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CHIRAL LEAVING GROUP: ASYMMETRIC SYNTHESIS OF LIMONENE AND BISABOLENE

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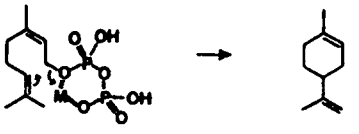
Abstract: The biogenetic-type asymmetric synthesis of limonene and bisabolenes is described. As model studies for the present asymmetric synthesis, the cyclization of catechol, biphenol and binaphthol mononeryl ethers **1**, **4**, and **5**, with organoaluminum reagents are executed to furnish limonene as a major product. Since the reaction of **1**, **4**, and **5** has proved to proceed much faster than that of neryl phenyl ether under the similar conditions, the rate acceleration is attributed to the novel metal-anchimeric assistance of the aluminum reagents bound with the neighboring hydroxyl group for effecting the generation of the allyl cation. This anchimeric effect is utilized for the enantioselective cyclization of (R)-(+)-1,1'-bi-2-naphthol mononeryl ether (**8**) upon treatment with modified aluminum reagent **9** to produce limonene with high optical purity (77% ee). In a similar fashion, (R)-(+)-binaphthol (*Z*,*Z*)-monofarnesyl ether **16a** undergoes the enantioselective cyclization to give β-bisabolene in 76% ee.

The structural diversity found in terpene metabolism is mostly elabolated by olefinic cyclizations of five basic acyclic precursors, isoprene units.[1] The biological strategy for construction of new C-C bonds involves intramolecular electrophilic alkylation of remote double bonds to a cationic center generated by the ionization of allylic pyrophosphate,[2] in which the enzyme may require a divalent cation, Mg^{2+} or Mn^{2+}, for catalytic activity.[3] Formation of limonene from geranyl and/or neryl precursors[1b,4] seems to provide a simple, yet enticing modal for related terpene biosynthesis, although the biogenetic route leading to limonene has not been elucidated so far. Actually, a number of regiochemical features of this simple cyclization have been delineated,[5] but the crucial enantioface differentiation taking place at the enzyme active site as well as the important role of a divalent metal to assist with C-O heterolysis of the allylic substrate have received scant attention.[6] Assuming that cyclization of neryl pyrophosphate to limonene is initiated by bidentate coordination of the pyrophosphate moiety to a metal (eq. 1), we have been intrigued for a number of years in the simulation of such a cyclization with asymmetric induction in organic chemistry. Here we wish to disclose the first asymmetric synthesis of monocyclic terpenes limonene and bisabolenes according to this line as illustrated in eq. 2.

The choice of leaving group would be crucial to realize our project. Among various neryloxy alcohols as substrates, neryloxy-substituted phenols seem to be



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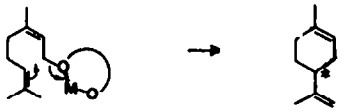
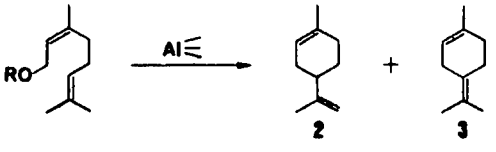
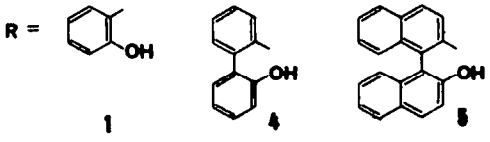


(2)

appropriate in view of the ready accessibility as well as the facile generation of the neryl cation through C-O bond scission by Lewis acids. Accordingly, mononeryl ether of catechol, biphenol, and binaphthol, 1, 4, and 5, were prepared from catechol, biphenol, and binaphthol, respectively, by simple monoalkylation with neryl bromide in the presence of base.

First, we have examined various metals for effecting the cyclization of catechol mononeryl ether (1). Treatment of 1 with ordinary Lewis acids such as $BF_3{\cdot}OEt_2$, $SnCl_4$, and $TiCl_4$ at -78 °C resulted in formation of complex reaction products. The use of $EtAlCl_2$ and Et_2AlCl gave similar results. However, when the neryl ether 1 was reacted with diisobutylaluminum hydride (DIBAH) in CH_2Cl_2 at -78 °C to room temperature, a mixture of limonene (2) and terpinolene (3) was cleanly produced in 53% yield in a ratio of 18:1. None of the acyclic components were detected in the crude reaction mixture by GLC analysis. Other organoaluminum reagents such as Me_3Al, Me_2AlOTf, and dialkylaluminum aryloxide were found to be effecient in the cyclization of 1, 4, and 5, as shown in Table I. Notably, the cyclization of neryl phenyl ether has proved to proceed much more slowly than





those of 1, 4, and 5, under similar conditions. Attempted reaction of neryl phenyl ether with diisobutylaluminum phenoxide in CH_2Cl_2 at room temperature for 1 day resulted in 50% recovery of the starting material. Thus, the remarkable rate acceleration observed herein should be ascribed to the novel metal-anchimeric assistance of the aluminum reagents bound with the neighboring hydroxyl group for effecting the ionization of the allylic substrates.

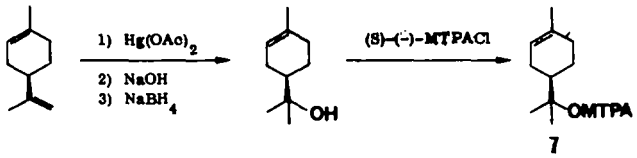
With the demonstration of the anchimeric effect of metal in terpene synthesis accomplished, our attention has been focused on the enantioselective cyclization of neryl precursors, a reaction that would provide access to a variety of terpenes in enantiomeric form. Prior to the execution of the cyclization experiments, we needed enantiomerically pure limonene as standard to determine the enantiomeric excess of the chiral limonene product by the optical rotation value. Unfortunately, so far no evidence is presented in the literatures showing that the limonene standard is enantiomerically pure. Since many commercially available terpenes are not always enantiomerically pure, we checked the optical purity of commercial D-limonene ($[\alpha]_D^{20}$ +115° (c 0.82, pentane); supplied from Wako Pure Chemical Indus-

Table I. Cyclyzation of the Mononeryl Ether 1, 4, and 5[a]

entry	ether	aluminum reagent	conditions[b]	chemical yield %[c] (ratio, 2 : 3)
1	1	DIBAH	A	53 (18 : 1)
2		Me_3Al		50 (12 : 1)
3		Me_2AlO-6		35 (17 : 1)
4		Me_2AlOTf		50 (5 : 1)
5	4	DIBAH	B	81 (8 : 1)
6		Me_3Al		76 (7 : 1)
7		6		63 (5 : 1)
8		Me_2AlOTf		69 (4 : 1)
9	5	DIBAH	C	77 (9 : 1)
10		Me_3Al		72 (7.5 : 1)
11		6		60 (7 : 1)
12		i-Bu_2AlO-		69 (8 : 1)

[a]All reactions were run on a 1 mmol scale using 1.2 equiv of aluminum reagent. [b]Conditions (°C (h)), A: -78 (0.5), room temperature (24); B: -78 (0.5), room temperature (10); C: -78 (0.5), room temperature (5). [c]Determined by capillary GLC (20-m OV-101, 100 °C) using 1-dodecene as an internal standard.

tries, Ltd.), which was found to be >98% enantiomerically pure. Its optical purity was substantiated by ^1H NMR analysis with Sievers' reagent[7] after converting to α-terpineol and then to the (-)-MTPA ester 7.



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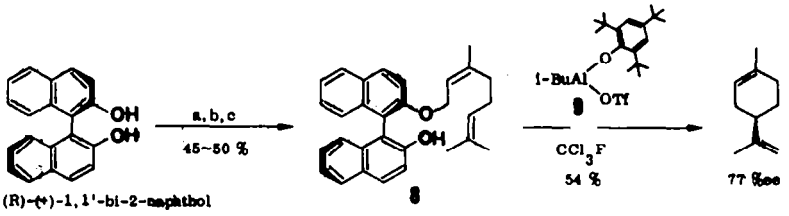
With the limonene standard at hand, we set out the enantioselective cyclization experiments. Thus, (R)-(+)-binaphthol mononeryl ether 8 ($[\alpha]_D^{20}$ +39.4° (c 0.77, THF)) was prepared in 45-50% yield by the monosilylation and alkylation of (R)-(+)-binaphthol as the chiral auxiliary.[8] Reaction of 8 with DIBAH under the standard conditions gave naturally occurring D-limonene (2) and 3 (ratio, 5:1) in



(R)-(+)-1,1'-bi-2-naphthol

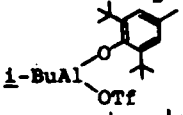
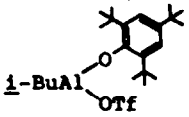
8

a) Me_3SiCl, NEt_3, b) NaH, neryl bromide, c) H_3O^+

58% yield with only moderate asymmetric induction (~12% ee). Since the optical yield generally tends to increase by lowering the reaction temperature, we have then sought to design more oxygenophilic aluminum reagents than DIBAH in order to conduct the reaction at low temperature. A trifluoromethanesulfonyl group was quickly found to be promising as a ligand of modified organoaluminum reagents to withdraw the electron on aluminum. The bulky 2,6-di-tert-butyl-4-alkylphenoxy group was also incorporated to make a monomeric aluminum species in solution, which should additionally enhance its oxygenophilicity. The highest enantioface

differentiation was finally achieved by the use of (2,4,6-tri-tert-butylphenoxy)-isobutylaluminum trifluoromethanesulfonate (9)[9] (3 equiv)[10] in fluorotrichloromethane (CCl_3F) at -130 °C for 3 h, producing D-limonene (54% yield) in 77% ee (Table II).

Table II. Asymmetric Synthesis of D-Limonene[a]

entry	aluminum reagent	conditions[b]	chemical yield %[c] (ratio, 2 : 3)[d]	D-Limonene $[\alpha]_D$ deg (c)[e]	optical yield % ee
1	i-Bu_2AlOTf	A	36 (3 : 1)	+45 (0.96)	39
2	i-$BuAl(OTf)_2$	B	27 (4 : 1)	+46 (0.46)	40
3		C	29 (5.2 : 1)	+74 (0.36)	64
4		D	58[f] (14 : 1)	+88 (1.44)	77

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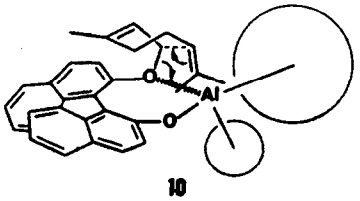
[a]All reactions were carried out on a 1 mmol scale using 3 equiv of aluminum reagent in CCl_3F. [b]Conditions (°C (h)), A: -130 (1), -100 (3), -94 (3), -78 (4); B: -130 (4), -100 (5), -94 (1), -78 (3); C: -130 (1), -78 (9); D: -130 (3). [c]Isolated by column chromatography on silica gel, unless otherwise specified. [d]Determined by capillary GLC analysis (20-m OV-101, 100 °C). [e]In pentane. [f]Determined by capillary GLC (100 °C) using veratrol as an internal standard.

The high sense of asymmetric induction observed herein may be envisioned as occurring through an intermediate 10, in which the cyclization of neryl cation would arise from an preferential anti-endo conformation.[11]



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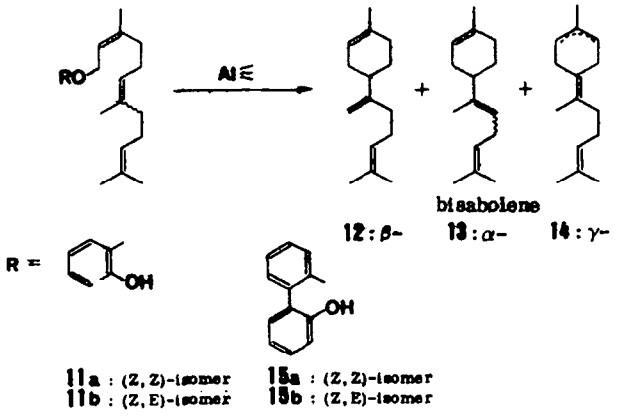
The present study has been successfully extended to the synthesis of bisabolenes[12] from the following ethers: catechol (Z,Z)-monofarnesyl ether (11a), its Z,E isomer 11b, biphenol (Z,Z)-monofarnesyl ether 15a, its Z,E isomer 15b, and (R)-(+)-1,1'-bi-2-naphthol (Z,Z)-monofarnesyl ether (16a), and its Z,E isomer 16b. These ethers were obtained by procedures similar to those in the preparation of 1, 4, and 8, respectively.[13] Reaction of these ethers with several organoaluminum reagents yielded a mixture of α-, β-, and γ-bisabolenes as listed in Table III. Noteworthy is the preferential formation of 12 from the Z,Z isomer 11a vs. 11b, since it implies that during deprotonation the aluminum reagents may be responsible for the discrimination of the stereochemistry of the farnesyl moiety. A similar tendency was also observed in the ratio of bisabolene products (Table III).

Futhermore, by switching the catechol or biphenol moiety to a chiral auxiliary and manipulating the modified organoaluminum reagents, asymmetric synthesis of bisabolenes appears feasible. Thus, exposure of (R)-(+)-binaphthol (Z,Z)-mononeryl ether 16a ($[\alpha]_D^{20}$ +28.6° (c 1.02, THF)) to the aluminum reagent 9 (3 equiv) in CCl_3F at -130 °C for 3 h led to the formation of bisabolenes (ratio of Z-α/β/Z-γ/E-γ/E-α = 3:74:1:1:21) in 52% yield, from which (+)-β-bisabolene was

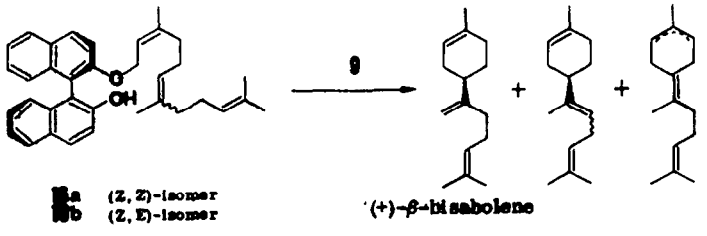
Table III. Cyclization of the Monofarnesyl Ether 11a, 11b, 15a, and 15b[a]

entry	ether	aluminum reagent[b]	conditions[d]	yield[e] %	ratio of bisabolenes[f] (Z-α, β, Z-γ, E-γ, E-α)
1	11a	DIBAH	A	42	3 : 84 : 1 : 2 : 10
2		6		27	3 : 84 : 1 : 2 : 10
3	11b	DIBAH		22	11 : 52 : 2 : 5 : 30
4		6		23	11 : 55 : 1 : 5 : 28
5	15a	DIBAH	B	85	5 : 77 : 1 : 3 : 14
6		6		64	4 : 80 : 1 : 3 : 12
7	15b	DIBAH		71	11 : 50 : 2 : 6 : 31
8		6		79	9 : 48 : 3 : 9 : 31
9	15a	9	C	62	4 : 69 : 2 : 2 : 23
10		9[c]	D	61	6 : 58 : 2 : 4 : 30
11	15b	9	E	67	8 : 45 : 2 : 9 : 36
12		9[c]	D	63	8 : 46 : 4 : 9 : 34

[a]All reactions were performed on a 1 mmol scale. [b]Using 1.2 equiv of aluminum reagent, unless otherwise indicated. [c]Using 3 equiv of the aluminum reagent. [d]Conditions (solvent, °C (h)), A: CH_2Cl_2, -78 (0.5), room temperature (24); B: CH_2Cl_2, -78 (0.5), room temperature (4); C: CCl_3F, -130 (0.5), -40 (1), -20 (2); D: CCl_3F, -130 (0.5), -100 (2), -78 (2); E: CCl_3F, -130 (0.5), -40 (6), -20 (2). [e]Isolated by column chromatography on silica gel. [f]Determined by capillary GLC (20-m OV-101, 150 °C).



separated by preparative TLC on $AgNO_3$-impregnated silica gel. This product was 76% enantiomerically pure, as determined by the comparison of authentic sample.[16] Unfortunately, attempted isolation of (+)-(E)-α-bisabolene was unsuccessful. The Z,E isomer 16b ($[\alpha]_D^{20}$ +34.3° (c 0.91, THF)) was also subjected to the analogous cyclization conditions providing (+)-β-bisabolene in 62% ee, as summarized in Table IV.



The terpene syntheses described above provide a new body of results that, coupled with certain other considerations, (1) indicate that six-membered ring is formed with a high degree of neighboring π-bond participation during C-O heterolysis of 7, thus allowing the remote chiral transfer efficiently and (2) suggest that overall process may involve conformationally rigid cationic structures.

Table IV. Asymmetric Synthesis of Bisabolenes[a]

entry	ether	aluminum reagent (equiv)	conditions[b]	yield[c] %	ratio of bisabolenes[d] (Z-α, β, Z-γ, E-γ, E-α)	β-bisabolene [α]D deg (c)[e]	β-bisabolene optical yield % ee
1	16a	9 (1.2)	A	56	6: 63 : 3: 4: 23	+47 (0.92)	62
2		(3)	B	52	3: 74 : 1: 1: 21	+56 (2.94)	76
3	16b	(3)	B	60	10: 39 : 2: 2: 47	+47 (1.50)	62

[a]All reactions were carried out on a 1 mmol scale in CCl_3F. [b]Conditions (°C (h)), A: -130 (0.5), -100 (1); B: -130 (3). [c]Isolated by column chromatography on silica gel. [d]Determined by capillary GLC (20-m OV-101, 150 °C). [e]In EtOH, see ref 12a.

Experimental Section

General. Infrared (IR) spectra were recorded on a Hitachi 260-10 spectrometer. ^1H NMR spectra were measured on a JNM-PMX 60 spectrometer. Carbon tetrachloride was used as the NMR solvent. Chemical shifts are expressed in parts per million downfield from internal tetramethylsilane (δ=0). Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. Analytical gas-liquid phase chromatography (GLC) was performed on a Hitachi 164 instrument equipped with a flame ionization detector with nitrogen as carrier gas and using a capillary column (20-m OV-101). Optical rotations were determined on JASCO DIP-140 digital polarimeter. For thin layer chromatographic (TLC) analysis, Merck precoated TLC plates (silica gel 60 GF_{254}) were used. The products were purified by preparative column chromatography on silica gel E. Merck Art 9385.

In experiments requiring dry solvents, ether and tetrahydrofuran (THF) were distilled from sodium-benzophenone. Benzene and hexane were dried over sodium metal. Dichloromethane was distilled from phosphorus pentoxide and stored over 4-Å molecular sieves. Pyridine and triethylamine were stored over potassium hydroxide pellets. Diisobutylaluminum hydride (DIBAH) in hexane (1.0 M) was a commercial product.

Preparation of Neryl Bromide. To a stirred solution of 7.71 g of nerol (50 mmol) in 150 mL of ether at -78 °C under N_2 was added 1.69 mL of phosphorus tribromide (18 mmol). The resulting solution was stirred at -78 °C for 30 min and stood at 0 °C for 10 h. The mixture was poured onto ice-water and extracted with hexane. The organic extracts were washed with saturated $NaHCO_3$ solution, dried over Na_2SO_4, and concentrated to give a crude neryl bromide (10.85 g, quantitative yield): ^1H NMR δ 1.61, 1.67, 1.77 (9H, CH_3-C=C), 3.90 (2H, d, J = 9 Hz, CH_2-Br), 5.07-5.62 (2H, m, CH=C). This was used without any purification.

Preparation of Catechol Mononeryl Ether (1). To a stirred suspension of 2.11 g of sodium hydride (50% in oil, 44 mmol) in 200 mL of THF at room temperature under N_2 was added 4.40 g of catechol (40 mmol) portionwise followed by a catalytic amount of hydroquinone. The mixture was stirred for 30 min. Twenty mL of hexamethylphosphoramide (HMPA) and 8.68 g of neryl bromide (40 mmol) were successively added. The whole mixture was stirred for 1 day. After decomposition of excess sodium hydride with 5 mL of methanol, the mixture was poured onto ice-water and extracted with ether. The combined organic layers were dried, concentrated, and purified by column chromatography on silica gel (20:1, hexane-ether as eluant) to give mononeryl ether 1 as an oil (4.40 g, 45%): TLC, R_f 0.33 (5:1, hexane-ether); ^1H NMR δ 1.58, 1.66, 1.77 (9H, CH_3-C=C), 4.35 (2H, d, J = 7 Hz, CH_2-O), 5.20-5.44 (2H, m, CH=C), 6.63 (4H, m, Ar-H).

Preparation of Biphenol Mononeryl Ether (4). To a solution of 3.72 g of biphenol (20 mmol) in 100 mL of 2-propanol in the presence of 2.47 g of potassium tert-butoxide (22 mmol) at room temperature was added 4.34 g of neryl bromide (20 mmol). The resulting mixture was stirred at room temperature for 1 day, poured onto saturated NaCl solution, and extracted with ether. The combined organic extracts were dried, concentrated, and purified by column chromatography on silica gel (10:1, hexane-ethyl acetate as eluant) to give mononeryl ether 4 (6.44 g, 50%) as an oil: TLC, R_f 0.40 (5:1, hexane-ethyl acetate); ^1H NMR δ 1.59, 1.63, 1.73 (9H, CH_3-C=C), 4.49 (2H, d, J = 7 Hz, CH_2-O), 4.98-5.46 (2H, m, CH=C), 6.75-7.37 (8H, m, Ar-H).

Preparation of Racemic 1,1'-Bi-2-naphthol Mononeryl Ether (5). An analogous procedure described for the preparation of catechol mononeryl ether (1) was utilized. To a stirred suspension of 1.06 g of sodium hydride (50% in oil, 22 mmol) in 100 mL of THF at room temperature under N_2 was added 5.73 g of racemic binaphthol (20 mmol) portionwise. After 30 min, 20 mL of HMPA followed by 4.34 g of neryl bromide (20 mmol) were added. The whole mixture was kept on stirring for 1 day. After excess sodium hydride was destroyed by addition of 5 mL of methanol at 0 °C, the mixture was poured onto iced-1 N HCl solution and extracted with benzene. The combined organic layers were dried, concentrated, and purified by column chromatography on silica gel (5:1, hexane-ether as eluant) to afford the

desired binaphthol mononeryl ether 5 in 25% yield (2.10 g) in addition to binaphthol dineryl ether (4.37 g, 39%), and unreacted binaphthol was recovered (1.71 g, 30%); binaphthol dineryl ether: TLC, R_f 0.57 (5:1, hexane-ether); 5: TLC, R_f 0.27 (5:1, hexane-ether), ^{1}H NMR δ 1.49 (3H, s, CH_3-C=C), 1.56 (6H, s, CH_3-C=C), 4.39 (2H, d, J = 7 Hz, CH_2-O), 4.71-5.19 (2H, m, CH=H), 6.77-7.83 (12H, m, Ar-H).

Preparation of Dimethylaluminum 2,6-Di-tert-butyl-4-methylphenoxide (6). To a solution of 264 mg of 2,6-di-tert-butyl-4-methylphenol (1.2 mmol) in 10 mL of dichloromethane at 0 °C under N_2 was added 1.2 mL of Me_3Al (1 M in hexane, 1.2 mmol). This mixture was stirred at 0 °C for 30 min to yield dimethylaluminum 2,6-di-tert-butyl-4-methylphenoxide (6), which was directly used for the cyclization experiments.

Preparation of Dimethylaluminum Trifluoromethanesulfonate. To a solution of 1.2 mL of Me_3Al (1 M in hexane, 1.2 mmol) in 10 mL of dichloromethane at -78 °C was added 106 μL of trifluoromethanesulfonic acid (1.2 mmol). The resulting mixture was stirred at -78 °C for 30 min and at 0 °C for 30 min under N_2, producing dimethylaluminum trifluoromethanesulfonate.

Reaction of Catechol Mononeryl Ether (1) with Organoaluminum Reagents. To a solution of 246 mg of 1 (1 mmol) in 10 mL of dichloromethane at -78 °C under N_2 was added 1.2 mL of DIBAH (1.2 mmol). The solution was stirred at -78 °C for 30 min and at room temperature for 1 day. After 200 μL of 1-dodecene was added as an internal standard by GLC analysis, the reaction mixture was poured onto 1 N HCl solution and extracted with dichloromethane. The combined organic layers were dried, concentrated and purified by short-path column chromatography on silica gel (pentane as eluant) to give a mixture of 2 and 3 (53% yield, TLC, R_f 0.58 (hexane)) in a ratio of 18:1 (limonene (2) (t_r = 2.77 min), terpinolene (3) (t_r = 3.25 min), and 1-dodecene (t_r = 5.73 min), by GLC analysis (100 °C)). The reaction of 1, 4, and 5, with other organoaluminum reagents were carried out in like manners as described above, and the results were listed in Table I.

Preparation of (R)-(+)-1,1'-Bi-2-naphthol Mononeryl Ether (8). To a solution of 5.73 g of (R)-(+)-binaphthol (20 mmol) in 200 mL of THF in the presence of 4.18 mL of triethylamine (30 mmol) at 0 °C under N_2 was added 2.80 mL of chlorotrimethylsilane (22 mmol). After stirring at 0 °C for 3 h, the mixture was poured onto cold-aq $NaHCO_3$ solution and extracted with benzene. The combined organic layers were dried and concentrated to afford (R)-(+)-binaphthol monosilyl ether almost exclusively. This crude ether was diluted with 390 mL of THF and then 1.06 g of sodium hydride (50% in oil, 22 mmol) was added portionwise at 0 °C under N_2. After stirring at 0 °C for 30 min, a solution of 4.77 g of neryl bromide (22 mmol) in 20 mL of THF followed by 30 mL of HMPA were added at 0 °C. The whole mixture was stirred at room temperature for 1 day. After remaining sodium hydride was destroyed with addition of 5 mL of methanol, the mixture was poured onto cold-1 N HCl solution and extracted with benzene. The combined organic layers were dried, concentrated, and purified by column chromatography on silica gel (5:1, hexane-ether as eluant) to give mononeryl ether 8 (3.96 g, 47%) as an oil: $[\alpha]_D^{20}$ +39.4° (c 0.77, THF).

Reaction of (R)-(+)-1,1'-Bi-2-naphthol Mononeryl Ether (8) with Diisobutylaluminum Trifluoromethanesulfonate. To a solution of 3 mL of DIBAH (3 mmol) in 30 mL of CCl_3F at -78 °C under N_2 was added 265 μL of trifluoromethanesulfonic acid (3 mmol). The mixture was stirred at -78 °C for 30 min and at 0 °C for 30 min, producing diisobutylaluminum trifluoromethanesulfonate. After cooling to -130 °C (external temperature, pentane-liquid N_2 bath), a solution of 422 mg of mononeryl ether 8 in 3 mL of CCl_3F was added dropwise. The solution was stirred at -130 °C for 1 h, at -100 °C (methanol-liquid N_2 bath) for 3 h, at -94 °C (hexane-liquid N_2 bath) for 3 h and -78 °C for 4 h. This was poured onto 1 N HCl solution and extracted with dichloromethane. The combined organic layers were dried, concentrated and purified by column chromatography on silica gel (pentane as eluant) to afford a mixture of limonene and terpinolene (48.8 mg, 36% yield, ratio, 3:1) which was determined by GLC analysis. The products were separated by pre-packed column chromatography (LiChroprep Si® 60 by Merck, pentane as eluant) to give D-(+)-limonene (2) (9.6 mg): $[\alpha]_D^{20}$ +45° (c 0.96, pentane).

Reaction of (R)-(+)-Binaphthol Mononeryl Ether 8 with (2,4,6-tri-tert-butylphenoxy)isobutylaluminum Trifluoromethanesulfonate (9). To a solution of 787 mg of tri-tert-butylphenol (3 mmol) in 30 mL of CCl_3F at 0 °C under N_2 was added 3 mL of DIBAH (3 mmol). The mixture was stirred at 0 °C for 30 min. After cooling to -78 °C, 265 μL of trifluoromethanesulfonic acid (3 mmol) was added and the mixture was stirred at -78 °C for 30 min and at 0 °C for 30 min. The aluminum reagent 9 was cooled to -130 °C (external temperature, pentane-liquid N_2 bath) and a solution of 422 mg of mononeryl ether 8 (1 mmol) in 3 mL of CCl_3F was added dropwise. The resulting solution was stirred at -130 °C for 3 h. After addition of 40 μL of veratrole (o-dimethoxybenzene) as an internal standard by GLC analysis, the mixture was poured onto 1 N HCl solution and extracted with dichloromethane. The combined organic layers were dried and concentrated to furnish a colorless oil (58% yield, limonene:terpinolene = 14:1, veratrole (t_r = 4.19 min)). Chromatography on silica gel (pentane as eluant) and subsequent separation of the products by pre-packed column chromatography (pentane as eluant) gave rise to D-limonene (2), (14.4 mg): $[\alpha]_D^{20}$ +88° (c 1.44, pentane).

^{1}H NMR Analysis of MTPA Ester of α-Terpineol with the Chiral Shift Reagnt. A published procedure was used for the preparation of α-terpineol.[14,15] Mercury acetate (637 mg, 2 mmol) was added to a solution of 272 mg of D-(+)-limonene (2

mmol) (supplied from Wako Pure Chemical Industries, Ltd.) in 8 mL of THF and 2 mL of water at 0 °C. The mixture was stirred at room temperature for 30 min. The reaction was then completed by adding 2 mL of a 3 M NaOH solution followed by 2 mL of a 0.5 M sodium borohydride solution in 3 M NaOH at room temperature. After stirring at room temperature for 45 min, the solution was saturated with potassium carbonate and then extracted with ether. The combined organic layers were dried, concentrated, and purified by column chromatography on silica gel (2:1, hexane-ether as eluant) to give a colorless oil of α-terpineol (112 mg, 36%): TLC, R_f 0.45 (3:1, hexane-ethyl acetate); ^{1}H NMR δ 1.11 (6H, s, CH_3-C-O), 5.19-5.45 (1H, br, CH=C).

(S)-(-)-α-Methoxy-(α-trifluoromethyl)phenylacetyl chloride ((S)-(-)-MTPA-Cl, 100 μL) was added to a solution of 23 mg of α-terpineol (0.15 mmol) in 1.5 mL of 1,2-dichloroethane in the presence of 0.1 g of 4-dimethylaminopyridine (DMAP, 0.82 mmol) at room temperature. The solution was heated at 70 °C for 12 h. After confirming the completion of the reaction by TLC, the solution was poured onto 1 N HCl solution and extracted with dichloromethane. The combined organic layers were dried, concentrated, and purified by column chromatography on silica gel (10:1, hexane-ether as eluant) to afford an oil of (S)-(-)-MTPA ester **7** (51 mg, 92%): TLC, R_f 0.65 (3:1, hexane-ethyl acetate); ^{1}H NMR δ 1.57 (6H, s, CH_3-C-O), 3.54 (3H, s, CH_3-O), 5.19-5.41 (1H, br, CH=C), 7.25-7.66 (5H, m, Ar-H).

The diastereomeric ester derived from the racemic limonene was also synthesized in a similar manner as described above. Upon addition of the chiral shift reagent Eu(hfc)$_3$ (Sievers' reagent),[7] the methoxyl absorption in ^{1}H NMR spectrum split into two peaks at δ 9.20 and 9.57 with equal intensities. The MTPA ester **7**, on the other hand, gave still a single methoxy signal even if the signal shifted down toward lower field than δ 9. Thus, commercial D-(+)-limonene has proved to be >98% enantiomerically pure.

Preparation of (Z,Z)- and (Z,E)-Farnesyl Bromide. (Z,Z)- and (Z,E)-farnesyl bromides were prepared in a fashion similar to the preparation of neryl bromide; (Z,Z)-farnesyl bromide: 91% yield; ^{1}H NMR δ 1.61 (3H, CH_3-C=C), 1.68 (6H, CH_3-C=C), 1.77 (3H, CH_3-C=C), 3.88 (2H, d, J = 9 Hz, CH_2-Br), 5.04-5.59 (3H, m, CH=C); (Z,E)-isomer: 97% yield; ^{1}H NMR δ 1.61-1.79 (12H, CH_3-C=C), 3.97 (2H, d, J = 8 Hz, CH_2-Br), 5.06-5.61 (3H, m, CH=C).

Preparation of Monofarnesyl Ethers 11a, 11b, 15a, 15b, 16a, and 16b. Monofarnesyl ethers **11a**, **11b**, **15a**, **15b**, **16a**, and **16b** were prepared by the procedures similar to those in the preparation of mononeryl ethers, **1**, **5**, and **6**, respectively; **11a**: 50% yield; TLC, R_f 0.35 (8:1, hexane-ethyl acetate); ^{1}H NMR δ 1.57 (3H, CH_3-C=C), 1.65 (6H, CH_3-C=C), 1.77 (3H, CH_3-C=C), 4.48 (2H, d, J = 7 Hz, CH_2-O), 5.02-5.57 (3H, m, CH=C), 6.50-6.91 (4H, m, Ar-H); **11b**: 55% yield; TLC, R_f 0.35 (8:1, hexane-ethyl acetate); ^{1}H NMR δ 1.55 (6H, CH_3-C=C), 1.63 (3H, CH_3-C=C), 1.76 (3H, CH_3-C=C), 4.44 (2H, d, J = 6 Hz, CH_2-O), 4.98-5.52 (3H, m, CH=C), 6.56-6.78 (5H, m, Ar-H); **15a**: 85% yield; TLC, R_f 0.27 (10:1, hexane-ethyl acetate); ^{1}H NMR δ 1.58 (3H, CH_3-C=C), 1.64 (6H, CH_3-C=C), 1.74 (3H, CH_3-C=C), 4.56 (2H, d, J = 7 Hz, CH_2-O), 4.99-5.49 (3H, m, CH=H), 6.85-7.37 (8H, m, Ar-H); **15b**: 95% yield; TLC, R_f 0.27 (10:1, hexane-ethyl acetate); ^{1}H NMR δ 1.55 (6H, CH_3-C=C), 1.64 (3H, CH_3-C=C), 1.70 (3H, CH_3-C=C), 4.44 (2H, d, J = 7 Hz, CH_2-O), 4.96-5.41 (3H, m, CH=C), 6.76-7.24 (8H, m, Ar-H); **16a**: 52% yield; TLC, R_f 0.32 (4:1, hexane-ethyl acetate); ^{1}H NMR δ 1.59 (6H, CH_3-C=C), 1.65 (6H, CH_3-C=C), 4.48 (2H, d, J = 7 Hz, CH_2-O), 4.83-5.34 (3H, m, CH=C), 6.96-7.93 (12H, m, Ar-H); $[\alpha]_D^{20}$ +28.6° (c 1.02, THF); **16b**: 59% yield; TLC, R_f 0.32 (4:1, hexane-ethyl acetate); ^{1}H NMR δ 1.52 (3H, CH_3-C=C), 1.58 (6H, CH_3-C=C), 1.66 (3H, CH_3-C=C), 4.47 (2H, d, J = 7 Hz, CH_2-O), 4.81-5.28 (3H, m, CH=C), 6.91-7.92 (12H, m, Ar-H); $[\alpha]_D^{20}$ +34.3° (c 0.91, THF).

Reaction of Catechol (Z,Z)-Monofarnesyl Ether (11a) with DIBAH. To a solution of 246 mg of **11a** (1 mmol) in 10 mL of dichloromethane at -78 °C under N_2 was added 1.2 mL of DIBAH (1.2 mmol). The solution was stirred at -78 °C for 30 min and at room temperature for 1 day, poured onto 1 N HCl solution and extracted with dichloromethane. The combined organic layers were dried, concentrated and purified by column chromatography on silica gel (hexane as eluant) to give a mixture of bisabolenes (85 mg, 42%, TLC, R_f 0.41 (hexane)) as an oil, the ratio of which was determined by GLC analysis (150 °C); **12**:**13**:**14** = 28:4.3:1.

The structures of **12**-**14** were confirmed by GLC comparison with those of the authentic samples: t_r((Z)-**13**) = 18.37 min, t_r(**12**) = 19.05 min, t_r((Z)-**14**) = 19.53 min, t_r((E)-**14**) = 20.57 min, t_r((E)-**13**) = 21.49 min; MS m/e; **12**: 204 (M^+), 119, 109, 95, 79, 69 (100%); Z-**13**: 204 (M^+), 121, 119, 109, 93 (100%); E-**13**: 204 (M^+), 121, 119, 109, 93 (100%); Z-**14**: 204 (M^+), 119, 107, 93 (100%); E-**14**: 204 (M^+), 135, 119, 107, 93 (100%).[17]

The authentic **12** and **14** were prepared according to the literature procedures.[12a,c] The synthesis of authentic **13** was made by the analogous method as described in the reference 12c.

Reaction of (R)-(+)-1,1'-Bi-2-naphthol (Z,Z)-Monofarnesyl Ether (16a) with 9. To the aluminum reagent **9** (3 mmol), prepared as stated previously, in 30 mL of CCl_3F at -130 °C under N_2 was added a solution of 490 mg of monofarnesyl ether **16a** (1 mmol) in 3 mL of CCl_3F dropwise. The mixture was stirred at -130 °C for 3 h, poured onto 1 N HCl solution, and extracted with dichloromethane. The combined organic layers were dried, concentrated, and purified by column chromatography on silica gel (hexane as eluant) to afford a mixture of bisabolenes (106 mg, 52% yield, ratio of Z-**13**/**12**/Z-**14**/E-**14**/E-**13** = 3:74:1:1:21 by GLC analysis (150 °C)) as an oil. Separation of bisabolenes by preparative TLC on $AgNO_3$-impregnated silica

gel (10:1, hexane-ether as eluant) gave β-bisabolene (12) (29.4 mg): $AgNO_3$-TLC, R_f 0.35 (10:1, hexane-ether); $[\alpha]_D^{20}$ +56° (c 2.94, EtOH).
Attempted isolation of (+)-(E)-α-bisabolene ((E)-16) was unsuccessful.

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