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Asymmetric total synthesis of rhinacanthin A

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ABSTRACT

Starting from a reduced lapachol compound, the total synthesis of rhinacanthin A in both racemic and enantioenriched forms is achieved in eight steps without forming any undesired β-lapachone derivatives. For the synthesis of enantioenriched rhinacanthin A, the introduction of the asymmetric center was carried out by using the catalytic asymmetric epoxidation of an unfunctional trisubstituted olefin using Shi's epoxidation diketal catalyst. The acidic treatment of a derived enantioenriched epoxynaphthol and the following CAN oxidation afforded the target molecule with high enantiomeric purity.

1. Introduction

Naturally occurring naphthoquinones, such as lapachol, and its related 1,2- and 1,4-naphthoquinones, are found as biologically active pharmacophores. Over the course of our studies on its antiproliferative activity,[1] we have previously reported a convenient total synthesis of rhinacanthin C, which has antitumor activity. To date, 15 naphthoquinones have been isolated from *Rhinacanthus nastus* (L.) Kurz (Acanthaceae), a shrub widely distributed in South China and India, which have been named rhinacanthins A–D and G–Q.[2] From the 15 rhinacanthins, optically active rhinacanthins A **1**, B, O, and P, can be distinguished from other rhinacanthins by the presence of a tricyclic ring system containing a 1,4-naphthoquinone and a 2,2-dimethyldihydropyran ring, as shown in Figure 1. Rhinacanthins B, O, and P, are esters of **1** and (2*E*,6*E*)-2,6-dimethyl-2,6-octadienoic acid or its derivatives (Fig. 1).

Although studies on the biological activity of rhinacanthins are available, synthetic studies on rhinacanthin A including an asymmetric synthesis have not been reported to date. For example, Campillo et al. reported the synthesis of β-lapachone derivatives from lapachol, and also reported that racemic rhinacanthin A *rac*-**1** (α-lapachone analogue) was obtained as a minor product in less than 1 % yield.[3] This prompted us to establish a synthetic route for *rac*-**1** and then to extend the synthetic path for the asymmetric synthesis of **1**. Herein we report the total synthesis of both racemic and optically active **1**. The introduction of the asymmetric center in the target molecule was carried out by the catalytic asymmetric epoxidation of reduced lapachol equivalent compound (trisubstituted olefin compound **X**) using a Shi epoxidation diketal catalyst (Figs. 2 and 3).

2. Results and discussion

2.1. Synthesis of racemic rhinacanthin A

The synthetic strategy toward **1** is shown in Figure 3. It is known that the epoxidation of lapachol by MCPBA preferentially affords a β-lapachone derivative with a trace amount of an α-lapachone derivative (Fig. 3, route A).[3] Thus, we planned our synthetic route to obtain precursor **Z** by the epoxidation of the reduced lapachol equivalent compound **X** followed by the intramolecular epoxide ring opening reaction of the epoxynaphthol, obtained from the deprotection of R′ in **Y**. For example, the selective removal of 2-O-protective group from *O*-R groups in **Y** was inevitable in order to obtain epoxynaphthol for the construction of **Z** (Fig. 3, route B). As for our actual experiment, we selected a TBS group for the 2-hydroxy protection in the reduced lapachol equivalent compound **2**. Initially we tried to prepare **4** by the metalation–substitution reaction of **3**, but the migration of the TBS group was observed and we obtained **5**; hence no desired product **4** was obtained. To overcome this obstacle, we selected a MOM group as a temporary protecting group during the introduction of a prenyl group and exchanged it with a TBS group before epoxidation, even though extra steps for the removal of the MOM group and protection of a TBS group were needed (Scheme 1).

As shown in Scheme 1, starting from 1,4-dimethoxy-2-hydroxynaphthalene **2**, 1,4-dimethoxy-2-(methoxymethoxy)naphthalene **6** was synthesized in high yield (93%) and converted to **7** by the metalation–substitution reaction in 84% yield. The exchange of a protecting group from MOM to TBS was straightforward as shown in Scheme 2. The labile hydroxy function in naphthol **8** under ambient conditions was immediately protected to the TBS ether. Epoxide formation of the prenyl function in **4** was carried out with MCPBA to afford **9**. Additionally, **7** and **8** were also converted to the corresponding epoxides **10** and **11**, respectively, because **10** and **11**

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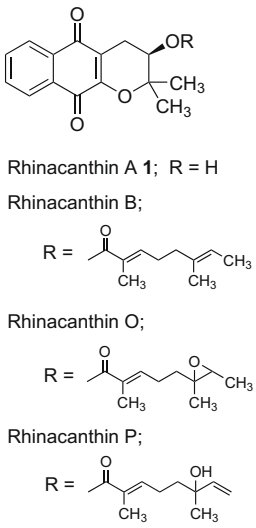


Figure 1. Chemical structures of rhinacanthin A, B, O, and P.

might also become appropriate candidates for the preparation of **12** (Scheme 2). The thus obtained epoxides were exposed to acidic conditions to afford **12**, the racemic **1** precursor. Treatment of **10** with 50% H_2SO_4 afforded **12** at most in 34% yield and with many by-products. One of them was identified as a ring-opened compound of the epoxide with no MOM signal on ^1H NMR analysis (compound **13** in Scheme 2). This indicated that the in situ preparation of epoxynaphthol **11** and the following acid-catalyzed intramolecular epoxide ring opening by only pH control were difficult. Furthermore, the epoxidation of **8** with MCPBA was unsatisfactory and gave undesired naphthoquinones as by-products, although **11** was formed in 65% yield. The one-pot reaction of TBS deprotection and the following intramolecular epoxide ring opening of **9** in acidic solution did not proceed at all. The ordinary deprotection of a TBS group in **9** and the ensuing acidic treatment of **11** at room temperature promoted the intramolecular ring opening of an epoxide function to afford **12** in high yield (92%). Finally, conversion of dimethoxynaphthalene **12** to *rac*-**1** was achieved by CAN oxidation in 88%. This material showed analytical and spectroscopic data consistent with those in the literature in all respects[2] (Scheme 2).

2.2. Synthesis of optically active rhinacanthin A

Next, our attention was focused on the preparation of the enantioenriched epoxide of **9** with an (*R*)-configuration and on achieving the asymmetric total synthesis of **1**. For the synthesis of (*R*)-**9**, it was necessary to achieve the highly enantioselective oxidation of an unfunctional trisubstituted olefin (prenyl group). To date, a number of useful methods for the asymmetric oxidation of olefins have been developed. One of them is a well known catalytic asymmetric epoxidation mediated by manganese-*N*′,*N*′-bis(salicylidene)ethylenediamine dianion (salen)Mn(III).[4] Another method is the chiral bishydroxamic acid–molybdenum (BHA–Mo)-mediated catalytic epoxidation developed by Yamamoto et al.[5] Furthermore, a highly enantioselective epoxidation of *trans* olefins or trisubstituted olefins using a fructose-derived diketal catalyst has recently been reported by Shi et al.[6] Using their procedures, epoxidations of **4** with (salen)Mn(III) complex, chiral BHA–Mo complex, Shi epoxidation diketal catalyst, and the appropriate oxidants were carried out. Chiral BHA ligand was prepared according to the literature,[5] and the commercially available (salen)Mn(III) complex and Shi epoxidation diketal catalyst were purchased (Tables 1 and 2).

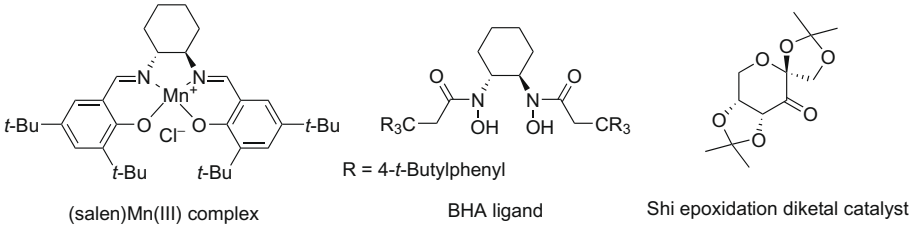


Figure 2. Structures of chiral ligands for asymmetric epoxidation.

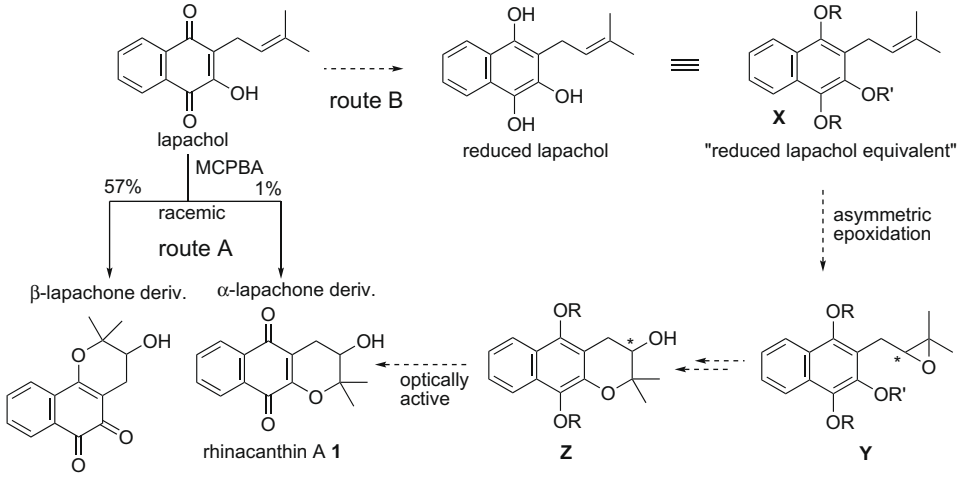
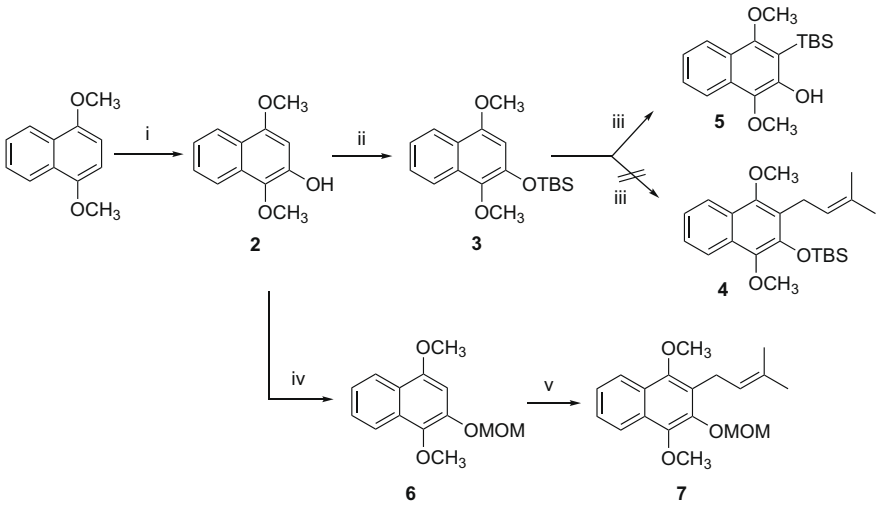


Figure 3. Synthetic strategy toward rhinacanthin A.

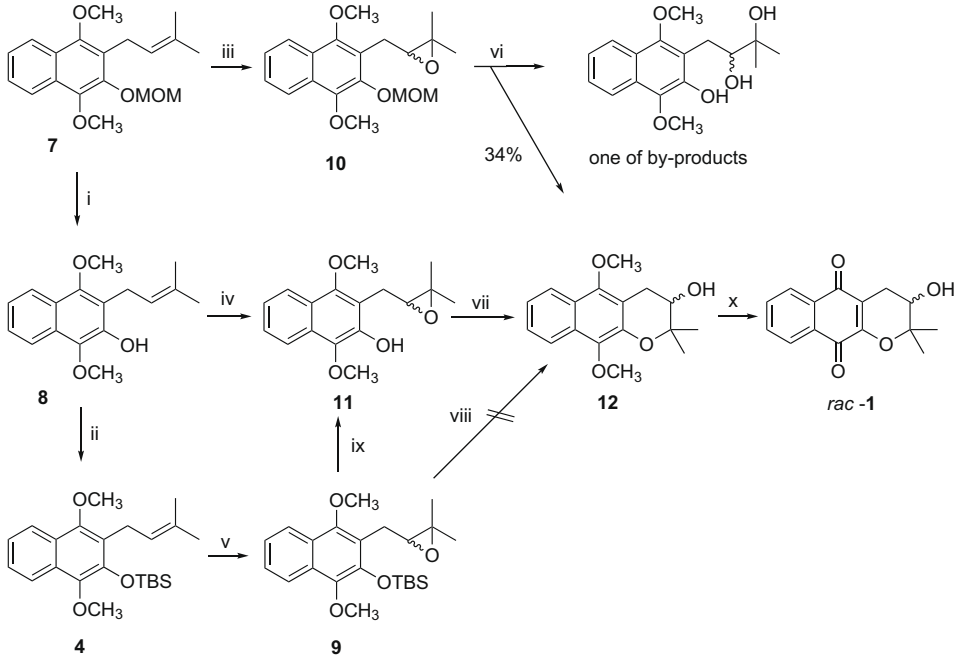


Scheme 1. Reagents and conditions: (i) (1) *sec*-BuLi, TMEDA, −78 °C, THF, 1 h; (2) $B(OCH_3)_3$, 3 h; (3) H_2O_2, AcOH, 16 h, 97%; (ii) TBSCl, imid, DMAP, DMF, 82%; (iii) *n*-BuLi, THF, 0 °C, 1 h, then prenyl bromide at −78 °C, 82%; (iv) NaH, MOMCl, DMF, 93%; (v) *n*-BuLi, THF, −78 °C, 1 h, then prenyl bromide, 84%.

As can be seen from Table 1, compound **4** was not a suitable substrate for both (salen)Mn(III)-catalyzed and chiral BHA–Mo-catalyzed reactions. The epoxide formation proceeded to some extent under all the different reaction conditions but the enantiodiscrimination was not satisfactory (Table 1). On the other hand, the chiral dioxirane species prepared in situ from the Shi epoxidation diketal catalyst and Oxone in buffered media promoted the epoxidation reaction to afford optically active **9** in good chemical yield with high enantioselectivity (Table 2). In reference to the Shi report, the absolute (*R*)-configuration of **9** was suggested.[6] The absolute configuration of the enantioenriched epoxide **9** was finally determined as (*R*) by comparing the measured specific rotation of synthetic **1** derived from TBS deprotection, acidic epoxide ring opening, and oxidation with CAN of enantioenriched **9**, with that of **1** reported by Wu et al.[2] (Scheme 3). Thus, (*R*)-**9** was converted to **1** via (*R*)-**12** as shown in Scheme 3. The enantiomeric excess of synthetic **1** (82% ee) was increased by recrystallization from hexane/AcOEt to afford enantiomerically pure **1** (>99% ee).

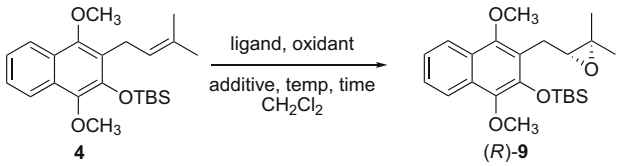
3. Conclusion

We have established the synthesis of racemic rhinacanthin A **1** via reduced lapachol equivalent compound **4** in 47% yield over eight steps from **2**. Using the same pathway for the racemic route, we have also achieved the asymmetric synthesis of **1** in 49% yield in eight steps from **2** with high enantiomeric purity. As for the introduction of the asymmetric center of (*R*)-**9**, the asymmetric epoxidation of **4** by a chiral dioxirane species prepared in situ from



Scheme 2. Reagents and conditions: (i) TFA, CH_2Cl_2, 0 °C, 2 h, 91%; (ii) NaH, TBSCl, DMF, 4 h, 90%; (iii) MCPBA, $NaHCO_3$ aq, $CHCl_3$, rt, 1 h, 98%; (iv) MCPBA, $CHCl_3$, rt, 1 h, 65%; (v) MCPBA, $NaHCO_3$ aq, $CHCl_3$, rt, 88%; (vi) 50% H_2SO_4, CH_2Cl_2, rt, 16 h, 34%; (vii) 50% H_2SO_4, CH_2Cl_2, rt, 2 h, 92%; (viii) 50% H_2SO_4, CH_2Cl_2, rt, 16 h; (ix) TBAF, AcOH, THF, rt, 1 h, quant; (x) CAN, CH_3CN, rt, 1 h, 88%.

Table 1

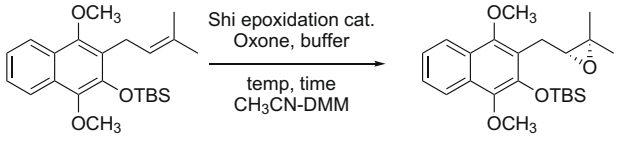


4 (*R*)-**9**

Entry	Ligand	Oxidant	Additive	Temp (°C)	Time (h)	Yield (%)	ee (%)
1	(salen)Mn(III)[a]	MCPBA	NMO	−40	16	13	49
2	(salen)Mn(III)[a]	MCPBA	NMO	−20	72	13	45
3	BHA–Mo[b]	CHP	—	0	18	36	43
4	BHA–Mo[b]	CHP	—	−5	42	23	30
5	BHA–Mo[b]	CHP	—	−10	40	29	33

[a] See the structure of (salen)Mn(III) in Figure 3.
[b] See the structure of BHA–Mo in Figure 3.

Table 2



4 (*R*)-**9**

Entry	Buffer[a]	Temp (°C)	Time (h)	Yield (%)	ee (%)
1	A	−10	5	58	83
2	B	−10	5	93	83
3	B	−10	2	71	83
4	A	rt	5	80	68

[a] Buffer A; 0.2 M K_2CO_3/AcOH pH 8.0; buffer B; 0.05 M $Na_2B_4O_7{\cdot}10H_2O$/4×10^{-4} M Na_2(EDTA)aq.

the Shi epoxidation diketal catalyst and Oxone in buffered media was found to be highly effective. The synthetic application of this methodology to the total synthesis of rhinacanthins B, O, and P is currently in progress.

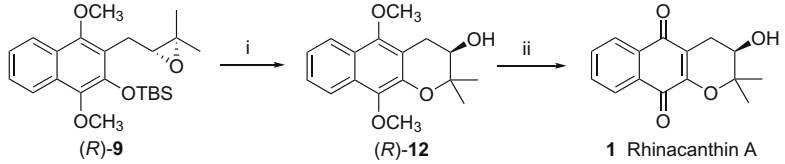
4. Experimental

4.1. General methods

All materials not explicitly mentioned were purchased from Wako Pure Chemical Products Co., Kanto Chemical Co., TCI Laboratory Chemicals Co., and Aldrich Chemical Co. ^{1}H NMR spectra were recorded on a JEOL JNM-ECP400 or JNM-ECP500 spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts are recorded in parts per million (ppm) relative to TMS. ^{13}C NMR spectra were proton decoupled and recorded on a JEOL JNM-ECP400 or JNM-ECP500 spectrometers using the carbon signal of the deuterated solvent as the internal standard. Mass spectra (MS) were obtained on JEOL JMS-700 instruments. Optical rotations were measured on a P-1020 (Japan Spectroscopic Co.) polarimeter at the sodium D-line and ambient temperature. Analytical HPLC was performed on a Waters 600E/484 unit and the wavelength detector was operated at 254 nm. Chiral HPLC analyses were performed using CHIRALPAK AD-H or CHIRALPAK-IC columns at room temperature unless stated otherwise. Enantiomeric purity assays using chiral HPLC columns were completed with both racemic and enantioenriched materials and were repeated at least once in order to ensure accuracy of the method used. Melting points were measured on a Yanaco micro melting point apparatus and are uncorrected. Flash chromatography was performed with silica gel (Wakosil C-200) obtained from Wako Pure Chemical Products Co. Analytical thin layer chromatography was performed on Merck Silica Gel 60 F_{254} aluminum sheets and the visualization was accomplished by UV lamp.

4.2. 2-Hydroxy-1,4-dimethoxynaphthalene 2

At first, *sec*-BuLi (60 mL, 60 mmol) was added to a solution of dehydrated tetrahydrofuran (THF) (140 mL) and *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) (9.0 mL, 60 mmol) at −80 °C under an argon atmosphere. The mixture was stirred for 15 min, and 1,4-dimethoxynaphthalene (3.76 g, 20 mmol) dissolved in THF (40 mL) was slowly added via a cannula. The yellow mixture was stirred for 1 h at 0 °C. To a separately prepared $B(OCH_3)_3$ (6.7 mL, 60 mmol) solution in THF (40 mL), the organolithium reagent prepared as stated above was added via a cannula over a period of 2 h at −80 °C, and then the mixture was stirred for 1 h at 0 °C. Next, AcOH (5 mL), and 30–35% H_2O_2 (11.6 mL) were added to the mixture. Stirring was continued for 16 h at room temperature, and then, the mixture was worked up as follows. The solvent was evaporated under reduced pressure, and water (50 mL) was added to the remaining residue. The aqueous layer was extracted with Et_2O. The combined organic layer was extracted with 5% aq KOH (50 mL × 5). The combined aqueous layer was adjusted to pH 6 at 0 °C. The aqueous mixture was saturated by NaCl solid, and



(*R*)-**9** (*R*)-**12** **1** Rhinacanthin A

82% ee
$[\alpha]_D^{24} = -10.8$ (*c* 1.0, $CHCl_3$)

83% ee
$[\alpha]_D^{25} = -6.1$ (*c* 1.0, $CHCl_3$)

82% ee
$[\alpha]_D^{25} = -14.0$ (*c* 1.0, $CHCl_3$)
lit.$[\alpha]_D^{25} = -12.9$ (*c* 1.0, $CHCl_3$)

Scheme 3. Reagents and conditions: (i) (1) TBAF, AcOH, THF, 0 °C; (2) 50% H_2SO_4, CH_2Cl_2, rt, 90%; (ii) CAN, CH_3CN, 0 °C, 87%.

extracted with Et_2O (50 mL × 5). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography (AcOEt/*n*-hexane = 1:2) to provide **2** as a pale yellow solid (3.94 g, 97%). Mp 94–95 °C, recrystallized from *n*-hexane/AcOEt. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.91 (s, 3H), 3.96 (s, 3H), 5.76 (m, 1H), 6.59 (s, 1H), 7.31 (td, 1H, *J* = 8.4, 1.1 Hz), 7.50 (td, 1H, *J* = 8.4, 1.1 Hz), 7.86 (d, 1H, *J* = 8.4 Hz), 8.16 (d, 1H, *J* = 8.4 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.7, 61.6, 96.7, 120.0, 121.5, 122.7, 122.8, 127.1, 128.4, 133.2, 145.4, 153.2.

4.3. 2-*tert*-Butyldimethylsilyloxy-1,4-dimethoxynaphthalene 3

Imidazole (855 mg, 12.6 mmol) and 4-(dimethylamino)pyridine (DMAP) (375 mg) were added to a solution of **2** (1.84 g, 9 mmol) in dehydrated *N*,*N*-dimethylformamide (DMF) (50 mL). The mixture was cooled to 0 °C, and *tert*-butylchlorodimethylsilane (TBSCl) (1.62 g, 10.8 mmol) was added slowly. The mixture was stirred for 3 h at room temperature and worked up. Next, satd aq $NaHCO_3$ (20 mL) and Et_2O were added at 0 °C and separated. The aqueous layer was extracted three times with Et_2O. The combined organic layer was washed with water, brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product (3.0 g) was purified by flash chromatography (AcOEt/*n*-hexane = 1:6) to provide 2.14 g of **3** (82%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.23 (s, 6H), 1.06 (s, 9H), 3.86 (s, 3H), 3.94 (s, 3H), 6.44 (s, 1H), 7.33 (td, 1H, *J* = 8.4, 1.5 Hz), 7.48 (td, 1H, *J* = 8.4, 1.5 Hz), 8.00 (d, 1H, *J* = 8.4 Hz), 8.13 (d, 1H, *J* = 8.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.5(2C), 18.4, 25.8(3C), 55.7, 60.7, 101.7, 121.1, 122.1, 122.2, 123.4, 126.7, 129.6, 138.4, 144.3, 152.2. HRMS (EI$^+$): *m/z* calcd for $C_{18}H_{26}O_3Si$: 318.1651; found: 318.1650.

4.4. 2-*tert*-Butyldimethylsilyl-3-hydroxy-1,4-dimethoxynaphthalene 5

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.48 (s, 6H), 0.92 (s, 9H), 3.89 (s, 3H), 3.91 (s, 3H), 6.05 (s, 1H), 7.31 (td, 1H, *J* = 8.1, 1.1 Hz), 7.47 (td, 1H, *J* = 8.1, 1.1 Hz), 7.88 (d, 1H, *J* = 8.1 Hz), 7.99 (d, 1H, *J* = 8.1 Hz).

4.5. 1,4-Dimethoxy-2-(methoxymethoxy)naphthalene 6

At first, NaH (1.6 g, 40 mmol, 60% dispersion in mineral oil) was slowly added to a solution of **2** (4.08 g, 20 mmol) in DMF (75 mL) at 0 °C. Gas evolution was observed, and the yellow suspension turned to a brown solution. After 1 h stirring at room temperature, MOMCl (3 mL, 40 mmol) was slowly added at 0 °C, and the mixture was warmed up to room temperature in 30 min. Next, satd aq NH_4Cl was carefully added to the reaction mixture. The reaction mixture was extracted with Et_2O, and the organic layer was washed with water, brine, dried over $MgSO_4$, and concentrated under reduced pressure. The remaining residue was purified by flash chromatography to afford **6** as a pale yellow oil (4.6 g, 93 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.59 (s, 3H), 3.94 (s, 3H), 3.97 (s, 3H), 5.31 (s, 2H), 6.77 (s, 1H), 7.37 (td, 1H, *J* = 8.4, 1.1 Hz), 7.50 (td, 1H, *J* = 8.4, 1.1 Hz), 8.04 (d, 1H, *J* = 8.4 Hz), 8.15 (d, 1H, *J* = 8.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.8, 56.4, 61.3, 96.6, 98.2, 121.2, 122.1, 122.5, 123.9, 126.8, 129.3, 137.9, 145.8, 152.4. HRMS (EI$^+$): *m/z* calcd for $C_{14}H_{16}O_4$: 248.1049; found: 248.1053.

4.6. 1,4-Dimethoxy-2-(methoxymethoxy)-3-(3-methylbut-2-enyl)-naphthalene 7

To a 0 °C stirred solution of **6** (1.08 g, 4.35 mmol) in THF (6.6 mL), *n*-BuLi (3.2 mL, 5.12 mmol, 1.6 M solution in hexane) was added dropwise under an argon atmosphere. After 2 h stirring at room temperature, the mixture was cooled to −80 °C, followed by dropwise addition of prenyl bromide (1 mL, 8.44 mmol). The mixture was allowed to warm up to room temperature in 30 min. AcOEt and satd aq NH_4Cl were added to the mixture and separated. The aqueous layer was extracted three times with AcOEt. The combined organic layer was washed with 1% aq $Na_2S_2O_3$, water, brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product (1.5 g) was purified by flash chromatography (AcOEt/*n*-hexane = 1:6) to provide 1.15 g of **7** as a yellow oil (84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.70 (s, 3H), 1.83 (s, 3H), 3.59 (s, 2H), 3.61 (s, 3H), 3.89 (s, 3H), 3.93 (s, 3H), 5.26 (s, 2H), 5.30 (m, 1H), 7.41–7.46 (m, 2H), 8.00–8.07 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.0, 24.3, 25.7, 57.6, 61.0, 62.1, 99.6, 121.7, 122.2, 123.3, 124.9, 125.0, 125.7, 127.3, 128.1, 131.5, 143.4, 145.6, 150.4. HRMS (EI$^+$): *m/z* calcd for $C_{19}H_{24}O_4$: 316.1675; found: 316.1676.

4.7. 2-Hydroxy-1,4-dimethoxy-3-(3-methylbut-2-enyl)naphthalene 8

To a 0 °C stirred solution of **7** (1.83 g, 5.8 mmol) in dehydrated dichloromethane (CH_2Cl_2) (20 mL), trifluoroacetic acid (TFA) (1.08 mL, 14.5 mmol) was slowly added. The mixture was stirred for 2 h at this temperature, and then quenched by the addition of water. The organic layer was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. The remaining residue was purified by flash chromatography (AcOEt/*n*-hexane = 1:6) to provide 1.43 g of **8** (91 %) as a brown oil. This compound was unstable in ambient air, and used in the next step (TBS-protection reaction of naphthol function) without any purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.71 (s, 3H), 1.84 (s, 3H), 3.58 (d, 2H, *J* = 7.0 Hz), 3.90 (s, 3H), 3.95 (s, 3H), 5.28–5.34 (m, 1H), 5.88 (s, 1H), 7.33 (td, 1H, *J* = 8.4, 1.5 Hz), 7.44 (td, 1H, *J* = 8.4, 1.5 Hz), 7.90 (d, 1H, *J* = 8.4 Hz), 8.01 (d, 1H, *J* = 8.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.9, 23.9, 25.7, 61.6, 62.3, 120.4, 122.0, 122.4, 122.6, 123.3, 123.4, 125.8, 126.8, 132.2, 136.4, 144.9, 150.7. HRMS (EI$^+$): *m/z* calcd for $C_{17}H_{20}O_3$: 272.1412; found: 272.1406.

4.8. 2-*tert*-Butyldimethylsilyloxy-1,4-dimethoxy-3-(3-metylbut-2-enyl)naphthalene 4

At first, NaH (123 mg, 3.08 mmol, 60% dispersion in mineral oil) was slowly added to a solution of **8** (600 mg, 2.2 mmol) in DMF (10 mL) at 0 °C. After 1 h stirring at room temperature, TBSCl (462 mg, 3.08 mmol) was added to the reaction mixture at 0 °C. After stirring for 1 h at room temperature, Et_2O and satd aq NH_4Cl were added and separated. The aqueous layer was extracted three times with Et_2O. The combined organic layer was washed with water, brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash chromatography to provide 764 mg of **4** (90%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.25 (s, 6H), 1.03 (s, 9H), 1.68 (s, 3H), 1.79 (s, 3H), 3.54 (d, 2H, *J* = 6.7 Hz), 3.82 (s, 3H), 3.87 (s, 3H), 5.24–5.28 (m, 1H), 7.36 (td, 1H, *J* = 8.4, 1.5 Hz), 7.42 (td, 1H, *J* = 8.4, 1.5 Hz), 7.99 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.0 (2C), 18.1, 18.8, 24.4, 25.6, 26.2(3C), 60.9, 62.0, 121.4, 122.2, 123.4, 123.9, 124.4, 125.5, 126.8, 127.9, 131.2, 141.3, 144.1, 150.5. HRMS (EI$^+$): *m/z* calcd for $C_{23}H_{34}O_3Si$: 386.2277; found: 386.2281.

4.9. 2-*tert*-Butyldimethylsilyloxy-1,4-dimethoxy-3-((3,3-dimethyloxiran-2-yl)methyl)-naphthalene 9 (racemate)

At first, 0.5 M aq $NaHCO_3$ (2.3 mL) was added to a stirred solution of **4** (447 mg, 1.16 mmol) in $CHCl_3$ (12 mL). Next, MCPBA (290 mg, 1.16 mmol; a commercially available 70% MCPBA was

used) was added to the mixture at 0 °C, and the mixture was stirred for 30 min at room temperature. After completion of the reaction, as monitored by TLC, the reaction mixture was worked up as follows; $CHCl_3$ and water were added at 0 °C. The separated organic layer was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (AcOEt/*n*-hexane = 1:6) to afford racemic epoxide **9** (409 mg, 88%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.22 (s, 3H), 0.30 (s, 3H), 1.05 (s, 9H), 1.30 (s, 3H), 1.44 (s, 3H), 3.08–3.13 (m, 3H), 3.83 (s, 3H), 3.93 (s, 3H), 7.38 (td, 1H, J = 8.2, 1.4 Hz), 7.45 (td, 1H, J = 8.2, 1.4 Hz), 8.01 (d, 1H, J = 8.2 Hz), 8.02 (d, 1H, J = 8.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.1, −3.8, 18.8, 19.1, 24.8, 25.5, 26.2 (3C), 58.7, 60.9, 62.5, 63.8, 121.5, 122.3, 123.4, 124.2, 124.4, 125.9, 128.4, 141.5, 144.0, 151.3. HRMS (EI$^+$): *m/z* calcd for $C_{23}H_{34}O_4Si$: 402.2226; found: 402.2222.

4.10. 1,4-Dimethoxy-2-methoxymethoxy-3-((3,3-dimethyloxiran-2-yl)methyl)naphthalene 10

At first, 0.5 M aq $NaHCO_3$ (3.2 mL) was added to a stirred solution of **7** (500 mg, 1.58 mmol) in $CHCl_3$ (16 mL). Next, MCPBA (400 mg, 1.6 mmol; a commercially available 70% MCPBA was used) was slowly added to the mixture at 0 °C, and the mixture was stirred for 30 min at room temperature. After the completion of the reaction, as monitored by TLC, the reaction mixture was worked up by addition of $CHCl_3$ and water at 0 °C, and extracted with $CHCl_3$. The organic layer was washed with 1% aq $Na_2S_2O_3$, 0.5 M aq $NaHCO_3$, and water, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography to afford **10** (514 mg, 98%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (s, 3H), 1.47 (s, 3H) 3.08–3.19 (m, 3H), 3.61 (s, 3H), 3.93 (s, 3H), 3.94 (s, 3H), 5.30 (d, 1H, J = 8.4 Hz), 5.31 (d, 1H, J = 8.4 Hz), 7.44 (td, 1H, J = 8.4, 1.4 Hz), 7.48 (td, 1H, J = 8.4, 1.4 Hz), 8.02 (d, 1H, J = 8.4 Hz), 8.08 (d, 1H, J = 8.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.1, 24.8, 25.2, 57.8, 59.0, 61.0, 62.5, 63.9, 99.7, 121.8, 122.3, 123.8, 125.2, 125.8, 126.1, 128.6, 143.4, 145.8, 151.2. HRMS (EI$^+$): *m/z* calcd for $C_{19}H_{24}O_5$: 332.1624; found: 332.1620.

4.11. 2-Hydroxy-1,4-dimethoxy-3-((3,3-dimethyloxiran-2-yl)-methyl)naphthalene 11

To a stirred solution of **9** (80.4 mg, 0.2 mmol) in THF (2.5 mL), AcOH (0.02 mL, 0.4 mmol) and tetrabutylammonium fluoride (TBAF) (0.4 mL, 0.4 mmol, 1 M solution in THF) were slowly added at 0 °C. The reaction was completed within several minutes, and the mixture was poured into water with crushed ice. The mixture was extracted twice with AcOEt, and the organic layer was washed with water, brine, dried over $MgSO_4$, and concentrated under reduced pressure. This material was utilized in the next step without any purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (s, 3H), 1.51 (s, 3H), 3.01 (dd, 1H, J = 13.9, 7.4 Hz), 3.13 (dd, 1H, J = 7.4, 4.4 Hz), 3.28 (dd, 1H, J = 13.9, 4.4 Hz), 3.94 (s, 3H), 3.97 (s, 3H), 6.46 (s, 1H), 7.36 (td, 1H, J = 8.4, 1.4 Hz), 7.46 (td, 1H, J = 8.4, 1.4 Hz), 7.96 (d, 1H, J = 8.4 Hz), 8.01 (d, 1H, J = 8.4 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.0 (2C), 24.8, 60.0, 61.4, 62.7, 64.2, 114.5, 120.7, 122.4, 123.3, 123.6, 126.2, 127.7, 137.1, 145.0, 151.2. HRMS (EI$^+$): *m/z* calcd for $C_{17}H_{20}O_4$: 288.1362; found: 288.1354.

4.12. 3,4-Dihydro-3-hydroxy-5,10-dimethoxy-2,2-dimethyl-2*H*-naphtho[2,3-*b*]pyran 12

The crude residue **11** prepared above was dissolved in CH_2Cl_2 (2.5 mL), cooled to 0 °C, and then a few drops of 50% H_2SO_4 were added. The mixture was stirred for 15 min at room temperature and worked up. Water and $CHCl_3$ were added to the mixture, and extracted. The organic layer was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash chromatography to provide **12** (53.0 mg) in 92% yield in two steps from **9** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (s, 3H), 1.45 (s, 3H), 1.87 (br s, 1H), 3.05 (dd, 1H, J = 13.9, 4.8 Hz), 3.25 (dd, 1H, J = 13.9, 4.0 Hz), 3.91 (s, 3H), 3.92 (dd, 1H, J = 4.8, 4.0 Hz), 3.96 (s, 3H), 7.34 (td, 1H, J = 8.4, 1.1 Hz), 7.42 (td, 1H, J = 8.4, 1.1 Hz), 7.95 (d, 1H, J = 8.4 Hz), 8.07 (d, 1H, J = 8.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 25.0, 27.3, 60.9, 61.2, 69.4, 71.8, 114.2, 121.4, 121.6, 122.8, 123.8, 125.8, 128.3, 138.6, 142.5, 150.1. HRMS (EI$^+$): *m/z* calcd for $C_{17}H_{20}O_4$: 288.1362; found: 288.1357.

4.13. 2-Hydroxy-3-((2,3-dihydroxy-3-methyl)butyl)-1,4-dimethoxynaphthalene by-product 13

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (s, 3H), 1.34 (s, 3H), 2.37 (s, 1H), 2.83 (dd, 1H, J = 10.3, 13.9 Hz), 3.22 (dd, 1H, J = 1.8, 13.9 Hz), 3.42 (s, 1H), 3.69 (dd, 1H, J = 1.8, 10.3 Hz), 3.88 (s, 3H), 3.94 (s, 3H), 7.17 (s, 1H), 7.35 (td, 1H, J = 8.4, 1.1 Hz), 7.45 (td, 1H, J = 8.4, 1.1 Hz), 7.96 (d, 2H, J = 8.4 Hz).

4.14. *rac*-1 (racemic rhinacanthin A)

To a stirred solution of **12** (24.1 mg, 0.08 mmol) in CH_3CN (1 mL) at 0 °C, diammonium cerium(IV) nitrate (CAN) (124 mg, 0.23 mmol) in water (0.5 mL) was added dropwise. The red-orange solution was stirred for 15 min at 0 °C, and worked up by addition of $CHCl_3$ and water. The aqueous layer was extracted with $CHCl_3$. The combined organic layer was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash chromatography to provide *rac*-**1** (18.9 mg, 88%). Mp 189–194 °C, recrystallization from *n*-hexane/AcOEt. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (s, 3H), 1.47 (s, 3H), 1.94 (br s, 1H), 2.68 (dd, 1H, J = 18.6, 5.0 Hz), 2.87 (dd, 1H, J = 18.6, 5.0 Hz), 3.88 (t, 1H, J = 5.0 Hz), 7.66 (td, 1H, J = 7.7 Hz, 1.4 Hz), 8.06 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 24.7, 25.8, 68.4, 80.4, 118.2, 126.0, 126.4, 131.1, 132.1, 133.1, 133.9, 153.7, 179.4, 184.3. HRMS (EI$^+$): *m/z* calcd for $C_{15}H_{14}O_4$: 258.0892; found: 258.0892.

4.15. 2-*tert*-Butyldimethylsilyloxy-1,4-dimethoxy-3-((3,3-dimethyloxiran-2-yl)methyl)naphthalene 9 (enantioenriched) (Table 1, entry 1)

A (Salen)Mn(III) complex (27.5 mg, 0.043 mmol) and 4-methylmorpholine N-oxide (NMO) (514.8 mg, 4.4 mmol) were added to a solution of **4** (340 mg, 0.88 mmol) in CH_2Cl_2 (7.5 mL), and then the mixture was cooled to −78 °C. Next, MCPBA (514.8 mg, 2.06 mmol; commercially available 70% MCPBA was used) was added to the mixture, and stirred for 3 h. The mixture was warmed up to −40 °C, stirred for 16 h, and worked up by the addition of $CHCl_3$ and satd aq NH_4Cl, and separated. The aqueous layer was extracted three times with $CHCl_3$. The combined organic layer was washed with 1% aq $Na_2S_2O_3$, 0.5 M aq $NaHCO_3$, and water, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography to afford enantioenriched **9** (46.9 mg, 13% yield). This material showed analytical and spectroscopic data consistent with those of *rac*-**9** in all respects except for enantiomeric purity. The enantiomeric excess was found to be 49% and was obtained by HPLC on a Chiralpak IC column (250 × 4.6 mm, i.d.) from Daicel Co., using *n*-hexane/isopropyl alcohol 97/3 as eluent (flow rate 1.0 mL/min) at 254 nm. The major enantiomer was eluted after 3.9 min, and the minor enantiomer was eluted after 4.2 min.

4.16. 2-*tert*-Butyldimethylsilyloxy-1,4-dimethoxy-3-((3,3-dimethyloxiran-2-yl)methyl)naphthalene 9 (enantioenriched) (Table 1, entry 3)

To a solution of BHA (26.3 mg, 0.025 mmol) in CH_2Cl_2 (1 mL) was added $MoO_2(acac)_2$ (5 mg, 0.02 mmol), and the mixture was stirred for 1 h at room temperature. To the resulting solution, **4** (193 mg, 0.5 mmol) in CH_2Cl_2 (0.5 mL) and cumene hydroperoxide (CHP) (0.18 mL, 1 mmol; a commercially available 80% CHP was used) were added at 0 °C and stirring was continued at the same temperature for 18 h. The process of oxidation was monitored by TLC, then the mixture was worked up by the addition of $CHCl_3$ and satd aq NH_4Cl and separated. The aqueous layer was extracted three times with $CHCl_3$. The combined organic layer was washed with 1% aq $Na_2S_2O_3$, water, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography to afford enantioenriched **9** (71.6 mg, 36% yield). This material showed analytical and spectroscopic data consistent with those of *rac*-**9** in all respects except enantiomeric purity. The enantiomeric excess was found to be 43% and was obtained by HPLC on a Chiralpak IC column (250 × 4.6 mm, i.d.) from Daicel Co., using *n*-hexane/isopropyl alcohol 97/3 as eluent (flow rate 1.0 mL/min) at 254 nm. The major enantiomer was eluted after 4.6 min, and the minor enantiomer was eluted after 4.8 min.

4.17. 2-*tert*-Butyldimethylsilyloxy-1,4-dimethoxy-3-((3,3-dimethyloxiran-2-yl)methyl)naphthalene 9 (enantioenriched) (Table 2, entry 2)

4 (193 mg, 0.5 mmol) was dissolved in acetonitrile/dimethoxymethane (CH_3CN/DMM) (7.5 mL, 1:2 v/v). Buffer (5 mL, 0.05 M solution of $Na_2B_4O_7{\cdot}10H_2O$ in 4×10^{-4} M aq Na_2(EDTA)), tetrabutylammonium hydrogen sulfate (7.5 mg, 0.02 mmol) and Shi epoxidation diketal catalyst (38.7 mg, 0.15 mmol) were added with stirring. The mixture was cooled to −10 °C. A solution of Oxone (425 mg, 0.69 mmol) in 4×10^{-4} M aq Na_2(EDTA) (3.5 mL) and 0.83 M aq K_2CO_3 (3.5 mL) were added dropwise separately over a period of 5 h. After stirring for 30 min, the mixture was quenched by addition of $CHCl_3$ and water. The mixture was extracted with $CHCl_3$ (15 mL × 3), washed with water, dried over $MgSO_4$, and purified by flash chromatography to afford enantioenriched **9** as a yellow oil (186.3 mg, 93% yield). This material showed analytical and spectroscopic data consistent with those of *rac*-**9** in all respects except enantiomeric purity. $[\alpha]_D^{24} = 10.8$ (*c* 1.0, $CHCl_3$). The enantiomeric excess was found to be 83% and was obtained by HPLC on a Chiralpak IC column (250 × 4.6 mm, i.d.) from Daicel Co., using *n*-hexane/isopropyl alcohol 97/3 as eluent (flow rate 1.0 mL/min) at 254 nm. The major enantiomer was eluted after 4.1 min, and the minor enantiomer was eluted after 4.5 min.

4.18. 3,4-Dihydro-3-hydroxy-5,10-dimethoxy-2,2-dimethyl-2*H*-naphtho[2,3-*b*]pyran 12 (enantioenriched)

To a stirred solution of **9** (201 mg, 0.5 mmol) in THF (2.6 mL), AcOH (0.06 mL, 1.0 mmol) and TBAF (0.5 mL, 0.5 mmol, 1 M solution in THF) were slowly added at 0 °C. The reaction was completed within several minutes, and the mixture was poured into water with crushed ice. The mixture was extracted twice with AcOEt, and the organic layer was washed with water, brine, dried over $MgSO_4$, and concentrated under reduced pressure. This material was utilized in the next step without any purification. The crude residue prepared above was dissolved in CH_2Cl_2 (6 mL), cooled to 0 °C, a few drops of 50% H_2SO_4 were added. The mixture was stirred for 1 h at room temperature and worked up. Next, $CHCl_3$ and water were added to the mixture. The organic layer was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash chromatography to provide enantioenriched **11** (129.4 mg, 90% yield). This material showed analytical and spectroscopic data consistent with those of *rac*-**12** in all respects except enantiomeric purity. $[\alpha]_D^{24} = 6.1$ (*c* 1.0, $CHCl_3$). The enantiomeric excess was found to be 83% and was obtained by HPLC on a Chiralpak AD-H column (250 × 4.6 mm, i.d.) from Daicel Co., using *n*-hexane/isopropyl alcohol 80/20 as eluent (flow rate 1.0 mL/min) at 254 nm. The major enantiomer was eluted after 6.7 min, and the minor enantiomer was eluted after 7.7 min.

4.19. Synthesis of 1

To a stirred solution of **11** (57.6 mg, 0.2 mmol) in CH_3CN (1.8 mL), CAN (296 mg, 0.81 mmol) in water (1.2 mL) was added dropwise at 0 °C. The red-orange solution was stirred for 5 min at 0 °C, and worked up by the addition of $CHCl_3$ and water. The aqueous layer was extracted with $CHCl_3$. The combined organic layer was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash chromatography to provide **1** (44.7 mg, 87% yield). This material showed analytical and spectroscopic data consistent with those of *rac*-**1** in all respects except enantiomeric purity. $[\alpha]_D^{24} = 14.0$ (*c* 1.0, $CHCl_3$). The enantiomeric excess was found to be 82% and was obtained by HPLC on a Chiralpak AD-H column (250 × 4.6 mm, i.d.) from Daicel Co., using *n*-hexane/isopropyl alcohol 80/20 as eluent (flow rate 1.0 mL/min) at 254 nm. The major enantiomer was eluted after 9.7 min, and the minor enantiomer was eluted after 10.5 min. The procedure to increase the enantiomeric purity of synthetic **1** was as follows; 66 mg of synthetic **1** was dissolved in 2.0 mL of hot AcOEt and diluted with a small amount of *n*-hexane. After 48 h, yellow crystals were collected by filtration. (59 mg). $[\alpha]_D^{24} = 20.0$ (*c* 0.99, $CHCl_3$). The enantiomeric excess was found to be >99% and was obtained by HPLC on a Chiralpak AD-H column (250 × 4.6 mm, i.d.) from Daicel Co., using *n*-hexane/isopropyl alcohol 80/20 as eluent (flow rate 1.0 mL/min) at 254 nm. The major enantiomer was eluted after 9.7 min, and the minor enantiomer was eluted after 10.5 min.

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