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# Unprecedented Rearrangement of a 4-Alkoxy-5-bromoalk-2-en-1-ol to a Cyclopentenone via an Iso-Nazarov Cyclization Process

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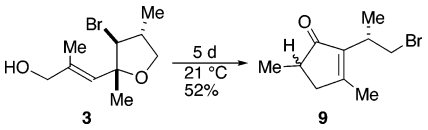
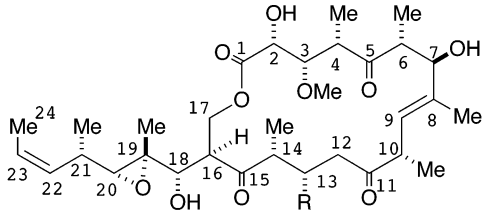



**3** **9**

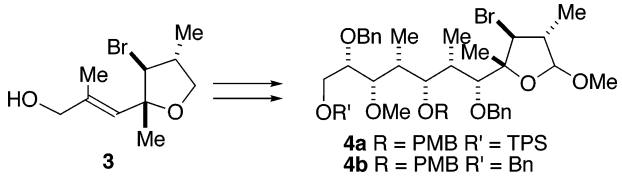
We report the structure determination of the product **9** of the rearrangement of the allylic alcohol **3** under very mild conditions, probably promoted by an acidic substance, and propose a reasonable mechanism for its formation.

For an ongoing project aimed at the total synthesis of the two related strongly antitumor agents, tedanolide **1** and 13-deoxytedanolide **2**,[1] using the non-aldol aldol process,[2] we prepared the optically active 3-bromotetrahydrofurfuryl propenol **3** by a method that we have described previously[3] to convert it into either of the two protected forms **4ab** of the top portion of the tedanolides[3] (Scheme 1). The conversion of the commercially available optically pure ester **5** into **3** proceeded without incident (Scheme 2). Thus, protection of the alcohol of **5** as the dimethoxytrityl group, conversion of the ester to the aldehyde, and a one-pot Wittig reduction sequence afforded the *E*-alkenol **6** in 86% yield for the four steps. Silylation of the alcohol of **6** and brominative cyclization as described[3] gave in

**SCHEME 1. Conversion of Allylic Alcohol 3 into Tedanolide Precursors 4ab**



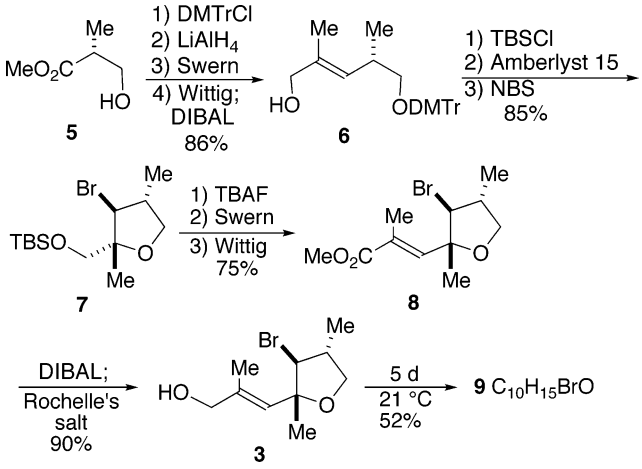

**1** R = OH Tedanolide
**2** R = H 13-Deoxytedanolide




**3**

**4a** R = PMB R' = TPS
**4b** R = PMB R' = Bn

**SCHEME 2. Preparation of 3 and Its Rearrangement to 9**




85% yield the 3-bromotetrahydrofuran **7** as the protected form of the *E*-alkene. Two-step conversion of the silyl ether of **7** to the aldehyde and Wittig olefination furnished the *E*-enoate **8** in 75% yield. Final DIBAL reduction of the ester of **8** using the normal workup with Rochelle's salt afforded the desired alcohol **3** in 90% yield. The spectroscopic data for **3** were identical to those we reported earlier.[3] However, when compound **3** was allowed to stand without solvent at 21 °C for 5 days, it completely rearranged to a new compound **9**, which could be isolated in a highly pure state in 52% yield. We report here the structural determination of this novel rearrangement product and the proposed mechanism for its formation.

It was clear from the chromatographic behavior and the proton NMR data that we had isolated a 1:1 mixture of two diastereomers. The low-resolution mass spectrum showed the presence of one bromine atom and a molecular formula of $C_{10}H_{15}BrO$ which indicated that the new compound was a dehydration product of compound **3**. The infrared spectrum showed no OH stretch but rather absorptions at 1694 and 1643 $cm^{-1}$, which indicated the possibility of an enone functionality, probably a cyclopentenone. The three quaternary carbons in the $^{13}C$ NMR spectrum at 211.1, 170.1, and 139.1 confirmed the existence of such an enone and implied that it was tetrasubstituted. But the

(1) (a) Isolation of tedanolide: Schmitz, F. J.; Gunasekera, S. P.; Yalamanchili, G.; Hossain, M. B.; van der Helm, D. *J. Am. Chem. Soc.* **1984**, *106*, 7251−7252. (b) Isolation of 13-deoxytedanolide: Fusetani, N.; Sugawara, T.; Matsunaga, S. *J. Org. Chem.* **1991**, *56*, 4971−4974. (c) Synthesis of tedanolide: Ehrlich, G.; Hassfeld, J.; Eggert, U.; Kalesse, M. *J. Am. Chem. Soc.* **2006**, *128*, 14038−14039. (d) Synthesis of 13-deoxytedanolide: Smith, A. B., III; Adams, C. M.; Lodise Barbosa, S. A.; Degnan, A. P. *J. Am. Chem. Soc.* **2003**, *125*, 350−351. Smith, A. B., III; Adams, C. M.; Lodise Barbosa, S. A.; Degnan, A. P. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 12042−12047. Julian, L. D.; Newcom, J. S.; Roush, W. R. *J. Am. Chem. Soc.* **2005**, *127*, 6186−6187.

(2) (a) Jung, M. E.; D'Amico, D. C. *J. Am. Chem. Soc.* **1993**, *115*, 12208−12209. (b) Jung, M. E.; D'Amico, D. C. *J. Am. Chem. Soc.* **1997**, *119*, 12150−12158. (c) Jung, M. E.; Marquez, R. *Tetrahedron Lett.* **1999**, *40*, 3129−3132. (d) Jung, M. E.; Lee, W. S.; Sun, D. *Org. Lett.* **1999**, *1*, 307−309. (e) Jung, M. E.; Sun, D. *Tetrahedron Lett.* **1999**, *40*, 8343−8346. (f) Jung, M. E.; van den Heuvel, A. *Tetrahedron Lett.* **2002**, *43*, 8169−8172. (g) Jung, M. E.; van den Heuvel, A.; Leach, A. G.; Houk, K. N. *Org. Lett.* **2003**, *5*, 3375−3378. (h) Jung, M. E.; van den Heuvel, A. *Org. Lett.* **2003**, *5*, 4705−4707.

(3) (a) Jung, M. E.; Karama, U.; Marquez, R. *J. Org. Chem.* **1999**, *64*, 663−665. (b) Jung, M. E.; Marquez, R. *Org. Lett.* **2000**, *2*, 1669−1672. (c) Jung, M. E.; Lee, C. P. *Tetrahedron Lett.* **2000**, *41*, 9719−9723. (d) Jung, M. E.; Lee, C. P. *Org. Lett.* **2001**, *3*, 333−336.

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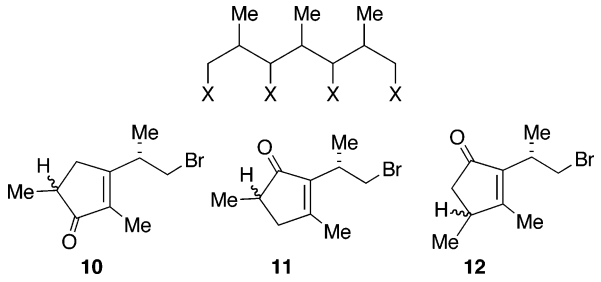
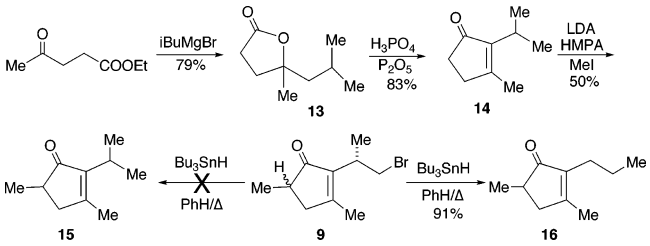
**SCHEME 3. Possible Structures for Rearrangement Product 9**



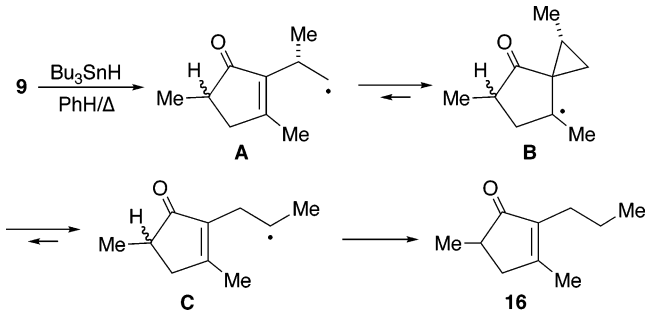

$^1$H NMR spectrum afforded the most information. It first lacked any absorption in the olefinic region, thereby confirming the tetrasubstituted alkene unit. It also showed two distinct ABX or ABC units each having a methyl group. Thus, there was an ABX pattern at $\delta$ 3.77, $\delta$ 3.54, and $\delta$ 2.98 which was adjacent to the methyl doublet at $\delta$ 1.27 (likely due to a Br−$CH_2$−CH-($CH_3$)−R unit). A second ABC pattern appeared at $\delta$ 2.75, $\delta$ 2.32, and $\delta$ 2.10 adjacent to the methyl doublet at $\delta$ 1.14 (probably a R−$CH_2$−CH($CH_3$)−R unit). The methyl singlet at $\delta$ 2.05 was likely attached to the enone. The chemical shift of all the upfield protons (except for the methyl groups) implied that the protons were likely allylic or α to a carbonyl group. Since the carbon skeleton of **3** is a polypropionate-type system, namely, a heptane backbone with alternating methyl and functional groups (Scheme 3), unless the backbone had undergone a significant rearrangement in which the skeleton had fragmented and recombined (unlikely under the mild conditions), there were two most likely products of the rearrangement, namely, the two cyclopentenones **10** and **11**. However, we thought that a methyl migration could have also taken place, and therefore the rearranged product **12** was also possible. These three structures all conformed to the NMR data. We carried out additional NMR experiments, namely, a NOESY experiment which showed no correlation between the allylic ring protons and the allylic side chain proton, which eliminated structure **10** which should have shown such correlation. We then conducted an HMBC experiment that showed correlation between the ketone carbonyl carbon and the allylic side chain proton but also a correlation between the upfield methyl group at $\delta$ 1.14 and the carbonyl carbon, which eliminated structure **12** which would not have that correlation. Thus it was likely that the 3-methylcyclopentenone **11** was the correct structure for the rearrangement product **9**.

To prove the structure, we decided to prepare an authentic sample of a simple derivative. Since 3-methyl-2-isopropylcyclopentenone **14** was known in the literature,[4] we decided to prepare its methylated derivative **15** and compare it to the product of simple debromination of **9**. Thus, addition of isobutylmagnesium bromide to ethyl levulinate gave in 79% yield the lactone **13** which was converted under acidic conditions into the known enone **14** in 83% yield (Scheme 4). Kinetic enolate formation and methylation gave the 5-methyl enone **15** in 50% unoptimized yield. When the bromide **9** was treated with tributylstannane in refluxing benzene, we isolated, in 91% yield, a compound that was clearly different from the expected

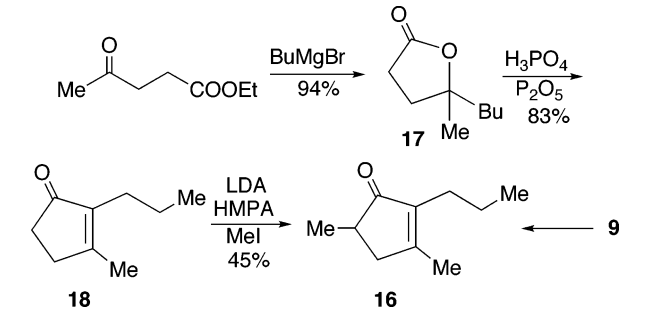
**SCHEME 4. Attempted Synthesis of Authentic Derivative 15**




**SCHEME 5. Radical Rearrangement**




**SCHEME 6. New Synthesis of Authentic Derivative 16**



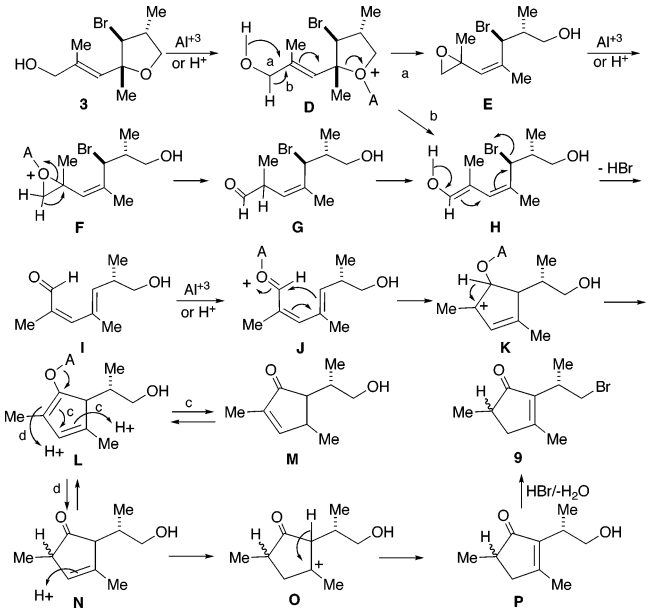

product **15**. Carbon and proton NMR allowed its assignment as the propyl analogue **16** of the expected isopropyl compound **15**. We propose (Scheme 5) that the primary homoallylic radical **A** generated by abstraction of the bromine atom from the rearrangement product **9** cyclizes onto the enone double bond (presumably via the tertiary cyclopropylcarbinyl radical **B**) and then reopens to generate the more stable secondary homoallylic radical **C** which abstracts hydrogen to afford the observed product **16**. Once we realized that the propyl analogue **16** was the product of debromination of **9**, we prepared it by an analogous route (Scheme 6). Addition of the butyl Grignard reagent to ethyl levulinate and dehydrative cyclization of the resulting known lactone **17**[4] gave the 2-propylenone **18** in 83% yield. Methylation of its kinetic enolate afforded the known 5-methyl compound **16**,[5] the spectra of which matched completely those of the same compound prepared by radical debromination of **9**. Thus the rearrangement product is indeed **9**.

Thus the allylic alcohol **3** underwent a remarkable rearrangement−cyclization process to afford the product **9**. We propose (Scheme 7) the following mechanism to account for this unusual transformation. First of all, there must have been traces of either aluminum(III) salts or acid present in the sample of **3** resulting

(4) (a) Kazmierczak, F.; Helquist, P. *J. Org. Chem.* **1989**, *54*, 3988−3992. (b) Sanganee, M. J.; Steel, P. G.; Whelligan, D. K. *Org. Biomol. Chem.* **2004**, *2*, 2393−2402. (c) Fujita, T.; Watanabe, S.; Suga, K.; Inaba, T. *J. Chem. Technol. Biotechnol.* **1979**, *29*, 100−106. (d) Rai, Ch.; Dev, S. *Experientia* **1955**, *11*, 114−115.

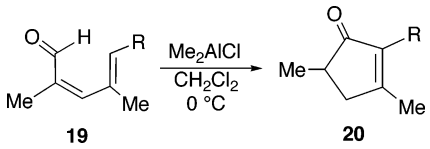
(5) Hermanson, J. R.; Hershberger, J. W.; Pinhas, A. R. *Organometallics* **1995**, *14*, 5426−5437.

**SCHEME 7. Proposed Mechanism for Formation of Rearrangement Product 9**



from the DIBAL reduction. We assume that these acidic impurities catalyze the conversion of **3** into **9**. Since a cyclopentenone product was formed by a cyclization, it seemed likely that some sort of Nazarov-type cyclization[6] might be occurring.[7,8] Coordination of the basic tetrahydrofurfuryl oxygen to the aluminum salt or proton would give the activated tertiary ether **D** which could open via attack of the allylic alcohol on the forming allylic tertiary carbocation to give the tertiary epoxide **E** (path a). A Lewis or Bronsted acid promoted rearrangement of the activated allylic epoxide **F** would give the aldehyde **G** which could enolize to form the dienol **H**. This dienol could also be generated directly from **D** by loss of the proton α to the alcohol (path b). Vinylogous $\beta$-elimination of the bromide from **H** would furnish the dienal **I** with loss of HBr. Iso-Nazarov-type cyclization of the activated aldehyde **J** would produce the very resonance-stabilized allylic carbocation **K** which would then deprotonate to give the cyclic dienol (or aluminate) **L**. Protonation at the $\gamma$-carbon would generate the kinetic cyclopentenone **M** (path c). It is well-known that under acidic or basic conditions such cyclopentenones rearrange via the $\beta,\gamma$-unsaturated enone to the opposite more stable tetrasubstituted cyclopentenone. Thus protonation of the enol **L** at the α-carbon would give the $\beta,\gamma$-unsaturated enone **N** which would protonate to give the carbocation **O** which would lose a proton to give the more stable enone **P**. Final conversion of the alcohol into the bromide with the generated HBr would then give the observed product **9**.

**SCHEME 8. Iso-Nazarov Cyclization to Give Cyclopentenones**



We have verified that purified **3** can be converted into the rearranged product **9** by treatment with aluminum reagents. Thus treatment of **3** with dimethylaluminum chloride at 23 °C for 5 days gave **9** in 30% yield. More interestingly, when **3** was treated with a catalytic amount of DIBAL in hexanes and then the solvent evaporated and the material let sit at 23 °C for 5 days, a 50% yield of **9** was obtained. When this reaction was stopped after 2 days, small amounts of the proposed intermediates **M** and **P** were obtained. Thus the production of **9** from pure **3** via the addition of exogenous aluminum reagents lends evidence for the proposed mechanism.

There is also some good literature precedent for this mechanism. Recently, Trauner[9] has reported the conversion of pentadienals similar to **I** to substituted cyclopentenones in a process he termed an "iso-Nazarov cyclization" (Scheme 8). Thus, several 5-aryl pentadienals **19** cyclized on treatment with dimethylaluminum dichloride under mild conditions to give the tetrasubstituted cyclopentenones. Therefore, we believe that we have discovered another example of this novel type of cyclization.

In summary, we have described the unexpected formation of a remarkable rearrangement product of the allylic alcohol **3**, namely, the cyclopentenone **9**. The structure was determined by both spectroscopic methods and synthesis of an authentic derivative. A reasonable mechanism for the formation of this product has been proposed. Further work on the use of these intermediates for the synthesis of the tedanolides is underway and will be reported in due course.

## Experimental Section

**2-(2-Bromo-1-methylethyl)-3,5-dimethylcyclopent-2-en-1-one, 9.** A solution of the ester **8**[3b] (0.98 g, 3.37 mmol) in diethyl ether (100 mL) was treated with a 1 M solution of DIBAL-H in hexane (8.4 mL, 8.40 mmol) at 21 °C. This reaction was quenched after 5 min by addition of a saturated Rochelle's salt solution (70 mL), followed by dilution with diethyl ether (50 mL) and addition of water (50 mL). The reaction was stirred at 21 °C until both phases were clearly separated and the organic layer was clear. After extraction, the separated organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude compound was kept at 21 °C for 5 days, and the resulting mixture was purified by flash column chromatography (silica gel, 6% ethyl acetate in hexane) to give 0.40 g (52%) of compound **9** as a colorless oil: one diastereomer of the mixture of diastereomers: $^1$H NMR $\delta$ 3.77 (dd, 1H, $J$ = 9.1, 2.2 Hz), 3.54 (dd, 1H, $J$ = 9.1, 4.6 Hz), 2.98 (m, 1H), 2.75 (m, 1H), 2.32 (m, 1H), 2.10 (m, 1H), 2.05 (s, 3H), 1.27 (d, 3H, $J$ = 7.0 Hz), 1.14 (d, 3H, $J$ = 7.4 Hz); $^{13}$C NMR $\delta$ 211.1, 170.1, 139.1, 40.8, 39.6, 36.6, 34.1, 17.3, 17.2, 16.3; IR (film) 2966, 2930, 2872, 1694, 1643, 1456, 1432, 1383, 1333, 1231, 954 cm$^{-1}$;

(6) Nazarov, I. N.; Torgov, I. B.; Terekhova, L. N. *Izv. Akad. Nauk S.S.S.R., Otd. Khim. Nauk.* **1942**, 200.

(7) For reviews, see: (a) Denmark, S. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 751−784. (b) Habermas, K. L.; Denmark, S. E.; Jones, T. K. *Org. React. (N.Y.)* **1994**, *45*, 1−158. (c) Ramaiah, M. *Synthesis* **1984**, 529−570. (d) Santelli-Rouvier, C.; Santelli, M. *Synthesis* **1983**, 429−442. (e) Tius, M. A. *Eur. J. Org. Chem.* **2005**, 2193−2206.

(8) For recent uses of the Nazarov cyclization, see: (a) Leikoski, T.; Kaunisto, J.; Alkio, M.; Aaltonen, O.; Yli-Kauhaluoma, J. *Org. Process Res. Dev.* **2005**, *9*, 629−633. (b) Mazzola, R. D., Jr.; White, T. D.; Vollmer-Snarr, H. R.; West, F. G. *Org. Lett.* **2005**, *7*, 2799−2801. (c) Aggarwal, V. K.; Belfield, A. J. *Org. Lett.* **2003**, *5*, 5075−5078. (d) Liang, G.; Gradl, S. N.; Trauner, D. *Org. Lett.* **2003**, *5*, 4931−4934. (e) Giese, S.; West, F. G. *Tetrahedron Lett.* **1998**, *39*, 8393−8396. (f) Fernandez Mateos, A.; Barba, A. L.; Coca, P.; Gonzalez, R.; Hernandez, C. T. *Synlett* **1995**, 409−410. (g) Denmark, S. E.; Wallace, M. A.; Walker, C. B., Jr. *J. Org. Chem.* **1990**, *55*, 5543−5545. (h) Marino, J. P.; Linderman, R. J. *J. Org. Chem.* **1981**, *46*, 3696−3702.

(9) Miller, A. K.; Banghart, M. R.; Beaudry, C. M.; Suh, J. M.; Trauner, D. *Tetrahedron* **2003**, *59*, 8919−8930.

EIMS, *m/z* 232 (9, $M^+$), 230 (9, $M^+$), 151 (31, $M^+ - Br$), 123 (8, $M^+ - Br - CO$), 41 (100). HRMS: calcd for $C_{10}H_{15}O$ ($M^+ - Br$), 151.1117; found 151.1125.

**5-Methyl-5-(2-methylpropyl)dihydrofuran-2[3*H*]-one, 13.** To a stirred solution of ethyl levulinate (1.0 g, 6.94 mmol) in dry benzene (3 mL) was added dropwise a 2.0 M solution of isobutylmagnesium bromide (3.81 mL, 7.63 mmol) in diethyl ether at 0 °C. The resulting solution was stirred for an additional 15 min at −5 to 0 °C and was then poured into a mixture of concentrated $H_2SO_4$ (2 mL) and ice (ca. 60 g). The mixture was extracted with ether (2 × 20 mL), and the extract was washed with water (40 mL) and 5% aq. $NaHCO_3$ (40 mL). Combining of the organic layers, followed by drying (anhydrous $MgSO_4$), concentration under vacuum, and flash column chromatography (silica gel, 25% ethyl acetate in hexane), yielded 0.85 g (79%) of the known lactone **13**[4] as a colorless oil: $^1$H NMR $\delta$ 2.62 (ddd, 1H, $J$ = 18.0, 9.4, 8.6 Hz), 2.55 (ddd, 1H, $J$ = 18.0, 9.3, 5.9 Hz), 2.08 (ddd, 1H, $J$ = 12.8, 9.3, 8.6 Hz), 2.00 (ddd, 1H, $J$ = 12.8, 9.4, 5.9 Hz), 1.82 (m, 1H), 1.62 (dd, 1H, $J$ = 14.4, 6.4 Hz), 1.57 (dd, 1H, $J$ = 14.4, 6.1 Hz), 1.39 (s, 3H), 0.98 (d, 3H, $J$ = 6.6 Hz), 0.95 (d, 3H, $J$ = 6.6 Hz); $^{13}$C NMR $\delta$ 176.8, 87.1, 49.4, 34.2, 28.9, 25.4, 24.4, 24.2, 24.0; IR (film) 2957, 1771, 1466, 1382, 1368, 1283, 1207, 1163, 1136, 938 cm$^{-1}$.

**3-Methyl-2-(2-methylethyl)-cyclopent-2-en-1-one, 14.** To a solution of $P_2O_5$ (6.1 g, 43.0 mmol) in 85% $H_3PO_4$ (4 mL) at 60−70 °C was added the lactone **13** (0.85 g, 5.44 mmol). Stirring of the mixture at 60−70 °C for 2 min resulted in a change of color from colorless to yellow-brown. The mixture was then stirred at 98 °C under argon for 6 h, after which the hot, dark red-brown mixture was poured onto ice (ca. 150 g). The mixture was extracted with ether (2 × 100 mL), and the combined extracts were washed with water (100 mL), dried over anhydrous $MgSO_4$, and concentrated under vacuum. The residue was purified by flash column chromatography (silica gel, 13% ethyl acetate in hexane) to give 0.62 g (83%) of the known cyclopentenone **14**[4] as a colorless oil: $^1$H NMR $\delta$ 2.79 (sep, 1H, $J$ = 7.1 Hz), 2.44 (m, 2H), 2.31 (m, 2H), 2.06 (s, 3H), 1.16 (d, 6H, $J$ = 7.1 Hz); $^{13}$C NMR $\delta$ 209.4, 168.8, 144.6, 34.5, 31.7, 24.7, 20.3 (2C's), 17.4; IR (film) 2961, 1695, 1637, 1385, 1340 cm$^{-1}$.

**3,5-Dimethyl-2-(2-methylethyl)-cyclopent-2-en-1-one, 15.** To a stirred solution of the cyclopentenone **14** (0.22 g, 1.56 mmol) and HMPA (0.35 mL, 2.02 mmol) in THF (10 mL) was added dropwise a 2.0 M solution of LDA (0.93 mL, 1.87 mmol) in THF at −78 °C. The mixture was then stirred for 30 min, after which iodomethane (0.19 mL, 3.11 mmol) was added to the reaction mixture. The solution was allowed to warm to 21 °C. After 10 h, the reaction was quenched by saturated $NH_4Cl$. The mixture was extracted with diethyl ether, dried over $MgSO_4$, and purified by flash column chromatography (silica gel, 13% ethyl acetate in hexane) to give 0.12 g (50%) of the methylated cyclopentenone **15** as a colorless oil: $^1$H NMR $\delta$ 2.78 (sep, 1H, $J$ = 7.1 Hz), 2.69 (dd, 1H, $J$ = 18.3, 6.8 Hz), 2.28 (m, 1H), 2.04 (dd, 1 H, $J$ = 18.3, 2.4 Hz), 2.04 (s, 3H), 1.16 (d, 3H, $J$ = 7.1 Hz), 1.15 (d, 3H, $J$ = 7.1 Hz), 1.13 (d, 3H, $J$ = 7.4 Hz); $^{13}$C NMR $\delta$ 211.8, 166.8, 143.4, 40.8, 39.6, 24.7, 20.4, 20.2, 17.3, 16.5; IR (film) 2960, 2929, 2872, 1696, 1639, 1457, 1436, 1385, 1340, 957 cm$^{-1}$.

**3,5-Dimethyl-2-propylcyclopent-2-enone, 16, from 9.** To a stirred solution of the bromide **9** (15 mg, 0.07 mmol) and tributylstannane (0.02 mL, 0.07 mmol) in benzene (5 mL) was added a catalytic amount of AIBN (1 mg). The mixture was heated under reflux for 2 h. The solution was allowed to cool to 21 °C and quenched by saturated $NH_4Cl$. The mixture was extracted with diethyl ether, dried over $MgSO_4$, and purified by flash column chromatography (silica gel, 13% ethyl acetate in hexane) to give 9 mg (91%) of the known cyclopentenone **16**[5] as a colorless oil: $^1$H NMR[10] $\delta$ 2.73 (dd, 1H, $J$ = 18.1, 6.7 Hz), 2.35 (m, 1H), 2.14 (t, 2H, $J$ = 7.5 Hz), 2.08 (dd, 1 H, $J$ = 18.1, 2.2 Hz), 2.03 (s, 3H), 1.40 (tq, 2H, $J$ = 7.5, 7.4 Hz), 1.15 (d, 3H, $J$ = 7.5 Hz), 0.87 (t, 3H, $J$ = 7.4 Hz); $^{13}$C NMR $\delta$ 212.3, 168.5, 139.4, 40.9, 39.7, 25.2, 21.8, 17.3, 16.9, 14.2; IR (film) 2961, 2931, 2871, 1698, 1646, 1456, 1436, 1385, 1354, 1334 cm$^{-1}$.

**5-Butyl-5-methyldihydrofuran-2[3*H*]-one, 17.** To a stirred solution of ethyl levulinate (1.0 g, 6.94 mmol) in dry benzene (3 mL) was added dropwise a 2.0 M solution of butylmagnesium bromide (4.16 mL, 8.32 mmol) in diethyl ether at 0 °C. The resulting solution was stirred for an additional 15 min at −5 to 0 °C and was then poured into a mixture of concentrated $H_2SO_4$ (2 mL) and ice (ca. 60 g). The mixture was extracted with ether (2 × 20 mL), and the extract was washed with water (40 mL) and 5% aq. $NaHCO_3$ (40 mL). Combining of the organic layers, followed by drying (anhydrous $MgSO_4$), concentration under vacuum, and flash column chromatography (silica gel, 25% ethyl acetate in hexane), yielded 1.02 g (94%) of the known lactone **17**[4c] as a colorless oil: $^1$H NMR $\delta$ 2.63 (ddd, 1H, $J$ = 18.0, 9.3, 8.0 Hz), 2.57 (ddd, 1H, $J$ = 18.0, 9.2, 6.6 Hz), 2.08 (ddd, 1H, $J$ = 12.8, 9.2, 8.0 Hz), 1.97 (ddd, 1H, $J$ = 12.8, 9.3, 6.6 Hz), 1.66 (m, 2H), 1.38 (s, 3H), 1.34 (m, 4H), 0.92 (m, 3H); $^{13}$C NMR $\delta$ 176.9, 86.9, 40.7, 32.9, 29.2, 26.0, 25.6, 22.9, 13.9; IR (film) 2936, 1770, 1458, 1382, 1205, 1161, 1137, 939 cm$^{-1}$.

**3-Methyl-2-propylcyclopent-2-en-1-one, 18.** To a solution of $P_2O_5$ (3.0 g, 21.1 mmol) in 85% $H_3PO_4$ (2 mL) at 60−70 °C was added the lactone **17** (0.4 g, 2.56 mmol). Stirring of the mixture at 60−70 °C for 2 min resulted in a change of color from colorless to yellow-brown. The mixture was then stirred at 98 °C under argon for 6 h, after which the hot, dark red-brown mixture was poured onto ice (ca. 75 g). The mixture was extracted with ether (2 × 50 mL), and the combined extracts were washed with water (50 mL), dried over anhydrous $MgSO_4$, and concentrated under vacuum. The residue was purified by flash column chromatography (silica gel, 13% ethyl acetate in hexane) to give 0.29 g (83%) of the known cyclopentenone **18**[4cd] as a colorless oil: $^1$H NMR $\delta$ 2.48 (m, 2H), 2.36 (m, 2H), 2.15 (t, 2H, $J$ = 7.6 Hz), 2.05 (s, 3H), 1.40 (tq, 2H, $J$ = 7.6, 7.3 Hz), 0.88 (t, 3H, $J$ = 7.3 Hz); $^{13}$C NMR $\delta$ 209.7, 170.2, 140.5, 34.3, 31.5, 25.0, 21.6, 17.2, 14.0; IR (film) 2960, 1698, 1648, 1442, 1385, 1072 cm$^{-1}$.

**3,5-Dimethyl-2-propylcyclopent-2-enone, 16.** To a stirred solution of the cyclopentenone **18** (0.20 g, 1.41 mmol) and HMPA (0.32 mL, 1.83 mmol) in THF (10 mL) was added dropwise a 2.0 M solution of LDA (0.92 mL, 1.83 mmol) in THF at −78 °C. The mixture was then stirred for 30 min, after which iodomethane (0.18 mL, 2.82 mmol) was added to the reaction mixture. The solution was allowed to warm to 21 °C. After 10 h, the reaction was quenched by saturated $NH_4Cl$. The mixture was extracted with diethyl ether, dried over $MgSO_4$, and purified by flash column chromatography (silica gel, 13% ethyl acetate in hexane) to give 0.10 g (45%) of the cyclopentenone **16** as a colorless oil: $^1$H NMR[10] $\delta$ 2.73 (dd, 1H, $J$ = 18.1, 6.7 Hz), 2.35 (m, 1H), 2.14 (t, 2H, $J$ = 7.5 Hz), 2.08 (dd, 1 H, $J$ = 18.1, 2.2 Hz), 2.03 (s, 3H), 1.40 (tq, 2H, $J$ = 7.5, 7.4 Hz), 1.15 (d, 3H, $J$ = 7.5 Hz), 0.87 (t, 3H, $J$ = 7.4 Hz); $^{13}$C NMR $\delta$ 212.3, 168.5, 139.4, 40.9, 39.7, 25.2, 21.8, 17.3, 16.9, 14.2; IR (film) 2961, 2931, 2871, 1698, 1646, 1456, 1436, 1385, 1354, 1334 cm$^{-1}$.

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**Supporting Information Available:** Spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) The proton NMR data given in ref 5 for compound **16** are incorrect, but the carbon NMR data match those of our synthetic material perfectly.