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Efficient Asymmetric Synthesis of *abeo*-Abietane-Type Diterpenoids by Using the Intramolecular Heck Reaction

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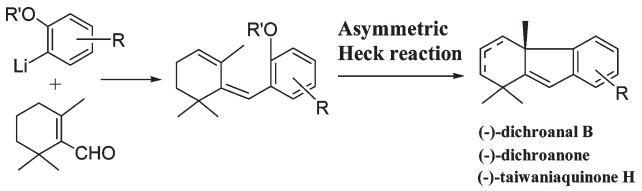

The synthesis of the *abeo*-abietane-type diterpenoids, i.e., (−)-dichroanal B, (−)-dichroanone, and taiwaniaquinone H, was achieved by using the intramolecular asymmetric Heck reaction. Our synthetic routes required fewer steps and gave a much higher overall yield and ee within shorter steps than those for racemic and antipodal forms reported to date (10, 12, and 13 steps with an overall yield of 50%, 40%, and 39%, and 94%, 98%, and 98% ee, respectively).

Introduction

Recently, diterpenes having an *abeo*-abietane (4a-methyltetrahydrofluorene) skeleton were identified as a new type of naturally occurring product. Among them, standishinal (**1**, Figure 1) isolated from *Thuja standishii* by Tanaka has been evaluated as a potential antitumor agent for treating breast cancer postmenopause because of its appreciable inhibitory activity against aromatase.[1a−d] Thus, other diterpenes possessing the same skeleton are expected to have promising activities for the treatment of female hormone-dependent cancers. Banerjee and his colleagues succeeded in the synthesis of dichroanal B (**2**), dichroanone (**3**), taiwaniaquinol B, and taiwaniaquinone D and H (**4**) using an intramolecular reductive Heck reaction.[1e,f] Later, Fillion and Fishlock adopted an intramolecular Friedel−Crafts/α-*tert*-alkylation domino reaction for the synthesis of taiwaniaquinol B.[1g] Moreover, Trauner's group reported the total synthesis of **3**, **4**, taiwaniaquinol B, and taiwaniaquinone D using the Nazarov triflation reaction.[1h] She's group recently reported the formal synthesis of **3** and taiwaniaquinol B.[1i] Meanwhile, we also achieved the synthesis of **1** and **2** using an acid-catalyzed aldol reaction and intramolecular Heck reaction, respectively.[1d,j] Very recently, Alvarez-Manzaneda's group reported the facile synthesis of **3** and **4**.[1k] In spite of these successful results of total synthesis, no asymmetric synthesis has been reported to date, except for that by Stoltz and his colleagues.[1l] However, it should be noted that (+)-**3** synthesized therein was the antipode of the naturally occurring compound. Against this background, we embarked on a study of *abeo*-abietane-type diterpenes using an intramolecular asymmetric Heck reaction of triflate **6**, as shown in Scheme 1. Herein, we report the first synthesis of the natural form of (−)-**2**, (−)-**3**, and (−)-**4** using the asymmetric intramolecular Heck reaction.

Results and Discussion

Initially, we planed to apply the asymmetric version of the intramolecular Heck reaction to the synthesis of *dl*-**2**

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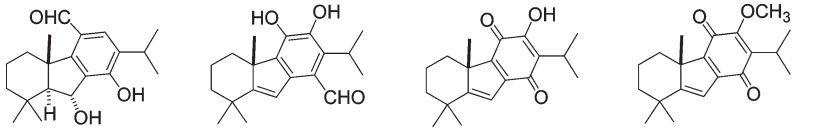


FIGURE 1. Structures of *abeo*-abietane-type diterpenoids.

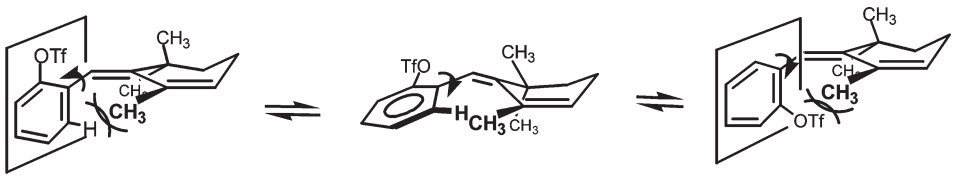
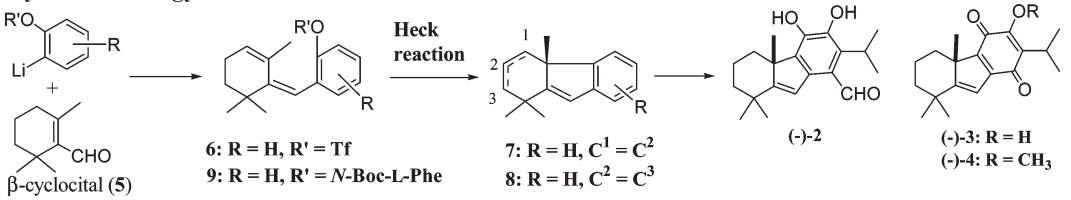


FIGURE 2. Equilibration of atropisomers.

SCHEME 1. Synthetic Strategy of *abeo*-Abietanes

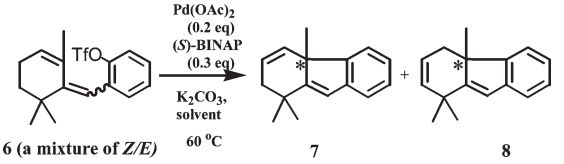


(Scheme 1).[1j] Namely, dienylalkyloxybenzene derivative prepared by the condensation of *β*-cyclocitral (**5**) and aryllithium was converted to the corresponding triflate via *O*-dealkylation and subsequent triflation. Thereafter, the asymmetric Heck reaction with a chiral ligand could annelate the B-ring to form the *abeo*-abietane skeleton. Further transformation of functional groups should afford the desired natural product.

Inspection with the Büchi molecular model of substrate **6** suggested the existence of two atropisomers, which is a disadvantage for the asymmetric reaction; however, the atropisomers were not analyzed by HPLC with a chiral column.[2] Thus, to evaluate the energy barrier that exists between two stable conformations, the triflate group of **6** was replaced with *N*-Boc-L-phenylalanine to give the α-amino ester **9**, the atropisomers of which were observed only at low temperature (−70 °C) in ^{1}H NMR spectroscopic analysis (see the Supporting Information). As the atropisomers were not observed at temperatures higher than −40 °C, the fast equilibrium between two atropisomers in **6** was confirmed. This phenomenon could be explained by considering the distorted boat-type conformation, which reduced the energy barrier between the atropisomers, as shown in Figure 2.[1j] Thus, it was confirmed that **6** could be employed as a substrate in the asymmetric Heck reaction, which should generally be performed at temperatures higher than 60 °C.

The asymmetric intramolecular Heck reaction of **6** (a mixture of *E*/*Z* isomers) was conducted as a model experiment under Shibasaki's condition where (*S*)-BINAP and potassium carbonate were adopted as a chiral ligand and base, respectively.[3] Fortunately, the annulated products

TABLE 1. Solvent Effect in the Intramolecular Asymmetric Heck Reaction of 6



	conditions				
entry[a]	solvent	time (h)	yield (%)[b]	**7**/**8**	% ee (**8**)[c]
1	toluene	40	70	38/62	49
2	THF	18	90	12/88	58
3	MeCN	17	89	52/48	69
4	DMF	7.5	90	25/75	97
5	DMA	7.5	87	80/20	96
6	NMP[d]	7.5	82	35/65	97

[a]The starting material **6** of *Z*/*E* 84/16 (entries 1 and 3) and *Z*/*E* 91/9, (entries 2 and 4−6) was used. [b]The yield was calculated from the *Z* isomer. [c]The ee value was determined by chiral HPLC. [d]NMP = *N*-methylpyrrolidinone.

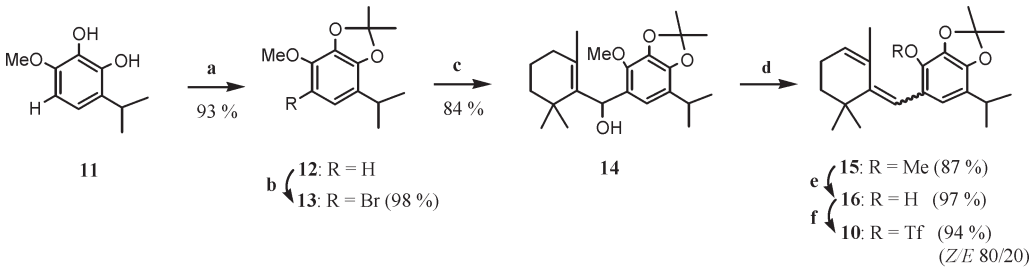
7 and **8** were attained in 70% yield with 49% ee at 60 °C (Table 1, entry 1).[4] Changing the solvent from toluene to aprotic polar solvents shortened the reaction period and increased both chemical and optical yields at the same temperature (Table 1, entries 2−6). The reaction in DMF gave the most satisfactory result, i.e., 90% yield with 97% ee (Table 1, entry 4). Since the dissociation of palladium and triflate in the Pd-complex could accelerate the Heck reaction with DMF as a solvent, high enatioselectivity in the

(2) The atropisomers did not separate at room temperature. The details of the existence of atropisomers will be published elsewhere.

(3) Takemoto, T.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1993**, *115*, 8477–8478.

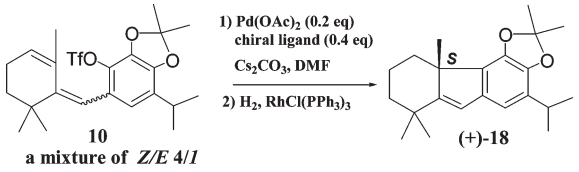
(4) The fate of the *E*-isomer was not traced, i.e., neither recovery of the *E*-isomer nor its decomposed products were detected.

SCHEME 2. Synthetic Route of 10

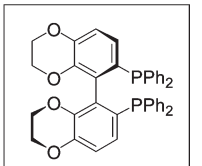


a: acetone, BF_3-Et_2O, Et_2O, **b**:NBS, CH_2Cl_2, **c**: *n*-BuLi, **5**, THF, **d**: HCl, MeOH, **e**: Dod-SH, NaH, DMF, 120 °C, **f**: Tf_2O, pyr.

TABLE 2. Heck Reaction of 10 with Chiral Ligands Having C_2-Symmetry



entry	chiral ligands	temp.	time (h)	yield[a]	%ee
1	(*R*)-BINAP	100 °C	25	83	76
2	(*R*)-BINAP	90 °C	45	84	76
3	(*R*)-BINAP	80 °C	90	83	77
4	(*R*)-BINAP	70 °C	150	81	77
5	(*R*)-Synphos	110 °C	4.5	86	94
6	(*R*)-Synphos	100 °C	6	85	94
7	(*R*)-Synphos	90 °C	9	72	97
8	(*R*)-Synphos	80 °C	26	72	98



(*R*)-Synphos (17)

[a]The numerical values show chemical yields (%) in the Heck reaction. The subsequent hydrogenation proceeded quantitatively.

amide-type solvent (DMF, DMA, and NMP) could be obtained by a route involving a cation intermediate.[5]

Finally, we applied the intramolecular Heck reaction to the asymmetric synthesis of (−)-**2** and (−)-**3** isolated from the roots of *Salvia dichroantha*[6] and (−)-**4** from *Taiwania cryptomerioides*.[7] Initially, we designed substrate **10** bearing a rigid acetonide group in the catechol moiety because the flexible isopropyl group employed in the racemic synthesis of **2** retarded the access of the palladium complex to a bulky chiral ligand. **10** was prepared by modifying a previously reported method[1j] (Scheme 2). Namely, **11**, commercially available, was treated with acetone in the presence of $BF_3 \cdot Et_2O$ to give the acetonide **12**, of which bromination with NBS afforded **13** in excellent yield. After lithiation of the bromide **13** with *n*-butyllithium, the aryllithium generated was reacted with β-cyclocitral (**5**) to afford the benzylic alcohol **14**. Dehydration of **14** by treatment with methanolic hydrochloric acid gave the diene **15** as a mixture of *E* and *Z* isomers (ca. 1:4). After demethylation of the methyl ether in **15** with dodecane thiol and sodium hydride in DMF,[8] the obtained phenolic compound **16** was converted to the triflate **10**.

The intramolecular asymmetric Heck reaction of triflate **10** (a mixture of *E*/*Z* isomers) was tried using palladium(II) acetate, chiral BINAP, and cesium carbonate in DMF at 100 °C, the hydrogenated product of which showed 76% ee (Table 2, entry 1). Marked temperature dependence to improve the ee was not observed in the Heck reaction with chiral BINAP (Table 2, entries 2−4). Among several other chiral phosphorus ligands having C_2-symmetry, such as (*S*)-6-MeO-BIP, (*S*,*S*)-chiraphos, and (*S*)-MOP, Synphos (**17**) exhibited a further improvement in ee and reaction time (Table 2, entries 5−8). This result could be attributed to the smaller dihedral angle of **17** (75°), which afforded more potent interaction between the ligand and substrate than that of BINAP (80°).[9] Moreover, temperature dependence was also observed in the reaction. Finally, it was found that the Heck reaction of **10** and successive hydrogenation gave **18** in good yield (< 86% in 2 steps) with excellent ee (94−98% ee) when (*R*)-**17** was used as a ligand.[10] The absolute configuration of (+)-**18** was confirmed to be *S* by single-crystal X-ray diffraction analysis after

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(6) Kawazoe, K.; Yamamoto, M.; Takaishi, Y.; Honda, G.; Fujita, T.; Sezik, E.; Yesilada, E. *Phytochemistry* **1999**, *50*, 493–497.
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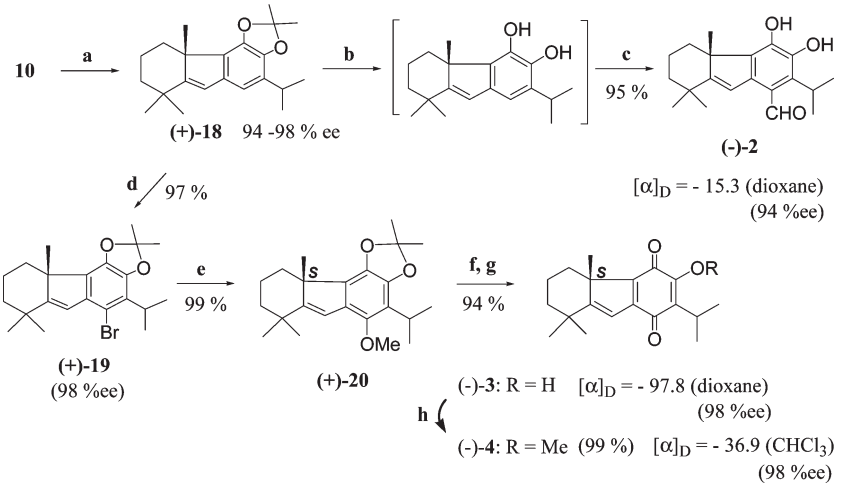
(9) Ozawa, F.; Kubo, A.; Matsumoto, Y.; Hayashi, T.; Nishioka, E.; Yanagi, K.; Moriguchi, K. *Organometallics* **1993**, *12*, 4188–4196.
(10) For economical reasons, the intermediate **18** (83%, 76% ee) obtained by the Heck reaction with (*R*)-BINAP and successive hydrogenation was recrystallized two times from isopropanol to increase the optical purity until > 98% ee. The recrystallized **18** (17%, 94−98% ee) was used for synthesis of (−)-**2**, (−)-**3**, and (−)-**4**.

SCHEME 3. Synthesis of (−)-2, (−)-3, and (−)-4[a]



[a]Reagents and conditions: (a) $Pd(OAc)_2$ (0.3 equiv), (*R*)-Synphos (0.4 equiv), Cs_2CO_3, DMF, then H_2, $RhCl(PPh_3)$; (b) HCl, MeOH, 60 °C; (c) BCl_3, $CHCl_2OCH_3$ (5 equiv), CH_2Cl_2, 0 °C; (d) NBS; (e) CuI, NaOMe, DMF, MeOH, 100 °C; (f) BBr_3 (4 equiv), CH_2Cl_2, −78 to 0 °C; (g) DDQ (1.1 equiv), CH_2Cl_2; (h) Me_3OBF_4, DIEA, CH_2Cl_2.

deriving to **19** with NBS. Because the *E*-isomer of **10** also afforded the desired product in 46% yield under Heck conditions, which indicated the existence of equilibrium between *E*/*Z* isomers, the *E*/*Z* mixture was used without any separation in the reactions.[11]

Finally, the acetonide of **18** (94.2%ee) was subjected to deprotection with HCl−MeOH followed by a Friedel−Crafts-type reaction with dichloromethoxymethane in the presence of BCl_3 to give (−)-**2** ($[\alpha]_D$ −15.3 (dioxane), lit. $[\alpha]_D$ −8.2[6]) in 92% yield. Treatment of **19** (98%ee) with sodium methoxide in the presence of CuI followed by removal of the acetonide and oxidation with DDQ afforded (−)-**3** ($[\alpha]_D$ −97 (dioxane), lit. $[\alpha]_D$ −99.3[6]), which was further transformed to (−)-**4** ($[\alpha]_D$ −36.9 ($CHCl_3$), lit. $[\alpha]_D$ −9.0[7]) on treatment with Meerwein reagent (Scheme 3).

Conclusions

In conclusion, we found an intramolecular asymmetric Heck reaction to be applicable to substrates which seem to exist as a mixture of two atropisomers. Using this reaction, we succeeded in the first asymmetric synthesis of naturally occurring *abeo*-abietane-type diterpenoids, (−)-**2**, (−)-**3**, and (−)-**4**, in 10, 12, and 13 steps with an overall yield of 50%, 40%, and 39%, respectively. Our routes gave a much higher overall yield and ee within shorter steps than those for racemic and antipodal forms reported to date.

Experimental Section

2-(2,6,6-Trimethylcyclohex-2-enylidenemethyl)phenyl Trifluoromethanesulfonate (6). *N*-phenylbis(trifluoromethanesulfonimide) (1.88 g, 5.04 mmol) was added to a solution of **C** (960 mg, 4.20 mmol) in dichloromethane (15 mL) at room temperature under a nitrogen atmosphere. The mixture was allowed to cool to 0 °C, and triethylamine (1.52 mL, 10.5 mmol) was added dropwise to the reaction mixture, which was stirred for 14 h at room temperature. The reaction mixture was then poured into a saturated aqueous solution of sodium hydrogen carbonate and extracted with diethyl ether. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 19/1) to afford **6** (1.39 g, 91%, *E*/*Z* = 9/91 mixture). Colorless oil; ^{1}H NMR of the *Z*-isomer (400 MHz, $CDCl_3$) δ 7.35−7.15 (m, 4H), 6.36 (s, 1H), 5.63 (m, 1H), 2.21 (m, 2H), 1.60 (t, J = 6.4 Hz, 2H), 1.42 (s, 3H), 1.18 (s, 6H); ^{13}C NMR of the *Z*-isomer (100 MHz, $CDCl_3$) δ 151.3, 147.6, 134.5, 132.7, 131.2, 130.7, 128.2, 127.6, 121.1, 114.1, 36.7, 36.3, 27.3 (2C), 24.0, 22.9; IR ($CHCl_3$) 2961, 2930, 1421, 1248, 1140, 903 cm^{-1}; HRMS calcd for $C_{17}H_{19}F_3O_3S$ (M^+) 360.1007, found 360.1002.

1,1,4a-Trimethyl-2,4a-dihydro-1*H*-fluorene (7) and 1,1,4a-Trimethyl-4,4a-dihydro-1*H*-fluorene (8). Potassium carbonate (128.0 mg, 0.93 mmol), (*S*)-BINAP (34.0 mg, 0.056 mmol), and palladium acetate (6.2 mg, 0.028 mmol) were added to a solution of **6** (66.8 mg, 0.19 mmol, *E*/*Z* = 9/91) in DMF (2.0 mL), and the resulting mixture was stirred for 10 min at room temperature under an argon atmosphere. The reaction mixture was allowed to warm to 60 °C and stirred for 7.5 h. After the reacton was complete, the mixture was poured into water and extracted with chloroform. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane) to afford the products **7** and **8** as a regioisomeric mixture (31.8 mg, 90% from the *Z*-isomer of **6**). This regioisomer could be separated by silica gel column chromatography into **7** and **8**.

7: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, J = 7.3 Hz, 1H), 7.25 (d, J = 7.3 Hz, 1H), 7.17 (dt, J = 7.3, 1.4 Hz, 1H), 7.12 (dt, J = 7.3, 1.4 Hz, 1H), 6.42 (s, 1H), 6.04 (ddd, J = 9.7, 2.7, 1.0 Hz, 1H), 5.56 (ddd, J = 9.7, 5.0, 2.7 Hz, 1H), 2.20 (ddd, J = 17.1, 5.0, 1.0 Hz, 1H), 1.97 (dt, J = 17.1, 2.3 Hz, 1H), 1.44 (s, 3H), 1.36 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 152.7, 142.3, 131.6, 126.7, 125.2, 124.4, 121.3, 121.2, 120.8, 53.3, 43.4, 35.2, 29.4, 27.1, 26.8; IR ($CHCl_3$) 3007, 2964, 1603, 1466 cm^{-1}; EI-MS *m*/*z* 210 (M^+, 22), 195 (100), 180 (28), 165 (41), 152 (13), 89 (16), 76 (10); HRMS calcd for $C_{16}H_{18}$ (M^+) 210.1409, found 210.1414. Anal. Calcd for $C_{16}H_{18}$: C, 91.37; H, 8.63. Found: C, 91.09; H, 8.65.

(***S***)**-8**: colorless oil; $[\alpha]^{23}_D$ −197.3 (*c* 1.65, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.26 (m, 2H), 7.21 (dt, J = 7.5, 1.2,

(11) The heating experiment of *E*-**10** in the absence of the palladium catalyst did not afford *Z*-**10**. The ee value of the product from the mixture of the *E*- and *Z*-isomers was as high as that from the *Z*-isomer only. Therefore, the ee value from the *E*-isomer should be equal to that from the *Z*-isomer.

1H), 7.13 (dt, J = 7.5, 1.2 Hz, 1H), 6.47 (s, 1H), 5.67 (ddd, J = 10.1, 5.8, 2.0 Hz, 1H), 5.54 (ddd, J = 10.1, 2.9, 0.7 Hz, 1H), 2.49 (dd, J = 16.6, 5.8 Hz, 1H), 1.83 (br dt, J = 16.6, 2.0 Hz, 1H), 1.38 (s, 3H), 1.31 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 153.7, 143.1, 137.5, 126.6 (2C), 124.2, 122.6, 121.3, 120.8, 49.7, 37.3, 36.4, 30.0, 28.6, 23.7; IR ($CHCl_3$) 3007, 2963, 2912, 2866, 1468, 1367 cm^{-1}; EI-MS m/z 210 (M^+, 39), 195 (100), 180 (39), 165 (56), 152 (15), 128 (12), 115 (12), 89 (27), 76 (14); HRMS calcd for $C_{16}H_{18}$ (M^+) 210.1409, found 210.1413. [97% ee, HPLC: Chiralcel OJ, *n*-hexane/*i*-PrOH = 200/1, 0.3 mL/min, t_R = 16.3 min [(−)-**8**], 18.3 min [(+)-**8**).]

4-Isopropyl-7-methoxy-2,2-dimethylbenzo[1,3]dioxole (12). Acetone (9.6 mL, 130.78 mmol) and boron trifluoride (6.60 mL, 52.31 mmol) were added to a solution of **11**[1] (2.38 g, 13.01 mmol) in diethyl ether (15.0 mL) at °C, and the resulting mixture was stirred at room temperature for 21.5 h under an argon atmosphere. After the reaction was complete, the mixture was quenched with water at 0 °C and extracted with chloroform. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 24/1) to afford **12** (2.70 g, 93%). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.60 (d, J = 8.6 Hz, 1H), 6.42 (d, J = 8.6 Hz, 1H), 3.85 (s, 3H), 2.95 (sept, J = 7.0 Hz, 1H), 1.69 (s, 6H), 1.22 (d, J = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.0, 141.9, 134.6, 126.1, 123.6, 118.3, 105.8, 56.2, 28.2, 25.8 (2C), 22.3 (2C); IR ($CHCl_3$) 2964. 1506, 1448, 1286, 1219, 1126 cm^{-1}; EI-MS m/z 222 (M^+, 32), 207 (100), 167 (13); HRMS calcd for $C_{13}H_{18}O_3$ (M^+) 222.1256, found 222.1260. Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.33; H, 8.09.

5-Bromo-7-isopropyl-4-methoxy-2,2-dimethylbenzo[1,3]dioxole (13). *N*-Bromosuccinimide (3.34 g, 18.80 mmol) was added to a solution of **12** (3.80 g, 17.08 mmol) in dichloromethane (70.0 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 1.5 h under an argon atmosphere. After the reacton was complete, silica gel was added to the mixture, and the mixture was concentrated in vacuo to remove the solvent. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 30/1) to afford **13** (5.02 g, 98%). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (s, 1H), 3.94 (s, 3H), 2.92 (sept, J = 7.0 Hz, 1H), 1.69 (s, 6H), 1.19 (d, J = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.6, 138.5, 137.7, 125.7, 122.0, 118.6, 106.3, 60.0, 28.1, 25.6 (2C), 22.0 (2C); IR ($CHCl_3$) 2963, 1483, 1441, 1377, 1273, 1117 cm^{-1}; EI-MS m/z 302 (M^+ + 2, 56), 300 (M^+, 57), 287 (99), 285 (100); HRMS calcd for $C_{13}H_{17}BrO_3$ (M^+) 300.0361, found 300.0366; Anal. Calcd for $C_{13}H_{17}BrO_3$: C, 51.84; H, 5.69. Found: C, 51.59; H, 5.72.

7-Isopropyl-4-methoxy-2,2-dimethyl-5-(2,6,6-trimethylcyclohexe-2-enylidenemethyl)benzo[1,3]dioxole (15). *n*-Buthyllithium (4.32 mL, 11.22 mmol, 2.6 M in hexane) was added dropwise to a solution of **13** (3.07 g, 10.20 mmol) in THF (30.0 mL) at −78 °C, and the solution was stirred for 1 h under an argon atmosphere. β-Cyclocitral (2.06 mL, 10.20 mmol, 80% pure) was added dropwise at −78 °C, and the mixture was stirred for 0.5 h at the same temperature and stirred for another 2 h at 0 °C. After the reaction was complete, the reaction mixture was quenched with a saturated aqueous solution of ammonium chloride and extracted with chloroform. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo to give the crude material. A methanol solution of hydrogen chloride (5−10%, 8.0 mL) was added to the crude material at 0 °C, and the resulting solution was stirred for 15 min at the same temperature. The reaction mixture was then diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo to remove the solvent. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 30/1) to afford **15** (3.16 g, 87%, E/Z = 20/80). Colorless oil; ^{1}H NMR of the Z-isomer (400 MHz, $CDCl_3$) δ 6.43 (s, 1H), 6.32 (s, 1H), 5.52 (m, 1H), 3.86 (s, 3H), 2.92 (sept, J = 7.0 Hz, 1H), 2.21−2.17 (m, 2H), 1.68 (s, 6H), 1.56 (t, J = 6.4 Hz, 2H), 1.52 (dd, J = 3.3, 2.0 Hz, 3H), 1.20 (d, J = 7.0 Hz, 6H), 1.14 (s, 6H); ^{13}C NMR of the Z-isomer (100 MHz, $CDCl_3$) δ 146.8, 145.0, 139.2, 136.8, 132.4, 128.4, 125.9, 123.9, 121.3, 117.7, 117.4, 60.0, 37.4, 36.0, 28.5, 27.4, 25.8 (2C), 24.1, 23.0, 22.6, 22.5 (2C); IR ($CHCl_3$) 3005, 2966, 1701, 1418, 1366, 1240 cm^{-1}; EI-MS m/z 356 (M^+, 100), 341 (51), 325 (9), 313 (13), 283 (17), 235 (23); HRMS calcd for $C_{23}H_{32}O_3$ (M^+) 356.2351, found 356.2348. Anal. Calcd for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.21; H, 8.96.

7-Isopropyl-2,2-dimethyl-5-(2,6,6-trimethylcyclohexe-2-enylidenemethyl)benzo[1,3]dioxol-4-ol (16). 1-Dodecanethiol (28.0 mL, 117.59 mmol) was added dropwise to a suspension of sodium hydride (5.13 g, 117.59 mmol, 55% in mineral oil) in DMF (15.0 mL) at 0 °C, and the solution was stirred for 10 min under an argon atmosphere. After 10 min, the solution of **15** (4.19 g, 11.76 mmol) in DMF (15.0 mL) was added dropwise to the resulting mixture at 0 °C, and the reaction mixture was stirred at 120 °C for 17.5 h. After the reaction was complete, the reaction mixture was quenched with an aqueous solution of 1 M hydrochloric acid at 0 °C and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo to remove the solvent. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 100/1) to afford **16** (3.91 g, 97%, E/Z = 20/80). Colorless oil; ^{1}H NMR of the Z-isomer (400 MHz, $CDCl_3$) δ 6.40 (s, 1H), 6.24 (s, 1H), 5.04 (m, 1H), 5.03 (s, 1H, OH), 2.92 (sept, J = 7.0 Hz, 1H), 2.24−2.19 (m, 2H), 1.69 (s, 6H), 1.58 (t, J = 6.4 Hz, 2H), 1.52−1.50 (m, 3H), 1.20 (d, J = 7.0 Hz, 6H), 1.17 (s, 6H); ^{13}C NMR of the Z-isomer (100 MHz, $CDCl_3$) δ 149.5, 144.7, 135.2, 133.1, 131.7, 130.3, 122.1, 120.6, 119.1, 118.0, 115.9, 37.6, 36.0, 28.2, 28.0, 27.2, 25.6 (2C), 23.8, 22.4 (2C), 22.1; IR ($CHCl_3$) 3518, 2963, 2924, 1452, 1377, 1248, 1151 cm^{-1}; EI-MS m/z 342 (M^+, 49), 327 (100), 299 (9), 285 (8), 221 (25); HRMS calcd for $C_{22}H_{30}O_3$ (M^+) 342.2195, found 342.2188.

7-Isopropyl-2,2-dimethyl-5-(2,6,6-trimethylcyclohexe-2-enylidenemethyl)benzo[1,3]dioxol-4-yl trifluoromethanesulfonate (10). Triflic anhydride (1.75 mL, 10.41 mmol) was slowly added to a solution of **16** (2.38 g, 6.94 mmol) in pyridine (20.0 mL) at 0 °C, and the reaction mixture was stirred at the same temperature for 1.5 h and stirred for another 2.0 h at room temperature under an argon atmosphere. After the reacton was complete, the reaction mixture was quenched with water at 0 °C and extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo to remove the solvent. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 50/1) to afford **10** (3.10 g, 94%, E/Z = 20/80). Colorless oil; ^{1}H NMR of the Z-isomer (400 MHz, $CDCl_3$) δ 6.52 (s, 1H), 6.22 (s, 1H), 5.58 (m, 1H), 2.96 (sept, J = 7.0 Hz, 1H), 2.22−2.18 (m, 2H), 1.70 (s, 6H), 1.58 (t, J = 6.4 Hz, 2H), 1.47 (m, 3H), 1.20 (d, J = 7.0 Hz, 6H), 1.14 (s, 6H); ^{13}C NMR of the Z-isomer (100 MHz, $CDCl_3$) δ 149.9, 148.9, 145.1, 138.3, 131.4, 129.0, 128.8, 128.0, 127.2, 121.3, 120.3, 114.4, 36.6, 36.0, 28.6, 27.2, 25.6 (2C), 23.9, 22.6, 22.1, 22.0 (2C); IR ($CHCl_3$) 2966, 2926, 1450, 1418, 1250, 1140, 1109, 1049 cm^{-1}; EI-MS m/z 474 (M^+, 55), 356 (100), 341 (67), 285 (87); HRMS calcd for $C_{23}H_{29}F_3O_5S$ (M^+) 474.1687, found 474.1684.

(*S*)-4-Isopropyl-2,2,7,7,10a-pentamethyl-8,9,10,10a-tetrahydro-7*H*-fluoreno[3,4-*d*][1,3]dioxole [(+)-18]. Palladium acetate (6.1 mg, 0.027 mmol) was added to a suspension of **10** (64.0 mg, 0.135 mmol), cesium carbonate (176.3 mg, 0.541 mmol), and (*R*)-synphos (**17**) (34.5 mg, 0.054 mmol) in DMF (2 mL). The reaction mixture was stirred for 26 h at 80 °C under an argon atmosphere. After the reacton was complete, the mixture was quenched with water, and the resulting mixture was extracted

with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (hexane/diethyl ether = 50/1) to afford the cyclized products as a regioisomeric mixture (33.1 mg, 72%). $RhCl(PPh_3)_3$ (23.6 mg, 0.026 mmol) was added to a solution of the cyclic compounds (33.1 mg, 0.102 mmol) in methanol (1.0 mL) under a nitrogen atmosphere. The nitrogen was replaced with hydrogen, and the resulting mixture was stirred for 24.5 h at room temperature. After the reacton was complete, the solvent was concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/diethyl ether = 50/1) to afford **18** (33.1 mg, 99%). Colorless crystal; mp 89−91 °C (*i*-PrOH); $[\alpha]^{26}_D$ +68.2 (*c* 2.67, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.59 (s, 1H), 6.22 (s, 1H), 3.30 (sept, J = 7.0 Hz, 1H), 2.32 (dd, J = 13.0, 1.5 Hz, 1H), 1.91 (tq, J = 13.0, 3.3 Hz, 1H), 1.66 (s, 6H), 1.55−1.64 (m, 2H), 1.43 (s, 3H), 1.25 (s, 6H), 1.23 (d, J = 7.0 Hz, 3H), 1.21 (d, J = 7.0 Hz, 3H), 1.11 (dt, J = 13.0, 4.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 142.6, 141.3, 136.8, 132.1, 127.5, 120.8, 116.8, 109.7, 50.2, 42.6, 36.5, 35.4, 31.3, 28.4, 25.8 (2C), 25.5, 22.5, 22.4, 21.1, 19.4; IR ($CHCl_3$) 2999, 2963, 2934, 1602, 1429, 1375, 1332 cm^{-1}; EI-MS m/z 326 (M^+, 100), 311 (70), 283 (16), 268 (21), 257 (55); HRMS calcd for $C_{22}H_{30}O_2$ (M^+) 326.2246, found 326.2247. Anal. Calcd for $C_{22}H_{30}O_2$: C, 80.94; H, 9.26. Found: C, 80.82; H, 9.45. [98% ee, HPLC: Chiralcel OD → OD-H, *n*-hexane, 0.1 mL/min, t_R = 72 min [(−)-**18**], 75 min [(+)-**18**.]

(−)-Dichroanal B [(−)-2]. A solution of (+)-**18** (33.5 mg, 0.10 mmol, 94% ee) in a hydrogen chloride methanol solution (3.0 mL, 5−10%) was stirred for 1 h at room temperature and then for another 8 h at 60 °C. After the reacton was complete, the mixture was concentrated in vacuo to remove the solvent. Next, boron trichloride (309 μL, 0.31 mmol, 1 M in dichloromethane) was added dropwise to a solution of the residue in dichloromethane (3.0 mL), and subsequent dichloromethyl methyl ether (46.6 μL, 0.52 mmol) was then added dropwise at −78 °C, and the resulting mixture was stirred for 1 h at the same temperature and for another 11 h at 0 °C. After the reacton was complete, the mixture was quenched with an aqueous solution of 1 M hydrochloric acid and extracted with chloroform. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo to remove the solvent. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 6/1) to afford (−)-**2** (30.8 mg, 95%). Yellow amorphous; $[\alpha]^{21}_D$ −15.3 (*c* 0.61, dioxane); ^{1}H NMR (400 MHz, C_5D_5N) δ 10.93 (s, 1H), 7.56 (s, 1H), 4.95 (br s, 2H), 4.44 (sept, J = 7.1 Hz, 1H), 2.90 (dd, J = 12.8, 1.5 Hz, 1H), 1.91 (qt, J = 13.7, 3.1 Hz, 1H), 1.70 (s, 3H), 1.63 (d, J = 7.1 Hz, 6H), 1.60−1.56 (m, 1H), 1.53−1.49 (m, 1H), 1.27 (s, 3H), 1.21 (s, 3H), 1.18−1.05 (m, 2H); ^{13}C NMR (100 MHz, C_5D_5N) δ 192.2, 167.5, 150.8, 143.0, 141.3, 139.7, 139.5, 121.3, 120.9, 51.5, 43.4, 36.7, 36.2, 31.9, 27.4, 25.9, 23.1, 23.0, 20.7, 20.1; IR ($CHCl_3$) 3524, 2969, 2934, 1670, 1589, 1458, 1275 cm^{-1}; EI-MS m/z 314 (M^+, 36), 300 (45), 283 (36), 271 (12), 258 (18), 245 (100), 231 (34); HRMS calcd for $C_{20}H_{26}O_3$ (M^+) 314.1882, found 314.1890.

(*S*)-5-Bromo-4-isopropyl-2,2,7,7,10a-pentamethyl-8,9,10,10a-tetrahydro-7*H*-fluoreno[3,4-*d*][1,3]dioxole [(+)-19]. *N*-Bromosuccinimide (67 mg, 0.38 mmol) was added to a solution of (+)-**18** (112 mg, 0.32 mmol) in dichloromethane (3.0 mL) at 0 °C, and the reaction mixture was stirred for 2 h at the same temperature. The reaction mixture was quenched with an aqueous solution of 1 M hydrochloric acid and extracted with chloroform. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo to remove the solvent. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 100/1) to give (+)-**19** (134 mg, 97%). Colorless crystal; mp 140−150 °C (*i*-PrOH); $[\alpha]^{26}_D$ +39.5 (*c* 1.59, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.33 (s, 1H), 3.42 (sept, J = 7.2 Hz, 1H), 2.31 (dd, J = 13.2, 3.2 Hz, 1H), 1.90 (tq, J = 13.0, 3.3 Hz, 1H), 1.65 (d, J = 0.8 Hz, 6H), 1.56−1.64 (m, 2H), 1.42 (s, 3H), 1.31−1.28 (m, 9H), 1.22 (s, 3H), 1.16−1.07 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 144.1, 141.3, 136.5, 132.6, 126.3, 121.3, 117.6, 106.7, 76.7, 51.7, 42.6, 36.4, 35.6, 31.6, 31.2, 25.64, 25.62, 25.4, 20.9, 20.5, 19.3; IR ($CHCl_3$) 3018, 2937, 1427, 1375, 1333, 1267, 1238, 1196 cm^{-1}; EI-MS m/z 404 (M^+, 64), 406 (61), 391 (31), 389 (31), 337 (85), 335 (88), 58 (100); HRMS calcd for $C_{22}H_{29}BrO_2$ (M^+) 404.1350, found 404.1354. Anal. Calcd for $C_{22}H_{29}BrO_2$: C, 65.18; H, 7.21. Found: C, 65.38; H, 7.25.

(*S*)-4-Isopropyl-5-methoxy-2,2,7,7,10a-pentamethyl-8,9,10,10a-tetrahydro-7*H*-fluoreno[3,4-*d*]dioxole [(+)-20]. Copper iodide (177 mg, 0.93 mmol) and a suspension of sodium methoxide (1.0 mL, 4.63 mmol, 28% in methanol) in DMF/methanol = 1/1 (10 mL) were added to a solution of (+)-**19** (313 mg, 0.77 mmol, 98% ee) in DMF (5.0 mL) at room temperature, and the resulting mixture was stirred at 100 °C for 28 h. The reaction mixture was added to water and extracted with diethyl ether. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo to remove the solvent. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 50/1) to afford (+)-**20** (272 mg, 99%). Colorless crystal; mp 135−138 °C (*i*-PrOH); $[\alpha]^{26}_D$ +47.9 (*c* 1.02, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.32 (s, 1H), 3.78 (s, 3H), 3.32−3.25 (sept, J = 7.2 Hz, 1H), 2.32−2.26 (dd, J = 12.8, 1.6 Hz, 1H), 1.96−1.84 (tq, J = 13.6, 3.2 Hz, 1H), 1.65 (d, J = 4.0 Hz, 6H), 1.63−1.53 (m, 2H), 1.42 (s, 3H), 1.31−1.27 (m, 9H), 1.21 (s, 3H), 1.15−1.07 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 144.3, 143.7, 138.2, 132.4, 127.4, 121.4, 117.1, 76.7, 62.6, 50.6, 50.5, 42.7, 36.5, 35.4, 31.3, 25.6, 25.5, 25.0, 21.4, 21.3, 21.1, 19.4; IR ($CHCl_3$) 3034, 3009, 2936, 2361, 2341, 1452, 1429, 1375, 1335, 1234, 1209, 1198 cm^{-1}; EI-MS m/z 356 (M^+, 80), 341 (37), 287 (100), 143 (10); HRMS calcd for $C_{23}H_{32}O_3$ (M^+) 356.2351, found 356.2344. Anal. Calcd for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.22; H, 9.00.

(−)-Dichroanone [(−)-3]. Boron tribromide (0.58 μL, 0.58 mmol) was added dropwise to a solution of (+)-**20** (41 mg, 0.12 mmol, 98% ee) in dichloromethane (5.0 mL) at 0 °C, and the reaction mixture was stirred for 1 h at the same temperature and then for another 14 h at room temperature under an argon atmosphere. After the reacton was complete, the mixture was quenched with an aqueous solution of 1 M hydrochloric acid at 0 °C and extracted with chloroform. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo to remove the solvent. Then, 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (32 mg, 0.14 mmol) was added to a solution of the residue in dichloromethane (3.0 mL) at room temperature, and the reaction mixture was stirred at room temperature for 1 h under an argon atmosphere. After the reacton was complete, the mixture was quenched with water and extracted with chloroform. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/diethyl ether = 14/1) to afford (−)-**3** (33 mg, 94%). Red amorphous; $[\alpha]^{21}_D$ −97.8 (*c* 0.14, dioxane); ^{1}H NMR (400 MHz, $CDCl_3$) (H of OH was not detected) δ 6.45 (s, 1H), 3.22 (sept, J = 7.0 Hz, 1H), 2.38 (dq, J = 13.0, 2.5 Hz, 1H), 1.92 (tq, J = 14.0, 3.5 Hz, 1H), 1.71 (br dq, J = 13.0, 2.5 Hz, 1H), 1.67−1.60 (m, 1H), 1.46 (s, 3H), 1.29 (s, 3H), 1.24 (s, 3H), 1.24 (dd, J = 7.0, 1.8 Hz, 6H), 1.15−1.06 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.7, 178.2, 177.1, 152.4, 148.9, 147.7, 122.7, 118.0, 55.3, 43.3, 37.3, 37.0, 30.9, 24.7, 23.9, 20.1, 20.0, 19.0; IR ($CHCl_3$) 3368, 2964, 2930, 2872, 2856, 1717, 1636, 1526, 1470, 1458, 1369, 1319 cm^{-1}; EI-MS m/z 300 (M^+, 93), 285 (85), 267 (9), 257 (29), 232 (48), 231 (79); HRMS calcd for $C_{19}H_{24}O_3$ (M^+) 300.1725, found 300.1723.

(−)-Taiwaniaquinone H [(−)-4]. *N*,*N*-Diisopropylethylamine (6.5 μL, 0.038 mmol) and Meerwein reagent (5.1 mg, 0.034 mmol) were added to a solution of (−)-**3** (9.4 mg, 0.031 mmol, 98% ee) in dichloromethane (1.0 mL) at room temperature, and the reaction mixture was stirred for 7 h under an argon atmosphere. After the reacton was complete, the mixture was quenched with an aqueous solution of 1 M hydrochloric acid at 0 °C and extracted with chloroform. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo to remove the solvent. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 9/1) to afford (−)-**4** (9.8 mg, 99%). Orange amorphous; $[\alpha]^{21}_{D}$ −36.9 (*c* 0.30, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.38 (s, 1H), 3.99 (s, 3H), 3.25 (sept, J = 7.0 Hz, 1H), 2.40 (dq, J = 13.1, 2.6 Hz, 1H), 1.92 (tq, J = 13.8, 3.4 Hz, 1H), 1.72−1.66 (m, 1H), 1.65−1.59 (m, 1H), 1.44 (s, 3H), 1.27 (s, 3H), 1.24, 1.23 (each d, J = 7.0 Hz, 3H), 1.22 (s, 3H), 1.08 (tt, J = 13.5, 3.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.3, 178.8, 175.7, 157.3, 150.5, 145.8, 136.0, 116.7, 61.3, 55.6, 43.3, 37.2, 36.7, 30.9, 24.8, 24.5, 20.7, 20.6, 20.1, 19.1; IR ($CHCl_3$) 3031, 1643, 1533, 1236, 1197 cm^{-1}; EI-MS m/z 314 (M^+, 100), 299 (97), 285 (14), 271 (24), 255 (57), 245 (56); HRMS calcd for $C_{20}H_{26}O_3$ (M^+) 314.1882, found 314.1889.

***O*-[2-(2,6,6-Trimethylcyclohex-2-enylidenemethyl)phenyl]-2-(*R*)-*tert*-butoxycarbonylamino-3-phenylpropionate (9).** To a solution of **C** (131 mg, 0.57 mmol) in dichloromethane (5.0 mL) were added *N*-Boc-D-phenylalanine (274 mg, 1.03 mmol) and WSC (220 mg, 1.15 mmol) at room temperature, and the mixture was stirred for 14 h at the same temperature under a nitrogen atmosphere. After the reacton was complete, the mixture was quenched with a saturated aqueous solution of ammonium chloride and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo to remove the solvent. The residue was purified with silica gel column chromatography (hexane/diethyl ether = 24/1) to give **9** (75 mg, 28%). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.12 (m, 8H), 6.94 (d, J = 7.9 Hz, 1H), 6.22 (s, 1H), 5.57 (s, 1H), 5.01 (d, J = 8.1 Hz, 1H, NH), 4.82−4.76 (m, 1H), 3.30 (dd, J = 11.0, 5.4 Hz, 1H), 3.12 (dd, J = 11.0, 6.9 Hz, 1H), 2.22−2.17 (m, 2H), 1.53 (t, J = 6.4 Hz, 2H), 1.42 (br s, 3H), 1.41 (s, 9H), 1.11 (s, 3H), 1.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 155.1, 149.8, 148.0, 136.1, 133.5, 132.0, 131.8, 129.7, 128.8, 127.6, 127.3, 125.8, 121.6, 115.84, 115.77, 80.1, 54.67, 54.65, 38.8, 37.1, 36.1, 28.5, 27.7, 24.0, 23.2; IR ($CHCl_3$) 2926, 1759, 1713, 1497, 1456, 1367, 1163 cm^{-1}; EI-MS m/z 475 (M^+, 1), 419 (29), 374 (8), 360 (19), 228 (45), 213 (67), 172 (100); HRMS calcd for $C_{30}H_{37}NO_4$ (M^+) 475.2723, found 475.2722.

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra for all new compounds, an ORTEP for **19**, and complete experimental details following the general procedures. This material is available free of charge via the Internet at http://pubs.acs.org.