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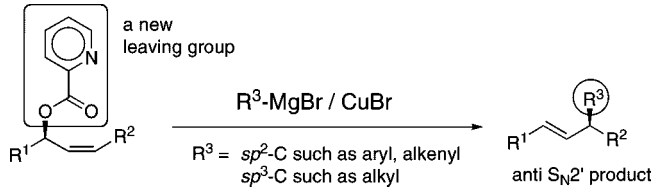
New General Method for Regio- and Stereoselective Allylic Substitution with Aryl and Alkenyl Coppers Derived from Grignard Reagents

Yohei Kiyotsuka, Yuji Katayama, Hukum P. Acharya, Tomonori Hyodo, and Yuichi Kobayashi*

Department of Biomolecular Engineering, Tokyo Institute of Technology, Box B52, Nagatsuta-cho 4259, Midori-ku, Yokohama 226-8501, Japan

ykobayas@bio.titech.ac.jp

Received November 5, 2008

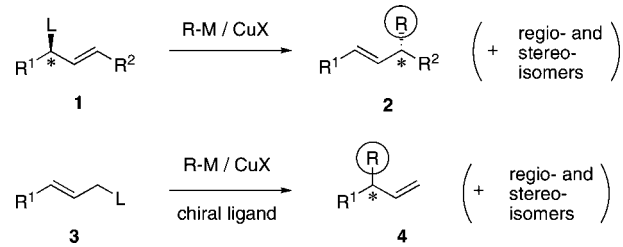


Allylic substitution with sp^2-carbon reagents (aryl and alkenyl anions) was realized by using allylic picolinates and copper reagents derived from RMgBr and CuBr·Me_2S to afford anti S_N2' products regio- and stereoselectively. Steric and electronic factors in the reagents and the size of the methylene substituents around the allylic moiety marginally affected the selectivity. The reaction system was compatible with alkyl reagents as well. Furthermore, the substitution was applied to construction of a quaternary center and synthesis of (−)-sesquichamaenol. Electron-withdrawing nature of the pyridyl group and chelation of the C(=*O*)-C_5H_4N to $MgBr_2$ generated in situ were found to be responsible for the high efficiency of the substitution.

Introduction

Copper-promoted substitution of allylic alcohol derivatives with hard nucleophiles is a potentially useful method for construction of C—C bond.[1] Generally, copper reagents prefer reaction at the γ position of the allylic moiety with inversion of stereochemistry. This propensity has stimulated intensive investigation shown in Scheme 1 to afford chiral compounds of structural types **2**[2−7] and **4**[8] from secondary and primary allylic substrates **1** and **3**, respectively. Among these types, we were attracted to the former because of the wider option in choosing substituents (i.e., R^1 and R^2 vs R^1 in the latter), which will provide a wider flexibility in designing synthesis of a target compound. We were also attracted by the availability of the various preparations of optically active allylic alcohols,[9] which are converted to allylic substrates **1**. However, the regio- and stereoselectivities of the former are highly susceptible to steric and electronic biases and nucleophilicity of the reagents. To improve the low reliability, the following leaving group/reagent systems have been developed to date: $C_6F_5CO_2$-,[2] 2,6-$F_2C_6H_3CO_2$- (in one occasion),[2f] and *o*-(Ph_2P(=O))$C_6H_4CO_2$-(*o*-DPPB oxide group)[3] with R_2Zn/CuCN·2LiCl; $(RO)_2P(O)O$-[4] with R_2Zn/CuCN·2LiCl; MsO in γ-mesyloxy-α,β-unsaturated

SCHEME 1. Two Types of Allylic Substitution[a]



[a] L = leaving group.

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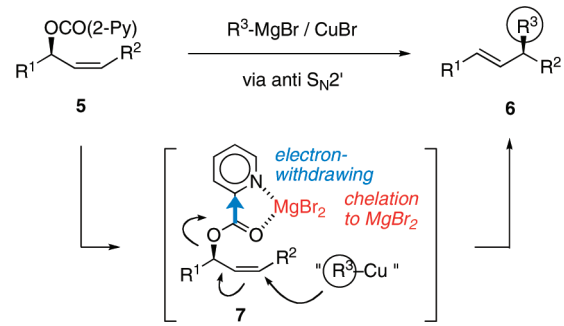
10.1021/jo802426g CCC: $40.75 © 2009 American Chemical Society
Published on Web 02/06/2009

esters[5] with $R_2Cu(CN)Li_2 \cdot BF_3$ or $RCu(CN)Li \cdot BF_3$; *o*-(Ph_2P)-$C_6H_4CO_2$- (*o*-DPPB group)[6] with $RMgX/CuBr \cdot Me_2S$, etc.[7] Among these leaving groups, the *o*-DPPB group shows especially excellent selectivity and reactivity even with a slightly excess quantity of the reagent and led to stereoselective synthesis of certain polyketides of deoxy-type and tocopherol.[10−12] However, the *o*-DPPB group is compatible mainly with alkyl reagents; additionally, the group is quite expensive. On the other hand, the other leaving groups require a large quantity of the reagents.[13]

The reaction systems mentioned above have been developed for alkyl reagents (sp^3-C reagents). Unfortunately, application of the systems to aryl and alkenyl reagents (sp^2-C reagents) has resulted in low selectivity and/or reactivity[4b,14] except for several reactive or sterically biased substrates.[2f,15,16] The low nucleophilicity of the sp^2-C reagents is responsible for the inefficient results.[17]

The drawback associated with the sp^2-C reagents prompted us to develop a totally new leaving group that is activated by a new mechanism. We selected the picolinoxy group (2-pyridyl-CO_2-), for which we expected double activation as illustrated in Scheme 2, i.e., (1) electrostatic activation by the electron-withdrawing pyridyl group as for the case of the C_6F_5 group in the $C_6F_5CO_2$ moiety and (2) dynamic activation by the carbonyl oxygen and the pyridyl nitrogen chelating to $MgBr_2$ that is generated in situ from R^3MgBr and CuBr. In addition, picolinic acid is quite inexpensive.[18] As communicated earlier, this hypothesis was found to be correct, giving anti S_N2' products **6** quite efficiently.[19] Herein, we present a full account of the allylic substitution with additional results. Furthermore, we disclose new results that include substitution with alkyl reagents, construction of a quaternary center, and synthesis of (−)-sesquichamaenol.

SCHEME 2. Expected Activations of the Picolinoxy Group in the Allylic Substitution



Results and Discussion

1. Preliminary Investigation. First, substitution was investigated by using racemic *cis* allylic picolinate **5a** ($R^1 = (CH_2)_2Ph$, $R^2 = CH_2OTBS$) and its *trans* isomer **15** with a phenyl copper reagent derived from PhMgBr (2 equiv) and $CuBr \cdot Me_2S$ (1 equiv) in THF at 0 °C for 1 h (Scheme 3). The S_N2' product **6a** was produced from **5a** with high regioselectivity (ca. 99:1) over the S_N2 product **8**[20] by ^1H NMR spectroscopy (Table 1, entry 2), whereas the *trans* isomer **15** produced a mixture of **6a** and the regioisomer **8** in a ratio of 60:40. Other byproducts such as alcohol **9** and the *cis* isomers of **6a** and **8** were not detected.[21] The amount of the reagent was also examined to find that reaction was completed even with 1.2 equiv of PhMgBr within 1 h (entry 4). However, we decided to use 2 equiv of RMgBr for further investigation to avoid any technical error.

Other phenyl coppers (Ph/Cu = 4:1 and 1:1) derived from PhMgBr (2 equiv) and $CuBr \cdot Me_2S$ (0.5 and 2 equiv, respectively) were also satisfactory reagents as presented in entries 1 and 3, thus indicating the practical merit that precise measurement of PhMgBr and $CuBr \cdot Me_2S$ is no longer necessary to attain good efficiency. The selectivity being independent of the

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(17) Recently, the regioselection of a racemic allylic *o*-DPPB ester with sp^2-C copper reagents such as those derived from PhMgBr and CH_2=C(Me)MgBr was improved by using CH_2Cl_2 in place of Et_2O or by slow addition, but the scope of substrates to be covered by the improved conditions and the chirality transfer (C.T.)[23] thereof are uncertain.[6b]

(18) Relative prices (Aldrich) of the major leaving groups as compared with picolinic acid (28 $/mol): $C_6F_5CO_2H$, 43 times; *o*-$(Ph_2P)C_6H_4CO_2H$, 330 times; *o*-$(Ph_2P(=O))C_6H_4CO_2H$, available by oxidation of *o*-$(Ph_2P)C_6H_4CO_2H$; $(EtO)_2P(O)Cl$, 4 times; cf. DCC 2.1 times.

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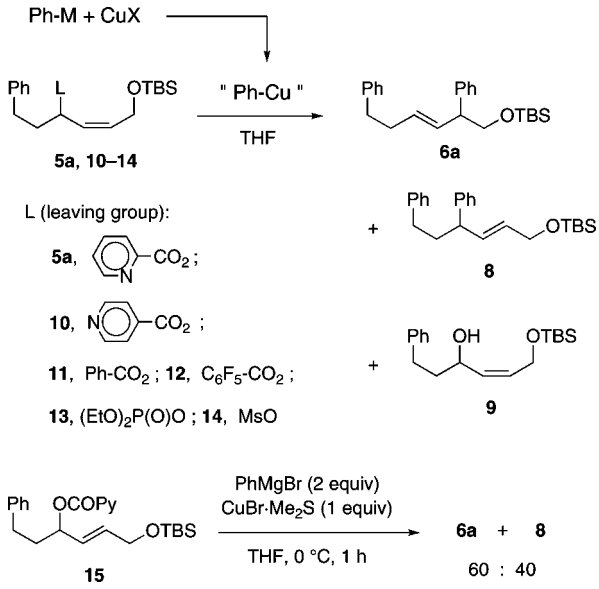
(20) Regioisomer **8** possessing the *trans* olefin in it was synthesized unambiguously. See entry 10 of Table 2 for the enantiomerically enriched version of **8** as (*S*)-**6e**.

SCHEME 3. Preliminary Study



Ph/Cu ratios is a rare case in the allylic substitution. In addition, the reactions were found to be successful at lower temperatures (see Table 2).

Copper bromide (CuBr) in place of $CuBr\cdot Me_2S$ and other copper salts (CuCl, CuI, CuCN) gave similarly good results (Table 1, entries 5−10). However, except for CuCN, the other reagents derived from CuX (X = Cl, Br, I) showed slightly decreased reactivity at lower temperatures (e.g., ca. 10% recovery of **5a**, entry 6).

We then carried out several reactions using substrates **10** and **11** to clarify the proposed mechanism. Reaction of isonicotinate **10** proceeded slowly even at somewhat higher temperatures (0 °C—rt) (entry 11), whereas benzoate **11** was inert under the same reaction conditions (entry 12). These results are consistent with the double activation we proposed for the picolinoxy group as mentioned above: chelation **5a** > **10**; electron-withdrawal **5a**, **10** > **11**.

2. Additional Study. Although we have achieved satisfactory results using PhMgBr as a reagent source, phenyl zinc reagents (Ph_2Zn and PhZnBr) derived from Ph-M (M = Li, MgBr) and $ZnBr_2$ (therefore one more step of the transmetalation is required) were briefly examined with scientific interest. Surprisingly, copper reagents derived from Ph_2Zn (prepared from PhLi and $ZnBr_2$) and $CuBr\cdot Me_2S$ and that from Ph_2Zn and $CuCN\cdot 2LiCl$ (Knochel reagent)[2a,c−f,4c,d,22] were ill-suited to **5a** (entries 15, 16). On the other hand, use of Ph_2Zn derived from PhMgBr and $ZnBr_2$ afforded the S_N2' product **6a** efficiently (entries 17, 18). These results indicate that $MgBr_2$ is a real species to which the picolinoxy group chelates. Additional evidence supporting the effect of $MgBr_2$ was obtained with $PhZnBr\cdot MgBr_2$ derived from PhMgBr and $ZnBr_2$, though the reaction was slightly less efficient (entries 19, 20).

Next, pentafluorobenzoate **12** and phosphonate **13** were subjected to the substitution with $PhMgBr/CuBr\cdot Me_2S$ to compare the reactivity of the picolinoxy group (entries 13, 14). The former produced alcohol **8** competitively, and the latter afforded a mixture of **6a** and the *cis* isomer as stated in footnote e of Table 1 (ca. 20%).[21] On the other hand, an attempted synthesis of mesylate **14** from the alcohol was unsuccessful, giving a mixture of products.

3. Chirality Transfer. We then studied the stereochemistry and chirality transfer (C.T.)[23] of the reaction using enantiomerically enriched allylic picolinate (*S*)-**5a**. Synthesis of (*S*)-**5a** is delineated in Scheme 4, in which other substrates that we have examined in Table 2 are also presented. Among them, (*S*)-**5c** was prepared as a complementary substrate of (*S*)-**5a**. Epoxy alcohol **17** was prepared from aldehyde **16** via the Sharpless asymmetric epoxidation using L-(+)-DIPT.[9a] The chloride **18** derived from **17** was converted according to the protocol published by Yadav[24] to the propargylic anion, which was trapped by paraformaldehyde to give diol **19** in 73% yield. Silylation followed by hydrogenation of the acetylene afforded alcohol **21** in good yield. Finally, condensation of **21** with $PyCO_2H$, DCC, and DMAP produced picolinate (*S*)-**5a**, which was 90% ee by chiral HPLC analysis. Picolinate (*S*)-**5b** (89% ee) was synthesized from **18** in a similar way. Next, aldehyde **26**, prepared from mannitol according to the literature procedure,[25] was subjected to Wittig reaction with $[Ph(CH_2)_3PPh_3]^+Br^-$ and $NaN(TMS)_2$ to afford an olefin, which was converted to diol **27** by hydrolysis in 68% yield. Selective silylation of the diol at the primary OH group followed by DCC-assisted condensation at the remaining secondary OH group with $PyCO_2H$ furnished (*S*)-**5c**, which was 95% ee by chiral HPLC analysis. Synthesis of (*S*)-**5d** commenced with the TBDPS ether[26] of natural ethyl (*S*)-lactate, which was converted to the propargyl alcohol derivative **30** in three steps. Reaction of an anion derived from **30** with paraformaldehyde afforded alcohol **31**, which was transformed to **32** by PMB protection followed by desilylation. Finally, esterification of **32** with $PyCO_2H$ followed by hydrogenation of the resulting ester **33** over Lindlar catalyst ($Pd/CaCO_3$, Pb-poisoned) afforded picolinate (*S*)-**5d** (97% ee by chiral HPLC analysis). Note that use of $Pd/BaSO_4$ and quinoline was not suited in this case since (*S*)-**5d** and quinoline was inseparable by chromatography on silica gel.

(21) The *cis* isomers of **6a** and **8** (i.e., **i** and **iii**) were synthesized by methods shown below. Isomer **i**: ^1H NMR (300 MHz, $CDCl_3$) δ−0.07 (s, 3 H),−0.06 (s, 3 H), 0.83 (s, 9 H), 2.26−2.49 (m, 2 H), 2.52−2.70 (m, 2 H), 3.62−3.79 (m, 3 H), 5.56 (dt, J = 11, 7 Hz, 1 H), 5.65 (dd, J = 11, 8 Hz, 1 H), 7.10−7.31 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ−5.37 (−),−5.35 (−), 18.4 (+), 26.0 (−), 29.8 (+), 35.8 (+), 46.5 (−), 67.9 (+), 125.9 (−), 126.3 (−), 128.1 (−), 128.32 (−), 128.34 (−), 128.5 (−), 130.6 (−), 130.9 (−), 142.0 (+), 142.9 (+). Isomer **iii**: ^1H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 3 H), 0.04 (s, 3 H), 0.89 (s, 9 H), 1.87−2.13 (m, 2 H), 2.47−2.68 (m, 2 H), 3.45−3.60 (m, 1 H), 4.15 (dd, J = 13, 4 Hz, 1 H), 4.27 (dd, J = 13, 5 Hz, 1 H), 5.54−5.66 (m, 2 H), 7.12−7.34 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ−5.08 (−),−5.05 (−), 18.4 (+), 26.0 (−), 33.7 (+), 38.5 (+), 43.3 (−), 59.7 (+), 125.9 (−), 126.2 (−), 127.4 (−), 128.4 (−), 128.5 (−), 128.6 (−), 130.0 (−), 134.1 (−), 142.1 (+), 144.7 (+).

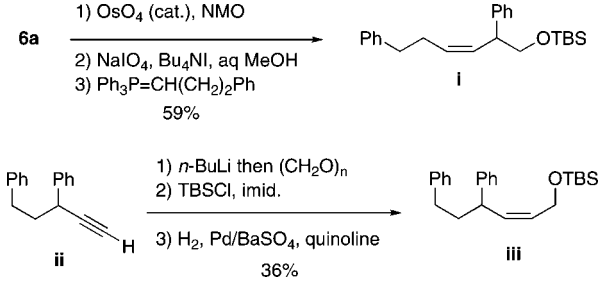


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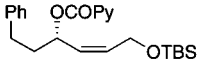
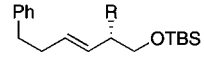
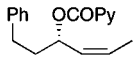
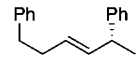
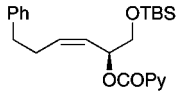
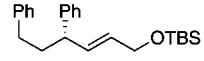
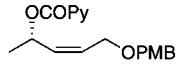
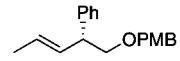
TABLE 1. Allylic Substitution of 5a and 10−13 with "Ph-Cu" derived from Ph-M and CuX

entry	substrate	reagent sources (equiv)	temp (°C)	time (h)	ratio of **6a**:**8**:**9**:**SM**[a]	yield (%)[b,c]
1	**5a**	PhMgBr (2), CuBr·Me_2S (0.5)	0	1	99:1:0:0	85
2	**5a**	PhMgBr (2), CuBr·Me_2S (1)	0	1	99:1:0:0	91
3	**5a**	PhMgBr (2), CuBr·Me_2S (2)	0	1.5	98:2:0:0	84
4	**5a**	PhMgBr (1.2), CuBr·Me_2S (0.5)	0	1	98:0:1:1	92
5	**5a**	PhMgBr (2), CuBr (0.5)	0	1	97:3:0:0	ND
6	**5a**	PhMgBr (3), CuBr (1.5)	−50 to −20	1	90:0:0:10	83
7	**5a**	PhMgBr (2), CuCl (0.5)	0	1	98:2:0:0	ND
8	**5a**	PhMgBr (2), CuI (0.5)	0	1	90:2:8:0	ND
9	**5a**	PhMgBr (2), CuCN (0.5)	0	1	96:0:2:2	88
10	**5a**	PhMgBr (3), CuCN (1.5)	−50 to −20	1	99:1:0:0	86
11	**10**	PhMgBr (2), CuBr·Me_2S (1)	0 to rt	13	46:0:0:54	ND
12	**11**	PhMgBr (2), CuBr·Me_2S (1)	0 to rt	20	0:0:0:100	
13	**12**	PhMgBr (2), CuBr·Me_2S (2)	0 to rt	18	60:0:40:0	ND
14	**13**	PhMgBr (3), CuBr·Me_2S (1)	0[d]	3	99[e]:1:0:0	90
15	**5a**	Ph_2Zn·2LiBr[f] (3), CuBr·Me_2S (1.5)	−15 to 0	4	31:0:46:23	ND
16	**5a**	Ph_2Zn·2LiBr[f] (3), CuCN·2LiCl (1.5)	−15 to 0	4	25:0:60:15	ND
17	**5a**	Ph_2Zn·2$MgBr_2$[g] (2), CuBr·Me_2S (1)	−15 to 0	1	99:1:0:0	91
18	**5a**	Ph_2Zn·2$MgBr_2$[g] (2), CuCN·2LiCl (1)	−15 to 0	1.5	85:1:5:10	ND
19	**5a**	PhZnBr·$MgBr_2$[g] (2), CuBr·Me_2S (1)	−15 to 0	1	85:2:0:13	ND
20	**5a**	PhZnBr·$MgBr_2$[g] (2), CuCN·2LiCl (1)	−15 to 0	1	93:1:0:6	ND

[a] SM: starting materials (substrates). Zero (0) is given in the cases where the product signal(s) was not detected by ^{1}H NMR spectroscopy. [b] Isolated yield of **6a** (and **8**, if produced). [c] ND: not determined. [d] Almost no reaction took place at −50 to −30 °C for 4 h. [e] An olefinic impurity (*cis* isomer in ca. 20%) was seen in the ^{1}H NMR spectrum. [f] Derived from PhLi and $ZnBr_2$. [g] Derived from PhMgBr and $ZnBr_2$.

TABLE 2. Allylic Substitution of Enantiomerically Enriched Allylic Picolinates

entry	substrate (%ee)	reagent (equiv)	CuBr·Me_2S (equiv)	temp. (°C)	time (h)	product[a,b]	yield (%)	C.T.[c] (%)
1	 (*S*)-**5a** (90% ee)	PhMgBr (2)	0.5	0	1	 (*R*)-**6a**, R = Ph	85	53
2	(*S*)-**5a** (90% ee)	PhMgBr (2)	0.5	–20 to –15	1	(*R*)-**6a**	84	71
3	(*S*)-**5a** (90% ee)	PhMgBr (2)	0.5	–60 to –40	1	(*R*)-**6a**	83	98
4	(*S*)-**5a** (90% ee)	PhMgBr (2)	1	–60 to –40	1	(*R*)-**6a**	89	98
5	(*S*)-**5a** (98% ee)	PhMgBr (2)	1	–60 to –40	1	(*R*)-**6a**	93	99
6	(*S*)-**5a** (97% ee)	PhMgBr (1.2)	0.5	–60 to –40	1	(*R*)-**6a**	83	98
7	(*S*)-**5a** (90% ee)	*o*-MeC_6H_4MgBr (2)	1	–60 to –40	1	(*R*)-**6b**, R = *o*-MeC_6H_4	81	99
8	(*S*)-**5a** (90% ee)	*o*-$MeOC_6H_4MgBr$ (2)	1	–60 to –40	1	(*R*)-**6c**, R = *o*-$MeOC_6H_4$	85	98
9	 (*S*)-**5b** (89% ee)	PhMgBr (2)	1	–60 to –40	1	 (*R*)-**6d**	86	99
10	 (*S*)-**5c** (95% ee)	PhMgBr (2)	1	–40	1	 (*S*)-**6e**	93	97
11	 (*S*)-**5d** (97% ee)	PhMgBr (2)	1	–60 to –40	1	 (*R*)-**6f**	83	99

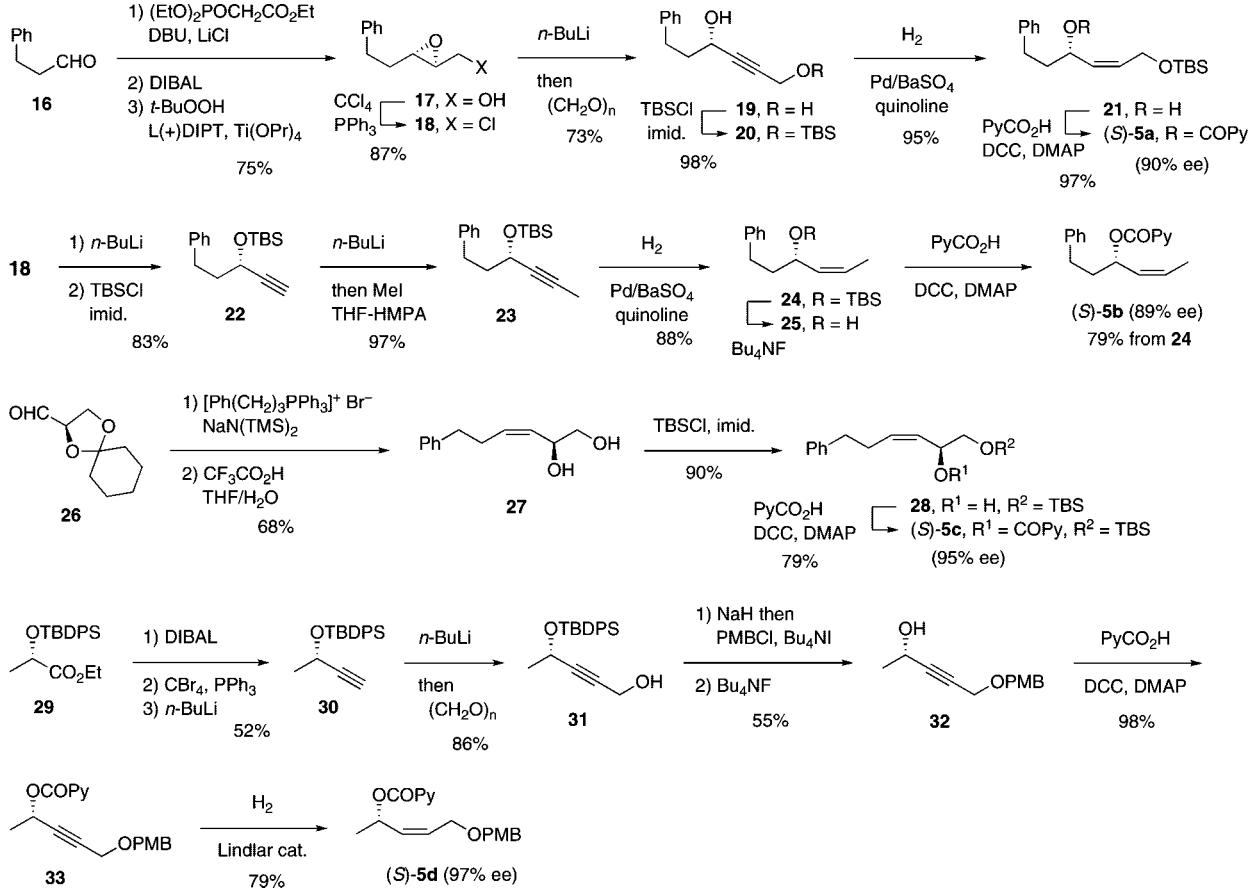
[a] Absolute configurations of **6a**, **6d**, and **6e** were determined unambiguously (for **6a**, see Scheme 5; for **6d**,**e**, see Experimental Section), while that of the products **6b**, **6c**, and **6f** were determined by analogy. [b] Regioselectivities of >98:2 were determined by ^{1}H NMR spectroscopy. [c] Chirality transfers were determined by chiral HPLC analysis of the derivatives.

Reaction of (*S*)-**5a** (90% ee) was carried out with the Ph/Cu reagents of 2/0.5 and 2/1 equiv (Table 2, entries 1−4). The absolute configuration of product **6a** in entry 4 was determined to be *R* by comparison of the $[\alpha]_D$ of the derived (*S*)-alcohol **34** ($[\alpha]^{25}_D$ −13 (*c* 0.12, $CHCl_3$)) with that of the (*R*)-alcohol reported ($[\alpha]^{23}_D$ +14.6 (*c* 1.03, $CHCl_3$)),[27,28] thus unambiguously establishing the anti S_N2' pathway (Scheme 5). The same configuration for the major enantiomers of entries 1−3 was assigned by comparison of the retention times on chiral HPLC. Unexpectedly, the C.T. of the reaction with the Ph/Cu (2/0.5

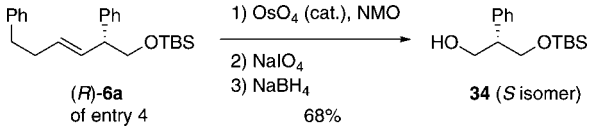
(27) Maruoka, K.; Ooi, T.; Nagahara, S.; Yamamoto, H. *Tetrahedron* **1991**, *47*, 6983–6998.

(28) In addition to (*R*)-**6a** (Table 2), the absolute configuration of (*R*)-**6d** and (*S*)-**6e** in Table 2, (*S*)-**6g** in Scheme 6, (*S*)-**6k** and (*S*)-**6m** in Scheme 7, and **41** in Scheme 8 was determined by transformation into known compounds. See the Experimental Section for (*R*)-**6d** and (*S*)-**6e**,**g**,**k**,**m**; Scheme 9 for **41**. Other products of the allylic substitution were assigned by analogy.

SCHEME 4. Preparation of Picolinates (*S*)-5a−d



SCHEME 5. Determination of the Absolute Configuration of (*R*)-6a

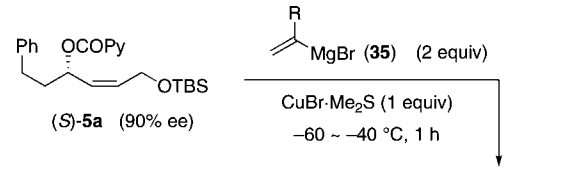


equiv) at 0 °C (corresponding to conditions of Table 1, entry 1) was unacceptable (entry 1). However, we were pleased to attain high level of C.T. (98%) at −60 to −40 °C (entry 3, cf. entry 2). High efficiency was also recorded with the Ph/Cu reagent at 2/1 equiv (entry 4). Additionally, reaction of entry 4 was successfully repeated with (*S*)-**5a** of 98% ee as presented in entry 5. High C.T. was also attained with a reduced quantity of the reagent (entry 6).

To clarify the steric as well as electronic effect on the selectivity and reactivity, the following reagents and picolinates were examined next. Substitution reactions with copper reagents derived from *o*-Me and *o*-MeO-C_6H_4MgBr proceeded well to produce the (*R*)-**6b** and (*R*)-**6c**, respectively (entries 7 and 8). Importantly, yield, C.T., and regioselectivity were little influenced by the substituent at the ortho position of the phenyl ring. Next, substrates (*S*)-**5b** and (*S*)-**5c** produced (*R*)-**6d** and (*S*)-**6e**, respectively, with efficiency comparable to that of (*S*)-**5a** (entries 9 and 10). These results clearly indicate that the anti S_N2' selectivity and the reactivity are not affected by any methylene substituents at the α and γ positions. An additional result presented in entry 11 is consistent with this generalization.

4. Alkenyl Reagents. We then investigated substitution of (*S*)-**5a** with three alkenyl reagents derived from the Grignard

SCHEME 6. Allylic Substitution of (*S*)-5a with Alkenyl Reagents 35 (R = H, C_5H_{11}, Ph)[a,b]



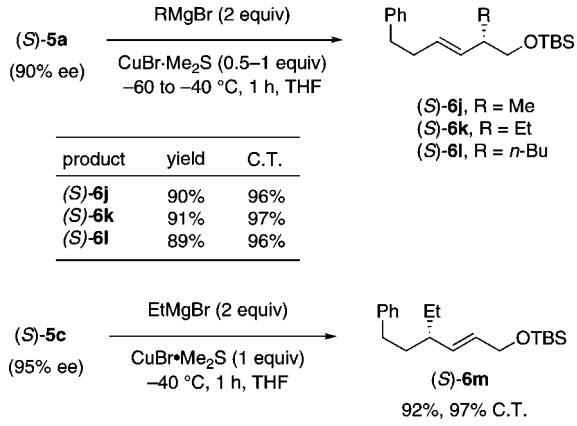
product	yield	C.T.
(*S*)-**6g**	81%	98%
(*R*)-**6h**	75%	97%
(*R*)-**6i**	85%	97%

[a] The stereochemistry of (*S*)-**6g** was determined as described in the Experimental Section, and that of (*R*)-**6h**,**i** was assigned by analogy. [b] Chirality transfer (C.T.) was determined by chiral HPLC.

reagents **35** (R = H, C_5H_{11}, Ph, each 2 equiv) and CuBr·Me_2S (1 equiv) (Scheme 6), which afforded anti S_N2' products (*S*)-**6g**, (*R*)-**6h**, and (*R*)-**6i**, respectively, in good yields with efficiencies similar to those of the aryl reagents. The anti S_N2' course of the reaction was established by the absolute configuration of (*S*)-**6g**, which was determined by derivation to the known compound as described in the Experimental Section. Since the vinyl copper reagent **35** of R = H is one of the least reactive reagents, it is reasonable that the high reactivity of the allylic picolinate compensates for the low reactivity[29] of the vinyl reagent.

(29) For example, refs 4b and 14a.

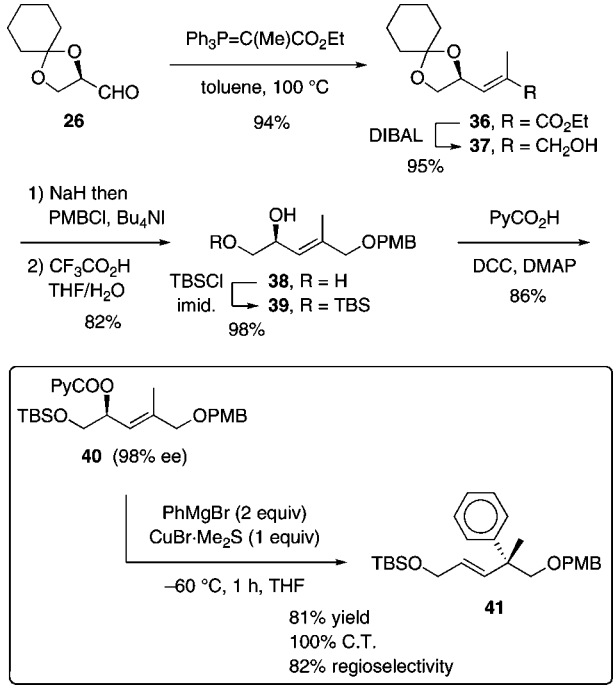
SCHEME 7. Allylic Substitution with Alkyl Reagents[a,b]



product	yield	C.T.
(S)-**6j**	90%	96%
(S)-**6k**	91%	97%
(S)-**6l**	89%	96%

[a] The stereochemistry of (*S*)-**6k** and (*S*)-**6m** was determined as described in the Experimental Section, and that of the other products was assigned by analogy. [b] Chirality transfer (C.T.) was determined by chiral HPLC.

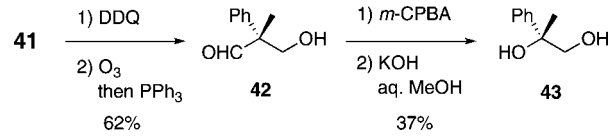
SCHEME 8. Construction of a Quaternary Center



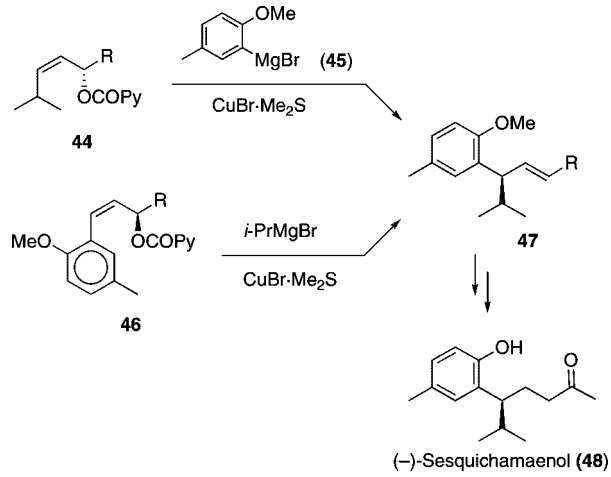
5. Alkyl Reagents. Alkyl copper reagents derived from RMgBr (R = Me, Et, *n*-Bu) and CuBr·Me_2S were subjected to substitution with (*S*)-**5a** according to the protocol developed for PhMgBr to afford (*S*)-**6j**−**l** with excellent regioselectivity and C.T. as shown in Scheme 7. Reaction of (*S*)-**5c** with EtMgBr proceeded as well to furnish (*S*)-**6m**, which is the regioisomer of (*S*)-**6k**. Comparison of the ^{1}H NMR spectra of (*S*)-**6k** and (*S*)-**6m** clearly indicated no contamination of the regioisomer in each product. The absolute configuration of (*S*)-**6k** and (*S*)-**6m** was determined by conversion to the known compounds (see Experimental Section), thus establishing anti S_N2' selection of the substitution.

6. Construction of a Quaternary Carbon. This subject was investigated using picolinate **40**, which was prepared by the procedure shown in Scheme 8. In brief, Wittig reaction of aldehyde **26** used in Scheme 4 with Ph_3P = C(Me)CO_2Et gave (*E*)-ester **36** stereoselectively, whereas use of the corresponding phosphonate resulted in somewhat worse stereoselection. Reduction of the ester with DIBAL followed by protection of the resulting alcohol **37** with PMBCl afforded the PMB ether, which was hydrolyzed to diol **38** in good yield. Monosilylation with TBSCl was followed by esterification with $PyCO_2H$ to afford the picolinate **40**, which was 98% ee by chiral HPLC analysis. Reaction of **40** with PhMgBr/CuBr·Me_2S was carried out under the conditions optimized above for (*S*)-**5a** to produce **41** in 81% yield with ∼100% C.T. and with 82% regioselectivity. The absolute configuration was determined by degradation to the known compound **43**[30] (Scheme 9), which established anti S_N2' substitution unambiguously. Previously, this issue was realized with alkyl reagents.[31,32]

SCHEME 9. Determination of the Absolute Configuration of 41



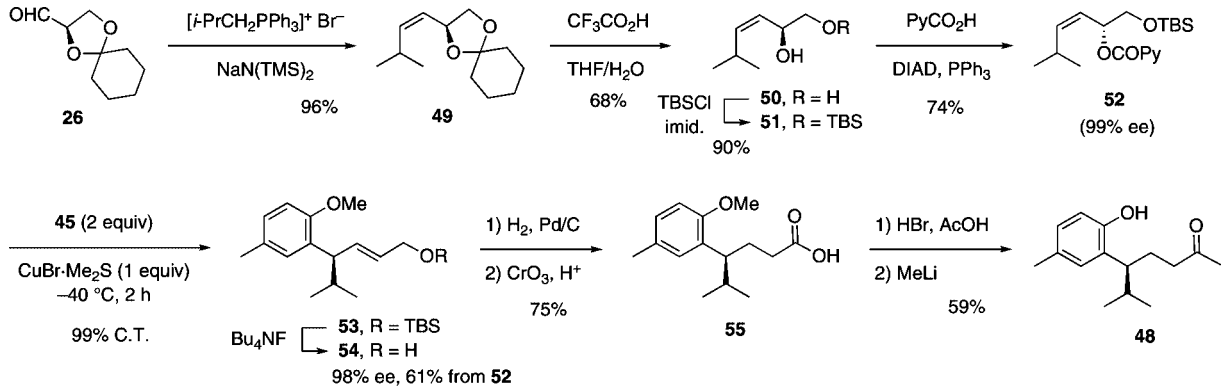
SCHEME 10. Two Possible Routes to the Key Intermediate 47



7. Synthesis of (−)-Sesquichamaenol. To apply the present allylic substitution reaction, we investigated synthesis of (−)-sesquichamaenol (**48** in Scheme 10), which was isolated from several kinds of woods.[32,33] Previously, several syntheses of racemic **48** have been reported,[32,34] whereas construction of the asymmetric center of **48** seems hardly attainable by using standard C−C bond-forming reactions such as enolate alkylation because of steric reasons. We envisioned two allylic substitutions to afford the key intermediate **47** (Scheme 10). Among these possibilities, picolinate **44** and the Grignard reagent **45** in the upper reaction are sterically more crowded than the picolinates/reagents described in the above paragraphs, whereas the lower reaction seemed difficult to effect regioselectively due to the conjugation of the double bond to the aromatic ring in **46** and

(30) Becker, H.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 448–451.
(31) (a) Nakamura, E.; Sekiya, K.; Arai, M.; Aoki, S. *J. Am. Chem. Soc.* **1989**, *111*, 3091–3093. (b) Spino, C.; Beaulieu, C. *Angew. Chem., Int. Ed.* **2000**, *39*, 1930–1932. (c) Kimura, M.; Tamazaki, T.; Kitazume, T.; Kubota, T. *Org. Lett.* **2004**, *6*, 4651–4654.
(32) Ando, M.; Ibe, S.; Kagabu, S.; Nakagawa, T.; Asao, T.; Takase, K. *J. Chem. Soc., Chem. Commun.* **1970**, 1538.
(33) (a) Kuo, Y.-H.; Yu, M.-T. *Chem. Pharm. Bull.* **1996**, *44*, 2150–2152. (b) Koorbanally, N. A.; Randrianarivelojosia, M.; Mulholland, D. A.; Van Ufford, L. Q.; Van den Berg, A. J. J. *J. Nat. Prod.* **2002**, *65*, 1349–1352.
(34) Singh, V.; Khurana, A.; Kaur, I.; Sapehiyia, V.; Kad, G. L.; Singh, J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1766–1768.

SCHEME 11. Synthesis of (−)-Sesquichamaenol (48)



due to the steric bulkiness at the olefinic carbon and the *i*-Pr group. Although both of the reactions are uncertain, we decided to investigate the upper possibility.

Aldehyde **26** was subjected to Wittig reaction with an ylide derived from $[i\text{-PrCH}_2\text{PPh}_3]^+\text{Br}^-$ and NaN(TMS)_2 to afford *cis* olefin **49** as the sole product by ^{1}H and ^{13}C NMR spectroscopy (Scheme 11). Cleavage of the acetal group and selective protection of the primary OH of diol **50** produced the TBS ether **51**. Subsequent Mitsunobu inversion with PyCO_2H, DIAD, and PPh_3 proceeded regioselectively to afford the key compound **52** (= **44** with CH_2OTBS as R) in 74% yield and with 99% ee by chiral HPLC analysis. Substitution of **52** with the reagent derived from **45** (2 equiv) and $\text{CuBr}\cdot\text{Me}_2\text{S}$ (1 equiv) at −40 °C for 2 h proceeded smoothly to furnish **53** regioselectively. Without purification, **53** was subjected to desilylation with Bu_4NF to afford alcohol **54** in 61% yield from **52** with 98% ee and 99% C.T. Acid **55** was obtained from **54** by reduction of the olefin and oxidation of the hydroxyl group. Finally, demethylation with HBr in hot AcOH followed by reaction with MeLi cleanly afforded (−)-sesquichamaenol (**48**), which was confirmed by ^{1}H and ^{13}C NMR spectra.[33] Note that **48** obtained by the reverse sequence (MeLi then HBr/AcOH) was contaminated by minor byproducts.

Next, the enantiomer of **52** was synthesized by DCC-assisted esterification of **51** with PyCO_2H and converted to *ent*-**53** as well (scheme not shown). This example demonstrates an easy access to the both enantiomers of picolinates for the allylic substitution from an available one enantiomer.

Conclusion

We have developed allylic substitution for aryl and alkenyl reagents for the first time using the picolinoxy group as a powerful leaving group. The reaction proceeded with high anti S_N2' selectivity and with efficient chirality transfer (C.T.). Almost the same result was observed with alkyl-MgBr/$\text{CuBr}\cdot\text{Me}_2\text{S}$ as well. Furthermore, construction of a quaternary carbon and synthesis of (−)-sesquichamaenol (**48**) have been achieved. Additionally, PyCO_2H, DCC, RMgBr, and $\text{CuBr}\cdot\text{Me}_2\text{S}$ are inexpensive, and both enantiomers of the starting allylic alcohols are easily available by asymmetric reactions and from natural sources. The concept of the chelation-induced activation of the picolinoxy leaving group seems applicable to other types of coupling reactions. We are continuing investigation along this line.

Experimental Section

General Procedure of the Allylic Substitution (Table 2, entry 4). To an ice-cold suspension of $\text{CuBr}\cdot\text{Me}_2\text{S}$ (18 mg, 0.088 mmol) in THF (3 mL) was added PhMgBr (0.20 mL, 0.90 M in THF, 0.18 mmol) dropwise. After 30 min of stirring, the resulting mixture was cooled to −60 °C. A solution of (*S*)-**5a** (36.5 mg, 0.0877 mmol, 90% ee) in THF (1 mL) was added to the mixture dropwise. The resulting mixture was allowed to warm to −40 °C over 1 h and diluted with hexane and saturated NH_4Cl with vigorous stirring. The layers were separated, and the aqueous layer was extracted with hexane twice. The combined extracts were washed with brine, dried over MgSO_4, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford (*R*)-**6a** (29 mg, 89%): $[\alpha]^{26}_D$ −7.7 (*c* 0.626, CHCl_3); IR (neat) 1255, 1102, 836, 698 cm^{-1}; ^{1}H NMR (300 MHz, CDCl_3) δ −0.06 (s, 3 H), −0.05 (s, 3 H), 0.84 (s, 9 H), 2.35 (dt, J = 6, 8 Hz, 2 H), 2.68 (dd, J = 8, 7.5 Hz, 2 H), 3.42 (ddd, J = 8, 7, 7 Hz, 1 H), 3.74 (dd, J = 10, 7 Hz, 1 H), 3.76 (dd, J = 10, 7 Hz, 1 H), 5.55 (dt, J = 15, 6 Hz, 1 H), 5.67 (dd, J = 15, 7 Hz, 1 H), 7.12−7.38 (m, 10 H); ^{13}C NMR (75 MHz, CDCl_3) δ −5.3, 18.4, 26.0, 34.8, 36.0, 51.4, 67.6, 125.8, 126.4, 128.26, 128.34, 128.6, 131.2, 142.1, 142.6; HRMS (FAB) calcd for $C_{24}H_{34}OSiNa$ [(M + Na)$^+$] 389.2277, found 389.2278. The enantiomeric information (88% ee, 98% C.T.) was determined by HPLC analysis of the corresponding alcohol: Chiralcel AD-H, hexane/*i*-PrOH = 98/2, 0.4 mL/min, t_R (min) = 47.7 (*S*), 49.1 (*R*).

Determination of the Absolute Configuration (Scheme 5). To an ice-cold solution of (*R*)-**6a** (120 mg, 0.327 mmol) in acetone/H_2O (4:1, 3 mL) were added NMO (50 mg, 0.43 mmol) and OsO_4 (0.33 mL, 0.02 M in *t*-BuOH, 0.0066 mmol). After 3 h at 0 °C, the mixture was diluted with H_2O and Et_2O. The layers were separated, and the aqueous layer was extracted with Et_2O twice. The combined extracts were dried over MgSO_4 and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford the corresponding diol (115 mg, 87%).

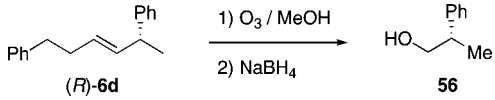
To an ice-cold solution of the above diol (110 mg, 0.244 mmol) in MeOH/H_2O (4:1, 2.5 mL) were added Bu_4NI (27 mg, 0.073 mmol) and NaIO_4 (68 mg, 0.32 mmol). After 3 h at 0 °C, NaBH_4 (40 mg, 1.06 mmol) was added to the mixture. The mixture was stirred at 0 °C for 30 min and diluted with saturated NH_4Cl and Et_2O. The layers were separated, and the aqueous layer was extracted with Et_2O twice. The combined extracts were washed with aqueous $\text{Na}_2\text{S}_2\text{O}_3$, dried over MgSO_4, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **34** (51 mg, 78%): $[\alpha]^{25}_D$ −13.0 (*c* 0.12, CHCl_3); cf. $[\alpha]^{23}_D$ +14.6 (*c* 1.03, CHCl_3) for the *R* enantiomer;[27] ^{1}H NMR (300 MHz, CDCl_3) δ 0.07 (s, 6 H), 0.91 (s, 9 H), 2.75 (dd, J = 7, 4 Hz, 1 H), 3.09 (ddd, J = 7, 7, 5 Hz, 1 H), 3.89 (ddd, J = 11, 7, 5 Hz, 1 H), 3.93 (d, J = 7 Hz, 2 H), 4.08 (ddd, J = 11, 7, 4 Hz, 1 H), 7.19−7.36 (m, 5 H). The ^{1}H NMR spectrum was identical with the data reported.[27]

(*R*,*E*)-1-[(*tert*-Butyldimethylsilyl)oxy]-2-(2-methylphenyl)-6-phenyl-3-hexene ((*R*)-6b) (Table 2, entry 7). Yield 81% from (*S*)-**5a** (90% ee), 89% ee, 99% C.T.; IR (neat) 1255, 1102, 837 cm^{-1}; ^{1}H NMR (300 MHz, CDCl_3) δ −0.04 (s, 3 H), −0.02 (s, 3 H), 0.85 (s, 9 H), 2.28−2.39 (m, 2 H), 2.33 (s, 3 H), 2.67 (dd, J = 8,

6 Hz, 2 H), 3.67−3.84 (m, 3 H), 5.50 (dt, J = 15, 7 Hz, 1 H), 5.64 (dd, J = 15, 6 Hz, 1 H), 7.11−7.32 (m, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.34, −5.30, 18.4, 19.9, 26.0, 34.8, 36.0, 46.6, 67.1, 125.8, 125.9, 126.1, 127.0, 128.3, 128.5, 130.3, 131.0, 131.2, 136.4, 140.6, 142.1; HRMS (FAB) calcd for $C_{25}H_{36}OSiNa$ [(M + Na)$^+$] 403.2433, found 403.2432. The enantiomeric information was determined by HPLC analysis of the corresponding alcohol: Chiralcel AD-H, hexane/*i*-PrOH = 97/3, 0.5 mL/min, t_R (min) = 39.0 (*S*), 40.7 (*R*).

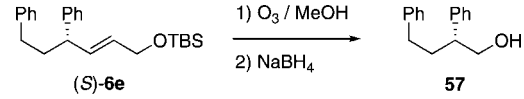
(*R*,*E*)-1-[(*tert*-Butyldimethylsilyl)oxy]-2-(2-methoxyphenyl)-6-phenyl-3-hexene ((*R*)-6c) (Table 2, entry 8). Yield 85% from (*S*)-**5a** (90% ee), 88% ee, 98% C.T.; $[\alpha]^{28}_D$ −9.7 (*c* 0.682, $CHCl_3$); IR (neat) 1241, 1103, 837, 751 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.041 (s, 3 H), −0.038 (s, 3 H), 0.84 (s, 9 H), 2.34 (dt, J = 7, 8 Hz, 2 H), 2.68 (dd, J = 8, 6 Hz, 2 H), 3.71 (dd, J = 10, 8 Hz, 1 H), 3.78 (dd, J = 10, 5 Hz, 1 H), 3.80 (s, 3 H), 3.85−3.93 (m, 1 H), 5.57 (dt, J = 16, 7 Hz, 1 H), 5.73 (dd, J = 16, 7 Hz, 1 H), 6.84 (dd, J = 8, 1 Hz, 1 H), 6.88 (ddd, J = 8, 8, 1 Hz, 1 H), 7.10 (dd, J = 8, 2 Hz, 1 H), 7.13−7.21 (m, 4 H), 7.22−7.29 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.3 (−), 18.4 (+), 26.0 (−), 34.8 (+), 36.1 (+), 44.5 (−), 55.4 (−), 66.5 (+), 110.6 (−), 120.5 (−), 125.7 (−), 127.2 (−), 128.3 (−), 128.6 (−), 128.9 (−), 130.7 (+), 130.9 (−), 131.1 (−), 142.3 (+), 157.1 (+); HRMS (FAB) calcd for $C_{25}H_{36}O_2SiNa$ [(M + Na)$^+$] 419.2382, found 419.2385. The enantiomeric information was determined by HPLC analysis of the corresponding alcohol: Chiralcel OD-H, hexane/*i*-PrOH = 97/3, 0.5 mL/min, t_R (min) = 45.2 (*S*), 54.1 (*R*).

(*R*,*E*)-1,5-Diphenyl-3-hexene ((*R*)-6d) (Table 2, entry 9). According to the typical procedure, a solution of (*S*)-**5b** (114 mg, 0.405 mmol, 89% ee) in THF (4 mL) was added to a mixture of CuBr·Me_2S (84 mg, 0.41 mmol) in THF (10 mL) and PhMgBr (0.86 mL, 0.95 M in THF, 0.82 mmol) at −60 °C, and the mixture was allowed to warm to −40 °C over 1 h to afford a mixture of (*R*)-**6d** and Ph_2 in a 83:17 ratio by ^{1}H NMR analysis (93 mg in total, 86% yield of (*R*)-**6d**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (d, J = 7 Hz, 3 H), 2.33 (dt, J = 7, 7 Hz, 2 H), 2.68 (t, J = 7 Hz, 2 H), 3.40 (dq, J = 7, 7 Hz, 1 H), 5.48 (dt, J = 15, 7 Hz, 1 H), 5.60 (dd, J = 15, 7 Hz, 1 H), 7.14−7.20 (m, 4 H), 7.23−7.28 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5 (−), 34.5 (+), 36.1 (+), 42.3 (−), 125.8 (−), 126.0 (−), 127.3 (−), 128.3 (−), 128.4 (−), 128.6 (−), 135.8 (−), 142.1 (+), 146.4 (+); HRMS (EI) calcd for 236.1565 $C_{18}H_{20}$ (M^+), found 236.1567.



Determination of the Absolute Configuration and C.T. A stream of O_3 in O_2 was gently bubbled into a solution of the mixture of (*R*)-**6d** and Ph_2 (222 mg in total, (*R*)-**6d**/Ph_2 = 81:19) in MeOH at −78 °C for 20 min. Excess O_3 remaining in the solution was purged by bubbling argon at −78 °C for 10 min and $NaBH_4$ (309 mg, 8.17 mmol) was added. After stirring for 1 h at −78 °C, the resulting mixture was allowed to warm to room temperature, and diluted with EtOAc and saturated NH_4Cl. The layers were separated, and the aqueous layer was extracted with EtOAc three times. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford alcohol **56**: 89% ee and 99% C.T. by HPLC analysis (Chiralcel OB-H, hexane/*i*-PrOH = 98/2, 0.2 mL/min, t_R (min) = 56.6 (*S*), 61.3 (*R*)); $[\alpha]^{28}_D$ −11.7 (*c* 1.2, $CHCl_3$); cf. $[\alpha]^{20}_D$ −10.8 (*c* 1.0, $CHCl_3$) for the *S* enantiomer of 78% ee;[35] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (d, J = 7 Hz, 3 H), 2.93 (tq, J = 7, 7 Hz, 1 H), 3.67 (d, J = 7 Hz, 2 H), 7.19−7.26 (m, 2 H), 7.28−7.34 (m, 3 H). The ^{1}H NMR spectrum of the product was identical with that reported.[35]

(*S*,*E*)-1-[(*tert*-Butyldimethylsilyl)oxy]-4,6-diphenyl-2-hexene ((*S*)-6e) (Table 2, entry 10). According to the typical procedure, a solution of (*S*)-**5c** (59 mg, 0.143 mmol, 95% ee) dissolved in THF (1 mL) was added to a mixture of CuBr·Me_2S (29 mg, 0.14 mmol) in THF (5 mL) and PhMgBr (0.27 mL, 1.07 M in THF, 0.287 mmol) at −40 °C, and the mixture was stirred −40 °C for 1 h to furnish (*S*)-**6e** (49 mg, 93%): $[\alpha]^{24}_D$ +14 (*c* 0.59, $CHCl_3$); IR (neat) 1254, 836, 776 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 6 H), 0.91 (s, 9 H), 2.05 (ddd, J = 8, 8, 8 Hz, 2 H), 2.48−2.68 (m, 2 H), 3.30 (ddd, J = 8, 8, 8 Hz, 1 H), 4.16 (d, J = 5 Hz, 2 H), 5.57 (dt, J = 15, 5 Hz, 1 H), 5.82 (dd, J = 15, 8 Hz, 1 H), 7.10−7.35 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.0 (−), 18.5 (+), 26.0 (−), 33.8 (+), 37.5 (+), 47.9 (−), 63.9 (+), 125.8 (−), 126.3 (−), 127.7 (−), 128.4 (−), 128.52 (−), 128.54 (−), 129.5 (−), 134.3 (−), 142.3 (+), 144.4 (+); HRMS (FAB) calcd for $C_{24}H_{34}OSiNa$ [(M + Na)$^+$] 389.2277, found 389.2287. The enantiomeric information (92% ee, 97% C.T.) was determined by HPLC analysis of the corresponding alcohol: Chiralcel AD-H, hexane/*i*-PrOH = 98/2, 0.3 mL/min, t_R (min) = 95.4 (*S*), 99.2 (*R*).



Determination of the Absolute Configuration. A stream of O_3 in O_2 was gently bubbled into a solution of (*S*)-**6e** (92 mg, 0.25 mmol) in MeOH at −78 °C for 20 min. Excess O_3 remaining in the solution was purged by bubbling argon at −78 °C, and $NaBH_4$ (95 mg, 2.51 mmol) was added at −78 °C. The cooling bath was removed. The mixture was stirred at room temperature for 1 h and diluted with saturated NH_4Cl. The resulting mixture was extracted with EtOAc three times. The combined extracts were dried over $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel (hexane/EtOAc) to furnish the alcohol **57** (56 mg, 99%): $[\alpha]^{24}_D$ −11 (*c* 0.41, $CHCl_3$); cf. $[\alpha]_D$ +6.92 (*c* 1.82, $CHCl_3$) for the (*S*)-enantiomer;[36] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (br s, 1 H), 1.81−2.12 (m, 2 H), 2.40−2.62 (m, 2 H), 2.73−2.88 (m, 1 H), 3.67−3.80 (m, 2 H), 7.05−7.40 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 33.5 (+), 33.7 (+), 48.2 (−), 67.7 (+), 125.9 (−), 127.0 (−), 128.25 (−), 128.39 (−), 128.45 (−), 128.8 (−), 142.0 (+), 142.1 (+). The ^{1}H NMR and ^{13}C NMR spectra were identical with the data reported.[36]

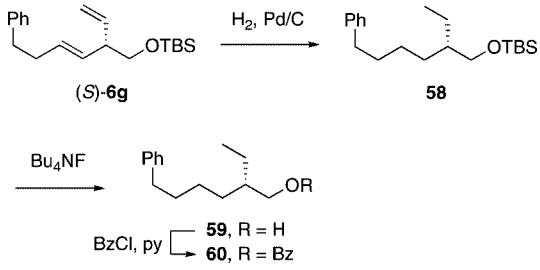
(*R*,*E*)-1-[(2-Phenylpent-3-enyloxy)methyl]-4-methoxybenzene ((*R*)-6f) (Table 2, entry 11). According to the typical procedure, a solution of (*S*)-**5d** (60.0 mg, 0.183 mmol, 97% ee) in THF (1 mL) was added to a mixture of CuBr·Me_2S (40 mg, 0.195 mmol) and PhMgBr (0.50 mL, 0.75 M in THF, 0.50 mmol) in THF (5 mL) at −60 °C. The resulting mixture was allowed to warm to −40 °C over 1 h and diluted with hexane and saturated NH_4Cl to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to give (*R*)-**6f** (43 mg, 83%): IR (neat) 1612, 1513, 1248 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.68 (d, J = 6 Hz, 3 H), 3.53−3.68 (m, 3 H), 3.80 (s, 3 H), 4.45 (s, 2 H), 5.51 (dq, J = 15, 6 Hz, 1 H), 5.63 (dd, J = 15, 7 Hz, 1 H), 6.85 (d, J = 8 Hz, 2 H), 7.15−7.23 (m, 5 H), 7.25−7.33 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.2 (−), 48.9 (−), 55.3 (−), 72.7 (+), 73.7 (+), 113.8 (−), 126.4 (−), 126.7 (−), 128.0 (−), 128.4 (−), 129.3 (−), 130.6 (+), 131.9 (−), 142.5 (+), 159.1 (+); HRMS (EI) calcd for $C_{19}H_{22}O_2$ (M^+) 282.1620, found 282.1627. The enantiomeric information (97% ee, 99% C.T.) was determined by HPLC analysis of the corresponding alcohol: Chiralcel AD-H; hexane/*i*-PrOH = 97/3, 0.3 mL/min, t_R (min) = 29.9 (*R*), 33.7 (*S*).

(*S*,*E*)-1-[(*tert*-Butyldimethylsilyl)oxy]-2-ethenyl-6-phenyl-3-hexene ((*S*)-6g) (Scheme 6). Yield 81%, 88% ee, 98% C.T.; IR (neat) 1256, 1104, 836 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 6 H), 0.90 (s, 9 H), 2.35 (dt, J = 7, 8 Hz, 2 H), 2.69 (dd, J =

(35) Xie, J.-H.; Zhou, Z.-T.; Kong, W.-L.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2007**, *129*, 1868–1869.

(36) Spino, C.; Gund, V. G.; Nadeau, C. *J. Comb. Chem.* **2005**, *7*, 345–352.

7, 6 Hz, 2 H), 2.87 (ddt, J = 8, 8, 7 Hz, 1 H), 3.54 (d, J = 7 Hz, 2 H), 4.98−5.08 (m, 2 H), 5.40 (dd, J = 16, 8 Hz, 1 H), 5.55 (dt, J = 16, 7 Hz, 1 H), 5.79 (ddd, J = 17, 11, 7 Hz, 1 H), 7.15−7.23 (m, 3 H), 7.25−7.32 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.2, 18.5, 26.0, 34.8, 36.0, 49.5, 66.6, 115.4, 125.8, 128.3, 128.5, 130.2, 131.3, 138.9, 142.1. The enantiomeric information was determined by HPLC analysis of the corresponding alcohol: Chiralcel AD-H, hexane/*i*-PrOH = 97/3, 0.3 mL/min, t_R (min) = 30.5 (*R*), 31.9 (*S*).



Determination of the Absolute Configuration. To a solution of (*S*)-**6g** (42 mg, 0.153 mmol) in MeOH and EtOAc (1:1, 2 mL) was added 10% Pd/C (20 mg). The mixture was stirred at room temperature for 2 h under H_2 atmosphere and filtered through a pad of Celite. The filtrate was concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **58** (40 mg, 94%): $[\alpha]^{28}_D$ 0 (*c* 0.80, $CHCl_3$); IR (neat) 1256, 1094, 835, 774 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 6 H), 0.85 (t, J = 7 Hz, 3 H), 0.89 (s, 9 H), 1.18−1.42 (m, 8 H), 1.54−1.66 (m, 1 H), 2.60 (t, J = 8 Hz, 2 H), 3.46 (d, J = 5 Hz, 2 H), 7.15−7.20 (m, 3 H), 7.23−7.30 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.3 (−), 11.3 (−), 18.4 (+), 23.6 (+), 26.0 (−), 26.7 (+), 30.4 (+), 32.0 (+), 36.0 (+), 42.0 (−), 65.3 (+), 125.6 (−), 128.3 (−), 128.5 (−), 143.0 (+).

To an ice-cold solution of **58** (40 mg, 0.125 mmol) in THF (1 mL) was added Bu_4NF (0.19 mL, 1.0 M in THF, 0.19 mmol). The reaction was carried out at room temperature for 3 h, and quenched by addition of saturated NH_4Cl. The organic phase was separated, and the aqueous phase was extracted with EtOAc three times. The combined organic layers were dried over $MgSO_4$ and concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish **59** (24 mg, 93%): $[\alpha]^{28}_D$ −1.2 (*c* 0.803, $CHCl_3$); IR (neat) 3351, 1453, 1030 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, J = 7 Hz, 3 H), 1.21 (br s, 1 H), 1.26−1.45 (m, 6 H), 1.56−1.68 (m, 3 H), 2.61 (t, J = 8 Hz, 2 H), 3.54 (d, J = 4 Hz, 2 H), 7.13−7.22 (m, 3 H), 7.23−7.30 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.2 (−), 23.4 (+), 26.7 (+), 30.4 (+), 31.9 (+), 36.0 (+), 42.0 (−), 65.3 (+), 125.7 (−), 128.3 (−), 128.5 (−), 142.8 (+).

To an ice-cold solution of **59** (24 mg, 0.117 mmol) in pyridine and CH_2Cl_2 (1:1, 1 mL) was added BzCl (0.027 mL, 0.233 mmol). The resulting mixture was stirred at room temperature overnight and diluted with EtOAc and H_2O. The excess reagent was quenched with *N*,*N*-dimethyl-1,3-propanediamine (0.050 mL, 0.40 mmol). The mixture was stirred at room temperature for 20 min. The organic phase was separated, and the aqueous phase was extracted with EtOAc three times. The combined organic layers were dried over $MgSO_4$ and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **60** (23 mg, 63%): $[\alpha]^{28}_D$ −1.8 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (t, J = 8 Hz, 3 H), 1.35−1.52 (m, 6 H), 1.58−1.77 (m, 3 H), 2.62 (t, J = 8 Hz, 2 H), 4.24 (d, J = 6 Hz, 2 H), 7.13−7.21 (m, 3 H), 7.22−7.30 (m, 2 H), 7.44 (dddd, J = 8, 8, 1, 1 Hz, 2 H), 7.56 (dddd, J = 8, 8, 1, 1 Hz, 1 H), 8.04 (ddd, J = 8, 1, 1 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.2 (−), 24.1 (+), 26.6 (+), 30.9 (+), 31.9 (+), 36.0 (+), 39.0 (−), 67.3 (+), 125.7 (−), 128.3 (−), 128.43 (−), 128.45 (−), 129.6 (−), 130.6 (+), 132.9 (−), 142.7 (+), 152.1 (+), 166.8 (+); HRMS (EI) calcd for $C_{21}H_{26}O_2$ (M^+) 310.1934, found 310.1933.

HPLC analysis (Chiralcel OB-H, hexane/*i*-PrOH = 98/2, 0.2 mL/min, t_R (min) = 32.6 (*S*), 33.8 (*R*)) showed that retention time of **60** thus synthesized was identical with that of **60** synthesized from (*S*)-**6k** (R = Et in Scheme 7) ((i) H_2, Pd/C, MeOH and EtOAc; (ii) Bu_4NF; (iii) BzCl, pyridine, CH_2Cl_2), while determination of the absolute configuration of (*S*)-**6k** was independently carried out as described below.

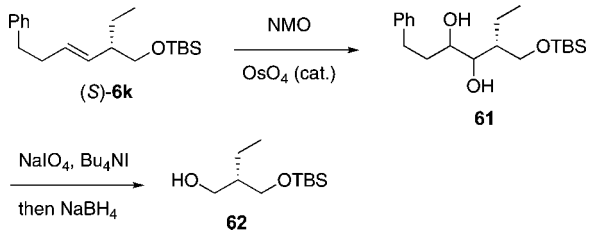
(*R*,*E*)-1-[(*tert*-Butyldimethylsilyl)oxy]-2-(1-pentylethenyl)-6-phenyl-3-hexene ((*R*)-6h) (Scheme 6). Yield 75%, 87% ee, 97% C.T.; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 3 H), 0.03 (s, 3 H), 0.88 (s, 9 H), 0.89 (m, 3 H), 1.21−1.48 (m, 6 H), 1.97 (t, J = 8 Hz, 2 H), 2.32 (ddd, J = 8, 8, 7 Hz, 2 H), 2.67 (t, J = 8 Hz, 2 H), 2.76 (ddd, J = 7, 7, 7 Hz, 1 H), 3.55 (dd, J = 10, 7 Hz, 1 H), 3.65 (dd, J = 10, 7 Hz, 1 H), 4.71 (s, 1 H), 4.78 (s, 1 H), 5.37 (dd, J = 15, 8 Hz, 1 H), 5.50 (dt, J = 15, 6 Hz, 1 H), 7.14−7.30 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.22 (−), −5.16 (−), 14.2 (−), 18.4 (+), 22.7 (+), 26.0 (−), 27.5 (+), 31.8 (+), 34.7 (+), 35.6 (+), 36.1 (+), 51.5 (−), 66.0 (+), 109.3 (+), 125.8 (−), 128.3 (−), 128.5 (−), 130.8 (−), 131.3 (−), 142.2 (+), 150.4 (+); HRMS (FAB) calcd for $C_{25}H_{42}OSiNa$ [$(M + Na)^+$] 409.2903, found 409.2905. The enantiomeric information was determined by HPLC analysis of the corresponding alcohol: Chiralcel AD-H, hexane/*i*-PrOH = 97/3, 0.3 mL/min, t_R (min) = 26.0 (*R*), 28.0 (*S*).

(*R*,*E*)-1-[(*tert*-Butyldimethylsilyl)oxy]-6-phenyl-2-(1-phenylethenyl)-3-hexene ((*R*)-6i) (Scheme 6). Yield 85%, 87% ee, 97% C.T.; IR (neat) 1256, 1103, 836 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.09 (s, 6 H), 0.79 (s, 9 H), 2.22−2.32 (m, 2 H), 2.60 (dd, J = 8, 8 Hz, 2 H), 3.28 (ddd, J = 7, 7, 6 Hz, 1 H), 3.52 (dd, J = 10, 7 Hz, 1 H), 3.62 (dd, J = 10, 6 Hz, 1 H), 4.96 (s, 1 H), 5.22 (s, 1 H), 5.44 (dd, J = 16, 7 Hz, 1 H), 5.52 (dt, J = 16, 6 Hz, 1 H), 7.04−7.33 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.3, −5.2, 18.4, 26.0, 34.7, 36.0, 50.2, 66.2, 113.7, 125.8, 126.7, 127.2, 128.1, 128.3, 128.6, 131.1, 131.3, 142.1, 142.6, 149.6; HRMS (FAB) calcd for $C_{26}H_{36}OSiNa$ [$(M + Na)^+$] 415.2433, found 415.2430. The enantiomeric information was determined by HPLC analysis of the corresponding alcohol: Chiralcel AD-H, hexane/*i*-PrOH = 97/3, 0.3 mL/min, t_R (min) = 47.6 (*S*), 59.9 (*R*).

(*S*,*E*)-1-[(*tert*-Butyldimethylsilyl)oxy]-2-methyl-6-phenyl-3-hexene ((*S*)-6j) (Scheme 7). Yield 90% from (*S*)-**5a** (90% ee), 86% ee, 96% C.T.; IR (neat) 1257, 1078, 837, 775 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 6 H), 0.89 (s, 9 H), 0.96 (d, J = 7 Hz, 3 H), 2.20−2.35 (m, 3 H), 2.67 (t, J = 7 Hz, 2 H), 3.34 (dd, J = 9, 7 Hz, 1 H), 3.46 (dd, J = 9, 6 Hz, 1 H), 5.35 (dd, J = 16, 7 Hz, 1 H), 5.49 (dt, J = 16, 7 Hz, 1 H), 7.14−7.21 (m, 3 H), 7.24−7.31 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.21, −5.18, 16.8, 18.5, 26.0, 34.7, 36.2, 39.4, 68.4, 125.8, 128.3, 128.6, 129.3, 133.6, 142.2. HRMS (FAB) calcd for $C_{19}H_{32}OSiNa$ [$(M + Na)^+$] 327.2120, found 327.2122. The enantiomeric information was determined by HPLC analysis of the corresponding alcohol: Chiralcel AD-H, hexane/*i*-PrOH = 97/3, 0.3 mL/min, t_R (min) = 30.0 (*R*), 31.3 (*S*).

(*S*,*E*)-1-[(*tert*-Butyldimethylsilyl)oxy]-2-ethyl-6-phenyl-3-hexene ((*S*)-6k) (Scheme 7). Yield 91% from (*S*)-**5a** (90% ee), 87% ee, 97% C.T.; IR (neat) 1256, 1103, 836 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 6 H), 0.82 (t, J = 7 Hz, 3 H), 0.89 (s, 9 H), 1.07−1.34 (m, 1 H), 1.46−1.62 (m, 1 H), 1.94−2.08 (m, 1 H), 2.28−2.38 (m, 2 H), 2.68 (dd, J = 7, 6 Hz, 2 H), 3.43 (dd, J = 10, 7 Hz, 1 H), 3.48 (dd, J = 10, 6 Hz, 1 H), 5.20 (dddd, J = 15, 8, 2, 2 Hz, 1 H), 5.48 (dt, J = 15, 7 Hz, 1 H), 7.13−7.35 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.2, 11.7, 18.5, 24.0, 26.0, 34.8, 36.3, 47.3, 66.9, 125.8, 128.3, 128.6, 130.9, 132.3, 142.2; HRMS (FAB) calcd for $C_{20}H_{34}OSiNa$ [$(M + Na)^+$] 341.2277, found 341.2269. The enantiomeric information was determined by HPLC analysis of the corresponding alcohol: Chiralcel AD-H, hexane/*i*-PrOH = 97/3, 0.3 mL/min, t_R (min) = 28.7 (*R*), 29.8 (*S*).

Determination of the Absolute Configuration. To an ice-cold solution of (*S*)-**6k** (110 mg, 0.345 mmol) in acetone/H_2O (4:1, 3.5 mL) were added NMO (53 mg, 0.45 mmol) and OsO_4 (0.175 mL, 0.02 M in *t*-BuOH, 0.0035 mmol). After 5 h at 0 °C, the mixture was diluted with H_2O and Et_2O. The layers were separated, and



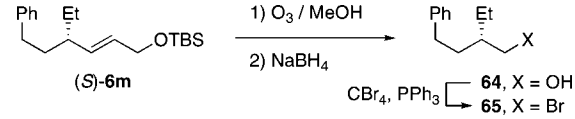
the aqueous layer was extracted with Et_2O twice. The combined extracts were dried over $MgSO_4$ and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **61** (105 mg, 85%).

To an ice-cold solution of **61** (55 mg, 0.16 mmol) in MeOH/H_2O (5:1, 2 mL) were added Bu_4NI (18 mg, 0.049 mmol) and $NaIO_4$ (48 mg, 0.22 mmol). After 4 h at 0 °C, $NaBH_4$ (20 mg, 0.53 mmol) was added to the mixture. The mixture was stirred at 0 °C for 30 min and diluted with saturated NH_4Cl and Et_2O. The layers were separated, and the aqueous layer was extracted with Et_2O twice. The combined extracts were washed with aqueous $Na_2S_2O_3$, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **62** (21 mg, 61%): $[\alpha]^{25}_D$ −10.0 (*c* 0.10, $CHCl_3$); cf. $[\alpha]^{26}_D$ −11.41 (*c* 1.42, $CHCl_3$);[371]^{1}H NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 6 H), 0.90 (s, 9 H), 0.92 (t, J = 8 Hz, 3 H), 1.19−1.35 (m, 2 H), 1.58−1.72 (m, 1 H), 2.92 (dd, J = 6, 4 Hz, 1 H), 3.60 (dd, J = 10, 7 Hz, 1 H), 3.60−3.68 (m, 1 H), 3.70−3.80 (m, 1 H), 3.81 (dd, J = 10, 4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.55, −5.49, 11.9, 18.2, 20.7, 25.9, 43.7, 66.7, 67.4.

(*S*,*E*)-1-[(*tert*-Butyldimethylsilyl)oxy]-2-butyl-6-phenyl-3-hexene ((*S*)-6l) (Scheme 7). Yield 89%, 86% ee, 96% C.T.; IR (neat) 1256, 1077, 837, 775 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 6 H), 0.82−1.00 (br s, 12 H), 1.16−1.35 (m, 5 H), 1.44−1.54 (m, 1 H), 2.03−2.16 (m, 1 H), 2.33 (dt, J = 7, 7 Hz, 2 H), 2.69 (t, J = 7 Hz, 2 H), 3.37−3.53 (m, 2 H), 5.21 (dd, J = 15, 8 Hz, 1 H), 5.48 (dt, J = 15, 7 Hz, 1 H), 6.85−7.22 (m, 3 H), 7.25−7.32 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.21, −5.17, 14.2, 18.5, 22.9, 26.0, 29.3, 30.9, 34.7, 36.2, 45.5, 67.2, 125.8, 128.3, 128.6, 130.6, 132.7, 142.2; HRMS (FAB) calcd for $C_{22}H_{38}OSiNa$ [(M + Na)$^+$] 369.2590, found 369.2594. The enantiomeric information was determined by HPLC analysis of the corresponding alcohol: Chiralcel AD-H, hexane/*i*-PrOH = 97/3, 0.3 mL/min, t_R (min) = 25.9 (*R*), 27.6 (*S*).

(*S*,*E*)-1-[(*tert*-Butyldimethylsilyl)oxy]-4-ethyl-6-phenyl-2-hexene ((*S*)-6m) (Scheme 7). Yield 92% from (*S*)-**5c** (95% ee), 92% ee, 97% C.T.; $[\alpha]^{23}_D$ +4.7 (*c* 0.42, $CHCl_3$); IR (neat) 1462, 1255, 1092, 837 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.099 (s, 3 H), 0.101 (s, 3 H), 0.86 (t, J = 7 Hz, 3 H), 0.93 (s, 9 H), 1.18−1.80 (m, 6 H), 1.87−2.00 (m, 1 H), 2.45−2.70 (m, 2 H), 4.19 (d, J = 5 Hz, 2 H), 5.43 (dd, J = 15, 8 Hz, 1 H), 5.55 (dt, J = 15, 5 Hz, 1 H), 7.12−7.22 (m, 3 H), 7.24−7.32 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.9 (−), 11.7 (−), 18.5 (+), 26.1 (−), 28.1 (+), 33.7 (+), 36.8 (+), 43.8 (−), 64.1 (+), 125.6 (−), 128.3 (−), 128.5 (−), 130.0 (−), 134.9 (−), 143.0 (+). The enantiomeric information was determined by HPLC analysis of the corresponding alcohol shown below.

Determination of C.T. To a solution of the above product (23 mg, 0.072 mmol) in THF (2 mL) was added Bu_4NF (0.14 mL, 1.0 M in THF, 0.14 mmol) dropwise. The reaction was carried out at room temperature for 1 h and quenched by addition of saturated NH_4Cl. The organic phase was separated, and the aqueous phase was extracted with EtOAc three times. The combined organic layers were dried over $MgSO_4$ and concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish **63** (14 mg, 95%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (t, J = 7 Hz, 3 H), 1.24−1.78 (m, 5 H), 1.88−2.02 (m, 1 H), 2.45−2.70 (m, 2 H), 4.13 (dd, J = 6, 1 Hz, 1 H), 5.46 (dd, J = 15, 9 Hz, 1 H), 5.64 (dt, J = 15, 6 Hz, 1 H), 7.14−7.22 (m, 3 H), 7.24−7.32 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.7 (−), 27.9 (+), 33.7 (+), 36.6 (+), 43.9 (−), 63.9 (+), 125.7 (−), 128.4 (−), 128.5 (−), 129.6 (−), 137.0 (−), 142.8 (+); HRMS (EI) calcd for $C_{14}H_{20}O$ (M^+) 204.1514, found 204.1516. The enantiomeric information (92% ee, 97% C.T.) was determined by chiral HPLC analysis: Chiralcel OB-H, hexane/*i*-PrOH = 98/2, 0.3 mL/min, t_R (min) = 31.8 (*R*), 33.8 (*S*).



Determination of the Absolute Configuration. A stream of O_3 in O_2 was gently bubbled into a solution of (*S*)-**6m** (78 mg, 0.245 mmol) in MeOH at −78 °C for 20 min. Excess O_3 remaining in the solution was purged by bubbling argon at −78 °C, and $NaBH_4$ (93 mg, 2.45 mmol) was added. The cooling bath was removed, and the solution was stirred at room temperature for 1 h. Saturated NH_4Cl was added to the solution, and the resulting mixture was extracted with EtOAc three times. The combined extracts were dried over $MgSO_4$ and concentrated to obtain a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to give alcohol **64** (38 mg, 87%): $[\alpha]^{23}_D$ 0 (*c* 0.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.92 (t, J = 7 Hz, 3 H), 1.36−1.54 (m, 2 H), 1.56−4.74 (m, 2 H), 2.64 (t, J = 8 Hz, 2 H), 3.60 (d, J = 5 Hz, 2 H), 7.14−7.33 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.3 (−), 23.3 (+), 32.6 (+), 33.5 (+), 41.8 (−), 65.3 (+), 125.9 (−), 128.6 (−), 142.9 (+). The ^{1}H NMR and ^{13}C NMR spectra were identical with the data reported.[38]

To an ice-cold solution of the above alcohol (25 mg, 0.14 mmol) in CH_2Cl_2 (5 mL) were added CBr_4 (56 mg, 0.169 mmol) and PPh_3 (48 mg, 0.183 mmol) portionwise. The mixture was stirred at 0 °C for 2 h and filtered through a pad of Celite. The filtrate was concentrated to afford a residual oil, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish bromide **65** (20 mg, 59%): $[\alpha]^{25}_D$ +6 (*c* 0.2, $CHCl_3$), *cf.* $[\alpha]_D$ +10.8 (*c* 1.5, $CHCl_3$) for the same enantiomer;[391]^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, J = 8 Hz, 3 H), 1.43−1.80 (m, 5 H), 2.53−2.73 (m, 2 H), 3.52 (d, J = 4 Hz, 2 H), 7.16−7.24 (m, 3 H), 7.25−7.34 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.9 (−), 25.2 (+), 33.0 (+), 34.1 (+), 38.8 (+), 40.5 (−), 125.9 (−), 128.4 (−), 128.5 (−), 142.2 (+); HRMS (EI) calcd for $C_{12}H_{17}Br$ (M^+) 242.0514, found 242.0518. The ^{1}H NMR and ^{13}C NMR spectra were identical with the data reported.[39]

(*S*,*E*)-Ethyl 2-Methyl-3-(1,4-dioxaspiro[4.5]decan-2-yl)prop-2-enoate (36). A solution of **26** (1.20 g, 7.05 mmol) and Ph_3P = C(Me)CO_2Et (3.06 g, 8.44 mmol) in toluene (15 mL) was stirred at 100 °C for 30 min. After being stirred at room temperature for 12 h, the solvent was removed to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish **36** (1.49 g, 94%): IR (neat) 1713, 1250, 929, 746 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, J = 7 Hz, 3 H), 1.20−1.80 (m, 10 H), 1.85 (s, 3 H), 3.58 (t, J = 8 Hz, 1 H), 4.04−4.22 (m, 3 H), 4.82 (q, J = 7 Hz, 1 H), 6.65 (d, J = 7 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.0 (−), 14.2 (−), 23.89 (+), 23.93 (+), 25.1 (+), 35.4 (+), 36.2 (+), 60.9 (+), 68.3 (+), 72.4 (−), 110.4 (+),

(37) Ihara, M.; Takahashi, M.; Taniguchi, N.; Yasui, K.; Fukumoto, K.; Kametani, T. *J. Chem. Soc., Perkin Trans. 1* **1989**, 897–903.

(38) Jones, R. V. H.; Standen, M. C. H. *Tetrahedron* **1998**, *54*, 14617–14634.

(39) Yang, Z.; Attygalle, A. B.; Meinwald, J. *Synthesis* **2000**, *13*, 1936–1943.

130.9 (+), 138.4 (−), 167.4 (+); HRMS (FAB) calcd for $C_{14}H_{22}O_4Na$ [$(M + Na)^+$] 277.1416, found 277.1416.

(*S*,*E*)-2-Methyl-3-(1,4-dioxaspiro[4.5]decan-2-yl)prop-2-en-1-ol (37). To a solution of ester **36** (271 mg, 1.20 mmol) in THF (10 mL) was added DIBAL (3.09 mL, 0.97 M in hexane, 3.00 mmol) dropwise at −78 °C. After being stirred at −78 to −60 °C for 15 min, the reaction was quenched with H_2O (0.34 mL, 12 mmol) and NaF (1.0 g, 24 mmol) at 0 °C with vigorous stirring. After 30 min of additional stirring, the resulting suspension was filtered through a pad of Celite with EtOAc. The filtrate was concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish alcohol **37** (242 mg, 95%): IR (neat) 3422, 1104, 930 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.2−1.8 (m, 10 H), 1.67 (s, 3 H), 2.3−2.6 (br s, 1 H), 3.47 (t, J = 8 Hz, 1 H), 3.92−4.11 (m, 3 H), 4.75−4.82 (m, 1 H), 5.42 (dt, J = 8, 2 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0 (−), 23.8 (+), 23.9 (+), 25.1 (+), 35.5 (+), 36.3 (+), 67.4 (+), 68.9 (+), 72.1 (−), 109.6 (+), 122.1 (−), 140.7 (+).

(*S*,*E*)-5-(4-Methoxybenzyloxy)-4-methylpent-3-ene-1,2-diol (38). To an ice-cold solution of **37** (255 mg, 1.20 mmol) in THF (10 mL) was added NaH (58 mg, 60% in mineral oil, 1.45 mmol). The mixture was stirred at room temperature for 30 min. Bu_4NI (90 mg, 0.24 mmol) and PMBCl (0.21 mL, 1.54 mmol) were added to the mixture. The reaction was carried out at room temperature for 12 h and quenched by addition of saturated NH_4Cl. The resulting mixture was extracted with hexane three times. The combined extracts were dried over $MgSO_4$ and concentrated. The residue was passed through a short column of silica gel (hexane/EtOAc) to afford the corresponding PMB ether, which was used for the next reaction without further purification.

A solution of the above ether in CF_3CO_2H (0.37 mL, 4.8 mmol), H_2O (1 mL), and THF (1 mL) was stirred at room temperature for 3 h and diluted with saturated $NaHCO_3$ and EtOAc. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined extracts were dried over $MgSO_4$ and concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish **38** (248 mg, 82% from **37**): IR (neat) 3364, 1515, 1208, 728 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.67 (s, 3 H), 3.40−3.65 (m, 2 H), 3.78 (s, 3 H), 3.83 (s, 2 H), 4.38 (s, 2 H), 4.58 (dt, J = 8, 3 Hz, 1 H), 5.40 (d, J = 8 Hz, 1 H), 6.86 (d, J = 9 Hz, 2 H), 7.23 (d, J = 9 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4 (−), 55.3 (−), 65.2 (+), 68.8 (−), 72.0 (+), 74.6 (+), 113.9 (−), 124.0 (−), 129.5 (−), 130.1 (+), 138.2 (+), 159.3 (+).

(*S*,*E*)-1-[(*tert*-Butyldimethylsilyl)oxy]-5-(4-methoxybenzyloxy)-4-methylpent-3-en-2-ol (39). To a solution of **38** (1.07 g, 4.24 mmol) and imidazole (959 mg, 6.36 mmol) in DMF (10 mL) at −40 °C was added TBSCl (346 mg, 5.08 mmol) in DMF (2 mL) dropwise. After 30 min at −40 °C, the resulting solution was diluted with saturated $NaHCO_3$ and EtOAc with vigorous stirring. The organic layer was separated, and the aqueous layer was extracted with EtOAc three times. The combined organic layers were dried over $MgSO_4$ and concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish **39** (1.40 g, 98%): IR (neat) 3437, 1514, 1249, 1110, 836 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.09 (s, 6 H), 0.91 (s, 9 H), 1.74 (d, J = 1 Hz, 3 H), 3.44 (dd, J = 10, 8 Hz, 1 H), 3.59 (dd, J = 10, 4 Hz, 1 H), 3.80 (s, 3 H), 3.89 (s, 2 H), 4.40 (s, 2 H), 4.47 (dt, J = 8, 4 Hz, 1 H), 5.43 (dq, J = 8, 1 Hz, 1 H), 6.87 (d, J = 9 Hz, 2 H), 7.26 (d, J = 9 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.33 (−), −5.26 (−), 14.5 (−), 18.4 (+), 25.9 (−), 55.3 (−), 66.7 (+), 69.0 (−), 71.6 (+), 75.1 (+), 113.8 (−), 125.5 (−), 129.4 (−), 130.4 (+), 137.0 (+), 159.2 (+); HRMS (FAB) calcd for $C_{20}H_{34}O_4SiNa$ [$(M + Na)^+$] 389.2124, found 389.2117.

(*S*,*E*)-1-[(*tert*-Butyldimethylsilyl)oxy]-5-(4-methoxybenzyloxy)-4-methylpent-3-en-2-yl Pyridine-2-carboxylate (40). To an ice-cold solution of **39** (100 mg, 0.30 mmol) in CH_2Cl_2 (3 mL) were added DCC (80 mg, 0.39 mmol), DMAP (44 mg, 0.36 mmol), and picolinic acid (44 mg, 0.36 mmol). The mixture was stirred at room temperature for 2 h and filtered through a pad of Celite. The filtrate was concentrated to afford a residual oil, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish **40** (121 mg, 86%): 98% ee by HPLC analysis (Chiralcel OD-H, hexane/*i*-PrOH = 97/3, 0.3 mL/min, t_R (min) = 50.4 (*S*), 61.5 (*R*)); IR (neat) 1718, 1513, 1247, 1131, 837 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ −0.01 (s, 3 H), 0.01 (s, 3 H), 0.80 (s, 9 H), 1.82 (s, 3 H), 3.73 (s, 3 H), 3.70−3.92 (m, 2 H), 3.86 (s, 2 H), 4.35 (s, 2 H), 5.57 (d, J = 9 Hz, 1 H), 5.89−5.98 (m, 1 H), 6.81 (d, J = 9 Hz, 2 H), 7.20 (d, J = 9 Hz, 2 H), 7.39 (dd, J = 8, 5 Hz, 1 H), 7.76 (dt, J = 8, 1 Hz, 1 H), 8.06 (d, J = 8 Hz, 1 H), 8.70 (dt, J = 5, 1 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.5 (−), 14.6 (−), 18.1 (+), 25.7 (−), 55.1 (−), 64.6 (+), 71.4 (+), 72.9 (−), 74.4 (+), 113.6 (−), 121.5 (−), 125.0 (−), 126.6 (−), 129.2 (−), 130.2 (+), 136.8 (−), 139.3 (+), 148.2 (+), 149.7 (−), 159.0 (+), 164.3 (+); HRMS (FAB) calcd for $C_{26}H_{38}NO_5Si$ [$(M + H)^+$] 472.2519, found 472.2518.

(*R*,*E*)-1-[(*tert*-Butyldimethylsilyl)oxy]-5-(4-methoxybenzyloxy)-4-methyl-4-phenylpent-2-ene (41). To an ice-cold suspension of $CuBr\cdot Me_2S$ (135 mg, 0.657 mmol) in THF (10 mL) was added PhMgBr (1.40 mL, 0.94 M in THF, 1.32 mmol). The mixture was stirred at 0 °C for 30 min and cooled to −60 °C. A solution of **40** (310 mg, 0.657 mmol, 98% ee) dissolved in THF (1 mL) was added to the mixture. The reaction was carried out −60 °C for 1 h and quenched by addition of saturated NH_4Cl. The resulting mixture was extracted with hexane three times. The combined extracts were dried over $MgSO_4$ and concentrated to obtain a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish **41** (227 mg, 81%): 98% ee, 100% C.T. by HPLC analysis (Chiralcel OJ-H, hexane/*i*-PrOH = 99/1, 0.3 mL/min, t_R (min) = 18.4 (*R*), 21.2 (*S*)); $[\alpha]^{30}_D$ +1.5 (*c* 0.40, $CHCl_3$); IR (neat) 1513, 1249, 1099, 836 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.12 (s, 6 H), 0.96 (s, 9 H), 1.49 (s, 3 H), 3.60 (d, J = 9 Hz, 1 H), 3.66 (d, J = 9 Hz, 1 H), 3.82 (s, 3 H), 4.26 (dd, J = 5, 2 Hz, 2 H), 4.48 (s, 2 H), 5.62 (dt, J = 16, 5 Hz, 1 H), 5.98 (dt, J = 16, 2 Hz, 1 H), 6.89 (d, J = 8 Hz, 2 H), 7.20−7.42 (m, 7 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.0 (−), 18.5 (+), 23.7 (−), 26.0 (−), 44.5 (+), 55.2 (−), 64.3 (+), 73.0 (+), 77.5 (+), 113.7 (−), 126.1 (−), 127.0 (−), 128.0 (−), 128.1 (−), 129.1 (−), 130.6 (+), 136.7 (−), 145.7 (+), 159.0 (+); HRMS (FAB) calcd for $C_{26}H_{38}O_3SiNa$ [$(M + Na)^+$] 449.2488, found 449.2493.

Determination of the Absolute Configuration (Scheme 9). To an ice-cold solution of **41** (578 mg, 1.35 mmol) in CH_2Cl_2 (13 mL) and H_2O (0.6 mL) was added DDQ (460 mg, 2.03 mmol). The mixture was stirred at 0 °C for 1 h, and diluted with saturated $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with Et_2O three times. The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was passed through a short column of silica gel (hexane/EtOAc) to afford a 1:1 mixture of the corresponding alcohol and *p*-$MeOC_6H_4CHO$ (573 mg in total, 69% yield of the alcohol), which was used for the next reaction without further purification.

A stream of O_3 in O_2 was gently bubbled into a solution of the 1:1 mixture of the alcohol and *p*-$MeOC_6H_4CHO$ (180 mg, 0.67 mmol) in MeOH at −78 °C for 20 min. Excess O_3 remaining in the solution was purged by bubbling argon at −78 °C for 10 min, and PPh_3 (200 mg, 0.76 mmol) was added. The cooling bath was removed, and the solution was stirred at room temperature for 2 h. The reaction was concentrated to obtain a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish **42** (43 mg, 90%): ^1H NMR (300 MHz, $CDCl_3$) δ 1.57 (s, 3 H), 3.72 (d, J = 11 Hz, 1 H), 4.09 (d, J = 11 Hz, 1 H), 7.20−7.45 (m, 5 H), 9.57 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.6 (−), 56.4 (+), 67.7 (+), 127.4 (−), 128.1 (−), 129.3 (−), 137.5 (+), 203.3 (−).

A solution of commercial *m*-CPBA (95 mg, 77% purity, 0.423 mmol) in CH_2Cl_2 (1 mL) was washed with buffer pH 7.6 and dried over $MgSO_4$. To a solution of **42** (43 mg, 0.28 mmol) in CH_2Cl_2 (5 mL) were added the dried *m*-CPBA (73 mg, ca. 100% purity,

0.45 mmol) and Na_2HPO_4 (40 mg, 0.28 mmol). The reaction was carried out at room temperature for 5 h and quenched by addition of H_2O. The mixture was extracted with Et_2O three times. The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel (hexane/EtOAc) to furnish the corresponding formate, which was used for the next reaction without further purification.

To a solution of the above formate in MeOH (1 mL) was added aqueous KOH (0.46 mL, 1.83 M, 0.85 mmol). The mixture was stirred at room temperature for 2 h and diluted with H_2O. The resulting mixture was extracted with Et_2O three times. The combined extracts were dried over $MgSO_4$ and concentrated to obtain a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish **43** (16 mg, 37%): $[\alpha]^{27}_D$ −2.9 (*c* 0.90, EtOH); cf. $[\alpha]^{23}_D$ −4.4 (*c* 0.96, EtOH) for the *R* enantiomer of 82% ee);[30] IR (neat) 3397, 1216, 1043, 759 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.53 (s, 3 H), 1.70−2.20 (br s, 1 H), 2.40−2.80 (br s, 1 H), 3.62 (d, J = 11 Hz, 1 H), 3.79 (d, J = 11 Hz, 1 H), 7.23−7.50 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.1 (−), 71.2 (+), 74.9 (+), 125.1 (−), 127.3 (−), 128.5 (−), 145.0 (+); HRMS (EI) calcd for $C_9H_{12}O_2$ (M^+) 152.0837, found 152.0839.

Synthesis of (−)-Sesqichamaenol (48).

(*S*,*Z*)-2-(3-Methylbut-1-enyl)-1,4-dioxaspiro[4.5]decane (49). To a suspension of $[i\text{-}PrCH_2PPh_3]^+Br^-$ (10.50 g, 26.2 mmol) in THF (35 mL) was added $NaN(TMS)_2$ (24.4 mL, 1.0 M in THF, 24.4 mmol) at 0 °C. The mixture was stirred 0 °C for 20 min and cooled to −78 °C. Aldehyde **26** (2.97 g, 17.5 mmol) was added to the mixture. The reaction was carried out first at −78 °C for 1 h and then at room temperature for 12 h, and quenched by addition of saturated NH_4Cl. The resulting mixture was extracted with hexane three times. The combined extracts were dried over $MgSO_4$ and concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **49** (3.52 g, 96%): IR (neat) 1108, 931 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.92 (d, J = 7 Hz, 3 H), 0.98 (d, J = 7 Hz, 3 H), 1.31−1.42 (m, 2 H), 1.50−1.66 (m, 8 H), 2.53−2.71 (m, 1 H), 3.47 (dd, J = 8, 8 Hz, 1 H), 4.02 (dd, J = 8, 6 Hz, 1 H), 4.82 (ddd, J = 8, 8, 6 Hz, 1 H), 5.25 (dd, J = 11, 9 Hz, 1 H), 5.42 (dd, J = 11, 10 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.0 (−), 23.7 (−), 23.9 (+), 24.0 (+), 25.2 (+), 27.3 (−), 35.6 (+), 36.4 (+), 69.3 (+), 71.8 (−), 109.7 (+), 125.1 (−), 142.2 (−).

(*S*,*Z*)-1-[(*tert*-Butyldimethylsilyl)oxy]-5-methylhex-3-en-2-ol (51). A solution of **49** (500 mg, 2.38 mmol) in CF_3CO_2H (0.73 mL, 9.5 mmol), H_2O (1 mL), and THF (1 mL) was stirred at room temperature for 12 h and diluted with saturated $NaHCO_3$ and EtOAc. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined extracts were dried over $MgSO_4$ and concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish diol **50** (210 mg, 68%): IR (neat) 3391, 1075, 756 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.92 (d, J = 7 Hz, 3 H), 0.96 (d, J = 7 Hz, 3 H), 2.50−2.69 (m, 1 H), 3.42 (dd, J = 12, 8 Hz, 1 H), 3.51 (dd, J = 12, 3 Hz, 1 H), 3.65 (br s, 2 H), 4.51 (ddd, J = 8, 8, 3 Hz, 1 H), 5.19 (dd, J = 11, 9 Hz, 1 H), 5.35 (dd, J = 11, 10 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.1 (−), 23.4 (−), 27.4 (−), 66.6 (+), 68.9 (−), 125.4 (−), 141.5 (−).

To a solution of the above diol **50** (915 mg, 7.03 mmol) and imidazole (1.59 g, 10.5 mmol) in DMF (10 mL) at −40 °C was added TBSCl (573 mg, 8.42 mmol) in DMF (4 mL) dropwise. After 2 h at −40 °C, the resulting solution was diluted with saturated NH_4Cl and EtOAc. The organic layer was separated, and the aqueous layer was extracted with EtOAc three times. The combined organic layers were dried over $MgSO_4$ and concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish **51** (1.54 g, 90%): IR (neat) 3424, 1106, 836, 777 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 6 H), 0.91 (s, 9 H), 0.94 (d, J = 7 Hz, 3 H), 0.99 (d, J = 7 Hz, 3 H), 2.56 (br s, 1 H), 2.53−2.69 (m, 1 H), 3.40 (dd, J = 10, 8 Hz, 1 H), 3.56 (dd, J = 10, 4 Hz, 1 H), 4.47 (ddm, J = 8, 8 Hz, 1 H), 5.19 (dd, J = 11, 9 Hz, 1 H), 5.39 (ddd, J = 11, 10, 1 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.3 (−), −5.2 (−), 18.4 (+), 23.2 (−), 23.5 (−), 26.0 (−), 27.5 (−), 67.2 (+), 68.6 (−), 125.4 (−), 141.4 (−).

(*R*,*Z*)-1-[(*tert*-Butyldimethylsilyl)oxy]-5-methylhex-3-en-2-yl Pyridine-2-carboxylate (52). To a solution of PPh_3 (2.15 g, 8.20 mmol) in THF (18 mL) at −78 °C were added picolinic acid (1.01 g, 8.20 mmol) and a solution of alcohol **51** (1.54 g, 6.30 mmol) in THF (3 mL). After 15 min, DIAD (1.66 mL, 7.87 mmol) was added dropwise. The solution was warmed to room temperature over 12 h and diluted with saturated $NaHCO_3$ and EtOAc. The organic layer was separated, and the aqueous layer was extracted with EtOAc three times. The combined organic layers were dried over $MgSO_4$ and concentrated to obtain a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish **52** (1.63 g, 74%): 99% ee by HPLC analysis (Chiralcel AD-H, hexane/*i*-PrOH = 98/2, 0.2 mL/min, t_R (min) = 25.4 (*S*), 26.2 (*R*)); $[\alpha]^{25}_D$ +18 (*c* 0.188, $CHCl_3$); IR (neat) 1718, 1247, 837 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ −0.02 (s, 3 H), 0.05 (s, 3 H), 0.84 (s, 9 H), 0.99 (d, J = 6 Hz, 6 H), 2.80−2.94 (m, 1 H), 3.76 (dd, J = 11, 5 Hz, 1 H), 3.89 (dd, J = 11, 7 Hz, 1 H), 5.36 (dd, J = 11, 9 Hz, 1 H), 5.50 (dd, J = 11, 11 Hz, 1 H), 5.97 (ddd, J = 9, 7, 5 Hz, 1 H), 7.45 (ddd, J = 8, 5, 1 Hz, 1 H), 7.82 (ddd, J = 8, 8, 2 Hz, 1 H), 8.11 (ddm, J = 8, 1 Hz, 1 H), 8.76 (ddm, J = 5, 2 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.48 (−), −5.46 (−), 18.2 (+), 22.7 (−), 23.1 (−), 25.7 (−), 27.4 (−), 64.9 (+), 72.4 (−), 121.8 (−), 125.0 (−), 126.6 (−), 136.8 (−), 143.6 (−), 148.3 (+), 149.7 (−), 164.2 (+); HRMS (FAB) calcd for $C_{19}H_{31}NO_3SiNa$ [$(M + Na)^+$] 372.1971, found 372.1968.

(*R*,*E*)-4-(2-Methoxy-5-methylphenyl)-5-methylhex-2-en-1-ol (54). To a suspension of $CuBr\cdot Me_2S$ (280 mg, 1.05 mmol) in THF (5 mL) was added Grignard reagent **45** (2.65 mL, 0.80 M in THF, 2.12 mmol) at 0 °C. The mixture was stirred at 0 °C for 20 min and cooled to −40 °C. Picolinate **52** (370 mg, 1.06 mmol) dissolved in THF (2 mL) was added to the mixture. The reaction was carried out at −40 °C for 2 h and quenched by addition of saturated NH_4Cl. The resulting mixture was extracted with hexane three times. The combined extracts were dried over $MgSO_4$ and concentrated to obtain a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **53**, which was used for the next reaction without further purification.

To a solution of the above compound **53** in THF (3 mL) was added Bu_4NF (1.8 mL, 1.0 M in THF, 1.8 mmol) dropwise. The solution was stirred at room temperature for 1 h and diluted with saturated NH_4Cl. The mixture was extracted EtOAc three times. The combined organic layers were dried over $MgSO_4$ and concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish alcohol **54** (152 mg, 61% from **52**): 98% ee, 99% C.T.; IR (neat) 3408, 1501, 1244, 1036, 804 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.73 (d, J = 7 Hz, 3 H), 0.95 (d, J = 7 Hz, 3 H), 1.56−1.86 (br s, 1 H), 1.90−2.30 (m, 1 H), 2.27 (s, 3 H), 3.33 (dd, J = 9, 9 Hz, 1 H), 3.78 (s, 3 H), 4.08 (dd, J = 6, 1 Hz, 2 H), 5.65 (dt, J = 15, 6 Hz, 1 H), 5.91 (dd, J = 15, 9 Hz, 1 H), 6.75 (d, J = 8 Hz, 1 H), 6.90−6.99 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7 (−), 21.1 (−), 31.8 (−), 49.8 (−), 55.7 (−), 63.7 (+), 111.0 (−), 127.1 (−), 129.1 (−), 129.5 (−), 129.6 (+), 132.5 (+), 135.1 (−), 155.0 (+). The enantiomeric information was determined by HPLC analysis: Chiralcel AD-H, hexane/*i*-PrOH = 99/1, 0.2 mL/min, t_R (min) 65.6 (*S*), 70.7 (*R*).

(*S*)-4-(2-Methoxy-5-methylphenyl)-5-methylhexanoic Acid (55). To a mixture of 10% Pd/C (75 mg, 0.070 mmol) in EtOAc (1 mL) was added **54** (152 mg, 0.649 mmol) in EtOAc (1 mL). The mixture was stirred at room temperature for 2 h under H_2 atmosphere and filtered through a pad of Celite. The filtrate was concentrated to afford the corresponding alcohol, which was used for the next reaction without further purification.

To an ice-cold solution of the above alcohol in acetone (4.3 mL) was added Jones reagent (0.28 mL, 4.7 M, 0.88 mmol) dropwise. The reaction was quenched by addition of *i*-PrOH and the aqueous layer was extracted EtOAc three times. The combined organic layers

were dried over $MgSO_4$ and concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish **55** (121 mg, 75% from **54**): $[\alpha]^{30}_D$ −4.17 (*c* 0.24, $CHCl_3$); IR (neat) 2957, 1244, 1037 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.73 (d, $J = 7$ Hz, 3 H), 1.00 (d, $J = 7$ Hz, 3 H), 1.74−1.96 (m, 3 H), 2.04−2.20 (m, 2 H), 2.27 (s, 3 H), 2.77 (dd, $J = 9$, 9 Hz, 1 H), 3.75 (s, 3 H), 6.74 (d, $J = 8$ Hz, 1 H), 6.88 (d, $J = 2$ Hz, 1 H), 6.96 (dd, $J = 8$, 2 Hz, 1 H) 9.5−11.0 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6 (−), 20.8 (−), 21.3 (−), 27.3 (+), 32.56 (+), 32.59 (−), 44.2 (−), 55.6 (−), 110.6 (+), 127.2 (−), 128.8 (−), 129.6 (−), 131.7 (−), 156.0 (−), 180.7 (+).

(−)-Sesquichamaenol (48). To an ice-cold solution of **55** (130 mg, 0.523 mmol) in AcOH (2.6 mL) was added 30% HBr in AcOH (1.31 mL). The mixture was refluxed for 2 h and poured into saturated $NaHCO_3$. The organic phase was separated, and the aqueous was extracted EtOAc three times. The combined organic layers were dried over $MgSO_4$ and concentrated to afford a residue, which was passed through a short column of silica gel (hexane/EtOAc) to afford the corresponding phenol (103 mg), which was used for the next reaction without further purification.

To a solution of the above phenol (103 mg) in Et_2O (5 mL) was added MeLi (2.19 mL, 1.02 M in Et_2O, 2.23 mmol) dropwise at −55 °C. After 3 h at −55 °C, the resulting solution was diluted with saturated NH_4Cl and EtOAc. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined extracts were dried over $MgSO_4$ and concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to furnish (−)-sesquichamaenol (**48**) (75 mg, 59% from **55**): $[\alpha]^{27}_D$ −8.1 (*c* 0.72, $CHCl_3$) and $[\alpha]^{27}_D$ −9.2 (*c* 0.72, CH_2Cl_2); cf. $[\alpha]^{25}_D$ −4.3 (*c* 0.6, $CHCl_3$)[33a] and $[\alpha]^{22}_D$ −5.95 (*c* 0.042, CH_2Cl_2);[33b] ^1H NMR (300 MHz, $CDCl_3$) δ 0.73 (d, $J = 7$ Hz, 3 H), 1.01 (d, $J = 7$ Hz, 3 H), 1.66−1.93 (m, *2* H), 2.05 (s, 3 H), 2.04−2.24 (m, 3 H), 2.25 (s, 3 H), 2.61 (ddd, $J = 12$, 9, 3 Hz, 1 H), 5.55 (br s, 1 H), 6.68 (d, $J = 8$ Hz, 1 H), 6.85 (d, $J = 8$ Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8 (−), 20.9 (−), 21.3 (−), 26.7 (+), 30.1 (−), 33.0 (−), 42.0 (+), 44.2 (−), 115.7 (−), 127.3 (−), 128.6 (−), 129.8 (+), 129.9 (+), 152.1 (+), 211.1 (+); HRMS (FAB) calcd for $C_{15}H_{22}O_2Na$ [$(M + Na)^+$] 257.1517, found 257.1512. The spectral data were consistent with those reported.[33]

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan and in part by a Grant-in-Aid for Young Scientists from JSPS.

Supporting Information Available: Synthesis of allylic picolinates (*S*)-**5a**,**b**,**c**,**d** (Scheme 4) and spectral data of compounds described herein. This material is available free of charge via the Internet at http://pubs.acs.org.

JO802426G