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Biomimetic Synthesis of Acid-Sensitive (−)-Caparrapi Oxide and (+)-8-Epicaparrapi Oxide Induced by Artificial Cyclases

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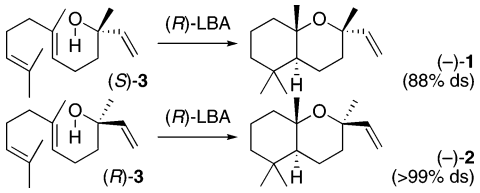
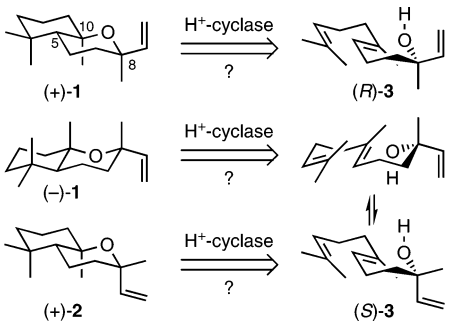
ABSTRACT



Asymmetric total syntheses of acid-sensitive (–)-caparrapi oxide (1) and (+)-8-epicaparrapi oxide (2) from farnesol (9) were achieved using Sharpless–Katsuki epoxidation and Lewis acid-assisted chiral Brønsted acid (chiral LBA)-induced polyene cyclization as key steps. Furthermore, (–)-1 could be directly synthesized from (*S*)-nerolidol (3) and (*R*)-LBA with 88% ds by reagent control which overcame substrate control, while (–)-2 was obtained from (*R*)-3 and (*R*)-LBA with >99% ds by the double-asymmetric induction.

Natural bicyclic sesquiterpene ethers such as (5*S*,8*S*,10*S*)-(−)- and (5*R*,8*R*,10*R*)-(+)-caparrapi oxides (**1**)[1,2] and 8-epi-caparrapi oxide (**2**)[3] can be formally derived by biomimetic proton-induced cyclization of (*S*)-(+)- or (*R*)-(−)-nerolidol (**3**) (Scheme 1). (−)-**1** has been isolated from the neutral fraction of the essential oil of *Ocotea caparrapi Nates* (Dugand).[1] On the other hand, (+)-**1** has been isolated from the sponge *Dysidea fragilis Montagu* (family Dysideidae).[2] 8-Epicaparrapi oxide **2** has been isolated as a minor constituent of the defense secretion of the termite *Amitermes evuncifer*.[3] Unfortunately, it has not yet been confirmed whether the absolute configuration of natural product **2** by analogy to (3*R*,5*R*,8*S*,10*R*)-(+)-3β-bromo-8-epicaparrapi oxide[4] is (5*R*,8*S*,10*R*)-(+). According to Zefirov and co-workers, the cyclization of (±)-**3** induced by 5 equiv of

Scheme 1. Formal Biosynthetic Routes for Bicyclic Sesquiterpene Ethers **1** and **2**



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(1) For the isolation of (−)-**1**, see: (a) Appel, H. H.; Brooks, C. J. W.; Campbell, M. M. *Perf. Essent. Oil Record* **1967**, 776−781. (b) Brooks, C. J. W.; Campbell, M. M. *Phytochemistry* **1969**, *8*, 215−218.

(2) For the isolation of (+)-**1**, see: Shen, Y.-C.; Hsieh, P.-W. *Chin. Pharm. J.* **1999**, *51*, 213−218.

(3) For the isolation of natural product **2**, see: (a) Wadhams, L. J.; Baker, R.; Howse, P. E. *Tetrahedron Lett.* **1974**, 1697−1700. (b) Baker, R.; Evans, D. A.; McDowell, P. G. *Tetrahedron Lett.* **1978**, 4073−1076.

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HSO_3F gives (±)-**2** diastereoselectively (via substrate control).[5] However, there have been no successful examples of the diastereoselective cyclization of (±)-**3** to (±)-**1**. Kametani and co-workers obtained a 1:1 diastereomeric mixture of (±)-**1** and (±)-**2** through the cyclization of *β*-hydroxy phenylselenide derived from 10,11-epoxynerolidol induced by 5.7 equiv of CF_3CO_2H.[6] To concisely synthesize (+)-**1** and (−)-**1** through the polyene cyclization of (*R*)-**3** and (*S*)-**3**, respectively, asymmetric control with artificial cyclases should be able to overcome substrate control, and both enantiomers of artificial cyclases should be readily available.

Recently, we demonstrated that Lewis acid assisted chiral Brønsted acids (chiral LBAs) prepared in situ from chiral alcohols and tin(IV) chloride were highly effective as artificial cyclases for the enantioselective biomimetic cyclization of polyprenoids.[7] For example, tri-, tetra-, and pentacyclic terpenpoids bearing a chroman skeleton give products with up to 91% ee by enantioselective cyclization of the corresponding 2-(polyprenyl)phenol derivatives induced by chiral catechol derivative **4**·$SnCl_4$ (Figure 1).[7f] We

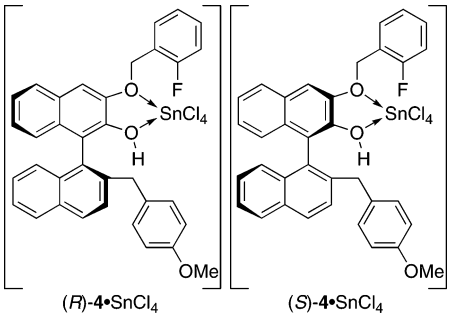
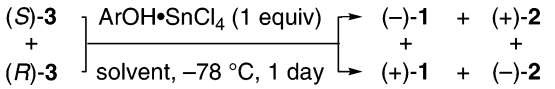


Figure 1. Artificial cyclases that are available in both enantiomeric forms.

describe here a concise total synthesis of acid-sensitive bicyclic sesquiterpenes (−)-**1** and (+)-**2** based on a biomimetic pathway induced by the chiral LBAs (*R*)-**4**·$SnCl_4$ and (*S*)-**4**·$SnCl_4$.[7]

First, the diastereoselective cyclization of (±)-**3**, which was obtained commercially, was examined with 1 equiv of the achiral LBA, 2-methoxyphenol (**5**)·$SnCl_4$, in dichloromethane at −78 °C (Table 1). Cyclization of (±)-**3** bearing an acid-sensitive allylic hydroxy group gave a complex

Table 1. Double-Asymmetric Induction in the Cyclization of (±)-**3** with (*R*)-**4**·$SnCl_4$



ArOH	solvent	yield[a] (%) 1+2	ratio[b] (+)-1/(−)-1/ (+)-2/(−)-2	from (*S*)-3[b] (−)-1/(+)-2	from (*R*)-3[b] (+)-1/(−)-2
5[c]	CH_2Cl_2	<10	18.5:18.5:31.5:31.5	37:63	37:63
5[c]	toluene	0			
(*R*)-**4**	CH_2Cl_2	32	0.4:8.2:9.9:81.5	45:55	<1:>99
(*R*)-**4**	toluene	13	0.4:27.5:3.7:68.4	88:12	<1:>99

[a] Isolated yield. [b] The ratio was determined by GC analysis (PEG and *β*-DM columns). [c] 2-Methoxyphenol (**5**).

reaction mixture, and the desired *trans*-fused 2-oxabicyclo-[4.4.0]decanes were obtained in less than 10% yield as a 37:63 mixture of (±)-**1** and (±)-**2**, which were stable under the reaction conditions. This diastereomeric ratio is due to substrate control. When (*R*)-**4** was used as a Brønsted acid instead of **5**, a 9:91 mixture of (−)-**1** (91% ee) and (−)-**2** (78% ee) was obtained in 32% yield. This result indicates that (+)-**2** and (−)-**2** were obtained from (*S*)-**3** and (*R*)-**3** with 55% and >99% diastereoselectivity, respectively. In the former case, low diastereoselectivity was observed due to the mismatch in asymmetric induction between substrate control and reagent control. In the latter case, high diastereoselectivity was observed due to the double asymmetric induction of substrate control and reagent control. The use of toluene in place of CH_2Cl_2 lowered the chemical yield of **1** and **2** but raised their enantioselectivities to 97% ee and 90% ee. Notably, (−)-**1** was obtained from (*S*)-**3** with 88% diastereoselectivity due to reagent control, which overcame substrate control. The activated proton in (*R*)-**4**·$SnCl_4$ preferentially attacked the *si* face of the terminal isoprenyl group because the OH/*π* interaction between (*R*)-**4**·$SnCl_4$ and **3** in the initial protonation step should be stronger in less polar solvents such as toluene.[7f]

To improve the chemical yield of **1** or **2**, (±)-(*E*)-3,7,11-trimethyl-6,10-dodecadiene-1,3-diol derivatives **6a**−**f**, which were less acid-sensitive than (±)-**3**, were examined as substrates for cyclization with (*R*)-**4**·$SnCl_4$ (Table 2). Although the cyclizations of 1,3-diol **6a** and 1-*tert*-butyldiphenylsilyl ether **6b** were carried out in the presence of 2 equiv of (*R*)-**4**·$SnCl_4$ in toluene at −78 °C for 1 day, no desired bicyclic ethers were obtained, probably due to the tight bidentate chelation between the substrates and $SnCl_4$ (entries 1 and 2). This undesirable chelation disturbs not only the generation of (*R*)-**4**·$SnCl_4$ but also the internal nucleophilic attack of the 3-hydroxy group in the final step of the cyclization of **6**.[8] In the course of screening various protecting groups for the 1-hydroxy group of **6a**, we found that 1-acylates such as 1-benzoate **6e** and 1-phenylacetate **6f** were effective for the cyclization of **6** and gave *trans*-fused

(4) For the isolation of (+)-**2**, see: (a) Faulkner, D. J. *Phytochemistry* **1976**, *15*, 1993−1994. (b) Kato, T.; Ishii, K.; Ichinose, I.; Nakai, Y.; Kumagai, T. *J. Chem. Soc., Chem. Commun.* **1980**, 1106−1109.

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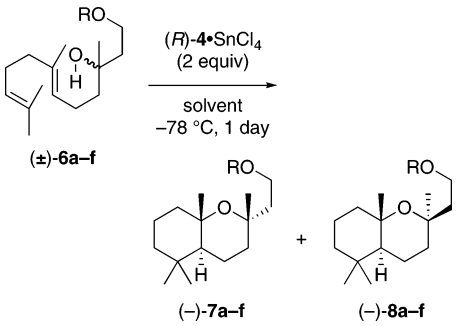
Table 2. Double-Asymmetric Induction in the Cyclization of (±)-**6** with (*R*)-**4**·$SnCl_4$



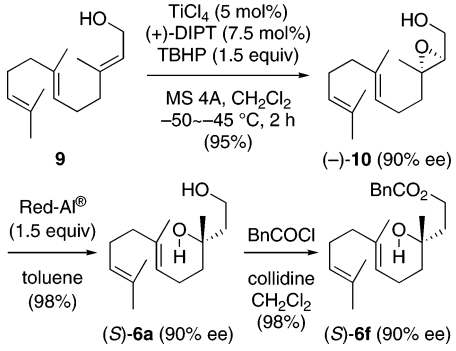
entry	R, **6**	solvent	yield (%)[a] **7** + **8**	ratio[b] (+)-**7**/(−)-**7**/ (+)-**8**/(−)-**8**
1	H, **6a**	toluene	0	
2	Si-*t*-$BuPh_2$, **6b**	toluene	0	
3	CO-*i*-Bu, **6c**	toluene	0	
4	$CO(CH_2)_2Ph$, **6d**	toluene	16	3.7:49.3:4.5:42.5
5	COPh, **6e**	toluene	21	5.8:49.2:4.0:41.0
6	COBn, **6f**	toluene	29	4.0:58.0:3.4:34.6
7	COBn, **6f**	CH_2Cl_2	78	8.5:38.5:8.7:44.3
8	COBn, **6f**	PrCl	41	3.1:48.9:2.6:45.4
9	COBn, **6f**	CH_2Cl_2−PrCl[c]	65	4.0:40.0:5.0:51.0

[a] Isolated yield. [b] The ratio was determined by GC (PEG column) and HPLC analyses (AD-H columns). [c] A 1:1 (v/v) mixed solvent.

2-oxabicyclo[4.4.0]decanes **7** and **8** (entries 5−9). Interestingly, aliphatic esters such as isovalerate **6c** were inert under the same reaction conditions (entry 3), and 3-phenylpropionate **6d** was less reactive than **6e** and **6f** (entry 4). These experimental data suggest the existence of some attractive interaction between Sn(IV) and a phenyl group of **6e** and **6f**.[8] The cyclization of (±)-**6f** with (*R*)-**4**·$SnCl_4$ gave a 62:38 mixture of (−)-**7f** (87% ee) and (−)-**8f** (82% ee) in 29% yield (entry 6). Judging from the enantioselectivity and chemical yield of **7** and **8**, (±)-**6f** gave slightly better results than (±)-**6e** (entry 5 versus entry 6). Next, the solvent effect was investigated in the cyclization of (±)-**6f** with (*R*)-**4**·$SnCl_4$ (entries 6−8): the enantioselectivity was higher in the order CH_2Cl_2 ≪ toluene < chloropropane, while the chemical yield of **7** and **8** increased in the order toluene < chloropropane ≪ CH_2Cl_2. Thus, chloropropane was superior to toluene with respect to both enantioselectivity and reactivity. Finally, when a 1:1 mixed solvent of chloropropane and CH_2Cl_2 was used, a 44:56 mixture of (−)-**7f** (82% ee) and (−)-**8f** (82% ee) was obtained in 65% yield (entry 9). These experimental results indicate that the substrate control of **6** is relatively lower than that of **3** because of little difference in the thermodynamic stabilities of **7** and **8** (Table 1 versus Table 2). Fortunately, **7f** and **8f** were easily separable by column chromatography on silica gel. In contrast, it was difficult to separate **1** and **2** without any chemical modification.[6]

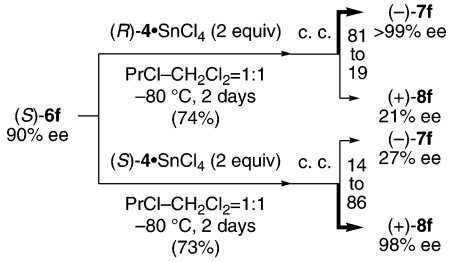
(*S*)-**6f** had to be prepared to synthesize (−)-**7f**, which is a synthetic precursor of (−)-caparrapi oxide **1**.[9] (*S*)-**6f** was prepared with 90% ee in 91% overall yield from farnesol (**9**) in three steps (Scheme 2): (a) Sharpless−Katsuki epoxidation of **9** to (2*S*,3*S*)-(−)-epoxyfarnesol (**10**) with 90% ee,[10] (b) regioselective reduction of (−)-**10** to (*S*)-**6a** (>99% regioselectivity) with Red-Al (65% sodium bis(2-methoxyethoxy)aluminum hydride in toluene),[11] and (c) regioselective acylation of (*S*)-**6a** with phenylacetyl chloride to (*S*)-**6f** (>99% regioselectivity).[12]

Scheme 2

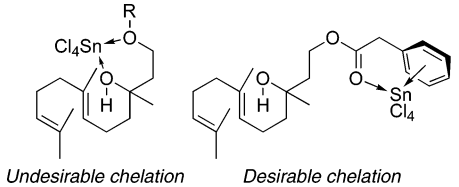


The asymmetric cyclization of (*S*)-**6f** induced by 2 equiv of (*R*)-**4**·$SnCl_4$ gave an 81:19 mixture of (−)-**7f** (>99% ee) and (+)-**8f** (21% ee) in 74% yield. On the other hand, the asymmetric cyclization of (*S*)-**6f** induced by 2 equiv of (*S*)-**4**·$SnCl_4$ gave a 14:86 mixture of (−)-**7f** (27% ee) and (+)-**8f** (98% ee) in 73% yield. These experimental results indicate that the substrate control of **6f** was much lower than the reagent control by **4**·$SnCl_4$. Optically pure (−)-**7f** and (+)-**8f** were easily separated by column chromatography on silica gel (Scheme 3).

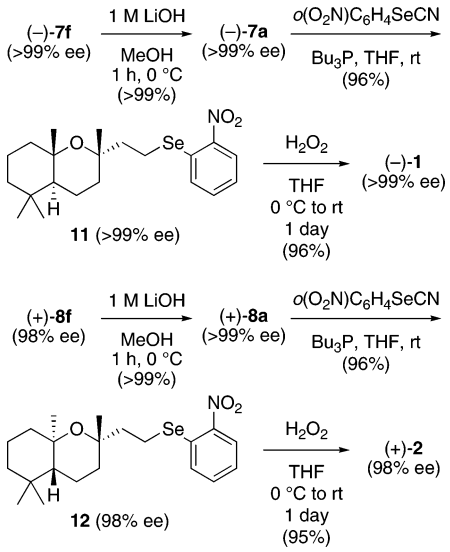
Scheme 3. Diastereoselective Preparation of (−)-**7f** and (+)-**8f** from (*S*)-**6f**



(8) Predicatable chelation structures of **6** with $SnCl_4$ are shown below. Further studies to elucidate the existence of some attractive interaction between Sn(IV) and a phenyl group of **6e** and **6f** are currently in progress in our laboratory, and our results will be reported in due course.



Scheme 4



Optically pure (−)-caparrapi oxide **1** was obtained in 92% overall yield from (−)-**7f** in three steps (Scheme 4): hydrolysis of (−)-**7f** to (−)-**7a** under basic conditions and subsequent Grieco elimination to (−)-**1** through alkyl *o*-nitrophenyl selenide **11**.[13] In the same manner, (+)-8-epicaparrapi oxide **2** (98% ee) was obtained in 91% overall yield from (+)-**8d**: (a) hydrolysis of (+)-**8f** to (+)-**8a** (>99%), (b) *o*-nitrophenylselenylation of **8a** (96%), and (c) oxidative elimination of **12** to (+)-**3** (95%).

In summary, we have demonstrated that the chiral LBA **4**·$SnCl_4$ is an artificial cyclase that is useful for both achiral and chiral substrates: (−)-caparrapi oxide **1** and (+)-8-epicaparrapi oxide **2** could be diastereoselectively synthesized from (*S*)-**6f** by the reagent control of (*R*)-**4**·$SnCl_4$ and (*S*)-**4**·$SnCl_4$, respectively, regardless of the chirality of (*S*)-**6f**. Furthermore, in the cyclization of (±)-**3** induced by (*R*)-**4**·$SnCl_4$, (−)-**1** was diastereoselectively obtained from (*S*)-**3** by reagent control which overcame substrate control, while (−)-**2** was highly diastereoselectively obtained from (*R*)-**3** by the double-asymmetric induction of substrate control and reagent control.

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Supporting Information Available: Experimental details and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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