6.7, 1 Hz), 1.74 (7-CH_{2endo}, d, 1H, J = 10.8 Hz), 1.38 (s, 3H), 0.76 (s, 3H); spin system assigned as $J_{1,5}$ = 4.5 Hz, $J_{1,7exo}$ = 6.2 Hz, $J_{3,4endo}$ = 10.6 Hz, $J_{3,4exo}$ = 6.7 Hz, $J_{4,4}$ = −19.3 Hz, $J_{4endo,5}$ = 4.5 Hz, $J_{4exo,5}$ = 13.5 Hz, $J_{4exo,7anti}$ = 1 Hz, $J_{5,7exo}$ = 5.4 Hz, $J_{7,7}$ = −10.8 Hz; ^{13}C NMR ($CDCl_3$, 100 MHz) δ C 214.3 (2-C), 44.9 (C-6); CH 69.6 (3-CH), 55.9 (1-CH), 40.5 (5-CH); CH_2 31.0 (4-CH_2), 24.5 (7-CH_2); CH_3 26.0 (*anti*), 21.6 (*syn*); MS (ESI QTOF) m/z 177.0915 (calcd for $[C_9H_{14}O_2 + Na]^+$, 177.0886).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00756.

NMR spectra for all compounds; crystal data for **4** and **6**; HPLC chromatogram for the chiral support determination of the er of **5** (PDF)

Crystallographic data for **4** and **7** (CIF)

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Notes

The authors declare no competing financial interest.

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(13) We have not examined whether a diastereomeric structure is obtained from reaction of **6** with **8**. Our overall observations confirm the presumption that the carbonyls of dione **6** are electrophilic, suggesting value for this dione as a general auxiliary for the α-hydroxyketone and quite probably other functional groups.

(14) In the presence of catalytic base, isomerization of 3-hydroxy-6,6-dimethylbicyclo[3.1.1]heptan-2-one to the 2-hydroxy-6,6-dimethylbicyclo[3.1.1]heptan-3-one was suggested. See footnote 10 of: Campos, K. R.; Lee, S.; Journet, M.; Kowal, J. J.; Cai, D.; Larsen, R. D.; Reider, P. J. *Tetrahedron Lett.* **2002**, *43*, 6957−6959. While none of our experiments suggests a preparative route to a 2-hydroxy-6,6-dimethylbicyclo[3.1.1]heptan-3-one, our limited study on the equilibration of **5** and **8** is not in conflict with the assertion that there are reaction circumstances that give a 2-hydroxy-6,6-dimethylbicyclo[3.1.1]heptan-3-one product.

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(18) The CAS registry number assigned currently to *rel*-**5** of [57089-70-0] cites a "phantom" compound, as a result of faithful CAS transcription of the incorrectly drawn structure found in: Bessière, Y.; El Gaïed, M. M.; Boussac, G. *Can. J. Chem.* **1975**, *53*, 738−747. The CAS registry number [477334-65-9] for (−)-**5** originates from its first preparation (but without characterization) by the oxidation of the silyl enol ether of nopinone, as described by Campos et al.[14]

(19) If the intention is to co-isolate diketone **6** from this reaction, the use of the minimum quantity of bisulfite necessary to clarify the mixture is advised.

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