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Catalytic Asymmetric Synthesis of a Versatile Intermediate for Diterpene Syntheses. Regioselective Olefin Insertion in Asymmetric Heck Reactions

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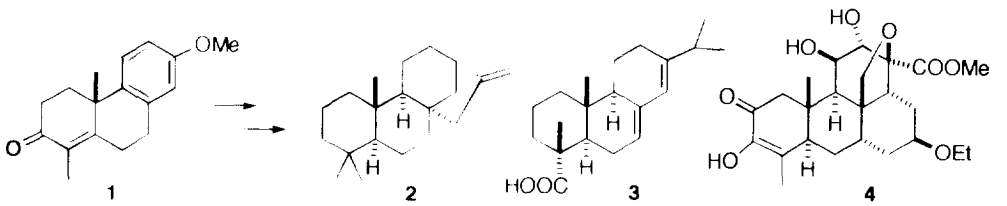
Abstract : We describe the details of the regioselective asymmetric cyclization of **5** to optically active **8** (95% ee), and the use of this tricyclic compound in the asymmetric synthesis of various diterpenes.

Since our first report on the asymmetric Heck reaction in 1989, we[1] and others[2] have demonstrated that this carbon-carbon bond-forming reaction is quite useful for the highly enantioselective synthesis of various compounds. The construction of polycyclic skeletons via the intramolecular Heck reaction is a particularly powerful application and has been used in the asymmetric synthesis of several complex natural products.[1e,f,g,k,p,q,2i] In these cases, however, there has been no issue of regioselectivity in the cyclization with only the 5-exo or 6-exo mode possible. The question remains as to whether regioselectivity in the cyclization of substrates containing both possible reaction pathways can be controlled and predicted. Herein we describe the details of the regioselective asymmetric cyclization of **5** to optically active **8** (95% ee), and the use of this tricyclic compound in the asymmetric synthesis of various diterpenes.[3]



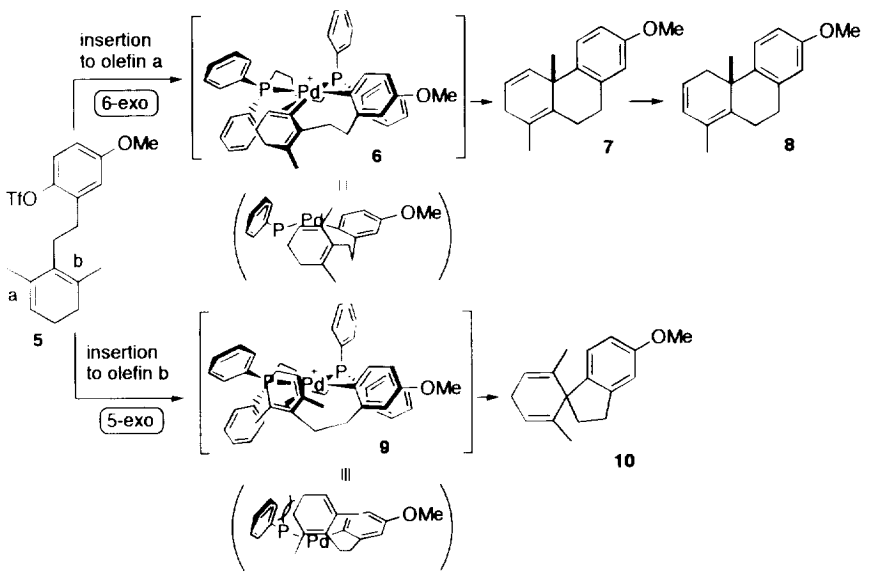
Scheme 1

The enone **1** is a versatile synthetic intermediate for a number of diterpenes such as kaurene (**2**), abietic acid (**3**) and bruceantin analog (**4**).[4] We planned the asymmetric synthesis of enone **1** from **5**, a substrate expected to yield the tetrahydrophenanthrene derivative **7** or its isomerized product **8** in a regioselective, asymmetric Heck cyclization. The 6-exo-cyclization was predicted using a molecular model with the assumptions that: (1) cyclization of the aryl triflate would proceed via a squareplanar cationic Pd(II) intermediate with a 16-electron configuration,[1f,o] and that (2) the insertion step would proceed through "in-plane" coordination of the olefin as suggested by Hoffmann *et al.*.[5] In principle, four insertion modes, 6-exo, 7-endo, 5-exo, and 6-endo, are possible for diene **5**; however, the 7-endo and 6-endo modes

Dedicated to the memory of Professor Hidemasa Takaya, deceased on 5 October 1995

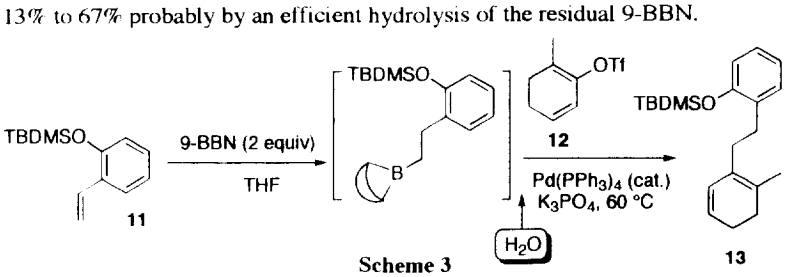
are disfavored by the severe tortional strain that results on "in-plane" coordination. As shown in Scheme 2, "in-plane" coordination leading to both the 6-exo and 5-exo products, **7** and **10**, respectively are possible.

Discrimination between the remaining two pathways relies on consideration of the steric environment generated by the chiral ligand. Extrapolating from the X-ray crystal structure of $PdCl_2$[(*R*)-binap], one would expect that the (*R*)-BINAP ligand forms an asymmetric environment about Pd with a phenyl group placed in close proximity to the olefin coordinating site.[2k] More steric repulsion would thus result between the phenyl group and the tetra-substituted olefin **b** (in **9**) than the trisubstituted olefin **a** (in **6**), and this was expected to give preferred formation of the desired optically active tricyclic compound **7**. To verify this prediction, the asymmetric Heck cyclization of **5** using (*R*)-BINAP was examined.



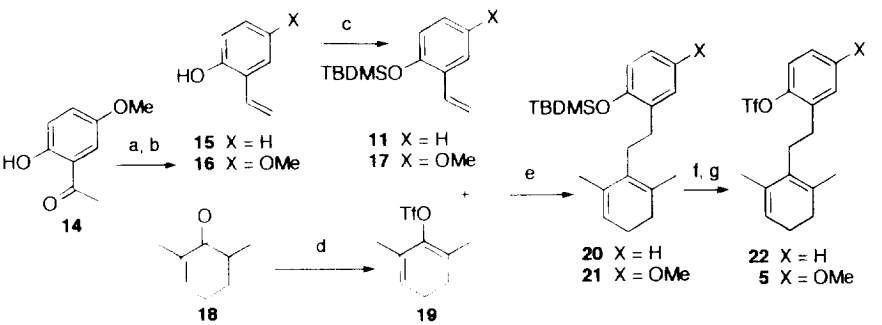
Scheme 2

Substrate **5** was planned to be synthesized using a Suzuki coupling[6] of an alkylborane and an alkenyl triflate as a key step. Initial examination of this coupling reaction using model substrates **11** and **12**, prepared from 2-vinylphenol[7] and 2-methyl-2-cyclohexenone respectively, were problematic. Excess 9-BBN was necessary for the complete conversion of **11** to its hydroboration product but caused formation of the reduced product, 2-methylcyclohexa-1,3-diene as well. Formation of this by-product suggests that the hydridoalkenylpalladium intermediate is formed on transmetallation with 9-BBN. Addition of water to the reaction mixture after the hydroboration of **11** was found to improve the yield of the coupling product **13** from 13% to 67% probably by an efficient hydrolysis of the residual 9-BBN.



Scheme 3

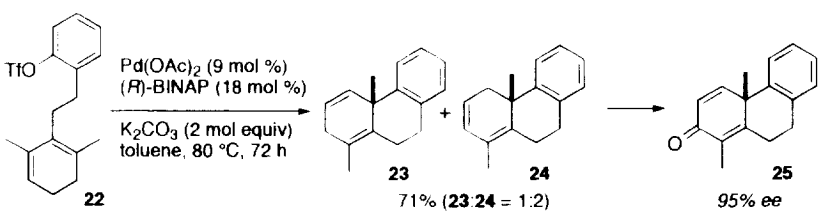
Using these modified conditions the coupling reaction of the vinyl phenol derivative **11** with triflate **19**, prepared from **18**,[8] also proceeded smoothly to afford **20** in 68% yield. Silyl ether **20** was then converted to triflate **22** in 65% yield by deprotection of the *tert*-butyldimethylsilyl group and trifluoromethanesulfonylation. Furthermore, synthesis of the methoxy-substituted substrate **5** was also achieved by the use of similar procedures starting from **14** (Scheme 4).



a) $LiAlH_4$, Et_2O, 23 °C; b) HMPA, 224 °C (81%, 2 steps); c) for **11**: TBDMSCl, imidazole, DMF (94%); for **17**: TBDMSCl, Et_3N, DMAP, CH_2Cl_2 (98%); d) LDA, THF, -78 °C, then Tf_2NPh, 0 °C (65%); e) For **20**, **11**, 9-BBN, THF, 23 °C then H_2O; **19**, $Pd(PPh_3)_4$ (cat.), K_3PO_4, 60 °C (68%); for **21**, **17**, 9-BBN, THF, 23 °C then H_2O; **19**, $Pd(PPh_3)_4$ (cat.), K_3PO_4, 60 °C (72%); f) TBAF, THF; g) Tf_2O, NEt_3, -78 °C (for **22**: 65%; for **5**: 63%, 2 steps)

Scheme 4

With these desired substrates **22** and **5** in hand, we first began to test reaction conditions for the asymmetric Heck reaction using the model substrate **22**. Treatment of diene **22** with $Pd(OAc)_2$ (9 mol %), (*R*)-BINAP[9] (18 mol %), and K_2CO_3 (2 mol equiv) in toluene at 80 °C for 72 h gave the desired 6-endo-cyclized products **23** and **24** in 71% chemical yield (**23**:**24** = 1:2). Oxidation of this inseparable mixture with CrO_3-3,5-dimethylpyrazole (CH_2Cl_2, 0 °C, 1 h)[10] afforded dienone **25** in 14% yield. HPLC analysis of **25** using chiral phase column (DAICEL CHIRALCEL OJ, hexane:2-propanol, 9:1) indicated that the enantiomeric excess of **25** was 95%.

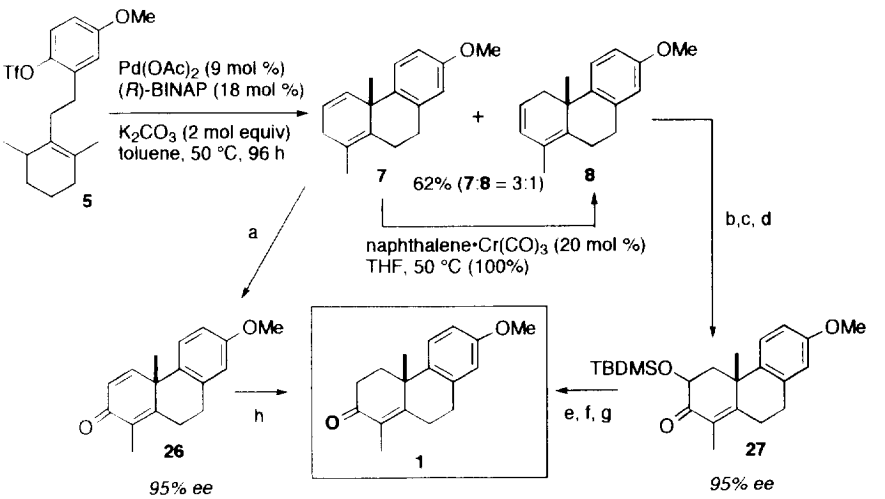


Scheme 5

Encouraged by this excellent asymmetric induction, we next examined the cyclization of **5**. Reaction of **5** under the similar conditions ($Pd(OAc)_2$: 9 mol %, (*R*)-BINAP: 18 mol %, and K_2CO_3: 3 mol equiv, in toluene at 80 °C for 12 h), however, gave the desired 6-endo-cyclized product **7** only in 36% chemical yield. The enantiomeric excess of **7** was determined to be 94% ee by HPLC analysis (DAICEL CHIRALCEL OJ, hexane:2-propanol, 9:1) after conversion to **26**. A small amount of **5** (16%) was

recovered under these conditions; however, prolonged reaction at this temperature did not improve the chemical yield of **7** possibly because of decomposition of the products and/or starting material. The use of other solvents, such as THF, DMF and 1,2-dichloroethane, and of another palladium complex, $Pd_2(dba)_3$•$CHCl_3$, gave less satisfactory results.[11] However, when the reaction temperature was decreased to 60 °C, the conjugated diene **8** was formed in 8% yield in addition to **7** (38%). Finally, reaction at 50 °C gave the best results with the combined yield of the desired 6-exo-cyclized products **7** and **8** increasing to 62% (**7** : **8** = 3:1) (**7** : $[\alpha]_D^{24}$ +174 (*c* 0.60, $CHCl_3$), **8** : $[\alpha]_D^{27}$ +363 (*c* 4.67, $CHCl_3$)).[12] *Asymmetric induction in this cyclization was 95% ee.*[13] The non-conjugated diene **7** (or a mixture of **7** and **8**) was cleanly isomerized to conjugated diene **8** in quantitative yield using catalytic naphthalene•$Cr(CO)_3$.[14] The specific rotation of **8** from this isomerization reaction was identical to that of the product from the Heck reaction suggesting no kinetic resolution occurred during the Pd-catalyzed isomerization process.[15] Thus 6-exo selective cyclization of **5** to **8** has been achieved with excellent enantioselectivity. The 5-exo-cyclized product **10** was not isolated in any case.

Conjugated diene **8** has been successfully converted to enone **1** ($[\alpha]_D^{27}$ +149 (*c* 1.21, $CHCl_3$), 95% ee).[13] As shown in Scheme 6, a diastereomeric mixture of the *cis*-diols obtained by the regioselective dihydroxylation of **8** was converted to the α-silyloxyenone **27** in good yield after selective protection and oxidation. Removal of the silyloxy group from **27** afforded enone **1**, with spectral data identical to that reported. The absolute stereochemistry of **1** was unequivocally determined to be (*S*) by comparison of its specific rotation with the reported value.[4d] This enone **1** was also obtained in one step from **26** by regioselective $RhCl(PPh_3)_3$-catalyzed hydrogenation.



a) CrO_3, 3,5-dimethylpyrazole, CH_2Cl_2, -78 °C (24%, 48% conversion yield); b) OsO_4, *t*-BuOH-H_2O, then $NaHSO_3$, pyridine (76%); c) TBDMSCl, DMAP, CH_2Cl_2 (94%); d) SO_3•Py, NEt_3, DMSO (90%); e) HF, MeCN-H_2O (70%); f) PhOC(=S)Cl, DMAP, MeCN; g) Bu_3SnH, AIBN, benzene, 90 °C (43%, 2 steps); h) H_2, $RhCl(PPh_3)_3$, benzene (79%).

Scheme 6

In conclusion, we have shown that a highly regio- and enantioselective intramolecular Heck reaction of **5** can be achieved, and conversion of the cyclized products to **1** provides a simple route to a useful intermediate for diterpene syntheses. This example suggests that consideration of the interactions resulting on "in-plane" olefin coordination in cationic complexes may be useful for the prediction of the regio- and enantioselectivity in asymmetric Heck reactions.

Experimental Section

Infrared (IR) spectra were measured on a JASCO A-300 diffraction grating infrared spectrophotometer. Nuclear magnetic resonance (NMR) spectra were recorded with a JEOL JNM-FX-270 NMR spectrometer with tetramethylsilane as an internal standard ($CDCl_3$). Mass spectra (MS) were obtained from a JEOL JMS-DX303, a JEOL JMS-D300 or a JEOL JMS-HX100 instrument. Optical rotation was measured on a JASCO DIP-140 polarimeter. In general, reactions were carried out in dry solvents under an argon atmosphere unless otherwise mentioned. Solvents were distilled before use. IR, NMR and MS data were obtained on all intermediates described herein using chromatographically homogeneous samples.

2-*tert*-Butyldimethylsilyloxystyrene 11 :

To a stirred solution of 2-hydroxystyrene **15** (2.07 g, 17.2 mmol) in DMF (15.0 mL) were added imidazole (3.47 g, 51.0 mmol) and *tert*-butyldimethylsilyl chloride (3.89 g, 25.8 mmol) at 0 °C. The reaction mixture was stirred at 23 °C for 1 hr, diluted with H_2O and extracted with EtOAc. The organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column (hexane) to give the silyl ether **11** (3.78 g, 94%) as a colorless oil. IR (neat) 1626, 1252 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.22 (s, 6 H), 1.02 (s, 9 H), 5.23 (dd, J = 10.9, 1.3 Hz, 1 H), 5.68 (dd, J = 17.8, 1.3 Hz, 1 H), 6.80 (brd, J = 7.6 Hz, 1 H), 6.94 (brdd, J = 7.6, 7.6 Hz, 1 H), 7.09 (dd, J = 17.8, 10.9 Hz, 1 H), 7.14 (ddd, J = 7.6, 7.6, 1.7 Hz, 1 H), 7.50 (dd, J = 7.6, 1.7 Hz, 1 H). MS *m/z* 234 (M^+), 177 (bp). Anal. Calc. for $C_{14}H_{22}OSi$: C, 71.49; H, 9.35. Found : C, 71.73; H, 9.46.

2-Methyl-1,5-cyclohexadienyl Trifluoromethanesulfonate 12 :

To a solution of LDA (10.0 mmol) in THF (30.0 mL) was gradually added a solution of 6-methyl-2-cyclohexen-1-one (1.00 g, 9.17 mmol) in THF (20.0 mL) at -78 °C, and the reaction mixture was stirred for 1 h at the same temperature. To this enolate solution was then added $PhNTf_2$ (3.28 g, 9.17 mmol) at -78 °C, and the whole reaction mixture was stirred at 0 °C for 1 h, and concentrated. The residue was purified by silica gel column (hexane) to give the triflate **12** (1.33g, 60%) as a colorless oil. IR (neat) 1673, 1418, 1212, 1143 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.84 (s, 3 H), 2.20-2.40 (m, 4 H), 5.82 (s, 2 H). MS *m/z* 242 (M^+), 196, 91 (bp).

1-(*tert*-Butyldimethylsilyloxy)-2-[2-(2-methyl-1,5-cyclohexadienyl)ethyl]benzene 13 :

To the styrene derivative **11** (266 mg, 1.15 mmol) was addded 9-BBN (0.5 *M* in THF, 4.6 mL, 2.30 mmol) at 0 °C. After stirring for 30 min at 23 °C, water (2.0 mL) was added to the solution. The solution was stirred for 20 min at 23 °C, and to this solution were added $Pd(PPh_3)_4$ (92.4 mg, 0.0800 mmol), K_3PO_4 (488 mg, 2.30 mmol), and a solution of the triflate **12** (186 mg, 0.769 mmol) in THF (1.5 mL). The resulting solution was stirred for 20 min at 60 °C, cooled, and extracted with ether. The organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by prep-TLC (hexane) to give the coupling product **13** (159 mg, 67%) as a colorless oil. ^1H NMR ($CDCl_3$) δ 0.27 (s, 6 H), 1.05 (s, 9 H), 1.61 (s, 3 H), 2.00-2.19 (m, 4 H), 2.31-2.41 (m, 2 H), 2.63-2.75 (m, 2 H), 5.66-5.75 (m, 1

H), 5.87 (brd, J = 9.6 Hz, 1 H), 6.75-6.94 (m, 2 H), 7.03-7.16 (m, 2 H). ^{13}C NMR ($CDCl_3$) δ -4.06, 18.31, 18.83, 22.99, 25.86, 29.65, 29.98, 31.83, 118.29, 120.79, 123.54, 126.63, 128.23, 128.48, 128.68, 130.60, 132.63, 153.53.

2,6-Dimethy-1,5-cyclohexadienyl Trifluoromethanesulfonate 19 :

To a solution of LDA (2.80 mmol) in THF (6.0 mL) was gradually added a solution of 2,6-dimethyl-2-cyclohexen-1-one **18** (318 mg, 2.56 mmol) in THF (6.0 mL) at -78 °C, and the reaction mixture was stirred for 1 h at the same temperature. To this enolate solution was then added $PhNTf_2$ (929 mg, 2.60 mmol) at -78 °C, and the whole reaction mixture was stirred at 0 °C for 1 h, and concentrated. The residue was purified by silica gel column (hexane) to give the triflate **19** (405 mg, 65%) as a colorless oil. IR (neat) 1619, 1417, 1211, 1143 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.82 (d, J = 2.0 Hz, 3 H), 1.86 (brs, 3 H), 2.08-2.30 (m, 4 H), 5.58 (brs, 1 H). MS m/z 256 (M^+), 107 (bp). HR MS (M^+): Calcd. for $C_9H_{11}F_3O_3S$: 256. 0381. Found: 256.0372.

1-(*tert*-Butyldimethylsilyoxy)-2-[2-(2,6-dimethyl-1,5-cyclohexadienyl)ethyl]benzene 20 :

To the styrene derivative **11** (347 mg, 1.50 mmol) was addded 9-BBN (0.5 *M* in THF, 6.0 mL, 3.00 mmol) at 0 °C. After stirring for 60 min at 23 °C, water (2.0 mL) was added to the solution. The solution was stirred for 30 min at 23 °C, and to this solution were added $Pd(PPh_3)_4$ (116 mg, 0.100 mmol), K_3PO_4 (637 mg, 3.00 mmol), and a solution of the triflate **19** (256 mg, 1.00 mmol) in THF (1.5 mL). The resulting solution was stirred for 10 min at 60 °C, cooled, and extracted with ether. The organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. The residue was pufified by prep-TLC (hexane) to give the coupling product **20** (234 mg, 68%) as a colorless oil. IR (neat)1655, 1599, 1253 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.25 (s, 6 H), 1.02 (s, 9 H), 1.61 (s, 3 H), 1.83 (s, 3 H), 1.97 (brs, 4 H), 2.47 (dd, J = 7.9, 7.9 Hz, 2 H), 2.58 (dd, J = 7.9, 7.9 Hz, 2 H), 6.84 (brs, 1 H), 6.72-6.91 (m, 2 H), 7.00-7.13 (m, 2 H). ^{13}C NMR ($CDCl_3$) δ -3.99, 18.39, 19.46, 20.34, 22.77, 25.90, 28.21, 30.33, 118.31, 120.49, 120.76, 126.58, 130.21, 130.35, 130.60, 132.58, 133.96, 153.67. MS m/z 342 (M^+), 221, 165 (bp). HR MS (M^+) : Calcd. for $C_{22}H_{34}OSi$: 342.2369. Found : 342.2397.

2-[2-(2,6-Dimethyl-1,5-cyclohexadienyl)ethyl]phenyl Trifluoromethanesulfonate 22 :

To a stirred solution of **20** (179 mg, 0.523 mmol) in THF (1.0 mL) was added TBAF (1.0 *M* in THF, 0.6 mL, 0.600 mmol) at 0 °C. The mixture was stirred at 23 °C for 5 min and concentrated. The residual oil was dissolved in CH_2Cl_2 (2.0 mL), and Et_3N (0.28 mL, 2.00 mmol) and Tf_2O (0.17 mL, 1.00 mmol) were added at -78 °C. The resulting mixture was stirred for 30 min at the same temperature, poured into ice-water, extracted with ether. The organic extracts were washed with brine and concentrated. The residue was purified by prep-TLC (hexane) to give **22** (122 mg, 65%) as a colorless oil. IR (neat) 1422, 1216, 1143 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.63 (s, 3 H), 1.83 (s, 3 H), 1.99 (brs, 4 H), 2.48 (dd, J = 9.9, 8.6 Hz, 2 H), 2.72 (dd, J = 9.9, 8.6 Hz, 2 H), 5.52 (brs, 1 H), 7.19-7.41 (m, 4 H). ^{13}C NMR ($CDCl_3$) δ 19.27, 20.11, 22.64, 28.59, 30.23, 30.23, 118.63 (q, J = 325 Hz), 121.06, 127.76, 128.15, 129.31, 131.09, 131.81, 133.33, 134.77, 148.18. MS m/z 360 (M^+), 257, 199, 121 (bp). HR MS (M+) Calcd. for $C_{17}H_{19}O_3SF_3$: 360.1008. Found : 360.1003.

(4a*S*)-1,4a-Dimethyl-2,4a,9,10-tetrahydrophenanthrene 23 and (4a*S*)-1,4a-Dimethyl-4,4a,9,10-tetrahydrophenanthrene 24 :

To a suspension of $Pd(OAc)_2$ (2.9 mg, 0.0129 mmol), (*R*)-BINAP (16.0 mg, 0.0257 mmol) and K_2CO_3(39.5 mg, 0.286 mmol) in toluene (0.5 mL) was added a solution of **22** (51.5 mg, 0.143 mmol) in

toluene (1.5 mL) at 23 °C. After degassing, the reaction mixture was stirred at 80 °C for 72 h under an argon atomosphere, cooled, diluted with ether, filtered through a layer of Florisil to remove the solid material, and concentrated. The residue was purified by prep-TLC (hexane) to give the tricyclic compound **23** and **24** (21.3 mg, 71%) as an isomeric mixture (**23** /**24** = 1 : 2). IR (neat) 1657, 1607 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.27 (s, 3 Hx2/3), 1.44(s, 3 Hx1/3), 1.75 (s, 3 Hx1/3), 1.81 (s, 3 Hx2/3), 2.09-2.94 (m, 6 H), 5.69-5.88 (m, 2 Hx2/3+1 Hx1/3), 6.19 (brd, J = 10.0 Hz, 1 Hx1/3). MS m/z 210 (M^+, bp), 195.

(4a*R*)-1,4a-Dimethyl-2-oxo-2,4a,9,10-tetrahydrophenanthrene 25 :

To a suspension of CrO_3 (50.0 mg, 0.500 mmol) in CH_2Cl_2 (0.5 mL) was added 3,5-dimethylpyrazole (48.1 mg, 0.500 mmol) in one portion at -20 °C. After stirring at -20 °C for 20 min, a solution of the isomeric mixture **23** and **24** (10.9 mg, 0.0519 mmol, **23**/**24** = 1 : 2) in CH_2Cl_2 (1.0 mL) was added and the reaction mixture was stirred for 1 h at 0 °C. After diluting with ether, celite was added. The mixture was stirred at 23 °C for 1 h, filtered through florisil, and concentrated. The residue was purified by silica gel column (50% ether in hexane) to give **25** (1.1 mg, 9%) as a pale yellow oil.

IR (neat) 1662 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.60 (s, 3 H), 1.98 (s, 3 H), 2.59-2.75 (m, 1 H), 2.84-3.22 (m, 3 H), 6.34 (d, J = 9.9 Hz, 1 H), 7.09-7.28 (m, 3 H), 7.41-7.46 (m, 1 H), 7.47 (d, J = 9.9 Hz, 1 H). ^{13}C NMR ($CDCl_3$) δ 10.53, 26.63, 31.56, 32.26, 43.76, 125.93, 126.61, 126.74, 126.86, 129.22, 129.33, 153.75, 185.26. MS *m/z* 224 (M^+, bp), 209, 196, 181.

2-Hydroxy-5-methoxystyrene 16 :

To a stirred solution of the 2'-hydroxy-5'-methoxyacetophenone **14** (9.88 g, 59.5 mmol) in ether (400 mL) was added $LiAlH_4$ (4.55 g, 120 mmol) at 0 °C, and the reaction mixture was stirred for 30 min at 23 °C. The reaction mixture was quenched by the slow addition of water, acidified with aq HCl, and extracted with ether. The organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. The residual oil was dissolved in HMPA (60.0 mL). The resulting mixture was stirred for 30 min at 224 °C, cooled, poured into ice-water and extracted with ether. The organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column (25% ether in hexane) to give the hydroxystyrene derivative **16** (81%, 7.22 g) as a colorless oil. IR (neat) 3397, 1624 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.78 (s, 3 H), 4.65 (brs, 1 H), 5.36 (dd, J = 1.3, 11.2 Hz, 1 H), 5.73 (dd, J = 1.3, 17.5 Hz, 1 H), 6.65-6.79 (m, 2 H), 6.91-6.95 (m, 1 H), 6.94 (dd, J = 11.2, 17.5 Hz, 1 H). ^{13}C NMR ($CDCl_3$) δ 55.80, 111.91, 114.65, 115.90, 116.73, 125.48, 131.46, 146.95, 153.82. MS *m/z* 150 (M^+, bp), 135, 107. HR MS (M^+) : Calcd. for $C_9H_{10}O_2$: 150.0681. Found: 150.0669.

2-*tert*-Butyldimethylsilyloxy-5-methoxystyrene 17 :

To a stirred solution of the hydroxystyrene derivative **16** (2.20 g, 14.7 mmol) in CH_2Cl_2 (50.0 mL) were added Et_3N (9.80 mL, 70.3 mmol), TBDMSCl (4.43 g, 29.4 mmol) and DMAP (171 mg, 1.40 mmol) at 0 °C. The reaction mixture was stirred for 14 h at 23 °C, poured into ice-water and extracted with ether. The extracts were washed sucessively with aq HCl, water, sat aq $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column (50% ether in hexane) to give the silyl ether **17** (3.83 g, 98%) as a colorless oil. IR (neat) 1626, 1216 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.17 (s, 6 H), 1.01 (s, 9 H), 3.78 (s, 3 H), 5.22 (dd, J = 1.0, 11.2 Hz, 1 H), 5.65 (dd, J = 1.0, 17.8 Hz, 1 H), 6.66-6.74 (m, 2 H), 7.03 (dd, J = 11.2, 17.8 Hz, 1 H), 7.01-7.04 (m, 1 H). ^{13}C NMR ($CDCl_3$) δ -4.26, 18.28, 25.82, 55.65, 110.57, 113.75, 114.36, 120.32, 129.49, 132.02, 146.90, 154.00. MS *m/z* 264 (M^+), 207 (bp), 191, 181. HR MS (M^+) Calcd. for $C_{15}H_{24}O_2Si$: 264.1545. Found: 264.1541.

1-(*tert*-Butyldimethylsilyloxy)-2-[2-(2,6-dimethyl-1,5-cyclohexadienyl)ethyl]-4-methoxybenzene 21 :
To the styrene derivative **17** (883 mg, 3.34 mmol) was addded 9-BBN (0.5 *M* in THF, 13.2 mL, 6.6 mmol) at 0 °C. After stirring for 40 min at 23 °C, water (5.0 mL) was added to the solution. The solution was stirred for 30 min at 23 °C, and to this solution were added $Pd(PPh_3)_4$ (197 mg, 0.170 mmol), K_3PO_4 (1.06 g, 5.0 mmol), and a solution of the triflate **19** (405 mg, 1.67 mmol) in THF (2.5 mL). The resulting solution was stirred for 20 min at 60 °C, cooled, extracted with ether. The organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. The residue was pufified by prep-TLC (hexane, pretreated with 1% Et_3N in hexane) to give the coupling product **21** (447 mg, 72%) as a colorless oil. IR (neat) 1608, 1582, 1225 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.23 (s, 6 H), 1.03 (s, 9 H), 1.66 (s, 3 H), 1.83 (s, 3 H), 2.00 (brs, 4 H), 2.40-2.50 (m, 2 H), 2.52-2.65 (m, 2 H), 3.75 (s, 3 H), 5.51 (brs, 1 H), 6.58-6.76 (m, 3 H). MS *m/z* 372 (M^+), 315, 251, 195 (bp), 179. HR MS (M^+) Calcd. for $C_{23}H_{36}O_2Si$: 372.2485. Found: 372.2485.

2-[2-(2,6-Dimethyl-1,5-cyclohexadienyl)ethyl]-4-methoxyphenyl Trifluoromethanesulfonate 5 :
To a stirred solution of **21** (352 mg, 0.945 mmol) in THF (2.0 mL) was added TBAF (1.0 *M* in THF, 1.1 mL, 1.1 mmol) at 0 °C. The mixture was stirred at 23 °C for 5 min and concentrated. The residual oil was dissolved in CH_2Cl_2 (3.5 mL), and Et_3N (0.56 mL, 4.00 mmol) and Tf_2O (0.32 mL, 2.00 mmol) were added at -78 °C. The resulting mixture was stirred for 30 min at the same temperature, poured into ice-water, extracted with ether. The organic extracts were washed with brine and concentrated. The residue was purified by prep-TLC (hexane) to give **5** (233 mg, 63%) as a colorless oil. IR (neat) 1419, 1213, 1143 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.66 (s, 3 H), 1.81 (s, 3 H), 1.99 (brs, 4 H), 2.45-2.58 (m, 2 H), 2.62-2.77 (m, 2 H), 3.80 (s, 3 H), 5.52 (brs, 1 H), 6.73-6.80 (m, 2 H), 7.15 (d, J = 9.2 Hz, 1 H). MS *m/z* 390 (M^+), 225, 137, 121 (bp), 91. HR MS (M^+) Calcd. for $C_{18}H_{21}F_3O_4S$: 390.1113. Found: 390.1114.

(4a*S*)-7-Methoxy-1,4a-dimethyl-2,4a,9,10-tetrahydrophenanthrene 7 and (4a*S*)-7-Methoxy-1,4a-dimethyl-4,4a,9,10-tetrahydrophenanthrene 8 :
To a suspension of $Pd(OAc)_2$ (2.7 mg, 0.0120 mmol), (*R*)-BINAP (14.9 mg, 0.0239 mmol) and K_2CO_3(55.1 mg, 0.399 mmol) in toluene (0.3 mL) was added a solution of **5** (52.1 mg, 0.133 mmol) in toluene (1.0 mL) at 23 °C. After degassing, the reaction mixture was stirred at 50 °C for 96 h under an argon atomosphere, cooled, diluted with ether, filtered through a layer of Florisil to remove the solid material, and concentrated. The residue was purified by prep-TLC (hexane) to give the tricyclic compuond **7** (15.0 mg, 47%) as a more polar fraction and **8** (4.9 mg, 15%) as a less polar fraction accompanied by recovery of the starting material (1.1 mg, 3%). The spectral data of **7** : IR (nujol) 1608, 1463 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.41 (s, 3 H), 1.75 (s, 3 H), 2.30-2.88 (m, 6 H), 3.77 (s, 3 H), 5.71 (ddd, J = 9.9, 4.0, 3.0 Hz, 1 H), 6.14 (brd, J = 9.9 Hz, 1 H), 6.58 (d, J = 2.6 Hz, 1 H), 6.76 (dd, J = 8.9, 2.6 Hz, 1 H), 7.29 (d, J = 8.9 Hz, 1 H). ^{13}C NMR ($CDCl_3$) δ 18.53, 23.74, 31.56, 33.01, 33.21, 39.55, 55.19, 112.36, 113.39, 122.14, 122.41, 127.08, 132.78, 135.02, 137.77, 137.93, 157.07. MS *m/z* 240 (M^+), 225, 210, 165 (bp). HR MS (M^+) Calcd. for $C_{17}H_{20}O$: 240.1515. Found: 240.1511. $[\alpha]_D^{24}$ +174 (*c* 0.60, $CHCl_3$).
To a stirred solution of **7** (4.2 mg, 0.0175 mmol) in THF (0.7 mL) was added naphthalene•$Cr(CO)_3$ (0.8 mg, 0.00350 mmol) at 23 °C. After degassing by freeze-pump-thaw cycles the reaction mixture was stirred for 6 h at 50 °C, cooled, passed through Florisil and concetrated. The residue was purified by silca gel column (hexane) to give the diene **8** (4.2 mg, 100%) as a colorless oil. The spectral data of **8** : IR(neat) 1655, 1609 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.25 (s, 3 H), 1.82 (s, 3 H), 2.12-2.28 (m, 2 H), 2.47 (dd, J = 5.9, 16.8 Hz, 1 H), 2.70-2.93 (m, 3 H), 3.80 (s, 3 H), 5.77(ddd, J = 2.0, 5.9, 9.2 Hz, 1 H), 5.87 (dd, J = 2.6, 9.2

Hz, 1 H), 6.65 (d, J = 2.6 Hz, 1 H), 6.78 (dd, J = 2.6, 8.6 Hz, 1 H), 7.18 (d, J = 8.6 Hz, 1 H). ^{13}C NMR ($CDCl_3$) δ 17.68, 24.42, 25.21, 31.54, 37.00, 38.96, 55.17, 112.53, 112.85, 122.32, 123.27, 127.55, 129.47, 136.78, 137.77, 138.87, 156.98. MS *m/z* 240 (M^+), 225 (bp), 210, 105. HR MS (M^+) Calcd. for $C_{17}H_{20}O$: 240.1515. Found: 240.1516. $[\alpha]_D^{27}$ +363 (*c* 4.67, $CHCl_3$).

(4a*R*)-7-Methoxy-1,4a-dimethyl-2-oxo-2,4a,9,10-tetrahydrophenanthrene 26 :

To a suspension of CrO_3 (30.0 mg, 0.300 mmol) in CH_2Cl_2 (0.5 mL) was added 3,5-dimethylpyrazole (28.8 mg, 0.300 mmol) in one portion at -30 °C. After stirring at -30 °C for 20 min, a solution of **7** (7.1 mg, 0.0295 mmol) in CH_2Cl_2 (0.5 mL) was added at -78 °C and the reaction mixture was stirred for 1 h at the same temperature. After diluting with ether, celite was added. The mixture was stirred at 23 °C for 1 hr, filtered through florisil, and concentrated. The residue was purified by silica gel column (50% ether in hexane) to give **26** (1.8 mg, 24%) as a pale yellow oil accompanied by recovery of starting material **7** (3.1 mg, 44%). IR (neat) 1659 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1..58 (s, 3 H), 1.98 (s, 3 H), 2.53-2.75 (m, 1 H), 2.81-3.19 (m, 3 H), 3.78 (s, 3 H), 6.32 (d, J = 10.2 Hz, 1 H), 6.67 (d, J = 2.6 Hz, 1 H), 6.81 (dd, J = 8.9, 2.6 Hz, 1 H), 7.35 (d, J = 8.9 Hz, 1 H), 7.43 (d, J = 10.2 Hz, 1 H). ^{13}C NMR ($CDCl_3$) δ 10.50, 26.58, 31.81, 32.28, 43.20, 55.26, 112.79, 113.86, 126.56, 126.95, 129.18, 132.31, 137.36, 153.85, 158.01, 159.10, 185.32. MS *m/z* 254 (M^+), 239, 57 (bp). HR MS (M^+) Calcd. for $C_{17}H_{18}O_2$: 254.1307. Found: 254.1320.

(4a*R*)-3-*tert*-Butyldimethylsilyloxy-7-methoxy-1,4a-dimethyl-2-oxo-2,3,4,4a,9,10-hexahydrophenanthrene 27 :

To a stirred solution of **8** (106 mg, 0.441 mmol) in ether (1.5 mL) was added OsO_4 (3.1 mL, 4.0 w/v% in *t*-BuOH, 0.500 mmol) at 0 °C. The reaction mixture was stirred for 20 min at 23 °C, diluted with pyridine (3.0 mL), quenched with aq $NaHSO_3$ and stirred for 7 h. The mixture was extracted with $CHCl_3$ and the extracts were dried (Na_2SO_4). Removal of solvent provided an oil which was purified by silica gel column (50% hexane in EtOAc) to give the diol (91.5 mg, 76%) as a diastereomeric mixture (2:1). IR (neat) 3386 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 3 Hx2/3), 1.40 (s, 3 Hx1/3), 1.70-1.82 (m, 1 H), 1.85 (s, 3 Hx2/3), 1.88 (s, 3 Hx1/3), 2.10-3.14 (m, 7 H), 3.67-4.13 (m, 2 H), 3.76 (s, 3 Hx2/3), 3.77 (s, 3 Hx1/3), 6.63-6.70 (m, 1 H), 6.76-6.88 (m, 1 H), 7.19 (d, J = 8.6 Hz, 1 Hx1/3), 7.27 (d, J = 7.6 Hz, 1 Hx2/3). ^{13}C NMR ($CDCl_3$) δ 17.00, 17.34, 23.31, 24.26, 29.98, 31.00, 31.45, 32.87, 37.86, 40.13, 40.31, 40.56, 55.11, 66.92, 67.12, 71.18, 71.65, 111.82, 112.54, 112.92, 113.78, 123.67, 124.64, 125.00, 126.88, 136.68, 137.56, 137.77, 138.40, 139.91, 140.05, 157.18, 157.43. MS *m/z* 274 (M^+), 259 (bp), 213. HR MS (M^+) Calcd. for $C_{17}H_{22}O_3$: 274.1569. Found: 274.1567.

To a stirred solution of the diol (78.4 mg, 0.286 mmol) in CH_2Cl_2 (3.0 mL) were added DMAP (97.7 mg, 0.800 mmol) and TBDMSCl (60.3 mg, 0.400 mmol)at 0 °C. The reaction mixture was stirred for 7 h at 23 °C, poured into ice-water and extracted with EtOAc. The extracts were washed successively with aq 10% HCl, water, sat aq $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column (10% ether in hexane) to give the silyl ether (104 mg, 94%) as a diastereomeric mixture (2:1). IR (neat) 3554, 1251, 1071 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 0.05 (s, 3 Hx2/3), 0.11(s, 3 Hx2/3), 0.17(s, 3 Hx1/3), 0.18 (s, 3 Hx1/3), 0.91 (s, 9 Hx2/3), 0.95 (s, 9 Hx1/3), 1.35 (s, 3 Hx2/3), 1.39 (s, 3 Hx1/3), 1.86 (s, 3 Hx2/3), 1.87(s, 3 Hx1/3), 2.10-2.18 (m, 1 H), 2.46-3.06 (m, 5 H), 3.58-3.66 (m, 1 Hx2/3), 3.72-3.79 (m, 1 Hx1/3), 3.76 (s, 3 Hx1/3), 3.77 (s, 3 Hx2/3), 3.85-3.90 (m, 1 Hx1/3), 4.02-4.12 (m, 1 Hx1/3), 6.53-6.62 (m, 1 H), 6.68-6.76 (m, 1 H), 7.16 (d, J = 8.6 Hz, 1 Hx1/3), 7.23 (d, J = 8.9 Hz, 1 Hx2/3). ^{13}C NMR ($CDCl_3$) δ -4.81, -4.35, 17.43, 18.01, 18.13, 23.13, 24.21, 25.84, 30.10, 31.13, 31.50, 32.87, 37.56, 39.88, 40.47,

40.56, 55.13, 68.29, 68.52, 71.20, 71.81, 111.73, 112.44, 112.78, 113.84, 123.63, 124.47, 124.60, 126.83, 136.98, 137.83, 138.53, 138.80, 139.46, 157.11, 157.45. MS *m/z* 331 (M^+-*t*-Bu), 239 (bp), 213, 147. HR MS (M^+) Calcd. for $C_{23}H_{36}O_3Si$: 388.2434. Found: 388.2448.

To a stirred solution of the silyl ether (100 mg, 0.258 mmol) in 2.7 mL of DMSO-Et_3N (2 : 1) was added SO_3•pyridine (410 mg, 2.60 mmol) at 0 °C. The reaction mixture was stirred for 40 min at 23 °C, poured into ice-water and extracted with ether. The extracts were washed successively with sat. aq NH_4Cl, sat. aq $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column (9% ether in hexane) to give the silyloxyketone **27** (89.7 mg, 90%) as a diastereomeric mixture (2:1). IR (neat) 1673, 1254, 1098 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.11 (s, 3 Hx2/3), 0.12 (s, 3 Hx2/3), 0.14 (s, 3 Hx1/3), 0.21 (s, 3 Hx1/3), 0.92 (s, 9 Hx2/3), 0.95 (s, 9 Hx1/3), 1.57 (s, 3 H), 1.85 (s, 3 Hx1/3), 1.87 (s, 3 Hx2/3), 2.36 (dd, *J* = 5.9, 5.9 Hz, 2 Hx2/3), 2.44-3.14 (m, 4 H + 2 Hx1/3), 3.79 (s, 3 H), 4.07 (dd, *J* = 5.9, 5.9 Hz, 1 Hx2/3), 4.50 (dd, *J* = 5.3, 13.5 Hz, 1 Hx1/3), 6.61-6.67 (m, 1 H), 6.75-6.83 (m, 1 H), 7.22 (d, *J* = 8.9 Hz, 1Hx1/3H), 7.28 (d, *J* = 8.9 Hz, 1 Hx2/3). ^{13}C NMR ($CDCl_3$) δ -5.26, -4.56, -4.32, 11.09, 11.23, 18.24, 18.56, 25.81, 25.88, 26.42, 27.17, 28.14, 30.05, 30.93, 32.76, 40.34, 40.58, 43.09, 46.24, 55.20, 112.58, 112.90, 112.97, 113.39, 125.91, 126.40, 126.54, 127.28, 136.53, 136.71, 136.80, 157.59, 157.70, 160.68, 161.44, 196.73, 198.00. MS *m/z* 329 (M^+-*t*-Bu, bp), 314, 147. HR MS (M^+-*t*-Bu) Calcd. for $C_{19}H_{25}O_3Si$: 329.1573. Found 329.1582.

(4a*R*)-7-Methoxy-1,4a-dimethyl-2-oxo-2,3,4,4a,9,10-hexahydrophenanthrene 1 :

From 27 : To a stirred solution of **27** (4.0 mg, 0.0104 mmol) in acetonitrile (0.2 mL) was added a mixture of 46% aq HF and acetonitrile (3:7, 0.2 mL) at 0 °C. The resulting mixture was stirred at the same temperature for 20 min, poured into ice-water, extracted with ether. The organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. The residure was purified by prep-TLC (25% ether in hexane) to give the ketoalcohol (2.0 mg, 70%). IR (neat) 3470, 1671 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.44 (s, 3 H), 1.89 (s, 3 H), 2.73-3.05 (m, 5 H), 3.14-3.26 (m, 1 H), 3.58 (s, 1 H), 3.78 (s, 3 H), 3.97 (dd, *J* = 5.3, 13.2 Hz, 1 H), 6.66 (d, *J* = 2.3 Hz, 1 H), 6.78 (dd, *J* = 2.3, 8.6 Hz, 1 H), 7.40 (d, *J* = 8.6 Hz, 1 H). ^{13}C NMR ($CDCl_3$) δ 11.32, 25.66, 31.43, 33.28, 40.00, 40.70, 55.26, 69.00, 112.18, 114.23, 125.01, 125.10, 134.23, 137.16, 158.29, 162.79, 199.62. MS *m/z* 272 (M^+), 257 (bp), 239. HR MS (M^+) Calcd. for $C_{17}H_{20}O_3$: 272.1413. Found: 272.1403.

To a stirred solution of the ketoalcohol (16.2 mg, 0.0596 mmol) in acetonitrile (0.4 mL) were added DMAP (48.0 mg, 0.400 mmol) and phenyl chlorothionoformate (28 μL, 0.200 mmol) at 0 °C. The reaction mixture was stirred for 1 h at 23 °C, passed through a silica gel pad and concentrated. To a stirred solution of the residual oil in benzene (0.7 mL) were added tributyltin hydride (54 μL, 0.200 mmol) and AIBN (3.0 mg, 0.0200 mmol) at 23 °C. The reaction mixture was stirred at 90 °C for 1 h, cooled and concentrated. The residue was diluted with dichloromethane (1.0 mL) and H_2O (0.5 mL). To the resulting suspension was added potassium hydrogen fluoride (7.0 mg) at 23 °C, and the mixture was stirred at this temperature for 2 h. It was then filtered, and the filtrate was washed with H_2O, dried (Na_2SO_4) and concentrated. The residue was purified by prep-TLC (50% ether in hexane) to give the enone **1** (6.6 mg, 43%) as a colorless oil.

From 26 : To a stirred solution of **26** (2.0 mg, 0.00787 mmol) in benzene (0.4 mL) was added $Rh(PPh_3)_3Cl$ (3.7 mg, 0.00400 mmol). The reaction mixture was stirred for 14 h at 23 °C under hydrogen atmosphere (1 atm), diluted with ether, passed through a Florosil pad and concentrated. The residue was

purified by silica gel column (25% ether in hexane) to give the enone **1** (1.6 mg, 79%) as a colorless oil. IR (neat) 1660 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.51 (s, 3 H), 1.84 (s, 3 H), 2.04 (ddd, J = 5.0, 14.5, 14.5 Hz, 1 H), 2.35 (ddd, J = 2.6, 5.0, 13.2 Hz, 1 H), 2.44-2.59 (m, 2 H), 2.64-3.08 (m, 4 H), 3.79 (s, 3 H), 6.65 (d, J = 2.5 Hz, 1 H), 6.80 (dd, J = 2.5, 8.7 Hz, 1 H), 7.21 (d, J = 8.7 Hz, 1 H). ^{13}C NMR ($CDCl_3$) δ 10.89, 27.14, 27.32, 30.21, 34.23, 36.35, 39.21, 55.52, 112.88, 126.69, 128.54, 136.93, 137.07, 157.52, 162.28, 198.20. MS *m/z* 256 (M^+), 241 (bp), 149. HR MS (M^+) Calcd. for $C_{17}H_{20}O_2$: 256.1463. Found: 256.1457. $[\alpha]_D^{27}$ +149 (*c* 1.21, $CHCl_3$).

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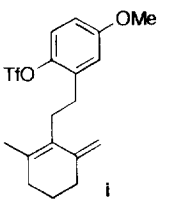
(11) Reaction using achiral 1,3-bis(diphenylphosphino)propane or triphenylphosphine as a ligand was quite slow (ca. 50% yield of the starting material was recovered after 72 h at 80 °C), and no cyclized product was isolated.

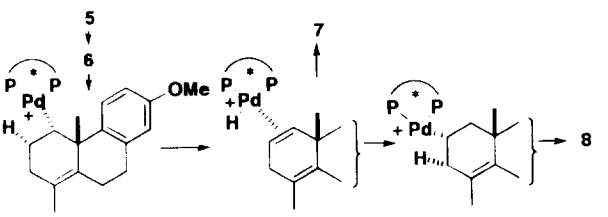
(12) Starting material **5** (3%) and its olefin-isomerized product **i** (4%) were also recovered, and formation of some highly polar materials was observed. These polar byproducts may be formed by thermal decomposition of **5** and/or the cyclized products. It is unlikely that a significant amount of the 5-*exo*-product **10** was formed and only this compound was selectively decomposed to the highly polar materials; however, there might be a possibility that a small amount of **10** was formed and decomposed under the reaction conditions.



(13) The enantiomeric excesses of **7** and **8** were determined by HPLC analysis (DAICEL CHIRALPAK AS, hexane:2-propanol, 9:1) after conversion to **1** via **27**.

(14) Sodeoka, M.; Satoh, S.; Shibasaki, M. *J. Am. Chem. Soc.* **1988**, *110*, 4823.

(15) Conjugated diene **8** could be formed by olefin isomerization through the hydridopalladium intermediate as shown below.



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