Stereocontrolled Assembly of Cis *or* Trans Angularly Substituted Hydrindenes by the Unactivated Intramolecular Diels−Alder Reaction

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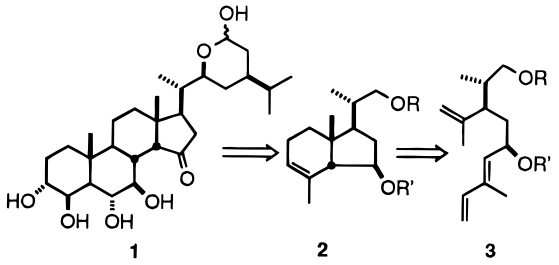
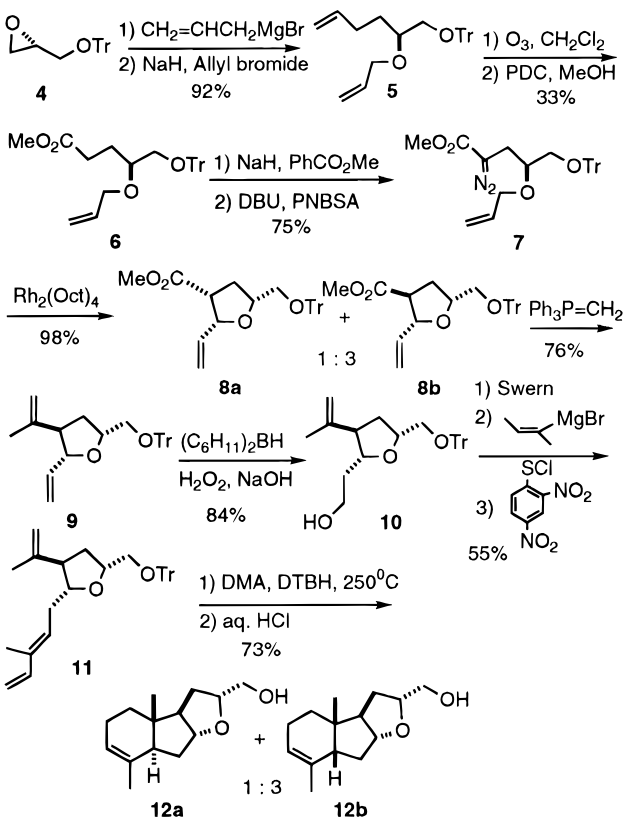
The unactivated intramolecular Diels−Alder reaction has become a powerful tool for the construction of polycyclic natural products. Nevertheless, the factors that govern diastereoselectivity in these cyclizations have not been fully understood. We here report that through the choice of the proper substituents, it is possible to make the unactivated intramolecular Diels−Alder reaction proceed to give *either* the cis angularly-substituted hydrindene **12b** or the trans product **19a**.

The activated intramolecular Diels−Alder reaction is a powerful tool for the construction of complex polycyclic natural products.[1,2] Since its introduction by Wilson in 1978,[3] the *unactivated* intramolecular Diels−Alder (UIDA) reaction[4] has also been widely used in natural product synthesis. In the context of a prospective total synthesis of the immune-suppressive steroid contignasterol (**1**), we envisioned a retrosynthetic dissection to **2** and thus to **3**. The difficulty with this approach was that it was well known[5−7] that trienes such as **3** often cyclize to give preferentially the (in this case undesired) trans ring fusion. We have therefore set out to explore substituent effects on the stereochemical course of the UIDA reaction. We now report that through the choice of the proper substituents, it is in fact possible to make the UIDA reaction proceed to give preferentially either the cis *or* the trans angularly-substituted 6/5 product.



Triene **11** was prepared from 1,2-epoxy-3-(triphenylmethoxy)propane (**4**) (Scheme 1). The epoxide was opened with allylmagnesium chloride, and the resultant secondary alcohol was alkylated with allyl bromide and NaH to give the trityl ether **5**. Selective ozonolysis of the more electron-rich alkene of **5** in CH_2Cl_2 followed by

Scheme 1



the oxidation with PDC[8] in MeOH gave the γ-alkoxy ester **6**. Diazo transfer[9,10] was then effected by benzoylation[11] of the ester **6** followed by exposure to DBU[12] and 4-nitrobenzenesulfonyl azide.[13]

Catalytic rhodium octanoate in CH_2Cl_2 at room temperature smoothly cyclized[14] α-diazo ester **7** to a mixture

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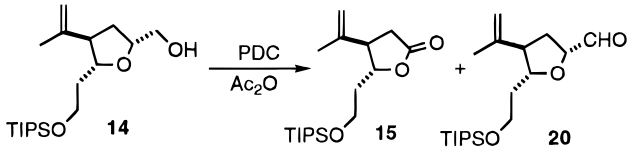
of **8a** and **8b**, in a ratio of 1:3. Transformation of **8b** into **9** was achieved by using a 4-fold excess of "salt-free" methylenetriphenylphosphorane.[15] Hydroboration and oxidation of **9** gave the primary alcohol **10**. Swern oxidation of **10** followed by addition of (1-methyl-1-propenyl)magnesium bromide gave the secondary allylic alcohol.

We next faced the problem of preparing selectively the *E*-diene. We reasoned that sigmatropic rearrangement of a sulfenate ester should establish the *E*-trisubstituted alkene, with subsequent sulfoxide elimination completing the diene. Indeed, dehydration[16] of allylic alcohol by 2,4-dinitrobenzenesulfenyl chloride gave the triene **11** (*E*:*Z* = 82:18).[17]

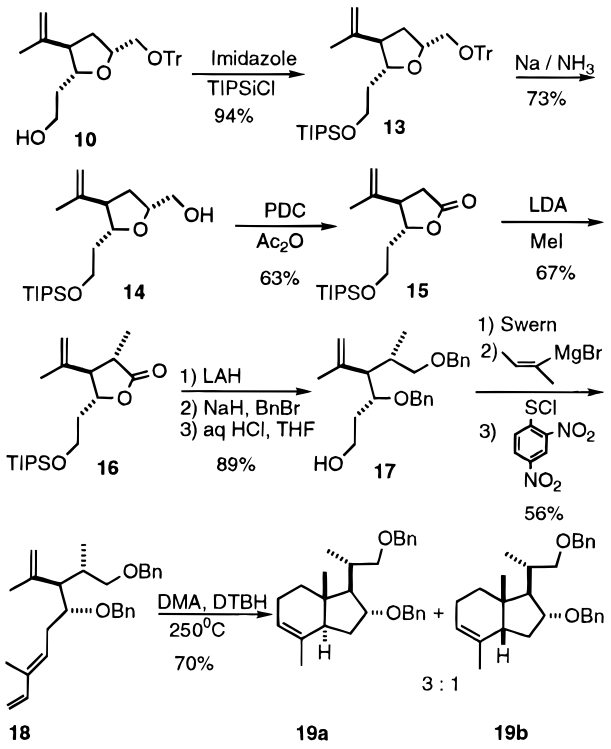
The triene **11** was cyclized[6a] by heating in dimethylaniline in a sealed tube with 2,5-di-*tert*-butylhydroquinone as a radical inhibitor at 250 °C for 24 h to give the tricycles **12a** (trans-fused) and **12b** (cis-fused) in a ratio of 1:3. The trityl group was cleaved when the reaction was worked up with 6 N aqueous hydrochloric acid to remove the dimethylaniline. The relative configuration of the cyclized products was assigned on the basis of the ^{1}H NMR spectra, with the chemical shifts of both the alkene proton (δ 5.17 vs δ 5.45) and the angular methyl group (δ 0.76 vs δ 0.95) further upfield in the trans diastereomer.[5−7] The observation of a *cis*-fused product predominating from the cyclization of **11** is in sharp contrast to the *trans* product established[5−7] for related acyclic trienes.

To confirm this, acyclic triene **18** was then prepared (Scheme 2) from the primary alcohol **10**. The alcohol **10** was silylated, and the trityl group was removed to give **14**. Our next objective was the oxidative cleavage of the primary alcohol to the lactone. Room-temperature oxidation with pyridinium dichromate[18] and acetic anhydride gave the lactone **15** and aldehyde **20** in a ratio of 2 to 1. We found that if alcohol **14** was added to a refluxing mixture of PDC and acetic anhydride in CH_2Cl_2 and DMF, the predominant product was lactone **15** (lactone:aldehyde = 10:1). We established this route to **18** because the diene of the primary alcohol from detritylation of **11** (Scheme 1) did not survive the PDC oxidation conditions.



The last stereogenic center of **18** (C-20, steroid numbering) was established by alkylation of lactone **15**. Thus, exposure to LDA followed by the addition of methyl iodide gave methylated lactone **16** as a single dominant diastereomer. The methylated lactone **16** was reduced with $LiAlH_4$, and the diol was protected with benzyl bromide. Desilylation followed by diene construction as before gave the triene **18** (*E*:*Z* = 86:14).[17]

Scheme 2



The triene **18** was heated in dimethylaniline at 250 °C for 24 h to give the cyclization products **19a** (trans-fused) and **19b** (cis-fused) in a ratio of 3:1. As expected,[5−7] the *trans* hydrindene was indeed the dominant product from cyclization of this acyclic triene. As before, the relative configuration of the cyclized products was assigned on the basis of the ^{1}H NMR spectra, with the chemical shifts of both the alkene proton (δ 5.24 vs δ 5.37) and the angular methyl group (δ 0.72 vs δ 0.89) further upfield in the trans diastereomer.[5−7]

This study confirms the previous experience[5−7] that the 6/5 unactivated intramolecular Diels−Alder reaction is closely balanced between cis vs trans ring-fused products. As can be seen from the cyclization of trienes **11** and **18**, it is possible to direct the unactivated intramolecular Diels−Alder reaction to give predominantly either the cis *or* the trans angularly-substituted 6/5 product. In pursuit of contignasterol (**1**), we are currently preparing 15-substituted trienes (steriod numbering) to investigate the influence of a substituent at that position on the diastereoselectivity of the cyclization.

Experimental Section[19]

Methyl 4-(2-Propenyloxy)-5-(triphenylmethoxy)pentanoate (6). At 0 °C, 100 mL of 2 M allylmagnesium chloride was added slowly to 1-[(triphenylmethoxy)methyl]oxirane (**4**) (30 g, 100 mmol) in 200 mL of dry THF. The reaction mixture was warmed to rt. After 4 h, the reaction mixture was sequentially partitioned between the aqueous 2 N HCl and 50% EtOAc/petroleum ether. The combined organic extract was washed sequentially with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. The combined organic extract was dried (Na_2SO_4) and concentrated to give 35 g of crude 1-(triphenylmethoxy)-5-hexen-2-ol.

NaH (14 g, 0.35 mol, 60% in mineral oil) was added in portions to the crude 1-(triphenylmethoxy)-5-hexen-2-ol (35 g)

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(16) To our knowledge, the Reich procedure has not previously been employed to prepare such an internally-substituted acyclic diene. For the development of this elimination procedure, see: (a) Reich, H. J.; Reich, I. L.; Wollowitz, S. *J. Am. Chem. Soc.* **1978**, *100*, 5981. (b) Suzuki T.; Sato, O.; Hirama, M.; Yamamoto, Y.; Murata, M. Yasumoto, T.; Harada, N. *Tetrahedron Lett.* **1991**, *32*, 4505.
(17) Although we report yields based on total (*E* + *Z*) triene, we expect that only the *E*-triene can cyclize.
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in 250 mL of dry THF at 0 °C. Allyl bromide (26 g, 0.21 mol) and Bu_4NI (200 mg) were then added. The reaction mixture was warmed to rt. After 4 h, the reaction mixture was partitioned between 2 N aqueous HCl and 50% EtOAc/petroleum ether. The combined organic extract was dried (Na_2SO_4) and concentrated to give 37 g of crude 6-(triphenylmethoxy)-5-(2-propenyloxy)-1-hexene (**5**) a colorless oil.

A solution of crude **5** (3.86 g, 10 mmol) in 30 mL of CH_2Cl_2 was stirred at −78 °C while 10 mmol of O_3 was passed through. Ph_3P (4.0 g, 15 mmol) was added, and the reaction mixture was warmed to rt for 2 h. Evaporation of the solvent and chromatography of the residue afforded 1.76 g of the aldehyde as a colorless oil (44% yield from 1,2-epoxy-3-(triphenylmethoxy)propane): TLC R_f (15% EtOAc/petroleum ether) = 0.43; ^{1}H NMR δ 9.74 (bs, 1H), 7.47 (m, 6H), 7.26 (m, 9H), 5.89 (m, 1H), 5.23 (m, 2H), 4.13 (m, 1H), 3.95 (m, 1H), 3.48 (m, 1H), 3.23 (dd, J = 5.1, 9.8 Hz, 1H), 3.12 (dd, J = 5.1, 9.8 Hz, 1H), 2.46 (m, 2H), 1.93 (m, 2H); ^{13}C NMR δ u 144.0, 116.8, 87.8, 71.1, 65.4, 40.0, 25.0; d 202.3, 134.9, 128.7, 127.8, 127.0, 77.3; IR (cm^{-1}) 3060, 2924, 1724, 1596, 1490, 1449, 1390, 1343, 1077, 900; MS *m/z* 323 (0.5), 259 (3), 243 (100), 165 (63), 127 (61), 105 (17); HRMS calcd for $C_{21}H_{23}O_3$ (n-C_6H_5) 323.1648, obsd 323.1729.

Pyridinium dichromate (40 g, 114 mmol) and MeOH (0.72 g) were added to the aldehyde (7.4 g, 18.5 mmol) in 40 mL of dry DMF. The reaction mixture was stirred at rt for 20 h. Ether (200 mL) and Celite (24 g) were added. The mixture was filtered, and the residue was washed with ether. The combined filtrate was washed with saturated aqueous NaCl and dried (Na_2SO_4). Evaporation of the solvent and chromatography of the residue afforded ester **6** as a colorless oil (5.7 g, 33% yield from **4**): TLC R_f (15% EtOAc/petroleum ether) = 0.50; ^{1}H NMR δ 7.43 (m, 6H), 7.28 (m, 9H), 5.89 (m, 1H), 5.23 (d, J = 17.1 Hz, 1H), 5.12 (d, J = 17.1 Hz, 1H), 4.12 (dd, J = 5.8, 12.7 Hz, 1H), 3.93 (dd, J = 5.8, 12.7 Hz, 1H), 3.62 (s, 3H), 3.47 (m, 1H), 3.19 (dd, J = 4.8, 9.7 Hz, 1H), 3.09 (dd, J = 4.8, 9.7 Hz), 2.35 (t, J = 7.4 Hz, 2H), 1.86 (m, 2H); ^{13}C NMR δ u 174.0, 144.0, 116.6, 86.7, 71.2, 65.6, 30.0, 27.4; d 51.4, 77.3, 126.9, 127.7, 128.7, 135.1; IR (cm^{-1}) 2927, 2871, 1738, 1597, 1471, 1448, 1346, 1261, 1171, 1078; MS *m/z* 430 (1), 353 (1), 259 (2), 243 (100), 189 (2), 131 (6), 115 (24); HRMS calcd for $C_{28}H_{20}O_4$ 430.2144, obsd 430.2149.

Methyl 2-Diazo-4-(2-propenyloxy)-5-(triphenylmethoxy)pentanoate (7). At 0 °C, NaH (3.18g, 76.4 mmol, 60% in mineral oil) was added to **6** (8 g, 18.6 mmol) in 50 mL of dry DME. After 10 min at 0 °C, methyl benzoate (5.21 g, 38.3 mmol) was added all at once, then the reaction mixture was heated to reflux for 10 h. The reaction was quenched by cautiously adding 1 N aqueous HCl, to pH = 4. The mixture was partitioned between 1 N aqueous HCl and 50% EtOAc/petroleum ether (3 × 40 mL). The combined organic extract was washed with saturated aqueous NaCl, dried (Na_2SO_4), concentrated, and chromatographed to give methyl 2-benzoyl-4-(2-propenyloxy)-5-(triphenylmethoxy)pentanoate (8.2g, 83% yield from **6**).

DBU (4.7 g, 30.8 mmol) was added to a solution of methyl 2-benzoyl-4-(2-propenyloxy)-4-(triphenylmethoxy)pentanoate (8.2 g, 15.4 mmol) in 40 mL of CH_2Cl_2 at 0 °C. After 10 min, 4-nitrobenzenesulfonyl azide (7.0 g, 30.8 mmol) was added. The reaction mixture was warmed to rt for 2 h and then sequentially partitioned between 0.5 M aqueous phosphate buffer (pH = 7.0) and CH_2Cl_2. The combined organic extract was dried (Na_2SO_4), concentrated, and chromatographed to give **7** (6.3 g, 75% yield from **6**) as a bright yellow oil: TLC R_f (15% EtOAc/petroleum ether) = 0.50; ^{1}H NMR δ 7.44 (m, 6H), 7.29 (m, 9H), 5.87 (m, 1H), 5.21 (m, 2H), 4.13 (dd, J = 5.6, 12.7 Hz, 1H), 3.95 (dd, J = 5.6, 12.7 Hz, 1H), 3.71 (s, 3H), 3.6 (m, 1H), 3.17 (d, J = 5.7 Hz, 2H), 2.57 (m, 2H); ^{13}C NMR δ u 143.8, 116.8, 87.3, 71.2, 64.8, 26.5; d 134.6, 128.6, 127.7, 127.0, 77.5, 51.8; IR (cm^{-1}) 2921, 2088, 1693, 1490, 1449, 1344, 1132, 1075.

Methyl (*R*,S*,R)-2-Ethenyl-5-[(triphenylmethoxy)-methyl]-2,3,4,5-tetrahydro-3-furancarboxylate (8a) and Methyl (*R*,R*,R**)-2-Ethenyl-5-[(triphenylmethoxy)-methyl]-2,3,4,5-tetrahydro-3-furancarboxylate (8b).** Diazo ester **7** (456 mg, 1 mmol) in a 25 mL round-bottom flask containing a magnetic stir bar was evaporated with toluene (3 × 7 mL). Methylene chloride was then added by filtration through a pad of anhydrous K_2CO_3. Dirhodium tetraoctanoate (1 mg) was added with stirring. The reaction was complete in 30 min. The reaction mixture was concentrated, and the residue was chromatographed to give 316 mg of **8a** (24% yield from **7**) and 103 mg of **8b** (74% yield from **7**). **8a**: TLC R_f (15% EtOAc/petroleum ether) = 0.41; ^{1}H NMR δ 7.47 (m, 6H), 7.26 (m, 9H), 5.76 (m, 1H), 5.29 (d, J = 17.0 Hz, 1H), 5.12 (d, J = 11.6 Hz, 1H), 4.61 (t, J = 8.1 Hz, 1H), 4.14 (m, 1H), 3.56 (s, 3H), 3.37 (m, 1H), 3.27 (m, 1H), 3.16 (m, 1H), 2.08 (t, J = 8.3 Hz, 2H); ^{13}C NMR δ u 171.8, 143.9, 117.2, 86.4, 66.2, 31.0; d 135.1, 128.6, 127.6, 126.8, 80.7, 78.5, 51.5, 48.3; IR (cm^{-1}) 3057, 2872, 2131, 1738, 1597, 1491, 1448, 1202, 1078. **8b**: TLC R_f (15% EtOAc/petroleum ether) = 0.48; ^{1}H NMR δ 7.45 (m, 6H), 7.29 (m, 9H), 5.92 (m, 1H), 5.36 (d, J = 17.2 Hz, 1H), 5.17 (d, J = 10.3 Hz), 4.47 (t, J = 7.0 Hz, 1H), 4.29 (m, 1H), 3.70 (s, 3H), 3.15 (m, 2H), 2.84 (q, J = 7.7 Hz, 1 H), 2.29 (m, 1H), 2.08 (m, 1H); ^{13}C NMR δ u 173.4, 144.0, 116.6, 86.5, 66.0, 32.7; d 137.1, 128.7, 127.7, 126.9, 83.0, 78.1, 51.9, 49.6; IR (cm^{-1}) 2921, 2872, 1738, 1597, 1490, 1449, 1366, 1273, 1170, 1077; MS *m/z* 428 (0.02), 398 (1), 351 (2), 259 (12), 243 (100), 165 (60), 123 (28), 105 (17); HRMS calcd for $C_{28}H_{28}O_4$ 428.1988, obsd 428.2279.

(*R*,R*,R)-2-Ethenyl-3-(methylethenyl)-5-[(triphenylmethoxy)methyl]-2,3,4,5-tetrahydrofuran (9).** NaHMDS (6.5 mL, 1 M in THF) was added to 2.4 g of methyltriphenylphosphonium bromide in 6 mL of dry THF at rt. The reaction mixture was stirred at rt for 30 min and then heated to reflux for 1 h. After the mixture was cooled to rt, **8b** (0.7 g, 1.64 mmol) in 4 mL of THF was added. After 8 h at rt, the mixture was partitioned between H_2O and 20% EtOAc/petroleum ether. The combined organic extract was dried (Na_2SO_4), concentrated, and chromatographed to give **9** (0.51g, 76% yield from **8b**): TLC R_f (10% EtOAc/petroleum ether) = 0.63; ^{1}H NMR δ 7.47 (m, 6H), 7.27 (m, 9H), 5.85 (m, 1H), 5.27 (d, J = 17.3 Hz, 1H), 5.13 (d, J = 10.4 Hz, 1H), 4.79 (m, 2H), 4.25 (m, 1H), 4.17 (t, J = 7.7 Hz, 1H), 3.18 (dd, J = 5.2, 9.5 Hz, 1H), 3.09 (dd, J = 5.2, 9.5 Hz, 1H), 5.56 (q, J = 8.7 Hz, 1H), 1.98 (m, 2 H), 1.73 (s, 3H); ^{13}C NMR δ u 144.1, 143.5, 116.2, 111.8, 86.4, 66.6, 34.1; d 138.1, 128.7, 127.7, 126.7, 83.7, 77.4, 51.7, 20.6; IR (cm^{-1}) 3059, 2916, 1645, 1597, 1490, 1449, 1222, 1076; MS *m/z* 410 (0.1), 354 (2), 333 (1), 298 (0.3), 277 (3), 259 (3), 243 (100), 165 (70), 137 (50); HRMS calcd for $C_{29}H_{30}O_2$ 410.2246, obsd 410.2491.

(*R*,R*,R)-3-(Methylethenyl)-5-[(triphenylmethoxy)-methyl]-2,3,4,5-tetrahydrofuran-2-ethanol (10).** At 0 °C, borane−dimethyl sulfide (0.15 mL,10 M) was added to cyclohexene (250 mg) in 1.5 mL of dry THF. The reaction mixture was stirred for 45 min at 0 °C and another 45 min at rt. Then **9** (500 mg) in 0.5 mL of dry THF was added to the reaction mixture. After 3 h, EtOH (673 mg), aqueous NaOH (0.5 mL, 3 M), and H_2O_2 (0.3 mL, 33%) were added. After 1 h, the mixture was partitioned between H_2O and 40% EtOAc/petroleum ether. The combined organic extract was dried (Na_2SO_4), concentrated, and chromatographed to give **10** (438 mg, 84% yield from **9**): TLC R_f (30% EtOAc/petroleum ether) = 0.37; ^{1}H NMR δ 7.48 (m, 6H), 7.45 (m, 9H), 4.79 (d, J = 6.1 Hz, 2H), 4.20 (m, 1H), 3.89 (dt, J = 3.0, 9.0 Hz, 1H), 3.79 (m, 2H), 3.11 (t, J = 5.9 Hz, 2H), 2.78 (bs, 1H), 2.52 (q, J = 9.0 Hz, 1H), 1.93 (m, 2H), 1.86 (m, 1H), 1.72 (s, 3H), 1.68 (m, 1H); ^{13}C NMR δ u 144.0, 143.8, 112.1, 86.5, 66.4, 61.6, 36.2, 33.7; d 128.7, 127.7, 126.9, 82.5, 77.7, 51.7, 20.1; IR (cm^{-1}) 3032, 2938, 1643, 1597, 1491, 1449, 1378, 1222, 1071, 899, 706; MS *m/z* 428 (1), 351 (1), 258 (1), 243 (100), 228 (4), 185 (2), 165 (35); HRMS calcd for $C_{29}H_{32}O_3$ 428.2351, obsd 428.2321.

Triene 11. At −78 °C, DMSO (1.07 g, 13.8 mmol) in 4 mL of CH_2Cl_2 was added dropwisely to 2.4 mL of 3.44 M $(COCl)_2$ in 3 mL of dry CH_2Cl_2. After 20 min, **10** (529 mg, 1.24 mmol) in 2 mL of CH_2Cl_2 was added. After 2 h at −78 °C, Et_3N (2.3 g) was added. After being warmed to rt over 1 h, the mixture was partitioned between saturated aqueous $NaHCO_3$ and CH_2Cl_2. The combined organic extract was dried (Na_2SO_4) and concentrated to give crude aldehyde as a light yellow oil.

A few drops of 2-bromo-2-butene (2.7 g, 20 mmol) in 4 mL of dry THF was added to 0.96 g of magnesium and a catalytic amount of I_2 in 15 mL of dry THF. The mixture was heated

to reflux to initiate the reaction. When the red color of I_2 had disappeared, the rest of the 2-bromo-2-butene solution was added dropwise. The reaction was kept at reflux for another 1 h to give 20 mL of 1 M 1-methyl-1-propenyl-2-magnesium bromide.

1-Methyl-1-propenyl-2-magnesium bromide (1 M in THF, 4 mL, 4 mmol) was added to the crude aldehyde in 4 mL of dry THF at rt. After 1 h, the mixture was partitioned between saturated aqueous NH_4Cl and EtOAc. The combined organic extract was dried (Na_2SO_4), concentrated, and chromatographed to give allylic secondary allylic alcohol as a light yellow oil (419 mg, 70% yield from **10**).

At 0 °C, 2,4-dinitrobenzenesulfenyl chloride (282 mg, 1.2 mmol), 0.5 mg of methylene blue, and Et_3N (202 mg, 2 mmol) were added to the allylic alcohol (419 mg) in 8 mL of dichloroethane. After 10 min at 0 °C, the mixture was heated to 80 °C for 4 h. After being cooled to rt, the reaction mixture was partitioned between saturated aqueous $NaHCO_3$ and CH_2Cl_2. The combined organic extract was dried (Na_2SO_4), concentrated, and chromatographed to give triene **11** as a light yellow oil (289 mg, 50% yield from **10**): TLC R_f (10% EtOAc/petroleum ether) = 0.75; ^{1}H NMR δ 7.49 (m, 6H), 7.46 (m, 9H), 6.75 (dd, J = 11.2, 10.5 Hz, 0.2H), 6.36 (dd, J = 10.7, 10.8 Hz, 0.8H), 5.64 (t, J = 7.2 Hz, 0.8H), 5.54 (t, J = 7.0 Hz, 0.2H), 5.07 (bd, J = 17.1 Hz, 1H), 4.91 (bd, J = 10.7 Hz, 1H), 4.77 (m, 2H), 4.19 (m, 1H), 3.84 (m, 1H), 3.11 (m, 2H), 2.53 (m, 2H), 2.42 (m, 1H), 1.95 (m, 2H), 1.72 (s, 3H), 1.71 (s, 3H); ^{13}C NMR δ u 144.5, 144.2, 135.4, 113.6, 111.7, 110.7, 86.4, 66.6, 34.2, 33.1 (trans), 32.2 (cis); d 141.5, 133.7, 128.8, 127.7, 126.9, 82.1, 77.3, 50.8 (trans), 50.7 (cis), 20.2 (trans), 19.8 (cis), 11.9; IR (cm^{-1}) 3032, 2916, 1643, 1597, 1490, 1448, 1221, 1075, 990, 897; MS m/z 465 (10), 386 (4), 243 (100), 215 (3), 165 (37); HRMS calcd for $C_{33}H_{36}O_2$ (M + H) 465.2794, obsd 465.2750.

Tricyclic Hydrindenes 12a and 12b. A mixture of triene **11** (142 mg, 0.31 mmol, E/Z ratio = 82:18) and 2,5-di-*tert*-butylhydroquinone (1 mg) in *N*,*N*-dimethylaniline (10 mL) was heated in a sealed tube at 250 °C for 24 h. After being cooled to rt, the reaction mixture was partitioned between EtOAc and, sequentially, 3 N aqueous HCl and saturated aqueous $NaHCO_3$. The combined organic extract was dried (Na_2SO_4), concentrated, and chromatographed to give pure **12b** (69 mg) and a mixture of **12a** and **12b** (34 mg) as colorless oils (73% overall yield). **12a:** TLC R_f (40% EtOAc/petroleum ether) = 0.22; ^{1}H NMR δ 5.17 (m, 1H), 4.48 (m, 1H), 4.18 (q, J = 9.3 Hz, 1H), 3.65 (m, 2H), 2.94 (bs, 1H), 2.36−1.68 (m, 6H), 1.67 (s, 3H), 1.57−1.25 (m, 4H), 0.76 (s, 3H); ^{13}C NMR δ u 138.0, 65.7, 35.2, 23.6, 23.4; d 119.1, 82.8, 82.7, 58.5, 56.7, 25.2, 20.9; MS m/z 222 (22), 191 (39), 181 (40), 167 (30), 147 (100); HRMS calcd for $C_{14}H_{22}O_2$ 222.1620, obsd 222.1601. **12b:** TLC R_f (40% EtOAc/petroleum ether) = 0.25; ^{1}H NMR δ 5.45 (dd, J = 3.8, 4.8 Hz, 1H), 4.58 (m, 1H), 3.92 (dt, J = 5.7, 11 Hz, 1H), 3.71 (m, 1H), 3.69 (m, 1H), 2.31 (m, 2H), 2.25 (bs, 1H), 1.94 (m, 3 H), 1.77 (m, 1H), 1.62 (s, 3H), 1.56 (m, 2H), 1.44 (m, 1H), 1.17 (m, 1H), 0.95 (s, 3H); ^{13}C NMR δ u 138.0, 65.9, 34.9, 34.1, 25.2, 21.4; d 120.5, 86.7, 84.3, 56.4, 54.8, 25.2, 22.2; IR (cm^{-1}) 3020, 2911, 1456, 1376, 1249, 1114, 1055; MS m/z 222 (24), 191 (10), 173 (15), 149 (11), 147 (50), 141 (100), 121 (8), 107 (30); HRMS calcd for $C_{14}H_{22}O_2$ 222.1620, obsd 222.1618.

(*R,*R**,*R**)-2-[2-[[Tris(methylethyl)silyl]oxy]ethyl]-3-(methylethenyl)-5-[(triphenylmethoxy)methyl]-2,3,4,5-tetrahydrofuran (13).** Imidazole (381 mg) and DMAP (10 mg) were added to **10** (400 mg, 0.93 mmol) in 5 mL of dry CH_2Cl_2. Then TIPSiCl (2.5 mL, 0.5 M in CH_2Cl_2) was added. After 4 h, the mixture was partitioned between H_2O and CH_2Cl_2. The combined organic layer was washed with saturated $NaHCO_3$, dried (Na_2SO_4), concentrated, and chromatographed to give **13** (510 mg, 94% yield from **10**): TLC R_f (15% EtOAc/petroleum ether) = 0.72; ^{1}H NMR δ 7.47 (m, 6H), 7.27 (m, 9H), 4.78 (s, 2H), 4.18 (m, 1H), 3.88 (m, 3H), 3.15 (m, 1H), 3.07 (m, 1H), 2.48 (q, J = 8.4 Hz, 1H), 1.92 (t, J = 7.5 Hz, 2 H), 1.82 (m, 2H), 1.72 (s, 3H), 1.08 (m, 21H); ^{13}C NMR δ u 144.3, 144.1, 111.6, 86.7, 66.7, 60.7, 38.2, 34.2; d 128.7, 127.6, 126.8, 78.8, 77.0, 51.6, 20.0, 17.9, 11.9; IR (cm^{-1}) 3061, 2942, 2845, 1644, 1597, 1490, 1449, 1382, 1090, 995.

(*R,*R**,*R**)-2-[2-[[Tris(methylethyl)silyl]oxy]ethyl]-3-(methylethenyl)-5-(hydroxymethyl)-2,3,4,5-tetrahydrofuran (14).** To a solution of **13** (150 mg, 0.26 mmol) in dry THF and EtOH (8 mL, 1:1 v/v) and condensed ammonia (15 mL) at −78 °C was added sodium metal (60 mg, 2.5 mmol) until the solution was blue. After 30 min at −78 °C, solid NH_4Cl was added until the blue color disappeared. The mixture was warmed to rt and then partitioned between H_2O and EtOAc. The combined organic extract was dried (Na_2SO_4), concentrated, and chromatographed to give **14** as a colorless oil (71 mg, 76% yield): TLC R_f (15% EtOAc/petroleum ether) = 0.33; ^{1}H NMR δ 4.79 (s, 2H), 4.09 (m, 1H), 3.94 (dt, J = 3.4, 8.6 Hz, 1H), 2.07 (t, J = 6.3 Hz, 1H), 1.92 (m, 2H), 1.85 (m, 1H), 1.73 (s, 3H), 1.68 (m, 1H), 1.06 (m, 21H); ^{13}C NMR δ u 144.2, 111.8, 65.4, 60.7, 37.9, 33.2; d 79.2, 78.2, 52.1, 20.1, 18.0, 12.0; IR (cm^{-1}) 3436, 2942, 2866, 1645, 1463, 1383, 1101, 1069; MS m/z 311 (2), 299 (55), 239 (3), 187 (13), 173 (100), 157 (18), 145 (35); HRMS calcd for $C_{19}H_{38}O_3Si$ (n + H) 343.2866, obsd 343.2671.

(*R,*R**)-3-(Methylethenyl)-4-[2-[[tris(methylethyl)silyl]-oxy]ethyl]-dihydrofuran-2-one (15).** Compound **15** (80 mg, 0.24 mmol) was added to a refluxing solution of pyridinium dichromate (356 mg, 0.95 mmol) and Ac_2O (292 mg, 2.88 mmol) in 1 mL of CH_2Cl_2 and 0.5 mL of DMF. After 2 h, Et_2O (10 mL) and Celite (3 g) were added. The mixture was filtered, and the residue was washed with ether. The combined filtrate was washed sequentially with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl and dried (Na_2SO_4). Evaporation of the solvent and chromatography of the residue afforded lactone **15** as a colorless oil (48 mg, 63% yield from **14**): TLC R_f (15% EtOAc/petroleum ether) = 0.62; ^{1}H NMR δ 4.90 (bs, 2H), 4.62 (dt, J = 3.1, 8.5 Hz, 1H), 3.85 (m, 2H), 2.86 (q, J = 8.4 Hz, 1H), 2.62 (m, 2H), 1.92 (m, 1H), 1.80 (m, 1H), 1.76 (s, 3H), 1.04 (m, 21H); ^{13}C NMR δ u 175.8, 141.5, 113.5, 59.3, 37.6, 34.1; d 79.9, 48.6, 19.5, 17.8, 11.8; MS m/z 327 (0.1), 297 (2), 283 (72), 253 (100), 239 (17), 211 (9), 187 (82), 157 (30), 145 (95), 131 (49), 103 (59); HRMS calcd for $C_{18}H_{34}O_3Si$ 327.2355, obsd 327.2486.

(*S,*R**,*R**)-2-Methyl-3-(methylethenyl)-4-[2-[[tris(methylethyl)silyl]oxy]ethyl]dihydrofuran-2-one (16).** LDA (0.4 mL, 0.5 M in THF) was added to the lactone **15** (160 mg, 0.5mmol) in 4 mL of dry THF at −78 °C. After 1 h, MeI (284 mg) was added. The mixture was warmed to rt. After 4 h, the mixture was partitioned between H_2O and EtOAc. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to give **16** as a colorless oil (113 mg, 67% yield from **15**): TLC R_f (10% EtOAc/petroleum ether) = 0.49; ^{1}H NMR δ 4.92 (d, J = 1.5 Hz, 2H), 4.87 (d, J = 6.9 Hz, 1H), 4.44 (dt, J = 2.8, 9.5 Hz, 1H), 3.80 (m, 2H), 2.54 (m, 1H), 2.37 (m, 1H), 1.84 (m, 1H), 1.69 (s, 3H), 1.67 (m, 1H), 1.14 (d, J = 6.8 Hz, 3H), 1.00 (m, 21H); ^{13}C NMR δ u 178.2, 139.8, 115.9, 59.4, 37.1; d 77.2, 58.3, 39.7, 18.5, 17.9, 13.1, 11.8; IR (cm^{-1}) 2943, 2867, 1781, 1462, 1382, 1220, 1171, 1100; MS m/z 341 (1), 297 978), 267 (100), 253 (37), 225 (5), 187 (33), 157 (29); HRMS calcd for $C_{19}H_{36}O_3Si$ 340.2434, obsd 340.2459.

(*R,*R**,*S**)-3,6-Dibenzyl-4-(methylethenyl)-5-methyl-1-hexanol (17).** $LiAlH_4$ (46 mg, 1.2 mmol) was added to **16** (100 mg, 0.3 mmol) in 4 mL of dry THF at 0 °C. After 3 h at rt, the mixture was partitioned between saturated aqueous NH_4Cl and EtOAc. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to give the diol as a colorless oil (96 mg, 94% from **16**): TLC R_f (40% EtOAc/petroleum ether) = 0.51; ^{1}H NMR δ 4.88 (bs, 1H), 4.81 (bs, 1H), 4.73 (bs, 1H), 4.20 (bs, 1H), 4.17−3.86 (m, 3H), 3.72 (m, 1H), 3.50 (m, 1H), 2.03 (m, 1H), 1.88 (m, 1H), 1.78 (m, 1H), 1.68 (m, 1H), 1.60 (d, J = 0.5 Hz, 3H), 1.08 (m, 21H), 0.87 (d, J = 6.9 Hz, 3H); ^{13}C NMR δ u 145.4, 114.0, 67.4, 64.2, 36.4; d 74.2, 57.6, 37.8, 20.8, 17.9, 16.6, 11.7; IR (cm^{-1}) 2961, 1642, 1464, 1382, 1260, 1088, 884, 801; MS m/z 283 (100), 253 (11), 211 (5), 171 (6), 157 (12), 135 (26); HRMS calcd for $C_{19}H_{40}O_3Si$ (n − H_2O) 326.2641, obsd 326.2652.

At 0 °C, NaH (10 mg, 60% in mineral oil) was added to the diol (20 mg) and benzyl bromide (31 mg) in 1 mL of dry THF. After 18 h at rt, the mixture was partitioned between water and EtOAc. The combined organic extract was dried (Na_2SO_4), concentrated, and chromatographed to give the diprotected benzyl ether as a colorless oil (29 mg, 97% yield from the

diol): TLC R_f (20% EtOAc/petroleum ether) = 0.84; ^{1}H NMR δ 7.31 (m, 10H), 4.93 (s, 1H), 4.70 (s, 1H), 4.56 (s, 2H), 4.46 (s, 2H), 3.82 (m, 3H), 3.44 (dd, J = 5.7, 9.1 Hz, 1H), 3.34 (dd, J = 5.7, 9.1 Hz, 1H), 2.52 (t, J = 7.3 Hz, 1H), 2.25 (m, 1H), 1.83 (m, 1H), 1.74 (s, 3H), 1.71 (m, 1H), 1.06 (m, 21H), 0.95 (d, J = 6.8Hz, 3H); ^{13}C NMR δ u 143.9, 139.0, 138.8, 114.3, 74.1, 72.9, 71.7, 60.1, 35.5; d 128.2, 127.8, 127.5, 127.3, 76.0, 50.8, 32.9, 23.7, 18.1, 14.9, 12.0; IR (cm^{-1}) 2942, 2866, 2360, 1460, 1496, 1453, 1365, 1259, 1097; MS *m*/*z* 373 (4), 283 (98), 229 (12), 187 (31), 157 (23), 145 (100); HRMS calcd for $C_{33}H_{52}O_3Si$ (n − C_3H_7) 481.3137, obsd 481.3141.

Aqueous 1 M HCl (1 mL) was added to the diprotected benzyl ether (40 mg, 0.076 mmol) in 1 mL of THF at rt. After 14 h, the mixture was partitioned between saturated aqueous $NaHCO_3$ and EtOAc. The combined organic extract was dried (Na_2SO_4), concentrated, and chromatographed to give **17** as a colorless oil (27 mg, 89% yield from **16**): TLC R_f (20% EtOAc/petroleum ether) = 0.29; ^{1}H NMR δ 7.32 (m, 10H), 4.96 (s, 1H), 4.71 (s, 1H), 4.60 (d, J = 11.1 Hz, 1H), 4.52 (d, J = 11.1 Hz, 1H), 4.47 (s, 2H), 3.83 (dt, J = 3.0, 7.7 Hz, 1H),3.78 (m, 2H), 3.35 (m, 2H), 2.61 (t, J = 7.4 Hz, 1H), 2.21 (m, 1H), 2.11 (m, 1H), 1.86 (m, 1H), 1.74 (s, 3H), 1.70 (m, 1H), 0.93 (d, J = 6.9 Hz, 3H); ^{13}C NMR δ u 143.6, 138.3, 114.5, 74.1, 73.0, 71.4, 60.5, 33.2; d 128.4, 128.3, 128.0, 127.7, 127.5, 78.0, 50.2, 33.0, 23.9, 15.1; IR (cm^{-1}) 3030, 2963, 1496, 1453, 1366, 1261, 1095, 1028.

(*R,*R**,*S**)-3-Methyl-6-(phenylmethoxy)-7-(methylethene)-8-methyl-9-(phenylmethoxy)-1,3-nonadiene (18).** Triene **18** was prepared as triene **11** (15 mg, 56% yield from **17**): TLC R_f (10% EtOAc/petroleum ether) = 0.56; ^{1}H NMR δ 7.3 (m, 10H), 6.73 (dd, J = 10.8, 11.2 Hz, 0.25H), 6.33 (dd, J = 10.7, 10.8 Hz, 0.75H), 5.63 (t, J = 7.2 Hz, 0.75H), 5.54 (t, J = 8.1 Hz, 0.25H), 5.09 (bd, J = 17.2 Hz, 1H), 4.92 (bs, 2H), 4.63 (bd, J = 10.3 Hz, 1H), 4.45 (s, 4H), 3.67 (m, 1H), 3.37 (m, 1H), 3.26 (m, 1H), 2.55−2.26 (m, 4H), 1.71 (s, 3H), 1.7 (s, 3H), 0.90 (d, J = 6.8 Hz, 3H); ^{13}C NMR δ u 143.8, 138.8, 135.1, 114.4, 113.4, 110.4, 74.6, 72.8, 71.4, 30.5; d 141.7, 134.0, 129.5, 128.3, 127.9, 127.8, 127.6, 127.4, 127.3, 79.0, 50.9, 32.7, 23.9, 19.9, 13.9, 11.9; MS *m*/*z* 405 (3), 313 (24), 205 (42), 189 (24); HRMS calcd for $C_{28}H_{36}O_2$ (n + H) 4.5,2793, obsd 405.2779.

Bicyclic Hydrindenes (19a and 19b). A mixture of triene **18** (10 mg, 0.029 mmol, *E*/*Z* ratio = 86:14) and 1,4-di-*tert*-butylhydroquinone (1 mg) in *N*,*N*-dimethylaniline (2 mL) was heated in a sealed tube at 250 °C for 24 h. After being cooled to rt, the reaction mixture was partitioned between ethyl acetate and, sequentially, 3 N aqueous HCl and saturated aqueous $NaHCO_3$. The combined organic extract was dried (Na_2SO_4), concentrated, and chromatographed to give a mixture of **19a** and **19b** as a colorless oil (7 mg, 70% yield). **19a** and **19b**: TLC R_f (15% EtOAc/petroleum ether) = 0.75; ^{1}H NMR δ 7.31 (m, 10H), 5.37 (bs, 0.25H, cis), 5.24 (bs, 0.75H, trans), 4.45 (m, 3H), 4.21 (m, 1H), 3.76 (m, 1H), 3.59 (m, 1H), 3.20 (t, 1H, J = 9.3 Hz), 2.36 (m, 1H), 2.01−1.82 (m, 4H), 1.63 (s, 3H), 1.45−1.25 (m, 4H), 1.11 (d, 3H, J = 6.4 Hz), 0.89 (s, 0.75H, cis), 0.72 (s, 2.25H, trans); ^{13}C NMR δ u 138.8, 138.4, 134.0, 75.4, 72.9, 71.5, 42.7, 36.2, 30.6; d 128.4, 128.3, 128.0, 127.6, 127.5, 127.4, 120.1, 84.6, 59.8, 48.9, 35.9, 20.9, 17.6, 14.1 (cis), 12.9 (trans); MS *m*/*z* 404 (3), 313 (24), 205 (42), 189 (24); HRMS calcd for $C_{28}H_{36}O_2$ 404.2715, obsd 404.1730.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for all new compounds are available (32 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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