Total Syntheses of the Cytotoxic Marine Natural Product, Aplysiapyranoid C[1]

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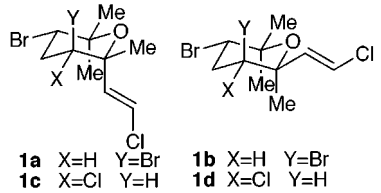
The first total syntheses of the cytotoxic marine natural product, aplysiapyranoid C, **1c**, are reported. The Wittig reaction of 4-methyl-3-pentenyltriphenylphosphorane with the THP ether of hydroxyacetone gave in 88% yield the *Z*-alkene **4** which was hydrolyzed to the alcohol **5** in 72% yield. Sharpless asymmetric epoxidation of **5** afforded the epoxy alcohol **6** in 91% yield and 81% ee. Opening of the epoxide of **6** with ammonium chloride in DMSO gave in 76% yield the chloro diol **7** which was converted to the primary TBS ether **8** in 95% yield. Opening of the epoxy alcohol **6** with HCl and $Ti(OiPr)_4$ afforded the desired chloro diol **7** as the minor product along with the rearranged chloromethyl diol **9**. This compound is presumably formed by opening of the protonated epoxide to give a butenyl cation which rearranges to the cyclopropylcarbinyl cation and is then trapped by chloride ion at the unsubstituted cyclopropyl carbon, regenerating the alkene. Cyclization of the TBS ether **8** with tetrabromocyclohexadienone (TBCO) afforded a mixture of all four possible cyclization products, the desired tetrahydropyrans **11a,b** and the tetrahydrofurans **12a,b** with the former being isolated in 70% yield. Hydrolysis of the TBS ether afforded the primary alcohols from which the desired isomer, **13**, could be isolated (24% overall from **8**). Swern oxidation furnished the aldehyde **14** which was subjected to the Takai chlorovinylation to give a mixture of aplysiapyranoid C **1c** and the reduced product, dechloroaplysiapyranoid C **15**. This dechlorination under these conditions is quite unusual. A second synthesis of aplysiapyranoid C avoided this problem. Selective protection of the more hindered tertiary alcohol of the chloro diol **7** afforded the primary alcohol **16** in which the tertiary alcohol was protected as the triethylsilyl ether. Swern oxidation, Takai reaction, and desilylation gave the dichloro alkenol **17** in 52% overall yield. In this case, only a small amount of the corresponding dechlorinated product was obtained. Final cyclization of **17** with TBCO afforded aplysiapyranoid C **1c** as the major product in an isolated yield of 43%. Thus we have completed two total syntheses of aplysiapyranoid C **1c** from the simple bromide **2** in eight or nine steps and good overall yield.

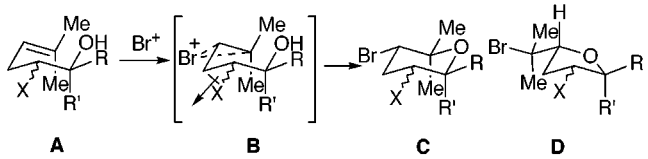
Introduction

The aplysiapyranoids A−D, **1a**−**d**, are four halogenated monoterpenes isolated by Kakisawa and co-workers from the marine mollusc *Aplysia kurodai* (Scheme 1).[3] These compounds, which have an unusual polyhalogenated tetrahydropyran structure, show good cytotoxicity against several cell lines.[3] For example, aplysiapyranoid D has exhibited an IC_{50} of 14 μg/mL vs human tumor cells (Moser), while the other aplysiapyranoids are somewhat less active (IC_{50}'s of 19−96 μg/mL vs standard cancer cell lines, e.g., Vero, MDCK, and B_{16} cells). We have previously reported the synthesis of the aplysiapyranoids A and D, **1a,d**, from simple achiral allylic alcohols.[4] The approach in those syntheses involved as key steps: (1) a Sharpless asymmetric epoxidation to give an epoxy alcohol, from which all three of the required stereocenters are ultimately derived; and (2) a stereoselective bromoetherification to furnish a product that is normally disfavored sterically but is favored in these cases due to a strong inductive effect on the homoallylic halogen atom.

Scheme 1



Scheme 2



This causes the normally disfavored opening of the intermediate bromonium ion at the more substituted carbon atom to occur to give the tetrahydropyran product in preference to the tetrahydrofuran product (Scheme 2). Thus, cyclization of the bis-homoallylic alcohol **A** having either a chlorine or a bromine atom in the homoallylic position with a source of positive bromine atom would afford the bromonium ion **B** (and its stereoisomer, see below), which could be opened at either the tertiary position to give the tetrahydropyran **C** or at the secondary center to give the tetrahydrofuran product **D**. We have shown[4] that the halogen atom is crucial in

(1) Presented at the 211th National American Chemical Society meeting, New Orleans, LA, March 1996, ORGN 319.
(2) American Chemical Society Arthur C. Cope Scholar, 1995.
(3) Kusumi, T.; Uchida, H.; Inouye, Y.; Ishitsuka, M.; Yamamoto, H.; Kakisawa, H. *J. Org. Chem.* **1987**, *52*, 4597.
(4) (a) Jung, M. E.; Lew, W. *J. Org. Chem.* **1991**, *56*, 1347. (b) Jung, M. E.; D′Amico, D.; Lew, W. *Tetrahedron Lett.* **1993**, *34*, 923.

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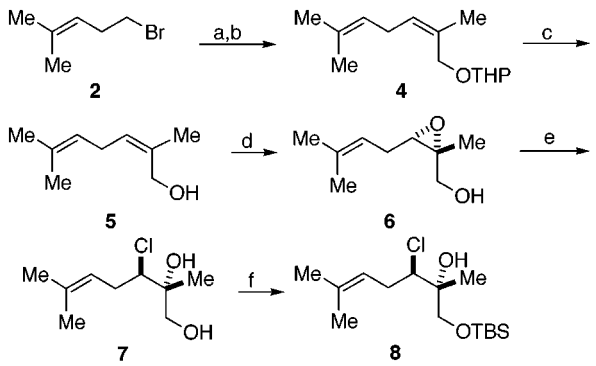
controlling this opening in the desired sense, namely to favor the normally disfavored opening[5] to give mainly the desired product **C**. We believe that the inversion of the normal opening of bromonium ions of this sort is due to the carbon−halogen dipole (shown in **B**) which destabilizes the carbocation at the secondary center proximal to the halogen atom and thereby inductively favors opening at the end distal to the halogen. This reaction sequence affords, in the case of aplysiapyranoid D, the all-equatorial isomer and, in the case of aplysiapyranoid A, a less stable isomer having an axial bromine atom. We now report herein the first two total syntheses of aplysiapyranoid C, **1c**, which has a structure possessing an equatorial chlorine atom and an axial 2-chlorovinyl group. These two syntheses of **1c** also utilize as key steps a Sharpless asymmetric epoxidation to produce an optically active epoxy alcohol and, after opening with chloride ion, a 3-chloro 1,2-diol which, after protection of the primary alcohol, then undergoes a similar stereoselective bromoetherification to afford once again the tetrahydropyran product in preference to the tetrahydrofuran one. Once more a chlorovinylation reaction (the Takai reaction) is used to produce the required vinyl chloride in both syntheses.

Results and Discussion

There are two possible ways to carry out the synthesis of aplysiapyranoid C based on our previous syntheses of aplysiapyranoids A and D. One can first start with the bromoetherification to give the tetrahydropyran system, prepare the aldehyde, and then carry out the chlorovinylation (Takai reaction), or one can invert the two key processes and effect first the chlorovinylation on an acyclic precursor and subsequently perform the bromoetherification as the final step in the synthesis. Since we had no strong reason to believe a priori that one route would be preferable to the other, we decided to look at both routes. As it turns out, although both were successful, the second procedure, namely first chlorovinylation and then bromoetherification, gave much better results.

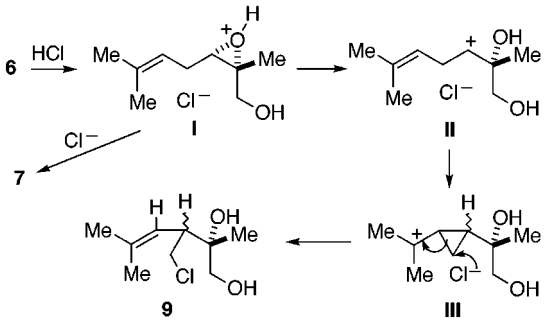
The syntheses both begin (Scheme 3) with the phosphonium bromide derived from the readily available 5-bromo-2-methyl-2-pentene **2**. In the formation of the phosphonium bromide, it was necessary to add a trace amount of tetramethylpiperidine (TMP) to the reaction to suppress migration of the double bond to form a 2-methyl-1-alkene. Although this less substituted double bond isomer would be expected to be less stable, it was found to be necessary to completely suppress its formation using a hindered base, since otherwise inseparable mixtures of products resulted. Under conditions reported by Still for similar substrates,[6] the phosphonium bromide was deprotonated with KHMDS in THF/HMPA, followed by Wittig reaction with the tetrahydropyranyl ether of hydroxyacetone **3**, to give only the *Z*-alkene **4** in 88% overall yield from **2**. The resulting adduct was deprotected using PPTS in ethanol to yield the allylic alcohol **5**.[7] Sharpless epoxidation of **5** was effected in 91% yield

Scheme 3



[a] (a) PPh_3, H_3CCN, 85 °C, 5 mol % TMP. (b) KHMDS, THF, HMPA, 25 °C; **3**, −78 °C to 25 °C, 88% based on **3**. (c) PPTS, EtOH, 60 °C, 72%. (d) D-(−)-DIPT, $Ti(OiPr)_4$, TBHP, CaH_2, SiO_2, CH_2Cl_2, −25 °C, 91% (81% ee). (e) NH_4Cl, $Ti(OiPr)_4$, DMSO, 25 °C, 76%. (f) TBSCl, ImH, DMF, 25 °C, 95%.

Scheme 4



using the modification of Zhou, which allows rapid asymmetric epoxidation of cis allylic alcohols, normally poor substrates in the Sharpless epoxidation.[8] The enantiomeric excess of the epoxy alcohol **6** obtained was determined to be 81% by the method of Alexakis.[9] The epoxy alcohol was opened by chloride ion using ammonium chloride and titanium tetraisopropoxide in DMSO[10] to give the chloro diol **7**, which was the branch point in the two syntheses. For the first synthesis, monoprotection of the diol at the primary alcohol was carried out under the usual conditions to give **8** in 95% yield.

We had observed a novel rearrangement in an earlier attempt to prepare the chloro diol **7** in the opening of the epoxy alcohol **6** with hydrogen chloride and titanium tetraisopropoxide in dichloromethane rather than with ammonium chloride in dimethyl sulfoxide (Scheme 4). In addition to the desired product **7** (20% yield), we also obtained the rearranged chloromethyl diol **9** as a 2.8:1 mixture of diastereomers in 45% yield. These compounds are presumably formed by protonation of the epoxide to give **I** which can be opened by chloride in an S_N2 process to give **7** or can open via an S_N1 process to give the butenyl cation **II** which is stabilized as the cyclopropylcarbinyl cation **III**. Opening of this cyclopropylcarbinyl cation with chloride ion at the unsubstituted carbon regenerates the alkene and produces the products **9**.

(5) (a) Broka, C. A.; Lin, Y.-T. *J. Org. Chem.* **1988**, *53*, 5876. (b) Corey, E. J.; Ha, D.-C. *Tetrahedron Lett.* **1988**, *29*, 3171. (c) Hashimoto, M.; Kan, T.; Nozaki, K.; Yanagiya, M.; Shirahama, H.; Matsumoto, T. *J. Org. Chem.* **1990**, *55*, 5088 and references in all of the above.

(6) Sreekumar, C.; Darst, K. P.; Still, W. C. *J. Org. Chem.* **1980**, *45*, 4260.

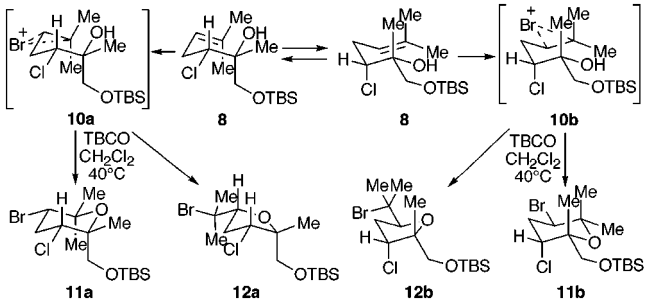
(7) Miyashita, N.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772.

(8) Wang, Z.-m.; Zhou, W.-s.; Lin, G.-q. *Tetrahedron Lett.* **1985**, *26*, 6221.

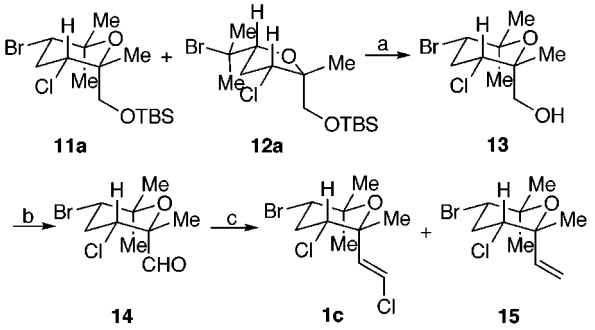
(9) Alexakis, A.; Frutos, J. C.; Mutti, S.; Mangeney, P. *J. Org. Chem.* **1994**, *59*, 3326.

(10) (a) Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557. (b) Chong, J. M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1560.

Scheme 5



Scheme 6



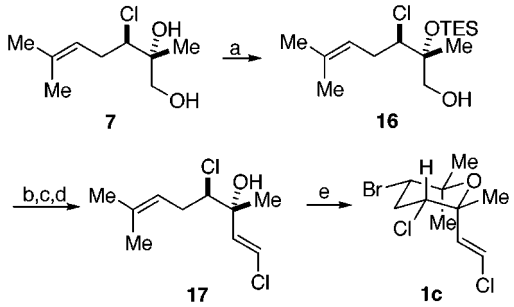
[a] (a) TBAF, THF, 0 °C; SiO_2, yield of **13** is 24% from **8**. (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to 0 °C, 98%. (c) $CrCl_2$, $CHCl_3$, THF, 60 °C, 68% of a 5:5:3 mixture of **1c**, **15**, and **14**.

For the first synthesis, the cyclization of **8** was carried out using tetrabromocyclohexadienone (TBCO) in dichloromethane at 40 °C, which yielded four products in good yield (Scheme 5). The two major products were determined on the basis of their ^{1}H NMR spectra to be the stereoisomeric tetrahydropyrans **11a,b**. The two other products have been assigned the tetrahydrofuran structures **12a,b**, based on comparison of their ^{1}H NMR spectra with those of similar compounds.[11] The formation of tetrahydropyrans **11a,b** is normally disfavored in cyclizations of substituted 4-pentenols with respect to the tetrahydrofurans due to the strong steric repulsion (1,3-diaxial-like interactions) in the transition states leading to these products. This mode of cyclization is favored by the inductive effect of the chlorine atom, which destabilizes build-up of positive charge at the proximal end of the bromonium ions **10ab** because of repulsion of the two positive dipoles. The major isomer present was the desired tetrahydropyran **11a** with both halogens equatorial, due presumably to steric hindrance in the transition state for cyclization leading to **11b** with an axial chlorine atom. We have observed both of these inductive and steric effects in similar cyclizations before.[4] Compound **11a** could not be separated cleanly, but a mixture of it and compound **12a** was isolated in 70% yield from the crude reaction mixture using silica gel chromatography.

The synthesis of aplysiapyranoid C was finished as follows (Scheme 6). Treatment of the mixture of **11a** and **12a** with TBAF removed the TBS groups to give, after flash chromatography on silica gel, the desired alcohol **13**. This alcohol was converted by a Swern oxidation into the aldehyde **14**, which was converted to the vinyl chloride using the method of Takai,[12] namely treatment

(11) Lew, Willard, Ph. D. dissertation, 1992, University of California, Los Angeles.

Scheme 7



[a] (a) DMTrCl, collidine, 0 °C; Et_3SiOTf (TESOTf), collidine, CH_2Cl_2, 40 °C; $C_{12}H_{25}SH$, CF_3COOH, 90% from **7**. (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to −20 °C, 88%. (c) $CrCl_2$, $CHCl_3$, THF, 60 °C, 69%. (d) HF·pyr, pyr, CH_2Cl_2, −20 °C, 86%. (e) TBCO, CH_3NO_2, 25 °C, 43%.

with chromous chloride and chloroform. Interestingly, we obtained a 1:1 mixture of aplysiapyranoid C **1c** along with compound **15**, in which the vinyl chloride has been reduced to a simple vinyl group. Presumably compound **15** is formed from **1c** in a reductive process carried out by the chromium(II) chloride. Whether the active reducing species is actually chromium(II) chloride or not is unknown. It is possible that the reduction of the vinyl chloride is carried out by a trace contaminant. It is known, for example, that chromium(II) chloride can undergo oxidative addition to vinyl chlorides in the presence of trace amounts of nickel(II) chloride.[13] Further work is underway to determine the cause of this unwanted reduction and to find ways to suppress it.

Thus this completes an eight-step synthesis of aplysiapyranoid C from the bromide **2**.

However, we have developed a somewhat better synthesis of **1c** by inverting the key steps as follows (Scheme 7). Conversion of the diol to the secondary triethylsilyl ether was carried out in a 3-step one-pot procedure by dimethoxytritylation of the primary alcohol, silylation of the tertiary alcohol, and deprotection with acid and dodecanethiol to give **16**. Swern oxidation furnished in 88% yield the aldehyde which was subjected to the Takai reaction to give a good yield of the desired *E*-vinyl chloride (with little interference by an intramolecular ene reaction).[14] Final removal of the silyl ether with HF·pyr afforded the tertiary alcohol **17** in 86% yield.[15] In this case, only a small amount (up to ∼10%) of the dechlorinated product was obtained in the chlorovinylation reaction, in marked contrast to the case with the aldehyde **14** above. We believe that the abnormal Takai reaction (to give the dechlorinated product **15**) must be due to the severe steric hindrance of this particular aldehyde (1,3-diaxial to a methyl group in a pyran ring system). We have not seen this abnormal process with other simple aldehydes.[16] Cyclization of the dichlorodienol **17** with TBCO in nitromethane gave a mixture of

(12) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408.

(13) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644.

(14) Takai reports such probelms with olefinic aldehydes giving products from ene reactions.[12]

(15) When less pyridine is used for the desilylation, the quaternary fluoride, formed by Markovnikov addition of HF to the trisubstituted alkene, is produced.

(16) The Takai reaction on several aldehydes, e.g., benzaldehyde, dodecanal, and 2-(decyloxy)-2-methylpropanal, gave only chlorovinylation with no dechlorinated product observed.

four products, from which aplysiapyranoid C **1c** [$[\alpha]^{25}_D$ = 58.4 (lit. 52)[3]] could be isolated in 43% yield by HPLC.[17]

In summary we have completed two efficient syntheses of aplysiapyranoid C, **1c**, utilizing as key steps a Sharpless asymmetric epoxidation and a diastereoselective bromoetherification. Further work in this area is in progress.

Experimental Section

General. ^{1}H NMR were recorded at 200, 360, 400, or 500 MHz and are so indicated. ^{13}C NMR were recorded at 90, 100, or 125 MHz, respectively, and are so indicated. Infrared spectra were recorded on an FTIR as a liquid film or as a thin crystalline film. High-resolution mass spectra (MS) were recorded on a double focusing instrument. Optical rotations were obtained at ambient temperature and referenced to the sodium D line (589 nm). Melting points were recorded on a Thomas-Hoover Unimelt and are uncorrected. ^{1}H NMR and ^{13}C NMR data are reported in parts per million (δ) downfield from tetramethylsilane, using the normal abbreviations.

Thin-layer chromatography (TLC) was performed using silica gel 60 F_{254} 0.2 mm plates. Visualization was accomplished using ultraviolet light or one of the following stains: 1. Ceric sulfate dihydrate (0.4 g) and ammonium molybdate tetrahydrate (4.0 g) in 10% aqueous sulfuric acid (100 mL). 2. Potassium permanganate (0.45 g) in water (100 mL). 3. Anisaldehyde (2 mL), acetic acid (10 mL), and sulfuric acid (2 mL) in 95% ethanol (85 mL). Flash chromatography was carried out using silica gel 60 (230−400 mesh). Solvent systems are reported as volume percent mixtures. Concentration or evaporation of solvent refers to removal at reduced pressure using a Büchi rotary evaporator and a Büchi aspirator pump. All inorganic solutions are aqueous and concentrations are indicated in percent weight, except for saturated sodium chloride and saturated sodium bicarbonate. The following solvents and reagents were distilled from the indicated agent under argon: tetrahydrofuran (THF) and diethyl ether from sodium benzophenone ketyl; dichloromethane, acetonitrile, and triethylamine from calcium hydride. Dimethyl sulfoxide (DMSO) was distilled from calcium hydride under reduced pressure. Chloroform was used as supplied by Fisher Scientific (certified A.C.S.). Chromium(II) chloride was used as supplied by Strem Chemicals or Aldrich Chemical. All other reagents were purified by literature procedures. All reactions were performed under argon unless otherwise noted.

(*E*)-2,6-Dimethylhepta-2,5-dien-1-ol, Tetrahydropyranyl Ether, 4. To a solution of 5-bromo-4-methyl-2-butene **2** (2.00 g, 12.27 mmol) dissolved in 25 mL of acetonitrile were added triphenylphosphine (3.22 g, 12.27 mmol) and tetramethylpiperidine (0.075 g, 0.53 mmol). The solution was refluxed under argon for 24 h and then cooled to room temperature. The bulk solvent was removed with a vigorous stream of nitrogen, followed by concentration in vacuo. The viscous oil was heated to 80 °C under argon and washed with 15 mL of benzene, cooled, and concentrated in vacuo. Hexamethylphosphoramide (HMPA, 4.4 mL) and tetrahydrofuran (THF, 43 mL) were added under argon, followed by a solution of 0.78 M potassium hexamethyldisilazide in THF (13.5 mL, 10.52 mmol), freshly prepared from potassium hydride and hexamethyldisilazane. The reaction was heated to 70 °C and then cooled to room temperature over 1 h with stirring. The resulting deep red solution was cooled to −78 °C, and 1-(tetrahydropyranyloxy)-2-propanone **3** (1.39 g, 8.76 mmol) was added dropwise to the reaction. After the reaction stirred for 20 min, the cold bath was removed, and the reaction was allowed to warm to room temperature over 3 h. The reaction was diluted with 40 mL of water and 15 mL of petroleum ether. Following separation of the layers, the aqueous layer was extracted with petroleum ether. The combined organic layers were dried ($MgSO_4$) and concentrated to give a semisolid. The crude product was dissolved in a minimum amount of warm hexane, allowing the solution to cool and filtering off the triphenylphosphine oxide crystals. The resulting hexane solution was concentrated by rotary evaporation. Flash chromatography over silica gel (5% ethyl acetate in hexane) afforded the *Z*-alkene **4** (1.74 g, 88%) as a colorless oil. ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.34 (br t, J = 7.2 Hz, 1H), 5.07 (t, J = 7.3 Hz, 1H), 4.59 (t, J = 3.5 Hz, 1H), 4.12 (d, J = 11.5 Hz, 1H), 4.11 (d, J = 11.5 Hz, 1H), 3.89 (m, 1H), 3.51 (m, 1H), 2.76 (dd J = 7.3, 7.3 Hz, 2H), 1.9−1.5 (m, 6H), 1.83 (s, 3H), 1.68 (s, 3H), 1.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.7, 131.6, 128.2, 122.8, 97.4, 65.3, 62.1, 30.6, 26.8, 25.6, 25.5, 21.7, 19.5, 17.6. IR (neat) 2942, 1453 cm^{-1}. HRMS calcd for $C_{14}H_{23}O_2$ (M^+ − H) 223.1698, found 223.1692.

(*E*)-2,6-Dimethylhepta-2,5-diene-1-ol, 5. The tetrahydropyranyl ether **4** (3.60 g, 16.0 mmol) was dissolved in 125 mL of absolute ethanol. Pyridinium *p*-toluenesulfonate (PPTS, 0.42 g, 1.6 mmol) was added, and the flask was capped and heated to 60 °C for 4 h. The solution was cooled to room temperature, and the solvent was removed by rotary evaporation. The crude product was dissolved in ether, washed with saturated sodium bicarbonate solution and then with brine, and then dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. The resulting oil was purified by flash chromatography over silica gel (20% ethyl acetate in hexane), followed by distillation to provide the alcohol **5** (1.623 g, 72%) as a colorless oil: bp 61−65 °C @0.21 mm Hg. ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.30 (br t, J = 7.5 Hz, 1H), 5.08 (br t, J = 7.1 Hz, 1H), 4.16 (d, J = 5.8 Hz, 2H), 2.75 (dd, J = 7.2, 7.2 Hz, 2H), 1.81 (s, 3H), 1.70 (s, 3H), 1.64 (s, 3H), 1.18 (br t, J = 5.8 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.2, 132.0, 127.2, 122.7, 61.6, 26.6, 25.6, 21.3, 17.7. IR (neat) 3324, 2971, 1674 cm^{-1}. HRMS calcd for $C_9H_{16}O$ (M^+) 139.1123, found 139.1117.

(2*R*,3*S*)-2-Methyl-3-(3-methyl-2-butenyl)oxiranemethanol, 6. Crushed calcium hydride (76 mg, 1.8 mmol) and activated silica gel (0.163 g, 2.7 mmol) were weighed under argon into a flask. Dry dichloromethane (110 mL) was added, and the reaction was cooled to −30 °C. Titanium tetraisopropoxide (4.1 mL, 19.2 mmol) and D-(−)-diisopropyl tartrate (5.6 mL, 26.2 mmol) were added, and the reaction was stirred for 15 min. A 4.77 M solution of *tert*-butyl hydroperoxide (7.2 mL, 34.3 mmol) was added, and the reaction was stirred an additional 15 min while maintaining the temperature between −30 °C and −20 °C. The allylic alcohol **5** (2.60 g, 18.5 mmol) was added to the reaction, and the reaction was placed in a −20 °C freezer for 18 h. The reaction was warmed to 0 °C, and a solution of sodium hydroxide (8.6 g, 0.21 mmol) in 30 mL of brine was added to the reaction, followed by addition of 30% hydrogen peroxide (21 mL, 0.19 mmol). After the reaction had stirred for 2 h, the reaction was warmed to room temperature and stirred an additional 7 h. The reaction was diluted with brine, and following separation of the layers, the aqueous layer was washed with methylene chloride. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to an oil. Flash chromatography over silica gel (30% ethyl acetate in hexane) provided the epoxy alcohol **6** (2.48 g, 90.6%) as a colorless oil: $[\alpha]^{25}_D$ = +22.8 (*c* 0.62, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.15 (br t, J = 6.0 Hz, 1H), 3.69 (d, J = 6.2 Hz, 2H), 2.87 (dd, J = 6.6, 6.6 Hz, 1H), 2.40 (m, 1H), 2.23 (m, 1H), 1.72 (s, 3H), 1.63 (s, 3H), 1.39 (s, 3H), 1.25 (t, J = 6.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.7, 118.7, 64.2, 64.0, 60.8, 27.4, 25.7, 20.2, 17.9; IR (neat) 3432, 2973, 1449 cm^{-1}. HRMS calcd for $C_9H_{17}O_2$ (M^+ + H) 157.1229, found 157.1233. ^{31}P NMR analysis of derivative[9] (10% C_6D_6 in C_6H_6, 162 MHz) δ 133.3 (90.3%), 132.1 (9.7%), 81% ee.

(2*R*,3*R*)-3-Chloro-2,6-dimethyl-5-heptene-1,2-diol, 7. To a solution of the epoxy alcohol **6** (1.00 g, 6.4 mmol) in dimethyl sulfoxide (DMSO, 64 mL) was added ammonium chloride (0.68 g, 12.7 mmol). Titanium tetraisopropoxide (2.05 mL, 9.58 mmol) was added dropwise, under argon, with vigorous stirring. The reaction became yellow within several minutes. After the reaction had stirred for 1.5 h at room temperature, ether (120 mL) was added, followed by slow addition of 5% H_2SO_4 (60 mL). After the layers separated, the aqueous layer was extracted with ether, and the organic layers were dried

(17) We thank Dr. Darko Kantoci of Loma Linda University for his assistance is this separation.

($MgSO_4$), filtered, and concentrated. Flash chromatography over silica gel (40% ethyl; acetate in hexane) provided the chloro diol **7** as white crystals (0.93 g, 76%): mp 36−37 °C. $[\alpha]^{25}_D = +33.9$ (*c* 0.66, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.23 (br t, J = 6.2 Hz, 1H), 4.16 (dd, J = 10.6, 3.0 Hz, 1H), 3.62 (d, J = 6.5 Hz, 2H), 2.51 (m, 1H), 2.49 (s, 1H), 2.35 (m, 1H), 2.00 (t, J = 6.5 Hz, 1H), 1.74 (s, 3H), 1.64 (s, 3H), 1.25 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.6, 120.3, 74.8, 70.8, 67.5, 31.8, 25.8, 20.2, 18.0. IR (neat) 3400, 2977, 1673.5, 1451 cm^{-1}. HRMS calcd for $C_9H_{18}ClO_2$ ($M^+ + H$) 193.1000, found 1193.0995.

(2*R*,3*R*)-3-Chloro-2,6-dimethyl-1-[(1,1-dimethylethyl)-dimethylsilyloxy]-5-hepten-2-ol, 8. To a solution of the chloro diol **7** (0.472 g, 2.45 mmol) in anhydrous dimethylformamide (5.5 mL) was added imidazole (0.416 g, 6.12 mmol) and *tert*-butyldimethylsilyl chloride. After the reaction had stirred at room temperature for 10 h, the reaction was quenched with hexane and water. After the layers were separated, the aqueous layer was extracted with hexanes. The organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography of the crude product over silica gel (5% ethyl acetate in hexane) provided 0.72 g of the silyl ether **8** as a colorless oil (95%). $[\alpha]^{25}_D = +22.8$ (*c* 0.62, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.23 (m, 1H), 4.04 (dd, J = 10.7, 2.9 Hz, 1H), 3.61 (d, J = 9.9 Hz, 1H), 3.60 (d, J = 9.9 Hz, 1H), 2.57−2.50 (m, 1H), 2.55 (s, 1H), 2.45−2.30 (m, 1H), 1.74 (s, 3H), 1.63 (s, 3H), 1.25 (s, 3H), 0.91 (s, 9H), 0.08 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.1, 120.9, 74.4, 70.0, 67.9, 31.5, 25.82, 25.77, 21.3, 18.2, 18.0, −5.51, −5.53. IR (neat) 3567, 2955, 1464 cm^{-1}. HRMS calcd for $C_{15}H_{32}ClO_2Si$ ($M^+ - H$) 307.1860, found 307.1858.

(2*R*,3*R*,5*S*)-5-Bromo-3-chloro-2,6,6-trimethyltetrahydropyran-2-methanol, 13. To a solution of the alkenol **8** (86.8 mg, 0.28 mmol) in dichloromethane (8.5 mL) was added tetrabromocyclohexadienone (TBCO, 139 mg, 0.34 mmol). The reaction flask was covered in aluminum foil and was stirred under argon at room temperature for 16 h. The reaction was quenched with ether (20 mL) and 1 N sodium hydroxide solution (10 mL). After the layers were separated, the aqueous layer was extracted with ether. The organic layers were dried ($MgSO_4$), filtered, and concentrated to an oil. Flash chromatography over silica gel (5% benzene in hexane) provided several fractions. The third fraction contained **11a** and **12a** and was concentrated to give an oil (76.3 mg, 70% yield). The oil was dissolved in THF (2.5 mL), and a THF solution of tetrabutylammonium fluoride (TBAF, 0.15 mL, 150 mmol) was added. After the reaction had stirred for 24 h, the reaction was concentrated to a semisolid. Flash chromatography over silica gel (20% ethyl acetate in hexane) provided the alcohol **13** as white crystals (18.1 mg, 24% based on **8**). mp 77−80 °C. $[\alpha]^{25}_D = +2.8$ (*c* 0.88, CH_2Cl_2). ^{1}H NMR (400 MHz, C_6D_6) δ 3.59 (m, 2H), 3.25 (dd, J = 12.9, 4.0 Hz, 1H), 3.19 (dd, J = 12.6, 4.5 Hz, 1H), 2.19 (ddd, J = 12.9, 12.9, 12.9 Hz, 1H), 2.00 (ddd, J = 13.1, 4.2, 4.2 Hz, 1H), 1.52 (s, 3H), 1.38 (s, 3H), 1.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 77.6, 76.6, 63.2, 61.3, 53.3, 37.7, 30.5, 25.4, 21.9. IR (neat) 3494, 2984 cm^{-1}. HRMS calcd for $C_9H_{17}O_2ClBr$ ($M^+ - H$) 271.0100, found 271.0103.

(2*R*,3*R*,5*S*)-5-Bromo-3-chloro-2,6,6-trimethyltetrahydropyran-2-carboxaldehyde, 14. To a solution of DMSO (60 μL, 0.77 mmol) in dichloromethane (1.5 mL) at −78 °C was added oxalyl chloride (50 μL, 0.57 mmol). The reaction was stirred for 30 min, at which point the alcohol **13** (0.104 g, 0.38 mmol) was added to the reaction as a dichloromethane solution (2.5 mL). After the reaction had stirred for an additional 30 min, triethylamine (0.20 mL, 1.4 mmol) was added. The reaction was warmed to 0 °C and quenched with a 10% solution of potassium dihydrogen phosphate. After the layers were separated, the aqueous layer was extracted with dichloromethane. The organic layers were dried ($MgSO_4$), filtered, and concentrated to a solid. Flash chromatography over silica gel provided the aldehyde **14** as white crystals (0.101 g, 98%). mp 49−50 °C. $[\alpha]^{25}_D = +78.3$ (*c* 0.46, $CHCl_3$). ^{1}H NMR (360 MHz, C_6D_6) δ 9.54 (br s, 1H), 3.21 (dd, J = 12.8, 4.0 Hz, 1H), 3.06 (dd, J = 12.7, 4.4 Hz, 1H), 2.42 (ddd, J = 12.9, 12.9, 12.9 Hz, 1H), 2.09 (ddd, J = 13.2, 4.3, 4.3 Hz, 1H), 1.12 (s, 3H), 1.09 (s, 3H), 1.03 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.7, 80.0, 77.5, 58.6, 52.9, 37.6, 29.3, 23.2, 22.4. IR (neat) 2988, 1736 cm^{-1}. HRMS calcd for $C_9H_{15}O_2ClBr$ ($M^+ + H$) 268.9944, found 268.9934.

Aplysiapyranoid C, 1c, and (2*R*,3*R*,5*S*)-5-Bromo-3-chloro-2-ethenyl-2,6,6-trimethyltetrahydropyran, 15. To a glass ampule containing chromium(II) chloride (27 mg, 0.22 mmol) was added the aldehyde **14** (9.9 mg, 0.037 mmol) in THF (0.4 mL) under argon. Chloroform was added (7 μL, 0.083 mmol), and the ampule was sealed under argon. The ampule was placed in a oil bath at 60 °C for 56 h, at which point the ampule was cooled to room temperature and opened, and the reaction was quenched with ether (2 mL) and water (2 mL). After the layers separated, the aqueous layer was extracted with ether, and the organic layers were dried ($MgSO_4$), filtered, and concentrated to give a yellow oil (7.5 mg, 68%) containing a 5:5:3 mixture of **1c**:**15**:**14**, as determined by ^{1}H NMR. The ^{1}H NMR for **1c** matched that reported in the literature.[3] Compound **15**: ^{1}H NMR (C_6D_6, 360 MHz) δ 6.11 (dd, J = 17.6, 11.2 Hz, 1H), 5.34 (d, J = 17.6 Hz, 1H), 5.04 (d, J = 11.1 Hz, 1H), 3.36 (dd, J = 12.6, 4.0 Hz, 1H), 3.24 (m, 1H), 2.30 (ddd, J = 12.6, 12.6, 12.6 Hz, 1H), 2.13 (m, 1H), 1.31 (s, 3H), 1.21 (s, 3H), 1.20 (s, 3H).

(2*R*,3*R*)-3-Chloro-2,6-dimethyl-2-(triethylsilyloxy)-5-hepten-1-ol, 16. A solution of 4,4′-dimethoxytrityl chloride (0.14 g, 0.73 mmol) in dichloromethane (4 mL) was prepared under argon, and the reaction was cooled to 0 °C. Collidine was added (0.2 mL, 1.5 mmol), followed by the chloro diol **7** (0.130 g, 0.68 mmol). After the reaction had stirred for 1.5 h, collidine was added (0.6 mL, 4.5 mmol), followed by triethylsilyl trifluoromethanesulfonate (0.5 mL, 2.2 mmol). The reaction was heated to 40 °C in an oil bath for 16 h, at which point the reaction was diluted with dichloromethane (5 mL) and quenched with saturated sodium bicarbonate solution (5 mL). After the layers were separated, the aqueous layer was extracted with dichloromethane, and the organic layers were dried ($MgSO_4$), filtered, and concentrated to a brown oil. The oil was redissolved in dichloromethane and filtered through silica gel in a filter funnel using 10% ethyl acetate in hexane. The resulting solution was concentrated to a yellow oil. The oil was dissolved in dichloromethane (10 mL), and to this solution was added dodecanethiol (0.35 mL, 1.5 mmol). The reaction was cooled to 0 °C, and trifluoroacetic acid (44 μL, 0.57 mmol) was added. After the reaction had stirred for 1.5 h, the reaction was quenched with saturated sodium bicarbonate solution (5 mL). After the layers were separated, the aqueous layer was extracted with dichloromethane, and the organic layers were dried ($MgSO_4$), filtered, and concentrated onto silica gel. Flash chromatography over silica gel (10% ethyl acetate in hexane) provided the silyl ether **16** as a colorless oil (0.186 g, 90%). $[\alpha]^{25}_D = +28.5$ (*c* 0.85, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.21 (br t, J = 7.5 Hz, 1H), 3.86 (dd, J = 11.1, 2.3 Hz, 1H), 3.65 (d, J = 11.1 Hz, 1H), 3.60 (d, J = 11.1 Hz, 1H), 2.65 (m, 1H), 2.34 (m, 1H), 1.85 (br s, 1H), 1.73 (s, 3H), 1.63 (s, 3H), 1.35 (s, 3H), 0.97 (t, J = 7.9 Hz, 9H), 0.65 (q, J = 7.9 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.0, 121.2, 77.9, 69.9, 67.7, 31.4, 25.8, 22.6, 18.0, 7.0, 6.7. IR (neat) 3428, 2957, 1458, 1238 cm^{-1}. HRMS calcd for $C_{15}H_{32}ClO_2Si$ ($M^+ + H$) 307.1860, found 307.1868.

(*E*)-(3*R*,4*R*)-1,4-Dichloro-3,7-dimethylocta-1,6-dien-3-ol, 17. A solution of DMSO (90 μL, 1.27 mmol) in dichloromethane (2 mL) under argon was cooled to −78 °C. Oxalyl chloride was added (80 μL, 0.92 mmol), and the reaction was stirred for 30 min. A solution of the alcohol **16** (0.183 g, 0.616 mmol) was added, and the reaction was stirred an additional 30 min. Triethylamine was added (0.26 mL, 1.87 mmol), and the reaction was stirred for 10 min, at which point the reaction was warmed to −20 °C and quenched with a 10% potassium dihydrogen phosphate solution. After the layers were separated, the aqueous layer was extracted with dichloromethane, and the organic layers were dried ($MgSO_4$), filtered, and concentrated. Flash chromatography over silica gel (5% ethyl acetate in hexane) provided the aldehyde (0.166 g, 88% yield). $[\alpha]^{25}_D = +9.4$ (*c* 1.10, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 360 MHz) δ 9.63 (s, 1H), 5.19 (br t, J = 7.0 Hz, 1H), 3.85 (dd, J = 10.5, 2.9

Hz, 1H), 2.63 (m, 1H), 2.36 (m, 1H), 1.73 (s, 3H), 1.62 (s, 3H), 1.40 (s, 3H), 0.97 (t, J = 7.8 Hz, 9H), 0.65 (q, J = 7.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.9, 135.1, 120.0, 81.5, 67.6, 30.7, 25.8, 21.2, 18.0, 6.9, 6.6. IR (neat) 2957, 1738, 1456, 1238 cm^{-1}. HRMS calcd for $C_{15}H_{30}ClO_2Si$ (M^+) 305.1704, found 305.1700.

To a mixture of chromium(II) chloride (0.37 g, 3.0 mmol) in THF (1.5 mL) under argon was added chloroform (98 μL, 1.17 mmol). The reaction was heated to 65 °C for 10 min, by which time the solution had turned dark red. The above aldehyde (0.139 g, 0.46 mmol) was added as a solution in THF (1.6 mL), and the reaction was stirred at 65 °C for 4.5 h. The reaction was cooled to room temperature, diluted with ether (5 mL), and quenched with water (6 mL). Using centrifugation to separate the layers, the organic layer was removed and the aqueous layer was extracted with ether. The organic layers were dried ($MgSO_4$), filtered, and concentrated to an oil. The oil was washed through silica gel in a fritted funnel using 1% ethyl acetate in hexane, and the resulting solution was concentrated to give the vinyl chloride as a colorless oil (0.1054 g, 69%).

The vinyl chloride (12.1 mg, 0.036 mmol) was dissolved in dichloromethane (3 mL) and cooled to 0 °C in a polyethylene tube open to air. Pyridine (50 μL) was added, and hydrogen fluoride−pyridine was added in portions, until TLC indicated that the reaction was complete (approximately 300 μL). The reaction was quenched with saturated sodium bicarbonate solution. After the layers were separated, the aqueous layer was extracted with dichloromethane, and the organic layers were dried ($MgSO_4$), filtered, and concentrated to an oil. Flash chromatography over silica gel (10% ethyl acetate in hexane) provided the dichloro alcohol **17** as a colorless oil (6.9 mg, 86%). $[\alpha]^{25}_D$ = +20.9 (*c* 0.118, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.36 (d, J = 13.3 Hz, 1H), 6.08 (d, J = 13.3 Hz, 1H), 5.21 (br t, J = 7.0 Hz, 1H), 3.81 (dd, J = 10.2, 3.4 Hz, 1H), 2.58 (m, 1H), 2.32 (m, 2H), 1.73 (s, 3H), 1.62 (s, 3H), 1.41 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.1, 134.9, 120.4, 120.2, 75.3, 71.7, 31.8, 25.7, 24.6, 18.1. IR (neat) 3459, 2977, 1622, 1451, 1267 cm^{-1}.

Aplysiapyranoid C, 1c. To a solution of the dichloroalkenol **17** (36.0 mg, 0.161 mmol) in nitromethane (1.1 mL) was added TBCO (135 mg, 0.33 mmol). The flask was covered with aluminum foil, and the reaction was stirred at room temperature under argon for 12 h. The reaction was diluted with dichloromethane (3 mL), then washed with sodium hydroxide solution (1 N). The organic solution was dried ($MgSO_4$), filtered, and concentrated to an oil. The oil was dissolved in hexane and filtered through a plug of silica gel using 5% ethyl acetate in hexane. The resulting solution was concentrated, and flash chromatography of the resulting oil (10% benzene in hexane) provided aplysiapyranoid C **1c** (21.1 mg, 43%). The ^{1}H NMR, ^{13}C NMR, and IR spectra of **1c** matched those reported in the literature.[3] Further purification was accomplished using reverse phase HPLC (acetonitrile/water). $[\alpha]^{25}_D$ = +58.4 (*c* 0.25, $CHCl_3$). lit. $[\alpha]^{25}_D$ = +52 (*c* 1.0, $CHCl_3$).[3]

(2*S*,3*RS*)-3-(Chloromethyl)-2,5-dimethyl-4-hexene-1,2-diol, 9. Using a gas dispersion tube, hydrogen chloride was bubbled into dichloromethane to give a solution 0.17 M in hydrogen chloride (titrated against 0.15 M sodium hydroxide). The hydrogen chloride solution (41 mL, 7.0 mmol) was cooled to −78 °C under argon. Titanium tetraisopropoxide (0.9 mL, 4.2 mmol) was added. To the cloudy solution was added the epoxy alcohol **6** (0.59 g, 3.8 mmol) as a solution in dichoromethane (6 mL). The reaction was placed in a −25 °C freezer for 12 h, followed by quenching with saturated sodium bicarbonate solution. After the layers were separated, the aqueous layer was extracted with dichloromethane. The organic layers were dried ($MgSO_4$), filtered, and concentrated onto silica gel. Flash chromatography over silica gel (40% ethyl acetate in hexane) provided the chloromethyl diol **9** as a 2.8:1 mixture of two diastereomers (0.33 g, 45%), as well as the expected chloro diol **7** (0.15 g, 20%). Major diastereomer of **9**: ^{1}H NMR (DMSO-d_6, 360 MHz) δ 5.05 (br d, J = 10.6 Hz, 1H), 3.96 (dd, J = 10.3, 3.1 Hz, 1H), 3.46 (dd, J = 10.5, 10.5 Hz, 1H), 3.19 (d, J = 10.8 Hz, 1H), 3.18 (d, J = 10.8 Hz, 1H), 2.63 (ddd, J = 10.5, 10.5, 3.1 Hz, 1H), 1.70 (s, 3H), 1.54 (s, 3H), 1.02 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 121.1, 74.6, 67.9, 47.7, 45.6, 26.2, 22.3, 18.6. Minor diastereomer of **9**: ^{1}H NMR (DMSO-d_6, 360 MHz) δ 4.93 (br d, J = 10.1 Hz, 1H), 3.96 (m, 1H), 3.51 (d, J = 8.5 Hz, 1H), 3.41 (d, J = 8.5 Hz, 1H), 3.33 (dd, J = 7.9, 5.4 Hz, 1H), 2.82 (m, 1H), 1.67 (s, 3H), 1.62 (s, 3H), 1.07 (s, 3H). IR (neat, mixture of diastereomers) 3410, 2980, 1470 cm^{-1}. HRMS (mixture of diastereomers) calcd for $C_9H_{18}ClO_2$ 193.0995, found 193.1000.

The structure of the major diastereomer of **9** was confirmed by preparation of the monoacetate. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.96 (br d, J = 9.9 Hz, 1H), 4.08 (d, J = 9.9 Hz, 1H), 4.04 (dd, J = 8.4, 6.7 Hz, 1H), 3.83 (d, J = 9.9 Hz, 1H), 3.49 (dd, J = 8.4, 6.7 Hz, 1H), 3.35 (m, 1H), 2.02 (s, 3H), 1.75 (s, 3H), 1.72 (s, 3H), 1.44 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 136.3, 120.6, 89.0, 76.9, 72.2, 47.6, 26.0, 22.0, 18.4, 17.9. IR (neat) 2977, 1738, 1447 cm^{-1}.

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Supporting Information Available: Copies of NMR spectra (23 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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