An Intramolecular Prins Double Cyclization Catalyzed by Silyl Triflates[1]

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Several intramolecular Prins double cyclizations are reported. The 2-alkyl 5-hepten-1,2-diols and their analogues, **9**−**11**, were prepared and oxidized to the aldehydes **6**−**8** under Swern conditions. Treatment of these α-hydroxy aldehydes with TBSOTf and a hindered base gave the products of an intramolecular Prins double cyclization, namely the 7-(silyloxy)-2-oxabicyclo[2.2.1]heptanes, **17**−**19**, in 84−92% yield. These compounds were formed as single diastereomers with only the anti silyl ethers being obtained. The cyclizations occur when five-membered rings are being formed and when the initially formed cation is highly stabilized. Other substrates do not cyclize, e.g., when the α-hydroxy aldehydes **20**−**22**, prepared from **26**−**28**, are treated under similar conditions, none of the corresponding cyclization products, **23**−**25**, were obtained.

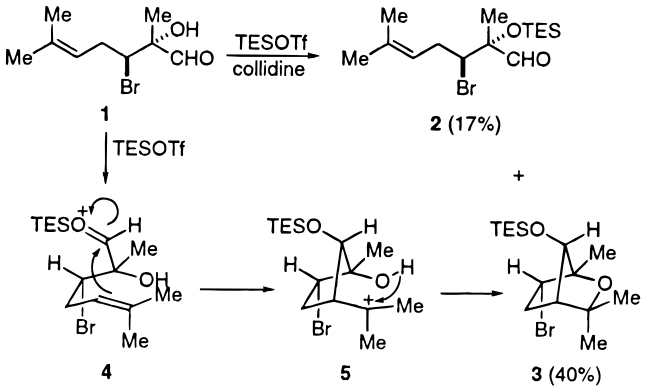
In the attempted protection of the α-hydroxy aldehyde **1** as the triethylsilyl ether, in addition to the expected product **2**, which was isolated in 17% yield, we isolated the double cyclization product **3** in 40% yield as the primary product.[4] We discovered that triethylsilyl triflate in the presence of collidine catalyzed an intramolecular Prins reaction presumably via the silylated aldehyde **4**, which was attacked by the trisubstituted alkene to produce the tertiary carbocation **5** as an intermediate which then was trapped by the alcohol in a second intramolecular cyclization (Scheme 1). We wanted to investigate the generality and scope of this novel reaction with related substrates. We also thought that a more hindered reagent such as *tert*-butyldimethylsilyl triflate (TBSOTf) might give a higher yield of **5** by discouraging the competing protection of the alcohol to give the analogue of **2** and thereby favoring the production of the analogue of **3**.

A search of the literature revealed only a few precedents for this kind of tandem reaction. Kiyooka demonstrated an intermolecular Prins reaction where a carbobenzyloxy-protected nitrogen formed the second bond, in that case resulting in a single ring.[5] In attempting an ene reaction starting from an acetal, Bertrand observed a mixture of products including one in which the liberated alcohol trapped the generated cation.[6] But the general use of an intramolecular Prins reaction to prepare 2-oxabicyclo[2.2.1]heptane-7-ol derivatives was unknown.

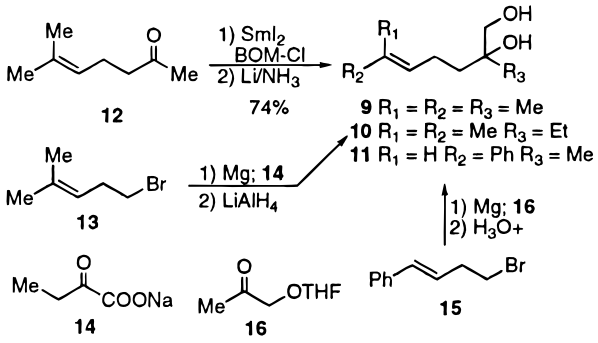
As a general method for accessing these δ-olefinic α-hydroxy aldehydes **6**−**8**, we chose to synthesize the diols **9**−**11** (Scheme 2) by a variety of routes and then to use the Swern oxidation[7] to produce the desired substrates. The diol **9** was available in two steps and 74% overall yield by coupling (benzyloxy)methyl chloride (BOM-Cl)[8] and 6-methyl-5-hepten-2-one (**12**) in the presence of samarium diiodide (88% yield) followed by dissolving metal reduction of the benzyl group (83% yield). The diol **10** was prepared by the addition of the Grignard reagent of the known[9] bromide **13** to sodium α-ketobutyrate (**14**) followed by hydride reduction. Finally the cinnamyl diol **11** was prepared by addition of the Grignard reagent of the known[10] bromide **15** to 1-[(tetrahydrofuranyl)oxy]acetone **16** followed by acidic hydrolysis.

Of the various possible oxidation methods, the Swern oxidation proved to be the most reliable, converting the diols **9**−**11** into the desired α-hydroxy aldehydes **6**−**8** in

Scheme 1



Scheme 2



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(4) D'Amico, D. C. Ph.D. Dissertation, University of California, Los Angeles, 1995.

(5) Kiyooka, S., Shiomi, Y., Kira, H., Kaneko, Y.; Tanimori, S. *J. Org. Chem.* **1994**, *59*, 1958.

(6) Bertrand, M., Rousmestant, M−L.; Sylvestre-Panthet, P. *J. Chem. Soc., Chem. Commun.* **1979**, 529.

(7) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.

(8) Imamoto, T., Takeyama, T.; Yokoyama, M. *Tetrahedron Lett.* **1984**, *25*, 3225.

(9) Biernacki, W.; Gdula, A. *Synthesis* **1979**, 37.

(10) McCormick, J. P.; Barton, D. L. *J. Org. Chem.* **1980**, *45*, 2566.

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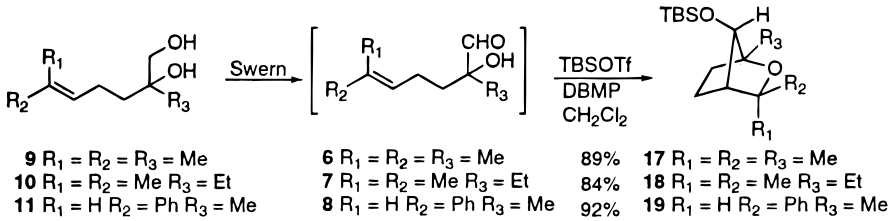
Scheme 3

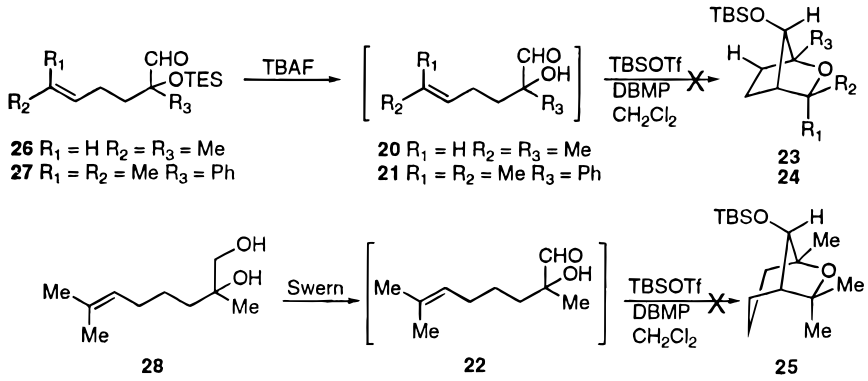


9 $R_1 = R_2 = R_3 = Me$ — **6** $R_1 = R_2 = R_3 = Me$ — 89% — **17** $R_1 = R_2 = R_3 = Me$

10 $R_1 = R_2 = Me\ R_3 = Et$ — **7** $R_1 = R_2 = Me\ R_3 = Et$ — 84% — **18** $R_1 = R_2 = Me\ R_3 = Et$

11 $R_1 = H\ R_2 = Ph\ R_3 = Me$ — **8** $R_1 = H\ R_2 = Ph\ R_3 = Me$ — 92% — **19** $R_1 = H\ R_2 = Ph\ R_3 = Me$

Scheme 4



26 $R_1 = H\ R_2 = R_3 = Me$ — **20** $R_1 = H\ R_2 = R_3 = Me$ — **23**

27 $R_1 = R_2 = Me\ R_3 = Ph$ — **21** $R_1 = R_2 = Me\ R_3 = Ph$ — **24**

28 — **22** — **25**

good yields. These compounds proved to be somewhat unstable, decomposing on attempted chromatography on silica gel and therefore were generally carried forward in dichloromethane solution to the next reaction, the key double cyclization.

As shown in Scheme 3, treatment of the α-hydroxy aldehydes **6**−**8** with *tert*-butyldimethylsilyl triflate and the hindered base 2,6-di-*tert*-butyl-4-methylpyridine (DBMP) afforded the desired intramolecular Prins products **17**−**19** in yields of 84−92% over the two steps from the diols **9**−**11**. Thus this intramolecular Prins double cyclization works well for systems forming five-membered rings in the initial step and where the initially formed cation is highly stabilized, e.g., tertiary or benzylic.

In all cases examined, the products were formed with high diastereoselectivity, with only the anti silyl ether being produced. This stereochemistry is presumably due to the other possible cyclization, which would give the silyl ether syn to the dimethyl-substituted carbocation, being subject to severe steric hindrance so that the observed cyclization is greatly favored (e.g., **4** → **5**).

However, not all substrates could be induced to undergo the double cyclization, even those with quite similar structures. For example (Scheme 4) the olefinic α-hydroxy aldehydes **20**−**22**[11] did not produce any of the desired materials, **23**−**25**, under these cyclization conditions. We believe that the cyclization of **20** failed because the disubstituted double bond was not sufficiently electron-rich. In the case of compound **21**, the bulky phenyl group α to the aldehyde may have created unfavorable steric hindrance to the cyclization. Finally, the cyclization of **22** to give compound **25** would have required the formation of a six-membered ring from the initial Prins reaction, a process which is known to be less facile.[12] Attempts to use stronger Lewis acids, e.g., various alkyl-substituted aluminum halides, did not give better results.

Thus, in summary, we have demonstrated a novel intramolecular Prins double cyclization reaction effective for a family of related α-hydroxy aldehydes with a properly spaced and electron-rich double bond. We have optimized this reaction to afford yields of 84−92% for the two steps from the corresponding diols including a Swern oxidation. Further research is currently underway in this area.

Experimental Section

General. Thin-layer chromatography (TLC) was performed using Merck silica gel 60 F_{254} 0.2 mm plates. Visualization was accomplished using ultraviolet light or the following stain: anisaldehyde (2 mL), acetic acid (10 mL), and sulfuric acid (2 mL) in 95% ethanol (85 mL). Flash chromatography was carried out using ICN Biomedicals silica gel 60 (230−400 mesh). Solvent systems are reported as volume percent mixtures. Concentration or evaporation of solvent refers to removal at reduced pressure using a Büchi rotary evaporator and an aspirator pump. All inorganic solutions are aqueous, and concentrations are indicated in percent weight, except for saturated sodium chloride, saturated sodium carbonate, and saturated ammonium chloride. The following solvents and reagents were distilled from the indicated agent under argon: tetrahydrofuran (THF) and diethyl ether from sodium benzophenone ketyl; dichloromethane, acetonitrile, and triethylamine from calcium hydride. Dimethyl sulfoxide (DMSO) was distilled from calcium hydride under reduced pressure. Oxalyl chloride was distilled just prior to use. All solvents were stored over calcium hydride.

2,6-Dimethyl-5-heptene-1,2-diol (9). To a 100 mL oven-dried round-bottom flask under argon were added 30 mL of 0.1 M samarium diiodide (3 mmol) in tetrahydrofuran (THF)

(11) The precursors to these substrates were prepared as follows (see Experimental Section for details). (a) Compound **26**: reaction of 5-hepten-2-one neat with TESCN (prepared from TESCl and TMSCN by the method of Bither, T. A., Knoth, W. H., Lindsey, R. V., Jr.; Sharkey, W. H. *J. Am. Chem. Soc.* **1958**, *80*, 4151) and the salt of 18-crown-6 and KCN as a catalyst. Cf. Corey, E. J., Crouse, D. N.; Anderson, J. E. *J. Org. Chem.* **1975**, *40*, 2140. The silyl cyanohydrin was then reduced with DIBAL to give **26**. (b) Compound **27**: alkylation of the anion of the triethylsilyl cyanohydrin of benzaldehyde with 5-bromo-2-methyl-2-pentene (**13**). Reduction afforded **27**. (c) Compound **28**: addition of the Grignard reagent of 5-bromo-2-methyl-2-pentene to [(2-ethoxyethoxy)methyl]methyloxirane in the presence of CuI followed by acidic hydrolysis gave **28**.

(12) (a) Snider, B. B. The Prins and Carbonyl Ene Reaction, Chapter 2.1 in *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 2, pp 527−561. (b) Santelli, M.; Pons, J.-M. *Lewis Acids and Selectivity in Organic Synthesis*; CRC Press: Boca Raton, FL, 1996; Chapter 2. (c) In this case, the simple ene product was obtained as the major product.

and then 6-methyl-5-hepten-2-one (**12**) (130 mg, 1.03 mmol) and benzyl chloromethyl ether (160 mg, 1.02 mmol). The solution was stirred for 1 h and the dark green color gradually faded to give a light yellow sediment. At this time 5 mL of 0.1 N HCl was added and the solution stirred for 10 min which allowed the solids to dissolve and gave a slightly cloudy pale yellow solution. The organic layer was separated, and the aqueous phase was extracted with 5 × 10 mL of ether. The organic phases were combined and washed with 5 mL each of water and of saturated NaCl and then dried over K_2CO_3. After the drying agent was removed by filtration, the solution was evaporated and the crude product was vacuum distilled in a Kugelrohr at 200 °C (1 mmHg) to give 242 mg of 6-methyl-1-(phenylmethoxy)-5-hepten-2-ol as a colorless oil, which was shown by ^{1}H NMR to be 92.9% pure, implying a yield of 87.9%: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40−7.25 (m, 5H), 5.12 (br t, J = 7.1 Hz, 1H), 4.67 (s, 2H), 3.35 (d, J = 9 Hz, 1 H), 3.30 (d, J = 9 Hz, 1H), 2.32 (br s, 1H), 2.04 (q, J = 7.8 Hz, 2H), 1.69 (s, 3H), 1.61 (s, 3H), 1.58 (m, 2H), 1.19 (s, 3H); ^{13}C NMR (50 MHz) δ 138.3, 131.5, 128.4, 127.6, 127.0, 125.0, 77.8, 73.5, 72.2, 39.0, 25.7, 23.7, 22.5, 17.6.

A 100 mL oven-dried flask with a septum-capped sidearm inlet was placed under a dry ice condenser connected to a drying tube. Dry THF (2.5 mL) was added under argon, and then 3.8 g of lithium wire cut into short pieces was added. The dry ice condenser was chilled to −60 °C, and gaseous ammonia was introduced by needle slowly through the septum on the side inlet, which gave a dark blue solution with stirring as the ammonia condensed. Enough ammonia was added to increase the volume of the solution to 5 mL. Then 6-methyl-1-(phenylmethoxy)-5-hepten-2-ol (150 mg, 0.60 mmol) in 2.5 mL of THF was added dropwise over 10 min. The solution was stirred for an additional 2 min, the dry ice condenser was removed, and 1.5 g of solid ammonium chloride was added with gentle stirring. The mixture was allowed to warm to room temperature very gradually to minimize foaming as the ammonia evaporated. Saturated NaCl and ether (20 mL each) were added, and the organic layer was separated. The aqueous phase was extracted with 4 × 10 mL of ether, and the combined organic phases were dried over K_2CO_3. After the drying agent was removed by filtration, Kugelrohr vacuum distillation at 150 °C (1 mmHg) gave 79 mg of the diol **9**, as a pure colorless oil (83.2% yield): ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.05 (br t, J = 7.0 Hz, 1H), 3.38 (d, J = 10.9 Hz, 1H), 3.34 (d, J = 10.9 Hz, 1H), 2.29 (br s, 2H), 1.99 (app q, J = 7.7 Hz, 2H), 1.62 (s, 3H), 1.55 (s, 3H), 1.45 (m, 2H), 1.11 (s, 3H); ^{13}C NMR (50 MHz) δ 132.0, 124.2, 73.0, 69.8, 38.5, 25.7, 23.2, 22.4, 17.6.

2-Ethyl-6-methyl-5-heptene-1,2-diol (10). A Grignard reagent was made in the usual manner from 5-bromo-2-methyl-2-pentene (**13**)[9] (1.47 g., 9.0 mmol) and Mg turnings (219 mg, 9.0 mmol) in 10 mL of dry THF. In another 50 mL oven-dried round-bottom flask with a stir bar was added sodium α-ketobutyrate (**14**) (744 mg, 6 0.0 mmol) and 10 mL of dry ether under a dry ice condenser with a drying tube. This flask was heated to 50 °C (reflux) in an oil bath, and the Grignard solution was added via a large bore needle over 5 min with stirring.[13] The solution was refluxed for 2 h and then chilled in an ice bath while 10 mL of 2 N HCl was carefully added with vigorous stirring. Over the next 15 min, the solids gradually dissolved. The organic phase was separated, the aqueous phase was extracted with 3 × 10 mL of ether, and the combined organic phases were dried over $MgSO_4$. The solution was filtered and evaporated, and the crude product was purified by column chromatography on silica gel with a gradient hexane to 1:5 ethyl acetate/hexane elution to give 411 mg of sodium 2-ethyl-2-hydroxy-6-methyl-5-heptenoate, as a colorless liquid which crystallized under refrigeration (32.9% yield). Higher yields can be obtained by using a slightly larger excess of the Grignard reagent.[13] The melting point of the product was determined to be 37−39 °C; however the product appeared to be somewhat hygroscopic and attempts at further drying with mild heat and high vacuum resulted in decomposition at about 70 °C: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.02 (t, J = 7.0 Hz, 1H), 2.2−1.5 (m, 6H), 1.59 (s, 3H), 1.52 (s, 3H), 0.85 (t, J = 7.4 Hz, 3H); ^{13}C NMR (50 MHz) δ 180.9, 132.0, 122.7, 77.4, 38.0, 31.7, 24.9, 21.8, 17.0, 7.1.

In a 25 mL oven-dried round-bottom flask with a reflux condenser and drying tube was placed 2 mL of 1 M lithium aluminum hydride (LAH, 2.0 mmol) in ether. Then sodium 2-ethyl-2-hydroxy-6-methyl-5-heptenoate (223 mg, 1.07 mmol) in 6 mL of ether was added dropwise with stirring which produced slight gas evolution. The solution was stirred for 15 min, and 5 mL of water was cautiously added to decompose the excess LAH. Then 5 mL of 10% H_2SO_4 was added slowly to clarify the solution. The organic phase was separated, and the aqueous phase was extracted with 3 × 5 mL of ether. The organic phases were combined and washed with 5 mL of water. The solution was then dried over Na_2SO_4 and filtered, the solution was evaporated, and the crude product was purified by column chromatography on silica gel with a gradient hexanes to 1:5 ethyl acetate/hexanes elution to give 179 mg of the diol **10** as a colorless oil (97.1% yield): ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.10 (br t, J = 6.4 Hz, 1H), 3.46 (s, 2 H), 2.03 (br s, 2H), 1.98 (m, 2H), 1.68 (s, 3H), 1.62 (s, 3H), 1.52 (m, 4H), 0.88 (t, J = 7.5 Hz, 3H); ^{13}C NMR δ 132.0, 124.2, 74.9, 67.6, 35.2, 28.4, 25.7, 22.0, 17.6, 7.8.

***(E)*-2-Methyl-6-phenyl-5-hexene-1,2-diol (11).** A Grignard reagent was made in the usual manner from 4-bromo-1-phenyl-1-butene (**15**) (1.71 g, 8.1 mmol) and Mg turnings (364 mg, 15.0 mmol) in 15 mL of dry THF. Then 1-[(tetrahydrofuran-2-yl)oxy]acetone (**16**) (1.3 g., 9.0 mmol) in 3 mL of dry THF was added dropwise with stirring. Stirring was continued in a 50 °C oil bath for 30 min. Then the flask was transferred to an ice bath and 8 mL of 2 N HCl was added carefully, followed by stirring at room temperature for 30 min. The organic phase was separated, and the aqueous phase was extracted with 2 × 5 mL of ether. The combined organic phases were washed with 4 mL of cold water and then dried over Na_2SO_4. The drying agent was removed by filtration, and the solution was evaporated down to a couple of milliliters. At this time 10 mL of 3:1:1 acetic acid/water/THF was added, and the solution was stirred overnight. The next day the solution was poured carefully into 40 mL each of ether and of saturated Na_2CO_3 which resulted in considerable bubbling. Additional saturated Na_2CO_3 was added to bring the pH of the solution to 7. The organic phase was separated, and the organic phase was extracted with 2 × 25 mL of ether. The combined organic phases were washed with 25 mL of saturated NaCl and dried over $MgSO_4$. The crude product in solution was filtered, evaporated, and purified by column chromatography on silica gel, eluting with hexanes to a 1:3 ethyl acetate/hexane gradient to give 925 mg of the diol as a colorless oil (55.4% yield) which began to crystallize into small white nodules at room temperature; the process was completed in the refrigerator overnight. The melting point of the product was determined to be 65−66 °C: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.35−7.07 (m, 5H), 6.35 (d, J = 15.8 Hz, 1H), 6.15 (dt, J = 15.8, 6.3 Hz, 1H), 3.42 (d, J = 11.0 Hz, 1H), 3.38 (d, J = 11.0 Hz, 1H), 2.24 (m, 2H), 2.17 (br s, 2H), 1.58 (m, 2H), 1.14 (s, 3H); ^{13}C NMR (50 MHz) δ 137.6, 130.5, 130.1, 128.5, 127.0, 125.9, 72.9, 69.8, 38.1, 27.4, 23.3.

5-Bromo-2-methyl-2-pentene (13).[9] A Grignard reagent was made in the usual manner from Mg turnings (2.43 g, 100 mmol), methyl iodide (14.6 g, 103 mmol), and 20 mL of dry ether in a 100 mL oven-dried round-bottom flask. The Grignard solution was cooled in an ice bath, and cyclopropyl methyl ketone (4.5 g, 53.5 mmol) in 5 mL of ether was added dropwise over 20 min which produced much foaming. The reaction flask was removed from the ice bath and stirred for 1 h at room temperature. The flask was then returned to the ice bath, 30 mL of saturated aqueous ammonium chloride was added gradually, and the solution was stirred for 15 min. The almost colorless organic phase was separated, and the aqueous phase was extracted with 4 × 20 mL of ether. The organic phases turned orange after the extraction due to the presence of the small amount of iodine which was used to initiate the Grignard reaction. The combined organic phases were shaken with 15 mL of water and a little $Na_2S_2O_3$ until the color faded. The organic phase was once again separated and washed with

(13) Christie, E. W.; McKenzie, A.; Ritchie, A. *J. Chem. Soc.* **1935**, 153.

20 mL each of water and saturated aqueous NaCl and then dried over $MgSO_4$. After filtration the solution was evaporated down to 5.4 g of a pale yellow oil in a 100 mL round-bottom flask, a stir bar was added, and the flask was placed in an ice bath. At this time 11.3 mL of 48% HBr (99.9 mmol) was added dropwise over 30 min with vigorous stirring, and then the solution was stirred for an additional 1 h to give a clear organic layer and whitish aqueous phase. TLC showed the second reaction to be complete with a new high-R_f spot. Water and ether (10 mL each) were then added, and the solution was stirred until the mixture clarified. The light yellow organic phase was separated, and the aqueous phase was extracted with 3 × 15 mL of ether. The organic phases were combined and washed with 10 mL each of water, 2% Na_2CO_3, water, and saturated NaCl, and the solution was dried over $MgSO_4$. After filtration to remove the drying agent, the solution was evaporated to give 7.44 g of the bromide **13**[9] as a pale yellow oil which was shown by ^{1}H NMR to contain 26% of residual ether, implying a yield of 67.3% for the two steps: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.06 (br t, J = 7.1 Hz, 1H), 3.27 (t, J = 7.3 Hz, 2H), 2.49 (dt, J = 7.3, 7.3 Hz, 2H), 1.65 (s, 3 H), 1.56 (s, 3 H).

4-Bromo-1-phenyl-1-butene (15).[10] Cyclopropyl phenyl ketone (1.46 g, 10 mmol) was added to 20 mL of methanol in a 100 mL oven-dried round-bottom flask which was cooled in an ice bath. Sodium borohydride (567 mg, 15 mmol) was then added carefully in small portions, and the solution was stirred for 15 min. At this time the solution was acidified to pH 3 with 2 N HCl using Congo Red as an indicator. The organic phase was separated, and the aqueous phase was extracted with 3 × 35 mL dichloromethane. The combined organic phases were dried over $MgSO_4$ and then filtered into a 250 mL round-bottom flask. The resultant solution was vacuum evaporated at 50 °C (50 mmHg) and then put in ice bath where 2.26 mL of 48% HBr (20 mmol) was added dropwise over 20 min with vigorous stirring. The solution was stirred for an additional 30 min at 0 °C and then for 15 min at room temperature. The solution was partitioned with 2 mL of water and 4 mL of ether, and the organic layer was separated. The aqueous phase was extracted with 3 × 4 mL of ether, and the combined organic phases were washed with 2 mL each of water, 2% Na_2CO_3, water, and saturated NaCl. The solution was dried over $MgSO_4$, filtered, and evaporated to give 1.911 g of the bromide **15**,[10] which was shown by ^{1}H NMR to contain 9% residual ether, implying a yield of 82.4% for the two steps: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.45−7.19 (m, 5H), 6.49 (d, J = 15.8 Hz, 1H), 6.18 (dt, J = 15.8, 6.8 Hz, 1H), 3.47 (t, J = 6.8 Hz, 2H), 2.79 (dt, J = 6.8, 6.4 Hz, 2H).

***exo*-7-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-1,3,3-trimethyl-2-oxabicyclo[2.2.1]heptane (17).** To a 25 mL oven-dried round-bottom flask under argon was added 1 mL of dichloromethane dried over CaH_2. Freshly distilled oxalyl chloride (254 mg, 2.0 mmol) was added, and the solution was chilled to −60 °C. Then dimethyl sulfoxide (DMSO, 312 mg, 4.0 mmol) which had been freshly distilled from CaH_2 was added over 5 min dropwise in 1 mL of dry dichloromethane with stirring. The resultant clear solution was stirred for an additional 5 min, and then the diol **9** (158 mg, 1.0 mmol) in 1 mL of dry dichloromethane was added dropwise with stirring. During this time the solution acquired a white slushy appearance and stirring was continued for an additional 15 min at −60 °C. Then diisopropylethylamine (DIPEA, 1.03 g, 8.0 mmol) which had been stored over KOH was added dropwise over 5 min and the reaction flask was removed from the cold bath and allowed to warm gradually to room temperature with stirring over 15 min. This was followed by the addition of 4 mL of water and stirring for another 10 min. The organic phase was separated, and the aqueous phase was extracted with 4 × 3 mL of dichloromethane. The organic phases were combined and washed with 6 mL each of 0.1 M HCl, water, dilute Na_2CO_3, water, and saturated NaCl, and then the solution was dried over $MgSO_4$. The crude aldehyde **6** in solution was filtered directly into a 25 mL oven-dried round-bottom flask with a stirbar, evaporated to about 3 mL, and flushed with argon. To this new solution were added 2,6-di-*tert*-butyl-4-methylpyridine (308 mg, 1.5 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (317 mg, 1.2 mmol) which produced a slight bit of fuming. After the reaction stirred for 20 min, a TLC showed a new high-R_f spot predominating. The solution was stirred for a total of 30 min. At this time 4 mL of 5% Na_2CO_3 was added, and the stirring was continued for an additional 10 min. The organic phase was separated, and the aqueous phase was extracted with 3 × 3 mL of dichloromethane. The organic phases were combined, washed with 2 × 3 mL of water and 3 mL of saturated NaCl, and then dried over $MgSO_4$ and filtered. The solution was evaporated, and the crude product was purified by column chromatography on silica gel with a pentane to 1:10 dichloromethane/pentane gradient. After vacuum evaporation at room temperature (380 mmHg) to just over the theoretical weight, the flask was left open to the air for 1 h which allowed the remainder of the elution solvent to evaporate and gave 241 mg of the ether **17** as a colorless liquid (89.1% yield for two steps): ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.84 (s, 1H), 1.85−1.78 (m, 2H), 1.75−1.66 (m, 1H), 1.63−1.56 (m, 1H), 1.38−1.32 (m, 1H), 1.11 (s, 6H), 1.10 (s, 3H), 0.81 (s, 9H), 0.00 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (50 MHz) δ 84.8, 79.9, 77.4, 50.6, 32.1, 29.7, 26.1, 25.7, 21.9, 18.0, 17.4, −4.8, −5.0.

***exo*-3,3-Dimethyl-7-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3-ethyl-2-oxa-bicyclo[2.2.1]heptane (18).** To a 25 mL oven-dried round-bottom flask under argon was added 1.5 mL of dichloro-methane dried over CaH_2. Freshly distilled oxalyl chloride (82 mg, 0.65 mmol) was added, and the flask was cooled to −50 °C. DMSO (100 mg, 1.29 mmol) distilled from CaH_2 in 1 mL of dry dichloromethane was then added dropwise over 5 min, and the solution was stirred for another 5 min. This was followed by the addition of 2-ethyl-6-methyl-5-hexene-1,2-diol (**10**) (74 mg, 0.43 mmol) in 1 mL of dichloromethane dropwise over the next 5 min which caused the solution to assume a white, slushy appearance. Stirring was continued at the same temperature for another 15 min. Then triethylamine (261 mg, 2.58 mmol) was added over 5 min and the solution was allowed to warm gradually to room temperature with stirring. At this time 4 mL of water was added and the reaction stirred for 10 min to give very pale yellow solution. The organic phase was separated, and the aqueous phase was extracted with 4 × 3 mL of dichloromethane. The organic phases were combined and washed with 3 mL each of 0.1 M HCl, water, dilute Na_2CO_3, water, and saturated NaCl. The crude aldehyde **7** in solution was dried over $MgSO_4$ and filtered directly into a fresh 25 mL oven-dried round-bottom flask, and its volume was reduced by rotary evaporation down to about 2 mL. The flask was flushed with argon, and 2,6-di-*tert*-butyl-4-methylpyridine (132 mg, 0.645 mmol) and then *tert*-butyldimethylsilyl triflate (165 mg, 0.54 mmol) were added. The reaction was substantially complete in 10 min by TLC and was stirred for an additional 1 h. At this time 4 mL of 5% $NaHCO_3$ was added and the solution was stirred for 10 min. The organic phase was separated, and the aqueous phase was extracted with 3 × 4 mL of ether. The organic phases were then combined and washed with 2 × 3 mL of water and then 3 mL of saturated NaCl, dried over $MgSO_4$, and filtered. After the solvent was removed on a Rotovap, the crude product was purified by column chromatography on silica gel with a pentane to 1:6 dichloromethane/pentane gradient. The product was vacuum evaporated at 40 °C (380 mmHg) to just above theoretical weight. Then the flask was left open and monitored by weight on a scale while the remainder of solvent was allowed to evaporate over 1 h which left 103 mg of the ether **18** as a colorless liquid (84.1% yield for two steps): ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.08 (s, 1H), 1.85−1.45 (m, 7H), 1.19 (s, 6H), 0.91 (t, J = 7.2 Hz, 3H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (50 MHz) δ 87.9, 77.3, 77.2, 50.3, 30.8, 29.6, 26.1, 25.7, 23.9, 21.4, 17.9, 8.5, −4.7, −5.0.

***exo*-7-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3-phenyl-2-oxabicyclo-[2.2.1]heptane (19).** To a 25 mL oven-dried round-bottom flask under argon was added 1.5 mL of dichloromethane dried over CaH_2. Freshly distilled oxalyl chloride (66 mg, 0.52 mmol) was added, and the flask was cooled to −50 °C. DMSO (82 mg, 1.05 mmol) distilled from CaH_2 in 1 mL of dry dichloromethane was then added dropwise over 5 min, and the solution was stirred for another 5 min. The

subsequent addition of 2-methyl-6-phenyl-5-hexene-1,2-diol (**11**) (54 mg, 0.26 mmol) in 1 mL of dichloromethane dropwise over the next 5 min caused the solution to assume a white, slushy appearance, and stirring was continued at the same temperature for another 15 min. Finally diisopropylethylamine (271 mg, 2.10 mmol) was added over 5 min and the solution was allowed to warm gradually to room temperature with stirring. At this time 4 mL of water was added and the solution was stirred for 10 min to give very pale yellow solution. The organic phase was separated, and the aqueous phase was extracted with 4 × 3 mL of dichloromethane. The organic phases were combined and washed with 3 mL each of 0.1 M HCl, water, dilute Na_2CO_3, water, and saturated NaCl. The solution was dried over $MgSO_4$ and filtered directly into a fresh 50 mL oven-dried round-bottom flask, and its volume was reduced by rotary evaporation down to about 5 mL. The flask was flushed with argon, and 2,6-di-*tert*-butyl-4-methylpyridine (108 mg, 0.53 mmol) and then *tert*-butyldimethylsilyl triflate (104 mg, 0.39 mmol) were added. The solution was stirred for 1.5 h until the starting material disappeared and a new high-R_f spot predominated on TLC. The reaction was neutralized with 4 mL 5% of Na_2CO_3 and stirred for 10 min. The organic phase was separated, and the aqueous phase was extracted with 3 × 4 mL of ether. The organic phases were then combined and washed with 2 × 3 mL of water and then 3 mL of saturated NaCl, dried over $MgSO_4$, and filtered. After the solvent was removed on a Rotovap, the crude product was purified by column chromatography on silica gel with a pentane to 1:5 dichloromethane/pentane gradient. The product was vacuum evaporated at 40 °C (380 mmHg) to just above theoretical weight. Then the flask was left open and monitored by weight on a scale while the remainder of solvent was allowed to evaporate over 1 h which left 76 mg of the ether **19** as a colorless liquid (91.7% yield for two steps): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40−7.19 (m, 5H), 4.75 (s, 1H), 3.78 (s, 1H), 2.23−2.10 (m, 2H), 1.94−1.50 (m, 3H), 1.39 (s, 3H), 0.92 (s, 9H), 0.00 (s, 3H), −0.03 (s, 3H); ^{13}C NMR (50 MHz) δ 143.4, 128.0, 126.6, 125.2, 84.1, 82.4, 48.7, 33.5, 27.5, 25.6, 17.9, 16.6, −4.8, −5.0.

(*E*)-2-Methyl-2-(triethylsilyloxy)-5-heptenal (26). (*E*)-Methyl 2-acetyl-4-hexenoate (2.0 g, 11.75 mmol) was added to a 50 mL round-bottom flask with a boiling chip together with 15 mL of DMSO and 450 mg of water. The solution was then refluxed for 3 h at 185 °C under a reflux condenser. The resultant orange brown solution was poured onto ice and extracted with 3 × 20 mL of pentane. The combined organic extractions were dried over Na_2SO_4, filtered, and evaporated. The crude product was then vacuum distilled in a Kugelrohr apparatus at 100−140 °C (130 mmHg) which gave 801 mg of (*E*)-5-hepten-2-one as a colorless liquid (57.1% yield): ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.55−5.31 (m, 2H), 2.48 (t, J = 7.2 Hz, 2H), 2.27 (dt, J = 6.8, 6.8 Hz, 2H), 2.13 (s, 3H), 1.62 (br s, 3H). (*E*)-5-Hepten-2-one (224 mg, 2.0 mmol) was added to a 10 mL oven-dried round-bottom flask together with triethylsilyl cyanide (333 mg, 2.36 mmol) and 1:1 potassium cyanide/18-crown-6 salt (33 mg, 0.1 mmol) as a catalyst. The neat mixture was stirred overnight under argon at 70 °C. The next day 4 mL of pentane and 2 mL of ice were added and the mixture was stirred for 5 min. Florisil (240 mg) was then added to absorb impurities, and the mixture was shaken and stirred for an additional 5 min. The organic phase was separated, and the aqueous phase was extracted with 3 × 4 mL of pentane. The organic phases were dried over $MgSO_4$, and the drying agent was removed by filtration into a 25 mL oven-dried round-bottom flask. The solution was evaporated down to about 3 mL and the flask flushed with argon and chilled to −45 °C whereupon 3 mL of 1 M DIBAL (3 mmol) in hexanes was added dropwise over 20 min. The flask was then transferred to an ice bath where it was stirred for 1 h. At this time, 2 mL each of ether and of saturated ammonium chloride were added and the solution was stirred for 30 min until the white precipitate had fully coagulated. Then 4 mL of 0.75 M H_2SO_4 was added and the solution was stirred for an additional hour. The organic phase was separated, and the aqueous phase was extracted with 2 × 3 mL of ether. The combined organic phases were then dried over $MgSO_4$ and filtered, and the solvent was removed in a Rotavap. The crude product was placed on a 1 × 10 cm silica column, eluting with pentane alone to give 300 mg of the aldehyde as a colorless liquid (58.5% yield): ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.48 (s, 1H), 5.42−5.20 (m, 2H), 2.10−1.85 (m, 2H), 1.63−1.48 (m, 2H), 1.55 (d, J = 6.8 Hz, 3H), 1.20 (s, 3H), 0.89 (t, J = 8.2 Hz, 9H), 0.54 (q, J = 7.8 Hz, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 205.0, 130.7, 125.4, 80.1, 39.4, 26.5, 22.9, 17.8, 6.9, 6.6.

6-Methyl-2-phenyl-2-[(triethylsilyl)oxy]-5-heptenal (27).[14] Powdered potassium cyanide (2.6 g, 40 mmol) was dried in a 50 mL pear-shaped flask in a Kugelrohr apparatus at 250 °C (1 mmHg) for 30 min. The apparatus was allowed to cool to 150 °C, and zinc iodide (47 mg, 0.15 mmol) was added. The mixture was then heated for an additional hour at heated for 1 h at 150 °C (1 mmHg). After the flask was cooled under argon, benzaldehyde (1.06 g, 10 mmol) in 40 mL of dry acetonitrile was added. Subsequent addition of triethylsilyl chloride (1.8 g, 12 mmol) caused fuming and turned the solution yellow. It was then stirred under argon overnight. The next day the yellow color had faded. The solvent was removed by evaporation, and the crude product, α-[(triethylsilyl)-oxy]phenylacetonitrile, was redissolved in 10 mL of ether. The ether solution was dried over $MgSO_4$, filtered, and vacuum evaporated at 50 °C (10 mmHg) to give 2.594 g of a pale yellow liquid. The crude product was chromatographed on silica gel, eluting with pentane to give 2.287 g of the cyanohydrin silyl ether as a colorless liquid (92.4% yield): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.67−7.37 (m, 5H), 5.49 (s, 1H), 0.96 (t, J = 7.8 Hz, 9H), 0.73 (q, J = 7.4 Hz, 6H). To a solution of lithium diisopropylamide made in situ from diisopropyl-amine (607 mg, 6.0 mmol) in 5 mL of dry THF and 4.58 mL of 1.2 M *n*-butyllithium (5.5 mmol) in hexanes at −70 °C in a 25 mL oven-dried round-bottom flask was added α-[(triethylsilyl)oxy]-phenylacetonitrile (1.237 g, 5.0 mmol) in 1 mL of THF dropwise over 5 min, and then the reaction was stirred for an additional 5 min. Then 5-bromo-2-methyl-2-pentene (**13**)[9] (815 mg, 5.0 mmol) was added and the reaction stirred an additional 10 min at −70 °C.[15] The reaction mixture was then allowed to warm to room temperature as stirring was continued for 1.5 h. At this time 5 mL of water was added and the organic phase was separated. The aqueous phase was extracted with 2 × 10 mL of dichloromethane, and the combined organic phases were dried over Na_2SO_4, filtered, and evaporated down to a thin orange syrup. The crude product was purified by column chromatography on silica gel, eluting with pentane. The volume of the elution solvent was reduced to 5 mL in a fresh 50 mL oven-dried round-bottom flask which was flushed with and chilled to −50 °C. To this flask was then added 8.8 mL of 1 M diisobutylaluminum hydride (DIBAL, 8.8 mmol) in hexanes dropwise over 20 min. Stirring was continued in an ice bath for an additional 2 h; then 20 mL of ether and 10 mL of saturated ammonium chloride were added. After the mixture stirred for an additional hour, 10 mL of 0.75 M H_2SO_4 was carefully added and the solution was stirred overnight. The next day the organic layer was separated and the aqueous phase was extracted with 3 × 10 mL of ether. The organic phases were combined, dried over $MgSO_4$, and filtered. After the solvent was removed by evaporation, the crude product was chromatographed on silica gel, eluting with pentane to give 560 mg of the aldehyde as a colorless oil (33.8% yield for the two steps): ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.54 (s, 1H), 7.40−7.24 (m, 5H), 5.0 (br t, J = 7.0 Hz, 1H), 2.0−1.6 (m, 2H), 1.61 (s, 3H), 1.47 (s, 3H), 1.27 (m, 2H), 0.97 (t, J = 7.4 Hz, 9H), 0.70 (q, J = 7.7 Hz, 6H).

2,7-Dimethyl-6-octene-1,2-diol (28).[16] A Grignard reagent was made in the usual manner from 5-bromo-2-methyl-2-pentene (**13**)[9] (358 mg, 2.2 mmol) and Mg turnings (73 mg, 3.0 mmol) in 3 mL of dry THF. The grayish yellow solution was cooled to −30 °C which precipitated a large amount of

(14) Rawal, V. H.; Rao, J. A.; Cava, M. P. *Tetrahedron Lett.* **1985**, *26*, 4275.
(15) Albright, J. D. *Tetrahedron* **1983**, *39*, 3207.
(16) Huynh, C.; Derguini-Boumechal, F.; Linstrumelle, G. *Tetrahedron Lett.* **1979**, 1503.

thick whitish sediment. To this mixture was added 38 mg of anhydrous copper(I) iodide, and then 2-[(1-ethoxyethoxy)methyl]-2-methyloxirane[17] (280 mg, 1.75 mmol) was added with stirring to give a purple-black color. The mixture was transferred to an ice bath, stirred for 1.5 h, and then poured into 6 mL each of saturated ammonium chloride and ice which resulted in significant bubbling. After the mixture stirred overnight at room temperature, the last of the solids finally dissolved and gave a blue solution. The organic phase was separated, and the aqueous phase was extracted with 3 × 10 mL of ether. The combined organic phases were evaporated to remove the ether, and 20 mL of THF was added. This solution was chilled in an ice bath, 20 mL of 0.5 N HCl was added, and the mixture was stirred for 1 h and then for 1 h at room temperature as a new TLC spot with very low R_f appeared. The solution was extracted with 4 × 10 mL of ether, and the combined organic phases were washed with 5 mL each of water and dilute Na_2CO_3. After the organic phase was dried over Na_2CO_3, it was filtered and evaporated at 60 °C (380 mmHg). The crude product was chromatographed on silica gel, and eluting with a gradient dichloromethane to 1:50 methanol/dichloromethane gave 201 mg of the diol **28** as a pale yellow oil (66.6% yield for the two steps): ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.09 (br t, J = 7.2 Hz, 1H), 3.74 (m, 2H), 1.96 (dt, J = 6.9, 6.9 Hz, 2H), 1.7 (br s, 2H), 1.67 (s, 3H), 1.58 (s, 3H), 1.44 (m, 4H), 1.15 (s, 3H).

(17) Ando, K.; Yamada, T.; Shibuya, M. *Heterocycles* **1989**, *29*, 2209.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of **9**−**11**, **17**−**19**, and **26** and ^{1}H NMR spectra of **13**, **15**, and **27**−**28** (20 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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