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First synthesis and absolute configuration of a β-farnesene-trimethoxystyrene conjugate isolated from *Pachypodanthium confine*

Masatsugu Koso [a], Takuya Tashiro [b], Mitsuru Sasaki [a], Hirosato Takikawa [a,*]

[a] Department of Agrobioscience, Graduate School of Agricultural Science, Kobe University, Rokkodai 1-1, Nada-ku, Kobe 657-8501, Japan
[b] Glycosphingolipid Synthesis Group, Laboratory for Immune Regulation, RIKEN Research Center for Allergy and Immunology, Hirosawa 2-1, Wako, Saitama 351-0198, Japan

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ABSTRACT

(*E*)-1-[3′-(4″,8″-Dimethylnona-3″,7″-dienyl)cyclohex-3′-enyl]-2,4,5-trimethoxybenzene (**1**), a β-farnesene-trimethoxystyrene conjugate, was isolated from *Pachypodanthium confine*. Its first synthesis was accomplished, and absolute configuration was determined to be *R*.

1. Introduction

In 2007, Mathouet and his co-workers isolated a β-farnesene-trimethoxystyrene conjugate, (*E*)-1-[3′-(4″,8″-dimethylnona-3″,7″-dienyl)cyclohex-3′-enyl]-2,4,5-trimethoxybenzene (**1**), and its (*Z*)-isomer from the bark of *Pachypodanthium confine*.[1] The structure of **1** is quite unique, because its basic framework has never been reported in natural products so far, and it appears to be synthesized by Diels–Alder reaction between β-farnesene and 2,4,5-trimethoxystyrene. To our knowledge, the most structurally similar natural products may be fissistin[2] and its derivatives[3] isolated from the Annonaceae and Zingiberaceae families. We can regard these natural products as β-myrcene-chalcone conjugates, and all these compounds exist as racemic form in nature. Interestingly, **1**, in contrast, is optically active, however, the absolute configuration of **1** has not yet been clarified. Although the biological activity of **1** has not been studied, fissistin and its derivatives show various biological and/or physiological activities. Therefore, **1** may exhibit some biological activities. We were interested in the unique structure and the expected functional profile of **1** and undertook a project to synthesize optically active **1**. We herein report the first synthesis and absolute configuration of **1** (Fig. 1).

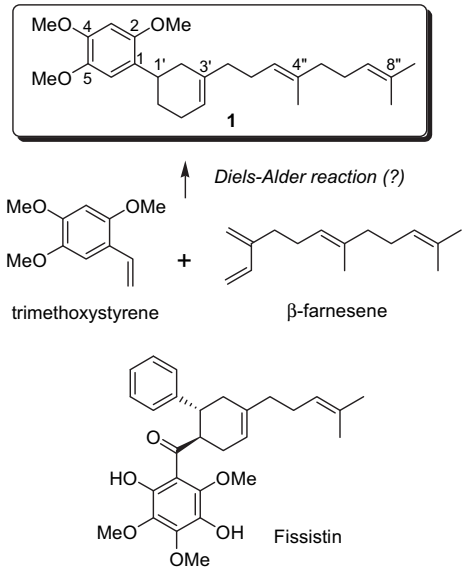

Figure 1. Structures of **1** and related compounds.

2. Results and discussion

Scheme 1 shows our synthetic plan for **1**. The crucial point in our synthesis was the preparation of the optically active form. The planned route needed to include an asymmetric reaction or an

* Corresponding author. Tel./fax: +81 78 803 5958.
E-mail address: takikawa@kobe-u.ac.jp (H. Takikawa).

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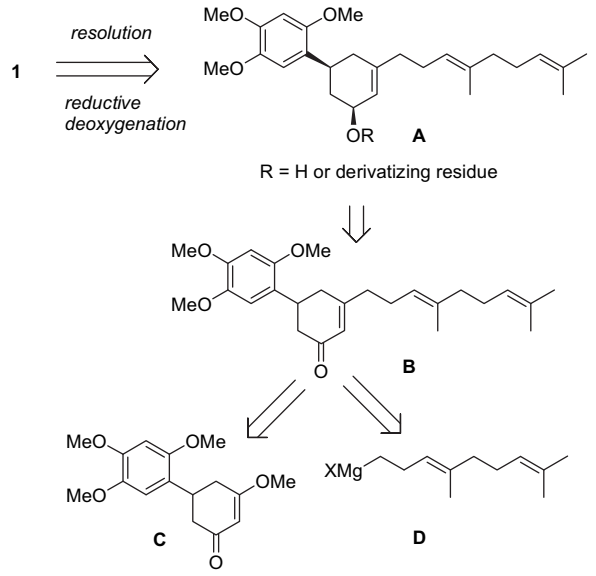
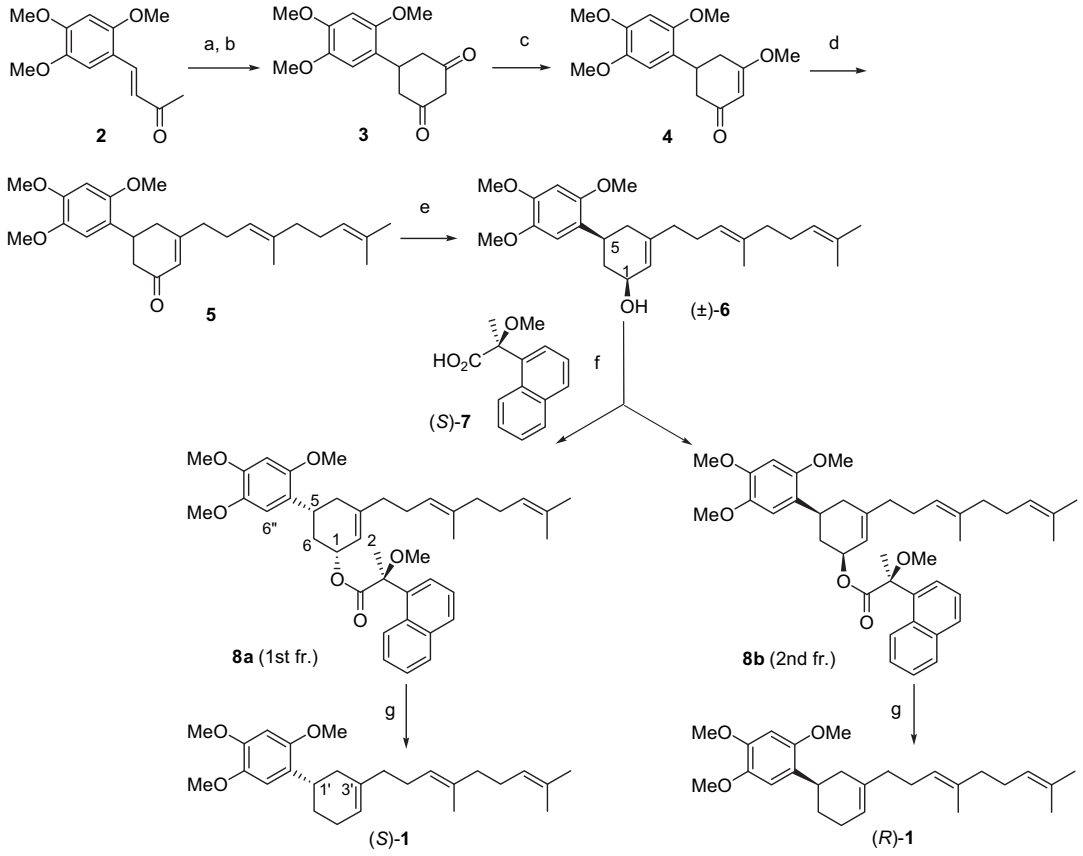


Scheme 1. Synthetic plan for **1**.

optical resolution at the appropriate stage, because it did not begin with an optically active starting material. For this purpose, we envisioned adopting the classical optical resolution of **A** by a diastereomer method based on our previous successful experience.[4] Another crucial step was the reductive deoxygenation of **A** to **1**. The intermediate **A** should be prepared by the diastereoselective reduction of **B**. For the synthesis of **B**, we assigned **C** and **D** as appropriate precursors. The enone **C** was obtainable according to the reported procedure.[5]

Scheme 2 shows our synthetic route to both enantiomers of **1**. First, we prepared the dione **3** (quant.) from the known enone **2**[6] according to the reported procedure.[5] The dione **3** was converted into the corresponding enol ether **4** (=**C**) by treatment with H_2SO_4 in MeOH (58% based on **2**). A reaction between **4** and homogeranylmagnesium bromide (=**D**) afforded the desired adduct **5** (=**B**; 59%). As mentioned above, we needed to carry out an optical resolution. For the conventional optical resolution, **5** was reduced under Luche conditions to give *cis*-allylic alcohol (±)-**6** (=**A**) as the sole diastereomer (91%). We confirmed the *cis*-relative configuration by observing NOE between 1-H and 5-H. It should be mentioned that reduction of **5** with L-Selectride® gave a ca. 1:3 mixture of (±)-**6** and its *trans*-isomer. In this case, equatorial attack of hydride was favored, while axial attack was predominant under Luche conditions. With the key intermediate (±)-**6** in hand, we attempted the classical resolution using a chiral derivatizing reagent. However, after discovering that MTPA ester was not suitable for the optical resolution, we found that Harada's reagent[7] [**7**, 2-methoxy-2-(naphthalen-1-yl)propionic acid] achieved successful results as follows. Condensation of (±)-**6** and (*S*)-**7** was performed with DCC in the presence of DMAP to give a diastereomeric mixture of **8a** and **8b**. Flash column chromatography did not easily separate these two diastereomers, but we did manage to obtain the less polar diastereomer **8a** (28%) and the more polar **8b** (23%). Application of a modified Mosher's method[8] enabled us to determine the absolute configurations of **8a** and **8b**. Figure 2 shows the crucial observed $\Delta\delta_{\mathbf{8a-8b}}$ values.



Scheme 2. Synthesis of (±)-**1**. Reagents and conditions: (a) dimethyl malonate, NaOMe, MeOH, reflux; (b) aq NaOH, reflux; aq HCl, reflux (quant.); (c) conc. H_2SO_4, MeOH, reflux (58% based on **2**); (d) homogeranylmagnesium bromide, THF, reflux (59%); (e) $NaBH_4$, $CeCl_3\cdot 7H_2O$, MeOH (91%); (f) **7**, DCC, DMAP,CH_2Cl_2 (28% for **8a**, 23% for **8b**) (g) Li, *t*-BuOH, NH_3, THF, [60% for (*S*)-**1**, 40% for (*R*)-**1**].

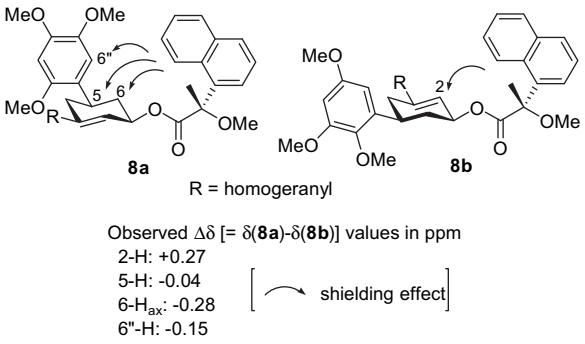


Figure 2. Absolute configurations of **8a** and **8b**.

The remaining subject was reductive deoxygenation. For this purpose, we preliminarily examined Barton–McCombie deoxygenation,[9] hydrogenolysis via a π-allylpalladium complex,[10] Zn–AcOH reduction,[10] and Birch reduction.[10] Our studies suggested that Birch reduction was the best suitable candidate. Therefore, we subjected the pure **8a** to a Birch reduction to furnish (*S*)-**1** (60%),[11] $[\alpha]_D^{25}$ −30 (*c* 0.18 in EtOH), {lit.[1] $[\alpha]_D^{20}$ +5 (*c* 0.6 in EtOH)}. The various spectral data of synthetic (*S*)-**1** are in good accord with those of the natural product.[1] Similarly, the pure **8b** was also converted into (*R*)-**1**,[11] $[\alpha]_D^{27}$ +30 (*c* 0.086 in EtOH). Although there was a considerable difference in the magnitude of the specific rotation between synthetic and natural **1**, we were able to determine the absolute configuration of the naturally occurring **1** to be *R*, because synthetic (*R*)-**1** and naturally occurring **1** were both dextrorotatory.

3. Conclusion

In conclusion, we accomplished the first synthesis of both enantiomers of (*E*)-1-[3′-(4″,8″-dimethylnona-3″,7″-dienyl)cyclohex-3′-enyl]-2,4,5-trimethoxybenzene (**1**) by employing an optical resolution using Harada's reagent as the key step. We were consequently able to determine the absolute configuration of naturally occurring **1** to be *R*. Bioassays employing our synthetic samples are now in preparation.

4. Experimental

4.1. General

Melting points were measured with YANAKO MP-S9 micromelting point apparatus. IR spectra were recorded with a Shimadzu IR-408 spectrophotometer. ^{1}H NMR spectra were recorded at 300 MHz on a JEOL JNM-AL300 spectrometer. The peak for $CHCl_3$ in $CDCl_3$ (δ 7.26) was used for the internal standard. Chemical shifts are reported in ppm on the δ scale and *J*-values are given in Hz. ^{13}C NMR spectra were recorded at 75 MHz on a JEOL JNM-AL300 spectrometer. The peak for $CDCl_3$ (δ 77.0) was used for the internal standard. Optical rotations were taken with a HORIBA SEPA-300 polarimeter. Mass spectra were measured with a JEOL JMS-SX102A. Flash chromatography was carried out on Kanto Chemical Co., Inc. Silica Gel 60 N (spherical, neutral, 40–50 μm). Column chromatography was carried out on Kanto Chemical Co., Inc. Silica Gel 60 N (spherical, neutral, 63–210 μm). TLC analyses were performed on Merck silica gel plates 60 F_{254}.

4.2. 5-(2,4,5-Trimethoxyphenyl)cyclohexane-1,3-dione (3)

To a solution of Na (4.8 g, 0.21 mol) in MeOH (60 mL), dimethyl malonate (9.2 g, 70 mmol) and **2** (11.0 g, 46.6 mmol) were added at room temperature under Ar. After stirring under reflux for 4 h, the reaction mixture was concentrated under reduced pressure. The residue was acidified with 3 M HCl, and extracted with $CHCl_3$. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under reduced pressure to give the residue (14 g). To this residue, was added a solution of NaOH (7.5 g, 0.19 mol) in water (140 mL). After stirring under reflux for 1 h, the reaction mixture was extracted with Et_2O. The aqueous layer was acidified with 3 M HCl, heated under reflux for 1 h, and extracted with $CHCl_3$. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under reduced pressure to give **3** (13 g, quant.) as orange semi-solid: IR (Nujol) 1630 (m, C=O) cm^{-1}; ^{1}H NMR δ 2.56 (dd, *J*=17.1, 4.5 Hz, 1.4H), 2.72 (dd, *J*=17.1, 11.7 Hz, 1.4H), 2.84 (d, *J*=7.5 Hz, 1.2H), 3.45 (s, 0.6H), 3.45–3.82 (m, 1H), 3.74 (s, 0.9H), 3.78 (s, 2.1H), 3.80 (s, 3H), 3.86 (s, 3H), 5.61 (s, 0.7H), 6.50 (s, 0.3H), 6.51 (s, 0.7H), 6.63 (s, 0.3H), 6.72 (s, 0.7H), 9.82 (br s, 0.7H); ^{13}C NMR δ 31.9, 33.7, 38.1, 45.5, 55.3, 56.0, 56.1, 56.8, 57.4, 97.6, 97.7, 103.8, 112.0, 112.1, 120.6, 121.7, 142.8, 142.9, 148.5, 148.9, 151.1, 151.5, 192.4, 203.7. Compound **3** was a mixture of keto and enol forms (ca. 3:7). Thus, signals due to the minor keto form might not be fully detected. HRMS (EI) *m*/*z* calcd for $C_{15}H_{18}O_5$: 278.1154, found 278.1153.

4.3. 3-Methoxy-5-(2,4,5-trimethoxyphenyl)cyclohex-2-en-1-one (4)

A solution of **3** (0.56 g, 2.0 mmol) and H_2SO_4 (5 drops) in MeOH (10 mL) was heated under reflux with stirring for 4 h. After removal of MeOH under reduced pressure, the residue was diluted with water, neutralized with 10% aq NaOH, and extracted with $CHCl_3$. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give **4** (7.90 g, 58%) as yellow solid: mp 106–108 °C; IR (Nujol) 1650 (m, C=O), 1600 (m, C=C) cm^{-1}; ^{1}H NMR δ 2.48–2.71 (m, 4H), 3.53–3.67 (m, 1H), 3.68 (s, 3H), 3.77 (s, 3H), 3.79 (s, 3H), 3.84 (s, 3H), 5.39 (s, 1H), 6.50 (s, 1H), 6.68 (s, 1H); ^{13}C NMR δ 33.3, 37.8, 42.4, 55.6, 55.9, 56.0, 56.7, 97.6, 101.7, 111.6, 121.9, 142.7, 148.3, 151.3, 178.3, 199.3; HRMS (EI) *m*/*z* calcd for $C_{16}H_{20}O_5$: 292.1311, found 292.1306.

4.4. (3′*E*)-3-(4′,8′-Dimethylnona-3′,7′-dienyl)-5-(2″,4″,5″-trimethoxyphenyl)cyclohex-2-en-1-one (5)

To a stirred solution of homogeranylmagnesium bromide, prepared from homogeranyl bromide (1.8 g, 7.8 mmol) and Mg (0.19 g, 7.8 mmol) in THF (20 mL), a solution of **4** (2.20 g, 7.53 mmol) in THF (20 mL) was added at room temperature. After stirring under gentle reflux for 2 h, the reaction mixture was quenched with satd aq NH_4Cl and extracted with $CHCl_3$. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give **5** (1.83 g, 59%) as a slightly orange oil: IR (film) 1660 (s, C=O), 1620 (m, C=C) cm^{-1}; ^{1}H NMR δ 1.58 (s, 3H), 1.60 (s, 3H), 1.66 (s, 3H), 1.94–2.10 (m, 4H), 2.17–2.39 (m, 4H), 2.40–2.66 (m, 4H), 3.52–3.64 (m, 1H), 3.79 (s, 3H), 3.82 (s, 3H), 3.87 (s, 3H), 5.02–5.12 (m, 2H), 5.94 (s, 1H), 6.53 (s, 1H), 6.71 (s, 1H); ^{13}C NMR δ 16.0, 17.6, 25.4, 25.6, 26.6, 34.7, 36.2, 38.0, 39.6, 43.0, 56.09, 56.14, 56.8, 97.8, 111.7, 122.5, 122.9, 124.0, 125.3, 131.4, 136.4, 142.9, 148.4, 151.4, 165.8, 200.0; HRMS (EI) *m*/*z* calcd for $C_{26}H_{36}O_4$: 412.2614, found 412.2601.

4.5. (1*S**,5*S**,3′*E*)-3-(4′,8′-Dimethylnona-3′,7′-dienyl)-5-(2″,4″,5″-trimethoxyphenyl)cyclohex-2-en-1-ol (6)

To a stirred and ice-cooled solution of **5** (0.45 g, 1.1 mmol) in MeOH (7 mL), $CeCl_3 \cdot 7H_2O$ (0.82 g, 2.2 mmol) and $NaBH_4$ (84 mg, 2.2 mmol) were added portionwise. After stirring for 10 min with warming to room temperature, the reaction mixture was quenched with satd aq NH_4Cl and extracted with $CHCl_3$. The organic layer was

washed with brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give **6** (0.41 g, 91%) as a pale yellow oil: IR (film) 3350 (s, O–H) cm^{-1}; ^1H NMR δ 1.60 (s, 6H), 1.60–1.68 (m, 2H), 1.67 (s, 3H), 1.93–2.21 (m, 11H), 3.24 (br t-like, J=10.8, 1H), 3.80 (s, 3H), 3.83 (s, 3H), 3.88 (s, 3H), 4.46 (m, 1H), 5.05–5.16 (m, 2H), 5.47 (s, 1H), 6.53 (s, 1H), 6.73 (s, 1H); ^{13}C NMR δ 16.0, 17.6, 25.6, 26.1, 26.7, 32.0, 35.9, 37.0, 38.7, 39.7, 56.2, 56.4, 56.7, 68.9, 97.9, 111.2, 123.8, 124.3, 124.8, 125.5, 131.3, 135.3, 140.8, 143.1, 147.7, 151.1; HRMS (EI) m/z calcd for $C_{26}H_{38}O_4$: 414.2770, found 414.2777.

4.6. (1*R*,5*R*,3′*E*)-3-(4′,8′-Dimethylnona-3′,7′-dienyl)-5-(2″,4″,5″-trimethoxyphenyl)cyclohex-2-enyl (*S*)-2-methoxy-2-(naphthalen-1-yl)propionate (8a) and (1*S*,5*S*,3′*E*)-3-(4′,8′-dimethylnona-3′,7′-dienyl)-5-(2″,4″,5″-trimethoxyphenyl)-cyclohex-2-enyl (*S*)-2-methoxy-2-(naphthalen-1-yl)-propionate (8b)

To a stirred solution of **6** (200 mg, 0.482 mmol) in dry CH_2Cl_2 (2 mL), (*S*)-**7** (0.55 g, 2.4 mmol), DCC (0.99 g, 4.8 mmol) and DMAP (59 mg, 0.48 mmol) were added successively under Ar. After stirring at room temperature for 4 d, the reaction mixture was quenched with satd aq NH_4Cl and filtered through Celite. The filtrate was extracted with $CHCl_3$. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography to give the less polar **8a** (86 mg, 28%), the more polar **8b** (69 mg, 23%), and a mixture of **8a** and **8b** (47 mg, 16%).

8a: $[\alpha]_D^{25}$ −11.9 (*c* 1.18, $CHCl_3$); IR (film) 1730 (s, C=O) cm^{-1}; ^1H NMR δ 1.37 (q-like, J=11.7 Hz, 1H, 6-H_{ax}), 1.56 (s, 3H, C=C–Me), 1.59 (s, 3H, C=C–Me), 1.67 (s, 3H, C=C–Me), 1.81–2.13 (m, 11H), 2.01 (s, 3H, 3-H_3), 3.10 (s, 3H, 2-OMe), 3.20 (m, 1H, 5-H), 3.73 (s, 3H, Ar-OMe), 3.77 (s, 3H, Ar-OMe), 3.86 (s, 3H, Ar-OMe), 5.01–5.13 (m, 2H, 3′- and 7′-H), 5.27 (s, 1H, 2-H), 5.61 (m, 1H, 1′-H), 6.47 (s, 1H, 3″-H), 6.48 (s, 1H, 6″-H), 7.41–7.45 (m, 3H, Np-H), 7.62 (d, J=6.6 Hz, 1H, Np-H), 7.80–7.87 (m, 2H, Np-H), 8.34–8.46 (m, 1H, Np-H); ^{13}C NMR δ 16.0, 17.6, 21.8, 25.6, 25.9, 26.7, 31.6, 33.4, 35.7, 37.0, 39.7, 51.0, 56.1, 56.4, 56.7, 72.9, 81.6, 97.8, 111.0, 120.1, 123.6, 124.3, 124.7, 124.9, 125.3, 125.6, 125.7, 126.2, 128.6, 129.3, 131.3, 134.1, 135.3, 135.4, 142.6, 143.0, 147.7, 151.0, 174.0; HRMS (EI) m/z calcd for $C_{40}H_{50}O_6$: 626.3607, found 626.3599.

8b: $[\alpha]_D^{22}$ −43.2 (*c* 0.806, $CHCl_3$); IR (film) 1730 (s, C=O) cm^{-1}; ^1H NMR δ 1.53 (s, 3H, C=C–Me), 1.60 (s, 3H, C=C–Me), 1.60–1.73 (m, 1H, 6-H_{ax}), 1.68 (s, 3H, C=C–Me), 1.79–2.13 (m, 11H), 1.98 (s, 3H, 3-H_3), 3.12 (s, 3H, 2-OMe), 3.24 (m, 1H, 5-H), 3.77 (s, 3H, Ar-OMe), 3.80 (s, 3H, Ar-OMe), 3.87 (s, 3H, Ar-OMe), 5.00 (br s, 1H, 2-H), 5.08 (m, 2H, 3′- and 7′-H), 5.60 (m, 1H, 1′-H), 6.50 (s, 1H, 3″-H), 6.63 (s, 1H, 6″-H, 6″-H), 7.41–7.51 (m, 3H, Np-H), 7.61 (d, J=6.6 Hz, 1H, Np-H), 7.80–7.88 (m, 2H, Np-H), 8.39–8.46 (m, 1H, Np-H); ^{13}C NMR δ 15.9, 17.7, 21.9, 25.7, 25.8, 26.7, 31.6, 33.8, 35.6, 36.8, 39.6, 51.0, 56.2, 56.4, 56.7, 72.9, 81.7, 97.8, 111.2, 120.0, 123.7, 124.3, 124.7, 125.0, 125.3, 125.6, 126.2, 128.7, 129.3, 131.3, 134.1, 135.3, 135.4, 142.4, 143.0, 147.8, 151.0, 174.0; HRMS (EI) m/z calcd for $C_{40}H_{50}O_6$: 626.3607, found 626.3612.

4.7. (1′*S*, 3″*E*)-1-[3′-(4″,8″-Dimethylnona-3″,7″-dienyl)-cyclohex-3′-enyl]-2,4,5-trimethoxybenzene [(*S*)-1]

To a solution of Li (20 mg, 2.9 mmol) in liq. NH_3 (2 mL), **8a** (24 mg, 38 μmol) and *t*-BuOH (0.10 g, 1.3 mmol) in dry THF (2 mL) was added at −78 °C under Ar. After stirring for 10 min, the reaction mixture was carefully poured into satd aq NH_4Cl and extracted with $CHCl_3$. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give (*S*)-**1** (9.1 mg, 60%) as a colorless oil: $[\alpha]_D^{25}$ −30 (*c* 0.18, EtOH); ^1H NMR δ 1.60 (s, 6H), 1.62–1.83 (m, 2H), 1.68 (s, 3H), 1.94–2.21 (m, 12H), 3.18 (m, 1H), 3.80 (s, 3H), 3.84 (s, 3H), 3.88 (s, 3H), 5.06–5.17 (m, 2H), 5.46 (s, 1H), 6.53 (s, 1H), 6.76 (s, 1H); ^{13}C NMR δ 16.0, 17.7, 25.7, 25.9, 26.4, 26.7, 28.7, 32.8, 35.7, 37.8, 39.7, 56.2, 56.6, 56.7, 98.0, 111.4, 120.4, 124.3, 124.4, 127.4, 131.3, 135.0, 137.8, 143.1, 147.4, 151.0; HRMS (FAB) m/z calcd for $C_{26}H_{38}O_3$: 398.2821, found 398.2829.

4.8. (1′*R*, 3″*E*)-1-[3′-(4″,8″-Dimethylnona-3″,7″-dienyl)-cyclohex-3′-enyl]-2,4,5-trimethoxybenzene [(*R*)-1]

In the same manner as described above, **8b** (39 mg, 62 μmol) was converted to (*R*)-**1** (10 mg, 40%): $[\alpha]_D^{27}$ +30 (*c* 0.086, EtOH); HRMS (FAB) m/z calcd for $C_{26}H_{38}O_3$: 398.2821, found 398.2820. NMR spectra of (*R*)-**1** were identical to those of (*S*)-**1**.

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10. The *O*-acetylated (±)-**6** was employed as a substrate for these reactions.
11. Synthetic **1** contained a small amount of inseparable impurity. The most probable structure of it was $\Delta^{4'}$-isomer.