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Enantio- and Diastereoselective Stepwise Cyclization of Polyprenoids Induced by Chiral and Achiral LBAs. A New Entry to (−)-Ambrox, (+)-Podocarpa-8,11,13-triene Diterpenoids, and (−)-Tetracyclic Polyprenoid of Sedimentary Origin

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Abstract: An enantio- and diastereoselective stepwise cyclization of polyprenoids induced by Lewis acid-assisted chiral Brønsted acids (chiral LBAs) and achiral LBAs is described. In particular, the absolute stereocontrol in the initial cyclization of polyprenoids to form an A-ring induced by chiral LBAs and the importance of the nucleophilicity of the internal terminator in polyprenoids for the relative stereocontrol in subsequent cyclization are demonstrated. (−)-Ambrox was synthesized via the enantioselective cyclization of (*E*,*E*)-homofarnesyl triethylsilyl ether with tin(IV) chloride-coordinated (*R*)-2-(*o*-fluorobenzyloxy)-2′-hydroxy-1,1′-binaphthyl ((*R*)-BINOL-*o*-FBn) and subsequent diastereoselective cyclization with $CF_3CO_2H{\cdot}SnCl_4$ as key steps. Protection of (*E*,*E*)-homofarnesol by a triethylsilyl group increased the enantioselectivity of chiral LBA-induced cyclization and both the chemical yield and diastereoselectivity in the subsequent cyclization. The enantioselective cyclization of homo(polyprenyl)arenes possessing an aryl group was also induced by (*R*)-BINOL-*o*-FBn·$SnCl_4$. Several optically active podocarpa-8,11,13-triene diterpenoids and (−)-tetracyclic polyprenoid of sedimentary origin were synthesized (75−80% ee) by the enantioselective cyclization of homo(polyprenyl)benzene derivatives induced by (*R*)-BINOL-*o*-FBn·$SnCl_4$ and subsequent diastereoselective cyclization induced by $BF_3{\cdot}Et_2O/EtNO_2$ or $CF_3CO_2H{\cdot}SnCl_4$.

Introduction

A variety of terpenoids are enzymatically synthesized by cyclization of polyprenoids such as farnesol, geranylgeraniol, and squalene in biological systems.[1] The stereospecific formation of polycyclic terpenoids may be rationalized by the Stork−Eshenmoser hypothesis.[2] The chemical simulation of this elegant biosynthetic process has been developed as an important methodology in organic synthesis.[3] van Tamelen's approach induced by the acid-catalyzed cyclization of chiral terminal epoxides of polyprenes[4] and Johnson's approach via the acid-catalyzed cyclization of polyprenic acetals derived from chiral diols[5] must be the most important contribution to this field. Alternative approaches to the biomimetic olefin cyclization are the treatment of polyprenoids with a variety of electrophiles such as proton, bromonium ion, acyl cation, Lewis acid, or mercuric salt.[3,6] We recently reported the first example of the enantioselective cyclization of polyprenyl alcohols induced by Lewis acid-assisted chiral Brønsted acids (chiral LBAs) (Scheme 1).[7] A hydroxy group in polyprenyl alcohols assists this polyene cyclization as a good nucleophilic internal terminator. However, hydroxy groups in a substrate may act as achiral LBAs in the presence of Lewis acid. Chiral LBAs should be designed so that the Lewis acid predominantly coordinates with a chiral Brønsted acid. Alternatively, protection of hydroxy groups in a substrate should help to avoid the generation of achiral LBA species. The nucleophilicity of the internal terminator may decrease due to its protection, and as a result, the reactivity of cyclization may decrease. To overcome these problems, an enantio- and diastereoselective stepwise cyclization of polyprenoids induced by chiral LBAs and stronger achiral LBAs was developed.

In the first stage, (−)-ambrox (**1A**)[8] was concisely synthesized via the enantioselective cyclization of (*E*,*E*)-homofarnesyltrialkylsilyl ethers (**4**: $\mathbb{P} = SiR_3$) induced by chiral LBAs and

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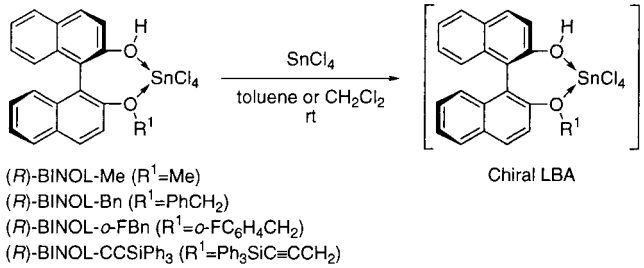
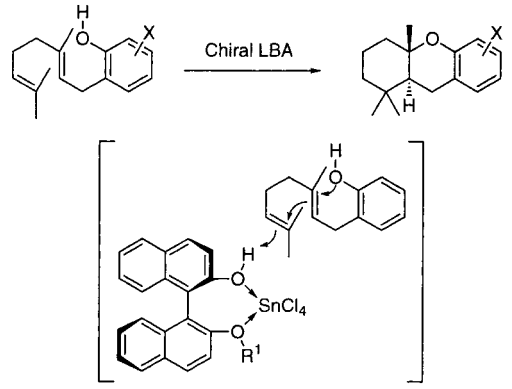
(8) Registered trademark of Firmenich S. A. for (−)-8α,12-epoxy-13,14,15,16-tetranorlabdane.

10.1021/ja0124865 CCC: $22.00

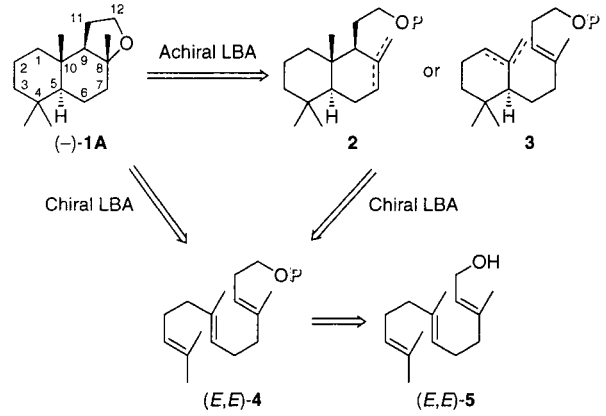
Scheme 1. Enantioselective Cyclization of Polyprenyl Alcohols Induced by Chiral LBA



(*R*)-BINOL-Me (R^1=Me)
(*R*)-BINOL-Bn (R^1=$PhCH_2$)
(*R*)-BINOL-*o*-FBn (R^1=*o*-$FC_6H_4CH_2$)
(*R*)-BINOL-CCSiPh$_3$ (R^1=$Ph_3SiC{\equiv}CCH_2$)



Scheme 2. Retrosynthesis of (−)-**1A**



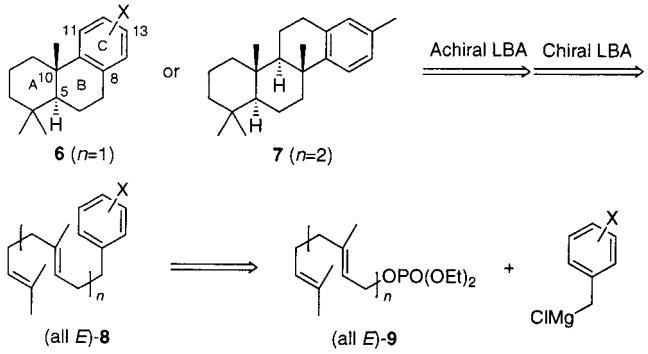
the subsequent diastereoselective cyclization of dicyclic and monocyclic products, **2** and **3**, induced by achiral LBAs as key steps (Scheme 2).

In the next stage, we applied this approach to a more challenging synthetic problem: the enantioselective cyclization of (*all-E*)-homo(polyprenyl)arenes (**8**) possessing an aryl group, which serves as a less-nucleophilic terminator than a hydroxy group (Scheme 3). Several optically active podocarpa-8,11,13-triene diterpenoids (**6**) and (−)-tetracyclic polyprenoid (**7**) of sedimentary origin were synthesized (75−80% ee) by the enantioselective cyclization of (*all-E*)-**8** induced by chiral LBAs and subsequent diastereoselective cyclization induced by achiral LBAs. Thus, the effectiveness of chiral LBAs for providing absolute stereocontrol in the initial cyclization of polyprenoids to form an A-ring and the importance of the nucleophilicity of the internal terminator in polyprenoids for the relative stereocontrol in the subsequent cyclization are demonstrated.[9]

Discussion

Protective Effect of a Hydroxy Group Terminator on LBA-Induced Cyclization of (*E*,*E*)-4: Total Synthesis of (−)-

Scheme 3. Retrosynthesis of Podocarpa-8,11,13-triene Diterpenoids (**6**) and Their Polycyclic Analogues



1A. Ambergris is a metabolic product that is found in the gut of some blue sperm whales (*Physeter macrocephalus L.*).[10] After several years of aging, ambergris is used in perfumery as a valuable ingredient in many fine fragrances because of its unique scent and fixative properties. One of the constituents of the ambergris tincture[11] is the labdane-like tricyclic ether **1A** that has a powerful amber-type aroma. As a consequence of the growing demand for ambergris-type odorants coupled with the almost complete worldwide ban on whaling, **1A** probably has become the most commercially important synthetic equivalent of scarce natural ambergris. For this reason, several syntheses of (−)-**1A** have been developed since it was initially prepared in 1950.[12] Most of them[13] use the terpene-type starting materials (−)-sclareol,[14] (−)-drimenol,[15] (+)-manool,[16] manoyl oxide,[17] (+)-abietic acid,[18] (−)-levopimaric acid,[19] and (−)-labdanolic acid.[20] In addition, diverse total syntheses of (±)-**1A** use biogenetic-type cyclizations from (*E*,*E*)-farnesic or (*E*)-monocyclofarnesic acids or their derivatives.[21] We describe here the concise enantioselective synthesis of (−)-**1A** using the enantioselective cyclization of (*E*,*E*)-**4** induced by chiral LBA[9,22] and the subsequent diastereoselective cyclization of **2** and **3** induced by achiral LBA as key steps (Scheme 2).

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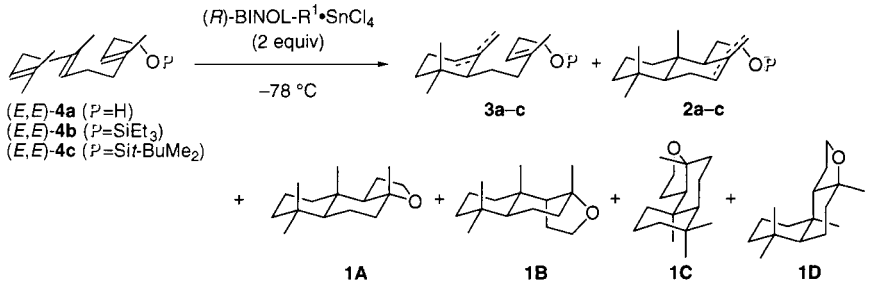
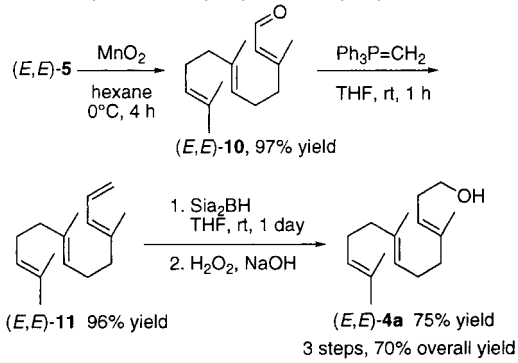
Table 1. Enantioselective Cyclization of (*E*,*E*)-Homofarnesol Derivatives **4** Induced by Chiral LBAs



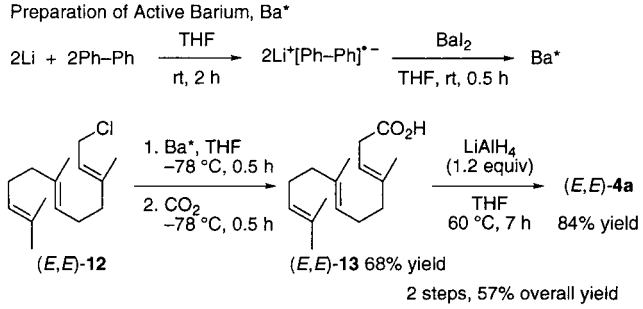
					GC ratio (Ee)			
entry	ℙ	R¹ of (*R*)-LBA	solvent, time (h)	yield (%)[b] **1A–D**	**1A**	**1B**	**1C**	**1D**
1[a]	H	Me	CH_2Cl_2, 72	54	56 (42% ee)	9	26	9
2	H	*o*-FBn	toluene, 72	29	64 (50% ee)	17	18	2
3	$SiEt_3$	*o*-FBn	toluene, 72	18	84 (76% ee)	6	11	0
4	$SiEt_3$	*o*-FBn	CH_2Cl_2, 72	32	56 (44% ee)	32	12	0
5	Si*t*-$BuMe_2$	*o*-FBn	toluene, 72	<1				

[a] Data in ref. 7. [b] Isolated yield of **1** is indicated. Starting material was completely consumed. Other main products were monocyclic compounds **3a**−**c** and dicyclic compounds **2a**−**c**.

Scheme 4. Preparation of (*E*,*E*)-**4a** from (*E*,*E*)-**5**



Scheme 5. Preparation of (*E*,*E*)-**4a** from (*E*,*E*)-**8**



(*E*,*E*)-Homofarnesol (**4a**: ℙ = H) was prepared in 70% overall yield in three steps from commercially available (*E*,*E*)-farnesol **(5)** by a slight modification of the method described by Leopold (Scheme 4).[23] In the first step, (*E*,*E*)-**5** was oxidized to (*E*,*E*)-farnesal (**10**) in hexane at 0 °C by using manganese(IV) oxide.[24] The stereoisomeric purity of product (*E*,*E*)-**6** was at least 99%. Next, the Wittig methylenation of (*E*,*E*)-**10** to (*E*,*E*)-4,8,12-trimethyl-1,3,7,11-tridecatetraene (**11**) was carried out with phenyllithium in THF. Finally, the selective hydroboration of (*E*,*E*)-**11** was carried out by adding disiamylborane, which was prepared from 2-methyl-2-butene and borane•THF in situ, to give (*E*,*E*)-**4a**.

A more concise preparation of (*E*,*E*)-**4a** was achieved by using the regio- and stereoselective carboxylation of allylic barium reagents as a key reaction (Scheme 5).[25] (*E*,*E*)-Farnesylbarium(II) was prepared directly by the reaction of in situ generated barium metal (Ba*) with commercially available (*E*,*E*)-farnesyl chloride (**12**) without loss of the double bond geometry. Treatment of (*E*,*E*)-farnesylbarium(II) with excess carbon dioxide gave (*E*,*E*)-4,8,12-trimethyl-3,7,11-tridecatrienoic acid (**13**) in 68% yield. The reduction of **13** with lithium aluminum hydride gave (*E*,*E*)-**4a** in 84% yield.[26] Thus, (*E*,*E*)-**4a** was obtained in 57% overall yield in two steps.

We have previously reported that the enantioselective cyclization of (*E*,*E*)-**4a** with tin(IV) chloride-coordinated (*R*)-2-hydroxy-2′-methoxy-1,1′-binaphthyl, (*R*)-BINOL-Me•$SnCl_4$, in dichloromethane gives a diastereomeric mixture (56:9:26:9 molar ratio) of tricyclic ethers, ambrox **1A**, *epi*-ambrox **1B**, **1C**, and **1D**, in 54% yield (entry 1, Table 1).[7] The ee of the resulting (−)-**1A** is 42%. To achieve the concise total asymmetric synthesis of **1a**, we reinvestigated the optimal conditions for the enantioselective cyclization of (*E*,*E*)-**4a** with tin(IV) chloride-coordinated (*R*)-2-alkoxy-2′-hydroxy-1,1′-binaphthyl, (*R*)-BINOL-R•$SnCl_4$. Representative results are summarized in Table 1. While the use of *o*-fluorobenzyl ether of (*R*)-BINOL [(*R*)-BINOL-*o*-FBn] instead of (*R*)-BINOL-Me in toluene gave higher enantioselectivity and diastereoselectivity, these values were still low (50% ee, 64% ds) (entry 2). Furthermore, the enantioselectivity and diastereoselectivity of (−)-**1A** were improved to 76% ee and 84% ds by using (*E*,*E*)-homofarnesyl triethylsilyl ether (**4b**) as a substrate (entry 3), but the yield of **1** was decreased to 18%. Other main products were monocyclic triethylsilyl ether **3b** and dicyclic triethylsilyl ether **2b**. In the

(22) The enantioselective cyclization of homofarnesyl triisopropylsilyl ether induced by chiral iron catalyst was presented in the Poster Session, see: Allemann, C.; Jenny, T. A. The 11th IUPAC Symposium on Organometallic Chemistry directed towards Organic Synthesis (OMCOS 11), Taipei (Taiwan), July 23, 2001, P007.

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Table 2. Diastereoselective Cyclization of a Mixture of **3b** and **2b** Induced by Acids

3b, **2b**, and others[a] —(Achiral LBA; $EtNO_2$, −78 °C)→ **1A + 1B + 1C + 1D**

entry	P	achiral LBA (equiv)	yield (%)[b] 1A–D	GC ratio (Ee) 1A	1B	1C	1D
1	$SiEt_3$	CF_3CO_2H (10)·$SnCl_4$ (2)	62[c]	76 (78% ee)	7	15	2
2	$SiEt_3$	CF_3CO_2H (10)	0[c]				
3	$SiEt_3$	$EtNO_2$ (excess)·$SnCl_4$ (2)	11[d]	79	6	14	1
4	$SiEt_3$	$EtNO_2$ (excess)·$SnCl_4$ (10)	15[c]	56	11	31	2
5	H	CF_3CO_2H (10)·$SnCl_4$ (2)	25[c]	65	9	23.5	2.5
6	Si*t*-$BuMe_2$	CF_3CO_2H (10)·$SnCl_4$ (2)	28[d]	74	7	17	2

[a] Starting material containing **3b**, **2b**, and other unknown compounds was prepared from (*E*,*E*)-**4b** [entry 3 in Table 1; GC ratio, **3b**:**2b**:others = 53(endo:exo = 55:45):30(endo:exo = 81:19):17]. [b] Isolated yield of **1** is indicated. [c] **3b** and **2b** were completely consumed. [d] **3b** and **2b** remained.

cyclization of (*E*,*E*)-homofarnesyl *tert*-butyldimethylsilyl ether (**4c**) with (*R*)-BINOL-*o*-FBn·$SnCl_4$, **3c** and **2c** were the main products but no tricyclic ether **1** was produced (entry 5). In screening several protective groups, we found that a triethylsilyl group was the most suitable with respect to the enantioselectivity of **1A** and diastereoselectivity of **1**. Although the use of dichloromethane increased the yield of **1**, the enantioselectivity and diastereoselectivity were reduced (entry 3 vs entry 4). It seems that the balance between the stability of the Si−O bond in **4** and the Brønsted acidity of chiral LBA is very important in this cyclization.

Next, the diastereoselective cyclization of a mixture of **3** and **2** with achiral acids was explored to increase the chemical yield of (−)-**1A**. Tricyclic ethers **1** were separated from the crude mixture obtained in the cyclization (entry 3 in Table 1) by column chromatography on silica gel, and alcohol products **3a** and **2a**, which were partially desilylated, were reprotected with chlorotriethylsilane before use as a starting material in the subsequent cyclization. As shown in Table 2, CF_3CO_2H (10 equiv)·$SnCl_4$ (2 equiv) in nitroethane gave the best result in the diastereoselective cyclization (**1**, 62% yield; **1A**, 76% ds; entry 1). The ee of (−)-**1A** was identical with that obtained in the initial enantioselective cyclization (see entry 3 in Table 1). The use of CF_3CO_2H or $SnCl_4$ alone did not give **1** in good yield, although **3b** and **2b** were completely consumed (entries 2 and 4). The diastereoselectivity of **1A** and the chemical yield of **1** in the subsequent cyclization of triethyl silyl ethers **3b** and **2b** with CF_3CO_2H·$SnCl_4$ were much better than those in the cyclization of desilylated alcohols (entry 1 vs entry 5). In screening several protective groups for the starting materials, the triethylsilyl group was the most suitable for diastereoselective cyclization (e.g., entry 1 vs entry 6).

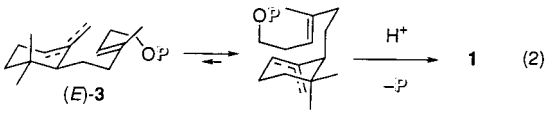
Finally, (−)-**1A** was obtained in 54% yield with 75% ee and 76% ds from (*E*,*E*)-**4b** through enantioselective cyclization, silylation, and diastereoselective cyclization (eq 1). Separation of **1** by column chromatography on silica gel was carried out only after the final step.

(*E*,*E*)-**4b** —(1. (*R*)-BINOL-*o*-FBn·$SnCl_4$, toluene, −78 °C, 1 day; 2. Et_3SiCl, imidazole, DMF; 3. CF_3CO_2H·$SnCl_4$, $EtNO_2$, −78 °C, 1 day; 4. Separation of **1**)→ **1A + 1B + 1C + 1D** (1)

1A:**1B**:**1C**:**1D**= 76 (75% ee):10:13:1
54% yield of **1** from (*E*,*E*)-**4b**

The following hypothesis is proposed for the enantioselective cyclization of (*E*,*E*)-**4b** with (*R*)-BINOL-*o*-FBn·$SnCl_4$. The enantioselective formation of an A-ring is rationalized by the Stork−Eschenmoser hypothesis,[2] which postulates a synchronous internal antiaddition via a chairlike conformation of the nascent cyclohexane ring, initiated by protonation at the terminal C(11)═C(12) bond. (*R*)-BINOL-*o*-FBn·$SnCl_4$ was almost inert in the subsequent cyclization of the resulting (*E*)-**3b** and **2b**. It is important to note that **1B** was obtained as a minor diastereomer. The following three pathways are essentially possible for the formation of **1B**: (1) epimerization from **1A** to **1B**, (2) the synchronous or nonsynchronous cyclization process of (3*Z*,7*E*)-**4a**, which is generated by isomerization of (3*E*,7*E*)-**4a**,[21a] and (3) the nonsynchronous cyclization process of (3*E*,7*E*)-**4a**. However, epimerization from **1A** to **1B** did not occur under these cyclization conditions based on control experiments. In addition, the cyclization of (3*Z*,7*E*)-**4b** was ruled out because no isomerization of (3*E*,7*E*)-**4b** to (3*Z*,7*E*)-**4b** occurred. Therefore, the formation of **1B** is explained by a synchronous or nonsynchronous cyclization process to form an AB-ring via a chair-boat transition state (the A/B-trans and 9,10-syn stereochemistry), conformational inversion of the B-ring cation from boat form to chair form, and subsequent cyclization of the C-ring.[6,27] For the other three diastereomers **1A**, **1C**, and **1D**, the reaction pathways can be rationalized by a totally synchronous or nonsynchronous cyclization process (Figure 1).

The stronger LBA CF_3CO_2H·$SnCl_4$ was required for the transformation from (*E*)-**3b** and **2b** to **1**. According to mechanistic studies by Snowden et al.,[21a] the FSO_3H-initiated cyclization of (*E*)-**3a** in 2-nitropropane gives a cis-fused AB-ring isomer, **1C**, as a major product. The diastereoselectivity is explained by the assumption that the side chain of (*E*)-**3b** is oriented axially in the major conformer (eq 2). In our case, a trans-fused AB-ring isomer **1A** was obtained as the major product by the cyclization of (*E*)-**3b** with CF_3CO_2H·$SnCl_4$ in nitroethane. The latter result with relatively milder acids can be rationalized by a nonsynchronous process in which the conformational inversion of the cyclohexyl cation generated by protonation occurs faster than B-ring closure.



Finally, the protective effect of a hydroxy group in (*E*,*E*)-**4a** was demonstrated in superacid-induced biogenetic polyene cyclization. According to the pioneering effort by Snowden et al.[21a] and Barrero et al.,[21b] ca. a 1:1 mixture of **1A** and **1B** is obtained in ca. 80% GC yield by the cyclization of (*E*,*E*)-**4a** induced by excess amounts of FSO_3H and $ClSO_3H$ in 1- or 2-nitropropane. Although the protection of (*E*,*E*)-**4a** with a trialkylsilyl group was unrelated to the diastereoselectivity, it was very effective for increasing the chemical yield of **1** (Table 3). In the cyclization of (*E*,*E*)-**4**, formation of the C-ring initiated by protonation at the C(3)═C(4) bond competes with the formation of **1**.[18] Protection of the hydroxy group in (*E*,*E*)-**4a** prevented this side reaction. Interestingly, the ratios of **1A** and **1B** in Table 3 are quite different from those in Tables 1 and 2. Epimerization from **1A** to **1B** did not occur even under these

(27) Corey, E. J.; Wood, H. B., Jr. *J. Am. Chem. Soc.* **1996**, *118*, 11982.

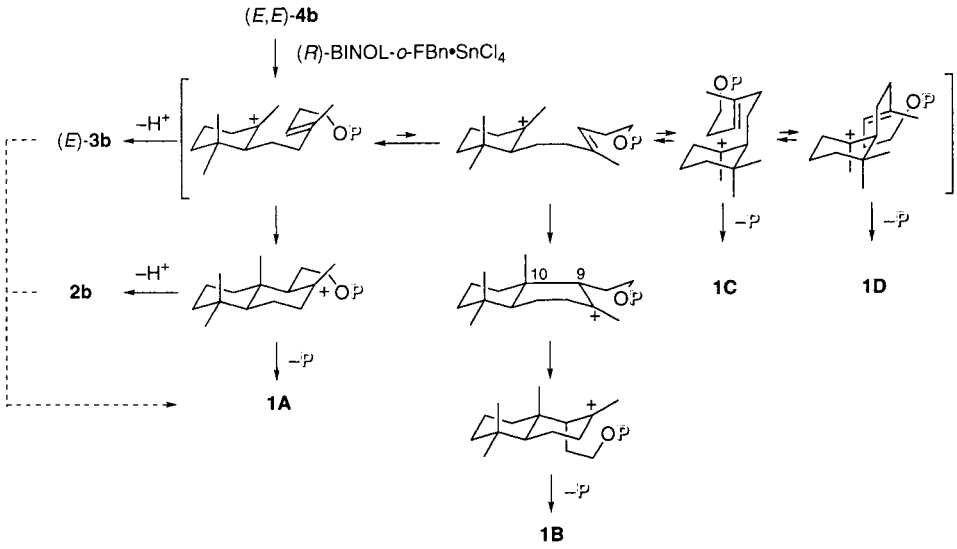


Figure 1. The enantioselective cyclization of (*E*,*E*)-**4b** induced by (*R*)-BINOL-*o*-FBn·$SnCl_4$: nonsynchronous pathway (Figure for synchronous pathway is omitted.).

Table 3. Diastereoselective Cyclization of (*E*,*E*)-**4**

(*E*,*E*)-**4** —(Acids; $EtNO_2$, –78 °C, 1 day)→ **1A** + **1B** + **1C** + **1D**

entry	ℙ	acids (equiv)	yield of **1** (%)[a]	**1A**:**1B**:**1C**:**1D**[b]
1	H	CF_3CO_2H (10)·$SnCl_4$ (2)	31	42:53:3:2
2	$SiEt_3$	CF_3CO_2H (10)·$SnCl_4$ (2)	69	43:50:5:2
3	$SiEt_3$	$ClSO_3H$ (10)	61	58:36:4:1
4	Si*t*-$BuMe_2$	$ClSO_3H$ (10)	87	54:46:0.4:0.4
5	Si*t*-$BuPh_2$	$ClSO_3H$ (10)	91	58:40:1:1

[a] Isolated yield. [b] GC ratio.

conditions based on control experiments. Therefore, the ratio of **1A** and **1B** would be controlled by the relative energies of the chair-chair and chair-boat transition states.

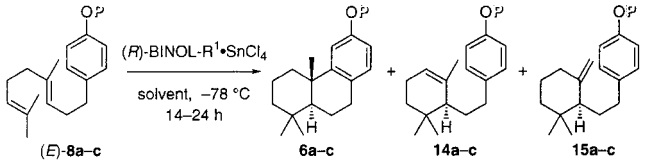
Enantioselective Cyclization of (*all-E*)-8. (*all-E*)-Homo(polyprenyl)arenes **8** were prepared in good yields by reaction of arylmethylmagnesium choride with polyprenyl diethyl phosphates (**9**) according to Butsugan's method (Scheme 3).[29]

Although cyclization via 2-(2-arylethyl)-1,3,3-trimethylcyclohexyl carbocations has been widely used to construct the B-ring of podocarpa-8,11,13-triene diterpenoids **6**,[30] there have been only a few reports on successive cyclizations of (*E*)-homogeranylbenzene derivatives **8** ($n = 1$) to **6**.[31] We initially studied the enantioselective cyclization of (*E*)-4-homogeranylphenol (**8a**) and its ether derivatives **8b** and **8c**[32] with (*R*)-BINOL-R^1·$SnCl_4$. Representative results are summarized in Table 4. Reaction of (*E*)-**8a** in dichloromethane with (*R*)-BINOL-Me·$SnCl_4$ at −78 °C for 14 h gave the desired trans tricyclic product **6a** in 87% yield and 38% ee (entry 1). The other products were single-cyclization products, **14a** and **15a**. The enantioselectivity of **6a** was improved to 49% ee by using toluene in place of dichloromethane, but the yield of **6a** was decreased and the yields of **14a** and **15a** were increased (entry 2). Furthermore, the enantioselectivity increased to 59% ee when (*E*)-**8b** was used in place of (*E*)-**8a** (entry 3). In screening several protective groups, R^1 in (*R*)-BINOL-R^1·$SnCl_4$ and ℙ in (*E*)-**8** ($n = 1$), we found that triphenylsilylpropargyl or the *o*-fluorobenzyl group and the *tert*-butyldiphenylsilyl group were the most suitable R^1 and ℙ, respectively, with regard to enantioselectivity (entries 6 and 7): the reaction of (*E*)-**8c** with (*R*)-BINOL-*o*-FBn·$SnCl_4$ gave *trans*-**6c** in 9% yield and 81% ee (entry 6). The relationship between enantioselectivity and R^1 is not clear. The steric bulkiness of ℙ may impair interaction between $SnCl_4$ and the basic oxygen atom of OℙP. The absolute configuration of *trans*-**6** shown in Table 4 was assigned to be 5*S* and 10*S* based on the known optical rotation.[30c] Notably, the tricyclic compounds **6a**−**c** obtained in the cyclization of (*E*)-**8a**−**c** were only trans isomers regardless of the reaction conditions.[30e,f] The monobenzoate of (*R*)-BINOL·$SnCl_4$, which was the most effective LBA for the enantioselective cyclization of 2-polyprenylphenol derivatives,[7] was inert in the cyclization of (*E*)-**8c**.

Although the enantiomeric purity of **14a**−**c** and **15a**−**c** could not be determined, we expected that they would be as pure as *trans*-**6a**−**c**, since no achiral stereoisomer was observed during the cyclization of (*E*)-**8a**−**c**. Thus, the diastereoselective cyclization of **14** and **15** with achiral LBA was explored to increase the chemical yield of **6**. After treating (*E*)-**8b** with (*R*)-BINOL-Bn·$SnCl_4$ at −78 °C for 3 days to completely consume (*E*)-**8b**, an achiral LBA, CF_3CO_2H·$SnCl_4$, was added to the reaction solution at the same temperature and the mixture was stirred for an additional day. As expected, the desired product **6b** was obtained in 62% ee and 86% yield from (*E*)-**8b** in a one pot procedure (cf. entry 4 in Table 4). Furthermore, the desilylation

(28) For preparation of **8**, see: Araki, S.; Sato, T.; Butsugan, Y. *J. Chem. Soc., Chem. Commun.* **1982**, 285.
(29) (a) Matsumoto, T.; Usui, S. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 212. (b) Matsumoto, T.; Suetsugu, A. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1450. (c) Axon, B. W.; Davis, B. R.; Woodgate, P. D. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2956. (d) Banik, B. K.; Chakraborti, A. K.; Ghatak, U. R. *J. Chem. Res. (S)* **1986**, 3391. (e) Banik, B. K.; Ghosh, S.; Ghatak, U. R. *Tetrahedron* **1988**, *44*, 6947. (f) Ghosh, S.; Banik, B. K.; Ghatak, U. R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3189 and references therein.
(30) For the cationic cyclization of homogeranylbenzene derivatives bearing regioselectivity- and/or diastereoselectivity-inducing auxiliaries, see: tosyl group (a) Janssen, C. G. M.; Godefroi, E. F. *J. Org. Chem.* **1982**, *47*, 3274. Trimethylsilyl group: (b) Janssen, C. G. M.; Godefroi, E. F. *J. Org. Chem.* **1984**, *49*, 3600. Cyano group: (c) Harring, S. R.; Livinghouse, T. *Tetrahedron* **1994**, *50*, 9229.
(31) King, F. E.; King, T. J.; Topliss, J. G. *J. Chem. Soc.* **1957**, 573.
(32) Although several ethers of **14e** and **15e** were examined regarding the second cyclization induced by CF_3CO_2H·$SnCl_4$ or BF_3·Et_2O, cis tricyclic compounds were produced as major products in all cases.

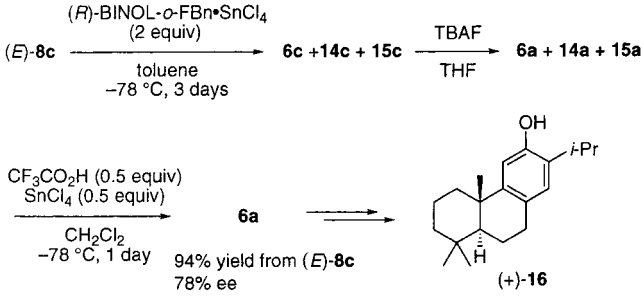
Table 4. Enantioselective Cyclization of (*E*)-**8a**−**c**



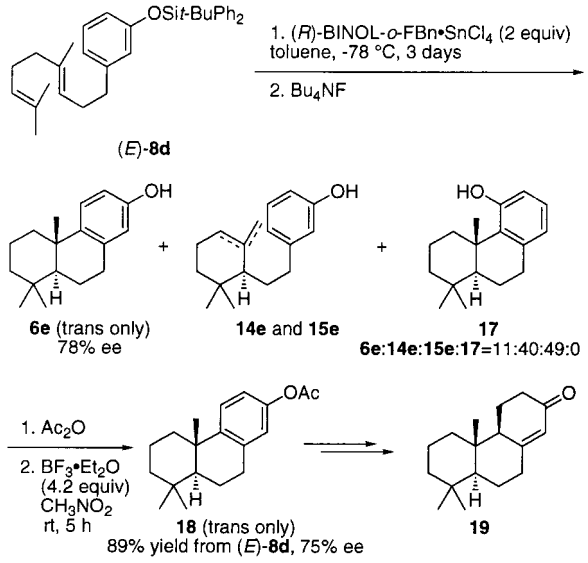
entry	8a–c(P)	R1, (R)-LBA (equiv)	solvent, time (h)	molar ratio[a] 6a–c [ee (%)][b]	14a–c	15a–c	8a–c
1[c]	**8a** (H)	Me (1.1)	CH_2Cl_2, 14	87 [38]	6	7	0
2[c]	**8a**	Me (1.1)	toluene, 14	28 [49]	40	32	0
3	**8b** (Me)	Me (2.0)	toluene, 19	10 [59]	36	36	18
4	**8b**	Bn (2.0)	toluene, 24	13 [61]	33	32	22
5[d]	**8c** (*t*-$BuPh_2Si$)	Me (2.0)	toluene, 24	13 [72]	35	35	17
6[d]	**8c**	*o*-FBn (2.0)	toluene, 48	9 [81]	44	47	0
7[d]	**8c**	PH_3SiCC (1.1)	toluene, 96	19 [80]	40	41	0

[a] Determined by GC and ^{1}H NMR analyses. [b] Determined by chiral HPLC analysis. [c] Product ratio was determined by GC and ^{1}H NMR analyses after acetylation of products. [d] Product ratio was determined by GC and ^{1}H NMR analyses after desilylation and acetylation of products.

Scheme 6. Enantioselective Synthesis of (5*S*,10*S*)-**6a**



Scheme 7. Enantioselective Synthesis of (5*S*,10*S*)-**18**



of a crude mixture of **6c**, **14c**, and **15c**, which were obtained in the enantioselective cyclization of (*E*)-**8c** induced by (*R*)-BINOL-*o*-FBn•$SnCl_4$, with tetrabutylammonium fluoride was highly effective at increasing the reactivity of the subsequent diastereoselective cyclization. Thus, the desired product **6a** was obtained in 78% ee and 94% yield from **2c** in three steps (Scheme 6; cf. entry 6 in Table 4). Since (±)-**6** has already been converted into (±)-ferruginol (**16**) by King[32] and Ghatak,[30d] the present method represents a formal and the first enantioselective total synthesis of (+)-**16**.

The enantioselective cyclization of (*E*)-1-homogeranyl-3-(*tert*-butyldiphenylsiloxy)benzene (**8d**) was also examined by using (*R*)-BINOL-*o*-FBn•$SnCl_4$ in toluene at −78 °C (Scheme 7). As expected, tricyclic product **6d** was obtained in 78% ee and in only the trans configuration, together with the monocyclization products **14d** and **15d**. However, the subsequent cyclization of desilylated compounds **14e** and **15e** with BF_3•Et_2O in nitromethane[31c] gave a 37:63 mixture of *trans*- and *cis*-**6e** together with a small amount of *trans*-**17**.[33] *Fortunately, we found that the cyclization of acetates of* ***14e*** *and* ***15e*** *under the same conditions gave (+)-13-acetoxypodocarpa-8,11,13-triene (****18****) with high diastereoselectivity (trans only) and regioselectivity (no detectable amount of* ***17****).* Thus, the desired product **18** was obtained in 75% ee and 89% yield from **8d**. This compound **18** can be easily converted into (+)-podocarpa-8(14)-en-13-one (**19**),[30a,34] a versatile intermediate for synthesis of naturally occurring diterpenes, e.g. isophyllocladene,[35a] phyllocladene,[35a] hibaone,[35b] manool,[35c] sclareol,[35c] manoyl oxide,[35c] isoabienol,[35d] *trans*-abienol,[35d] and anticopalic acid.[35e,f] Therefore, the present work can be regarded as the enantioselective total synthesis of the above natural diterpenes.

In 1990, Azevedo's group found a ring-C monoaromatic tricyclic terpene, 13-methylpodocarpa-8,11,13-triene (**6f**), in a Tasmanian tasmanite sediment.[36] Four years later, Albrecht's group reported the isolation of a series of chiral tetracyclic (**7**), pentacyclic, hexacyclic (**20**), heptacyclic, and octacyclic homologues, from Eocene Messel shale (Germany), which appear to be the remnants of an ancient family of cyclopolyprenoids.[37] Very recently, Corey's group achieved the asymmetric synthesis of **7** and **20** using the diastereoselective Lewis acid-catalyzed polycyclization of polyunsaturated oxiranes.[38] To demonstrate

(33) (a) Bartltrop, J. A.; Rogers, N. A. *J. Chem. Soc.* **1958**, 2566. (b) Church, R. F.; Ireland, R. E.; Marshall, J. A. *J. Org. Chem.* **1966**, *31*, 2526.

(34) (a) Duc, D. K. M.; Fetizon, M.; Lazare, S. *J. Chem. Soc., Chem. Commun.* **1975**, 282. (b) Duc, D. K. M.; Fetizon, M.; Flament, J. P. *J. Chem. Soc., Chem. Commun.* **1972**, 886; *Tetrahedron* **1975**, *31*, 1897. (c) Wenkert, E.; Mahajan, J. R.; Nussim, M.; Schenker, F. *Can. J. Chem.* **1966**, *44*, 2575. (d) Vlad, P. F.; Russo, A. G.; Kuang-fang, C. *Zh. Obsch. Chim. (Engl. Ed.)* **1969**, *39*, 423. (e) Manh, D. D. K.; Fetizon, M.; Kone, M. *Tetrahedron* **1975**, *31*, 1903. (f) Ohloff, G. *Justus Liebigs Ann. Chem.* **1958**, *615*, 134.

(35) Azevedo, D. A.; Aquino Neto, F. R.; Simoneit, B. R. T. *Org. Mass Spectrom.* **1990**, *25*, 475 and references therein.

(36) Schaeffer, P.; Poinsot, J.; Hauke, V.; Adam, P.; Wehrung, P.; Trendel, J.-M.; Albrecht, P.; Dessort, D.; Connan, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1166.

(37) Corey, E. J.; Luo, G.; Shouzhong, L. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1126.

(38) Corey, E. J.; Staas, D. D. *J. Am. Chem. Soc.* **1998**, *120*, 3526.

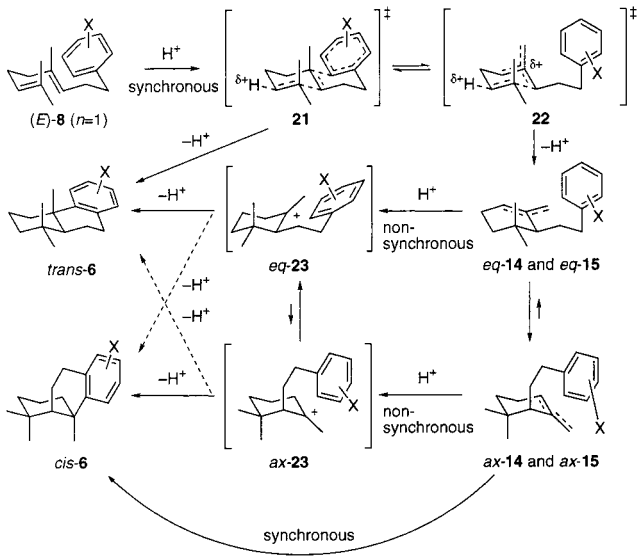
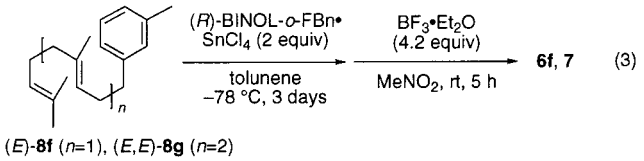
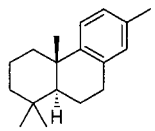


Figure 2. Possible reaction paths for the acid-induced cyclization of (*E*)-**8** ($n = 1$).

the generality of our synthetic strategy, polycyclic terpenes **6f** and **7** were concisely synthesized by using the (*R*)-BINOL-*o*-FBn·$SnCl_4$-induced enantioselective cyclization of 3-homo-(polyprenyl)toluenes as a key step (eq 3). An achiral LBA, $SnCl_4$·CF_3CO_2H/CH_2Cl_2, as well as BF_3·$Et_2O/MeNO_2$, was effective for the second step.





6f

6f: 83% yield, 88% trans, 80% ee
$[\alpha]^{26.9}_D$=33.8 (*c* 1.54, $CHCl_3$)

7: 65% yield, 77% ee
$[\alpha]^{26.5}_D$=–35.6 (*c* 0.43, $CHCl_3$)[37]

Our extensive results in the present investigation on the stereochemistry of the acid-induced polyene cyclization of (*E*)-**8** ($n = 1$) provide some important generalizations.[30,39] The possible reaction paths are shown in Figure 2. Initial cyclization of (*E*)-**8** induced by (*R*)-BINOL-*o*-FBn·$SnCl_4$ should take place through a synchronous pathway involving transition states (TSs) **21** and **22** enantioselectively: TS-**21** stereospecifically leads to *trans*-**6**, while TS-**22** leads to a mixture of **14** and **15**. (*E*)-4-Homogeranylphenol **8a** was completely consumed in toluene in the presence of 1.1 equiv of (*R*)-BINOL-Me·$SnCl_4$ (Table 4, entry 2), while the corresponding ethers (*E*)-**8b** and (*E*)-**8c** remained in ca. 20% yield even in the presence of 2 equiv of (*R*)-BINOL-R^1·$SnCl_4$ (Table 4, entries 3−5). These experimental results may indicate that protection of a hydroxy group in (*E*)-**8a** suppresses not only the second cyclization to form the B-ring but also the initial cyclization to form the A-ring. *Thus, an aryl moiety in (E)-8 may serve not only as a nucleophilic internal terminator to form the B-ring but also as a remote promoter of cyclization to form the A-ring (a secondary effect) via TS-21.* Furthermore, the stereochemistry in the subsequent cyclization of **14** and **15** strongly depends on the nucleophilicity of their terminal benzene ring. Their side chain should be orientated axially in the major conformer as well as that of (*E*)-**3** (see eq 2).[21a] Benzene rings without an electron-donating substituent, para to the site of electrophilic attack, would be not sufficiently nucleophilic to react through the synchronous pathways; rather, they may require complete protonation to a carbocation *eq*-**23** which reacts with high stereoselectivity by a nonsynchronous pathway due to the minimum steric effects giving *trans*-**6**: e.g. the second cyclization of **14a**−**c**, **15a**−**c**, and acetates of **14e** and **15e** leads only to *trans*-**6**. With an electron-donating substituent, the synchronous pathway through *ax*-**14** and *ax*-**15** or the nonsynchronous pathway through *ax*-**23** would predominate over the nonsynchronous pathway through *eq*-**14**: e.g. the second cyclization of **14e** and **15e** gave a 37:63 mixture of *trans*- and *cis*-**6e**.

(39) (a) Mori, K.; Tamura, H. *Liebigs Ann. Chem.* **1990**, 361. (b) Zoretic, P. A.; Fang, H.; Ribeiro, A. A.; Dubay, G. *J. Org. Chem.* **1998**, *63*, 1156.

Conclusions

We have demonstrated that chiral LBAs are effective for absolute stereocontrol in the initial cyclization of polyprenoids to form an A-ring and that the nucleophilicity of the internal terminator in polyprenoids is important for relative stereocontrol in the subsequent cyclization induced by achiral LBAs. Nonenzymatic enantioselective polyene cyclization of (*E*,*E*)-**4b** and (*all-E*)-**8** is a very attractive alternative to multistep synthesis from naturally occurring chiral synthons. (−)-Ambrox **1A** was concisely synthesized by the enantio- and diastereoselective cyclization of (*E*,*E*)-**4b**, which was prepared by adding a carbon to commercially available (*E*,*E*)-**5** or (*E*,*E*)-**12**. Alcohol protection of (*E*,*E*)-**4a** by a triethylsilyl group increased the enantioselectivity of chiral LBA-induced cyclization and both the chemical yield and diastereoselectivity in the subsequent cyclization. The enantioselective and diastereoselective cyclization of (*all-E*)-**8**, which possesses an aryl group, was also induced by chiral and achiral LBAs. Several optically active podocarpa-8,11,13-triene diterpenoids **6** and (−)-tetracyclic polyprenoid **7** of sedimentary origin were synthesized (75−80% ee). Further studies on the rational design of "chiral Brønsted acid catalysts" based on the concept of LBA may lead to practical artificial cyclases for the asymmetric synthesis of a wide range of polycyclic terpenoids.

Experimental Section

General Methods. High-performance liquid chromatography (HPLC) was done with Shimadzu 10A instruments using Daicel CHIRALCEL OD-H (4.6 mm × 25 cm) or OC (4.6 mm × 25 cm). GC analysis was done with Shimadzu 17A instruments using γ-TA (0.25 mm × 30 m) or PEG (0.25 mm × 25 m). Low-resolution mass spectra were obtained by direct insertion for CI (isobutane) on a Shimadzu GC/MS instrument (GC-17A) and QP-5050A (column: TC-1 (0.25 mm × 30 m)). All experiments were carried out under an atmosphere of dry argon. Benzene, hexane, toluene, and dichloromethane were freshly distilled from calcium hydride. Tin(IV) chloride was distilled under argon. Other simple chemicals were of commercially available analytical grade quality.

Enantioselective Synthesis of (−)-Ambrox 1A Using the Enantioselective Cyclization of (*E*,*E*)-4b Induced by (*R*)-BINOL-*o*-FBn·$SnCl_4$ and the Subsequent Diastereoselective Cyclization Induced by CF_3CO_2H·$SnCl_4$ (Eq 1). To a solution of (*R*)-BINOL-*o*-FBn (240 mg, 0.6 mmol) in toluene (6 mL) was added a 1.0 M solution of tin(IV) chloride (0.6 mL, 0.6 mmol) in toluene at room temperature, and

the solution was stirred for 5 min. After the solution of (*R*)-BINOL-*o*-FBn·$SnCl_4$ prepared in situ as above was cooled to −78 °C, (*E*,*E*)-**4b** (105.2 mg, 0.3 mmol) was added dropwise. The reaction mixture was stirred at −78 °C for 3 days, quenched with saturated aqueous $NaHCO_3$, and extracted with ether. The combined organic phase was dried over anhydrous $MgSO_4$ and concentrated. To a solution of the crude product in DMF (2 mL) were added imidazole (41 mg, 0.6 mmol) and chlorotriethylsilane (83 μL, 0.5 mmol) at 0 °C, and the reaction mixture was allowed to warm to ambient temperature. After being stirred for 5 h, the reaction mixture was quenched with water (2 mL) twice and extracted with ether. The combined organic phase was washed with brine (2 mL), dried over $MgSO_4$, and concentrated. To a mixed solution of trifluoroacetic acid (231 μL, 3 mmol) and tin(IV) chloride (1.0 M solution in toluene, 0.6 mL, 0.6 mmol) in nitroethane (4 mL) was added a solution of the crude product in nitroethane (2 mL) at −78 °C. After being stirred for 1 day, the reaction mixture was quenched with saturated aqueous $NaHCO_3$, extracted with ether, dried over $MgSO_4$, and concentrated. The residue was purified as a diastereomeric mixture of **1A**−**D** (54% yield) by column chromatography on silica gel (eluent, hexanes−ether 20:1). Compounds **1A**−**D** were not isolated, and their identification was effected by comparison of their ^{1}H and ^{13}C NMR data with those of authentic samples.[22b] The product distribution presented in eq 1 was determined by GC (PEG). The absolute stereochemistry of **1A** was ascertained by comparison of GC (γ-TA) data with that of (−)-ambrox (Aldrich). GC (PEG, 100 kPa, column temperature 120 °C, injection temperature 200 °C) t_R = 14.7 (**1B**), 15.5 (**1D**), 17.6 (**1A**), and 19.5 (**1C**) min; GC (γ-TA, 75 kPa, column temperature 130 °C, injection temperature 200 °C) t_R = 59.1 (major enantiomer of **1B**), 60.1 (minor enantiomer of **1B**), 61.3 (major enantiomer of **1D**), 63.0 (minor enantiomer of **1D**), 68.3 ((−)-**1A**), 70.2 ((+)-**1A**), 75.0 (major enantiomer of **1C**), and 77.8 (minor enantiomer of **1C**) min.

Although compounds **3** and **2** were not also isolated, ^{1}H and ^{13}NMR spectroscopic properties of the corresponding alcohols were identical with those reported.[19,21a,39] ^{1}H NMR chemical shifts of olefinic protons in **3b** and **2b** and their GC/MS data are provided as follows: ^{1}H NMR ($CDCl_3$) *endo*-**3b**: δ 5.27 (brs, 1H); *exo*-**3b**: δ 4.53 (s, 1H), 4.75 (s, 1H); *endo*-**2b**: δ 5.40 (brs, 1H); *exo*-**2b**: δ 4.75 (s, 1H), 4.81 (s, 1H). GC/MS [CI, 116 kPa, column temperature 70 °C for 5 min and then warming to 250 °C (+10 °C/min), injection temperature 150 °C] t_R = 20.0 (*exo*-**3b**), 20.2 (*endo*-**3b**), 20.5 (*exo*-**2b**), 20.8 (*endo*-**2b**) min; *m*/*z* M^+ + 1, 351.

General Procedure for the Enantioselective Cyclization of (*all-E*)-8 Induced by (*R*)-BINOL-R^1·$SnCl_4$. To a solution of (*R*)-BINOL-R^1 (0.4 mmol) in toluene (4 mL) was added a 1.0 M solution of tin(IV) chloride (0.4 mL, 0.4 mmol) in hexane at room temperature, and the solution was stirred for 5 min. After the solution of (*R*)-BINOL-R^1·$SnCl_4$ prepared in situ as above was cooled to −78 °C, (*all-E*)-**8** (0.2 mmol) was added dropwise over a period of 1 min. The reaction mixture was stirred at −78 °C for 3 days, quenched with saturated aqueous $NaHCO_3$, and extracted with ether. The combined organic phases were dried over anhydrous $MgSO_4$ and concentrated. The crude product was purified as a mixture of **6**, **14**, and **15** by column chromatography on silica gel (eluent, hexanes−ether). These compounds were used for the subsequent cyclization without further separation to give **6**, **14**, and **15** as a mixture, which were separable to **6** and a mixture of **14** and **15**.

Representative Procedure for the Desilylation of 14 and 15. To a solution of a mixture of **6c**, **14c**, and **15c**, which were obtained in the above reaction, in THF (1 mL) was added dropwise a 1 M solution of tetrabutylammonium fluoride (TBAF) in THF (0.2 mL, 0.2 mmol) at room temperature. After being stirred for 1 h, the reaction mixture was quenched with brine and extracted with ether. The combined oragnic phases were dried over anhydrous $MgSO_4$ and concentrated. The crude product was purified as a mixture of **6a**, **14a**, and **15a** by column chromatography on silica gel (eluent, hexanes−ether).

Procedure for the Diastereoselective Cyclization of 14a and 15a Induced by Achiral LBA, CF_3CO_2H·$SnCl_4$. To a solution of a mixture of **6a**, **14a**, and **15a**, which were obtained in the above reaction, in dichloromethane (2 mL) was successively added a 1 M solution of tin(IV) chloride in hexane (0.1 mL, 0.1 mmol) and trifluoroacetic acid (7.7 μL, 0.1 mmol) at −78 °C. The reaction mixture was stirred at −78 °C for 1 days, quenched with saturated aqueous $NaHCO_3$, and extracted with ether. The combined organic phases were dried over anhydrous $MgSO_4$ and concentrated. The crude product was purified by column chromatography on silica gel (eluent, hexanes−ether) to give **6a** in 94% over yield from (*E*)-**8c** in three steps.

General Procedure for the Diastereoselective Cyclization of 14 and 15 Induced by BF_3·Et_2O.[41] Boron trifluoride·diethyl etherate (0.84 mmol) was added to a solution of an acetylated mixture of **6e**, **14e**, and **15e**, which were obtained in the above enantioselective cyclization of (*E*)-**8d**, in nitromethane (3 mL) at room temperature. The reaction mixture was stirred at room temperature for 5 h, quenched with saturated aqueous $NaHCO_3$, and extracted with ether. The combined organic phases were dried over anhydrous $MgSO_4$ and concentrated. The crude product was purified by column chromatography on silica gel (eluent, hexanes−ether) to give **18** in 89% over yield from (*E*)-**8d** in four steps.

The diastereoselective cyclization of a mixture of products, which were obtained in the enantioselective cyclization of (*E*)-**8f** and (*E*)-**8g**, was also perofrmed in the same manner as above. Polycyclic compound **7** was purified by the oxidatitive treatment of byproducts including carbon−carbon double bonds with *m*-chloroperbenzoic acid in dichloromethane and subsequent column chromatography on silica gel (eluent: hexanes−ether).

Analytical data for these new compounds are provided in the following paragraphs.

(+)-(5*S*,10*S*)-12-Hydroxypodocarpa-8,11,13-triene (6a): GC/MS (CI, 70 °C for 5 min, warm to 10 °C/min, and then 250 °C for 7 min) t_R = 18.6 min for acetate of **6a**, *m*/*z* M^+ + 1, 287; HPLC (Daicel OD-H column, hexane-*i*-PrOH 20:1, flow rate = 0.5 mL/min) t_R = 27.7 (acetate of (−)-**6a**), 31.2 (acetate of (+)-**6a**) min; IR (film) 3500−3000 (OH), 2990, 1610, 1584 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.92 (s, 3H), 0.94 (s, 3H), 1.16 (s, 3H), 1.12−1.90 (m, 8H), 2.16 (d, J = 12.6 Hz, 1H), 2.69−2.92 (m, 2H), 4.9 (br, 1H), 6.57 (dd, J = 2.4, 8.7 Hz, 1H), 6.73 (d, J = 2.4 Hz, 1H), 6.89 (d, J = 8.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 19.1, 19.3, 21.6, 24.7, 29.6, 33.3, 33.4, 37.8, 41.6, 50.2, 111.0, 112.6, 127.4, 129.9, 151.6, 153.2; $[\alpha]^{26.2}_D$ 22.3 (*c* 1.07, $CHCl_3$). Anal. Calcd for $C_{17}H_{24}O$: C, 83.55; H, 9.90. Found: C, 83.57; H, 9.86.

6-Homo(*p*-hydroxybenzyl)-1,5,5-trimethylcyclohexene (14a) and 3,3-dimethyl-1-methylene-2-homo(*p*-hydroxybenzyl)cyclohexane (15a): Compounds **14a** and **15a** could not be separated by column chromatography on silica gel. GC/MS (CI, 70 °C for 5 min, warm to 10 °C/min, and then 250 °C for 7 min) t_R = 17.8 (acetate of **14a**), 18.1 (acetate of **15a**) min, *m*/*z* M^+ + 1, 287; ^{1}H NMR ($CDCl_3$) δ 0.82 (s, 3H (**15a**)), 0.88 (s, 3H (**14a**)), 0.90 (s, 3H (**15a**)), 0.97 (s, 3H (**14a**)), 1.01−2.62 (m, 9H (**14a**) and 11H (**15a**)), 1.67 (s, 3H (**14a**)), 4.53 (s, 1H), 4.60 (s, 1H (**15a**)), 4.82 (s, 1H (**15a**)), 5.30 (brs, 1H (**14a**)), 6.74 (d, J = 8.1 Hz, 2H), 7.04 (d, J = 8.1 Hz, 2H).

(+)-(5*S*,10*S*)-12-Methoxypodocarpa-8,11,13-triene (6b):[30c,42] GC/MS (CI, 70 °C for 5 min, warm to 10 °C/min, and then 250 °C for 7 min) t_R = 17.4 min, *m*/*z* M^+ + 1, 259; HPLC (Daicel OD-H column, hexane-*i*-PrOH 100:1, flow rate = 0.3 mL/min); t_R = 16.5 ((−)-enantiomer), 22.7 ((+)-enantiomer) min; IR (film) 2900, 1615, 1510, 1250, 1044 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (s, 3H), 0.95 (s, 3H), 1.14−1.91 (m, 8H), 1.19 (s, 3H), 2.19−2.29 (m, 1H), 2.71−2.94 (m, 2H), 3.78 (s, 3H), 6.63−6.69 (m, 1H), 6.81 (s, 1H), 6.96 (d, J = 8.4 Hz, 1H); $[\alpha]^{26.3}_D$ 21.0 (*c* 0.36, $CHCl_3$) for 61% ee; lit. $[\alpha]_D$ 65,[42] 72.[30c]

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6-Homo(*p*-methoxybenzy)-1,5,5-trimethylcyclohexene (14b) and 3,3-dimethyl-1-methylene-2-homo(*p*-methoxybenzyl)cyclohexane (15b): Compounds **14b** and **15b** could not be separated by column chromatography on silica gel. GC/MS (CI, 70 °C for 5 min, warm to 10 °C/min, and then 250 °C for 7 min) t_R = 17.4 (**14b**), 17.6 (**15b**) min, *m*/*z* $M^+ + 1$, 259; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (s, 3H (**15b**)), 0.88 (s, 3H (**14b**)), 0.90 (s, 3H (**15b**)), 0.97 (s, 3H (**14b**)), 1.01−2.62 (m, 9H (**14b**) and 11H (**15b**)), 1.68 (s, 3H (**15b**)), 3.80 (s, 3H), 4.62 (s, 1H (**15b**)), 4.82 (s, 1H (**15b**)), 5.30 (brs, 1H (**14b**)), 6.82 (d, *J* = 8.7 Hz, 2H), 7.10 (d, *J* = 8.7 Hz, 2H).

12-*tert*-Butyldiphenylsiloxypodocarpa-8,11,13-triene (6c), 6-homo[*p*-(*tert*-butyldiphenylsiloxy)benzyl]-1,5,5-trimethylcyclohexene (14c), and 3,3-dimethyl-1-methylene-2-homo[*p*-(butyldiphenylsiloxy)benzyl]cyclohexane (15c): Crude compounds of **6c**, **14c**, and **15c**, which were produced in the enantioselective cyclization of **8c** induced by (*R*)-BINOL-R^1·$SnCl_4$, were transformed into acetates of **6a**, **14a**, and **15a**, respectively, by desilylation with TBAF and acetylation with acetic anhydride in the presence of triethylamine to determine the product ratio of **6c**, **14c**, and **15c** and the ee value of **6c**.

13-*tert*-Butyldiphenylsiloxypodocarpa-8,11,13-triene (6d), 6-Homo[*m*-(*tert*-butyldiphenylsiloxy)benzyl]-1,5,5-trimethylcyclohexene (14d), and 3,3-Dimethyl-1-methylene-2-homo[*m*-(butyldiphenylsiloxy)benzyl]cyclohexane (15d): Crude compounds of **6d**, **14d**, and **15d**, which were produced in the enantioselective cyclization of **8d** induced by (*R*)-BINOL-*o*-FBn·$SnCl_4$, were transformed into **6e**, **14e**, and **15e**, respectively, by desilylation with TBAF to determine the product ratio of **6e**, **14e**, and **15e** and the ee value of **6e**.

(+)-(5*S*,10*S*)-13-Hydroxypodocarpa-8,11,13-triene (6e):[43] GC/MS (CI, 70 °C for 5 min, warm to 10 °C/min, and then 250 °C for 7 min) t_R = 17.8 min, *m*/*z* $M^+ + 1$, 245; HPLC (Daicel OD-H column, hexane-*i*-PrOH 20:1, flow rate = 0.5 mL/min) t_R = 16.0 ((−)-(5*R*,10*R*)), 18.3 ((+)-(5*S*,10*S*)) min; IR (film) 3400−3050 (OH), 2935, 1607, 1497 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (s, 3H), 0.94 (s, 3H), 1.15 (s, 3H), 1.16−1.90 (m, 8H), 2.19−2.28 (m, 1H), 2.73−2.94 (m, 2H), 4.54 (brs, 1H), 6.50 (d, *J* = 2.7 Hz, 1H), 6.60 (dd, *J* = 2.7, 8.7 Hz, 1H), 7.11 (d, *J* = 8.7 Hz, 1H); $[\alpha]^{24.0}_D$ 45.1 (*c* 0.42, $CHCl_3$) for 78% ee; lit. $[\alpha]_D$ 61 (*c* 1.3).[43]

6-Homo(*m*-hydroxybenzyl)-1,5,5-trimethylcyclohexene (14e) and 3,3-dimethyl-1-methylene-2-homo(*m*-hydroxybenzyl)cyclohexane (15e): Compounds **14e** and **15e** could not be separated by column chromatography on silica gel. GC/MS (CI, 70 °C for 5 min, warm to 10 °C/min, and then 250 °C for 7 min) t_R = 16.7 (**14e**), 16.9 (**15e**) min, *m*/*z* $M^+ + 1$, 245; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (s, 3H (**15e**)), 0.88 (s, 3H (**14e**)), 0.92 (s, 3H (**15e**)), 0.98 (s, 3H (**14e**)), 1.10−3.00 (m, 9H (**14e**) and 11H (**15e**)), 1.70 (s, 3H (**14e**)), 4.62 (s, 1H (**15e**)), 4.82 (s, 1H (**15e**)), 5.30 (s, 1H (**14e**)), 6.80−7.20 (m, 4H), the OH signal was not observed.

(+)-(5*S*,10*S*)-11-Hydroxypodocarpa-8,11,13-triene (17): GC/MS (CI, 70 °C for 5 min, warm to 10 °C/min, and then 250 °C for 7 min) t_R = 17.4 min, *m*/*z* $M^+ + 1$, 245; HPLC (Daicel OC coulmn, hexane-*i*-PrOH 80:1, flow rate = 0.3 mL/min) t_R = 28.2 ((+)-enantiomer), 30.4 ((−)-enantiomer) min; IR (film) 3700−3000 (OH), 1576, 1456, 1264 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (s, 3H), 0.96 (s, 3H), 1.34 (s, 3H), 1.17−1.86 (m, 8H), 2.84 (t, *J* = 4.5 Hz, 2H), 3.11 (dt, *J* = 13.5, 3.0 Hz, 1H), 4.69 (s, 1H), 6.42 (d, *J* = 8.1 Hz, 1H), 6.60 (d, *J* = 8.1 Hz, 1H), 6.92 (t, *J* = 8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.9, 19.4, 19.9, 22.2, 32.9, 33.74, 33.75, 36.5, 39.4, 41.4, 52.9, 100.0, 113.9, 122.3, 125.9, 138.9, 154.1; $[\alpha]^{26.5}_D$ 12.2 (*c* 0.27, $CHCl_3$) for 73% ee. Anal. Calcd for $C_{17}H_{24}O$: C, 83.55; H, 9.90. Found: C, 83.51; H, 9.91.

(+)-(5*S*,10*S*)-13-Acetoxypodocarpa-8,11,13-triene (18): HPLC (two linear Daicel OD-H columns, hexane-*i*-PrOH 80:1, 0.3 mL/min) t_R = 34.9 ((−)-enantiomer), 45.9 ((+)-enantiomer) min; IR (film) 2900, 1759 (C═O), 1493, 1368, 1210 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (s, 3H), 0.94 (s, 3H), 1.17 (s, 3H), 1.18−1.92 (m, 8H), 2.27 (s, 3H), 2.22−2.30 (m, 1H), 2.82−2.92 (m, 2H), 6.72 (s, 1H), 6.80 (d, *J* = 8.4 Hz, 1H), 6.72 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.8, 19.2, 21.2, 21.6, 24.9, 30.3, 33.3, 33.4, 37.6, 38.8, 41.6, 50.1, 118.5, 121.2, 125.5, 136.8, 147.7, 147.9, 169.8; $[\alpha]^{24.0}_D$ 15.1 (*c* 0.86, $CHCl_3$). Anal. Calcd for $C_{19}H_{26}FO_2$: C, 79.68; H, 9.15. Found: C, 79.73; H, 9.12.

(+)-13-Methylpodocarpa-8,11,13-triene (6f):[44] HPLC (two linear Daicel OD-H columns, hexane-*i*-PrOH 400:1, 0.2 mL/min) t_R = 38.9 ((−)-enantiomer), 41.4 ((+)-enantiomer) min; IR (film) 2900, 1497, 1474, 1375, 1040, 814 cm^{-1}; 0.92 (s, 3H), 0.94 (s, 3H), 1.02−1.91 (m, 8H), 1.18 (s, 3H), 2.22−2.30 (m, 1H), 2.26 (s, 3H), 2.79−2.95 (m, 2H), 6.86 (s, 1H), 6.93 (d, *J* = 8.1 Hz, 1H), 7.15 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.0, 19.3, 20.8, 21.6, 24.9, 30.3, 33.3, 33.4, 37.5, 38.9, 41.7, 50.5, 124.3, 126.4, 129.5, 134.5, 135.1, 147.3; $[\alpha]^{26.9}_D$ 33.8 (c 1.54, $CHCl_3$).

(−)-(4a*S*,4b*R*,10b*R*,12a*S*)-1,2,3,4,4a,4b,5,6,10b,11,12,12a-Dodecahydro-1,1,4a,8,10b-pentamethylchrysene (7):[37,44] IR (film) 2900, 1460 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.85 (s, 3H), 0.8−1.9 (m, 13H), 0.86 (s, 3H), 0.92 (s, 3H), 1.15 (s, 3H), 1.18 (s, 3H), 2.26 (s, 3H), 2.30−2.40 (m, 1H), 2.70−2.90 (m, 2H), 6.85 (s, 1H), 6.94 (d, *J* = 8.4 Hz, 1H), 7.14 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.3 (C16′), 18.0 (C9), 18.6 (C17), 19.1 (C13), 20.8 (C4′), 21.4 (C20′), 26.2 (C12′), 30.8 (C8), 33.3 (C19), 33.3 (C20), 37.6 (C15), 37.8 (C11), 39.8 (C16), 40.7 (C12), 42.0 (C18), 55.3 (C10), 56.3 (C14), 124.5 (C5), 126.5 (C4), 129.3 (C2), 134.4 (C3), 135.0 (C7), 147.6 (C6); $[\alpha]^{26.5}_D$ −35.6 (*c* 0.43, $CHCl_3$); the ee value (77%) was measured on the known optical rotation value; lit. $[\alpha]^{23}_D$ -46 (*c* 0.74, $CHCl_3$).[37]

Supporting Information Available: Experimental procedures and characterization data for (*R*)-BINOL-R^1, (*E*,*E*)-**4**, and (*all-E*)-**8** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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