Enantioselective Biomimetic Cyclization of Isoprenoids Using Lewis Acid-Assisted Chiral Brønsted Acids: Abnormal Claisen Rearrangements and Successive Cyclizations

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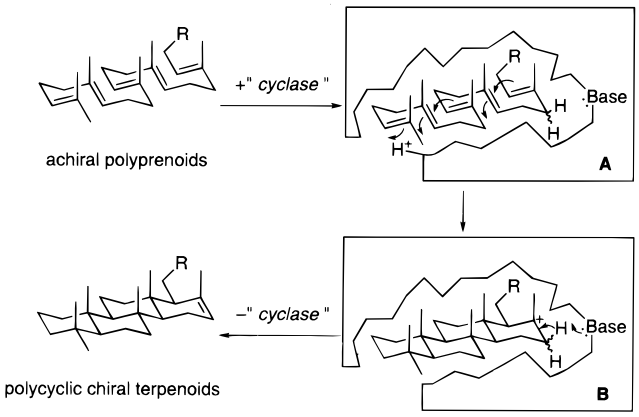
Abstract: Syntheses of polycyclic isoprenoids have been achieved by several groups; however, no general "biomimetic" method has yet been reported. In this paper we describe the biomimetic cyclization of simple isoprenoids to polycyclic isoprenoids using Lewis acid-assisted chiral Brønsted acids, "chiral LBAs". This is the first example of a proton-induced enantioselective ene cyclization in synthetic chemistry. Geranyl phenyl ethers, *o*-geranylphenols, and geranylacetone derivatives were directly cyclized at −78 °C in the presence of (*R*)-binaphthol derivatives and tin tetrachloride. During the cyclization, [1,3] abnormal Claisen rearrangement often took place. The enantioselectivities were up to 90% ee. Compounds bearing a farnesyl group could also be cyclized under the same conditions to give the natural products (−)-Ambrox and (−)-chromazonarol. These chiral LBAs recognize a trisubstituted terminal olefin enantiotopically and generate site-selective carbocations on the substrates. The absolute stereochemistry of the cyclization is discussed with model studies using DFT calculations on the B3LYP/LANL2DZ level.

Introduction

Many isoprenoids (over 30 000 compounds) have been characterized, identified, and reported. They play important roles in stabilizing membranes, and in the construction of signal transduction networks, visual pigments, antibiotics, etc.[1,2] Isoprenoids have extraordinarily diverse structures, which are created by enzymes called "cyclases". Various polycyclic isoprenoids are generated from simple linear polyene substrates such as geranyl pyrophosphate, farnesyl pyrophosphate, geranylgeranyl pyrophosphate, and squalene. The fundamental skeletons of polycyclic isoprenoids have many chiral centers including quaternary carbons and are mainly constructed by such cyclases in a single cyclization reaction,[3] recognized as an enzyme-controlled asymmetric ene reaction (Scheme 1). Diverse families of isoprenoid structures, often formed from the same substrate in an enzyme-specific manner, are thought to be based on these four steps:[4] (1) generation of the carbocation, (2) control over the conformation of the substrate, (3) stabilization of intermediates, and (4) quenching of the final carbocation. Carbocations generated on substrates are stabilized during the successive cyclization. Shifts of hydrogens and/or alkyl groups often take place, and the final carbocations are quenched to give the product. Generation of the carbocation is the most important step, since this is truly the first step in achieving complete absolute and relative stereoselectivity. There are three primary routes by which carbocations are generated: pyrophosphate elimination, olefin protonation, and epoxide ring opening.[1] In mono- and sesquiterpene biosyntheses, most initial carbocations are generated by pyrophosphate elimination. Some of the triterpenes such as sterols are biosynthesized by diastereoselective cyclization of enantiopure 2,3-oxidosqualene through epoxide opening. The protonation of olefin is the most important route especially in the biosyntheses of longer isoprenoids.

Scheme 1. A Hypothetical Simple Cyclization Catalyzed by a "Cyclase"



No catalyst with a cavity analogous to that of a natural enzyme has yet been designed in synthetic chemistry. The most important feature required for an artificial cyclase is that asymmetric induction in the protonation of the terminal isoprenyl group of isoprenoids, and the successive cyclization without

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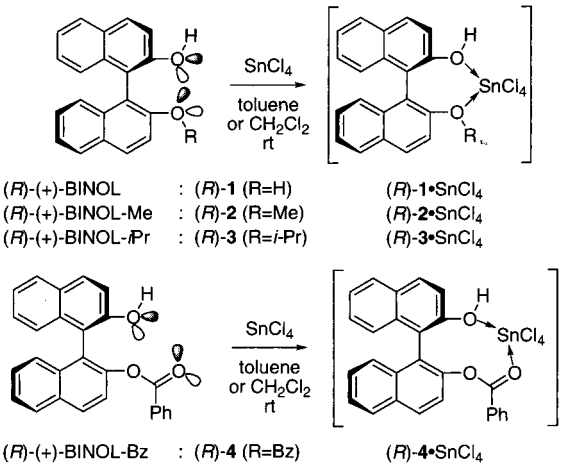
an enzymatic cavity must be done at low temperature to control the substrate conformation. The stereochemical implications of polyene cyclizations initiated by protonation at the terminal C−C double bond can be explained by the Stork−Eschenmoser hypothesis,[5] which postulates synchronous internal anti additions via chairlike conformations of nascent cyclohexane rings. Computational[6] and preparative studies[7] on the cyclization that begins with epoxide opening have been done to reveal that the first step must be the concerted step; however, the concertedness of the overall ring-forming process is a matter of debate.[8] Despite extensive studies on acid-catalyzed diastereoselective polyene cyclizations using chiral auxiliaries[9] and antibody-catalyzed diastereoselective cyclization,[10] enantioselective processes using synthetic chiral catalysts have not yet been reported.

We have found that the Lewis acid-assisted chiral Brønsted acids (chiral LBAs)[11,12] serve as chiral Brønsted acid catalysts and reagents. The coordination of a Lewis acid to a Brønsted acid restricts directional access to the proton and increases the Brønsted acidity. And the chiral LBAs, which are generated from chiral Brønsted acids, provide us the useful protons surrounded by chiral environments. We have previously reported enantioselective protonations[11a,b] of silyl enol ethers using an optically active (*R*)-2,2′-dihydroxy-1,1′-binaphthyl ((*R*)-BINOL or (*R*)-**1**·$SnCl_4$ complex, as well as its catalytic version[11c] using (*R*)-2-hydroxy-2′-methoxy-1,1′-binaphthyl ((*R*)-BINOL-Me or (*R*)-**2**·$SnCl_4$ complex as a catalyst and 2,6-dimethylphenol as an achiral proton source.[12] Recent research has revealed the isomerization[11g] of TBDMS enol ethers under the same conditions and indicates the existence of carbocation intermediates. The aliphatic substrates such as geranyltrimethyltin and *meso*-enediol disilyl ether were also enantiomerically protonated by chiral LBA.[11e,f] We report here that (*R*)-LBAs, (*R*)-**1**−**4**·$SnCl_4$ (Scheme 2), are useful as artificial geranyl and farnesyl cyclases.

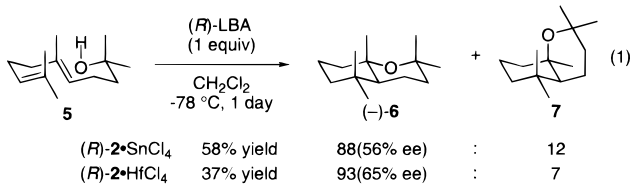
Scheme 2. In Situ Preparation of (*R*)-**1**−**4**·$SnCl_4$



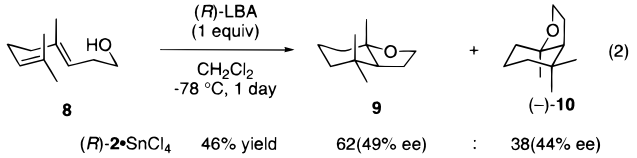
Our chiral LBAs gave their protons to the terminal trisubstituted olefin of simple isoprenoids enantiotopically to initiate ene cyclizations.

Results and Discussion

Cyclization of Polyolefinic Alcohols. First, the enantioselective cyclization of geranyl derivatives was examined using (*R*)-LBAs, (*R*)-**1**−**4**·$SnCl_4$, in dichloromethane at −78 °C. For example, the reaction of dienol **5**, prepared by methylation of geranyl acetone, with 1 equiv of (*R*)-**2**·$SnCl_4$ gave a diastereomeric mixture of decalins **6** and **7** in 58% yield (*trans*-**6**:*cis*-**7** = 88:12), and the enantiomeric excess of the major isomer **6** was 56% (eq 1). The use of (*R*)-**2**·$SnCl_4$ gave slightly better



enantioselectivity than the use of (*R*)-**1**·$SnCl_4$. This tendency is similar to that in the enantioselective protonation reported earlier.[12] The Lewis acids such as hafnium tetrachloride and zirconium tetrachloride were usable in the enantioselective cyclization, but were not completely dissolved in the reaction solution. The cyclization of homogeraniol (**8**) with (*R*)-**2**·$SnCl_4$ successfully proceeded to give trans-fused bicyclic compound **9** as a major isomer with 49% ee (eq 2). Compound **9** is known to be a natural product.[13]



(−)-Ambrox (**12**), which is found in Givenchy's Extravagance d'Amarige, for example, is the most important commercial substitute for ambergris,[14] due to its unique olfactive and fixative

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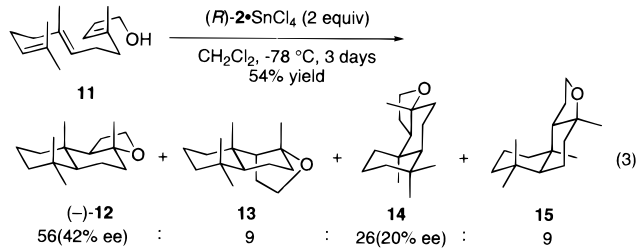
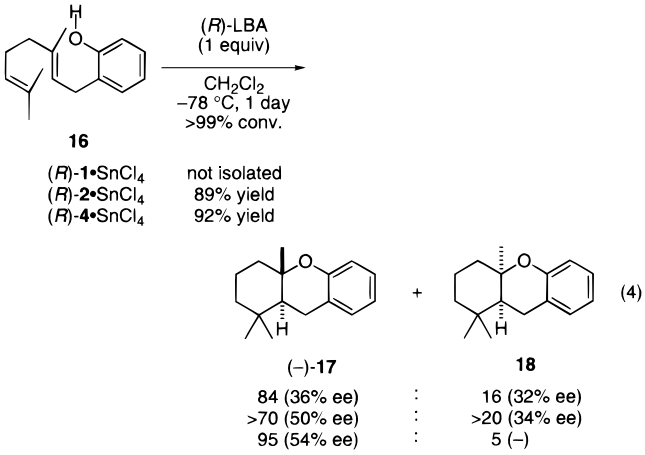
properties. Its scarcity has been a stimulus for chemical synthesis.[8,15] The successful preparation of (−)-**12** was achieved by the enantioselective cyclization of homofarnesol (**11**) promoted with (*R*)-**2**·$SnCl_4$, although the enantioselectivity and diastereoselectivity were moderate (eq 3). Minor products **13**−



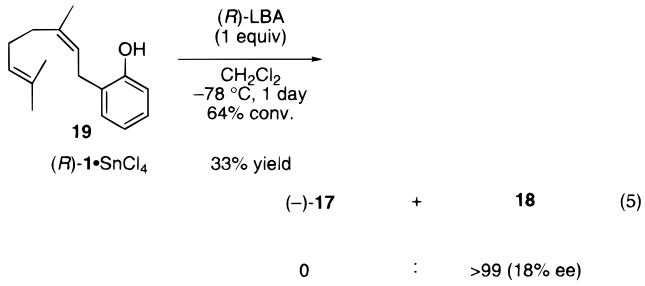
15 obtained were also identified by comparison with authentic samples.[15g,h] Homofarnesol (**11**) was produced from commercially available nerolidol in two steps according to the known procedure.[16] This three-step total synthesis of (−)-Ambrox is shorter than any previously reported enantioselective total synthesis.[8,15]

Cyclization of Polyolefinic Phenol Derivatives. The catalytic activity of chiral LBAs is inhibited to some degree by a hydroxy group which serves as an internal nucleophilic terminator in polyolefinic alcohols. To investigate the present cyclization system in detail, we chose more reactive *o*-geranylphenol (**16**). The cyclization of **16** with (*R*)-**1**·$SnCl_4$ in dichloromethane at −78 °C was completed within a day, and the trans-fused tricyclic compound **17** was obtained as a major diastereomer (84% ds) (eq 4).[17] However, the optical yield of **17** was only 36% ee.



The enantioselectivity was improved to 50% ee by using (*R*)-**2**·$SnCl_4$.[11c] Among various (*R*)-BINOL derivatives screened, we found that (*R*)-**4**·$SnCl_4$ prepared from the monobenzoyl ester of (*R*)-BINOL and tin tetrachloride was the most effective for controlling the absolute and relative stereochemistries in this cyclization (54% ee, 95% ds). It seems that the stereoselectivity depends on the reactivity of the chiral LBA as a promoter; the reactivities decreased in the order (*R*)-**1**·$SnCl_4$, (*R*)-**2**·$SnCl_4$, and (*R*)-**4**·$SnCl_4$. The cyclization was accelerated by the coordination of tin tetrachloride to several Brønsted acids, although the reaction proceeded slowly even in the presence of tin tetrachloride alone. Unfortunately, (*R*)-**4**·$SnCl_4$ was not effective for the cyclization of aliphatic substrates **5**, **8**, and **11**, probably because its Brønsted acidity is too low.

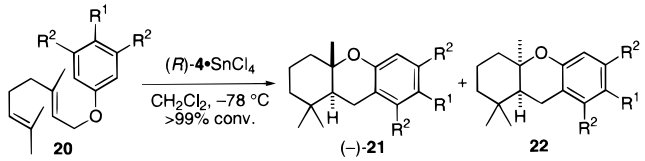
On the other hand, the cis-fused bicyclic compound **18** was observed as the major product under the same conditions using nerylphenol (**19**) (eq 5). However, the conversion and enantio-



selectivity were slightly lower than in the previous cases, and undesired monocyclic products were also produced, probably because cyclization was unfavorable.

In further studies, we found that **21** was obtained with much better selectivity from the reaction of geranyl phenyl ether **20** ($R^1 = R^2 = H$) with (*R*)-**4**·$SnCl_4$ (Table 1, entry 1). The proton in (*R*)-**4**·$SnCl_4$ is strong enough to promote the reaction and yet weak enough to control the reaction to achieve a higher ee. Surprisingly, the reaction proceeded smoothly even in the presence of 20 mol % (*R*)-**4**·$SnCl_4$ to give **21** with 77% ee and 98% ds (entry 2). Other examples are summarized in Table 1.

Table 1. Enantioselective Cyclization of Geranyl Ary Ether **20**



	20		(*R*)-LBA **4**	time	**21**		ratio[c]
entry	R^1	R^2	(equiv)	(day)	yield (%)[a]	ee (%)[b]	**21**:**22**
1	H	H	1.1	1	98 (79)	69	98:2
2	H	H	0.2	4	98 (76)	77	98:2
3	F	H	1.1	1	98	63	94:6
4	F	H	0.2	4	72	79	70:30
5	Cl	H	1.1	1	99	65	98:2
6	Cl	H	0.2	4	97	82	97:3
7	Br	H	1.1	1	87	63	94:6
8	Br	H	0.2	4	85 (71)	87	89:11
9	Br	H	0.15	6	94	90	95:5
10	Me	H	1.1	1	92	62	95:5
11	Me	H	0.2	4	94	67	97:3
12	OMe	H	1.1	1	84	70	95:5
13	OMe	H	0.2	4	92	42	94:6
14	H	Me	1.1	1	80	62	89:11
15	H	Me	0.2	4	82	46	91:9

[a] Unless otherwise noted, GC yields are indicated. Isolated yields are indicated in parentheses. [b] Ee values were determined by GC or HPLC analysis of isolated pure product. [c] Ratios were determined by GC or HPLC analysis of crude products in which other minor products were included.

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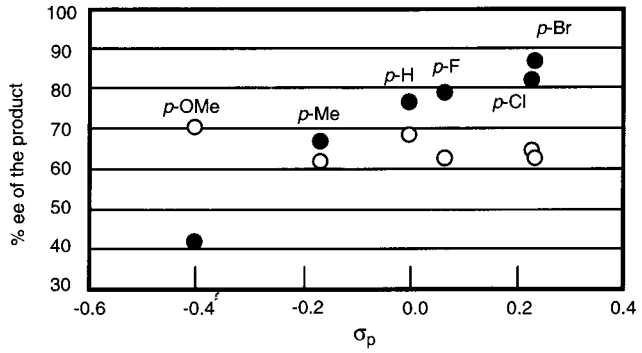


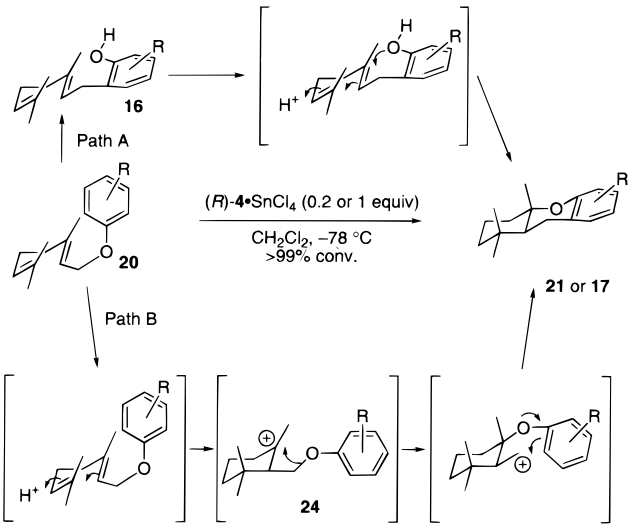
Figure 1. Percent ee value observed in the cyclization of **20** with (*R*)-**4**·$SnCl_4$ at −78 °C in CH_2Cl_2 as a function of the σ_p parameter for R^1 in **20**. (○) and (●) refer to the use of a stoichiometric amount of (*R*)-**4**Sn·Cl_4 and the use of a catalytic amount (20 mol %) of (*R*)-**4**·$SnCl_4$, respectively.

The use of (*R*)-**4**·$SnCl_4$ without exception resulted in the highest enantioselectivity and diastereoselectivity; however, the catalytic use of (*R*)-**4**·$SnCl_4$ for substrates **20** with electron-donating groups (R^1 = OMe, R^2 = H) or bulky groups (R^1 = H, R^2 = Me) on their phenols reduced the enantioselectivity (entries 12−15). The reaction on substrates **20** with electron-withdrawing groups on their phenols (R^1 = Br, R^2 = H), in contrast, gave **21** and increased the enantioselectivity to 87% ee (entry 8) and 90% ee (entry 9). These results indicate the importance of performing the reaction under mild conditions appropriate for each substrate to achieve maximal enantioselectivity and diastereoselectivity. The relative stereochemistry of the major product **21** was determined to be trans on the basis of the similarity of the ^1H and ^{13}C NMR spectra to those of **21** (R^1 = H, R^2 = Me), which had been assigned as trans by an X-ray analysis (see the Supporting Information). The absolute stereochemistry of **21** produced by (*R*)-LBAs is speculated to be (4a*S*,9a*S*) on the basis of the absolute stereopreference on the enantioselective cyclization of **11**.

A plot of the ee value observed in the cyclization of **20** with (*R*)-**4**·$SnCl_4$ as a function of the σ_p parameter[18] for the substituent R^1 on the aromatic ring in **20** is shown in Figure 1. Interestingly, the ee value observed in the reaction with catalytic amounts of the (*R*)-LBA was increased in proportion to the σ_p parameter. The ee value observed in the reaction with a stoichiometric amount of the (*R*)-LBA, however, was about 60−70% ee and was independent of the σ_p parameter. These phenomena can be understood by assuming that the catalytic use of LBA and weak Lewis basicity of the oxygen atom in **20** relatively suppress the undesired coordination of LBA or tin tetrachloride with the oxygen atom during the cyclization. Nevertheless, it is not clear why there is a difference between stoichiometric and catalytic amounts of LBA.

Geranyl phenyl ether **20** is more reactive than **16**, probably because of the lack of a hydroxy group in the former. The existence of the hydroxy group in the substrate reduces the catalytic activity of LBA by its coordination with tin tetrachloride. Although it is surmised that the reaction of geranyl aryl ether **20** takes place via [1,3]-rearrangement (abnormal Claisen rearrangement)[19] and cyclization, it is not clear which of these two steps occurs first (Scheme 3). Nevertheless, it is reasonable to suppose that the reaction takes place via abnormal Claisen

Scheme 3. Possible Pathways from Geranyl Phenyl Ethers **20** to the Tricyclic Products **21** or **17**



rearrangement before subsequent cyclization (path A). While we have not yet found any direct evidence of intermediates, we have a suggestive finding for path A: Although it is known that abnormal Claisen rearrangements generally do not occur smoothly,[19] the use of (*R*)-**2**·$FeCl_3$ for the reaction of **20** (R^1 = R^2 = H) gave **16** in 76% yield, and trace amounts of **21** and **22** were also observed. On the contrary, it seems that phenoxy migration after proton-induced cyclization (path B) is unfavorable because the C−O bond cleavage with the generation of unstable primary carbocation formation is quite unlikely.

Control experiments were performed with the metal halides tin tetrachloride, hafnium tetrachloride, and gallium trichloride under the same conditions as in Table 1, and the results are shown in Table 2. Although all three metal halides could promote the ene cyclization as Lewis acid (entries 1, 8, and 13), high enantioselectivity was not observed without a hydroxy group on the ligands (entries 6, 7, 10, 11, 15, and 16). The presence of OH on the ligand is not quite essential as stated since ligands **29** and **30** gave modest enantiomeric excesses (11−19%). No reactivity was observed using hafnium tetrachloride or gallium trichloride with aprotic bidentate ligand (*R*)-**28** (entries 11 and 16). Interestingly, the product ratio in the ene reaction is mostly dependent on the metal. The use of tin tetrachloride and its coordinate complexes produced **17** selectively, and the use of (*R*)-**2**·$SnCl_4$ and (*R*)-**4**·$SnCl_4$ produced **17** with good enantiomeric excesses (entries 2 and 5). In contrast, the use of hafnium tetrachloride, zirconium tetrachloride, and their coordinate complexes were realtively less selective for producing **17**, and their use as chiral LBA was also less effective. For example, (*R*)-**2**·$HfCl_4$ and (*R*)-**2**·$ZrCl_4$ produced monocyclization product **25** in 23% and 27% yields, respectively, together with **17** (entries 9 and 17). In both cases, the cis isomer of **26**, which was generated via a stepwise cyclization from **25**,[21] was observed along with other isomers. Interestingly, (*R*)-**2**·$GaCl_3$ generated unrearranged cyclic compound **26** in high yield but with low enantiomeric excess (entry

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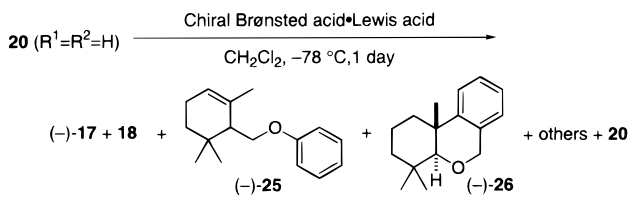
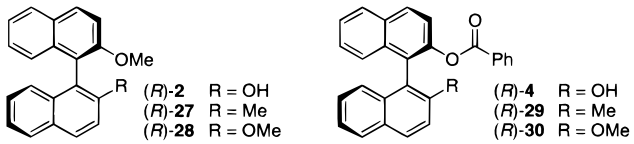
Table 2. Enantioselective Cyclization of Geranyl Phenyl Ether **20** (R^1=R^2=H) Using Various Combinations of Chiral Brønsted Acids[a] and Lewis Acids



entry	chiral Brønsted acid•Lewis acid	ratio[b] 17	18	25	26	others[c]	20
1	$SnCl_4$	89	3	0	0	8	0
2	(*R*)-**2**•$SnCl_4$	83 (46)	10	4	0	3	0
3	(*R*)-**27**•$SnCl_4$	83 (0)	5	0	0	12	0
4	(*R*)-**28**•$SnCl_4$	65 (0)	2	0	0	33	0
5	(*R*)-**4**•$SnCl_4$	98 (79)	2	0	0	0	0
6	(*R*)-**29**•$SnCl_4$	94 (19)[d]	6	0	0	0	0
7	(*R*)-**30**•$SnCl_4$	96 (11)[d]	4	0	0	0	0
8	$HfCl_4$	53	37	5	0	5	0
9	(*R*)-**2**•$HfCl_4$	23 (46)	11	23 (50)	0	43[e]	0
10	(*R*)-**27**•$HfCl_4$	26 (0)	19	13 (0)	0	42[e]	0
11	(*R*)-**28**•$HfCl_4$	0	0	0	0	0	>99
12	(*R*)-**4**•$HfCl_4$	69 (0)	8	0	0	23	0
13	$GaCl_3$	16	19	2	57	6	0
14	(*R*)-**2**•$GaCl_3$	4	2	2	82 (11)	10	0
15	(*R*)-**27**•$GaCl_3$	11 (0)	4	0	81 (0)	4	0
16	(*R*)-**28**•$GaCl_3$	0	0	0	0	0	>99
17	(*R*)-**2**•$ZrCl_4$	35 (38)	19	27	0	19[e]	0

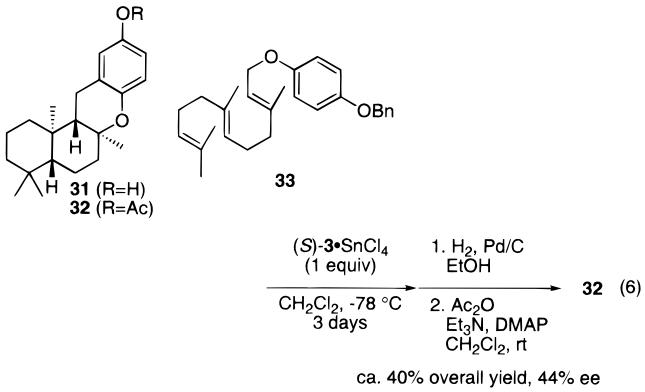
[a] The compounds **27**−**30** are not actually Brønsted acids, but we refer to them as "Brønsted acids" by analogy. [b] Unless otherwise noted, GC yields are indicated. Ee values are indicated in parentheses and were determined by GC or HPLC analysis of isolated pure product. [c] Trace amounts of chlorinated products, which were observed on GC−MS, are included in "others". [d] Enantioselectivity was reversed to give the (+)-enantiomer. [e] The cis isomer of **26** was included.



14). Hafnium tetrachloride, gallium trichloride, and zirconium tetrachloride may have the limited ability to promote abnormal Claisen rearrangement prior to the cyclization, and produce unrearranged cyclic compounds as a result. As mentioned above, (*R*)-**2**•$FeCl_3$ under the same conditions gave only abnormal Claisen-rearranged **16**. Taken together, these results suggest that whether the rearrangement takes place is largely based on the properties of Lewis acids themselves.[19]

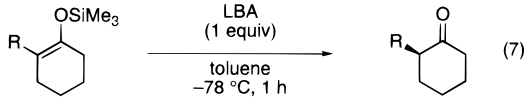
We now have several candidates to use in making a variety of chiral LBA reagents with various activities, although those containing tin tetrachloride are still the first choice.

To demonstrate the effectiveness of chiral LBA-promoted enantioselective cyclization, we synthesized acetate **32** of (−)-chromazonarol (**31**), a minor constituent of the brown Pacific seaweed, *Dictyopteris undulata*,[22] biomimetically from the corresponding farnesyl derivatives. The cyclization of 4-benzyloxyphenyl farnesyl ether (**33**) with (*S*)-**3**•$SnCl_4$[11e] gave the desired tetracyclic compound **32** as a major diastereomer in 44% ee after debenzylation and acylation (eq 6).



We simultaneously control four chiral centers including two quaternary carbons with the enantioselective ene cyclization. Syntheses of (−)-Ambrox and (−)-chromazonarol acetate indicate that these (*R*)-LBAs approach the *re* face of a trisubstituted terminal olefin uniformly. The number of cyclizations and the diastereoselectivity are dependent on the spontaneous conformation of substrates in media at low temperature. Enzymes control this with cavities made by aromatic residues, which also stabilize carbocations on intermediates. The design and construction of a cavity is a possible next step to achieve a higher yield and enantioselectivity.

DFT Calculations. In the previous report,[12] the properties of (*R*)-**1**•$SnCl_4$ and (*R*)-**2**•$SnCl_4$ were discussed and estimated using DFT calculations. (*R*)-**4**•$SnCl_4$ was the most efficient in the enantioselective ene reaction of geranyl aryl ethers **20**. However, less reactive substrates such as **5**, **8**, and **11** were not cyclized under the same conditions, probably because (*R*)-**4**•$SnCl_4$ was not sufficiently acidic to cyclize them. In contrast, the enantioselective protonation of "thermodynamic" trimethylsilyl enol ether **34** derived from 2-phenylcyclohexanone did not proceed using (*R*)-**4**•$SnCl_4$ (eq 7), although silyl enol ethers



34 (R=Ph)	(*R*)-**1**•$SnCl_4$:	>99% yield, 98% ee[12]
	(*R*)-**2**•$SnCl_4$:	>99% yield, 97% ee[12]
	(*R*)-**4**•$SnCl_4$:	trace, –
	(*R*)-**35**•$SnCl_4$:	trace, –
36 (R=Me)	(*R*)-**1**•$SnCl_4$:	>99% yield, 42% ee[25]
	(*R*)-**4**•$SnCl_4$:	>99% yield, 37% ee[25]
	(*R*)-**35**•$SnCl_4$:	>99% yield, 44% ee[25]

should be more reactive than simple olefins for accepting protons. What is responsible for this difference? We estimated it using Becke's three-parameter hybrid method and the Lee−Yang−Parr correlation functional (B3LYP), and all charges shown in this paper were evaluated by the natural population analysis (NPA).[23]

The optimized structure of a monobenzoate of biphenol (biphenol-Bz)•$SnCl_4$ complex as a model structure of (*R*)-**4**•$SnCl_4$ was determined at the B3LYP/LANL2DZ[24] level to understand this difference (Figure 2). The calculations predict that the chelation of biphenol-Bz with tin tetrachloride occurs at equatorial−equatorial sites. The bipyramidal coordination includes four chlorines and two oxygens, one each from the

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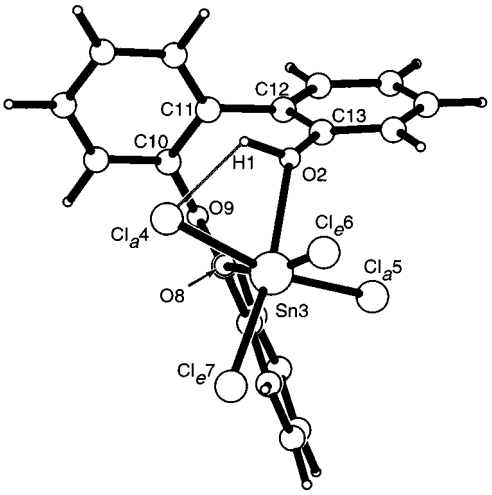

Figure 2. Optimized structures of the biphenol-Bz·$SnCl_4$ complex ("*e*" = equatorial, "*a*" = apical). Calculated on the B3LYP/LANL2DZ level (total energy −1 012.474 715 52 au). Selected distances (Å): H1−O2 = 0.981, H1−Cl_a4 = 2.440, O2−Sn3 = 2.419, Sn3−Cl_a4 = 2.402, Sn3−Cl_a5 = 2.376, Sn3−Cl_e6 =2.361, Sn3−Cl_e7 = 2.365, Sn3−O8-(carbonyl) = 2.331. Torsion angles (deg): H1−O2−Sn3−Cl_a4 = −11.2, C10−C11−C12−C13 = −97.8.

carbonyl and the hydroxy groups. The acidic proton is likely to be located at pseudoaxial sites parallel to an apical axis of the tin atom, and electrostatic interaction between the acidic protons and the apical chlorides is expected. Surprisingly, the axial angle (the torsion angle C10−C11−C12−C13) of the biphenol moiety is −97.8°, which is almost 40° larger than those of biphenol·$SnCl_4$ (−52.9°)[12] and monomethyl ether of biphenol (biphenol-Me)·$SnCl_4$ (−53.3°),[12] and the activated proton is in the center of the chiral environment as a result. The acidity of the protons was truly enhanced by coordinated tin tetrachloride (charge on the proton 0.541) compared to the proton on a phenol (charge on the proton 0.489). As expected, the extent of the enhancement was a little less than with biphenol·$SnCl_4$ and biphenol-Me·$SnCl_4$ (charge on each proton 0.546 and 0.549, respectively).[12]

This sterically crowded chiral LBA may provide a proton to a trisubstituted olefin such as the terminal olefin of linear isoprenoid groups in the enantioselective ene cyclization, however, not to a four-substituted olefin such as silyl enol ethers in the enantioselective protonation.[12] Similar results were observed using (*R*)-2,2′-dihydroxy-3,3′-dimethyl-1,1′-binaphthyl (**35**) (eq 7). (*R*)-**35**·$SnCl_4$ complex, which has bulky groups near the activated protons, promoted the enantioselective ene reaction on **20** (R^1 = H, R^2 = Me) under the same conditions to produce **21** (R^1 = H, R^2 = Me) in 59% yield (47% ee), while the chiral LBA showed no reactivity in the enantioselective protonation with trimethylsilyl enol ether **34**. Additionally, the reagent (*R*)-**35**·$SnCl_4$ exhibited 44% ee selectivity and regular reactivity on protonation of a trimethylsilyl enol ether, **36**, derived from 2-methylcyclohexanone (42% ee using (*R*)-**1**·$SnCl_4$),[25] which is a sterically less bulky substrate than the silyl enol ether **34** (eq 7). The relatively small silyl enol ether **36** was also accessible to the proton on (*R*)-**4**·$SnCl_4$ to produce 2-methylcyclohexanone (37% ee) (eq 7). All these results confirm our explanations.

This cascade reaction can produce up to four chiral centers at once; however, the enantioselectivity must be determined at the initial protonation step on the terminal trisubstituted olefin of the substrates. Geometry optimization at the B3LYP/LANL2DZ level of the reaction models, such as biphenol·$SnCl_4$ complex with 2-methyl-2-butene, exhibited a coordinated complex, **A**, to produce major enantiomers and a coordinated complex, **B**, to produce minor enantiomers (Figure 3). In the optimized structure **A**, the methyl group, $C5H_3$, of 2-methyl-2-butene is located above the space which is surrounded by the phenyl ring at the left in the figure and its adjacent apical Cl4. In the optimized structure **B**, the $C5H_3$ of the olefin which is located on the phenyl ring at the right would cause severe steric repulsion. Torsion angles H1−O2−Sn3−Cl4, 39.2° and 38.5°, shown in Figure 3, are much larger than those of biphenol·$SnCl_4$ and biphenol-Me·$SnCl_4$ (−5.9° and −2.2°, respectively).[12] This phenomenon can be attributed to interaction between the proton and π electrons of the olefin. Total energies were also calculated to understand the outcome of the enantioselective reaction. ΔE was appraised by comparing the two total energies, and the value would represent $\Delta\Delta G^{\ddagger}$ between $\Delta G^{\ddagger}$ producing the major enantiomer and $\Delta G^{\ddagger}$ producing the minor enantiomer of the reaction model. The estimated $\Delta\Delta G^{\ddagger}$ was −0.72 kcal/mol, and the evaluated ee value based on the Curtin−Hammett rule at −78 °C was 73% ee.[26] The result in the cyclization of **20** (R^1 = H, R^2 = Me) using (*R*)-**1**·$SnCl_4$ was 58% ee in toluene at −78 °C. Thus, the actual reaction seemed to be adequately reflected by the calculation models.

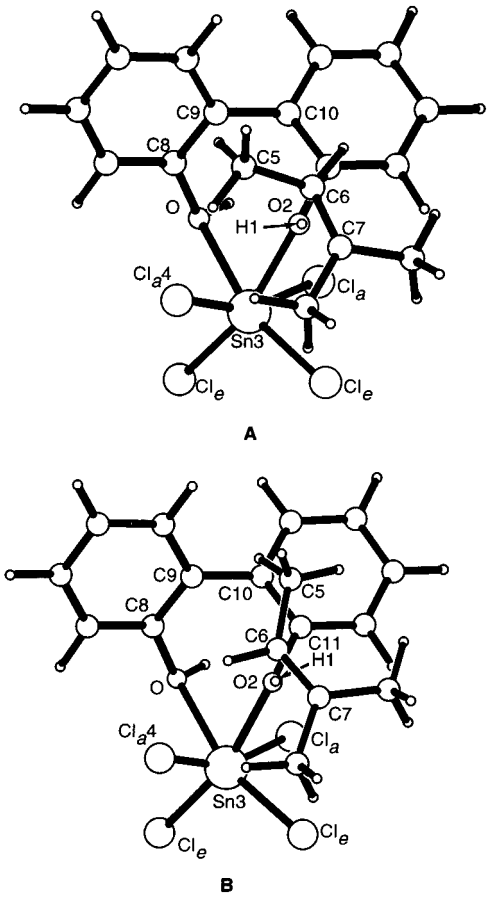

Figure 3. Optimized structures **A** and **B** of the biphenol·$SnCl_4$ complex with 2-methyl-2-butene, which respectively produce the major enantiomer and the minor enantiomer ("*e*" = equatorial, "*a*" = apical). Calculated on the B3LYP/LANL2DZ level. (**A**) Total energy −873.637 155 338 au). Selected distances (Å): H1−C6 = 2.153, H1−C7 = 2.361. Torsion angles (deg): H1−O2−Sn3−Cl_a4 = 39.2, C8−C9−C10−C11 = −51.5. (**B**) Total energy −873.636 010 472 au). Selected distances (Å): H1−C6 = 2.193, H1−C7 = 2.405. Torsion angles (deg): H1−O2−Sn3−Cl_a4 = 38.5, C8−C9−C10−C11 = −52.0.

(25) Unpublished results.

(26) Enders, D. *Chemtech* **1981**, 504.

The optimized structure **A** leads to the predominant approach of (*R*)-LBAs to the *si* face of a terminal linear isoprenyl group.

Conclusion

In summary, an enzyme-like reagent-controlled ene reaction was achieved with chiral BINOL derivative·$SnCl_4$ complexes. These reagents, which we call artificial cyclases, catalyzed the cyclization of simple nonactivated isoprenoids with 40−90% ee. The number of cyclizations and diastereoselectivities primarily depends on the spontaneous conformation of the substrates in media at low temperature. Asymmetric recognition of chiral LBAs for terminal olefin to generate the initial carbocation can control the absolute stereochemistry for the successive cyclization. On the other hand, enzymes control this by cavities made of aromatic residues, which also stabilize carbocations on the substrate.[27]

Nonenzymatic enantioselective polyene cyclizations are very attractive alternatives to the multistep synthesis from naturally occurring chiral synthons. Further studies on the rational design of "chiral proton catalysts" based on the concept of chiral LBA are expected to provide practical artificial cyclases for the asymmetric synthesis of a wide range of polycyclic isoprenoids. This chiral proton-initiated asymmetric ene reaction may also be found to be an efficient general synthetic method soon.

Experimental Section

General Procedures. Infrared (IR) spectra were recorded on a Shimadzu FT-IR 8100 spectrometer. ^{1}H NMR spectra were measured on a Varian Gemini-300 or VXR 500 spectrometer. Tetramethylsilane was used as internal standard for ^{1}H NMR (δ 0.00 ppm), $CDCl_3$ for ^{13}C NMR (δ 77.00 ppm), and $CF_3C_6H_5$ for ^{19}F NMR (δ −63.90 ppm). High-performance liquid chromatography (HPLC) was done with Shimadzu 10A instruments using 4.6 mm × 25 cm Daicel CHIRALCEL OJ, OD-H, AD, and AS. GC analysis was done with Shimadzu 17A instruments using γ-TA (0.25 mm × 20 m), β-DA (0.25 mm × 20 m), β-DM (0.25 mm × 20 m), and PEG (0.25 mm × 25 m). Optical rotations were measured on a JASCO DIP-1000 digital polarimeter. Melting points were determined using a Yanaco MP-J3. All experiments were carried out under an atmosphere of dry argon. For thin-layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF^{254}, 0.25 mm) were used. The products were purified by preparative column chromatography on silica gel E. Merck 9385. Microanalyses were accomplished at the School of Agriculture, Nagoya University. FAB mass spectral analyses were accomplished at the Graduate School of Engineering, Nagoya University. In experiments requiring dry solvents, ether and tetrahydrofuran (THF) were purchased from Aldrich Chemical Co. as "anhydrous" and stored over 4A molecular sieves. Benzene, hexane, toluene, and dichloromethane were freshly distilled from calcium hydride. Tin tetrachloride was distilled under argon. Other simple chemicals were purchased and used.

Enantioselective Cyclization of (*E*)-2,6,10-Trimethyl-5,9-undecadien-2-ol (5)[28] Promoted by (*R*)-2·$SnCl_4$[11c] (Representative Procedure). To a solution of **2** (66.0 mg, 0.22 mmol) in distilled dichloromethane (4 mL) was added a 1.0 M solution of tin tetrachloride in dichloromethane (20 μL, 0.2 mmol) at −78 °C under argon. After the mixture was stirred for several minutes at the same temperature, **5**[28] (23.6 mg, 0.1 mmol) was added dropwise at −78 °C. After the resulting mixture was stirred for 3 days at −78 °C, pyridine (16 μL, 0.2 mmol) was added. Then the mixture was poured onto a saturated $NaHCO_3$ solution and extracted with ether. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated. The crude product was purified by silica gel column chromatography (eluent, hexane:CH_2Cl_2 = 4:1) to give **6** (56% ee) and **7**, which were separable, as a 88:12 diastereomeric mixture (58% yield). Identification of compounds **6** and **7** was effected by comparison of their ^{1}H NMR data with those of authentic samples.[29] GC (β-TA, 100 kPa, column temperature 50 °C for 3 min and then warm to 150 °C (+1 °C/min)) t_R = 36.9 (**7**), 38.4 ((+)-**6**), 39.0 ((−)-**6**) min.

***trans*-Octahydro-2,2,5,5,8a-pentamethyl-2*H*-1-benzopyran (6):**[28,29] 56% ee; TLC (hexane:CH_2Cl_2 = 4:1) R_f = 0.11; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.78 (s, 3H), 0.90 (s, 3H), 1.18 (s, 3H), 1.27 (s, 3H), 1.29 (s, 3H), 1.20−1.80 (m, 11H); $[\alpha]^{25.1}_D$ = −5.32° (c = 0.37, $CHCl_3$).

***cis*-Octahydro-2,2,5,5,8a-pentamethyl-2*H*-1-benzopyran (7):** TLC (hexane:CH_2Cl_2 = 4:1) R_f = 0.18; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.96 (s, 3H), 1.06 (s, 3H), 1.20 (s, 3H), 1.22 (s, 3H), 1.33 (s, 3H), 1.10−1.75 (m, 10H), 1.85−1.95 (m, 1H).

Enantioselective Cyclization of (*E*)-Homogeraniol (8)[30] Promoted by (*R*)-2·$SnCl_4$. The cyclization of **8** was carried out according to the above representative procedure under the conditions shown in eq 2. The crude products were purified by column chromatography on silica gel (eluent, hexane:CH_2Cl_2 = 4:1 → 0:1) to give **9** (49% ee) and **10** (44% ee), which were separable, as a 62:38 diastereomeric mixture (46% yield). Identification of compounds **9** and **10** was effected by comparison of their ^{1}H NMR data with those of **6**, **7**, **12**, **13**, **14**, and **15**.[15,16] GC (γ-TA, 30 kPa, column temperature 85 °C) t_R = 28.8 (minor isomer of **9**), 30.2 (major isomer of **9**), 31.7 ((+)-**10**), 33.7 ((−)-**10**) min.

***trans*-Octahydro-4,4,7a-trimethylbenzofuran (9):** 49% ee; TLC (CH_2Cl_2) R_f = 0.27; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.85 (s, 3H), 0.96 (s, 3H), 1.07 (s, 3H), other resonances could be not discerned; ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.19, 23.51, 32.76, 33.12, 40.97, 56.23, other resonances could be not discerned; LR FAB^+-MS m/z 168 ($[M]^+$, $C_{11}H_{20}O_1$ requires 168.3).

***cis*-Octahydro-4,4,7a-trimethylbenzofuran (10):** 44% ee; TLC (CH_2Cl_2) R_f = 0.28; IR (film) 3856, 3651, 2928, 1509, 1491, 1221, 773 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.92 (s, 3H), 1.02 (s, 3H), 1.33 (s, 3H), 1.12−1.63 (m, 6H), 1.90−1.99 (m, 2H), 3.72−3.86 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.96, 27.09, 28.62, 29.39, 30.43, 33.59, 34.39, 53.93, 63.90, other resonances could be not discerned; LR FAB^+-MS m/z 168 ($[M]^+$, $C_{11}H_{20}O_1$ requires 168.3); $[\alpha]^{25.1}_D$ = −14.5° (c = 0.10, $CHCl_3$).

Enantioselective Cyclization of (*E*,*E*)-4,8,12-Trimethyl-3,7,11-tridecatrien-1-ol (11)[16] Promoted by (*R*)-2·$SnCl_4$. The cyclization of **11**[16] was carried out according to the above representative procedure under the conditions shown in Scheme 3. The crude products were purified by column chromatography on silica gel (eluent, hexane:CH_2Cl_2 = 4:1 to hexanes:EtOAc = 10:1) to give four diastereomeric products of **12**−**15** as a mixture (54% yield, $[\alpha]^{25.1}_D$ = −8.83° (c = 0.25, $CHCl_3$)). Compounds **12**−**15** were not isolated, and their identification was effected by comparison of their ^{1}H and ^{13}C NMR data with those of authentic samples (Tables 3 and 4). The product distribution presented in eq 3 was determined by GC (PEG). The absolute stereochemistry of **12** was ascertained by comparison of GC (γ-TA) data with those of (−)-Ambrox (Aldrich). GC (PEG, 100 kPa, column temperature 120 °C for 5 min and then warm to 220 °C (+1 °C/min)) t_R = 16.83 (**13** or **15**), 17.09 (**15** or **13**), 19.24 (**12**), 20.75 (**14**) min; GC (γ-TA, 75 kPa, colum temperature 120 °C for 3 min and then warm to 150 °C (+1 °C/min)) t_R = 60.55 (**13** and **15**), 64.14 ((−)-**12**), 65.75 ((+)-**12**), 70.46 (minor enantiomer of **14**), 71.82 (major enantiomer of **14**) min.

Preparation of *o*-Geranylphenol (16)[31] and *o*-Nerylphenol (19).[31] Both compounds were produced with simple methods reported previously. See ref 31.

General Procedure for the Preparation of Geranyl Aryl Ether 20.[32] To a stirred suspension of sodium hydride (60% in oil, 176 mg, 4.4 mmol) in THF (20 mL) at room temperature under argon

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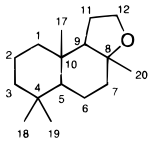
Table 3. ^{13}C NMR Assignments (δ [ppm], $CDCl_3$, 126 MHz) for **12**−**15**[a]



12–15

C(*n*)	**12**[b]	**13**[c]	**14**[d]	**15**[d]
C(1)	39.768 (39.95)*	38.676 (38.7)	27.066 (27.1)	41.122 (41.2)
C(2)	18.417 (18.39)	18.514 (18.5)	18.994 (19.0)	18.233 (18.3)
C(3)	42.451 (42.43)	42.317 (42.3)	35.520 (35.5)	42.554 (42.6)
C(4)	33.080 (33.06)	33.590 (33.6)	34.057 (34.1)	33.280 (33.2)
C(5)	57.272 (57.25)	46.724 (46.7)	52.635 (52.5)	48.611 (48.7)
C(6)	20.669 (20.64)	20.420 (20.4)	23.400 (23.4)	21.391 (21.4)
C(7)	39.969 (39.73)*	35.781 (35.8)*	38.700 (38.7)	36.279 (36.4)
C(8)	79.916 (79.91)	80.820 (80.8)	78.866 (78.9)	80.104 (80.2)
C(9)	60.136 (60.11)	59.014 (59.0)	58.589 (58.6)	49.060 (49.2)
C(10)	36.206 (36.18)	36.030 (36.0)*	37.656 (37.7)	36.103 (36.2)
C(11)	22.647 (22.62)	28.850 (28.9)	25.057 (25.1)	23.491 (23.6)
C(12)	64.986 (64.97)	64.081 (64.1)	64.409 (64.4)	64.081 (64.1)
C(17)	21.154 (21.13)	21.761 (21.8)**	29.687 (29.7)	25.870 (25.9)
C(18)	33.590 (33.58)	32.928 (32.9)	33.280 (33.3)	27.873 (28.0)
C(19)	21.154 (21.23)	28.829 (22.8)**	31.411 (31.4)	34.458 (34.5)
C(20)	15.049 (15.03)	27.709 (27.7)	20.614 (20.6)	22.046 (22.1)

[a] The reference data are indicated in parentheses. Entries marked with a single asterisk are interchangeable, and those marked with double asterisks are interchangeable. [b] Reference 15k. [c] Reference 15i. [d] Reference 15h.

Table 4. ^1H NMR Assignments (δ [ppm], $CDCl_3$, 500 MHz) for **12**−**15**[a]

C(*n*)	**12**[b]	**13**[c]
CH_3	0.831, s (0.83, s)	0.816, s (0.83, s)
CH_3	0.838, s (0.84, s)	0.890, s (0.90, s)
CH_3	0.876, s (0.88, s)	1.099, s (1.10, s)
C(20)H_3	1.085, s (1.09, s)	1.373, s (1.38, s)
C(12)*H*H	3.824, q, J = 8.5 Hz (3.83, q, J = 8 Hz)	3.77, q, J = 8.5 Hz (3.77, q, J = 8.5 Hz)
C(12)H*H*	3.915, dt, J = 4.0, 8.5 Hz (3.92, m)	3.864, m (3.86, m)

C(*n*)	**14**[d]	**15**[d]
CH_3	0.890, s (0.89)	0.924, s (0.92, s)
CH_3	1.143, s (1.14)	0.960, s (0.96, s)
CH_3	1.155, s (1.155s)	1.056, s (1.06, s)
C(20)H_3	1.177, s (1.18)	1.143, s (1.14, s)
C(12)*H*H	3.812, q, J = 8.0 Hz (3.81, q, J = 8.6 Hz)	3.801, q, J = 8.0 Hz (3.80, q, J = 7.9 Hz)
C(12)H*H*	3.885, dt, J = 3.0, 8.0 Hz (3.88, dt, J = 3.6, 8.6 Hz)	3.864, m (3.86, dt, J = 3.5, 7.9 Hz)

[a] The reference data are indicated in parentheses. [b] Reference 15j. [c] Reference 15g. [d] Reference 15h.

atmosphere was added aryl alcohol (4.0 mmol) portionwise followed by a catalytic amount of hydroquinone. The mixture was stirred for 0.5 h. Hexamethylphosphoramide (HMPA, 2 mL) and geranyl chloride (0.74 mL, 4.0 mmol) were successively added. The whole mixture was stirred for 1 day. After decomposition of excess sodium hydride with methanol (0.5 mL), the mixture was poured onto ice−water and extracted with ether. The combined organic layers were dried, concentrated, and purified by column chromatography on silica gel (hexane−CH_2Cl_2 as eluent) to give geranyl aryl ether (ca. 50%). Physical properties and analytical data of the ethers are given below.

Geranyl Phenyl Ether (20 (R^1 = R^2 = H)):[33a,b] TLC (hexane:CH_2Cl_2 = 4:1) R_f = 0.3; IR (film) 2924, 1601, 1497, 1238, 752, 691 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.61 (s, 3H), 1.68 (s, 3H), 1.74 (s, 3H), 2.02−2.20 (m, 4H), 4.54 (d, J = 6.6 Hz, 2H), 5.06−5.14 (m, 1H), 5.50 (tq, J = 6.6, 1.5 Hz, 1H), 6.89−6.97 (m, 3H), 7.25−7.31 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.64, 17.69, 25.69, 26.26, 39.53, 64.67, 114.61, 119.48, 120.52, 123.78, 129.36, 131.79, 141.11, 158.80.

Geranyl *p*-Fluorophenyl Ether (20 (R^1 = F, R^2 = H)):[33c] TLC (hexane:CH_2Cl_2 = 4:1) R_f = 0.3; IR (film) 2918, 1507, 1379, 1294, 1244, 1221, 1210, 1096, 1005, 828 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.60 (s, 3H), 1.68 (s, 3H), 1.72 (s, 3H), 2.02−2.19 (m, 4H), 4.49 (d, J = 6.6 Hz, 2H), 5.04−5.13 (m, 1H), 5.47 (tq, J = 6.6, 1.2 Hz, 1H), 6.84 (dd, J = 9.0, 4.5 Hz, 2H), 6.96 (t, J = 9.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.64, 17.69, 25.67, 26.25, 39.51, 65.41, 115.54 (J = 2.3 Hz), 115.66, 115.83, 119.34, 123.73, 131.82, 141.32, 154.90, 155.55, 158.71; ^{19}F NMR (282 MHz, $CDCl_3$) δ −125.17.

Geranyl *p*-Chlorophenyl Ether (20 (R^1 = Cl, R^2 = H)):[33b,d] TLC (hexane:CH_2Cl_2 = 4:1) R_f = 0.3; IR (film) 2924, 1491, 1287, 1238, 1169, 1094, 1005, 824 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.60 (s, 3H), 1.68 (s, 3H), 1.73 (s, 3H), 2.04−2.18 (m, 4H), 4.51 (d, J = 6.6 Hz, 2H), 5.04−5.13 (m, 1H), 5.46 (tq, J = 6.6, 1.2 Hz, 1H), 6.84 (d, J = 9.0 Hz, 2H), 7.22 (d, J = 9.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.68, 17.70, 25.69, 26.24, 39.51, 65.13, 115.95, 119.11, 123.70, 125.37, 129.22, 131.87, 141.54, 157.42.

Geranyl *p*-Bromophenyl Ether (20 (R^1 = Br, R^2 = H)):[33d] TLC (hexane:CH_2Cl_2 = 4:1) R_f = 0.3; IR (film) 2926, 1489, 1237, 1001, 822 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.60 (s, 3H), 1.68 (s, 3H), 1.73 (s, 3H), 2.02−2.18 (m, 4H), 4.50 (d, J = 6.6 Hz, 2H), 5.04−5.12 (m, 1H), 5.46 (tq, J = 6.6, 1.5 Hz, 1H), 6.79 (d, J = 9.2 Hz, 2H), 7.36 (d, J = 9.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.67, 17.70, 25.69, 26.22, 39.50, 65.04, 112.66, 116.47, 119.03, 123.68, 131.87, 132.15, 141.58, 157.90.

Geranyl *p*-Tolyl Ether (20 (R^1 = Me, R^2 = H)):[33b] TLC (hexane:CH_2Cl_2 = 4:1) R_f = 0.3; IR (film) 2969, 2923, 2859, 1510, 1238, 1013, 818 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.60 (s, 3H), 1.68 (s, 3H), 1.72 (s, 3H), 2.02−2.18 (m, 4H), 2.28 (s, 3H), 4.51 (d, J = 5.7 Hz, 2H), 5.09 (t, J = 6.0 Hz, 1H), 5.49 (t, J = 6.0 Hz, 1H), 6.82 (d, J = 8.7 Hz, 2H), 7.08 (d, J = 8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.63, 17.69, 20.46, 25.68, 26.29, 39.54, 64.86, 114.49, 119.66, 123.83, 129.73, 129.80, 131.76, 140.95, 156.70.

Geranyl *p*-Methoxyphenyl Ether (20 (R^1 = OMe, R^2 = H)):[33b,e] TLC (hexane:CH_2Cl_2 = 1:1) R_f = 0.4; mp 36.0 °C; IR (KBr) 2913, 1514, 1240, 1034, 1009, 826 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.61 (s, 3H), 1.68 (s, 3H), 1.72 (s, 3H), 2.02−2.18 (m, 4H), 3.77 (s, 3H), 4.49 (d, J = 6.3 Hz, 2H), 5.10 (t, J = 5.7 Hz, 1H), 5.49 (t, J = 5.7 Hz, 1H), 6.81−6.87 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 16.62, 17.68, 25.67, 26.29, 39.54, 55.70, 65.46, 114.55, 115.62, 119.75, 123.83, 131.74, 140.92, 153.00, 153.71.

Geranyl 3,5-Xylyl Ether (20 (R^1 = H, R^2 = Me)): TLC (hexane:CH_2Cl_2 = 4:1) R_f = 0.3; IR (film) 2919, 1613, 1595, 1323, 1293, 1167, 1154, 1057, 828 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.61 (s, 3H), 1.68 (s, 3H), 1.73 (s, 3H), 2.02−2.18 (m, 4H), 2.28 (s, 6H), 4.50 (d, J = 6.6 Hz, 2H), 5.06−5.14 (m, 1H), 5.49 (t, J = 5.7 Hz, 1H), 6.55 (s, 2H), 6.59 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.61, 17.68, 21.45, 25.67, 26.29, 39.54, 64.58, 112.36, 119.63, 122.31, 123.83, 131.75, 139.07, 140.91, 158.88. Anal. Calcd for $C_{18}H_{26}O$: C, 83.67; H, 10.14. Found: C, 83.68; H, 10.12.

Typical Procedure for the Enantioselective Cyclization of *o*-Geranylphenol (16),[31] ***o*-Nerylphenol (19),**[31] **or Geranyl Aryl Ether 20 Promoted by (*R*)-4·$SnCl_4$.** The cyclization of **16**,[31] **19**,[31] or **20**[32] was carried out according to the above representative procedure under the conditions shown in eqs 4 and 5 and Table 1. The crude product was purified by silica gel column chromatography (eluent, hexane:CH_2Cl_2 = 1:0 → 10:1 → 5:1) to give **17** (**21**) and **18** (**22**) as a diastereomeric mixture. Identification of compounds **17** (**21**) and **18** (**22**) was effected by comparison of their ^1H NMR data with those of authentic samples (Table 5).[17] The product mixture distribution is presented in eqs 4 and 5 and Table 1. Retention times (min) are (GC (γ-TA, 100 kPa, column temperature 130 °C)) t_R = 11.1 (**18**), 14.9 (**25**), 15.7 (cis isomer of **26**), 23.8 (**17**), 33.7 ((−)-**26**), 34.9 ((+)-**26**) min.

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Table 5. ^{1}H NMR Assignments (δ [ppm], $CDCl_3$, 300 MHz) for $(CH_3)_2C$ and CH_3C of **21**, **22**, **26**, and the Cis Isomer of **26**

R^1	R^2	**21**	**22**
H	H	0.92, 1.01, 1.23	0.65, 0.97, 1.21
F	H	0.89, 1.00, 1.19	0.65, 0.95, 1.26
Cl	H	0.89, 0.99, 1.19	0.65, 0.95, 1.18
Br	H	0.89, 0.99, 1.19	0.63, 0.95, 1.18
Me	H	0.90, 0.99, 1.20	0.65, 0.95, 1.19
OMe	H	0.90, 0.99, 1.20	0.66, 0.95, 1.18
H	Me	0.92, 1.01, 1.18	0.63, 0.96, 1.17
		26	cis isomer of **26**
		0.94, 1.02, 1.28	0.65, 100, 1.27

The physical properties and analytical data of other tricyclic ethers **21** and **22** thus obtained are listed below. Stereochemistries of diastereomers **21** and **22** were assigned by comparison with ^{1}H NMR spectra for $(CH_3)_2C(1)$ and $CH_3C(4a)$ of **21** (R^1 = H, R^2 = Me) and **22** (R^1 = H, R^2 = Me) (see Table 3).

***trans*-2,3,4,4a,9,9a-Hexahydro-1,1,4a-trimethyl-1*H*-xanthene (17, 21 ($R^1 = R^2$ = H)):**[17] TLC (hexane:CH_2Cl_2 = 4:1) R_f = 0.25; HPLC (OD-H, hexane, 1.0 mL/min) t_R = 9.3 ((+)-**17**), 11.5 ((−)-**17**) min; GC (β-DM, 50 kPa, column temperature 150 °C) t_R = 28.1 ((−)-**17**), 29.9 ((+)-**17**); IR (film) 2934, 1584, 1487, 1456, 1246 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (s, 3H), 1.01, (s, 3H), 1.23 (s, 3H), 1.25−1.76 (m, 6H), 1.93−2.01 (m, 1H), 2.61 (dd, J = 13.0, 16.1 Hz, 1H), 2.72 (dd, J = 5.6, 16.1 Hz, 1H), 6.75−6.86 (m, 2H), 7.07 (d, J = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.78, 19.84, 20.68, 23.25, 32.10, 33.38, 40.00, 41.49, 48.06, 117.01, 119.60, 122.64, 127.10, 129.63, 153.25, the resonance of C(4a) could not be discerned; $[\alpha]^{25.2}_D$ = −26.4° (c = 0.25, $CHCl_3$) for sample **17** of 50% ee.

***cis*-2,3,4,4a,9,9a-Hexahydro-1,1,4a-trimethyl-1*H*-xanthene (18, 22 ($R^1 = R^2$ = H)):**[17b] TLC (hexane:CH_2Cl_2 = 4:1) R_f = 0.26; HPLC (OD-H, hexane, 1.0 mL/min) t_R = 5.6 (major enantiomer), 6.4 (minor enantiomer) min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.65 (s, 3H), 0.97 (s, 3H), 1.21 (s, 3H), 1.20−2.20 (m, 7H), 2.73−2.80 (m, 1H), 3.04 (dd, J = 8.0, 18.0 Hz, 1H), 6.72−6.85 (m, 2H), 7.05 (d, J = 6.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.06, 21.37, 23.56, 26.99, 32.24, 33.94, 39.53, 41.60, 44.37, 75.20, 117.05, 119.76, 122.02, 126.63, 28.89, 154.45.

***trans*-2,3,4,4a,9,9a-Hexahydro-7-fluoro-1,1,4a-trimethyl-1*H*-xanthene (21 (R^1 = F, R^2 = H)):** TLC (hexane:CH_2Cl_2 = 4:1) R_f = 0.25; GC (γ-TA, 100 kPa, column temperature 130 °C) t_R = 26.8 ((±)-enantiomer) min; GC (β-DM, 75 kPa, column temperature 120 °C for 5 min and then warm to 150 °C (+0.5 °C/min)) t_R = 52.0 ((−)-enantiomer), 55.8 ((+)-enantiomer) min; IR (film) 2936, 1439, 1242, 1221, 1102, 810 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (s, 3H), 1.00 (s, 3H), 1.19 (s, 3H), 1.22−1.70 (m, 5H), 1.92−1.98 (m, 1H), 1.92−1.98 (m, 1H), 2.58 (dd, J = 22.8, 12.9 Hz, 1H), 2.68 (dd, J = 16.8, 5.7 Hz, 1H), 6.64−6.71 (m, 1H), 6.73−6.79 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.66, 19.73, 20.60, 23.49, 32.03, 33.34, 39.88, 41.42, 47.79, 113.76 (J = 22.7 Hz), 115.33 (J = 21.2 Hz), 117.69 (J = 8.0 Hz), 123.73, 149.21, 156.44 (J = 235.5 Hz), the resonance of C(4a) could not be discerned; ^{19}F NMR (282 MHz, $CDCl_3$) δ −124.55; LR FAB$^+$-MS m/z 248 ([M]$^+$, $C_{16}H_{21}OF$ requires 248.3); $[\alpha]^{24.4}_D$ = −22.44° (c = 0.27, $CHCl_3$) for a sample of 58% ee.

***cis*-2,3,4,4a,9,9a-Hexahydro-7-fluoro-1,1,4a-trimethyl-1*H*-xanthene (22 (R^1 = F, R^2 = H)):** TLC (hexane:CH_2Cl_2 = 4:1) R_f = 0.26; GC (γ-TA, 100 kPa, column temperature 130 °C) t_R = 13.1 ((±)-enantiomer) min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.65 (s, 3H), 0.95 (s, 3H), 1.26 (s, 1H), other resonances could not be discerned; ^{19}F NMR (282 MHz, $CDCl_3$) δ −123.42.

***trans*-2,3,4,4a,9,9a-Hexahydro-7-chloro-1,1,4a-trimethyl-1*H*-xanthene (21 (R^1 = Cl, R^2 = H)):** TLC (hexane:CH_2Cl_2 = 4:1) R_f = 0.25; GC (β-DM, 50 kPa, column temperature 160 °C) t_R = 55.0 ((−)-enantiomer), 58.8 ((+)-enantiomer) min; IR (film) 2936, 1482, 1458, 1250, 1102, 1042, 812 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (s, 3H), 0.99 (s, 3H), 1.19 (s, 3H), 1.22−1.70 (m, 5H), 1.66 (dd, J = 5.4, 12.9 Hz, 1H), 1.92−1.98 (m, 1H), 2.56 (dd, J = 12.9, 16.5 Hz, 1H), 2.67 (dd, J = 5.4, 16.5 Hz, 1H), 6.68 (d, J = 8.1 Hz, 1H), 6.91−7.05 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.72, 20.60, 23.21, 32.02, 33.37, 39.84, 41.38, 47.75, 118.30, 124.22, 127.07, 129.16, 151.90, other resonances could not be discerned; LR FAB$^+$-MS m/z 264 ([M]$^+$, $C_{16}H_{21}OCl$ requires 264.8); $[\alpha]^{27.4}_D$ = −25.4° (c = 0.33, $CHCl_3$) for a sample of 65% ee.

***cis*-2,3,4,4a,9,9a-Hexahydro-7-chloro-1,1,4a-trimethyl-1*H*-xanthene (22 (R^1 = Cl, R^2 = H)):** TLC (hexane:CH_2Cl_2 = 4:1) R_f = 0.26; GC (β-DM, 50 kPa, column temperature 160 °C) t_R = 26.5 ((±)-enantiomer) min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.65 (s, 3H), 0.95 (s, 3H), 1.18 (s, 3H), other resonances could not be discerned.

***trans*-2,3,4,4a,9,9a-Hexahydro-7-bromo-1,1,4a-trimethyl-1*H*-xanthene (21 (R^1 = Br, R^2 = H)):** TLC (hexane:CH_2Cl_2 = 4:1) R_f = 0.25; GC (β-DM, 75 kPa, column temperature 160 °C for 5 min and then warm to 170 °C (+0.1 °C/min)) t_R = 54.4 ((−)-enantiomer), 57.0 ((+)-enantiomer) min; IR (film) 2936, 1576, 1482, 1248, 812, 656 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (s, 3H), 0.99 (s, 3H), 1.19 (s, 3H), 1.22−1.70 (m, 5H), 1.92−1.98 (m, 1H), 2.57 (dd, J = 12.6, 16.2 Hz, 1H), 2.67 (dd, J = 5.7, 16.2 Hz, 1H), 6.63 (d, J = 8.4 Hz, 1H), 7.12−7.20 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.70, 19.73, 20.61, 23.15, 32.02, 33.37, 39.82, 41.35, 47.71, 77.63, 111.55, 118.81, 124.84, 129.96, 132.10, 152.43; $[\alpha]^{24.4}_D$ = −35.2° (c = 0.6, $CHCl_3$) for a sample of 63% ee. Anal. Calcd for $C_{16}H_{21}OBr$: C, 62.14; H, 6.84; Found: C, 62.21; H, 6.85.

***cis*-2,3,4,4a,9,9a-Hexahydro-7-bromo-1,1,4a-trimethyl-1*H*-xanthene (22 (R^1 = Br, R^2 = H)):** TLC (hexane:CH_2Cl_2 = 4:1) R_f = 0.26; GC (β-DM, 75 kPa, column temperature 160 °C for 5 min and then warm to 170 °C (+0.1 °C/min)) t_R = 27.4 ((±)-enantiomer) min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.63 (s, 3H), 0.95 (s, 3H), 1.18 (s, 1H), 2.73 (d, J = 18.0 Hz, 1H), 3.00 (dd, J = 7.8, 18.0 Hz, 1H), other resonances could not be discerned.

***trans*-2,3,4,4a,9,9a-Hexahydro-1,1,4a,7-tetramethyl-1*H*-xanthene (21 (R^1 = Me, R^2 = H)):** TLC (hexane:CH_2Cl_2 = 4:1) R_f = 0.25; GC (γ-TA, 100 kPa, column temp. 140 °C) t_R = 24.9 ((±)-enantiomer) min; GC (β-DM, 75 kPa, column temp. 150 °C for 5 min and then warm to 170 °C (+1 °C/min)) t_R = 22.1 ((−)-enantiomer), 22.8 ((+)-enantiomer) min; IR (film) 2932, 1409, 1240, 812 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (s, 3H), 0.99 (s, 3H), 1.20 (s, 3H), 1.25−1.37 (m, 1H), 1.44−1.68 (m, 4H), 1.68 (dd, J = 5.4, 12.9 Hz, 1H), 1.91−1.98 (m, 1H), 2.25 (s, 3H), 2.56 (dd, J = 12.0, 15.0 Hz, 1H), 2.66 (dd, J = 5.7, 15.0 Hz, 1H), 6.66 (d, J = 9.0 Hz, 2H), 6.87 (s, 1H), 6.88 (d, J = 9.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.74, 19.78, 20.49, 20.66, 23.19, 32.09, 33.35, 39.98, 41.48, 48.11, 116.72, 122.27, 127.74, 128.69, 129.99, 150.92, the resonance of C(4a) could not be discerned; $[\alpha]^{25.3}_D$ = −33.9° (c = 0.5, $CHCl_3$) for a sample of 62% ee. Anal. Calcd for $C_{17}H_{24}O$: C, 83.55; H, 9.90; Found: C, 83.53; H, 9.93.

***cis*-2,3,4,4a,9,9a-Hexahydro-1,1,4a,7-tetramethyl-1*H*-xanthene (22 (R^1 = Me, R^2 = H)):** TLC (hexane:CH_2Cl_2 = 4:1) R_f = 0.26; GC (γ-TA, 100 kPa, column temperature 140 °C) t_R = 11.4 ((±)-enantiomer) min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.65 (s, 3H), 0.95 (s, 3H), 1.19 (s, 1H), 2.24 (s, 3H), 2.71 (d, J = 18.0 Hz, 1H), 2.99 (dd, J = 9.0, 18.0 Hz, 1H), 6.63 (d, J = 8.7 Hz, 1H), other resonances could not be discerned.

***trans*-2,3,4,4a,9,9a-Hexahydro-7-methoxy-1,1,4a-trimethyl-1*H*-xanthene (21 (R^1 = MeO, R^2 = H)):** TLC (hexane:CH_2Cl_2 = 1:1) R_f = 0.37; GC (γ-TA, 100 kPa, column temperature 160 °C for 5 min and then warm to 180 °C (+1 °C/min)) t_R = 18.7 ((±)-enantiomer) min; GC (β-DM, 70 kPa, column temperature 150 °C) t_R = 72.8 ((−)-enantiomer), 76.0 ((+)-enantiomer) min; IR (film) 2934, 1497, 1227 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (s, 3H), 0.99 (s, 3H), 1.20 (s, 3H), 12.4−1.38 (m, 1H), 1.44−1.68 (m, 4H), 1.70 (dd, J = 5.9, 12.8 Hz, 1H), 1.91−1.97 (m, 1H), 2.58 (dd, J = 12.9, 16.2 Hz, 1H), 2.69 (dd, J = 5.7, 16.2 Hz, 1H), 3.75 (s, 3H), 6.60−6.66 (m, 2H), 6.68 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.67, 19.76, 20.61, 23.60, 32.07, 33.32, 39.93, 41.47, 48.05, 55.66, 113.11, 114.12, 117.46, 123.18, 147.19, 152.83, the resonance of C(4a) could not be discerned; $[\alpha]^{23.3}_D$ = −33.2° (c = 0.38, $CHCl_3$) for a sample of 70% ee. Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29; Found: C, 78.45; H, 9.30.

***cis*-2,3,4,4a,9,9a-Hexahydro-7-methoxy-1,1,4a-trimethyl-1*H*-xanthene (22 (R^1 = MeO, R^2 = H)):** TLC (hexane:CH_2Cl_2 = 1:1) R_f = 0.39; GC (γ-TA, 100 kPa, column temperature 160 °C for 5 min and then warm to 180 °C (+1 °C/min)) t_R = 10.8 ((±)-enantiomer) min;

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.66 (s, 3H), 0.95 (s, 3H), 1.18 (s, 3H), 3.00 (dd, J = 8.0, 17.9 Hz, 1H), 3.75 (s, 3H), other resonances could not be discerned; ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.07, 20.64, 23.96, 26.84, 32.25, 33.94, 39.56, 41.61, 44.40, 55.67, 112.50, 113.48, 117.46, other resonances could not be discerned.

***trans*-2,3,4,4a,9,9a-Hexahydro-1,1,4a,6,8-pentamethyl-1*H*-xanthene (21 (R^1 = H, R^2 = Me)):** TLC (hexane:CH_2Cl_2 = 4:1) R_f = 0.25; GC (γ-TA, 100 kPa, column temperature 150 °C) t_R = 23.6 ((±)-enantiomer) min; GC (β-DA, 80 kPa, column temperature 150 °C for 3 min and then warm to 170 °C (+0.2 °C/min)) t_R = 43.9 ((−)-enantiomer), 45.5 ((+)-enantiomer) min; IR (film) 2932, 1580, 1321, 1304, 1103 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (s, 3H), 1.01 (s, 3H), 1.18 (s, 3H), 1.25−1.38 (m, 1H), 1.45−1.65 (m, 4H), 1.67 (dd, J = 5.3, 13.1 Hz, 1H), 1.88−2.02 (m, 1H), 2.20 (s, 3H), 2.23 (s, 3H), 2.29 (dd, J = 13.5, 16.4 Hz, 1H), 2.57 (dd, J = 5.0, 16.4 Hz, 1H), 6.47 (s, 1H), 6.55 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.10, 19.62, 19.76, 20.62, 20.79, 20.97, 32.08, 33.39, 39.93, 41.58, 48.13, 76.31, 115.16, 118.24, 122.116, 136.36, 137.04, 152.91; $[\alpha]^{23.2}_D$ = −20.6° (c = 0.36, $CHCl_3$) for a sample of 41% ee. Anal. Calcd for $C_{18}H_{26}O$: C, 83.67; H, 10.14. Found: C, 83.65; H, 10.17.

***cis*-2,3,4,4a,9,9a-Hexahydro-1,1,4a,6,8-pentamethyl-1*H*-xanthene (22 (R^1 = H, R^2 = Me)):** TLC (hexane:CH_2Cl_2 = 4:1) R_f = 0.26; GC (γ-TA, 100 kPa, column temperature 150 °C) t_R = 10.6 ((±)-enantiomer) min; ^{1}H NMR ($CDCl_3$) δ 0.63 (s, 3H), 0.96 (s, 3H), 1.17 (s, 3H), 2.19 (s, 3H), 2.23 (s, 3H), 2.60 (d, J = 16.5 Hz, 1H), 2.72 (dd, J = 6.0, 16.5 Hz, 1H), 6.45 (s, 1H), 6.54 (s, 1H), other resonances could not be discerned; ^{13}C NMR (65 MHz, $CDCl_3$) δ 18.09, 21.42, 23.57, 26.94, 32.27, 33.96, 39.55, 41.67, 44.49, 114.53, 116.74, 127.33, 129.82, 152.20, other resonances could not be discerned.

3-Phenoxymethyl-2,4,4-trimethylcyclohexene (25): TLC (hexane:CH_2Cl_2 = 4:1) R_f = 0.25; GC (β-DM, 50 kPa, column temperature 150 °C) t_R = 19.9 ((−)-**25**), 20.7 ((+)-**25**) min; IR (film) 2917, 1601, 1586, 1497, 1474, 1456, 1242, 752, 691 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (s, 3H), 1.01, (s, 3H), 1.23 (s, 3H), 1.25−1.76 (m, 6H), 1.93−2.01 (m, 1H), 2.61 (dd, J = 13.0, 16.1 Hz, 1H), 2.72 (dd, J = 5.6, 16.1 Hz, 1H), 6.77 (d, J = 8.6 Hz, 1H), 6.75−6.86 (m, 2H), 7.07 (d, J = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.99, 23.13, 27.07, 27.44, 31.88, 32.29, 49.35, 67.85, 114.52, 120.41, 123.00, 129.35, 132.77, 158.89; LR FAB$^+$-MS m/z 230 ([M]$^+$, $C_{16}H_{22}O$ requires 230.3); $[\alpha]^{25.2}_D$ = −20.1° (c = 0.30, $CHCl_3$) for sample **25** of 53% ee.

***trans*-6a,7,8,9,10,10a-Hexahydro-7,7,10a-trimethyl-6*H*-Dibenzo[*b,d*]pyran (26):** TLC (hexane:CH_2Cl_2 = 4:1) R_f = 0.28; IR (film) 2928, 1732, 1489, 1449, 1293, 1285, 1221, 1042, 750 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (s, 3H), 1.02, (s, 3H), 1.28 (s, 3H), 1.23−1.85 (m, 6H), 2.20−2.30 (m, 1H), 2.61 (dd, J = 13.0, 16.1 Hz, 1H), 2.72 (dd, J = 5.6, 16.1 Hz, 1H), 6.72−6.88 (m, 2H), 7.03−7.17 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.93, 21.85, 24.51, 32.95, 37.22, 41.86, 47.81, 64.05, 116.28, 119.81, 124.27, 126.97, 155.58, other resonances could not be discerned; LR FAB$^+$-MS m/z 230 ([M]$^+$, $C_{16}H_{22}O$ requires 230.3); $[\alpha]^{22.8}_D$ = −20.1° (c = 0.10, $CHCl_3$) for sample **26** of 43% ee.

***cis*-6a,7,8,9,10,10a-Hexahydro-7,7,10a-trimethyl-6*H*-Dibenzo[*b,d*]-pyran (cis isomer of 26):** TLC (hexane:CH_2Cl_2 = 4:1) R_f = 0.28; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.65 (s, 3H), 1.02, (s, 3H), 1.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.94, 22.57, 32.69, 33.43, 35.96, 37.33, 42.75, 48.34, 63.00, 116.02, 119.76, 124.33, 126.91, other resonances could not be discerned.

Preparation of 1-Benzyloxy-4-((*E,E*)-farnesyloxy)benzene (33). **33** was prepared from farnesyl chloride and monobenzylhydroquinone according to a slight modification of the literature procedure.[31] To a stirred suspension of sodium hydride (60% in oil, 7 mmol) in THF (20 mL) at room temperature under argon was added 4-benzyloxyphenol (6 mmol). The mixture was stirred for 30 min. HMPA (2 mL) and farnesyl chloride (7 mmol) were successively added. After being stirred at room temperature for 1 h, the whole mixture was warmed to reflux for 6 h. After decomposition of excess sodium hydride with methanol (1 mL), the mixture was poured onto ice−water and extracted with ether. The combined organic layers were dried, concentrated, and purified by column chromatography on silica gel (eluent, hexane:CH_2Cl_2 = 5:1 to hexane:EtOAc = 20:1) to give **33** as a 9:1 2*E*−2*Z* mixture of white solid (ca. 50%). Finally, **33** was isolated by recycling preparative HPLC (LC-908 (Japan Analytical Industry Co., Ltd.): column, JAIGEL-1H+JAIGEL-2H; eluent, $CHCl_3$): mp 65.2−65.8 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.61 (s, 6H), 1.69 (s, 3H), 1.73 (s, 3H), 1.95−2.20 (m, 8H), 4.49 (d, J = 6.6 Hz, 2H), 5.02 (s, 2H), 5.06−5.16 (m, 2H), 5.50 (dt, J = 1.2, 6.5 Hz, 1H), 6.86 (d, J = 9.4 Hz, 2H), 6.91 (d, J = 9.4 Hz, 2H), 7.28−7.48 (m, 5H). Anal. Calcd for $C_{28}H_{36}O_2$: C, 83.12; H, 8.97. Found: C, 83.14; H, 8.93.

Enantioselective Cyclization of 33 Promoted by (*S*)-3·SnCl$_4$.[11e] The cyclization of **33** was carried out according to the above representative procedure under the conditions shown in eq 6. The crude product produced in the reaction of **33** was partially purified by silica gel column chromatography (eluent, hexanes:EtOAc = 20:1) to remove highly polar compounds and a monoisopropyl ether of (*S*)-BINOL.[11e] Then, the benzyl group of the product was cleaved by stirring for 12 h at room temperature in the presence of a catalytic amount of Pd/C in ethanol under a hydrogen atmosphere. The crude product of **31** was transformed to the corresponding acetate **32** by using acetic anhydride and pyridine in dichloromethane. Finally, acetate **32** was purified by silica gel column chromatography (eluent, hexanes:EtOAc = 30:1 to 20:1). Identification of compounds **31** and **32** was effected by comparison of their ^{1}H NMR spectra with those of authentic samples.[17b,34] The enantiomeric excess of **32** was determined by HPLC (OD-H, hexane:*i*-PrOH = 200:1, 1.0 mL/min): t_R = 16.9 ((+)-**32**) and 26.5 ((−)-**32**) min.

(−)-Chromazonarol acetate (32):[22] ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85−1.80 (m, 11H), 0.87 (s, 3H), 0.90 (s, 3H), 0.93 (s, 3H), 1.22 (s, 3H), 2.08 (dt, J = 13.0, 3.5 Hz, 1H), 2.29 (s, 3H), 2.628 (d, J = 10.5 Hz, 1H), 2.631 (d, J = 7.0 Hz, 1H), 6.72−6.81 (m, 3H); $[\alpha]^{30.4}_D$ = −45.55° (c = 0.06, $CHCl_3$) for >99% ee of (−)-**32** [(−)-**32** was isolated by recycling preparative HPLC (Tosoh Co., Ltd.; column, OD (Daicel); eluent, hexane:*i*-PrOH = 200:1)].

Computational Methods

The geometries of all the structures have been optimized using the hybrid B3LYP[24] as implemented in the Gaussian98[35] package on SGI Indigo2 Impact R10000. The optimized structure of biphenol-Bz·SnCl$_4$ was verified by vibrational frequency analysis at the same level. We used a LANL2DZ basis set for our studies because heavy metal atoms are well expressed using the ECP-type basis sets. Diffuse functions and polarization functions on O and Cl ($\alpha_{O,diffuse}$ = 0.0483, $\alpha_{O,polarization}$ = 0.85, $\alpha_{Cl,diffuse}$ = 0.0845, $\alpha_{Cl,polarization}$ = 0.60) and polarization functions on Sn ($\alpha_{Sn,polarization}$ = 0.183) were used.[36] What conditions are suited to the tasks was considered carefully in the case of enantioselective protonation using chiral LBAs.[11h] And all charges were calculated using the NBO program.[23]

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Supporting Information Available: X-ray data for **21** (R^1 = H, R^2 = Me) and optimized geometry in **Z**-matrix form (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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