Diels–Alder Reactions of β-Stannyl Enones: Synthesis of Δ^3-Carene, Isosesquicarene, and Other Bicyclo[4.1.0]hept-3-enes

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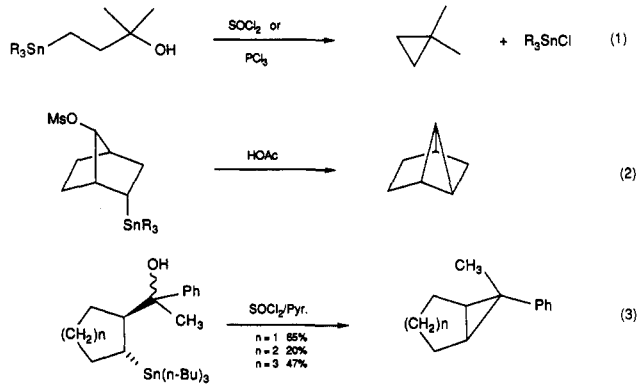
Various *trans*-β-stannyl enones, *trans*-3-(tributylstannyl)-2-propenal, and *trans*-ethyl 3-(tributylstannyl)-2-propenoate were prepared and found to readily undergo Diels–Alder reactions with 1,3-dienes. The cycloaddition occurs with maintenance of trans tin/carbonyl stereochemistry to give high yields of adducts. The carbonyl moieties of the cycloadducts were converted to alcohols or epoxides which are subsequently transformed into bicyclo[4.1.0]hept-3-enes including Δ^3-carene and isosesquicarene via 1,3-elimination of the tributylstannyl group and a leaving group.

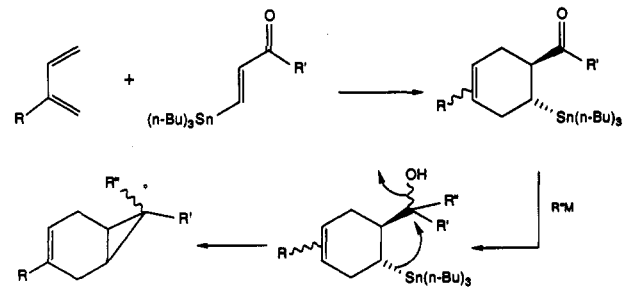
The bicyclo[4.1.0]heptane ring system is found in a variety of natural products and has been fundamental in a number of physical organic studies. We envisioned a novel synthetic entry into compounds in this series involving as key reactions Diels–Alder cycloadditions and 1,3-eliminations involving γ-hydroxy stannanes and related compounds.

In 1970 Davis and co-workers reported that γ-stannyl tertiary alcohols upon treatment with thionyl chloride or phosphorus trichloride underwent 1,3-eliminations to produce cyclopropanes (eq 1).[1] The solvolysis of γ-stannyl



mesylates to produce cyclopropanes was reported that same year by Kuivala.[2] In a subsequent study by the Davis group it was established that the reaction proceeds with inversion of configuration at both carbon centers; of the various 7-stannylnorbornyl mesylates only the diastereomer shown in eq 2 gave cyclopropane products upon solvolysis.[3] A number of synthetic applications of these cyclopropane-forming reactions have appeared.[4–6] In a recent study Fleming reaffirmed the double inversion nature of these reactions but noted that attempts to fuse a *gem*-dimethylcyclopropane onto a saturated ring by using BF_3·2HOAC met with failure.[6] At the time of the Fleming report we had observed in our laboratory that the use of thionyl chloride/pyridine on appropriate γ-stannyl alcohol

Scheme I



substrates produced gem-disubstituted cyclopropanes in ring fusion with five-, six-, and seven-membered rings (eq 3).[7]

Since the trialkylstannyl group is known to have a small electron-donating inductive effect when attached to carbon, unactivated vinyl and acetylenic stannanes would be expected to be poor dienophiles in cycloadditions with electron-rich dienes.[8] Trialkylethenylstannanes undergo cycloaddition with tetraphenylcyclopentadiene, a diene known to react readily with eletron-rich dienophiles.[9,10] (Trimethylstannyl)acetylenes and bis(trimethylstannyl)-acetylene also undergo Diels–Alder reactions with the electron-poor hexachlorocyclopentadiene.[11] The same stannylacetylenes have been found to undergo cycloadditions with tetraphenylcyclopentadiene, α-pyrones, and 3,6-diphenyltetrazine followed by spontaneous expulsion of carbon monoxide, carbon dioxide, and nitrogen, respectively, to give substituted aromatic stannanes.[12] Replacing the alkyl groups attached to a vinyltin with halogens reverses the electron-donating inductive effect; trichlorovinylstannane readily adds in a Diels–Alder fashion to 1,3-butadienes.[13]

It appeared to us that the electron-withdrawing properties of an attached carbonyl group might be sufficient to activate a vinylstannane toward participation in Diels–Alder reactions with electron-rich dienes.[14] Furthermore, the adducts from such reactions should reflect the stereochemistry of the starting enone and, in the case of trans enones, should have the stannyl group and a latent

(1) Davis, D. D.; Chambers, R. L.; Johnson, H. T. *J. Organomet. Chem.* **1970**, *25*, C13–C16.
(2) Kuivala, H. G.; Scarpa, N. M. *J. Am. Chem. Soc.* **1970**, *92*, 6990.
(3) Davis, D. D.; Johnson, H. T. *J. Am. Chem. Soc.* **1974**, *96*, 7576.
(4) Peterson, D. J.; Robbins, M. D.; Hansen, J. R. *J. Organomet. Chem.* **1974**, *73*, 237. Peterson, D. J.; Robbins, M. D. *Tetrahedron Lett.* **1977**, *18*, 4045. Pommier, J.; Kuivala, H. G. *J. Organomet. Chem.* **1974**, *73*, 237.
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(6) Fleming, I.; Urch, C. J. *Tetrahedron Lett.* **1984**, *24*, 4591. Fleming, I.; Rowley, M. *Ibid.* **1985**, *25*, 3857.
(7) Johnson, C. R.; Kadow, J. F. *Tetrahedron Lett.* **1984**, *25*, 5255.
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(9) Arbuzov, B. A.; Shapshinskaya, L. A.; Kudryavtseva, M. I. *Izv. Akad. Nauk. SSSR* **1961**, *12*, 2161; *Chem. Abstr.* **1962**, *57*, 11223e.
(10) Trialkylethenylsilanes are also unreactive in Diels–Alder reactions with electron-rich dienes (Curico, R. F. *J. Org. Chem.* **1971**, *36*, 929).
(11) Seyferth, D.; Evnin, A. B. *J. Am. Chem. Soc.* **1967**, *89*, 1468.
(12) Seyferth, D.; Sarafidis, G.; Evnin, A. B. *J. Organomet. Chem.* **1964**, *2*, 417, 437. Evnin, A. B.; Seyferth, D. J. *J. Am. Chem. Soc.* **1967**, *89*, 952. Neumann, W. P.; Kleiner, F. G. *Liebigs Ann. Chem.* **1968**, *716*, 29.
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(14) Jousseaume, B. *J. Chem. Soc., Chem. Commun.* **1984**, 1452.

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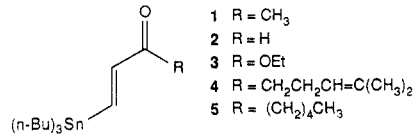
oxygen leaving group (the carbonyl group) appropriately disposed to yield fused cyclopropanes (Scheme I).

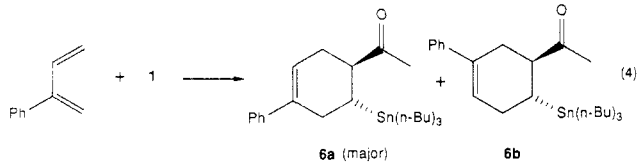
Results and Discussion

Compounds 1–5 have been found to be excellent dienophiles; they are not highly reactive, but with time the Diels–Alder reactions tend to go to completion and result in minimal amounts of byproducts. Heating 1 with 2-



1 R = CH_3
2 R = H
3 R = OEt
4 R = $CH_2CH_2CH{=}C(CH_3)_2$
5 R = $(CH_2)_4CH_3$

phenyl-1,3-butadiene in toluene at 105 °C in the presence of hydroquinone provided the adducts **6a** and **6b** in 87% yield (eq 4). HPLC analysis showed the products to be



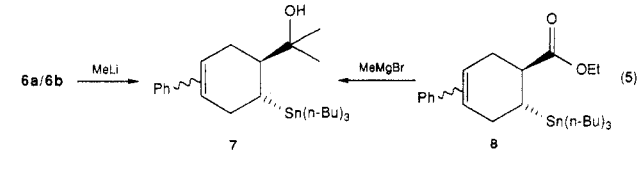
6a (major) 6b

a 5:1 mixture of regioisomers. The major isomer was assumed to be **6a** with the phenyl group in the 4-position since the carbonyl is expected to provide the dominant directing influence.[15] Treatment of enone 1 and 2-phenyl-1,3-butadiene in dichloromethane with 1 equiv of aluminum trichloride over the range −78 to 0 °C gave **6a** and **6b** in 72% yield with the same major isomer, but the product ratio was now 106:1.

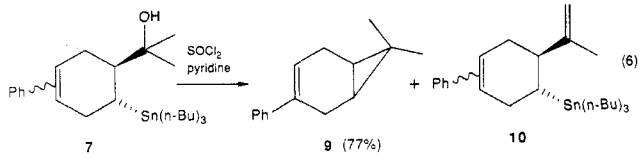
When Diels–Alder reactions with these stannyl enones are performed, it is convenient to employ excess diene to ensure complete consumption of the dienophile since the adducts and dienophile generally exhibited similar chromatographic behavior. In all of the thermal Diels–Alder reactions of enones 1–4 that we examined, only traces of tin-containing sideproducts were detectable by TLC analysis.

The combination of 2-phenyl-1,3-butadiene and *cis*-4-(tributylstannyl)-3-buten-2-one resulted in a mixture of two adducts that were different from those (**6a** and **6b**) obtained by the cycloaddition of the corresponding trans enone 1. The absence of crossover products indicated that our supposition of preservation of dienophile geometry during the reaction was valid.

Addition of methyllithium to the mixture of adducts **6** followed by flash chromatography gave the alcohols **7** in 72% yield (eq 5). These alcohols were also obtained from the addition of methylmagnesium iodide to ester **8** (eq 5).



7 8



7 9 (77%) 10

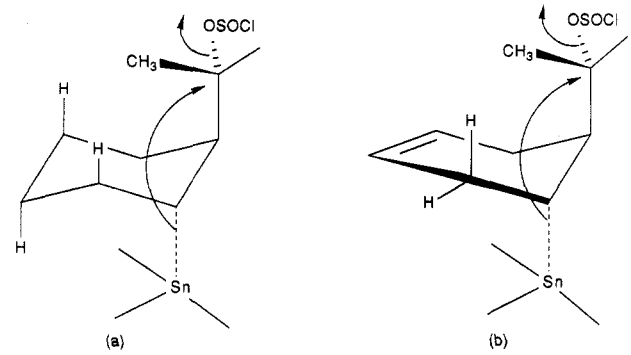
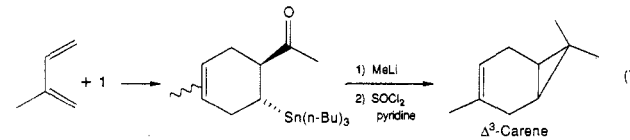


Figure 1. Steric conjestion in (a) formation of bicyclo[4.1.0]-heptanes compared with (b) formation of bicyclo[4.1.0]hept-3-enes.

Treatment of **7** (a mixture of regioisomers) with excess thionyl chloride/pyridine in THF resulted in 77% yield of cyclopropane **9** (eq 6). Note that the regioisomer problem disappears due to the symmetry of the fused three-membered ring. The trans relationship of the carbinol and stannyl groups permits an inversion at each reacting carbon atom in the 1,3-elimination process. It is noteworthy that the yields of **9** and related bicyclo-[4.1.0]hept-3-enes (see below) are considerably improved over those observed in a previous study[7] dealing with the production of bicyclo[4.1.0]heptanes. One rationale for this is that the presence of the double bond in the cyclohexene substrates relieves some steric strain in the transition state leading to cyclopropane formation (Figure 1).

There are a few technicalities concerning the above reactions that are useful to note. For the purposes of cyclopropane formation, separation of the alcohols from starting ketones is not absolutely necessary since the ketones are not reactive under the thionyl chloride conditions. In some cases nonpolar cyclopropanes, e.g., **9**, and the related olefinic byproducts, e.g., **10**, are chromatographically similar. In such cases, Kugelrohr distillation will easily separate the more volatile cyclopropane from the less volatile tributylstannyl-containing byproduct. In the cases of more polar cyclopropanes, separation of the product from tributyltin chloride by chromatography can be tedious. This problem can be alleviated by pouring the thionyl chloride reaction mixture into water containing potassium fluoride; insoluble polymeric tributyltin fluoride is formed.[16]

Several simple naturally occurring substances have been produced by utilizing the general strategy. Reaction of enone **1** with isoprene followed by addition of methyllithium and then treatment with thionyl chloride gave pure Δ^3-carene (**12**) (eq 7). In the previous synthesis of this



11 12

material, isomeric carenes were obtained.[17] A short synthesis of isosesquicarene (**15**) is shown in Scheme II; this direct, 3-step, but nonstereocontrolled, synthesis of isosesquicarene can be compared to a recent 20-step stereocontrolled synthesis from tropone.[18] We have examined

(15) Hennis, H. E. *J. Org. Chem.* **1963**, *28*, 2570. Hosomi, A.; Saito, M.; Sakurai, H. *Tetrahedron Lett.* **1980**, *21*, 355. Carruthers, W. Some Modern Methods of Organic Synthesis; Cambridge University: Cambridge, England, 1978; p 201. See also; Fleming, I.; Percival, A. *J. Chem. Soc., Chem. Commun.* **1976**, 681.

(16) Leibner, J. E.; Jacobus, J. *J. Org. Chem.* **1979**, *44*, 449.

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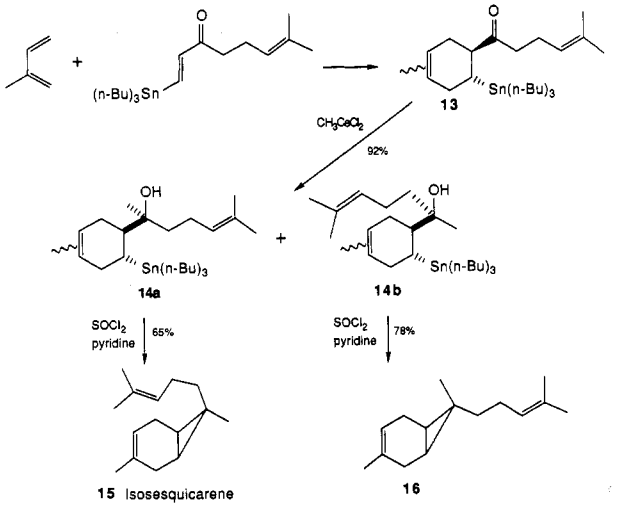
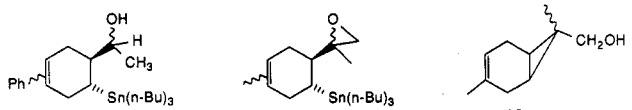
(18) Uyehara, T.; Yamada, J.; Kato, T.; Bohlmann, F. *Tetrahedron Lett.* **1983**, *24*, 4445.

Scheme II



several variants of Scheme II leading to isosesquicarene. Reaction of 4-methyl-3-pentenylmagnesium bromide with ketone **11** provided alcohols **14a** and **14b** in yields of 16 and 30%, respectively; the major product (42%) was **17**, resulting from hydride transfer. This situation was improved by use of "4-methyl-3-pentenylcerium dichloride".[19] The formation of the reduction product was suppressed, the total yield of adducts increased from 46% to 82%, but the major product was the stereoisomeric pair leading to the isomer of the desired target. These results lead us to the more efficient synthesis outlined in Scheme II.

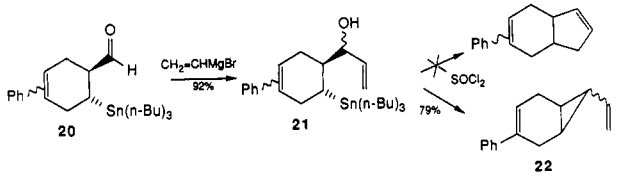
In the cyclopropanation examples noted above, cationic character has been induced at a tertiary center by treatment of tertiary alcohols with thionyl chloride. The acid-promoted ring opening of an appropriate epoxide should lead in like manner to cyclopropanation. Accordingly, ketone **11** was treated with dimethylsulfonium methylide[20] to provide epoxides **18** in 82% yield. Treatment of the latter with pyridine hydrochloride in acetonitrile produced cyclopropanes **19** (85%) as a mixture of diastereomers. Epoxides **18** upon treatment with trimethylsilyl halides (I, Br, Cl) and trimethylsilyl triflate gave complex mixtures.



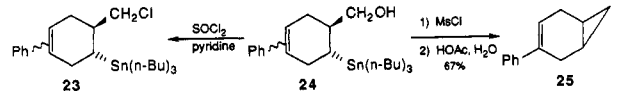
The generation of an allylic cationic center γ to a stannyl group conceptually could lead either to three- or five-membered-ring products (Scheme III). Adduct **20** (90%) was obtained from 2-phenyl-1,3-butadiene and dienophile **2** as a 6.7:1 mixture of regioisomers. Addition of vinylmagnesium bromide to **20** gave allylic alcohols **21** (91%). The latter upon treatment with thionyl chloride yielded exclusively vinylcyclopropanes **22**; no five-membered-ring products were detected.

Reduction of cycloadducts **20** with sodium borohydride gave primary alcohols **24** (93%). Treatment of **24** with thionyl chloride/pyridine gave only trace amounts of cyclopropane **25**; the major product was the primary chloride **23**. Mesylation of **24** followed by solvolysis in hot acetic acid/water gave cyclopropane **25** in 67% yield (Scheme IV). It is noteworthy that the bicyclo[4.1.0]hept-3-ene obtained by this procedure is isomeric with that to be

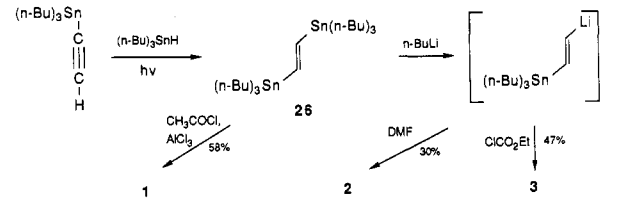
Scheme III



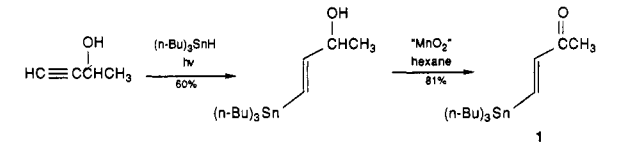
Scheme IV



Scheme V



Scheme VI



expected by treatment of 1-methyl-1,4-cyclohexadiene with carbenoids (attack at the more highly substituted double bond).

Synthesis of the Dienophiles. By use of the procedure of Corey and Wollenberg,[21] *trans*-1,2-bis(tributylstannyl)ethylene (**26**) was prepared by the addition of tributylstannane to tributylstannylacetylene. Treatment of **26** with 1 equiv of butyllithium followed by excess ethyl chloroformate gave **3**[22] in 47% yield (Scheme V). With a related procedure using dimethylformamide, aldehyde **2** was obtained in 30% yield (Scheme V).

The aluminum chloride promoted Friedel–Crafts reaction of *trans*-1,2-bis(tributylstannyl)ethylene (**26**) with acid chlorides was found to be a versatile route to the desired enones (Scheme V). Enone **5** is a synthon for the lower side chain of prostaglandins. Small amounts of cis enones were also produced but could be removed by flash chromatography.

A more effective method[23] for the synthesis of larger quantities of **1** is illustrated in Scheme VI. Aldehyde **2** was prepared from propargyl alcohol by a similar route. Addition of 4-methyl-3-butenylmagnesium bromide to **2** followed by MnO_2 oxidation provided an effective route to dienophile **4** (74% from **2**).

Experimental Section

***trans*-4-(Tributylstannyl)-3-buten-2-ol.** A mixture of 3-butyn-2-ol (7.009 g, 0.1 mol) and tributyltin hydride (32 g, 0.11 mol) was stirred under an argon atmosphere in a Pyrex flask 6 cm from a GE 275-W mogul-based sunlamp for 7 h. The mixture was then heated from 20 to 125 °C over 30 min in an oil bath. The mixture was cooled to room temperature, and a small amount

(19) Inamoto, T.; Sugiura, Y.; Takiyama, T. *Tetrahedron Lett.* **1984**, *25*, 4233.
(20) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.
(21) Corey, E. J.; Wollenberg, R. H. *J. Am. Chem. Soc.* **1974**, *96*, 5581. Corey, E. J.; Wollenberg, R. H. *J. Org. Chem.* **1975**, *40*, 3788.
(22) For the synthesis of related compounds, see: Piers, E.; Chong, J. M.; Morton, H. E. *Tetrahedron Lett.* **1981**, *22*, 4905. Stille, J. K.; Labadie, J. W. *Tetrahedron Lett.* **1983**, *24*, 4283. Seitz, D. E.; Lee, S. H. *Tetrahedron Lett.* **1981**, *22*, 4909. Chenard, B. L.; Van Zyl, C. M.; Sanderson, D. R. *Tetrahedron Lett.* **1986**, *27*, 2807.
(23) Collins, P. W.; Jung, C. J.; Gasiecki, A.; Pappo, R. *Tetrahedron Lett.* **1978**, 3187.

of hexane was added. The crude product was chromatographed on a silica gel column [54 × 7 cm, 1 kg of silica gel 60 (230–400 mesh, EM reagents)]. The column was eluted with 50:1 hexane/EtOAc until nonpolar tin impurities (TLC R_f = 0.95, 25:1 hexane/EtOAc) were removed; elution was continued until the undesired isomers (TLC R_f = 0.25, 25:1 hexane:EtOAc) had been nearly completely eluted and the desired trans isomer (TLC R_f = 0.13, 25:1 hexane/EtOAc) had just begun to appear. The solvent polarity was increased to 15:1 hexane/EtOAc until the desired compound had been completely collected. Three fractions were collected. The first fraction contained 5.480 g (15%) of an oil identified by ^{1}H NMR as a mixture containing *cis*-4-(tributylstannyl)-3-buten-2-ol and 3-(tributylstannyl)-3-buten-2-ol. Fraction 2 contained 5.408 g (15%) of a mixture containing mainly the desired trans isomer contaminated with the two isomers collected in fraction 1. Fraction 3 contained 21.568 g (60%) of pure *trans*-4-(tributylstannyl)-3-propen-2-ol as a colorless oil: IR (neat, NaCl) 3320, 2920, 1605, 1460, 1118, 1065, 982 cm^{-1}; ^{1}H NMR (CCl_4) δ 6.07 (m, 2 H) 4.20 (bm, 1 H) 2.57 (bs, 1 H) 1.67–0.80 (bm, 30 H). The silica gel column could be reused immediately for the same separation. Alternatively, the separation could be done by injecting 15 g of crude product onto a single Waters Prep 500 cartridge and eluting the undesired isomers with 80:1 hexane/EtOAc. Increasing solvent polarity would give the pure trans in similar yields as the flash column. Although the thermal reaction between alkynols and tributyltin hydride catalyzed by AIBN has been used to prepare similar compounds,[24] in this case we found the reaction occasionally to be violently exothermic.

***trans*-4-(Tributylstannyl)-3-buten-2-one (1). A.** "Active MnO_2"[25] and *trans*-4-(tributylstannyl)-3-buten-2-ol (21.00 g, 58.1 mmol, in hexane (1.5 L)) were stirred with a mechanical stirrer for 44 h under an argon atmosphere at room temperature. The mixture was allowed to stand for 27 h and was filtered through Celite. Flash chromatography using 80:1 hexane/EtOAc followed by 50:1 hexane/EtOAc gave 17.22 g (82%) of **1** as a clear oil: IR $CHCl_3$) 2930, 1669, 1569, 1465, 1250, 991 cm^{-1}; ^{1}H NMR (CCl_4) δ 7.4 (d, J = 20 Hz, 1 H) 6.4 (d, J = 20 Hz, 1 H), 2.17 (s, 3 H) 2.8–0.73 (m, 27 H); ^{13}C NMR ($CDCl_3$) δ 197.0, 150.4, 146.3, 28.7, 27.0, 25.5, 13.3, 9.5. Anal. Calcd for $C_{16}H_{32}OSn$: C, 53.51; H, 8.98. Found: C, 53.69; H, 8.88.

B. Anhydrous aluminum chloride (1.330 g, 10 mmol) was added to a solution of *trans*-1,2-bis(tributylstannyl)ethylene[21] (6.057 g, 10 mmol) and acetyl chloride (0.834 g, 11 mmol) in dichloromethane (35 mL) at −78 °C under an argon atmosphere. The reaction mixture was stirred for 30 min at −70 °C, allowed to warm to 0 °C over a period of 1 h, poured into 100 mL of water containing KF (10 g), and stirred vigorously for 5 min. The mixture was extracted with one 150-mL portion of diethyl ether followed by two 100-mL portions of diethyl ether. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation. Flash chromatography using 100:1 petroleum ether/EtOAc gave two product fractions. The faster eluting fraction contained a mixture of *cis*- and *trans*-4-(tributylstannyl)-3-buten-2-one (TLC R_f = 0.45 and 0.36; 25:1 hexane/EtOAc) as a clear oil (0.507 g, 14%). An analytical sample of the pure cis alkene was obtained by repeated flash chromatography: IR (NaCl, neat) 2960, 1691, 1508, 1185 cm^{-1}; ^{1}H NMR (CCl_4) δ 7.08 (s, 2 H) 2.29 (s, 3 H) 1.63–0.70 (bm, 27 H). Anal. Calcd for $C_{16}H_{32}OSn$: C, 53.51; H, 8.98. Found: C, 53.69; H, 8.88. The slower eluting fraction contained pure *trans*-4-(tributylstannyl)-3-buten-2-one as a clear oil (2.097 g, 58%) with spectral characteristics identical with those described earlier. Integration of the olefinic protons in a 300-MHz ^{1}H NMR spectrum of the crude reaction product showed that the ratios of *trans*- to *cis*-4-(tributylstannyl)-3-buten-2-one formed in the reaction was 95:5.

***trans*-3-(Tributylstannyl)-2-propenal (2). A.** *trans*-3-(Tributylstannyl)-2-propen-1-ol[24] (4.900 g, 14.1 mmol) and activated MnO_2 (12.3 g, 141.5 mmol) were stirred in 150 mL of petroleum ether for 2 h. Additional MnO_2 (5.0 g, 57.5 mmol) was added and the reaction stirred for 2.5 h. The mixture was filtered through Celite, concentrated on a rotary evaporator, and flash chromatographed with 80:1 hexane/EtOAc to give 4.85 g (80%) of a slightly green oil: IR (neat, NaCl) 2929, 1695, 1468, 1190, 1070 cm^{-1}; ^{1}H NMR (CCl_4) δ 9.09 (d, J = 7 Hz, 1 H) 7.60 (d, J = 20 Hz, 1 H) 6.50 (doublet of doublets, J = 7 Hz, 20 Hz, 1 H) 1.83–0.66 (bm, 27 H). Anal. Calcd for $C_{15}H_{30}OSn$: C, 52.21; H, 8.76. Found: C, 52.30; H, 8.87.

B. Butyllithium (17.2 mmol) in hexane was added dropwise with stirring to a solution of *trans*-bis(1,2-tributylstannyl)-ethylene[21] (9.920 g, 16.4 mmol) in 20 mL of THF at −78 °C. After 45 min the above mixture was added via transfer needle to a solution of DMF (11.99 g, 164.0 mmol) in 15 mL of THF at −78 °C. The reaction mixture was allowed to warm to 0 °C over a period of 2 h and then quenched with water. The mixture was extracted three times with diethyl ether, and the combined extracts were dried over anhydrous $MgSO_4$. Flash chromatography with 70:1 hexane/EtOAc gave 1.690 g (30%) of a slightly green, clear oil. The physical characteristics were identical with those described previously.

***trans*-Ethyl 3-(Tributylstannyl)propenoate (3).** Butyllithium (15.5 mmol) in hexane was added to a solution of *trans*-1,2-bis(tributylstannyl)ethylene[21] (9.340 g, 15.4 mmol) in THF (15 mL) at −78 °C. Ethyl chloroformate (16.71 g, 154 mmol) in THF (15 mL) at −78 °C was added dropwise via transfer needle. The reaction mixture was then stirred for 5 min at −78 °C, allowed to warm to 0 °C over 30 min, quenched with water, and extracted three times with diethyl ether. The combined organic extracts were dried over anhydrous $MgSO_4$ and flash chromatographed with 40:1 petroleum ether/EtOAc to give 2.793 g (47%) of a colorless oil: IR (NaCl, neat) 2924, 1728, 1592, 1205, 1151 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.58 (d, J = 19 Hz, 1 H) 6.17 (d, J = 19 Hz, 1 H) 4.15 (q, J = 7 Hz, 2 H) 2.0–0.60 (bm, 30 H). The spectral data agreed with literature values.[26]

(1*E*)-7-Methyl-1-(tributylstannyl)-1,6-octadien-3-ol. A solution of 1-bromo-4-methyl-3-pentene[27] (2.56 g, 15.7 mmol) in 4 mL of diethyl ether was added dropwise over 5 min to a rapidly stirred mixture of 70–80 mesh magnesium powder (0.382 g, 15.7 mmol) in 7 mL of anhydrous diethyl ether at 2 °C. After 15 min the cooling bath was removed, and the solution was stirred for an addition 45 min. The Grignard solution was cooled to −20 °C, and a solution of **2** in 4 mL of diethyl ether at −20 °C was added dropwise via syringe over 3 min. The reaction was allowed to warm to 0 °C over 30 min and poured into 40 mL of saturated aqueous NH_4Cl. The mixture was extracted with three 80-mL portions of diethyl ether, dried over anhydrous $MgSO_4$, and flash chromatographed to give 2.71 g (87%) of the product as a clear oil: IR (NaCl, neat) 3340 (b), 2905, 1600, 1440, 982 cm^{-1}; ^{1}H NMR (CCl_4) δ 6.03 (m, 2 H) 5.1 (t, J = 6 Hz, 1 H) 4.0 (bm, 1 H) 2.27–0.60 (bm, 38 H).

(1*E*)-7-Methyl-1-(tributylstannyl)-1,6-octadien-3-one (4). Activated MnO_2 (5.27 g, 60.6 mmol) was added with stirring to a solution of (2.60 g, 6.06 mmol) in 50 mL of hexane at room temperature. After 19 h, additional MnO_2 (5.27 g, 60.6 mmol) and hexane (20 mL) were added. A final portion of MnO_2 (2.5 g, 28.8 mmol) was added 3 h later. After stirring for 4.5 h, the reaction mixture was filtered through Celite by using diethyl ether as a wash. Flash chromatography with 70:1 petroleum ether/EtOAc gave 2.203 g (85%) of a colorless oil: IR (neat, NaCl) 2920, 1700, 1678, 1571, 1378, 992 cm^{-1}; ^{1}H NMR (CCl_4/Me_4Si) δ 7.43 (d, J = 20 Hz, 1 H) 6.44 (d, J = 20 Hz, 1 H) 5.10 (t, J = 6 Hz, 1 H) 2.73–1.90 (m, 3 H) 1.65 (bs, 6 H) 1.66–0.60 (bm, 29 H). Anal. Calcd for $C_{21}H_{40}OSn$: C, 59.03; H, 9.44. Found: C, 59.30; H, 9.34.

***trans*-1-(4- and 3-phenyl-6-(tributylstannyl)-3-cyclohexenyl)-1-ethanone (6a and 6b). A.** 2-Phenyl-1,3-butadiene[28] (1.95 g, 15 mmol), hydroquinone (20 mg), and **1** (3.000 g, 8.35 mmol) in toluene (3 mL) were placed under an argon atmosphere in a flask equipped with a water condenser. The mixture was heated in an oil bath at 105 °C for 22 h, whereupon additional diene (0.5 g, 3.8 mmol) was added. Heating was continued for 15 h (37 h total). The toluene was removed under vacuum, and the product was isolated by flash chromatography using 70:1 petroleum ether/ethyl acetate as eluent to give 3.551 g (87%) of

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a clear oil: IR (NaCl, neat) 3030 (m), 2920 (s), 1710, 1650 (w), 1600, 1500, 1460, 1362, 1263 cm^{-1}; ^1H NMR (CCl_4) δ 7.18 (s, 5 H) 5.98 (bs, 1 H) 2.93–2.2 (m, 5 H) 2.12 (s, 3 H) 1.73–0.67 (m, 27 H). Anal. Calcd for $C_{26}H_{44}OSn$: C, 63.56; H, 9.03. Found: C, 63.36; H, 8.82. Analytical HPLC (2% EtOAc/98% hexane; 2 mL/min flow rate) showed that the product was a mixture of two isomers (retention times, 4.8 min (**6a**) and 3.9 min (**6b**); ratio = 5.1:1; α = 1.64).

B. Aluminum chloride (0.067 g, 0.50 mmol) was added to a stirring solution of 2-phenyl-1,3-butadiene[28] (0.130 g, 1.00 mmol) and **1** (0.18 g, 0.5 mmol) in dichloromethane (3 mL) at −78 °C. The mixture was allowed to warm to 0 °C over a period of 1 h, poured into 5 mL of water, and extracted with three 15-mL portions of dichloromethane. The combined organic extracts were dried over anhydrous $MgSO_4$ and flash chromatographed with 70:1 hexane/EtOAc to give 0.177 g (72%) of a colorless oil with spectral characteristics similar to those described previously. Analytical HPLC (2% EtOAc/98% hexane) showed the presence of two isomers in a ratio of 106:1. Co-injection showed that the major compound was the same as the major isomer obtained from the thermal Diels–Alder reaction.

***cis*-1-(4- and 3-phenyl-6-(tributylstannyl)-3-cyclohexenyl)-1-ethanone.** *cis*-4-(Tributylstannyl)-3-buten-2-one (0.250 g, 0.70 mmol) and 2-phenyl-1,3-butadiene (0.272 g, 2.09 mmol) in toluene (2 mL) were refluxed for 21 h. The toluene was removed under vacuum. Analytical HPLC (2% EtOAc/98% hexane) showed the presence of two compounds in a ratio of 1:11.8. Flash chromatography with 70:1 hexane/EtOAc gave 0.238 g (70%) of a colorless oil: IR (neat, NaCl) 3025, 2920, 1710, 1161, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.20 (s, 3 H) 6.00 (S, 1 H) 2.95–2.20 (m, 4 H) 2.13 (s, 3 H) 2.15–2.90 (m, 11 H) 1.66–0.6 (bm, 28 H). Anal. Calcd for $C_{26}H_{42}OSn$: C, 63.82; H, 8.65. Found: C, 64.02; H, 8.53. Injecting the crude cis adducts simultaneously with the adducts derived from cycloaddition with the *trans*-4-(tributylstannyl)-2-buten-1-one showed the presence of four distinct compounds.

***trans*-1-(3- and 4-methyl-6-(tributylstannyl)-3-cyclohexenyl)-1-ethanone (11).** Isoprene (10 mL, 6.81 g, 100 mmol) was added to a solution of (*E*)-4-(tributylstannyl)-3-buten-2-one (**1**) (4.000 g, 11 mmol), hydroquinone (20 mg), and toluene (10 mL) in a glass bomb. The mixture was sealed under an argon atmosphere at room temperature and heated at 90 °C for 48 h. After the mixture cooled to room temperature, additional isoprene (10 mL) was added and the bomb was resealed. The reaction mixture was again heated at 90 °C for 48 h and cooled to room temperature, and the toluene was removed under vacuum. The product was flash chromatographed with 100:1 petroleum ether/ethyl acetate to give 4.48 g (95%) of a mixture of *trans*-1-(3- and 4-methyl-6-(tributylstannyl)-3-cyclohexenyl)-1-ethanone as a clear oil: IR ($CHCl_3$) 2930, 1709, 1465, 1380, 1355, 1280, 1235, 1140 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.4 (bm, 1 H) 2.14 (s, 3 H) 1.64 (bs, 3 H) 2.95–1.95 (bm, 5 H) 1.95–0.60 (bm, 28 H); ^{13}C NMR ($CDCl_3$) δ 211.9, 211.6, 135.4, 132.2, 122.5, 119.3, 51.6, 50.9, 53.8, 33.5, 29.4, 27.5, 26.6, 25.8, 23.5, 23.4, 21.3, 20.8, 13.6, 9.2. Anal. Calcd for $C_{21}H_{40}OSn$: C, 59.04; H, 9.44. Found: C, 58.97; H, 9.64. The ratio of isomers was approximately 1.2:1 as determined from the relative heights of similar peaks in the ^{13}C NMR spectrum.

***trans*-Ethyl 3- and 4-Phenyl-6-(tributylstannyl)-3-cyclohexenecarboxylate (8).** *trans*-Ethyl 3-(tributylstannyl)-propenoate (**2**) (2.120 g, 5.45 mmol), 2-phenyl-1,3-butadiene[28] (1.060 g, 8.20 mmol), and hydroquinone (15 mg) were refluxed in toluene (3 mL) for 12 h. The mixture was concentrated and flash chromatographed with 50:1 hexane/EtOAc to give a crude product which ^1H NMR showed still contained some starting **3**. The crude product was placed in 3 mL of toluene with 2-phenyl-1,3-butadiene (1.060 g, 8.20 mmol) and hydroquinone (15 mg). The mixture was refluxed for 24 h, and then an additional 0.70 g (5.38 mmol) of diene was added. The mixture was refluxed for 24 h, concentrated, and purified by MPLC with 90:1 hexane/EtOAc to give 1.802 g (64%) of a colorless oil: IR (NaCl, neat) 2926, 1734, 1655, 1375, 1178 cm^{-1}; ^1H NMR (CCl_4) δ 7.17 (s, 5 H) 5.93 (bs, 1 H) 4.07 (q, J = 8 Hz, 2 H) 2.97–2.23 (bm, 5 H) 1.93–0.66 (bm, 31 H).

***trans*-3- and *trans*-4-Phenyl-6-(tributylstannyl)-3-cyclohexenecarboxaldehyde (20).** A solution of 2-phenyl-1,3-butadiene[28] (1.70 g, 13.0 mmol), hydroquinone (25 mg), and *trans*-3-(tributylstannyl)propenal (**2**) (2.250 g, 6.52 mmol) in toluene (3 mL) was placed under an argon atmosphere in a flask equipped with a water condenser. The flask was heated in an oil bath at a temperature of 100 °C for 13 h. The toluene was removed under vacuum. Flash chromatography using 70:1 petroleum ether/ethyl acetate gave the product as a clear yellow oil (2.779 g, 90%): IR (NaCl, neat) 3025, 2920, 1728, 1650, 1601, 1462, 1070, 745 cm^{-1}; ^1H NMR (CCl_4) δ 10.09 (s, 1 H) 7.2 (s, 5 H) 6.02 (bs, 1 H) 3.02–2.07 (m, 5 H) 2.07–0.70 (bm, 28 H). Anal. Calcd for $C_{25}H_{40}OSn$: C, 63.18; H, 8.48. Found: C, 63.47; H, 8.73. Analytical HPLC (2% EtOAc/98% hexane; 2 mL/min flow rate) showed the product to be a mixture of two cycloadducts (retention times, 3.25 min and 2.88 min; ratio = 6.67:1; α = 1.42).

***trans*-5-Methyl-1-(3- and 4-methyl-6-(tributylstannyl)-3-cyclohexenyl)-4-hexen-1-one (13).** Isoprene (15 mL, 10.2 g, 150 mmol) was added to a solution of **4** (1.80 g, 4.21 mmol), hydroquinone (20 mg), and toluene (10 mL) in a glass bomb. The mixture was sealed under an argon atmosphere and heated in an oil bath for 24 h at 95–100 °C. The bomb was cooled to room temperature, and additional isoprene (8 mL 5.44 g, 80 mmol) was added. The reaction was heated for an additional 5.5 h at 95–100 °C. The toluene was removed under vacuum. Flash chromatography with 110:1 hexane/EtOAc gave 1.897 g (91%) of a clear oil: IR (neat, NaCl) 2920, 1711, 1455, 1378, 1076 cm^{-1}; 300-MHz ^1H NMR ($CDCl_3$) δ 5.48, 5.42 (bs, 1 H) 5.10.

***trans*-2-(3- and 4-phenyl-6-(tributylstannyl)-3-cyclohexenyl)-2-propanol (7). A.** A mixture of *trans*-ethyl 3- and 4-phenyl-6-(tributylstannyl)-3-cyclohexenecarboxylate (**8**) (1.802 g, 3.47 mmol) in 3 mL of diethyl ether was added via syringe to a solution of methylmagnesium iodide formed from magnesium metal (0.340 g, 13.9 mmol) and iodomethane (1.97 g, 13.9 mmol) in 15 mL of diethyl ether at 0 °C. The mixture was stirred for 10 min at 0 °C, warmed to reflux over 30 min, refluxed 1 h, and finally allowed to stir 1 h at room temperature. The mixture was quenched with saturated aqueous NH_4Cl and the mixture extracted three times with diethyl ether. The combined organic extracts were dried over anhydrous $MgSO_4$ and flash chromatographed with 70:1 hexane/EtOAc to give 0.925 g (53%) of a colorless oil: IR (NaCl, neat) 3580, 3467, 2920, 1655, 1600, 1464, 745 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.60 (bs, 5 H) 6.05 (bs, 1 H) 3.17–0.67 (bm, 40 H). Anal. Calcd for $C_{26}H_{46}OSn$: C, 64.17; H, 9.18. Found: C, 64.37; H, 9.25. Analytical HPLC (2% hexane/98% EtOAc) showed the product to be a mixture of two isomers in a ratio of 1:5.6.

B. Methyllithium (1.56 M, 3.05 mL, 4.76 mmol) in diethyl ether was added to 10 mL of diethyl ether under an atmosphere of argon, and the solution was cooled to −78 °C. A mixture of compounds **6** (1.559 g, 3.17 mmol) in 3 mL of diethyl ether at −78 °C was added via syringe. The mixture was stirred for 30 min at −78 °C, and 20 mL of saturated aqueous NH_4Cl was added. The mixture was extracted with three 75-mL portions of diethyl ether, and the combined organic extracts were dried over anhydrous $MgSO_4$. Flash chromatography with 70:1 petroleum ether/EtOAc gave **7** (1.156 g, 72%) as a colorless oil.

7,7-Dimethyl-3-phenylbicyclo[4.1.0]hept-3-ene (9). Thionyl chloride (0.22 mL, 0.36 g, 3 mmol) was added dropwise to a solution of pyridine (0.316 g, 4 mmol) and **7** (0.505 g, 1 mmol) in THF (4 mL) with stirring under an argon atmosphere in an ice-water bath. After 1.5 h the reaction mixture was poured into water (15 mL) and extracted with three 40-mL portions of hexane. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated by rotary evaporation. Flash chromatography using pentane as eluent gave 0.203 g of crude product which was distilled in a Kugelrohr tube at 85 °C (1 Torr) to give the product as a clear oil (0.152 g, 77%): IR ($CHCl_3$) 3060, 2870, 1660, 1600, 1495, 1445, 1430 cm^{-1}; ^1H NMR (CCl_4) δ 7.18 (s, 5 H) 5.87 (bs, 1 H) 3.0–1.88 (m, 4 H) 1.1 (s, 3 H) 0.83 (s, 3 H) 1.0–0.63 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 142.8, 134.7, 128.2, 126.5, 125.2, 123.4, 28.4, 22.3, 21.7, 18.7, 17.2, 16.9, 13.4; HRMS m/z 198.1409 (M^+) (calcd for $C_{15}H_{18}$, 198.1408). The residue in the distillation flush was identified by ^1H NMR as a mixture of *trans*-1-phenyl-5-(2-propenyl)-4-(tributylstannyl)cyclohexene and *trans*-1-phenyl-4-(2-propenyl)-5-(tributylstannyl)cyclohexene (**10**).

***trans*-2-(3- and 4-methyl-6-(tributylstannyl)-3-cyclohexenyl)-2-propanol.** A solution of **11** (2.00 g, 4.7 mmol) in diethyl ether (2 mL) at −78 °C was added via syringe to a 1.4 M

solution of MeLi (10 mL, 14 mmol) in diethyl ether at −78 °C under an argon atmosphere. After stirring for 65 min at −78 °C, the mixture was poured into 100 mL of saturated aqueous NH_4Cl. The mixture was extracted with three 200-mL portions of diethyl ether, and the combined organic extracts were dried over anhydrous $MgSO_4$. MPLC with 75:1 hexane/ethyl acetate gave 1.710 g (82%) of a clear oil: IR ($CHCl_3$) 3618 (w), 2920 (s), 1465 (m), 1378 (m), 1130 (m) cm^{-1}; ^1H NMR (CCl_4) δ 5.3 (s, 1 H) 1.6 (s, 3 H) 2.4–0.63 (m, 40 H). Anal. Calcd for $C_{22}H_{44}OSn$: C, 59.61; H, 10.00. Found: C, 59.78; H, 10.22.

7,7-Dimethylbicyclo[4.1.0]hept-3-ene (Δ^3-Carene) (12). Thionyl chloride (0.494 mL, 6.8 mmol) was added dropwise via syringe to a solution of the above mixture of alcohols (1.000 g, 2.20 mmol) and pyridine (0.73 mL, 9.0 mmol) in THF (8 mL) at −15 °C under an atmosphere of argon. After addition was complete, the temperature was maintained at −5 °C for 55 min. The mixture was poured into water (25 mL) and extracted three times with 60-mL portions of pentane. The combined organic extracts were dried over anhydrous $MgSO_4$ and filtered. Most of the pentane was removed by distillation at atmospheric pressure through a glass Vigreaux column to leave approximately 3 mL of solution which was flash chromatographed on 40 g of silica gel by using pentane as eluent. Most of the pentane was removed by distillation at atmospheric pressure through a glass Vigreaux column. The product was collected in a dry-ice-cooled bulb by heating to 100 °C in a Kugelrohr oven under water aspirator pressure. The distillate was a clear liquid (0.251 g, 82%): IR ($CDCl_3$) 2870, 1450, 1379, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.2 (1 H) 2.66–1.47 (m, 7 H) 1.03 (s, 3 H) 0.77 (s, 3 H) 1.00–0.50 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 131.4, 119.5, 28.4, 25.0, 23.6, 20.8, 18.7, 16.8, 13.2. The spectral data were in agreement with literature values.[29] ^1H NMR showed the residue in the distilling flask to be *trans*-2-(3- and 4-methyl-6-(tributylstannyl)-3-cyclohexenyl)propene.

***trans*-1-(3- and 4-phenyl-6-(tributylstannyl)-3-cyclohexenyl)ethanol (17).** Sodium borohydride (0.216 g, 5.7 mmol, 8 equiv) was added to a solution of **6a** and **6b** (1.400 g, 2.86 mmol) in ethanol (8 mL) at 0 °C. Additional sodium borohydride (0.216 g, 5.7 mmol) was added after 1.5 and 5.5 h had elapsed. After a total time of 7 h at 0 °C, the reaction mixture was poured into water (15 mL) and extracted with three 60-mL portions of diethyl ether. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated by rotary evaporation. ^1H NMR of the crude product showed the presence of approximately 20% starting material, so the mixture was reexposed to the reducing agent. The crude product was dissolved in 10 mL of ethanol and 4 mL of THF. The solution was cooled to 0 °C, and sodium borohydride (0.6 g, 15.8 mmol) was added. The reaction was allowed to warm to room temperature after 30 min and allowed to stir for an additional 9.5 h. The reaction mixture was poured into water (15 mL) and extracted with three 60-mL portions of diethyl ether. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated by rotary evaporation. Flash chromatography using 60:1 petroleum ether/ethyl acetate gave 1.020 g (72%) of a white gum: IR (CCl_4) 3630, 3480, 2925, 1652, 1550, 1465, 1249 cm^{-1}; ^1H NMR (CCl_4) δ 7.23 (s, 5 H) 6.03 (bs, 1 H) 3.66 (bs, 1 H) 2.83–0.5 (m, 36 H). Anal. Calcd for $C_{26}H_{44}OSn$: C, 63.56; H, 9.03. Found: C, 63.77; H, 8.84.

***trans*-6-Methyl-2-(3- and 4-methyl-6-(tributylstannyl)-3-cyclohexenyl)-5-hexen-2-ol (14a and 14b).** Cerium trichloride heptahydrate (1.20 g, 3.22 mmol) was heated at 150 °C for 2 h at 0.08 Torr in a round-bottom flask with vigorous stirring.[19] The dried cerium trichloride was then allowed to cool *completely* to room temperature. Anhydrous THF (10 mL) was added, and the suspension was stirred for 2 h under an atmosphere of argon. The suspension was cooled to −78 °C, and methyllithium (0.0178 g, 2.56 mmol) in 2.0 mL of diethyl ether was added dropwise over 2 min. The solution was stirred for 35 min at −78 °C, and then a solution of **13** (1.00 g, 2.02 mmol) in 4 mL of the THF at −78 °C was added via syringe. The reaction was stirred for 2.5 h at −78 °C, and then 15 mL of saturated aqueous NH_4Cl was added. The mixture was allowed to warm to room temperature and then filtered through Celite by using diethyl ether. The mixture was extracted twice with diethyl ether, and the organic extracts (400 mL total volume) were dried with $MgSO_4$. Flash chromatography with 110:1 hexane/EtOAc gave three fractions. Fraction one contained the faster eluting alcohols (**14a**, isomers as a result of the position of the ring methyl) as a colorless oil: 0.677 g, 65%; TLC R_f = 0.44, 25:1 hexane/EtOAc; IR (neat, NaCl) 3525 (b), 2920, 1680 (w), 1455, 1375 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.53–4.93 (bm, 2 H) 2.33–0.57 (bm, 40 H). The third fraction contained the slower eluting alcohols (**14b**, isomers as a result of the ring methyl) as a colorless oil: 0.282 g, 27%; TLC R_f = 0.30, 25:1 hexane/EtOAc; IR (neat, NaCl) 3619, 3540, 2920, 1682 (w), 1455, 1375, 1090 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.53–4.90 (bm, 2 H) 2.33–0.60 (bm, 40 H). The second fraction contained a mixture of both pairs of diastereomers as a slightly cloudy oil (0.012 g, 1%).

3,7-Dimethyl-*endo*-7-(4-methyl-3-pentenyl)bicyclo[4.1.0]-hept-3-ene (Isosesquicarene) (15). Thionyl chloride (0.06 mL, 98 mg, 0.82 mmol) was added dropwise to a stirring solution of **14a** (the faster eluting pair of diastereomers) (0.338 g, 0.661 mmol) and pyridine (0.209 g, 2.64 mmol) in THF (4 mL) at 2 °C. The mixture was stirred for 40 min and poured into 40 mL of water. The mixture was extracted with hexane (3 × 60 mL) and dried over anhydrous $MgSO_4$. The solvent was removed on a rotary evaporator, and the crude product was flash chromatographed to give an oil that was a mixture of compounds. Distillation into a dry-ice-cooled bulb from a Kugelrohr oven (80–120 °C, 0.1 Torr) gave 89 mg (66%) of pure isosesquicarene (uncontaminated by other stereoisomers): IR (neat) 2920, 1487, 1360, 781 cm^{-1}; ^1H NMR (CCl_4) δ 5.37–4.87 (bm, 2 H) 2.5–1.57 (m, 6 H) 1.57–1.4 (m, 9 H) 1.03 (s, 3 H) 1.22–0.50 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 131.6, 130.8, 125.5, 119.7, 28.3, 25.7, 25.5, 25.1, 23.6, 21.0, 20.4, 19.6, 17.7, 17.5; HRMS m/z 204.1880 (M^+) (calcd for $C_{15}H_{14}$, 204.1877). The spectral data were consistent with literature values.[18] The distillation flask contained 44 mg (13%) of an oil tentatively identified by ^1H NMR as a mixture of compounds resulting from the elimination of water from the starting material.

4,7-Dimethyl-*exo*-7-(4-methyl-3-pentenyl)bicyclo[4.1.0]-hept-3-ene (16). Thionyl chloride (0.110 mL, 0.179 g, 1.5 mmol) was added dropwise to a solution of **14b** (the slower eluting pair of diastereomers) (0.640 g, 1.25 mmol) and pyridine (0.39 g, 5.0 mmol) in THF (4 mL) stirring at 2 °C. The reaction was stirred for 30 min and poured into 40 mL of water. The mixture was worked up as above. Distillation into a dry-ice-cooled bulb from a Kugelrohr oven (80–100 °C, 0.1 Torr) gave 0.199 (78%) of 4,7-dimethyl-*exo*-7-(4-methyl-3-pentenyl))bicyclo[4.1.0]hept-3-ene (uncontaminated by other isomers): IR (NaCl, neat) 2916, 1687, 1440, 1378, 780 cm^{-1}; ^1H NMR (CCl_4) δ 5.63–4.87 (bm, 2 H) 2.66–1.73 (bm, 6 H) 1.73–1.43 (m, 6 H) 1.4–1.0 (m, 2 H) 0.93–0.43 (m, 2 H) 0.73 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 131.6, 130.8, 125.1, 119.7, 42.7, 25.7, 25.5, 24.9, 23.6, 20.9, 18.0, 17.6, 16.2, 10.3; HRMS m/z 204.1879 (M^+) (calcd for $C_{15}H_{24}$, 204.1877). The spectral data were consistent with literature values.[18] The distillation flask contained 100 mg of an oil tentatively identified by ^1H NMR as a mixture of compounds resulting from the elimination of water from the starting material.

***trans*-1-Methyl-1-(3- and 4-methyl-6-(tributylstannyl)-3-cyclohexenyl)oxirane (18).** Sodium hydride as a 50% oil dispersion (0.247 g, 5.1 mmol) was placed in an oven-dried flask and rinsed three times with 5 mL-portions of pentane. The remaining pentane was removed under a flow of argon, and 8 mL of dry Me_2SO was added. The mixture, after heating at 70 °C until gas evolution ceased, was cooled to room temperature, and 10 mL of dry THF was added via syringe. The solution was cooled with an ice–salt bath, and trimethylsulfonium iodide[20] (1.050 g, 5.3 mmol), dissolved in Me_2SO (3.5 mL), was added via syringe. The mixture was stirred for 1 min, and then **11** (2.000 g, 4.68 mmol) in THF (3 mL) was added via syringe followed by a 1-mL rinse of THF. The mixture was stirred for 10 min in the ice–salt bath followed by 30 min at room temperature. The reaction mixture was poured into water (100 mL) and extracted with two 150-mL portions of pentane followed by one extraction with 100 mL of 10:1 pentane/diethyl ether. The combined organic extracts were dried over anhydrous $MgSO_4$ and purified by MPLC using 80:1 petroleum ether/ethyl acetate to give the product (1.680 g, 82%) as a clear oil: IR (NaCl, neat) 2920, 1682, 1462, 1377, 1070

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cm^{-1}; ^1H NMR (CCl_4) δ 5.37 (bs, 1 H) 2.48 (bs, 2 H) 1.62 (bs, 3 H) 2.2–0.7 (m, 33 H). Anal. Calcd for $C_{22}H_{42}OSn$: C, 59.88; H, 9.59. Found: C, 60.16; H, 9.73.

***exo*- and *endo*-7-(Hydroxymethyl)-3,7-dimethylbicyclo[3.1.0]hept-3-ene (19).** Solid pyridine hydrochloride (0.191 g, 1.65 mmol) was added to a solution of **18** (0.485 g, 1.1 mmol) in 4 mL of acetonitrile at room temperature under an argon atmosphere. Additional pyridine hydrochloride (0.191 g, 1.65 mmol) was added 40 min after the start of the reaction and again 2 h after the initial addition. After a total reaction time of 4 h had elapsed, the solution was poured into 20 mL of water containing 1 g of KF and shaken for 2 min. The mixture was extracted with three 60-mL portions of diethyl ether, and the combined organic extracts were dried over anhydrous $MgSO_4$. Flash chromatography using 9:1 hexane/ethyl acetate followed by Kugelrohr distillation (90–110 °C, 1 Torr) gave a clear oil (0.142 g, 85%): IR (NaCl, neat) 3340, 2875, 1686, 1440, 1380, 1015 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.37 (bs, 1 H) 3.5, 3.33 (s, 2 H) 2.63 (bs, 1 H) 2.13 (m, 4 H) 1.97 (bs, 3 H) 1.17, 0.9 (s, 3 H) 1–0.73 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 131.4, 119.4, 73.2, 63.3, 25.0, 24.6, 23.6, 23.0, 21.0, 20.6, 20.0, 18.2, 15.7, 13.9, 8.7. Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; 10.59. Found: C, 78.72; H, 10.65. The product was a 1.3:1 mixture of two isomers as determined by the ^1H NMR integration of the hydroxymethyl resonances.

***trans*-1-(3- and 4-phenyl-6-(tributylstannyl)-3-cyclohexenyl)-2-propen-1-ol (21).** THF (5 mL) was placed in a flask containing 70–80-mesh magnesium powder under an argon atmosphere and heated to reflux. The heat source was removed, and 1 drop each of dibromomethane and vinyl bromide was added to initiate the reaction. Vinyl bromide (0.90 g, 8.42 mmol) in THF (3 mL) was added at a rate sufficient to keep the reaction temperature between 40 and 50 °C. The reaction mixture was stirred for 15 min after the last of the vinyl bromide had been added and allowed to cool to 35 °C. A mixture of *trans*-(3- and 4-phenyl-6-(tributylstannyl)-3-cyclohexene)carboxaldehyde (**20**) (2.000 g, 4.21 mmol) in THF (3 mL) was added dropwise at room temperature. The reaction mixture was slowly heated to reflux over 30 min and then maintained at reflux for 15 min. The heat source was removed, and the reaction mixture was allowed to cool for 30 min. The mixture was poured into 70 mL of saturated aqueous ammonium chloride and extracted with three 90-mL portions of diethyl ether. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, concentrated by rotary evaporation, and flash chromatographed by using 40:1 hexane/EtOAc to give 1.943 g (92%) of a clear oil: IR (NaCl, neat) 3520, 2922, 1648, 1601, 1497, 1465, 747 cm^{-1}; ^1H NMR (CCl_4) δ 7.23 (s, 5 H) 7.17–5.02 (m, 4 H) 4.13 (bs, 1 H) 2.83–0.66 (bm, 34 H). Analytical HPLC (2% EtOAc/98% hexane; 2 mL/min flow rate) showed the presence of four isomers (retention times 4.75, 5.0, 5.7, and 6.25 min; ratio = 43:13:77:1).

***exo*- and *endo*-3-Phenyl-7-ethenylbicyclo[4.1.0]hept-3-ene (22).** Thionyl chloride (0.95 mL, 0.155 g, 1.3 mmol) was added dropwise to a solution of pyridine (0.316 g, 4.0 mmol) and *trans*-1-(3- and 4-phenyl-6-(tributylstannyl)-3-cyclohexenyl)-2-propen-1-ol (**21**) (0.503 g, 1 mmol) in THF at 2 °C. The reaction mixture was stirred for 55 min and poured into 30 mL of water that contained 2.6 g of KF. The separatory funnel was shaken for 2 min, and the mixture was extracted with three 80-mL porions of pentane. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation. Flash chromatography using pentane as eluent followed by Kugelrohr distillation (110–120 °C, 0.5 Torr) gave 0.155 g (79%) of a clear oil: IR (NaCl, neat) 3020, 2898, 2838, 1649, 1601, 1499, 1449, 745 cm^{-1}; ^1H NMR (CCl_4) δ 7.17 (s, 5 H) 5.8 (bs, 1 H) 5.66–4.63 (m, 3 H) 2.83–2.37 (bm, 4 H) 1.7–1.07 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 142.6, 141.6, 134.7, 134.2, 133.5, 128.2, 126.8, 125.2, 123.2, 121.4, 116.1, 110.9, 25.6, 24.5, 24.0, 23.6, 22.5, 21.9, 20.1, 18.5, 14.2, 13.0. Anal. Calcd for $C_{15}H_{16}$: C, 91.78; H, 8.22. Found: C, 91.56; H, 8.19. ^{13}C NMR indicated the product was a mixture of isomers.

***trans*-(3- and 4-phenyl-6-(tributylstannyl)-3-cyclohexenyl)methanol (24).** Sodium borohydride (0.714 g, 18.9 mmol, 20 equiv) was added to a solution of *trans*-(3- and 4-phenyl-6-(tributylstannyl)-3-cyclohexene)carboxaldehyde (**20**) (1.800 g, 3.78 mmol) in ethanol (8 mL) at 2 °C. The reaction was stirred for 2 h, poured into 30 mL of water, and extracted with three 60-mL portions of dichloromethane. The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated by rotary evaporation. Flash chromatography using 25:1 petroleum ether/EtOAc gave the product as an amorphous white solid (1.680 g, 93%): mp 57.5–59 °C; IR (NaCl, neat) 3638, 3470, 2921, 1652, 1601, 1469, 1070 cm^{-1}; ^1H NMR (CCl_4) 7.18 (s, 5 H) 5.98 (bs, 1 H) 3.5 (bs, 2 H) 2.73–0.63 (bm, 34 H). Anal. Calcd for $C_{25}H_{42}OSn$: C, 62.91; H, 8.87. Found: C, 63.07; H, 8.70.

***trans*-4-(Chloromethyl)-1-phenyl-5-(tributylstannyl)-cyclohexene and *trans*-5-(Chloromethyl)-1-phenyl-4-(tributylstannyl)cyclohexene (23).** Thionyl chloride (0.359 g, 3.02 mmol) and pyridine (0.597 g, 7.50 mmol) were added to a solution of **24** (0.720 g, 1.51 mmol) in THF (3 mL) at 2 °C. The mixture was allowed to warm to room temperature and stirred for 3 h. Thionyl chloride (0.180 g, 1.51 mmol) was added, and the reaction mixture was stirred for 1.5 h. Additional thionyl chloride (0.180 g, 1.51 mmol) and pyridine (0.303 g, 3.83 mmol) were added, and the reaction was stirred for 2.5 h. The reaction was poured into water (30 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and flash chromatographed to give two fractions. Fraction one was placed in a Kugelrohr oven and heated to 133 °C at 0.5 Torr to give 49 mg (19%) of the cyclopropane **25** with physical properties identical with those previously described. Fraction two contained 0.388 (52%) of an oil identified as a mixture of the title compounds: ^1H NMR (CCl_4) δ 7.23 (s, 5 H) 6.01 (bs, 1 H) 3.87 (m, 2 H) 2.63 (m, 2 H) 2.20 (m, 2 H) 1.70–0.65 (bm, 29 H); IR (NaCl, neat) 3021, 1648, 1601, 1462, 1068 cm^{-1}.

3-Phenylbicyclo[4.1.0]hept-3-ene (25). Methanesulfonyl chloride (0.395 g, 3.45 mmol) was added to a mixture of **24** (0.550 g, 1.15 mmol) dissolved in pyridine (3.5 mL) at room temperature. The reaction was stirred for 11 h. The black reaction mixture was poured into a separatory funnel containing 20 mL of water and 150 mL of diethyl ether. The mixture was shaken, and the water layer was removed. The organic layer was extracted with the two 40-mL portions of 5% aqueous HCl. The three aqueous layers were combined and extracted with 50 mL of diethyl ether. This ether layer was extracted with 20 mL of 5% aqueous HCl and combined with the first organic layer. The extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporator. The nonpolar impurities were removed by flash chromatography using 25:1 hexane/EtOAc followed by 1:1 hexane/EtOAc as eluent. The crude product was concentrated by rotary evaporation, and glacial acetic acid (8 mL) containing water (0.1 mL) was added. The mixture was heated in an oil bath at 60 °C for 3.3 h. The acetic acid was neutralized with saturated aqueous $NaHCO_3$ and extracted with three 150-mL portions of pentane. The combined organic extracts were dried over anhydrous $MgSO_4$ and flash chromatographed by using pentane as eluent. Kugelrohr distillation (75–145 °C, 0.7 Torr) gave 0.132 g (67%) of 3-phenylbicyclo[4.1.0]hept-3-ene as a clear liquid: IR (neat, NaCl) 3020 (s), 2898 (s), 2839 (s), 1601, 1493, 1448, 1020, 701 cm^{-1}; ^1H NMR (CCl_4) δ 7.13 (s, 5 H), 5.70 (bs, 1 H) 2.77–2.37 (bm, 4 H) 1.33–0.80 (bm, 2 H) 0.66–0.230 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 143.0, 133.3, 128.1, 126.6, 125.2, 121.2, 26.3, 25.1, 10.1, 8.5, 6.3; HRMS m/z 170.1088 (M^+) (calcd for $C_{13}H_{14}$, 170.1095).

***trans*-1-(Tributylstannyl)-1-octen-3-one (5).** Anhydrous aluminum chloride (0.533 g, 4.00 mmol) was added to a solution of *trans*-1,2-bis(tributylstannyl)ethylene (**26**) (2.423 g, 4.00 mmol) and hexanoyl chloride (0.592 g, 4.40 mmol) in dichloromethane (40 mL) at −70 °C under an argon atmosphere. The mixture was stirred for 30 min at −70 °C and then allowed to warm to 0 °C over a period of 1 h. The mixture was poured into 100 mL of water containing KF (10g) and stirred vigorously for 10 min. The mixture was extracted with one 150-mL portion of diethyl ether followed by two 100-mL portions of diethyl ether. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation. Flash chromatography using 70:1 petroleum ether/EtOAc gave two product fractions. The faster eluting fraction contained a mixture of mainly *trans*-1-(tributylstannyl)-1-octen-3-one (TLC R_f = 0.56; 50:1 hexane/EtOAc) contaminated with *cis*-1-(tributylstannyl)-1-octen-3-one (TLC R_f = 0.69; 50:1 hexane/EtOAc) as a clear oil (0.206 g, 12%). An analytical sample of the cis alkene was obtained by flash chromatography: ^1H NMR (CCl_4) 7.03 (s, 2 H) 2.47 (t, J = 5 H, 2 H) 1.76–0.77 (bm, 36 H). The slower eluting fraction contained pure *trans*-1-(tributylstannyl)-1-octen-3-one as a clear oil (0.841

g, 49%): IR (neat, NaCl) 2924, 1695, 1678, 1570, 1462, 992 cm^{-1}; ^1H NMR (CCl_4) δ 7.37 (d, J = 19 Hz, 1 H) 6.38 (d, J = 19 Hz, 1 H) 2.47 (t, J = 6 Hz, 2 H) 1.90–0.70 (bm, 36 H). Anal. Calcd for $C_{20}H_{40}OSn$: C, 57.85; H, 9.71. Found: C, 58.09; H, 9.87.

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Supplementary Material Available: Experimental procedures for the preparation of the following substances: *trans*-1-(2-(tributylstannyl)-3-cyclohexenyl)-1-ethanone, *trans*-1-(3- and 4-(phenylthio)-6-(tributylstannyl)-3-cyclohexenyl)-1-ethanone, *trans*-2-(4-(phenylthio)-6-(tributylstannyl)-3-cyclohexenyl)-2-propanol, 7,7-dimethyl-3-(phenylthio)bicyclo[4.1.0]hept-3-ene, *exo*- and *endo*-7-methyl-3-phenylbicyclo4.1.0]hept-3-ene, *trans*-1-(3- and 4-methyl-6-(tributylstannyl)-3-cyclohexenyl)-1-phenylethanol, *exo*- and *endo*-3,7-dimethyl-7-phenylbicyclo[4.1.0]hept-3-ene, and *trans*-3,4-dimethyl-6-(tributylstannyl)-3-cyclohexenecarboxaldehyde (6 pages). Ordering information is given on any current masthead page.

Enzymatic and Chemical Oxidations of Leurosine to 5′-Hydroxyleurosine

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The major product obtained when leurosine was oxidized by microorganisms, copper oxidase enzyme systems, benzoquinone, and DDQ has been identified as a mixture of chromatographically inseparable 5′-hydroxyleurosine isomers. The leurosine oxidation product is only one of several possible positional carbinolamine isomers. The precise location of the carbinolamine functionality was clearly determined by carbon-13 NMR spectral analysis of 5′-deuterioleurosine obtained by sodium borodeuteride reduction of the carbinolamine. By virtue of the oxidants employed, it is likely that leurosine is first oxidized to a nitrogen centered cation-radical which loses hydrogen to form an iminium derivative that adds water. The possible occurrence of equilibrium mixtures of isomeric iminium intermediates in the oxidation reaction mixture was excluded by spectral analysis of the product formed when leurosine oxidations were conducted in deuterium oxide.

Introduction

Leurosine (1) is the most abundant dimeric antitumor alkaloid isolated from the Madagascar periwinkle (*Catharanthus roseus* G. Don, Apocynaceae, also known as *Vinca rosea* L.), and it is closely related in structure to the clinically used antineoplastic alkaloids vincristine and vinblastine. The Vinca alkaloids have been used in the treatment of human neoplasms for nearly 3 decades. However, surprisingly little is known about the types of oxidative transformations these alkaloids undergo, or of the possible roles that biotransformations play in their mechanism(s) of action and/or dose limiting toxicities.[1-3] Considerable evidence incidates that the Vinca alkaloids and their derivatives are extensively converted to other products in living systems,[4-6] but nothing is presently known about the structural changes which occur or the activities of presumed oxidation products.

Microbial transformations of monomeric Vinca alkaloids led to an understanding of the chemistry and biochemistry of alkaloid biotransformations. Aspidosperma and Iboga alkaloids were readily oxidized by unknown enzymes of a bacterium,[7] copper oxidases (ceruloplasmin, laccases),[8] peroxidase,[9] cytochrome P-450,[10] and chemical mimics of the enzyme systems. For example, vindoline (7) underwent one-electron oxidation[8] leading to the formation of a reactive iminium intermediate,[11] which by intramolecular etherification formed an enamine that isomerized and dimerized. Benzoquinone and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and photochemical oxidations mimicked the enzyme reactions by providing the same types of oxidation products. Among other products obtained by microbiological transformation, vindoline gave high yields of a phenol formed by methyl ether cleavage[12] and a carbinolamine formed by oxidation of 14,15-dihydrovindoline.[13] Work with vindoline was essential in clarifying the chemical and biochemical features of Vinca alkaloid biotransformations and in illustrating the broad range of oxidative reactions possible with these compounds.

These efforts have now been extended to the unsymmetrical dimeric Vinca alkaloid leurosine. Leurosine presented a much more complicated case because it contains both Aspidosperma and Iboga alkaloid systems linked to one another in its dimeric structure. Leurosine was readily converted to a major common product by microbiological, enzymatic, and chemical oxidizing systems. This report details the formation and characterization of the new carbinolamine product 5′-hydroxyleurosine (4) and reveals that in this dimer the Iboga ring system is more susceptible to enzymatic and chemical oxidation.

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