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SYNTHESES AND NMR ANALYSES OF THE EIGHT GEOMETRIC ISOMERS OF 3,6,8-DODECATRIEN-1-OL, SUBTERRANEAN TERMITE TRAIL PHEROMONE

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Abstract: Eight geometric isomers of 3,6,8-dodecatrien-1-ol **1**, the trail-following pheromone of subterranean termites (Reticulitermes sp. Banks), were synthesized via a Wittig olefination reaction. The convergent syntheses of **1** consisted of a combination of two fragments, each containing an olefin with a fixed configuration, by formation of a third double bond to give a mixture of two geometric isomers. The mixtures of **1** were resolved by recycle high-performance liquid chromatography methods. ^{1}H and ^{13}C NMR peak assignments of the individual isomers were accomplished by homonuclear COSY, and one-bond CH correlation spectroscopy.

Introduction

The semiochemical which is responsible for eliciting trail-following behavior in the subterranean termite, Reticulitermes virginicus, has been isolated and its structure determined to be (Z,Z,E)-3,6,8-dodecatrien-1-ol[1]. This material is nonspecies specific, being attractive to other Reticulitermes spp., and to termites of other genera, i.e., Coptotermes, Trinervitermes, Amitermes and Schedorhinotermes.[2] The nonspecificity of this pheromone is unusual since, generally, insect pheromones that have been characterized are species specific and are unique for each species within a genus. The response of the subterranean termites to this pheromone suggests a surprising conservation of receptor site specificity for the pheromone eliciting trail-following behavior. However, when these termites are offered a choice between conspecific and heterospecific pheromone trails of equivalent concentration, the conspecific trail is preferred.[3] It is proposed that isomeric or homologous blends of pheromones or other species specific cues may be involved in the species specificity of the trail-following behavior.

So far, five possible isomers of 3,6,8-dodecatrien-1-ol **1** have been synthesized, and tested individually for their biological activity.[4] However, all eight geometric isomers have not yet been synthesized and their activity compared. Comparison of the biological activity of the eight isomers, singly and in combination, may shed light on the possible factors determining recruitment and orientation of individual termites in colonies where species distributions overlap geographically, i.e., in trail recognition

by sympatric species.

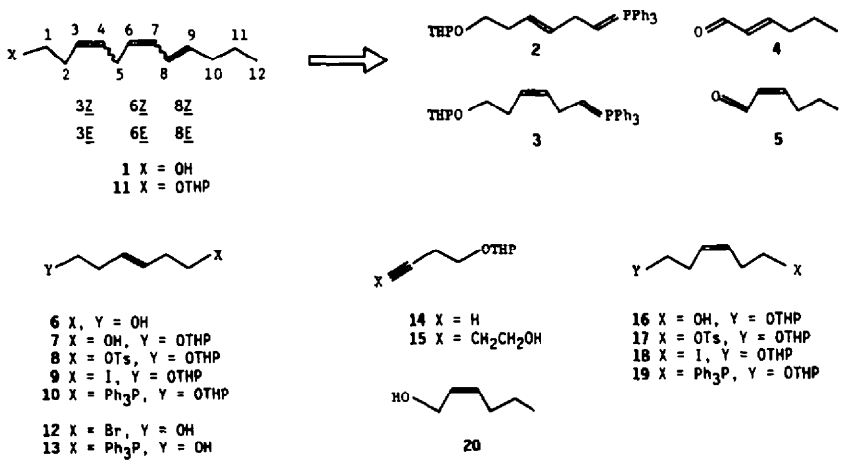
Described herein is the route for the synthesis of all geometric isomers of **1**. Also, ^{13}C and ^{1}H spectral peak assignments of the individual isomers are presented as a basis for structural and spectral assignments of other pheromones and biologically active unsaturated alcohols and fatty acids.[5] Also described are preparative recycle high-performance liquid chromatography[6] (R-HPLC) resolution of these unsaturated alcohols which are frequently difficult to resolve by usual methods.[7]

Synthesis

Wittig olefin syntheses appeared to be the most general and direct route to the eight geometric isomers of 3,6,8-dodecatrien-1-ol **1**. Other synthetic methods are either too stereospecific[8] or lack the generality[1b,5a,9] necessary for the syntheses of all stereoisomers.

The convergent syntheses of **1**, summarized in Scheme 1, combine two fragments, an alkenylphosphorane (**2** or **3**) and 2-hexenal (**4** or **5**), which are either commercially available or obtained through stereospecific synthesis in a few steps. The combination of these fragments affords (6Z)- and (6E)-isomeric mixtures, which are resolved chromatographically by recycle-HPLC.

Scheme 1



The phosphorane **2** was prepared from (E)-β-hydromuconic acid in six steps. (E)-β-Hydromuconic acid was reduced with lithium aluminum hydride (LAH) to the diol **6**, followed by conversion of **6** to the mono-THP ether **7** by the addition of 3,4-dihydro-2H-pyran and camphorsulfonic acid in methylene chloride. The mono-ether **7** was converted into a tosylate **8** with p-toluenesulfonyl chloride and pyridine followed by the displacement of tosylate by iodide using sodium iodide in acetone to afford **9**. The iodide **9** was refluxed for 18 h in benzene with triphenylphosphine to form **10**.

The phosphonium iodide **10** was converted into the corresponding ylide **2** by reaction with lithium hexamethyldisilazide (1.5 equiv.) in tetrahydrofuran (THF). The ylide was then treated with 1.5 equiv. of (E)-2-hexenal **4** to afford the 3,6,8-dodecatrien-1-ol **1** (15.4%) and its THP ether **11** (80.2%) after chromatographic purification on silica gel. The THP ether **11** was cleaved with pyridinium p-toluenesulfonate (PPTS)[10] in ethanol to give **1** (88% from **11**). The combined overall yield of **1** was 86% from **9**. After taking advantage of the stereochemistry present in the readily available starting materials, i.e., (E)-β-hydromuconic acid and **4**, (3E,6Z,8E)- and (3E,6E,8E)-isomers of **1** (mixture A) were synthesized in seven steps.

In an attempt to develop a shorter route to the above isomers of **1**, monobromide[11] **12** was prepared from the diol **6** in 44% yield, and was submitted to the Wittig reaction as described above without protection of the hydroxyl group. The gummy phosphonium bromide salt[7b] **13** does not react as readily as **10** with lithium hexamethyldisilazide (2.4 equiv.) in THF, and the overall yield of **1** from **12** was 36%.

Two isomers of **1** with (3Z)- and (8Z)-configuration, i.e., (3Z,6Z,8Z)- and (3Z,6E,8Z)-isomers (mixture B), were prepared from the corresponding phosphorane **3** and (Z)-2-hexenal **5** in the same manner as described above. The phosphorane **3**, derived from the alcohol **16**, was prepared from 3-butyn-1-ol THP ether **14** in five steps. The alkyne **14** was reacted with ethyl magnesium bromide (1.1 equiv.) in THF, and the subsequent treatment of the Grignard solution with excess ethylene oxide (4 equiv.) afforded the monoprotected 3-hexyn-1,6-diol **15** (51%). The alkyne **15** was then converted into the monoprotected (Z)-3-hexen-diol **16** (92%) by hydrogenation [1b] with Lindlar catalyst in ethanol poisoned with quinoline. The (Z)-configuration of **16** was confirmed by NMR spectral analysis and comparison with the (E)-alkene **7** as follows: (1) coupling constant of the olefinic protons of **16**, 11 Hz (**7**, 15 Hz); (2) chemical shifts of the olefinic carbons of **16**, 129.5 and 127.5 ppm (**7**, 130.1 and 128.1 ppm); and (3) chemical shifts of the allylic carbons of **16**, 30.5 and 27.9 ppm (**7**, 35.9 and 33.0 ppm).

The hexenal **5** was prepared by oxidation of the (Z)-2-hexen-1-ol **20** with excess activated manganese dioxide[5c,13,14] in dry methylene chloride. The oxidation of **20** went with 95% retention of (Z)-configuration, and the aldehyde **5** (recovered in 72% yield) was used immediately for the Wittig reaction as a mixture without isolation of the product from **20**. The (Z)-configuration of **5** was confirmed by NMR analyses and comparison with the (E)-hexenal **4** as follows: (1) coupling constant of the olefinic protons of **5**, 11 Hz (**4**, 16 Hz); (2) chemical shift of the aldehydic proton of **5**, 10.1 ppm (**4**, 9.45 ppm); and (3) ^{13}C spectra of the aldehydic, olefinic, and allylic carbons of **5**, 190.9d, 153.1d, 130.3d and 29.8t (**4**, 194.0d, 158.7d, 133.0d and 34.5t). The same oxidation reaction run in dry acetone gave 50% yield of aldehyde in Z:E (4:1) mixture.

The Wittig reactions between **3** and **4**, and between **2** and **5** afforded two other

mixtures, i.e., (3Z,6Z,8E)- and (3Z,6E,8E)-isomers (mixture C), and (3E,6Z,8Z)- and (3E,6E,8Z)-isomers (mixture D), respectively. The approximate ratio of the two isomers, (6Z):(6E), in each of the four mixtures was determined to be 7:3, favoring the (6Z)-configuration, determined from integration of the $C^5\underline{H}_2$ allylic and olefinic ^1H resonances.

The electron impact mass spectra of the four isomeric mixtures of 1 had the same fragmentation peaks as those obtained from the isolated trail-following pheromone,[16] i.e., m/z 180, 133, 119, 105, 91, 79, 67, 55 and 43. The spectra showed a molecular ion at m/z 180, and a pattern characteristic of a straight-chain primary alcohol with conjugated double bonds. Other smaller fragmentation peaks, i.e., m/z 162, 149, 121, 105 and 93 were also present, and were as described previously for the 3,6,8-dodecatrien-1-ol.[1a] Results of M^+ measurements by high resolution mass spectrometry (HRMS) were as follows: calcd. for $C_{12}H_{20}O_1$: m/z 180.1515, Found: m/z 180.1520 (mixture A); m/z 180.1514 (mixture B); m/z 180.1515 (mixture C); m/z 180.1517 (mixture D). Ultraviolet (UV) spectroscopy showed a strong absorption peak at 234 nm (in methanol) for all four isomeric mixtures.

Resolution of the Isomers by Recycle-HPLC

Complete baseline separations of the two components in each of the three isomeric mixtures, i.e., mixtures B, C and D, were accomplished on a normal-phase recycle HPLC. A mobile phase of hexane-acetone (9:1), at a flow rate of 3.2 mL/min, and recycling at intervals of 64 to 90 min, resolved the isomers (2 to 7 mg) in 4 to 14 recycles (Table 1). Mixture A, which was unresolvable on a normal phase column, was resolved on a reversed-phase recycle-HPLC, with a solvent system of acetonitrile:water (8:2), at a flow rate of 3.4 mL/min. The recycling was carried out at 45 min intervals and a complete baseline separation of the two components in mixture A was obtained in four recycles.[22]

Table 1. Resolution of the eight geometric isomers of 3,6,8-dodecatrien-1-ol by recycle-HPLC.

		Reversed Phase R-HPLC						Normal Phase R-HPLC				
		mg[a]	mg[b]	Interval (min)[c]	No. recycle[d]			mg[a]	mg[b]	Interval (min)[c]	No. recycle[d]	
Mixture A	(3E,6Z,8E)[e]	17	10.6	45	4	Mixture B	(3Z,6E,8Z)[e]	5	1.3	90	14	
	(3E,6E,8E)		3.5				(3Z,6Z,8Z)		2.5			
						Mixture C	(3Z,6Z,8E)[e]	7	3.8	64	4	
							(3Z,6E,8E)		1.6			
						Mixture D	(3E,6E,8Z)[e]	2	0.4	78	12	
							(3E,6Z,8Z)		0.7			

[a]Amount (mg) of isomeric mixture chromatographed.

[b]Amount (mg) of resolved isomer recovered.

[c]Interval in minutes between recycles.

[d]Number of times recycled until baseline resolution of isomers.

[e]Isomer with shorter retention time in a mixture.

NMR Analyses

The ^{1}H spectral assignments for the eight isomers of **1** were made by analyzing the COSY spectra (Table 2). The four geometric isomers with conjugated (6Z,8E)- or (6E,8Z)-double bonds had six well resolved olefinic proton signals. The values of the coupling constants between $C^{3}H$ and $C^{4}H$, $C^{6}H$ and $C^{7}H$, and $C^{8}H$ and $C^{9}H$, indicated the configurations of these double bonds. The coupling constants of (Z)- and (E)-double bonds were ca. 11 and 15 Hz, respectively. The chemical shifts of conjugated olefinic protons of these isomers had the following characteristics: (1) the terminal protons ($C^{6}H$ and $C^{9}H$) on a (Z)-double bond, i.e., $C^{6}H$ of a (6Z,8E)-isomer and $C^{9}H$ of a (6E,8Z)-isomer, had chemical shifts of 5.24-5.33 ppm; (2) the terminal $C^{6}H$ and $C^{9}H$ protons on an (E)-double bond, i.e., $C^{6}H$ of a (6E,8Z)-isomer and $C^{9}H$ of a (6Z,8E)-isomer, had chemical shifts of 5.62-5.69 ppm; (3) the internal $C^{7}H$ and $C^{8}H$ protons on a (Z)-double bond, i.e., $C^{7}H$ of a (6Z,8E)-isomer and $C^{8}H$ of a (6E,8Z)-isomer, had chemical shifts of 5.95-5.99 ppm; and (4) the internal $C^{7}H$ and $C^{8}H$ protons on an (E)-double bond, i.e., $C^{7}H$ of a (6E,8Z)-isomer and $C^{8}H$ of a (6Z,8E)-isomer, had chemical shifts of 6.28-6.33 ppm.

The $C^{6}H$ and $C^{9}H$ proton chemical shifts of the four other isomers with (6E,8E)- and (6Z,8Z)-conjugated double bonds partially overlapped with the signals of the isolated $C^{3}=C^{4}$ double bond. Overlapping of signals was also observed between the $C^{7}H$ and $C^{8}H$ protons of these four isomers. Interesting differences in the chemical shifts of the proton signals were observed when a (6Z,8Z)-diene was converted to a (6E,8E)-diene as follows: (1) the terminal $C^{6}H$ and $C^{9}H$ proton signals shifted downfield by 0.08-0.16 ppm, i.e., $C^{6}H$ (5.38 and 5.42 ppm) and $C^{9}H$ (5.48 and 5.50 ppm) of (6Z,8Z)-isomers shifted to $C^{6}H$ (5.53 and 5.54 ppm) and $C^{9}H$ (5.58 ppm) of (6E,8E)-isomers; and (2) the internal $C^{7}H$ and $C^{8}H$ protons shifted upfield by 0.23-0.28 ppm, i.e., $C^{7}H$ (6.27 and 6.29 ppm) and $C^{8}H$ (6.24 and 6.27 ppm) of (6Z,8Z)-isomers shifted to $C^{7}H$ (6.01 and 6.03 ppm) and $C^{8}H$ (5.99 and 6.01 ppm) of (6E,8E)-isomers.

The chemical shifts for the $C^{2}H_{2}$ and $C^{10}H_{2}$ allylic protons depended on the configuration of the neighboring double bond. The allylic proton signals shifted 0.05-0.13 ppm downfield when the configuration of the olefin was changed from an (E) to a (Z)-configuration. The $C^{5}H_{2}$ allylic proton chemical shift also depended on the configuration of the neighboring double bonds, i.e., $C^{5}H_{2}$ of the (3Z,6Z,8Z)-isomer (2.96 ppm) had a chemical shift further downfield than that of the (3E,6E,8E)-isomer (2.78 ppm) and its signal moved to a higher field as the (Z)-double bonds at C^{3} and C^{6} positions were converted to (E)-double bonds.

The ^{13}C spectral assignments for the eight geometric isomers were based on the one-bond CH correlation experiments (Table 3). The olefinic carbon resonances of the four isomers with conjugated (6Z,8E)- or (6E,8Z)-double bonds having well resolved olefinic proton signals were unambiguously assigned from their carbon-proton cross peaks. The olefinic carbon assignments based on the CH correlation experiments for the

Table 2. Proton spectral assignments for the eight geometric isomers of 3,6,8-dodecatrien-1-ol

	$C^1\underline{H}_2$	$C^2\underline{H}_2$	$C^3\underline{H}$	$C^4\underline{H}$	$C^5\underline{H}_2$	$C^6\underline{H}$	$C^7\underline{H}$	$C^8\underline{H}$	$C^9\underline{H}$	$C^{10}\underline{H}_2$	$C^{11}\underline{H}_2$	$C^{12}\underline{H}_3$
(3E, 6Z, 8E)	3.62t 6Hz	2.27q 6,7Hz	5.43dtt 15,7,1Hz	5.56dtt 15,7,1Hz	2,89t 7Hz	5.29dt 11,7Hz	5.99t 11Hz	6.28ddq 15,11,1Hz	5.69dt 15,7Hz	2.07q 7Hz	1.41tq 7Hz	0.90t 7Hz
(3E, 6E, 8E)	3.63t 6Hz	2.27q 6,7Hz	5.42dtt 16,7,1Hz	5.54m	2.78t 7Hz	5.54m	6.01m 14Hz	6.01m 14Hz	5.58m	2.03q 7Hz	1.38tq 7Hz	0.89t 7Hz
(3Z, 6Z, 8Z)	3.66t 7Hz	2.36q 7Hz	5.41m 11,8Hz	5.56dt 11,8Hz	2.96t 8Hz	5.38m 9,8Hz	6.27m 9Hz	6.27m 9Hz	5.50dt 9,7Hz	2.15q 7Hz	1.40tq 7Hz	0.90t 7Hz
(3Z, 6E, 8Z)	3.66t 7Hz	2.34q 7Hz	5.46dtt 11,7,1Hz	5.59dtt 11,7,1Hz	2.88t 7Hz	5.62dt 15,7Hz	6.33ddq 15,11,1Hz	5.95t 11Hz	5.33dt 11,8Hz	2.13q 8,7Hz	1.39tq 7Hz	0.91t 7Hz
(3Z, 6Z, 8E)	3.66t 6Hz	2.37q 6,7Hz	5.41dtt 11,7,2Hz	5.56dtt 11,7,2Hz	2.94t 7Hz	5.24dt 11,7Hz	5.97t 11Hz	6.31ddq 15,11,1Hz	5.69dt 15,7Hz	2.08q 7Hz	1.41tq 7Hz	0.90t 7Hz
(3Z, 6E, 8E)	3.65t 6Hz	2.34q 6,7Hz	5.44dtt 11,7,2Hz	5.56m	2.84t 7Hz	5.53m	6.03m 14,10Hz	5.99m 14,10Hz	5.58m	2.02q 7Hz	1.38tq 7Hz	0.88t 7Hz
(3E, 6Z, 8Z)	3.62t 6Hz	2.27q 6,7Hz	5.44m 15,6Hz	5.55dtt 15,6,1Hz	2.90t 6Hz	5.42m	6.29tq 11,1Hz	6.24tq 11,1Hz	5.48dt 11,8Hz	2.15q 8,7Hz	1.40tq 7Hz	0.91t 7Hz
(3E, 6E, 8Z)	3.64t 6Hz	2.28q 6,7Hz	5.43dtt 15,7,1Hz	5.58dtt 15,7,1Hz	2.82t 7Hz	5.63dt 15,7Hz	6.31ddq 15,11,1Hz	5.96t 11Hz	5.33dt 11,8Hz	2.13q 8,7Hz	1.40tq 7Hz	0.91t 7Hz

Table 3. Carbon spectral assignments for the eight geometric isomers of 3,6,8-dodecatrien-1-ol

	C^1	C^2	C^3	C^4	C^5	C^6	C^7	C^8	C^9	C^{10}	C^{11}	C^{12}
(3E, 6Z, 8E)	62.0t	35.9t	126.5d	131.7d	30.8t	126.8d	129.3d	125.3d	135.3d	34.9t	22.4t	13.7q
(3E, 6E, 8E)	62.0t	35.9t	126.9d	131.6d	35.5t	129.6d	131.2d	130.1d	133.0d	34.6t	22.5t	13.7q
(3Z, 6Z, 8Z)	62.2t	30.8t	125.8d	130.7d	25.9t	129.1d	124.0d	123.3d	132.7d	29.5t	22.7t	13.7q
(3Z, 6E, 8Z)	62.2t	30.8t	126.2d	130.2d	30.7t	131.8d	126.1d	128.4d	130.6d	29.7t	22.8t	13.7q
(3Z, 6Z, 8E)	62.2t	30.8t	125.7d	131.0d	26.1t	127.1d	129.0d	125.4d	135.3d	34.9t	22.5t	13.7q
(3Z, 6E, 8E)	62.0t	30.7t	126.1d	130.4d	30.4t	129.5d	130.8d	130.1d	133.0d	34.6t	22.5t	13.7q
(3E, 6Z, 8Z)	61.9t	35.9t	126.7d	131.5d	30.6t	128.8d	124.3d	123.3d	132.7d	29.5t	22.7t	13.7q
(3E, 6E, 8Z)	62.0t	35.9t	127.0d	131.5d	35.8t	131.8d	126.5d	128.4d	130.7d	29.7t	22.8t	13.7q

other four isomers with (6E,8E)- and (6Z,8Z)-conjugated double bonds having overlapping olefinic proton signals were verified using an empirical rule for the conjugated olefins.[12]

According to this rule if an E-configuration of the $C^b=C^c$ double bond in $C^a-C^b=C^c-C^d=C^e$ diene system is changed to a Z-configuration without altering the $C^d=C^e$ double bond, the carbon signals of C^a, C^b, C^c and C^d are shifted upfield by ca. 5, 2.5, 2 and 5 ppm, respectively, and the signal of C^e is shifted downfield by ca. 2 ppm (Table 4). Changing a Z-configuration of a $C^b=C^c$ bond to an E-configuration, therefore, will shift the carbon signals of C^a, C^b, C^c and C^d in the opposite direction, i.e., downfield, by ca. 5, 2.5, 2 and 5 ppm, respectively, and the C^e signal upfield by ca. 2 ppm. The shifts in the carbon signals were as predicted by this rule whether C^5 or C^{10} was chosen as the allylic carbon C^a, and whether the $C^6=C^7$ or $C^8=C^9$ double bond was chosen to be converted in configuration as $C^b=C^c$ double bond.

Table 4. Differences in chemical shifts (ppm) of the allylic and olefinic carbons between two isomers of 3,6,8-dodecatrien-1-ol

	C^a_5	C^b_6	C^c_7	C^d_8	C^e_9
(A) Conversion at $C^6=C^7$					
3E, 6Z, 8E → 3E, 6E, 8E	4.7	2.8	1.9	4.8	2.3
3Z, 6E, 8Z → 3Z, 6Z, 8Z	4.8	2.7	2.1	5.1	2.1
3Z, 6Z, 8E → 3Z, 6E, 8E	4.3	2.4	1.8	4.7	2.3
3E, 6E, 8Z → 3E, 6Z, 8Z	5.2	3.0	2.2	5.1	2
Averaged values[a]	4.8± 0.5	2.7± 0.3	2.0± 0.2	5.0± 0.2	2.2± 0.2
	C^a_{10}	C^b_9	C^c_8	C^d_7	C^e_6
(B) Conversion at $C^8=C^9$					
3E, 6Z, 8E → 3E, 6Z, 8Z	5.4	2.6	2	5	2
3E, 6E, 8Z → 3E, 6E, 8E	4.9	2.3	1.7	4.7	2.2
3Z, 6Z, 8E → 3Z, 6Z, 8Z	5.4	2.6	2.1	5	2
3Z, 6E, 8Z → 3Z, 6E, 8E	4.9	2.4	1.7	4.7	2.3
Averaged values[b]	5.2± 0.3	2.5± 0.2	1.9± 0.2	4.9± 0.2	2.1± 0.2

[a]Averaged differences in chemical shift between 6Z,8E and 6E,8E, and between 6E,8Z and 6Z,8Z isomers.

[b]Averaged differences in chemical shift between 6Z,8E and 6Z,8Z, and between 6E,8Z and 6E,8E isomers.

EXPERIMENTAL

All reactions were carried out under an argon atmosphere using freshly distilled solvents under anhydrous conditions. Preparative flash chromatography[17] was carried out with silica gel (Kieselgel 60H, E. Merck A.G. West Germany) with a hexane-ethyl acetate solvent system, and analytical TLC was performed on silica gel plates (HPTLC, Fertigplatten Kieselgel 60 F_{254}, Art. 5628 and RP-2 $F_{254\ S}$, Art 13726, Merck).

Mixtures B, C and D of **1** were resolved using a Model LC-908 high-performance preparative recycle liquid chromatograph (R-HPLC) with ultraviolet (UV) and refractive index (RI) detectors (Japan Analytical Industry, Tokyo, Japan). A normal phase column [Develosil 60 (10 μm), Nomura Chemical, Tokyo, Japan; 25 cm X 20 mm I.D.] was used for the preparative separation of isomers. Mixture A was resolved on a Model LC-09 recycle liquid chromatograph equipped with a JAI-ODS I reversed phase column, 20 X 250 mm (Japan Analytical Industry, Tokyo).[22]

^1H and ^{13}C NMR were recorded on a Bruker AM-500 spectrometer at 500 and 125 MHz, respectively. Chemical shifts in parts per million (ppm) for ^1H spectra were referenced to 0.2% $C\underline{H}Cl_3$ (^1H=7.25 ppm) in the deuterochloroform used as the solvent, the ^{13}C spectra were referenced to the central signal of the solvent (^{13}C=77 ppm). The spectral assignments of the products were completed using homonuclear COSY[18] and one-bond CH correlation spectroscopy[19], which are both in routine use. Each resolved isomer was used for ^1H spectral peak assignments, and the four mixtures (A, B, C and D) for the ^{13}C spectral peak assignments. The proton multiplicity for each carbon resonance was based on DEPT experiments.[20] Infrared spectra were obtained on a Nicolet 510 FT-IR spectrometer. Mass spectra were recorded on an AEI MS-12 spectrometer, with electron impact of 70 eV (EI). Molecular ion (M^+) obtained by HRMS was analyzed on a Kratos MS50 spectrometer, with 70 eV (EI) in the mass range between 68.9952 and 793.2764 mass units. Both measurements were obtained by direct introduction of the sample on a probe into the ion source.

Syntheses

(E)-3-Hexene-1,6-diol 6. (E)-β-Hydromuconic acid (7.2 g, 0.05 mol) in THF (160 mL) was added dropwise into a stirring slurry of LAH (13.5 g, 0.36 mol) in THF (120 mL) at room temperature. The temperature was allowed to rise during the addition of the acid. After stirring for 18 h at room temperature, the solution was cooled under ice, and neutralized by dropwise addition of dilute sulfuric acid. The hydrolyzed reaction mixture was extracted with ether (3 X 200 mL), and the combined organic extract was concentrated and purified by Kugelrohr distillation (bp 100-110 °C, 0.9 mm) to afford 3.99 g (69%) of **6** as colorless oil: ^1H NMR δ ppm: 3.60 ($C^1\underline{H}_2$, $C^6\underline{H}_2$), 2.23 ($C^2\underline{H}_2$, $C^5\underline{H}_2$), 5.48 ($C^3\underline{H}$, $C^4\underline{H}$). ^{13}C NMR ppm: 35.9 (t), 61.6 (t), 129.5 (d).

6-Tetrahydropyranyloxy-(E)-3-hexen-1-ol 7. To a stirring solution of **6** (0.5 g, 4.3 mmol), and 3,4-dihydro-2H-pyran (0.43 g, 5.2 mmol) in methylene chloride (9 mL), (1R)-(-)-10-camphorsulfonic acid (0.010 g, 0.043 mmol) was added, and stirred for 2 h. The mixture was dissolved in ether (12 mL), and washed with saturated brine (4 mL), saturated potassium bicarbonate (4 mL), and water (8 mL). The organic layer was concentrated, and submitted to silica gel chromatography to afford the mono-protected hexendiol **7** (61%). ^{1}H NMR δ ppm: 3.57 (C^1H_2, dt, J=7, 7), 2.23 (C^2H_2, q, J=7), 5.44 and 5.53 (C^3H, C^4H, dt, J=15, 7), 2.28 (C^5H_2, q, J=7), 3.40 and 3.71 (C^6H_2, dt, J=10, 7), THP ether 1.44-1.55 (4H, m), 1.63-1.70 (1H, m), 1.75-1.8 (1H, m), 3.45 (1H, m), 3.82 (1H, m), 4.53 (1H, m). ^{13}C NMR ppm: 19.6 (t), 25.4 (t), 30.6 (t), 33.0 (t), 35.9 (t), 61.7 (t), 62.4 (t), 66.9 (t), 98.8 (d), 128.1 (d), 130.1 (d).

6-Iodo-(E)-3-hexen-1-ol THP ether 9. The alcohol **7** (1.3 g, 6.5 mmol) and pyridine (6 mL) were cooled to -5 °C and tosyl chloride (1.6 g, 8.5 mmol) was gradually added with stirring, keeping the temperature ≤ 0 °C. After leaving the mixture at 7 °C overnight, it was poured into ice water (30 mL), and extracted with ether (3 X 30 mL). The combined organic layer was successively washed with 2.5 N HCl (2 X 30 mL), and saturated brine (2 X 15 mL) until neutral pH, dried over anhydrous sodium sulfate, and concentrated in vacuo to yield a colorless oil (98%). The tosylated hexenol **8** (2.3 g, 6.4 mmol) was dissolved in dry acetone (20 mL), NaI (2.0 g, 13 mmol) was added and the mixture was stirred overnight at room temperature. The brown suspension was poured into hexane (15 mL), filtered through a short column of silica gel, and concentrated in vacuo to give **9** (98% from **8**) ^{1}H NMR δ ppm: 3.12 (C^1H_2, t, J=7), 2.54 (C^2H_2, q, J=7), 5.44 and 5.54 (C^3H, C^4H, dt, J=15, 7), 2.29 (C^5H_2, q, J=7), 3.41 and 3.74 (C^6H_2, dt, J=10, 7). ^{13}C NMR ppm: 5.7 (t), 19.6 (t), 25.4 (t), 30.7 (t), 32.9 (t), 36.7 (t), 62.3 (t), 66.9 (t), 98.7 (d), 129.6 (d), 130.3 (d).

6-Bromo-(E)-3-hexen-1-ol. **12** Triphenylphosphine (1.1 g, 4.3 mmol) was added gradually over 2.5 h to a magnetically stirred solution of diol **6** (0.50 g, 4.3 mmol), and carbon tetrabromide (1.43 g, 4.3 mmol) in anhydrous ether (20 mL). After completion of the triphenylphosphine addition, the reaction mixture was stirred for 1 h. Thereafter, dry pentane (20 mL) was added, and stirring was continued for an additional 5 min. The reaction mixture was chromatographed on silica gel (5 g) and the recovered product was distilled with Kugelrohr (75 °C, 0.3 mm) to obtain **12** in 44% yield. ^{1}H NMR δ ppm: 3.60 (C^1H_2, t, J=6), 2.25 (C^2H_2, q, J=6), 5.48 (C^3H, C^4H, m), 2.53 (C^5H_2, q, J=7), 3.35 (C^6H_2, t, J=7). ^{13}C NMR ppm: 33.2 (t), 36.3 (t), 36.4 (t), 62.2 (t), 130.2 (d), 130.3 (d).

(E)-2-Hexenal 4. ^{1}H NMR δ ppm: 9.45 (C^1H, d, J=8), 6.06 (C^2H, dd, J=16, 8), 6.80 (C^3H, dt, J=16, 7), 2.26 (C^4H_2, q, J=7), 1.49 (C^5H_2, tq, J=7), 0.91 (C^6H_3, t, J=7). ^{13}C NMR ppm: 13.5 (q), 21.0 (t), 34.5 (t), 133.0 (d), 158.7 (d), 194.0 (d).

(Z)-2-Hexenal 5. To a solution of (Z)-2-hexen-1-ol (1.0 g, 10.0 mmol) in dry methylene chloride (80 mL), manganese dioxide (13.5 g, 154.8 mmol) was added, and vigorously stirred overnight. The mixture was filtered through a short column of silica gel, dried over anhydrous magnesium sulfate, and concentrated on a rotary evaporator to give 0.98 g of a mixture containing 72% hexenal **3** and 28% alcohol. This colorless oil was directly submitted to the Wittig reaction without any further purification. ^1H NMR δ ppm: 10.05 ($C^1\underline{H}$, d, J=8), 5.94 ($C^2\underline{H}$, dd, J=11, 8), 6.61 ($C^3\underline{H}$, dt, J=11, 8), 2.56 ($C^4\underline{H}_2$, q, J=8), 1.52 ($C^5\underline{H}_2$), 0.94 ($C^6\underline{H}_3$). ^{13}C NMR ppm: 13.5 (q), 22.3 (t), 29.8 (t), 130.3 (d), 153.1 (d), 190.9 (d). FT-IR (chloroform): 1674.8, 2740.0, and 2822.1 cm^{-1}.

6-Tetrahydropyranyloxy-3-hexyn-1-ol 15. To a solution of 3-butyn-1-ol THP ether **14** (10 g, 64.8 mmol) in THF (100 mL), ethyl magnesium bromide[21] (1.1 equiv) was added dropwise, and heated for 1 h at 40-45 °C. The resulting Grignard solution was cooled to 4 °C, and was treated dropwise with excess ethylene oxide (ca. 4 equiv) dissolved in cold THF (50 mL). The mixture was allowed to stir at 4 °C for 30 min and, thereafter, the cooling bath was removed, and temperature allowed to rise to room temperature over 3 h. The solution was poured into a 2N HCl solution (280 mL), and was extracted with ether (4 X 250 mL). The combined ether layer was extracted with saturated brine (250 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo. The recovered oil was purified by silica gel to afford the mono-protected 3-hexyn-1,6 diol **15** (6.52 g, 51%). ^1H NMR δ ppm: 3.65 ($C^1\underline{H}_2$, dt, J=6, 4), 2.39 and 2.44 ($C^2\underline{H}_2$, $C^5\underline{H}_2$, m), 3.52 and 3.78 ($C^6\underline{H}_2$, dt, J=10, 7). ^{13}C NMR ppm: 19.5 (t), 20.2 (t), 23.2 (t), 25.4 (t), 30.6 (t), 61.2 (t), 62.4 (t), 66.0 (t), 98.8 (d), 77.7 (s), 79.4 (s).

6-Tetrahydropyranyloxy-(Z)-3-hexen-1-ol 16. To a reaction vessel containing Lindlar Catalyst ($Pd{\cdot}CaCO_3{\cdot}Pb$) (0.72 g), ethanol (100 mL), and quinoline (14 drops), hydrogen was admitted to replace the air, and pressure was equalized to 1 atm. To this stirring solution of catalyst, **15** (3.6 g, 18 mmol) was added, and hydrogen consumption was monitored over a period of 3 h. After completion of the hydrogen consumption, the mixture was filtered through a short column of silica gel to remove the catalyst, concentrated in vacuo, and distilled with Kugelrohr (94-102 °C, 0.55 mm) to afford **16** (3.32 g, 92%). ^1H NMR δ ppm: 3.61 ($C^1\underline{H}_2$, dt, J=6, 5), 2.32 ($C^2\underline{H}_2$, q, J=7), 5.48 and 5.57 ($C^3\underline{H}$, $C^4\underline{H}$, dt, J=11, 7), 2.37 ($C^5\underline{H}_2$, q, J=7), 3.40 and 3.77 ($C^6\underline{H}_2$, dt, J=9, 7). ^{13}C NMR ppm: 19.5 (t), 25.3 (t), 27.9 (t), 30.5 (t), 30.6 (t), 61.9 (t), 62.2 (t), 66.7 (t), 98.8 (d), 127.5 (d), 129.5 (d).

Wittig Reaction. A mixture of alkenyl iodide **9** or **18** (1.0 g, 3.2 mmol) and triphenylphosphine (0.93 g, 3.5 mmol) in dry benzene (2 mL) was stirred, and refluxed at 90 °C (bath temperature) for 24 h. To this reaction mixture, cooled to room temperature, dry ether (2 mL) was added, and the supernatant liquid was pipetted away from the phosphonium salt **10** or **19**. The viscous oil **10** or **19** under constant stream of argon was stirred in dry THF (12 mL), and was treated at room temperature with lithium hexamethyldisilazide (ca. 4.8 mmol), which had been prepared from hexamethyldisilazane

and n-butyllithium in dry n-pentane. The stirring was continued until almost all of the salt dissolved, and the solution turned deep red (1 h). The solution was cooled to -30 °C for 20 min and 2-hexenal (**4** or **5**, ca. 4.8 mmol) in dry THF (4 mL) was added dropwise while the temperature was held between -30 to -25 °C. The reaction mixture was maintained at this temperature for 30 min and, thereafter, the dry ice-acetone bath was removed, and brought back up to room temperature over 2 h. After completion of the reaction, the mixture was poured into ice water (30 mL), and was extracted with hexane (3 X 50 mL). The combined organic layer was washed with 1 N HCl (30 mL), saturated sodium carbonate (15 mL), and saturated brine (2 X 30 mL). The extract was dried over anhydrous sodium sulfate, concentrated, and chromatographed on silica gel (20 g) to obtain the THP ether **11** (ca. 80%) and 3,6,8-dodecatrien-1-ol **1** (ca. 15%).

Hydrolysis of 3,6,8-dodecatrien-1-ol THP ether 11. A solution of THP ether **11** (0.20 g, 0.76 mmol) and pyridinium p-toluenesulfonate (PPTS) (0.019 g, 0.076 mmol) in ethanol (6 mL) was stirred at 55 °C (bath temperature) for 3 h. The solvent was evaporated in vacuo, and the residue was chromatographed on a silica gel column to afford **1** (0.12 g, 88%).

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22. After the fractions containing the resolved isomers were concentrated to remove most of the acetonitrile, the remaining aqueous fractions (ca. 20 mL) were extracted with methylene chloride (3 X 30 mL) and concentrated in vacuo to recover the purified isomers. Freeze drying or evaporation of water from the collected fractions resulted in lower recovery of the resolved isomers.