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Bioorganic & Medicinal Chemistry 13 (2005) 5055–5065
Bioorganic & Medicinal Chemistry

Biomimetic synthesis of acid-sensitive (−)- and (+)-caparrapi oxides, (−)- and (+)-8-epicaparrapi oxides, and (+)-dysifragin induced by artificial cyclases

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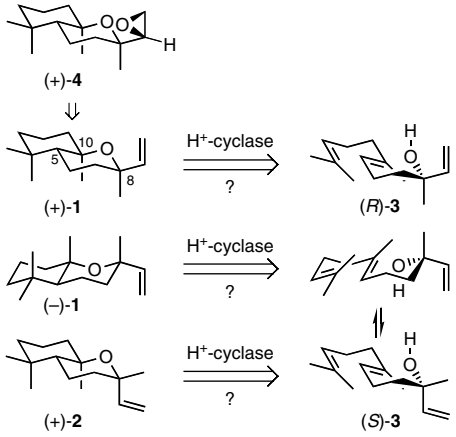
Received 14 March 2005; accepted 12 April 2005
Available online 4 May 2005

Dedicated to Professor Koji Nakanishi in honor of his receipt of the Tetrahedron Prize.

Abstract—Asymmetric total syntheses of acid-sensitive (−)- and (+)-caparrapi oxides (**1**) and (+)-8-epicaparrapi oxide (**2**) from farnesol (**10**) are achieved using Sharpless–Katsuki epoxidation and Lewis acid-assisted chiral Brønsted acid (chiral LBA)-induced polyene cyclization as key steps. The relative configuration of (+)-dysifragin (**4**) is determined by a single-crystal X-ray diffraction and its total synthesis is accomplished by the diastereoselective epoxidation of (+)-**1**. Furthermore, (−)-**1** can be directly synthesized from (*S*)-nerolidol (**3**) and (*R*)-LBA with 88% ds by reagent control, which overcame substrate control, while (−)-**2** is obtained from (*R*)-**3** and (*R*)-LBA with >99% ds by the double asymmetric induction.

1. Introduction

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-epicaparrapi oxide (**2**)[3] can be formally derived by biomimetic proton-induced cyclization of (*S*)-(+)- or (*R*)-(−)-nerolidol (**3**) (Scheme 1). Compounds (−)-**1** has been isolated from the neutral fraction of the essential oil of *Ocotea caparrapi Nates* (Dugand).[1] On the other hand, (+)-**1** and (+)-dysifragin (**4**) have been isolated from the sponge *Dysidea fragilis Montagu* (family Dysideidae).[2] However, the absolute and relative stereochemistry of (+)-**4** has not been determined. 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



Scheme 1. Formal biosynthetic routes for bicyclic and tricyclic sesquiterpene ethers **1**, **2**, and **4**.

5 equiv of 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

Keywords: Biomimetic synthesis; Caparrapi oxides; 8-Epicaparrapi oxide; Dysifragin.
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doi:10.1016/j.bmc.2005.04.029

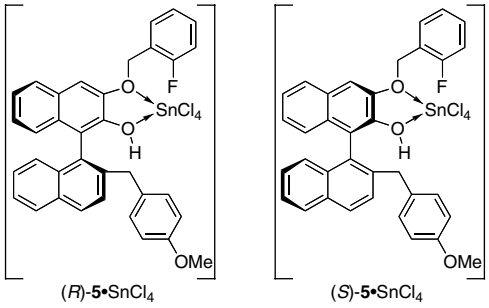


Figure 1. Artificial cyclases that are available in both enantiomeric forms.

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 terpenoids 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 **5**·$SnCl_4$ (Fig. 1).[7f] We describe here a concise total synthesis of acid-sensitive bicyclic sesquiterpenes (−)-**1**, (+)-**1**, and (+)-**2** based on a biomimetic pathway induced by the chiral LBAs (*R*)-**5**·$SnCl_4$ and (*S*)-**5**·$SnCl_4$ and the diastereoselective transformation from (+)-**1** to (+)-**4**.[8] The absolute stereochemical structure of (+)-**4** was established by ^{13}C NMR spectroscopic method and X-ray diffraction.

2. Results and discussion

First, the diastereoselective cyclization of (±)-**3**, which was obtained commercially, was examined with 1 equiv of the achiral LBA, 2-methoxyphenol (**6**)·$SnCl_4$, in dichloromethane at −78 °C (Table 1, entry 1). Cyclization of (±)-**3** bearing an acid-sensitive allylic hydroxy group gave a complex 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: transition-state assembly TS-**B** is more favorable than transition-state assembly TS-**A** due to the steric difference between 3-vinyl group and 3-methyl group of (±)-**3** (Fig. 2). When (*R*)-**5** was used as a Brønsted acid instead of **6**, a 9:91 mixture of (−)-**1** (91% ee) and (−)-**2** (78% ee) was obtained in 32% yield (entry 3). 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*)-**5**·$SnCl_4$ preferentially attacked the *si*-face of the terminal isoprenyl group because the OH/π interaction between (*R*)-**5**·$SnCl_4$ and **3** in the initial protonation step should be stronger in less polar solvents like toluene.[7f]

To improve the chemical yield of **1** or **2** (±)-(*E*)-3,7,11-trimethyl-6,10-dodecadiene-1,3-diol derivatives **7a**–**f**, which were less acid-sensitive than (±)-**3**, were examined as substrates for cyclization with (*R*)-**5**·$SnCl_4$ (Table 2). Although the cyclizations of 1,3-diol **7a** and 1-*tert*-butyldiphenylsilyl ether **7b** were carried out in the presence of 2 equiv of (*R*)-**5**·$SnCl_4$ in toluene at −78 °C for 1 day, no desired bicyclic ethers were obtained, probably due to

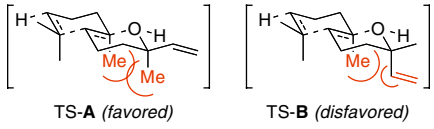
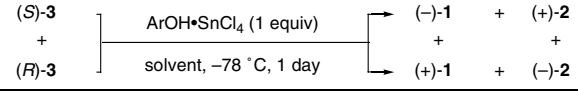


Figure 2. Two transition-state assemblies TS-**A** and TS-**B** in the proton-induced cyclization of (±)-**3**.

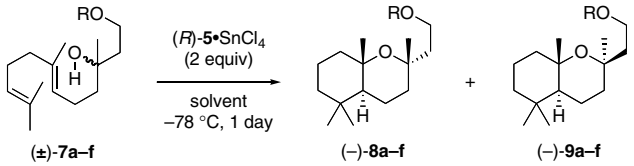
Table 1. Double asymmetric induction in the cyclization of (±)-**3** with (*R*)-**5**·$SnCl_4$



Entry	ArOH	Solvent	Yield [%][a] **1** + **2**	Ratio[b] (+)-**1**:(−)-**1**:(+)-**2**:(−)-**2**	Ratio **1**:**2**	Ee [%] (rotn.) **1**,**2**	From (*S*)-**3** (−)-**1**:(+)-**2**	From (*R*)-**3** (+)-**1**:(−)-**2**
1	**6**[c]	CH_2Cl_2	<10	18.5:18.5:31.5:31.5	37:63	—	37:63	37:63
2	**6**[c]	Toluene	0	—	—	—	—	—
3	(*R*)-**5**	CH_2Cl_2	32	0.4:8.2:9.9:81.5	9:91	91 (−), 78 (−)	45:55	<1:>99
4	(*R*)-**5**	Toluene	13	0.4:27.5:3.7:68.4	28:32	97 (−), 90 (−)	88:12	<1:>99

[a] Isolated yield.
[b] The ratio was determined by GC analysis (PEG and β-DM columns).
[c] 2-Methoxyphenol (**6**).

Table 2. Double asymmetric induction in the cyclization of (±)-**7** with (*R*)-**5**·$SnCl_4$



Entry	R, **7**	Solvent	Yield (%)[a] **8** + **9**	Ratio[b] (+)-**8**:(−)-**8**:(+)-**9**:(−)-**9**	Ratio **8**:**9**	Ee (%) (−)-**8**, (−)-**9**
1	H, **7a**	Toluene	0	—	—	—
2	Si*t*-$BuPh_2$, **7b**	Toluene	0	—	—	—
3	CO*i*-Bu, **7c**	Toluene	0	—	—	—
4	$CO(CH_2)_2Ph$, **7d**	Toluene	16	3.7:49.3:4.5:42.5	53:47	86, 81
5	COPh, **7e**	Toluene	21	5.8:49.2:4.0:41.0	55:45	79, 82
6	COBn, **7f**	Toluene	29	4.0:58.0:3.4:34.6	62:38	87, 82
7	COBn, **7f**	CH_2Cl_2	78	8.5:38.5:8.7:44.3	47:53	64, 67
8	COBn, **7f**	PrCl	41	3.1:48.9:2.6:45.4	52:48	88, 89
9	COBn, **7f**	CH_2Cl_2–PrCl[c]	65	4.0:40.0:5.0:51.0	44:56	82, 82

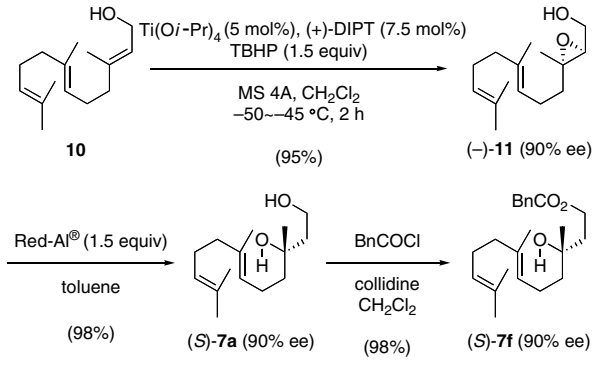
[a] Isolated yield.
[b] The ratio was determined by GC (PEG column) and HPLC analyses (AD-H columns).
[c] A 1:1 (v/v) mixed solvent.

the tight bidentate-chelation between the substrates and $SnCl_4$ (entries 1 and 2). This undesirable chelation disturbs not only the generation of (*R*)-**5**·$SnCl_4$ but also the internal nucleophilic attack of the 3-hydroxy group in the final step of the cyclization of **7**.[9] In the course of screening various protecting groups for the 1-hydroxy group of **7a**, we found that 1-acylates such as 1-benzoate **7e** and 1-phenylacetate **7f** were effective for the cyclization of **7** and gave *trans*-fused 2-oxabicyclo[4.4.0]-decanes **8** and **9** (entries 5–9). Interestingly, aliphatic esters such as isovalerate **7c** were inert under the same reaction conditions (entry 3), and 3-phenylpropionate **7d** was less reactive than **7e** and **7f** (entry 4). These experimental data suggest the existence of some attractive interaction between Sn(IV) and a phenyl group of **7e** and **7f**.[9] The cyclization of (±)-**7f** with (*R*)-**5**·$SnCl_4$ 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 **8** and **9**, (±)-**7f** gave slightly better results than (±)-**7e** (entry 5 vs entry 6). Next, the solvent effect was investigated in the cyclization of (±)-**7f** with (*R*)-**5**·$SnCl_4$ (entries 6–8): the enantioselectivity was higher in the order $CH_2Cl_2 \ll$ toluene < chloropropane, while the chemical yield of **8** and **9** increased in the order toluene < chloropropane $\ll CH_2Cl_2$. 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 (−)-**8f** (82% ee) and (−)-**9f** (82% ee) was obtained in 65% yield (entry 9). These experimental results indicate that the substrate control of **7** is relatively lower than that of **3** because of little difference in the thermodynamic stabilities of **8** and **9** (Table 1 vs Table 2). Fortunately, **8f** and **9f** were easily separable by column chromatography on silica gel. In contrast, it was difficult to separate **1** and **2** without any chemical modification.[6]

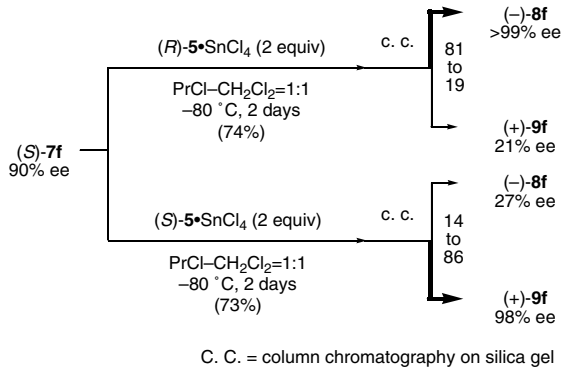
Compound (*S*)-**7f** had to be prepared to synthesize (−)-**8f**, which is a synthetic precursor of (−)-caparrapi oxide **1**.[10] (*S*)-**7f** was prepared with 90% ee in 91% overall yield from farnesol (**10**) in three steps (Scheme 2): (a) Sharpless–Katsuki epoxidation of **10** to (2*S*,3*S*)-(−)-epoxyfarnesol (**11**) with 90% ee,[11] (b) regioselective reduction of (−)-**11** to (*S*)-**7a** (>99% regioselectivity) with Red-Al® (65% sodium bis(2-methoxyethoxy)aluminum hydride in toluene),[12] and (c) regioselective acylation of (*S*)-**7a** with phenylacetyl chloride to (*S*)-**7f** (>99% regioselectivity).[13]

The asymmetric cyclization of (*S*)-**7f** induced by 2 equiv of (*R*)-**5**·$SnCl_4$ gave an 81:19 mixture of (−)-**8f** (>99% ee) and (+)-**9f** (21% ee) in 74% yield. On the other hand, the asymmetric cyclization of (*S*)-**7f** induced by 2 equiv of (*S*)-**5**·$SnCl_4$ gave a 14:86 mixture of (−)-**8f** (27% ee) and (+)-**9f** (98% ee) in 73% yield. These experimental results indicate that the substrate control of **7f** was much lower than the reagent control by **5**·$SnCl_4$. Optically pure (−)-**8f** and (+)-**9f** were easily separated by column chromatography on silica gel (Scheme 3).

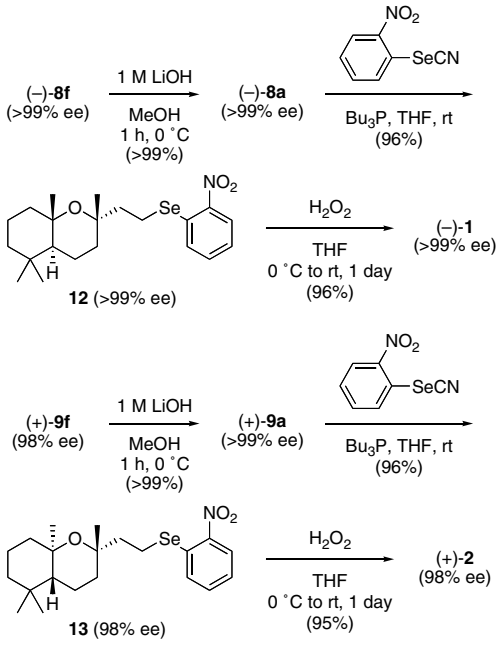
Optically pure (−)-caparrapi oxide **1** was obtained in 92% overall yield from (−)-**8f** in three steps (Scheme 4): hydrolysis of (−)-**8f** to (−)-**8a** under basic conditions and subsequent Grieco elimination to (−)-**1** through alkyl *o*-nitrophenyl selenide **12**.[14] In the same manner, (+)-8-epicaparrapi oxide **2** (98% ee) was obtained in



Scheme 2. Preparation of (*S*)-**7f**.



Scheme 3. Diastereoselective preparation of (−)-**8f** and (+)-**9f** from (*S*)-**7f**.

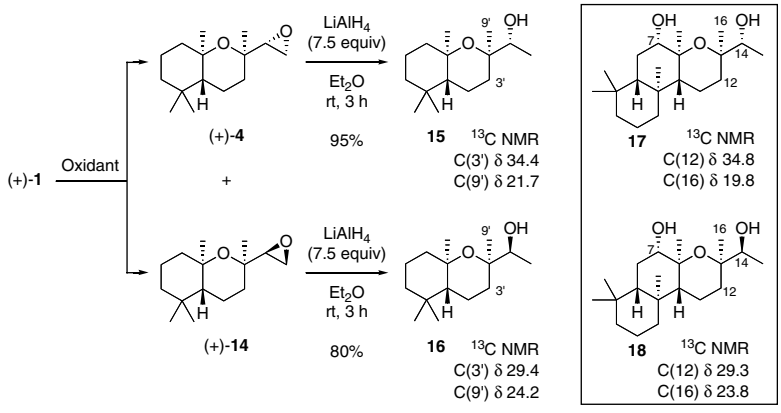


Scheme 4. Synthetic transformation from (−)-**1** and (+)-**2** to (−)-**8f** and (+)-**9f** using Grieco's method.[14]

91% overall yield from (+)-**9d**: (a) hydrolysis of (+)-**9f** to (+)-**9a** (>99%), (b) *o*-nitrophenylselenylation of **9a** (96%), and (c) oxidative elimination of **13** to (+)-**3** (95%).

(+)-Caparrapi oxide **1** and its epoxide, (+)-dysifragin **4**, have been isolated from the sponge *Dysidea fragilis* Montagu.[2] However, the absolute and relative stereochemistry of (+)-**4** is not determined. To elucidate the structure of (+)-**4**, it was necessary to synthesize diastereomeric epoxides of (+)-**1** in enantiomerically pure form. Diastereoselective epoxidation of (+)-**1**, which was synthesized from (+)-**11** as above, was examined with various oxidants. The representative results are shown in Table 3. In most cases, unfortunately, the diastereomer of (+)-**4**, (+)-**14**, was obtained as a major product. However, two diastereomers were easily separated by flash column chromatography on silica gel. Peroxytrifluoroacetic acid prepared from urea hydrogen peroxide and trifluoroacetic anhydride in situ gave the best result: (+)-**4** was obtained with 50% ds (entry 1). ^{1}H NMR, ^{13}C NMR, and IR spectra and absolute values of the specific rotation for synthetic product (+)-**4** and for natural dysifragin[2] were nearly identical. Based on the Rodriguez' ^{13}C NMR method for the determina-

Table 3. Diastereoselective epoxidation of (+)-**1**



Entry	Oxidant (equiv)	Additives (equiv)	Solvent	Temp (°C), time (h)	Yield (%)[a] (+)-**4** + (−)-**14**	Ratio[b] (+)-**4**:(−)-**14**
1[a]	H_2O_2·$(H_2N)_2CO$ (10) $(CF_3CO)_2O$ (2.5)	K_2HPO_4 (8.8)	CH_2Cl_2	23, 3	97	50:50
2	*m*CPBA (1.5)	—	CH_2Cl_2	23, 24	96	45:55
3[b]	Oxone (5) Acetone (10)	Na_2CO_3 (5)	EtOAc–water	23, 16	70	37:63
4[c]	H_2O_2 (4)	$MeReO_3$ (0.015) 3-Cyanopyridine (0.3)	Pyridine	23, 72	95	35:65

[a] Ref. 18.
[b] Ref. 19.
[c] Ref. 20.

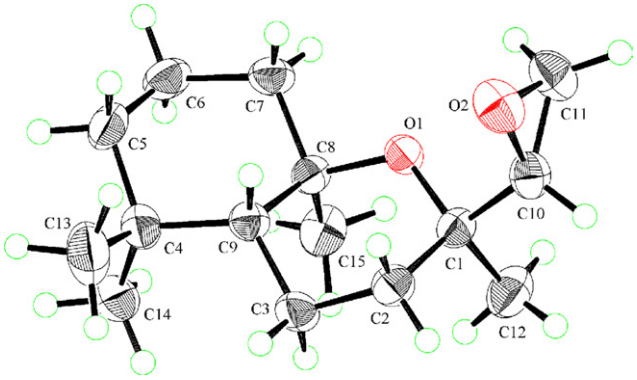


Figure 3. X-ray diffraction of (+)-**4**.

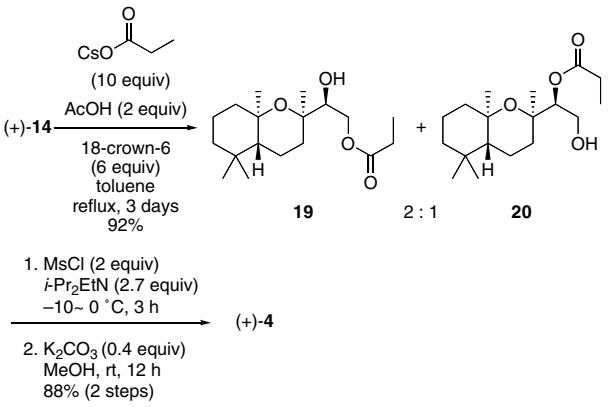
tion of C(14) configuration of 8,13-epoxylabdane-7, 14-diols, **17** and **18**,[16] the relative stereochemistries of (+)-**4** and (+)-**14** were presumed by ^{13}C NMR spectral analysis of **15** and **16**, which were transformed from (+)-**4** and (+)-**14**, respectively, by the regioselective reductive cleavage using lithium aluminum hydride (Table 3): the C(3′) and C(9′) chemical shifts of **15** were analogous to the C(12) and C(16) chemical shifts of **17**, while the C(3′) and C(9′) chemical shifts of **16** were analogous to the C(12) and C(16) chemical shifts of **18**.

Fortunately, the relative stereochemical structure of (+)-**4** was determined by its X-ray diffraction (Fig. 3), and it was ascertained that the Rodriguez' ^{13}C NMR method[16] was also useful for determination of analogous chemical structures like dysifragin.

Unnatural diastereomer (+)-**14** could be transformed to (+)-**4** with three steps in 81% yield according to the Prieto's method[17] (Scheme 5): the treatment of **14** with cesium propionates as the epoxide-cleaving agent gave a 2:1 molar mixture of regioisomeric propionates, **19** and **20**, that was mesylated and methanolyzed to produce the inverted epoxide (+)-**4**. Thus, (+)-**4** was obtained in 88% over all yield from (+)-**1**.

3. Conclusions

In summary, we have demonstrated that the chiral LBA **5**·$SnCl_4$ 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*)-**7f** by the reagent control of (*R*)-**5**·$SnCl_4$ and (*S*)-**5**·$SnCl_4$, respectively, regardless of the chirality of (*S*)-**7f**. Furthermore, in the cyclization of (±)-**3** induced by (*R*)-**5**·$SnCl_4$, (−)-**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. (+)-Dysifragin **4** was synthesized from (+)-**1** in high yield and its structure was fully determined by X-ray diffraction.



Scheme 5. Inversion from (+)-**14** to (+)-**4**.

4. Experimental

4.1. General methods

Infrared (IR) spectra were recorded on a JASCO FT/IR 460 plus spectrometer. ^1H NMR spectra were measured on a Varian Gemini-2000 (300 MHz) or Varian INOVA-500 (500 MHz) spectrometer at ambient temperature. Data were recorded as follows: chemical shift in parts per million from internal tetramethylsilane on the δ scale, multiplicity (s = singlet; d = doublet; t = triplet; m = multiplet), coupling constant (hertz), integration, and assignment. ^{13}C NMR spectra were measured on a Varian Gemini-2000 (75 MHz) or Varian INOVA-500 (125 MHz) spectrometer. Chemical shifts were recorded in parts per million from the solvent resonance employed as the internal standard (deuterochloroform at 77.00 ppm). High-performance liquid chromatography (HPLC) analysis was conducted using Shimadzu LC-10 AD coupled diode array-detector SPD-MA-10A-VP and chiral column of Daicel CHIRALCEL OD-H (4.6 mm × 25 cm) or Daicel CHIRALPAK AD-H (4.6 mm × 25 cm). Optical rotations were measured on a JASCO DIP-1000 digital polarimeter. GC analysis was performed with Shimadzu 17A instruments using PEG (0.25 mm × 25 m). All experiments were carried out under an atmosphere of dry nitrogen. 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 column chromatography on silica gel (E. Merck Art. 9385). High resolution mass spectral analysis (HRMS) was performed at Chemical Instrument Center, Nagoya University. In experiments that required dry solvent, ether and tetrahydrofuran (THF) were purchased from Aldrich or Wako as the 'anhydrous' and stored over 4 Å molecular sieves. Hexane, toluene, 1-chloropropane, and dichloromethane were freshly distilled from calcium hydride. Tin(IV) chloride was distilled under nitrogen. Other simple chemicals were analytical-grade and obtained commercially.

4.2. Preparation of chiral catechol derivatives (chiral BA of (*S*)-5 and (*R*)-5)[7f]

Chiral catechols (*S*)- and (*R*)-**5** were prepared from (*R*)-BINOL and (*S*)-BINOL, respectively.

4.3. Diastereoselective cyclization of *trans*-nerolidol induced by chiral LBA 5·$SnCl_4$ (Table 1)

To a solution of chiral catechol (*R*)-**5** (154 mg, 0.30 mmol) or 2-methoxyphenol (**6**, 33 mL, 0.30 mmol) in toluene or CH_2Cl_2 (6 mL) was added a 1 M solution of tin(IV) chloride in hexane (for toluene as reaction solvent) or CH_2Cl_2 (for CH_2Cl_2 as reaction solvent) (300 mL, 0.30 mmol) under N_2 at room temperature, and the mixture was stirred for 5 min. After the solution was cooled to −78 °C, *trans*-nerolidol (85 mL, 0.30 mmol) was added dropwise. The reaction mixture was stirred for 1 day, quenched with saturated aqueous $NaHCO_3$, and extracted with ether. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated. The crude product was purified by column chromatography on silica gel (eluent: hexane–ether = 50:1–30:1) to give bicyclic compounds containing a small amount of unknown products. Compounds **1** and **2** could not be separated by column chromatography on silica gel.[6] See Table 1 in the paper for yield of bicyclic compounds.

4.4. Total synthesis of (5*S*,8*S*,10*S*)-(−)-caparrapi oxide (1) and (5*R*,8*S*,10*R*)-(+)-epicaparrapi oxide (2) from farnesol (10)

4.4.1. (2*S*,3*S*)-(−)-Epoxyfarnesol (11).[11b,d] A mixture of powdered, activated 4 Å molecular sieves (20 mg), and CH_2Cl_2 (1 mL) was cooled to −20 °C. L-(+)-Diisopropyl tartrate (L-(+)-DIPT, 18 mg, 0.075 mmol, Aldrich) and Ti(O*i*-Pr)$_4$ (14 mg, 15 mL, 0.05 mmol, distilled) were added sequentially. After the mixture was cooled to −50 °C, TBHP (400 mL, 1.50 mmol, 3.74 M in toluene) was added and the resulting mixture was stirred for 30 min, whereupon freshly distilled *trans, trans*-farnesol (222 mg, 1.00 mmol) was added. Stirring was maintained for 2 h at −50 to −45 °C. Diluted with 10% aqueous tartaric acid solution (5 mL) and stirred at same temperature for further 30 min, and the reaction mixture was allowed to warm to room temperature and the stirring was continued for 1 h. Extracted with CH_2Cl_2 (3 × 10 mL) and washed with water, dried over anhydrous Na_2SO_4 and concentrated. To a residual oil in ether (10 mL) was added aqueous 1 M NaOH (3 mL) and the mixture was stirred at 0 °C for 30 min. Extracted with ether (3 × 10 mL), washed with NH_4Cl and brine, dried over anhydrous $MgSO_4$, and concentrated. The crude product was purified by column chromatography on silica gel (eluent: hexane–ethyl acetate = 4:1) to give **11** (226 mg, 0.95 mmol, 95% yield with 90% ee). TLC (hexane–EtOAc, 2:1) $R_f = 0.40$; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.31 (s, 3H), 1.45–1.75 (m, 2H), 1.61 (s, 6H), 1.68 (s, 3H), 1.95–2.14 (m, 7H), 2.99 (dd, $J = 4.5$, 6.6 Hz, 1H), 3.69 (ddd, $J = 4.8$, 6.6, 11.7 Hz, 1H), 3.81 (ddd, $J = 4.5$, 7.5, 11.7 Hz, 1H), 5.05–5.13 (m, 2H). Determination of the ee value of **11** via mosher ester: A mixture of 4-(dimethylamino)pyridine (DMAP, 5 mg, 0.04 mmol) and Et_3N (27 mL) in CH_2Cl_2 (140 mL) was treated with **10** (9.8 mg, 0.04 mmol). Immediately, (+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPACl, 8 mL) was added. After 30 min, quenched with water, dried, and concentrated. The residue was through pipette column on silica gel to give MTPA ester of epoxyfarnesol (90% ee). TLC (hexane–EtOAc, 4:1) $R_f = 0.46$; ^{1}H NMR analysis focused on the M or AB part of the ABM pattern, ^{1}H NMR (C_6D_6, 300 MHz) δ 0.97 (s, 3H), 1.22–1.45 (m, 2H), 1.50 (s, 3H), 1.56 (s, 3H), 1.68 (s, 3H), 1.90–2.20 (m, 8H), 2.74 (dd, $J = 4.5$, 7.2 Hz, 1H, M part of ABM pattern, major diastereomer, while appearing of minor diastereomer at δ 2.84), 3.43 (s, 3H), 4. 04 (dd, $J = 7.2$, 12.0 Hz, 1H, A part of ABM pattern, major diastereomer, while appearing of minor diastereomer at δ 3.87), 4.18 (dd, $J = 4.5$, 12.0 Hz, 1H, B part of ABM pattern, major diastereomer, while appearing of minor diastereomer at δ 3.91), 5.08 (t, $J = 7.2$ Hz, 1H), 5.21 (t, $J = 7.2$ Hz, 1H), 7.00–7.13 (m, 3H), 7.71 (d, $J = 7.8$ Hz, 2H).

4.4.2. (*S*)-3,7,11-Trimethyl-6,10-dodecadiene-1,3-diol (7a).[12] A 100-mL flask was charged with (−)-**11** (1.458 g, 6.12 mmol) and dry toluene (17 mL). The mixture was stirred under N_2 at 0 °C during the addition of Red-Al® (Kanto, 65% sodium bis(2-methoxyethoxy)aluminum hydride in toluene, 1.95 mL, 6.50 mmol). The reaction was allowed to warm to room temperature, over 3 h, at which time TLC analysis of an acidified sample disclosed the formation of single polar product. The reaction was cooled to 0 °C and quenched by addition of 2-propanol (2 mL). Acidification with 5% aqueous HCl was followed by phase separation and washing the organic layer with water and brine and drying over anhydrous $MgSO_4$. The residue was purified by column chromatography on silica gel (eluent: hexane–ethyl acetate = 2:1) to give **7a** (1.440 g, 5.99 mmol, 98% yield) as colorless oil. TLC (hexane–EtOAc, 1:1) $R_f = 0.16$; IR (film) 3550–3150, 2973, 2929, 2858, 1436, 1379, 1110, 1049 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.26 (s, 3H), 1.54–1.71 (m, 3H), 1.60 (s, 3H), 1.63 (s, 3H), 1.68 (s, 3H), 1.81 (ddd, $J = 4.8$, 7.5, 15.0 Hz, 1H), 1.97–2.14 (m, 6H), 2.34 (br s, 1H), 2.78 (br s, 1H), 3.86–3.95 (m, 2H), 5.08 (t, $J = 7.0$ Hz, 1H), 5.15 (t, $J = 7.0$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.6, 17.3, 22.3, 25.3, 26.1, 26.3, 39.4, 41.3, 42.0, 58.8, 72.9, 123.9, 124.0, 130.7, 134.6; $[\alpha]_D^{22.3}$ 0.80 (*c* 2.0, $CHCl_3$) for 90% ee; HRMS (FAB) *m*/*z* calcd for $C_{15}H_{28}O_2Na$ (M+Na) 263.1987, found 263.1980.

4.5. Selective silylation or acylation of 1-hydroxy group of 7a[13]

4.5.1. (±)-1-*tert*-Butyldimethylsiloxy-3,7,11-trimethyl-6,10-dodecadiene-3-ol (7b). To a solution of **7a** (1.010 g, 4.20 mmol) and imidazole (572 mg, 8.4 mmol) in *N*,*N*-dimethylformamide (DMF, 8 mL) was added slowly *tert*-butylchlorodiphenylsilane (1.196 mL, 4.60 mmol) in DMF (2 mL) at room temperature. After stirring 3 h at rt, quenched with water, extracted with hexane, washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by column chromatography on silica gel (eluent: hexane–ethyl acetate = 10:1) to give **7b** (2.01 g, 4.20 mmol, 100% yield) as colorless oil. TLC (hexane–EtOAc, 4:1) $R_f = 0.44$; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.06 (s, 9H), 1.24 (s, 3H), 1.50–1.85 (m, 4H), 1.60 (s, 6H), 1.68 (s, 3H), 1.94–2.12

(m, 6H), 3.71 (s, OH), 3.92 (t, J = 7.2 Hz, 2H), 5.08–5.16 (m, 2H), 7.37–7.44 (m, 6H), 7.68–7.71 (m, 4H).

4.5.2. (±)-1-Isovaleryloxy-3,7,11-trimethyl-6,10-dodecadiene-3-ol (7c). To a solution of **7a** (159 mg, 0.66 mmol), 2,4,6-collidine (114 mL, 0.86 mmol) in CH_2Cl_2 (1.3 mL) at −78 °C under N_2 was added isovaleryl chloride (105 mL, 0.86 mmol) dropwise and stirred for 5 h at −78 °C. Then 1 M HCl was poured into this mixture, extracted with hexane (twice), washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by column chromatography on silica gel (eluent: hexane–ethyl acetate = 10:1) to give **7c** (204 mg, 0.63 mmol, 95% yield) as colorless oil. TLC (hexane–EtOAc, 4:1) R_f = 0.30; IR (film) 3600–3250 (br, OH), 2968, 2930, 2872, 1726 (C=O), 1523, 1436, 1385, 1296, 1120, 1049 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.79 (d, J = 6.3 Hz, 3H), 1.06 (s, 3H), 1.34–1.39 (m, 2H), 1.44 (s, 3H), 1.46 (s, 3H), 1.52 (s, 3H), 1.67 (dt, J = 1.5, 6.9 Hz, 2H), 1.80–2.03 (m, 9H), 4.08 (t, J = 6.9 Hz, 2H), 4.90–5.01 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.9, 17.6, 22.3 (2C), 22.5, 25.6 (2C), 26.5, 26.8, 39.6, 39.7, 42.1, 43.4, 60.9, 71.7, 123.9, 124.1, 131.3, 135.4, 173.1; HRMS (FAB) m/z calcd for $C_{20}H_{36}O_3Na$ (M+Na) 347.2562, found 347.2572.

4.5.3. (±)-1-(3-Phenylpropionyloxy)-3,7,11-trimethyl-6,10-dodecadiene-3-ol (7d). To a solution of **7a** (180 mg, 0.75 mmol), 2,4,6-collidine (130 mL, 0.98 mmol) in CH_2Cl_2 (1.5 mL) at −78 °C under N_2 was added hydrocinnamoyl chloride (146 mL, 0.98 mmol) dropwise and stirred for 5 h at −78 °C. Then 1 M HCl was poured into this mixture, extracted with hexane (twice), washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by column chromatography on silica gel (eluent: hexane–ethyl acetate = 8:1) to give **7d** (265 mg, 0.71 mmol, 95% yield) as colorless oil. TLC (hexane–EtOAc, 4:1) R_f = 0.28; IR (film) 3600–3250 (br, OH), 2972, 2928, 2863, 1728 (C=O), 1454, 1383, 1046, 929 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.18 (s, 3H), 1.46–1.52 (m, 2H), 1.59 (s, 3H), 1.61 (s, 3H), 1.67 (s, 3H), 1.78 (dt, J = 2.1, 7.2 Hz, 2H), 1.96–2.07 (m, 7H), 2.61 (t, J = 7.8 Hz, 2H), 2.93 (t, J = 7.8 Hz, 2H), 4.23 (t, J = 6.9 Hz, 2H), 5.06–5.14 (m, 2H), 7.16–7.20 (m, 3H), 7.24–7.29 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.9, 17.5, 22.4, 25.6 (2C), 26.5, 26.7, 30.8, 35.8, 39.5, 42.0, 61.2, 71.6, 123.9, 124.1, 126.1, 128.1 (2C), 128.3 (2C), 131.2, 135.3, 140.2, 172.8; HRMS (FAB) m/z calcd for $C_{24}H_{36}O_3Na$ (M+Na) 395.2562, found 395.2576.

4.5.4. (±)-1-Benzoxy-3,7,11-trimethyl-6,10-dodecadiene-3-ol (7e). To a solution of **7a** (240 mg, 1.0 mmol), pyridine (105 mL, 1.3 mmol) in CH_2Cl_2 (2 mL) at −78 °C under N_2 was added benzoyl chloride (151 mL, 1.3 mmol) dropwise and stirred for 10 h at −78 °C. Then 1 M HCl was poured into this mixture, extracted with hexane (twice), washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by column chromatography on silica gel (eluent: hexane–ethyl acetate = 10:1) to give **7e** (327 mg, 0.95 mmol, 95% yield) as colorless oil. TLC (hexane–EtOAc, 4:1) R_f = 0.23; IR (film) 3600–3250 (br, OH), 2972, 2928, 2858, 1714 (C=O), 1452, 1279, 1114 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.29 (s, 3H), 1.50–1.70 (m, 2H), 1.60 (s, 3H), 1.62 (s, 3H), 1.68 (s, 3H), 1.79 (s, 1H), 1.96–2.15 (m, 8H), 4.50 (t, J = 7.0 Hz, 2H), 5.08 (t, J = 7.0 Hz, 1H), 5.14 (t, J = 7.0 Hz, 1H), 7.43 (t, J = 7.5 Hz, 2H), 7.56 (t, J = 7.5 Hz, 1H), 8.02 (d, J = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.0, 17.7, 22.5, 25.7, 26.6, 27.0, 39.6, 39.8, 42.2, 61.7, 71.9, 123.9, 124.1, 128.3 (2C), 129.5 (2C), 130.2, 131.5, 132.9, 135.6, 166.6; HRMS (FAB) m/z calcd for $C_{22}H_{32}O_3Na$ (M+Na) 367.2249, found 367.2245.

4.5.5. (*S*)-1-Phenylacetoxy-3,7,11-trimethyl-6,10-dodecadiene-3-ol (7f). To a solution of **7a** (841 mg, 3.50 mmol), 2,4,6-collidine (604 mL, 4.55 mmol) in CH_2Cl_2 (7 mL) at −78 °C under N_2 was added phenyl acetyl chloride (602 mL, 4.55 mmol) dropwise and stirred for 5 h at −78 °C. Then 1 M HCl was poured into this mixture, extracted with hexane (twice), washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by column chromatography on silica gel (eluent: hexane–ethyl acetate = 10:1) to give **7f** (1.23 mg, 3.43 mmol, 98% yield) as colorless oil. TLC (hexane–EtOAc, 4:1) R_f = 0.22; HPLC (two linear OD-H columns, hexane–*i*-PrOH = 40:1, flow rate = 0.5 mL/min) t_R = 20.2 min for (*S*)-**7f**, 21.2 min for (*R*)-**7f**; IR (film) 3650–3150 (br, OH), 2968, 2925, 2855, 1734 (C=O), 1454, 1257, 1142, 757 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) d 1.17 (s, 3H), 1.45–1.53 (m, 2H), 1.60 (s, 3H), 1.61 (s, 3H), 1.68 (s, 3H), 1.81 (t, J = 6.9 Hz, 2H), 1.95–2.08 (m, 7H), 3.62 (s, 2H), 4.26 (t, J = 6.9 Hz, 2H), 5.05–5.14 (m, 2H), 7.28–7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) d 15.9, 17.5, 22.4, 25.6, 26.5, 26.6, 39.5 (2C), 41.3, 41.9, 61.6, 71.5, 123.9, 124.1, 127.0, 128.4 (2C), 129.1 (2C), 131.2, 133.7, 135.3, 171.4; $[\alpha]_D^{22.3}$ −1.7 (c 2.0, $CHCl_3$) for 90% ee; HRMS (FAB) m/z calcd for $C_{23}H_{34}O_3Na$ (M+Na) 381.2406, found 381.2409.

4.6. General procedure for the diastereoselective cyclization of 6 induced by chiral LBA 5·$SnCl_4$ (Table 2)

To a solution of chiral catechol (*R*)-**5** (103 mg, 0.20 mmol) in toluene or CH_2Cl_2 or *n*-PrCl (2 mL) was added a 1 M solution of tin(IV) chloride in hexane (for toluene as reaction solvent) or CH_2Cl_2 (for CH_2Cl_2 or *n*-PrCl as reaction solvent) (200 mL, 0.20 mmol) at room temperature, and the mixture was stirred for 5 min. After the solution was cooled to −78 °C, 1.0 M solution of **7** in toluene (for toluene as reaction solvent) or CH_2Cl_2 (for CH_2Cl_2 or *n*-PrCl as reaction solvent) (100 mL, 0.10 mmol) was added dropwise. The reaction mixture was stirred for 1 day, 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: hexane–ether = 10:1 → 5:1 → 2:1) to give bicyclic compounds, chiral catechol, and monocyclic compounds. Further column chromatography (see below for conditions of each compound) of bicyclics gave **8** and **9**. Yields, ratio, and enantioselectivity of bicyclics are described in Table 2.

4.6.1. (2′*S*,4′a*S*,8′a*S*)-(−)-2-(2′,5′,5′,8′a-Tetramethyloctahydrochromen-2′-yl)ethyl 3-phenylpropionate (8d). TLC (hexane–EtOAc, 4:1) $R_f = 0.68$; column chromatography, hexane–Et_2O = 20:1; HPLC (two linear AD-H columns, hexane–*i*-PrOH = 250:1, flow rate = 0.5 mL/min) $t_R = 45.1$ min for (+)-**8d**, 47.2 min for (−)-**8d**; GC (PEG, column temp 210 °C, 120 kPa) $t_R = 54.3$ min; IR (film) 2992, 2938, 2868, 1725 (C=O), 1455, 1377, 1134, 1101, 976 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.75 (s, 3H), 0.88 (s, 3H), 1.13–1.82 (m, 10H), 1.24 (s, 3H), 1.25 (s, 3H), 2.61 (t, $J = 7.8$ Hz, 2H), 2.94 (t, $J = 7.8$ Hz, 2H), 4.18 (ddd, $J = 6.3$, 8.4, 11.1 Hz, 1H), 4.25 (ddd, $J = 6.3$, 8.7, 11.1 Hz, 1H), 7.19–7.21 (m, 3H), 7.28–7.31 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.2, 20.0, 20.8, 23.5, 28.1, 30.9, 32.2, 33.4, 36.0, 36.9, 41.4, 41.5, 43.5, 54.1, 61.5, 72.1, 74.9, 126.2, 128.3 (2C), 128.4 (2C), 140.6, 173.1; HRMS (FAB) *m*/*z* calcd for $C_{24}H_{36}O_3Na$ (M+Na) 395.2562, found 395.2576.

4.6.2. (2′*S*,4′a*S*,8′a*S*)-(−)-2-(2′,5′,5′,8′a-Tetramethyloctahydrochromen-2′-yl)ethyl benzoate (8e). TLC (hexane–EtOAc, 12:1) $R_f = 0.40$; column chromatography, hexane–Et_2O = 25:1–20:1; HPLC (AD-H column, hexane–*i*-PrOH = 200:1, flow rate = 1.0 mL/min) $t_R = 7.9$ min for (+)-**8e**, 8.7 min for (−)-**8e**; GC (PEG, column temp 210 °C, 120 kPa) $t_R = 31.6$ min; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.77 (s, 3H), 0.89 (s, 3H), 1.16–1.71 (m, 11H), 1.28 (s, 3H), 1.31 (s, 3H), 1.83 (ddd, $J = 6.0$, 8.4, 13.8 Hz, 1H), 1.94 (ddd, $J = 6.0$, 8.1, 13.2 Hz, 1H), 4.44 (ddd, $J = 2.4$, 6.0, 11.1 Hz, 1H), 4.50 (ddd, $J = 1.8$, 8.1, 11.1 Hz, 1H), 7.43 (t, $J = 1.5$, 7.5 Hz, 2H), 7.55 (dd, $J = 1.5$, 7.5 Hz, 1H), 8.03 (dd, $J = 1.5$, 7.5 Hz, 2H).

4.6.3. (2′*S*,4′a*S*,8′a*S*)-(−)-2-(2′,5′,5′,8′a-Tetramethyloctahydrochromen-2′-yl)ethyl phenylacetate (8f). TLC (hexane–EtOAc–CH_2Cl_2, 4:1:1) $R_f = 0.62$; column chromatography, hexane–Et_2O = 15:1; HPLC (two linear AD-H columns, hexane–*i*-PrOH = 250:1, flow rate = 0.5 mL/min) $t_R = 39.7$ min for (+)-**8f**, 41.2 min for (−)-**8f**; GC (PEG, column temp 210 °C, 120 kPa) $t_R = 39.0$ min; IR (film) 2975, 2936, 1726, 1523, 1426, 1045 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.75 (s, 3H), 0.87 (s, 3H), 1.07–1.60 (m, 11H), 1.22 (s, 3H), 1.24 (s, 3H), 1.66 (ddd, $J = 6.3$, 8.4, 13.8 Hz, 1H), 1.78 (ddd, $J = 6.3$, 8.4, 13.8 Hz, 1H), 3.60 (s, 2H), 4.20 (ddd, $J = 6.3$, 8.4, 11.1 Hz, 1H), 4.26 (ddd, $J = 6.3$, 8.7, 11.1 Hz, 1H), 7.23–7.24 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.1, 20.7 (2C), 23.4, 28.0, 32.0 (2C), 36.7 (2C), 41.4 (2C), 43.3, 54.0, 61.8, 72.0, 74.6, 126.9, 128.4 (2C), 129.7 (2C), 134.1, 171.7; $[\alpha]_D^{22.8}$ −8.2 (*c* 1.0, $CHCl_3$) for >99% ee; HRMS (FAB) *m*/*z* calcd for $C_{23}H_{34}O_3Na$ (M+Na) 381.2406, found 381.2409.

4.6.4. (2′*S*,4′a*R*,8′a*R*)-(+)-2-(2′,5′,5′,8′a-Tetramethyloctahydrochromen-2′-yl)ethyl 3-phenylpropionate (9d). TLC (hexane–EtOAc, 4:1) $R_f = 0.66$; column chromatography, hexane–Et_2O = 15:1; HPLC (AD-H column, hexane–*i*-PrOH = 250:1, flow rate = 1.0 mL/min) t_R = 9.8 min for (−)-**9d**, 14.0 min for (+)-**9d**; GC (PEG, column temp 210 °C, 120 kPa) $t_R = 56.8$ min; IR (film) 2982, 2938, 2870, 1726 (C=O), 1456, 1375, 1180, 1100, 974 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.77 (s, 3H), 0.89 (s, 3H), 1.14 (s, 3H), 1.17–1.80 (m, 19H), 1.25 (s, 3H), 2.05 (quintet, $J = 7.5$ Hz, 1H), 2.61 (t, $J = 7.8$ Hz, 2H), 2.95 (t, $J = 7.8$ Hz, 2H), 4.15–4.27 (m, 2H), 7.19–7.21 (m, 3H), 7.28–7.32 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.2, 20.2, 20.8, 23.1, 30.5, 31.0, 32.2, 33.5, 36.0, 38.1, 39.4, 41.4, 42.0, 53.5, 61.9, 72.3, 75.3, 126.2, 128.3 (2C), 128.5 (2C), 140.5, 173.0; HRMS (FAB) *m*/*z* calcd for $C_{24}H_{36}O_3SeNa$ (M+Na) 395.2562, found 395.2576.

4.6.5. (2′*S*,4′a*R*,8′a*R*)-(+)-2-(2′,5′,5′,8′a-Tetramethyloctahydrochromen-2′-yl)ethyl Benzoate (9e). TLC (hexane–Et_2O–CH_2Cl_2, 12:1) $R_f = 0.32$; column chromatography, hexane–Et_2O = 20:1–15:1; HPLC (AD-H column, hexane–*i*-PrOH = 200:1, flow rate = 1.0 mL/min) t_R = 8.1 min for (−)-**9e**, 9.5 min for (+)-**9e**; GC (PEG, column temp 210 °C, 210 kPa) $t_R = 34.4$ min; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.78 (s, 3H), 0.90 (s, 3H), 1.12–1.70 (m, 10H), 1.23 (s, 3H), 1.32 (s, 3H), 1.84–1.95 (m, 2H), 2.17–2.30 (m, 1H), 4.40–4.51 (m, 2H), 7.43 (t, $J = 7.5$ Hz, 2H), 7.55 (t, $J = 7.5$ Hz, 1H), 8.04 (dd, $J = 1.5$, 7.5 Hz, 2H).

4.6.6. (2′*S*,4′a*R*,8′a*R*)-(+)-2-(2′,5′,5′,8′a-Tetramethyloctahydrochromen-2′-yl)ethyl phenylacetate (9f). TLC (hexane–Et_2O–CH_2Cl_2, 4:1:1) $R_f = 0.60$; column chromatography, hexane–Et_2O = 15:1–10:1; HPLC (AD-H column, hexane–*i*-PrOH = 250:1, flow rate = 1.0 mL/min) $t_R = 9.4$ min for (−)-**9f**, 12.8 min for (+)-**9f**; GC (PEG, column temp 210 °C, 120 kPa) $t_R = 40.1$ min; IR (film) 2976, 2936, 1727, 1523, 1426, 1045 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.76 (s, 3H), 0.88 (s, 3H), 1.11 (s, 3H), 1.12–1.82 (m, 12H), 1.24 (s, 3H), 2.05 (dd, $J = 5.7$, 8.1 Hz, 1H), 2.09 (dd, $J = 6.0$, 7.5 Hz, 1H), 3.60 (s, 2H), 4.15 (ddd, $J = 6.6$, 8.1, 11.1 Hz, 1H), 4.25 (ddd, J = 6.0, 8.4, 11.1 Hz, 1H), 7.24–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.1, 20.1, 20.8, 23.1, 30.5, 32.2, 33.4, 37.9, 39.3, 41.4, 41.5, 42.0, 53.3, 62.3, 72.2, 75.2, 127.0, 128.5 (2C), 129.3 (2C), 134.1, 171.6; $[\alpha]_D^{23.4}$ 23 (*c* 1.0, $CHCl_3$) for 98% ee; HRMS (FAB) *m*/*z* calcd for $C_{23}H_{34}O_3Na$ (M+Na) 381.2406, found 381.2409.

4.6.7. (2′*S*,4′a*S*,8′a*S*)-(−)-2-(2′,5′,5′,8′a-Tetramethyloctahydrochromen-2′-yl)ethanol (8a). To a solution of **8f** (100 mg, 0.58 mmol) in methanol (2 mL) at 0 °C was added 1 M aqueous LiOH (870 mL, 0.87 mmol). After stirring for an additional 1 h poured into brine and extracted with ether (twice). The combined organic phases were dried over anhydrous $MgSO_4$ and concentrated. The crude product was through pipette column on silica gel to give **8a** (139 mg, 0.58 mmol, 100% yield) as colorless oil. TLC (hexane–EtOAc, 2.5:1) $R_f = 0.37$; IR (film) 3550–3250 (br, OH), 2975, 2941, 2872, 1711, 1523, 1427, 1046, 929 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.77 (s, 3H), 0.90 (s, 3H), 1.21–1.75 (m, 13H), 1.29 (s, 3H), 1.32 (s, 3H), 3.72–3.88 (m, 2H), 4.04 (t, $J = 5.0$ Hz, OH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.1, 20.0, 20.8, 23.3, 27.6, 32.1, 33.4, 37.3, 41.3, 41.7, 45.8, 54.2, 59.7, 76.0, 76.1; $[\alpha]_D^{23.4}$ −6.4 (*c* 1.0, $CHCl_3$) for >99% ee; HRMS (FAB) *m*/*z* calcd for $C_{15}H_{28}O_2Na$ (M+Na) 263.1987, found 263.1980.

4.6.8. (2′*S*,4′a*S*,8′a*S*)-(−)-*o*-Nitrophenyl-2-(2′,5′,5′,8′a-tetramethyloctahydrochromen-2′-yl)ethylselenide (12). To a stirring solution of **8a** (166 mg, 0.69 mmol) and *o*-nitrophenyl selenocyanate (384 mg, 1.73 mmol) in dry THF (3 mL) under N_2 at room temperature was added tri-*n*-butylphosphine (427 mL, 1.73 mmol). After stirring for 3 h, quenched with ethanol and concentrated. The crude product was purified by column chromatography on silica gel (eluent: hexane–ether = 15:1) to give **12** (282 mg, 0.66 mmol, 96% yield) as yellow oil. TLC (hexane–EtOAc, 4:1) $R_f = 0.54$; HPLC (OD-H column, hexane–*i*-PrOH = 80:1, flow rate = 1.0 mL/min) $t_R = 6.7$ min for (+)-**12**, 8.0 min for (−)-**13**; IR (film) 2976, 2932, 1515, 1426, 1335, 1046, 929 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.78 (s, 3H), 0.90 (s, 3H), 1.16–1.73 (m, 11H), 1.28 (s, 3H), 1.30 (s, 3H), 1.78 (ddd, $J = 5.7$, 10.8, 13.4 Hz, 1H), 1.87 (ddd, $J = 5.7$, 11.1, 13.4 Hz, 1H), 2.97 (dt, $J = 5.8$, 12.4 Hz, 1H), 3.06 (dt, $J = 5.8$, 12.4 Hz, 1H), 7.30 (ddd, $J = 1.2$, 7.2, 8.2 Hz, 1H), 7.52 (ddd, $J = 1.2$, 7.2, 8.2 Hz, 1H), 7.74 (dd, $J = 1.2$, 8.2 Hz, 1H), 8.30 (dd, $J = 1.2$, 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.3, 20.1, 20.5, 20.8, 23.5, 27.4, 32.3, 33.5, 36.8, 41.5, 41.7, 44.5, 54.3, 73.2, 75.0, 125.0, 126.4, 129.2, 133.5, 134.4; $[\alpha]_D^{23.7}$ −9.0 (*c* 1.0, $CHCl_3$) for >99% ee; HRMS (FAB) *m*/*z* calcd for $C_{21}H_{31}O_3SeNa$ (M+Na) 448.1367, found 443.1383.

4.6.9. (5*S*,8*S*,10*S*)-(−)-Caparrapi oxide (1).[1,2,15] To a solution of **12** (276 mg, 0.65 mmol) in THF (15 mL) was slowly added 30% aqueous hydrogen peroxide (592 mL) at 0 °C. Stirring was maintained for 1 day at room temperature. Water was added, extracted with ether (twice), washed with water, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by column chromatography on silica gel (eluent: hexane–ether = 10:1) to give **1** (139 mg, 0.625 mmol, 96% yield) as colorless oil. TLC (hexane–EtOAc, 4:1) $R_f = 0.45$; GC (PEG, column temp 60 °C, 60 kPa) $t_R = 109.8$ min; GC (β-DM column, column temp 70 °C, 70 kPa) $t_R = 104.9$ min for (+)-**1**, $t_R = 108.6$ min for (−)-**1**; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.79 (s, 3H), 0.86 (s, 3H), 1.15–1.84 (m, 11H), 1.29 (s, 3H), 1.30 (s, 3H), 4.92 (dd, $J = 1.5$, 10.7 Hz, 1H), 5.15 (dd, $J = 1.5$, 17.4 Hz, 1H), 5.89 (dd, $J = 10.7$, 17.4 Hz, 1H); $[\alpha]_D^{22.7}$ −19 (*c* 0.065, $CHCl_3$) for >99% ee.

4.6.10. (2′*S*,4′a*R*,8′a*R*)-(+)-2-(2′,5′,5′,8′a-Tetramethyl-octahydrochromen-2′-yl)ethanol (9a). To a solution of **9f** (22 mg, 0.061 mmol) in methanol (1 mL) at 0 °C was added 1 M aqueous LiOH (92 mL, 0.092 mmol). After stirring for an additional 1 h poured into brine and extracted with ether (twice). The combined organic phases were dried over anhydrous $MgSO_4$ and concentrated. The crude product was through pipette column on silica gel to give **9a** (14.6 mg, 0.061 mmol, 100% yield) as colorless oil. TLC (hexane–EtOAc, 2.5:1) $R_f = 0.20$; IR (film) 3550–3250 (br, OH), 2976, 2941, 2872, 1523, 1427, 1046, 926 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.67 (s, 3H), 0.74 (s, 3H), 1.00–1.60 (m, 11H), 1.11 (s, 3H), 1.17 (s, 3H), 1.76–1.90 (m, 2H), 3.23 (br s, OH), 3.60 (quintet, $J = 5.1$ Hz, 1H), 3.79 (ddd, $J = 4.8$, 9.0, 11.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.6, 20.0, 20.5, 24.0, 28.8, 31.9, 33.7, 35.1, 41.5, 42.3, 44.0, 50.0, 60.0, 74.6, 75.5; $[\alpha]_D^{23.1}$ 29 (*c* 1.0, $CHCl_3$) for 98% ee; HRMS (FAB) *m*/*z* calcd for $C_{15}H_{28}O_2Na$ (M+Na) 263.1987, found 263.1978.

4.6.11. (2′*S*,4′a*R*,8′a*R*)-(+)-*o*-Nitrophenyl-2-(2′,5′,5′,8′a-tetramethyloctahydrochromen-2′-yl)ethyl-selenide (13). To a stirring solution of **9a** (19.2 mg, 0.080 mmol) and *o*-nitrophenyl selenocyanate (44.4 mg, 0.200 mmol) in dry THF (1 mL) under N_2 at room temperature was added tri-*n*-butylphosphine (49 mL, 0.200 mmol). After stirring for 3 h, quenched with ethanol and concentrated. The crude product was purified by column chromatography on silica gel (eluent: hexane–ether = 10:1) to give **13** (32.4 mg, 0.076 mmol, 95% yield) as yellow oil. TLC (hexane–EtOAc, 4:1) $R_f = 0.48$; IR (film) 2977, 2932, 1520, 1425, 1335, 1046, 929 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.78 (s, 3H), 0.90 (s, 3H), 1.18–1.90 (m, 12H), 1.24 (s, 3H), 1.28 (s, 3H), 2.19 (ddd, $J = 4.2$, 12.0, 14.1 Hz, 1H), 2.96 (dt, $J = 5.1$, 10.6 Hz, 1H), 3.06 (dt, $J = 3.9$, 106 Hz, 1H), 7.31 (ddd, $J = 1.5$, 6.9, 9.5 Hz, 1H), 7.52 (ddd, $J = 1.5$, 6.9, 9.5 Hz, 1H), 7.59 (dd, $J = 1.5$, 8.4 Hz, 1H), 8.31 (dd, $J = 1.5$, 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.1, 20.2, 20.8, 21.3, 22.9, 30.0, 32.2, 33.5, 37.9, 38.9, 41.4, 42.1, 53.3, 73.4, 75.4, 125.2, 126.4, 129.2, 133.6, 134.4; $[\alpha]_D^{23.7}$ 29 (*c* 1.0, $CHCl_3$) for 98% ee; HRMS (FAB) *m*/*z* calcd for $C_{21}H_{31}O_3SeNa$ (M+Na) 448.1367, found 448.1367.

4.6.12. (5*R*,8*S*,10*R*)-(+)-Epicaparrapi oxide (2).[4a,15] To a solution of **13** (21.3 mg, 0.050 mmol) in THF (1 mL) was slowly added 30% aqueous hydrogen peroxide (46 mL) at 0 °C. Stirring was maintained for 1 day at room temperature. Water was added, extracted with ether (twice), washed with water, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by column chromatography on silica gel (eluent: hexane–ether = 10:1) to give **2** (10.6 mg, 0.048 mmol, 96% yield) as colorless oil. TLC (hexane–EtOAc, 4:1) $R_f = 0.45$; GC (PEG, column temp 60 °C, 60 kPa) $t_R = 114.4$ min; GC (β-DM column, column temp 80 °C, 100 kPa) $t_R = 61.1$ min for (+)-**2**, $t_R = 66.6$ min for (−)-**2**; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.73 (s, 3H), 0.89 (s, 3H), 1.18–1.67 (m, 10H), 1.14 (s, 3H), 1.22 (s, 3H), 2.18–2.28 (m, 1H), 4.91 (dd, $J = 1.0$, 11.1 Hz, 1H), 4.97 (dd, $J = 1.0$, 18.0 Hz, 1H), 6.02 (dd, $J = 11.1$, 18.0 Hz, 1H); $[\alpha]_D^{23.0}$ 43 (*c* 1.1, EtOH) and $[\alpha]_D^{22.5}$ 48 (*c* 1.0, $CHCl_3$) for 98% ee.

4.7. Diastereoselective epoxidation of (+)-1 with peroxytrifluoroacetic acid (Table 3, entry 1)

To a stirred mixture of urea hydrogen peroxide (144 mg, 1.5 mmol), potassium hydrogen phosphate (230 mg, 1.32 mmol) and (+)-**1** (33 mg, 0.15 mmol) in CH_2Cl_2 (2 mL) was added trifluroacetic anhydride (54 mL, 0.38 mmol) dropwise at 0 °C. The resulting mixture was allowed to warm to room temperature and stirred for additional 3 h. A saturated solution of sodium hydrogen carbonate (1 mL) was added to neutralize the acids present and an aqueous layer was then extracted with CH_2Cl_2 (twice). The combined organic

layers were washed with water, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane–diethyl ether = 15:1–10:1) to give (+)-dysifragin (**4**, 17.5 mg, 0.073 mmol, 49% yield) as amorphous solid and its (+)-epimer (**14**, 17.3 mg, 0.073 mmol, 49% yield) as amorphous solid, respectively.

4.7.1. (+)-Dysifragin (4).[2] TLC (hexane–EtOAc, 4:1) $R_f = 0.55$; IR (film) 2998, 2938, 2868, 1459, 1377, 1101 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.78 (s, 3H), 0.89 (s, 3H), 1.19–1.71 (m, 11H), 1.22 (s, 3H), 1.28 (s, 3H), 2.65 (dd, $J = 4.0$, 5.5 Hz, 1H), 2.76 (dd, $J = 3.0$, 5.5 Hz, 1H), 2.82 (dt, $J = 3.0$, 4.0 Hz, 1H); For ^{13}C NMR ($CDCl_3$, 125 MHz), see Table 4; $[\alpha]_D^{21.3}$ 13 (*c* 1.3, $CHCl_3$) for 98% ee; HRMS (FAB) *m*/*z* calcd for $C_{23}H_{34}O_3Na$ (M+Na) 261.1830, found 261.1833.

4.7.2. (+)-Epidysifragin (14). TLC (hexane–EtOAc, 4:1) $R_f = 0.49$; IR (film) 2997, 2934, 2863, 1457, 1378, 1222, 1209, 1101 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.77 (s, 3H), 0.90 (s, 3H), 1.20–1.70 (m, 11H), 1.23 (s, 3H), 1.29 (s, 3H), 2.66 (dd, $J = 4.0$, 5.0 Hz, 1H), 2.71 (dd, $J = 3.0$, 5.0 Hz, 1H), 2.87 (dt, $J = 3.0$, 4.0 Hz, 1H); For ^{13}C NMR ($CDCl_3$, 125 MHz), see Table 4; $[\alpha]_D^{21.5}$ 15 (*c* 0.080, $CHCl_3$) for 98% ee; HRMS (FAB) *m*/*z* calcd for $C_{23}H_{34}O_3Na$ (M+Na) 261.1830, found 261.1827.

4.7.3. (1*R*,2′*R*,4′a*R*,8′a*R*)-1-(2′,5′,5′,8′a-Tetramethyloctahydrochromen-2′-yl)ethanol (15).[16] To a solution of (+)-**4** (10 mg, 0.04 mmol) in Et_2O (2 mL) was added $LiAlH_4$ (11 mg, 0.3 mmol) at 0 °C, and allowed to warm to room temperature. After being stirred for 3 h at the same temperature, excess $LiAlH_4$ was decomposed with EtOAc, then with H_2O at 0 °C. Anhydrous Na_2SO_4 was added and stirred for 30 min at room temperature. The resulting mixture was filtered, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by flash column chromatography on silica gel (eluent: hexane–diethyl ether = 5:1) to give **15** (9 mg, 0.038 mmol, 95% yield) as colorless oil. TLC (hexane–EtOAc, 4:1) $R_f = 0.45$; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.76 (s, 3H), 0.89 (s, 3H), 1.06 (d, $J = 6.6$ Hz, 1H), 1.15 (s, 3H), 1.20–1.66 (m, 11H), 1.27 (s, 3H), 2.76 (d, $J = 5.1$ Hz, OH), 3.26–3.41 (m, 1H); For ^{13}C NMR ($CDCl_3$, 75 MHz), see Table 4.

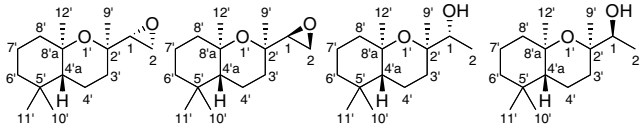
4.7.4. (1*S*,2′*R*,4′a*R*,8′a*R*)-1-(2′,5′,5′,8′a-Tetramethyloctahydrochromen-2′-yl)ethanol (16).[16] To a solution of (+)-**14** (12 mg, 0.05 mmol) in Et_2O (2 mL) was added $LiAlH_4$ (11 mg, 0.3 mmol) at 0 °C, and allowed to warm to room temperature. After being stirred for 3 h at the same temperature, excess $LiAlH_4$ was decomposed with EtOAc, then with H_2O at 0 °C. Anhydrous Na_2SO_4 was added and stirred for 30 min at room temperature. The resulting mixture was filtered, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by flash column chromatography on silica gel (eluent: hexane–diethyl ether = 5:1) to give **16** (9.6 mg, 0.04 mmol, 80% yield) as colorless oil. TLC (hexane–EtOAc, 4:1) $R_f = 0.36$; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.77 (s, 3H), 0.90 (s, 3H), 1.04 (d, $J = 6.3$ Hz, 1H), 1.10–1.82 (m, 11H), 1.20 (s, 3H), 1.32 (s, 3H), 3.05 (s, OH), 3.48 (ddd, $J = 2.0$, 6.9, 13.6 Hz, 1H); For ^{13}C NMR ($CDCl_3$, 75 MHz), see Table 4.

4.7.5. X-ray crystallographic analysis of (+)-4. Compound (+)-**4** was crystallized without any solvents at −25 °C. Crystal data: $C_{15}H_{26}O_2$, $M = 238.36$, crystal dimensions $0.30 \times .20 \times 0.07$ mm^3, orthorhombic, space group $P2_12_12_1$ (#19), $a = 6.9005$ (19), $b = 11.488$ (3), $c = 17.729$ (5) Å, $V = 1405.4$ (7) Å^3, $Z = 4$, $D_c = 1.127$ g/cm^3, $T = 223$ K. X-ray crystallographic analysis was performed with a Bruker SMART APEX CCD diffractometer (graphite monochromator, MoKα radiation, $\lambda = 0.71073$ Å). The structure was solved by direct methods and expanded using Fourier techniques. Three thousand six hundred and fifty one reflections were independent and unique, and 2018 with $I > 2\sigma(I)$ ($2\theta_{max} = 29.09°$) were used for the solution of the structure. The non-hydrogen atoms were refined anisotropically. $R = 0.0544$ and $Rw = 0.1110$.

Crystallographic data have been deposited with Cambridge Crystallographic Data Centre: Deposition number CCDC 265385 for (+)-**4**. Copy of the data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; Fax: +44 1223 336033; e-mail deposit@ccdc.cam.ac.uk).

4.7.6. Epoxide inversion from (+)-14 to (+)-4.[17] Cesium propionate (168 mg, 0.6 mmol) and 18-crown-6 (95 mg, 0.36 mmol) were added to the flask and removed moistures under high-vacuum pressure (0.04 mmHg) while stirring overnight. Dry toluene (4 mL) and freshly distilled AcOH (7 mL, 0.12 mmol) were added to the flask and the mixture was vigorously stirred. When the

Table 4. ^{13}C chemical shifts (δ) of (+)-**4**, (+)-**14**, **15**, and **16**



(+)-**4** (+)-**14** **15** **16**

C(*n*)	(+)-**4**	(+)-**14**	Δδ((+)-**4**, (+)-**14**)	**15**	**16**	Δδ((+)-**15**, (+)-**16**)
C(1)	59.8	59.9	−0.1	**75.7**	**73.2**	**+2.5**
C(2)	43.9	43.8	+0.1	16.3	15.3	+1.0
C(2′)	70.7	71.2	−0.5	75.2	76.4	−1.2
C(3′)	33.7	33.6	+0.1	**34.4**	**29.4**	**+5.0**
C(4′)	20.0	20.0	±0	20.0	20.0	±0
C(4′a)	53.0	53.7	−0.7	54.1	54.5	−0.4
C(5′)	33.5	33.6	−0.1	33.4	33.4	±0
C(6′)	41.4	41.5	−0.1	41.5	41.4	+0.1
C(7′)	15.9	15.7	+0.2	16.0	15.7	+0.3
C(8′)	41.4	41.5	−0.1	41.7	41.7	±0
C(8′a)	75.0	75.3	−0.3	75.1	75.8	−0.7
C(9′)	23.7	23.5	+0.2	23.4	23.2	+0.2
C(10′)	32.0	32.1	−0.1	32.1	32.1	±0
C(11′)	20.8	20.8	±0	20.8	20.8	±0
C(12′)	24.6	24.2	+0.4	**21.7**	**24.2**	**−2.5**

solids dispersed, (+)-**14** (14 mg, 0.06 mmol) was added, and the resulting mixture was heated to reflux for 3 days. Poured in to aqueous $NaHCO_3$ and extracted with EtOAc (three times). The combined organic layers were washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was through pipette column on silica gel to give a mixture of regioisomeric propionates, **19** and **20** (2:1 on TLC, 17 mg, 0.055 mmol, 92% yield), and used next step without further purification. Distilled MsCl (10 mL, 0.11 mmol) was added to a stirred solution of **19**, **20**, *N*,*N*-diisopropylethylamine (26 μL, 0.15 mmol), and DMAP (15 mg, 0.12 mmol) in CH_2Cl_2 was added dropwise at −10 °C. The reaction mixture was stirred for additional 3 h at −10 to 0 °C, quenched with NH_4Cl (aq), and the aqueous layer was extracted with Et_2O (twice). The combined organic layer was washed with water, dried over anhydrous $MgSO_4$, concentrated, and used in next step without further purification. To a mixture of regioisomeric mesylates were added MeOH (2.5 mL) and K_2CO_3 (4 mg, 0.022 mmol), and stirred for 12 h at room temperature. After the reaction was completed, the resultant mixture was passed through a short-column chromatography on silica gel, and concentrated under reduced pressure. The residue was purified on flash column chromatography on silica gel (eluent: hexane–diethyl ether = 10:1) to give (+)-**4** (11.5 mg, 0.048 mmol, 88% yield in two steps) as amorphous solid.

Acknowledgments

Financial support for this project was provided by SORST, Japan Science and Technology Agency (JST), JSPS.KAKENHI (15205021), the Mitsubishi Foundation, the Uehara Memorial Foundation, the Kowa Life Science Foundation, and the 21st Century COE program 'Nature-Guided Materials Processing' of MEXT. We also acknowledge Dr. Manabu Hatano for the single-crystal X-ray analysis.

References and notes

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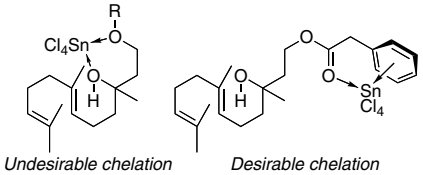
9. Predictable chelation structures of **7** with $SnCl_4$ are shown below. Further studies to elucidate the existence of some attractive interaction between Sn(IV) and a phenyl group of **7e** and **7f** are currently in progress in our laboratory, and our results will be reported in due course



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