JOC*Note*

Study on the Base-Catalyzed Reverse Vinylogous Aldol Reaction of (4a*β*,5*β*)-4,4a,5,6,7,8-Hexahydro-5-hydroxy-1,4a-dimethylnaphthalen-2(3*H*)-one under Robinson Annulation Conditions

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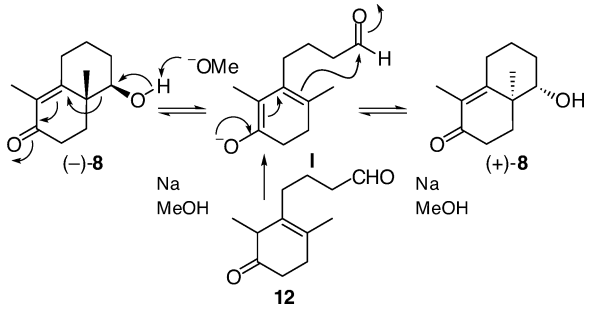
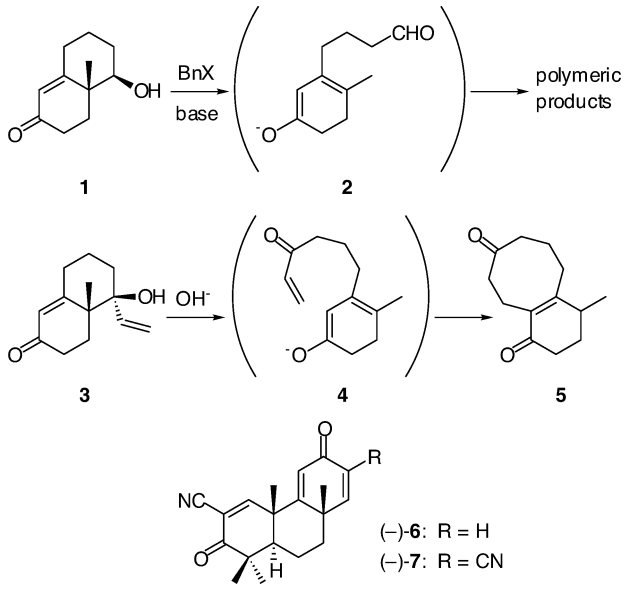


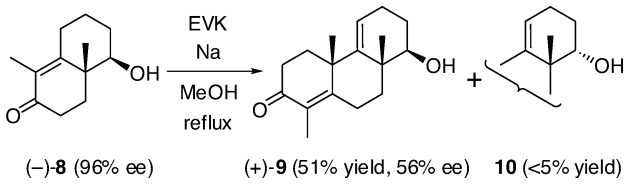
We have proposed a pathway for the base-catalyzed reverse vinylogous aldol reaction of (−)-(4a*β*,5*β*)-4,4a,5,6,7,8-hexahydro-5-hydroxy-1,4a-dimethylnaphthalen-2(3*H*)-one [(−)-**8**] under Robinson annulation conditions. For confirmation, 4-(2,6-dimethyl-3-oxocyclohex-1-enyl)butanal (**11**) and 4-(2,6-dimethyl-5-oxocyclohex-1-enyl)butanal (**12**), both of which potentially produce enolate **I**, were synthesized regioselectively. Unexpectedly, **11** gave a complex mixture, including only a trace amount of (±)-**8** (less than 5% yield), under these basic conditions. To the contrary, **12** cleanly afforded (±)-**8** in 66% yield. This result provides evidence for our proposed mechanism of the above reaction.

It is well-known that racemic hydroxy enone **1**, which is derived from a Wieland−Miescher ketone, gives polymeric products via the proposed enolate **2** under base-catalyzed benzylation conditions.[1] Enolate **2** is presumed to arise from **1** by a vinylogous retro-aldol reaction. Moreover, **1** cannot be ketalized because of a similar acid-catalyzed vinylogous retro-aldol reaction.[2] Also, it has been reported that hydroxy enone **3** gives the ring-enlargement product **5** via the presumed enolate

SCHEME 1



SCHEME 2



4, produced by a base-catalyzed vinylogous retro-aldol reaction (Scheme 1).[3]

In connection with the synthesis of optically active tricyclic compounds having cyano-bis-enone functionalities [e.g., (−)-**6** and (−)-**7**], which represent a series of novel and orally active anti-inflammatory and cancer-chemopreventive agents,[4,5] we have found that hydroxy enone (−)-**8**[5,6] [96% enantiomeric excess (ee); $[\alpha]^{26}_{D}$ −170° (*c* 1.2, $CHCl_3$)] is racemized and epimerized under Robinson annulation conditions [ethyl vinyl ketone and sodium methoxide in methanol (reflux, 12 h)] to afford (+)-**9** [51% yield; 56% ee; $[\alpha]^{27}_{D}$ +50° (*c* 2.0, $CHCl_3$)], **10** (<5% yield), and recovered **8** in racemic form [33% yield, $[\alpha]^{28}_{D}$ +2.4° (*c* 8.6, $CHCl_3$), Scheme 2].[5] We speculate that racemization and C-5 epimerization of (−)-**8** occur via an interesting base-catalyzed *reverse* vinylogous aldol reaction shown in Scheme 3. It is reasonable that enolate **I**, potentially derived from conjugated and/or deconjugated aldehydes **11** and **12** (Scheme 4), is a common intermediate for this reverse vinylogous aldol reaction, although we were not able to isolate these aldehydes from the reaction mixture. Therefore, for confirmation of this pathway, we now describe the regioselective

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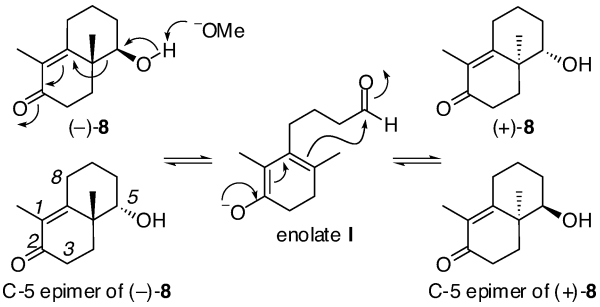
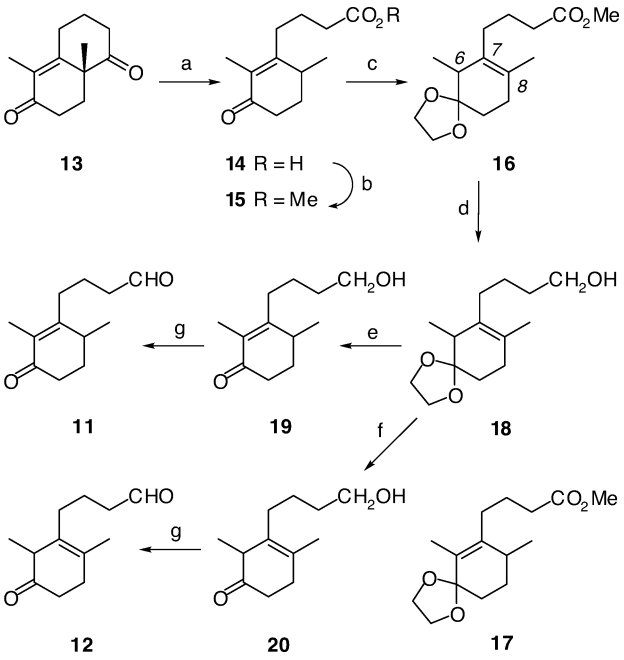
SCHEME 3



SCHEME 4 [a]



[a] Key: (a) aqueous NaOH, 82%; (b) H_2SO_4, MeOH, 71%; (c) *p*-TsOH, ethylene glycol, PhH, 54%; (d) $LiAlH_4$, Et_2O, 89%; (e) aqueous HCl, MeOH, 98%; (f) PPTS, aqueous acetone, 64%; and (g) CrO_3, pyridine, CH_2Cl_2, 77% for **11** and 68% for **12**.

synthesis of unknown aldehydes **11** and **12** and their behavior under these reaction conditions.

Because aldehydes **11** and **12** would presumably be unstable under both basic and acidic conditions, we adopted the sequence shown in Scheme 4 in which neutral oxidation conditions were employed. In this fashion, both aldehydes **11** and **12** were synthesized regioselectively by this sequence.

Methyl ester **15** was prepared from known acid **14**[7] under sulfuric acid−methanol conditions, which in turn was derived from diketone **13**[6] with a 2% aqueous NaOH solution (58% yield from **13**). Ketalization of **15** with ethylene glycol in the presence of pyridinium *p*-toluenesulfonate (PPTS) in benzene[8] gave an inseparable mixture of **16** and **17** in 53% yield. Interestingly, the use of *p*-TsOH gave only ketal **16** in 54% yield. The structure of **16** was confirmed by the observation of an NOE between the ketal protons and the C-6 methyl group (NOESY one-dimensional experiment). Reduction of **16** with $LiAlH_4$ in Et_2O afforded alcohol **18** in 89% yield. Deketalization of **18** with aqueous HCl conditions gave only the conjugated

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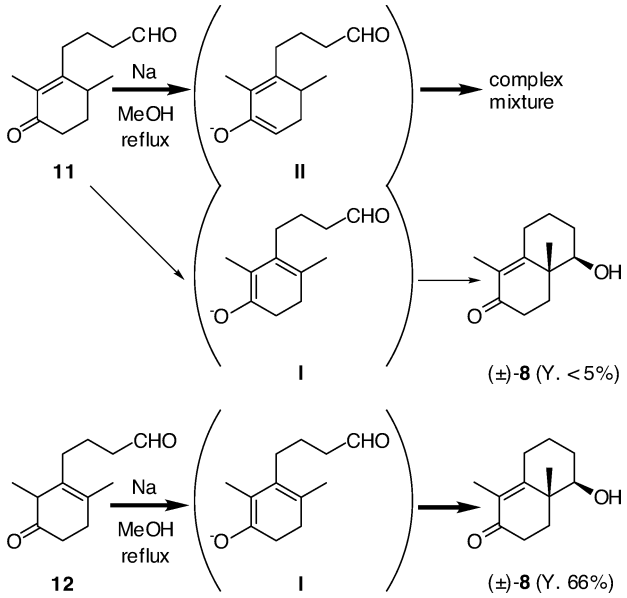
SCHEME 5



enone **19** in 98% yield. In contrast, deketalization of **18** using PPTS in aqueous acetone[8] produced deconjugated enone **20** (64% yield) and **19** (11% yield),[9] which were separable by flash column chromatography. Oxidation of **19** and **20** with CrO_3 and pyridine in CH_2Cl_2[10] afforded **11** and **12** in 77 and 68% yield, respectively.

Interestingly, we found that **12** gave (±)-**8**[6] in 66% yield under the same Robinson annulation conditions used for **9**, while **11** gave a complex product mixture including only trace amounts of (±)-**8** and **11** (each less than 5% yield). We rationalize these results in Scheme 5. Although the conjugated aldehyde **11** forms two enolates, **I** and **II**, under basic conditions, we believe that the formation of **II** is kinetically preferable to **I**. Because **II** cannot give the vinylogous aldol condensation product (±)-**8**, it affords a complex mixture, including only a trace amount of (±)-**8**. However, because the deconjugated aldehyde **12** is predominantly enolized to produce enolate **I**, which then cyclizes to (±)-**8**, **12** is cleanly converted to (±)-**8** in good yield.[11]

This result provides evidence for our proposed mechanisms on the base-catalyzed reverse vinylogous aldol reaction of (−)-**8** under Robinson annulation conditions that the common intermediate is the enolate **I**.

(9) GC-MS indicated that the ratio of **20** and **19** at the end of the reaction was 85:15.
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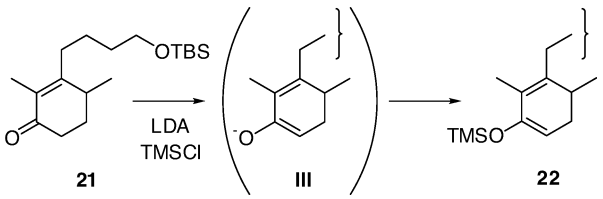
(11) For confirmation of our speculation about the different outcomes from **11** and **12**, we envisioned an enolate trapping experiment under kinetic enolate formation conditions using **21**, which was prepared from **19** with TBSCl in the presence of imidazole in DMF (85% yield). Enone **21** was treated with LDA and TMSCl in THF at −78 °C for 1 min to give silyl ether **22** (92% yield).[12] This result shows that enolate **III** is produced kinetically from **21** and supports our belief that aldehyde **11** gives a complex product mixture via kinetic enolate **II** (Scheme 5).



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Experimental Section

Methyl 4-(2,6-Dimethyl-3-oxocyclohex-1-enyl)butyrate (15). To a solution of 4-(2,6-dimethyl-3-oxocyclohex-1-enyl)butyric acid (**14**)[7] (4.12 g, 19.6 mmol) in MeOH (170 mL) was added concd H_2SO_4 (10.7 mL) dropwise. The resultant mixture was stirred at reflux for 45 min. After the removal of the solvent (ca. 100 mL), the reaction mixture was diluted with water (150 mL) and extracted with a mixture of Et_2O and CH_2Cl_2 (2:1; 3 × 80 mL). The combined organic extracts were worked up according to the standard method to give a yellow oil (4.26 g). This was purified by flash column chromatography [hexanes/EtOAc (2:1)] to give **15** as a yellow oil (3.10 g, 71%). ^{1}H NMR ($CDCl_3$) δ 3.65 (3H, s), 2.34 (2H, t, J = 7.32 Hz), 1.73 (3H, s), 1.16 (3H, d, J = 6.95 Hz); ^{13}C NMR ($CDCl_3$) δ 199.3, 173.6, 162.1, 130.9, 51.7, 33.9, 33.7, 33.5, 32.6, 29.6, 23.1, 17.9, 11.0. HREIMS calcd for $C_{13}H_{20}O_3$: 224.1412. Found: 224.1417. Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.78; H, 9.13.

Methyl 4-(6,8-Dimethyl-1,4-dioxaspiro[4,5]dec-7-en-7-yl)-butyrate (16). A mixture of **15** (1.22 g, 5.44 mmol), *p*-TsOH (188 mg, 0.99 mmol), and ethylene glycol (11 mL) in anhydrous benzene (65 mL) was heated under reflux with a Dean−Stark apparatus overnight. The benzene and ethylene glycol layers were separated. To the ethylene glycol layer was added water (15 mL), and this was extracted with a mixture of Et_2O and CH_2Cl_2 (2:1; 3 × 15 mL). The extracts were combined with the original benzene layer. The organic mixture was worked up according to the standard method to give an oil (1.63 g) that was purified by flash column chromatography [hexanes/EtOAc (2.5:1)] to give **16** as a yellow oil (790.8 mg, 54%). ^{1}H NMR (CD_3OD) δ 3.93 (4H, m), 3.65 (3H, s), 2.31 (2H, t, J = 7.14 Hz), 1.60 (3H, s), 1.03 (3H, d, J = 6.96 Hz); ^{13}C NMR (CD_3OD) δ 176.0, 133.7, 127.0, 112.0, 65.5, 65.2, 52.1, 42.2, 34.3, 31.9, 31.4, 28.0, 24.8, 18.9, 17.0. HREIMS calcd for $C_{15}H_{24}O_4$: 268.1675. Found: 268.1675. Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.14; H, 9.01. Found: C, 67.10; H, 9.13.

4-(6,8-Dimethyl-1,4-dioxaspiro[4,5]dec-7-en-7-yl)butan-1-ol (18). To a solution of **16** (301 mg, 1.12 mmol) in anhydrous Et_2O (40 mL) was added $LiAlH_4$ (372 mg, 9.54 mmol) with cooling to 0 °C. The resultant mixture was stirred for 2 h at rt. To the reaction mixture was added successively water (0.9 mL), a 40% aqueous NaOH solution (0.3 mL), and water (0.9 mL). After the formation of a white precipitate, the reaction mixture was decanted and dried over $MgSO_4$. Removal of the solvent in vacuo gave **18** (240.4 mg, 89%) as a colorless oil, which was used for the next reaction without further purification. An analytically pure sample was obtained by flash column chromatography [hexanes/EtOAc (1:2)] as a colorless oil. ^{1}H NMR (CD_3OD) δ 3.94 (4H, m), 3.53 (2H, t, J = 6.41 Hz), 1.62 (3H, s), 1.04 (3H, d, J = 6.95 Hz); ^{13}C NMR (CD_3OD) δ 134.4, 126.0, 111.9, 65.3, 65.1, 62.9, 42.1, 33.6, 32.0, 31.7, 27.9, 25.8, 18.8, 16.9. HREIMS calcd for $C_{14}H_{24}O_3$: 240.1725. Found: 240.1720. Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07. Found: C, 69.83; H, 10.18.

3-(4-Hydroxybutyl)-2,4-dimethylcyclohex-2-enone (19). To a solution of **18** (148.1 mg, 0.62 mmol) in MeOH (26 mL) was added a 1 N aqueous HCl solution (9.9 mL) dropwise. The resultant mixture was stirred at reflux for 45 min. After the removal of MeOH, the reaction mixture was diluted with water (35 mL) and extracted with a mixture of Et_2O and CH_2Cl_2 (2:1; 3 × 15 mL). The combined organic extracts were worked up according to the standard method to give **19** (118.7 mg, 98%) as a yellow oil, which was used for the next reaction without further purification. An analytically pure sample was obtained by flash column chromatography [hexanes/EtOAc (1:2)] as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 3.65 (2H, t, J = 6.0 Hz), 1.73 (3H, s), 1.16 (3H, d, J = 6.96 Hz); ^{13}C NMR ($CDCl_3$) δ 199.6, 163.6, 130.4, 62.5, 33.7, 33.6, 33.1, 33.0, 29.6, 24.3, 17.9, 11.0. HREIMS calcd for $C_{12}H_{20}O_2$: 196.1463. Found: 196.1455. Anal. Calcd for $C_{12}H_{20}O_2 \cdot {}^1/_{10}H_2O$:[13] C, 72.76; H, 10.28. Found: C, 72.96; H, 10.30.

3-(4-Hydroxybutyl)-2,4-dimethylcyclohex-3-enone (20). A solution of **18** (87.5 mg, 0.36 mmol) and PPTS (42 mg, 0.17 mmol) in acetone (5.0 mL) and water (0.6 mL) was stirred at reflux for 2 h. After the removal of acetone, the resultant mixture was diluted with a mixture of Et_2O and CH_2Cl_2 (2:1; 35 mL) and then worked up according to the standard method to give an oil (66.3 mg). This was purified by flash column chromatography [hexanes/EtOAc (1:2)] to give **20** as a colorless oil (45.6 mg, 64%) and **19** (8.0 mg, 11%). **20**: ^{1}H NMR (CD_3OD) δ 3.57 (2H, t, J = 6.22 Hz), 2.74 (1H, m), 1.76 (3H, s), 1.21 (3H, d, J = 7.2 Hz); ^{13}C NMR (CD_3OD) δ 217.0, 134.2, 128.6, 62.8, 47.7, 37.5, 33.5, 32.4, 31.3, 25.7, 19.1, 17.1. HREIMS calcd for $C_{12}H_{20}O_2$: 196.1463. Found: 196.1460. Anal. Calcd for $C_{12}H_{20}O_2 \cdot {}^1/_8H_2O$:[13] C, 72.60; H, 10.28. Found: C, 72.78; H, 10.26.

4-(2,6-Dimethyl-3-oxocyclohex-1-enyl)butanal (11). To a stirred solution of anhydrous CH_2Cl_2 (20 mL) and anhydrous pyridine (1.25 mL) was added CrO_3 (763 mg, 7.63 mmol). The deep burgundy solution was stirred for 15 min at rt. At this time, a solution of **19** (261 mg, 1.33 mmol) in a small amount of CH_2Cl_2 was added. After stirring for an additional 15 min, the solution was decanted and the remaining tarry black residue was washed with a mixture of Et_2O and CH_2Cl_2 (2:1; 3 × 10 mL). The combined organic extracts were washed with a 5% aqueous NaOH solution (3 × 10 mL) and a 5% aqueous HCl solution (3 × 10 mL) and then worked up according to the standard method to give an oil (233 mg). This was purified by flash column chromatography [hexanes/EtOAc (1:1)] to give **11** (200 mg, 77%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 9.80 (1H, t, J = 1.28 Hz), 1.76 (3H, s), 1.18 (3H, d, J = 7.33 Hz); ^{13}C NMR ($CDCl_3$) δ 201.7, 199.3, 162.0, 131.0, 43.8, 33.8, 33.5, 32.5, 29.6, 20.3, 18.0, 11.2. HREIMS calcd for $C_{12}H_{18}O_2$: 194.1307. Found: 194.1311. Anal. Calcd for $C_{12}H_{18}O_2 \cdot {}^1/_4H_2O$:[13] C, 72.51; H, 9.38. Found: C, 72.40; H, 9.19.

4-(2,6-Dimethyl-5-oxocyclohex-1-enyl)butanal (12). The title compound was prepared from **20** according to the same procedure followed for **11**, resulting in a colorless oil (68%). ^{1}H NMR ($CDCl_3$) δ 9.78 (1H, t, J = 1.5 Hz), 2.72 (1H, m), 1.73 (3H, s), 1.22 (3H, d, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 214.4, 202.3, 132.3, 128.4, 46.6, 43.7, 36.7, 31.7, 30.1, 20.9, 19.2, 17.2. HREIMS calcd for $C_{12}H_{18}O_2$: 194.1307. Found: 194.1307. Anal. Calcd for $C_{12}H_{18}O_2 \cdot {}^1/_2H_2O$:[13] C, 70.90; H, 9.42. Found: C, 70.70; H, 9.20.

Conversion of 4-(2,6-Dimethyl-5-oxocyclohex-1-enyl)butanal (12) into (±)-(4a*β*,5*β*)-4,4a,5,6,7,8-Hexahydro-5-hydroxy-1,4a-dimethylnaphthalen-2(3*H*)-one [(±)-8]. To **12** (39.0 mg, 0.20 mmol) was added a 1.28 M solution of sodium methoxide in MeOH (0.39 mL). The resultant mixture was stirred at reflux for 20 min. The reaction mixture was diluted with water (20 mL) and extracted with a mixture of Et_2O and CH_2Cl_2 (2:1; 3 × 15 mL). The combined organic extracts were then washed with a saturated aqueous NH_4Cl solution (10 mL) and brine (10 mL), dried over $MgSO_4$, and filtered. Removal of the solvent in vacuo gave an oil (30.7 mg) that was purified by flash column chromatography [hexanes/EtOAc (1:2)] to give (±)-**8**[6] (25.9 mg, 66%) as a colorless oil. ^{1}H and ^{13}C NMR, IR, UV, and MS spectra of this compound were identical with those of the authentic sample.

3-[4-(*tert*-Butyldimethylsilyloxy)butyl]-2,4-dimethylcyclohex-2-enone (21). A solution of **19** (62.5 mg, 0.32 mmol), *tert*-butyldimethylsilyl chloride (TBSCl) (72 mg, 0.48 mmol), and imidazole (65 mg, 0.95 mmol) in anhydrous DMF (0.6 mL) was stirred at rt overnight. The reaction mixture was diluted with water. The aqueous mixture was extracted with a mixture of Et_2O and CH_2Cl_2 (2:1; 3 × 15 mL). The extract was washed with a saturated aqueous NH_4Cl solution (twice) and brine (twice), dried over $MgSO_4$, and filtered. Removal of the solvent in vacuo gave an oil (122 mg) that was purified by flash column chromatography [hexanes/EtOAc (5:1)] to give **21** (83.7 mg, 85%) as a colorless

(13) Extensive drying did not remove the water present in the sample.

oil. ^{1}H NMR ($CDCl_3$) δ 3.62 (2H, t, J = 5.86 Hz), 2.51 (2H, m), 2.34 (2H, m), 2.06 (2H, m), 1.75 (1H, m), 1.74 (3H, s), 1.55 (4H, m), 1.17 (3H, d, J = 7.3 Hz), 0.87 (9H, s), 0.03 (6H, s); ^{13}C NMR ($CDCl_3$) δ 199.4, 163.6, 130.4, 62.7, 33.7, 33.6, 33.12, 33.08, 29.7, 26.1, 24.3, 18.4, 17.9, 11.0, −5.2. HRMS (ESI+) calcd for $C_{18}H_{34}O_2Si$ + H: 311.2406. Found: 311.2409

1-[4-(*tert*-Butyldimethylsilyloxy)butyl]-2,6-dimethyl-3-(trimethylsilyloxy)-cyclohexa-1,3-diene (22). To a solution of 2 M LDA (0.16 mL, 0.32 mmol) in dry THF (0.42 mL) was added a solution of TMSCl (257 mg, 2.37 mmol) in THF (0.47 mL), followed by the dropwise addition of a solution of **21** (73.7 mg, 0.237 mmol) in THF (0.47 mL) in a dry ice−2-propanol bath. After 1 min, dry Et_3N (0.47 mL) was added followed by quenching with a saturated aqueous $NaHCO_3$ solution. The mixture was extracted with a mixture of Et_2O and CH_2Cl_2 (2:1; 3 × 10 mL). The extract was washed with water (twice) and a 0.1 N aqueous citric acid solution (once), dried over $MgSO_4$, and filtered. Removal of the solvent in vacuo gave **22** (83.2 mg, 92%) as an oil. ^{1}H NMR (C_6D_6) δ 4.78 (1H, dd, J = 2.75 and 6.41 Hz), 3.55 (2H, t, J = 5.86 Hz), 2.48 (1H, ddd, J = 2.93, 7.32, and 16.11 Hz), 2.30 (1H, m), 2.03 (1H, m), 1.90 (1H, m), 1.86 (3H, s), 1.53 (4H, m), 1.03 (3H, d, J = 6.95 Hz), 0.98 (9H, s), 0.19 (9H, s), 0.07 (6H, s); ^{13}C NMR (C_6D_6) δ 150.5, 141.5, 125.3, 97.9, 63.4, 33.6, 32.44, 32.38, 30.2, 26.5, 26.4, 18.9, 17.3, 12.8, 0.6, −4.8. HRMS (ESI+) calcd for $C_{21}H_{42}O_2Si_2$ + H: 383.2802. Found: 383.2801.

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Supporting Information Available: General experimental procedures, UV, IR, and MS spectra for **11**, **12**, **15**, **16**, and **18**−**22**, and ^{1}H and ^{13}C NMR spectra for **11**, **12**, and **19**−**22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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