Tetrahedron Vol. 49, No. 9, pp. 1773-1782, 1993
Printed in Great Britain

0040-4020/93 $6.00+.00

Asymmetric Heck Reaction-Anion Capture Process. A Catalytic Asymmetric Synthesis of the Key Intermediates for the Capnellenols

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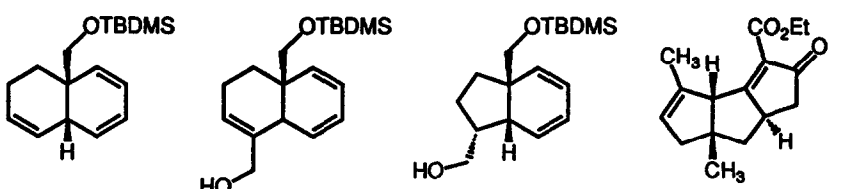
(*Received in Japan* 4 *November* 1992)

Abstract *: A catalytic asymmetric synthesis of the key intermediates* ***4*** *and* ***15*** *for the capnellenols has been achieved through an asymmetric Heck reaction followed by the acetate anion capture process. Furthermore, the above reaction has been successfully applied to an asymmetric Heck reaction -amine capture process.*

In 1989 we succeeded in demonstrating the first example of a catalytic asymmetric synthesis through the Heck reaction,[1] leading to catalytic asymmetric syntheses of **1** of 92% ee,[2,3] **2** of 92% ee,[3] **3** of 86% ee[4] and **4** of 80% ee.[5,6] Herein, we report a detailed account of the catalytic asymmetric synthesis of the key intermediates **4** and **15** for $\Delta^{9(12)}$-capnellene-3β,8β,10α-triol **7** and $\Delta^{9(12)}$-capnellene-3β,8β,10α,14-tetraol **10** as well as a catalytic asymmetric synthesis of the amine **33**. These syntheses feature an asymmetric Heck reaction followed by the anion capture process.[7]

Figure 1

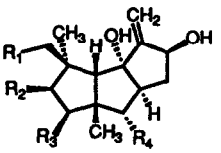


1 2 3 4

Dedicated to Professor Shun-ichi Yamada on the occasion of his 77th birthday.

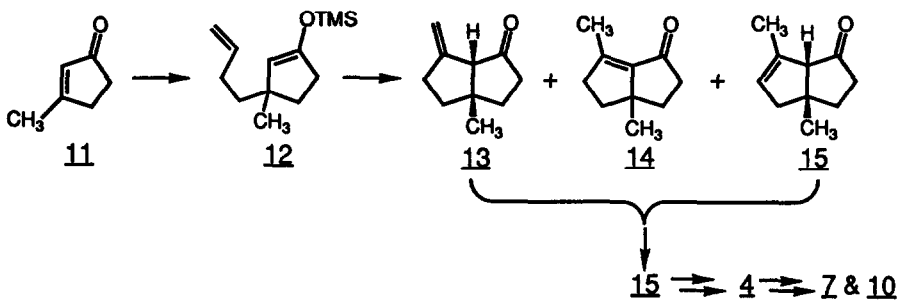
Capnellenols are sesquiterpene alcohols **5-10**, isolated from sun-dried colonies of the soft coral *Capnella imbricata*.[8] These substances appear to have protective roles against fish predation and invasion by microorganisms, larvae, and algae.[9] In 1986 we completed the first total syntheses of (±)-$\Delta^{9(12)}$-capnellene-8β,10α-diol **5**, (±)-$\Delta^{9(12)}$-capnellene-3β,8β,10α-triol **7** and (±)-$\Delta^{9(12)}$-capnellene-3β,8β,10α,14-tetraol **10** starting with 3-methyl-2-cyclopenten-1-one **11**.[10] In these syntheses, the Saegusa-Ito reaction[11] was successfully applied to the silyl enol ether **12** as a key step, providing the cyclized products **13**, **14** and **15** in a ratio of 0.4 : 3.6 : 1.0 (79% yield). The mixture then underwent DBU-catalyzed isomerization in refluxing benzene to afford only **15** in 92% yield, which was effectively converted to the racemic capnellenols via the tricyclic intermediate **4**.[12]

Figure 2



5, $R_1=R_2=R_3=R_4=H$
6, $R_1=R_3=R_4=H$, $R_2=OH$
7, $R_1=R_2=R_4=H$, $R_3=OH$
8, $R_1=R_2=R_3=H$, $R_4=OH$
9, $R_1=R_3=H$, $R_2=R_4=OH$
10, $R_2=R_4=H$, $R_1=R_3=OH$

Scheme 1

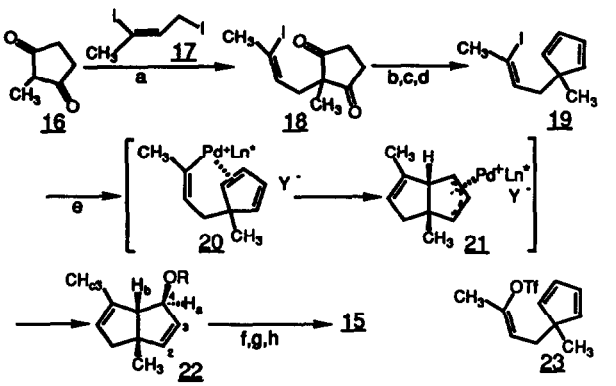


We reasoned that treatment of **19** with a palladium catalyst bearing an asymmetric ligand in the presence of a silver salt and some oxygen nucleophile (ROH) would regioselectively afford the optically active bicyclic compound **22**, a potential intermediate for **15**, via the π-allylpalladium intermediate **21**.[13] The reaction would proceed via the 16-electron Pd^+ intermediate **20** formed by abstraction of I^-,[2] thereby making possible effective discrimination of the two olefinic double bonds to give **22** of high enantiomeric excess. The regiochemistry of **22** was expected to be efficiently controlled by steric factors. The requisite prochiral alkenyl iodide **19** was readily synthesized in 61% overall yield starting with **16** as shown in Scheme 2.

With the aim of application to an asymmetric synthesis, reactions utilizing (diphenylphosphino)ethane (DIPHOS) as an achiral ligand were first investigated. After several attempts, it was found that exposure of **19** to $Pd(OAc)_2$ (5.8 mol %), DIPHOS (5.7 mol %) and tetrabutylammonium acetate (1.72 equiv) in CH_3CN (60 °C, 112 hr) gave **22** (R=Ac) (52%) in a highly stereo- and regiocontrolled manner. The reaction did not proceed in the absence of tetrabutylammonium acetate probably owing to the stability of the π-allylpalladium intermediate **21**. The stereochemical assignment for **22** (R=Ac) followed from the ^{1}H-NMR, which showed J_{ab} = 0.8 Hz. The coupling constant (J_{ab}= ca. 8 Hz) was expected for the other epimer. Furthermore, irradiation of H_a showed an enhancement of H_b(1.1%) and H_c (1.1%). The regio- and stereoselectivity are in accord with our expectation that an acetate anion should attack the π-allylpalladium complex **21** from the face opposite palladium[13] at C-4. The acetate **22** (R=Ac) was transformed into the key synthetic intermediate **15**

for (±)-7and (±)-**10** by the sequence : (1) LiOH in aqueous THF (89%); (2) PCC-MS4A in CH_2Cl_2 (95%); (3) 10% Pd-C in 10 % aqueous KOH-EtOH under H_2 (83%)[14] as shown in Scheme 2. The spectral data of (±)-**15** thus obtained were idential with those of an authentic sample.[10] The synthesis described above is an improved synthetic route to (±)-**7** and (±)-**10** in terms of the use of a catalytic amount of $Pd(OAc)_2$, because the former syntheses required stoichiometric quantities of $Pd(OAc)_2$.[10]

Scheme 2



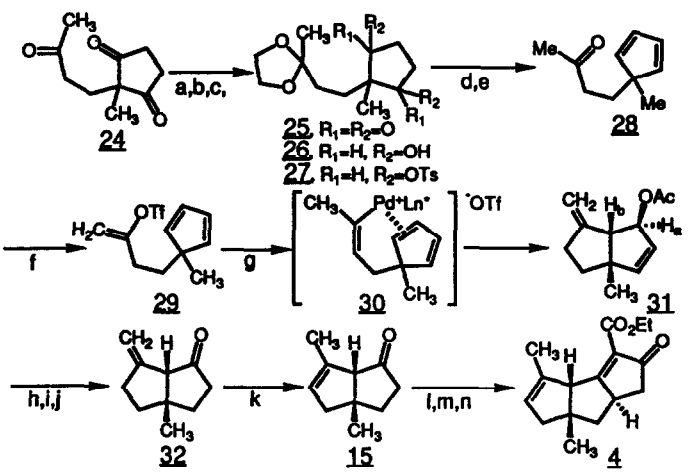
(a) Bu_4NOH, dioxane, H_2O (74%); (b) $NaBH_4$ (100%); (c) TsCl, DMAP, pyridine (96%); (d) Al_2O_3, $ClCH_2CH_2Cl$ (86%); (e) $Pd(OAc)_2$, DIPHOS, Bu_4NOAc, CH_3CN (52%); (f) LiOH, aq. THF (89%); (g) PCC, MS4A, CH_2Cl_2 (95%); (h) 10% Pd-C, 10% aq. KOH, EtOH, H_2 (83%).

The Heck reaction-anion capture process was next applied to a catalytic asymmetric synthesis. However, addition of a silver salt to the reaction medium, which appears to be essential to obtain a cyclized product of a high ee via a 16-eleectron Pd^+ intermediate,[2] was found to cause the decomposition of **19**, probably owing to the presence of the cyclopentadiene moiety. For this reason, **22** (R=Ac) was obtained with only a low ee. For example, treatment of **19** with $[Pd(allyl)Cl]_2$ (10 mol %), (*R,R*)-CHIRAPHOS (10 mol %) and tetrabutylammonium acetate (2.9 equiv) in toluene (60 °C, 144 hr) provided **22** (R=Ac) of 20% ee in 61% yield, and use of (*S*)-BINAP gave **22** of 26% ee in 39% yield. Furthermore, the use of TlOAc as a base[15] afforded the less satisfactory results. Assignment of the absolute configuration was achieved by application of the CD exciton chirality method to the corresponding benzoate, and the enantiomeric excess was unequivocally determined by the ^{1}H-NMR spectrum of the corresponding MTPA ester.

In order to overcome the above-mentioned problem, we undertook a catalytic asymmetric cyclization utilizing the corresponding trisubstituted alkenyl triflate **23**, which was expected to lead to the 16-electron Pd^+ intermediate efficiently even in the absence of a silver salt,[16] producing **22** (R=Ac) with high ee. The synthesis of **23**, however, turned out to be unsuccessful. For example, none of **23** was obtained from **28** under various reaction conditions. Thus, we turned our attention to a catalytic asymmetric cyclization of the prochiral alkenyl triflate **29**. The requisite alkenyl triflate **29** was readily prepared in 42% overall yield starting with **24** as shown in Scheme 3.

Treatment of **29** with $Pd(OAc)_2$ (10 mol %), DIPHOS (10 mol %) and tetrabutylammonium acetate (2.9 equiv) in toluene at 50 °C was found to give the expected product **31** in 61% yield as a sole product. The structure of **31** was determined from the ^{1}H-NMR spectrum, which showed J_{ab}= ~ 0 Hz. With this result in hand, a catalytic asymmetric synthesis of **31** was next examined. First of all, the use of (*S*)-BINAP[17] in toluene (50 °C) was found to afford **31** of 26% ee in 79% yield. Assignment of the absolute configuration was achieved by application of CD exciton chirality method to the corresponding benzoate, and the enantiomeric excess was unequivocally determined by the ^{1}H-NMR spectrum of the corresponding MTPA ester. In order to obtain a much higher enantiomeric excess, solvent effects were carefully examined. After several attempts, we

Scheme 3



(a) $(TMSOCH_2)_2$, TMSOTf (77%); (b) $NaBH_4$; (c) TsCl, DMAP, pyridine; (d) DBU (88%); (e)TsOH, acetone (88%); (f) LDA, Tl_2NPh (71%); (g) $Pd(OAc)_2$, (*S*)-BINAP, Bu_4NOAc, DMSO (89%); (h) NaOMe (85%); (i) PDC, MS3A (95%); (j) CuBr, Red-Al, *s*-BuOH, THF. (83%); (k) DBU (90%); (l) LDA, $ICH_2C(OMe)=CHCO_2Et$ (85%); (m) 30% $HClO_4$, Et_2O (90%); (n) NaOEt, EtOH (85%).

found that the use of DMSO gave **31** of 80% ee (50 °C). The results are summarized in Table 1. Furthermore, temperature effects were also examined utilizing DMSO as a solvent. However, it was found that the reaction at 20 °C did not improve the enantiomeric excess, giving **31** of 80% ee in 77% yield. In order to obtain a better result, other various bidentate ligands were further utilized in DMSO (20 °C). The use of BINAP, however, was found to give the best enantiomeric excess (80% ee). The results are summarized in Table 2. The Heck reaction of a prochiral alkenyl iodide is relatively fast when AgOAc is used, indicating that the Pd^+AcO^- intermediate is formed effectively, but the ee of the product is low.[2] Therefore, it is noteworthy that **31** was obtained with a high ee even in the presence of excess tetrabutylammonium acetate.

The asymmetric Heck reaction-acetate anion capture process described above was further optimized. After several attempts, we were pleased to find that treatment of **29** with $Pd(OAc)_2$ (1.7 mol %), (*S*)-BINAP (2.1 mol %) and tetrabutylammonium acetate (1.7 equiv) in DMSO at 20 °C for 2.5 hr produced **31** of 80% ee in 89% yield. The cyclized product **31** was then converted to **15** through **32** : $[\alpha]^{20}_D$ +532° (*c* 0.85, $CHCl_3$) (80% ee), the key intermediate for **7** and **10**, in a four-step process (60% overall yield) (Scheme 3).

Table 1. Solvent Effects on the Catalytic Asymmetric Synthesis of **31**[a]

run	solvent	time (hr)	yield (%)	ee (%)
1	toluene	3.0	79	26
2	MeCN	7.0	51	51
3	dioxane	2.0	59	65
4	DMF	40.5	32	67
5	DMSO	0.5	73	80

[a] $Pd(OAc)_2$ (5 mol %), (*S*)-BINAP (6.4 mol %) and tetrabutylammonium acetate (2.9 equiv) were used at 50 °C.

Table 2. Ligand Effects on the Catalytic Asymmetric Synthesis of 31[a]

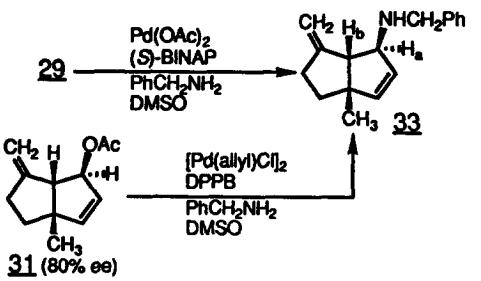
run	ligand	time (hr)	yield (%)	ee (%)
1	(*S*)-BINAP	1.0	77	80
2	(*S,S*)-DIOP	2.0	67	8
3	(*R,R*)-CHIRAPHOS	2.0	44	17
4	(*S,S*)-BPPM	0.5	61	58[b]
5	(*S,R*)-BPPFA	0.5	68	26

[a] $Pd(OAc)_2$ (5 mol %), a ligand (6.4 mol %) and $Bu_4N^+ {}^-OAc$ (2.9 equiv) (DMSO, 20 °C). [b] The antipode of **31** was formd.

The spectral data of **15** thus obtained were identical with those of an authentic sample.[10] The bicyclic intermediate **15** was further transformed into the ABC ring system **4** : $[\alpha]^{21}_D$ +530° (*c* 1.00, $CHCl_3$) (80% ee) in a three-step process (65% overall yield) as shown in Scheme 3. The spectral data of **4** were also identical with those of an authentic sample.[10] This is the first example of a catalytic asymmetric synthesis of a polycyclopentanoid.[18] On the other hand, treatment of **32** with DBU under the milder reaction conditions is known to give **14**, a key intermediate for **5**, as a major product.[10]

In addition, treatment of the prochiral alkenyl triflate **29** with $Pd(OAc)_2$ (5.0 mol %) (*S*)-BINAP (6.3 mol %) and benzylamine (2.0 equiv) in DMSO at 20 °C for 2 hr gave the allylic amine **33** of 81% ee in 76% yield : $[\alpha]^{20}_D$ +9.30° (*c* 0.83, $CHCl_3$). The stereo- and regiochemistry were unequivocally determined from the ^{1}H-NMR spectrum, which showed J_{ab}= ~ 0 Hz. The enantiomeric excess was determined as follows. The allylic acetate **31** of 80% ee was treated with $[Pd(allyl)Cl]_2$ (5 mol %), 1,4-bis(diphenylphoshpino)butane (DPPB) (6 mol %) and benzylamine (2.0 equiv) in DMSO at 20 °C for 2 hr gave **33** in 54% yield : $[\alpha]^{20}_D$ +9.22° (*c* 1.05, $CHCl_3$) (80% ee). Thus, the enantiomeric excess of **33** obtained directly from **29** as well as the absolute configuration was determined.

Scheme 4



Thus, we have achieved a catalytic asymmetric synthesis of the key intermediates **4** and **15** for the capnellenols by the use of the asymmetric Heck reaction followed by an acetate anion capture process. Furthermore, an asymmetric Heck reaction-amine capture process has been also achieved. Further studies along this line are in progress.

Experimental Section

Infrared (IR) spectra were measured on a JASCO A-300 diffraction grating infrared spectrophotometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded with a JEOL JNM-FX-100 NMR spectrometer or JEOL JNM-GX-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. ^{1}H NMR and MS data were obtained on all intermediates described herein using chromatographically homogeneous samples.

(*Z*)-1,3-Diiodo-2-butene (17). To a solution of (*Z*)-1-hydroxy-3-iodo-2-butene[19] (2.10 g, 10.6 mmol) in CH_2Cl_2 (30 ml) was added Et_3N (9.0 ml, 64.5 mmol) and CH_3SO_2Cl (6.0 ml, 77.6 mmol) at -30 °C. The reaction mixture was stirred for 0.5 hr (-30 °C), quenched (ether, 200 ml) at rt, and filtered. The filtrate was concentrated to give an oily residue. To a solution of the oily residue in acetone (45 ml) was added NaI (2.10 g, 14.0 mmol) at 0 °C. The reaction mixture was stirred at rt for 3 hr, quenched (ether, 200 ml), and filtered. The filtrate was concentrated and purified by silica gel column (hexane) to give **17** (3.0 g, 92%) as a pale yellow oil : ^{1}H NMR δ 2.50 (d, *J*=1.2 Hz, 3H), 3.85 (d, *J*=8.0 Hz, 2H), 5.70 (tq, *J*=8.0, 1.2 Hz, 1H) ; IR (neat) : 1630, 1420, 1290, 1145 cm^{-1} ; MS m/z 308 (M^+), 181 (bp) ; HRMS (M^+) calcd for $C_4H_6I_2$ 307.8559, found 307.8543.

2-[(*Z*)-3-Iodo-2-butenyl]-2-methyl-1,3-cyclopentanedione (18). To a solution of **16** (1.00 g, 8.9 mmol) in aqueous Bu_4NOH (40 wt.%, 6.1 ml, 9.4 mmol) was added **17** (2.96 g, 9.6 mmol) in dioxane (10 ml) at rt. The reaction mixture was stirred for 45 hr at r.t., diluted with AcOEt, washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column (AcOEt-hexane, 1 : 5) to give **18** (1.94 g, 74%) as a colorless oil : ^{1}H NMR δ 1.16 (s, 3H), 2.42 (dq, *J*=7.0, 1.5 Hz, 2H), 2.50 (dt, *J*=1.5, 1.5 Hz), 2.80 (broad s, 4H), 5.30 (tq, *J*=7.0, 1.5 Hz, 1H) ; IR (neat) : 1720, 1700 cm^{-1} ; MS m/z 250, 165(M^+-I, bp) ; HRMS (M^+-I) calcd for $C_{10}H_{13}O_2$ 165.0916, found 165.0937.

5-[(*Z*)-3-Iodo-2-butenyl]-5-methylcyclopentadiene (19). To a solution of **18** (926 mg, 3.17 mmol) in MeOH (6 ml) was added $NaBH_4$ (263 mg, 6.92 mmol) at 0 °C. The reaction mixture was stirred for 1 hr at 0 °C, quenched (acetone), diluted with H_2O, extracted (ether). The combined extracts were dried (Na_2SO_4), and concentrated. The oily residue was purified by silica gel column to give the diol (938 mg, 100%) as a colorless oil. To a suspension of TsCl (7.33 g, 38.5 mmol) in pyridine (6 ml) was added the diol (938 mg) in CH_2Cl_2 (6 ml) and DMAP (10 mg) at 0 °C. The reaction mixture was stirred for 20 hr at rt, diluted (CH_2Cl_2), successively washed with 10% aqueous H_2SO_4 and brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column (AcOEt-hexane, 1 : 4) to give the ditosylate (1.60 g, 84%) as a yellow oil. A suspension of the ditosylate (1.60 g) and Al_2O_3[20] (23 g) in 1,2-dichloroethane (23 ml) was refluxed with stirring for 5 hr. The reaction mixture was filtered, and the filtrate was concentrated The residue was purified by silica gel column (hexane) to give **19** (613mg, 89%) as a pale yellow oil : ^{1}H NMR δ 1.16 (s, 3H), 2.35 (dq, *J*=6.6, 1.5 Hz, 2H), 2.44 (dt, *J*=1.5, 1.5 Hz, 3H), 5.05 (tq, *J*=6.6, 1.5 Hz, 1H), 6.24 (s, 4H) ; IR (neat) : 2950 cm^{-1} ; MS m/z 260 (M^+), 181, 133, 69 (100) ; HRMS (M^+) calcd for $C_{10}H_{13}I$ 260.0062, found 260.0046.

(1*S, 4*S**, 5*S**)-4-Acetoxy-1,6-dimethyl-*cis*-bicyclo[3.3.0]octa-2,6-diene (22).** A mixture of **19** (46.1 mg, 0.177 mmol), $Pd(OAc)_2$ (2.3 mg, 10.2 μmol), DIPHOS (4.0 mg, 10.1 μmol) and Bu_4NOAc (92 mg, 0.31 mmol) in CH_3CN (1.5 ml) was stirred at 60 °C for 114 hr and the reaction mixture was directly purified by silica gel column (ether-hexane, 1 : 12) to give **22** (R=Ac) (17.6 mg, 52%) as a colorless oil : ^{1}H NMR δ 1.28 (s, 3H), 1.70-1.84 (broad s, 3H), 2.04 (s, 3H), 2.10–2.30 (m, 2H), 2.50-2.70 (broad d, *J* = 0.8 Hz, 1H), 5.00-5.20 (broad s, 1H), 5.38 (dd, *J*=2.2, 0.8 Hz, 1H), 5.58 (dd, *J*=2.2, 5.5 Hz, 1H), 5.86 (d, *J*=5.5 Hz, 1H) ; IR (neat) : 1735 cm^{-1} ; MS m/z 149, 133 (M^+-AcO, bp) ; HRMS (M^+-AcO) calcd for $C_{10}H_{13}$ 133.1017, found 133.0992.

(1*R, 5*R**)-5,8-Dimethyl-*cis*-bicyclo[3.3.0]oct-7-en-2-one (15).** To a solution of **22** (25.0 mg, 0.130 mmol) in THF (0.5 ml) was added LiOH (12 mg, 0.50 mmol) in H_2O (0.5 ml). The reaction mixture was stirred at rt for 48 hr, diluted with brine, extracted with ether. The organic extracts were dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column (ether-hexane, 1 : 1) to give the alcohol (17.4 mg, 89%) as a colorless oil. To a solution of the alcohol (17.0 mg, 0.113 mmol) in CH_2Cl_2 (1.2 ml) was added PCC (26.5 mg, 0.123 mmol) and MS4A (100 mg). The reaction mixture was stirred at rt for 2 hr, diluted with ether, and directly purified by silica gel column (ether-hexane, 1 : 4) to give the enone (15.8 mg, 95%) as a colorless oil. To a solution of the enone (6 mg, 0.041 mmol) in EtOH (0.18 ml) was added 10% Pd-C (0.6 mg) and 10 % aqueous KOH solution (0.02 ml). The reaction mixture was stirred for 15 min at rt under hydrogen atmosphere and filtered. The filtrate was concentrated to give an oily

residue, which was purified by silica gel column (ether-hexane, 1 : 8) to give **15** (5.1 mg, 83%) as a colorless oil : ^{1}H NMR δ 1.25 (s, 3H), 1.96 (m, 5H), 2.16–2.43 (m, 4H), 2.57 (broad s, 1H), 5.32 (broad s, 1H) ; IR (neat) : 1740, 1450, 1410, 1380 cm^{-1} ; MS m/z 150 (M^+), 121, 107, 94 (bp), 79 ; HRMS (M^+) calcd for $C_{10}H_{14}O$ 150.1043, found 150.1033. These spectral data were identical with those of an authentic sample.[10]

(1*S*, 4*S*, 5*S*)-4-Acetoxy-1,6-dimethyl-*cis*-bicyclo[3.3.0]octa-2,6-diene (22). A mixture of **19** (60.0 mg, 0.231 mmol), $[Pd(allyl)Cl]_2$ (4.2 mg, 11.4 μmol), (*R*,*R*)-CHIRAPHOS (9.8 mg, 23 μmol) and Bu_4NOAc (202 mg, 0.67 mmol) in toluene (2.0 ml) was stirred at 60 °C for 144 hr, and the reaction mixture was directly purified by silica gel column (ether-hexane, 1 : 12) to give **22** (27.0 mg, 61%) as a colorless oil. The spectral data were identucal with those of (±)-**22**. The corresponding MTPA ester showed that **22** thus obtained was 20% ee, and the absolute configuration was determined utilizing the corresponding benzoate.

2-(3,3-Ethylenedioxybutyl)-2-methyl-1,3-cyclopentanedione (25). To a solution of **24**[21] (145.0 mg, 0.797 mmol), 1,2-bis(trimethylsilyloxy)ethane (0.22 ml, 0.897 mmol) in CH_2Cl_2 (0.8 ml) was gradually added TMSOTf (15 μl, 0.078 mmol) at -78 °C. The reaction mixture was stirred for 1.5 hr at the same temperature, quenched by the addition of pyridine (0.1 ml), poured into satd. aqueous $NaHCO_3$ solution with vigorous stirring (-78 °C → rt), and extracted with ether. The organic extracts were dried (Na_2SO_4 and Na_2CO_3) and concentrated.. The residue was purified by silica gel column (EtOAc-hexane, 1 : 2.5) to give **25** (138 mg, 77%) in colorless oil : ^{1}H NMR δ 1.10 (s, 3H), 1.26 (s, 3H), 1.40-1.90 (m, 4H), 2.76 (s, 4H), 3.80–4.00 (m, 4H) ; IR (neat) : 1720 cm^{-1} ; MS m/z 226 (M^+), 211, 125, 99, 87 (bp) ; HRMS (M^+) calcd for $C_{12}H_{18}O_4$ 226.1205, found 226.1178.

1,3-Bis(*p*-toluenesulfonyloxy)-2-(3,3-ethylenedioxybutyl)-2-methylcyclopentane(27). To a solution of **25** (6.218 g, 27.5 mmol) in MeOH (44 ml) was added $NaBH_4$ (1.248 g, 33 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 0.5 hr and rt for 0.5 hr, quenched by the addition of acetone, diluted with H_2O, and extracted with ether. The organic extracts were dried (Na_2SO_4), and concentrated. The oily residue was purified by silica gel column (ether) to give **26** (6.330 g, 100 %) as a colorless oil. To a solution of **26** (6.330 g, 27.5 mmol) in pyridine (18.9 ml) was added TsCl (22.5 g, 118 mmol) and DMAP (10 mg). The reaction mixture was stirred at rt for 34 hr, diluted with CH_2Cl_2, and successively washed with satd. aqueous $CuSO_4$ solution, satd. aqueous $NaHCO_3$ solution and brine. The CH_2Cl_2 layer was dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column (EtOAc-hexane, 1 : 2) to give **27** (13.317 g, 90%) as a colorless oil : ^{1}H NMR δ 0.80 (s, 3H), 1.14 (s, 3H), 1.10–2.20 (m, 8H), 2.44 (s, 6H), 3.80-4.00 (m, 4H), 4.40-4.70 (m, 2H), 7.34 (d, J = 8.0 Hz, 4H), 7.80 (d, J = 8.0 Hz, 4H) ; IR (neat) : 2950, 1360, 1180 cm^{-1} ; MS m/z 523 (M^+-CH_3), 367, 91 (bp) ; HRMS (M^+-CH_3) calcd for $C_{12}H_{31}O_8S_2$ 523.1461, found 523.1462

5-Methyl-5-(3-oxobutyl) cyclopentadiene (28). A solution of **27** (2.51 g, 4.67 mmol) and DBU (2.7 ml) in benzene (6 ml) was refluxed with stirring for 5 days, and the reaction mixture was directly purified by silica gel column (ether-hexane, 1 : 5) to give **28** (890 mg, 98%) as a colorless oil. To a solution of **28** (1.00 g, 5.15 mmol) in acetone (9 ml) was added TsOH (10 mg). The reaction mixture was stirred for 11 hr at rt, diluted with hexane, successively washed with satd. aqueous $NaHCO_3$ solution and brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column (ether-hexane, 1 : 15) to give **28** (630 mg, 82%) as a colorless oil : ^{1}H NMR δ 1.16 (s, 3H), 2.04 (s, 3H), 1.08–2.28 (m, 4H), 6.00-6.30 (m, 4H) ; IR (neat) : 1720 cm^{-1} ; MS m/z 150 (M^+), 92 (100) ; HRMS (M^+) calcd for $C_{10}H_{14}O$ 150.1045, found 150.1050.

5-Methyl-5-(3-trifluoromethanesulfonyloxy-3-buten-1-yl) cyclopentadiene (29). To a solution of LDA (0.997 mmol) in THF (13 ml) was guradually added **28** (124.9 mg, 0.831 mmol) in THF (14 ml) at -78 °C, and the reaction mixture was stirred for 80 min at the same temperature. To this enolate solution was then added $PhNTf_2$ (386.0 mg, 1.08 mmol) in THF (14 ml) at -78 °C, and the whole reaction mixture was stirred at 0 °C for 3 hr and at rt for 16 hr, and concentrated. The residue was purified by silica gel column (hexane) to give **29** (165.9 mg, 71 %) as a colorless oil : ^{1}H NMR δ 0.96 (s, 3H), 1.40–1.70 (m, 2H), 1.80–2.00 (m, 2H), 4.30 (m, 1H), 4.70 (d, J = 3.8 Hz, 1H), 5.80-6.20 (m, 4H) ; IR (neat) : 1415, 1210, 1140 cm^{-1} ; MS m/z 282 (M^+), 93 (bp) ; HRMS (M^+) calcd for $C_{11}H_{13}O_3SF_3$ 282.0537, found 282.0514.

(1*S*, 4*S*, 5*S*)-4-Acetoxy-1-methyl-6-methylene-*cis*-bicyclo[3.3.0]oct-2-ene (31). A mixture of **29** (240 mg, 0.993 mmol), $Pd(OAc)_2$ (3.8 mg, 16.8 μmol), (*S*)-BINAP (13.2 mg, 21.2 μmol) and Bu_4NOAc (512 mg, 1.70 mmol) in DMSO (4 ml) was stirred at rt for 1 hr, and the reaction mixture was directly purified by silica gel column to give **31** (170.0 mg, 89%) as a pale yellow oil : ^1H NMR δ 1.26 (s, 3H), 1.40–1.90 (m, 2H), 2.04 (s, 3H), 2.10–2.40 (m, 2H), 2.50-2.70 (broad s, 1H), 5.00 (broad s, 1H), 5.10 (broad s, 1H), 5.40 (broad s, 1H), 5.70 (dd, J = 6.0, 2.0 Hz, 1H), 5.90 (d, J = 6.0 Hz, 1H) ; IR (neat) : 1740 cm^{-1} ; MS m/z 149 (M^+-Ac), 132 (bp), 117 ; HRMS (M^+-Ac) calcd for $C_{10}H_{13}O$ 149.0966, found 149.0983. The corresponding MTPA ester showed that **31** thus obtained was 80% ee, and the absolute configuration was determined utilizing the corresponding benzoate.

(1*R*, 5*R*)-5,8-Dimethyl-*cis*-bicyclo[3.3.0]oct-7-en-2-one (15). To a solution of **31** (34.0 mg, 0.177 mmol, 80% ee) in THF (1 ml) was added NaOMe (27.0 mg, 0.5 mmol) at 0 °C. The reaction mixture was stirred for at the same temperature 18 hr, diluted with brine, and extracted with ether. The ether extracts were dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column (ether-hexane, 2 : 3) to give the allylic alcohol (22.7 mg, 85%) as a colorless oil. To a solution of the allylic alcohol (59.0 gm, 0.39 mol) in CH_2Cl_2 (4.5 ml) was added PDC (238.0 mg, 0.755 mmol) and MS3A (510 mg) at 0 °C. The reaction mixture was stirred for 5 hr at rt, diluted with ether, and filtered through florisil. The filtrate was concentrated, and the residue was purified by silica gel column (ether-hexane, 2 : 3) to give the enone (55.0 mg, 95%) as a colorless oil. To a solution of CuBr (208.0 mg, 1.45 mmol) in THF (1 ml) was added Red-Al (70% toluene solution, 0.42 ml, 1.45 mmol) was added at -20 °C, and the reaction mixture was stirred for 0.5 hr (-20 °C). To the resulting mixture was gradually added 2-butanol (0.3 ml) and then the enone (33.4 mg, 0.226 mmol) in THF (2 ml) at -78 °C. The whole reaction mixture was stirred at -20 °C for 35 min, quenched by the addition of satd. aqueous NH_4Cl solution, diluted with H_2O and ether, stirred for a while, and extracted with ether. The ether extracts were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column (ether-hexane, 1 : 6) to give the ketone **32** (28.0 mg, 83%) as a colorless oil. To a solution of the ketone **32** (131.0 mg, 0.873 mmol) in benzene (1.5 ml) was added DBU (0.25 ml), and the reaction mixture was refluxed with stirring for 12 hr, neutralized with 10% aqueous HCl, and extracted with ether. The ether extracts were successively washed with satd. arqeous $NaHCO_3$ solution and brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column (ether-hexane, 1 : 6) to give **15** (123 mg, 90%) as a colorless oil. The spectral data were identical with those of an authentic sample.[10] $[\alpha]^{20}_D$ +532° (*c* 0.85, $CHCl_3$).

(1*R*, 6*R*, 8*S*)-3-Ethoxycarbonyl-8,11-dimethyltricyclo[6.3.0.0^{2,6}]undecane-2,10-dien-4-one (4). To a solution of LDA (2.66 mmol) in THF (3.5 ml) was added **15** (200 mg, 1.33 mmol, 80% ee) in THF (0.6 ml) over 5 min at -78 °C, and the reaction mixture was stirred for 45 min at -78 °C. To this enolate solution was then added ethyl-4-iodo-3-methoxycrotonate (720.0 mg, 2.67 mmol) in THF (0.3 ml). The whole reaction mixture was stirred for 0.5 hr at- 60 °C and for 0.5 hr at rt, quenched by the addition of satd. aqueous NH_4Cl solution, extracted with ether. The organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column (ether-hexane, 1 : 6) to give the mono-alkylated product (331 mg, 85%) as a colorless oil. To a solution of the mono-alkylated product (331 mg, 1.13 mmol) in ether (4 ml) was added 30 % $HClO_4$, and the reaction mixture was stirred for 12 hr at rt, quenched by the addtion of satd. aqueous $NaHCO_3$ solution, and extracted with ether. The ether layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column (ether-hexane, 1 : 3) to give the β-keto ester (284 mg, 90%) as a colorless oil. To a solution of the β-keto ester (284 mg, 1.02 mmol) in EtOH (3 ml) was added NaOEt (1.53 *M* EtOH solution, 1 ml, 1 53 mmol) at rt. The reaction mixture was stirred for 1 hr at the same temperature, and neutralized with 10% aqueous HCl. After evaporation of EtOH, the aqueous layer was extracted with ether, and the ether extracts were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column (EtOAc-hexane, 1 : 2) to give **4** (226 mg, 85%) : ^1H NMR δ 1.08 (d, J=12.8 Hz, 1H) 1.26 (s, 3H), 1.36 (t, J=7.0 Hz, 3H), 1.73 (m, 3H), 2.00-2.24 (m, 2H), 2.44 (dd, J =4.6, 2.2 Hz, 2H), 2.70 (dd, J=18, 6.km5 Hz, 1H), 3.10 (m, 1H), 3 75 (broad s, 1H), 4.32 (q, J = 7.0 Hz, 2H), 5.40 (m, 1H) ; IR (neat) · 1750, 1720, 1450 cm^{-1} ; MS m/z 260 (M^+), 215, 214 (M^+-EtOH, bp), 199, 145, 143, 91, 77 ; HRMS (M^+) calcd

for $C_{16}H_{20}O_3$ 260.1410, found 260.1405. $[\alpha]^{21}_D$ +530° (*c* 1.00, $CHCl_3$). The spectral data were identical with those of an authentic sample.[10]

(1*S*, 4*S*, 5*S*)-4-(*N*-benzylamino)-1-methyl-6-methylene-*cis*-bicyclo[3.3.0]oct-2-ene (33). a) A mixture of **29** (30.1 mg, 0.107 mmol) $Pd(OAc)_2$ (1.2 mg, 5.3 μmol), (*S*)-BINAP (4.18 mg, 6.7 μmol) and benzylamine (0.023 ml, 0.213 mmol) in DMSO (2 ml) was stirred at rt for 2 hr, and the reaction mixture was directly purified by silica gel column (AcOEt-hexane, 1 : 10) to give **33** (19.4 mg, 76%) as a pale yellow oil : ^{1}H NMR δ 1.26 (s, 3H), 1.46–1.53 (m, 1H), 1.57 (broad s, 1H), 1.66–1.71 (m, 1H), 2.20-2.23 (m, 2H), 2.53 (s, 1H), 3.60 (d, *J*=2.2 Hz, 1H), 3.82 (d, *J*=13 Hz, 1H), 3.95 (d, *J*=13 Hz, 1H), 4.83 (s, 1H), 4.87 (s, 1H), 5.59 (d, *J* = 5.5 Hz, 1H), 5.70 (dd, *J*=5.5, 2.2 Hz, 1H), 7.22-7.38 (m, 5H) ; ^{13}C NMR δ 157.4, 141.6, 140.4, 130.9, 128.4, 128.2, 126.9, 105.6, 73.9, 60.0, 56.7, 51.9, 38.0, 33.2, 28.3 ; IR (neat) : 2947, 1654, 1452 cm^{-1} ; MS m/z 239 (M^+), 224, 148, 91 (bp) ; $[\alpha]^{20}_D$ +9.30° (*c* 0.83, $CHCl_3$).

b) A mixture of **31** (28.4 mg, 0.161 mmol, 80% ee), $[Pd(allyl)Cl]_2$ (1.47 mg, 4.0 μmol), 1,4-bis(diphenylphosphino)butane (4.12 mg, 9.7 μmol) and benzylamine (0.04 ml, 0.322 mmol) in DMSO (1 ml) was stirred at rt 2 hr, and the reaction mixture was directly purified by silica gel column (AcOEt-hexane, 1 : 10) to give **33** (21.0 mg, 54%) as a pale yellow oil. The sprctral data were identical with those of an authentic sample. $[\alpha]^{20}_D$ +9.22° (*c* 1.05, $CHCl_3$).

Acknowledgment. This study was financially supported by Grant-in-Aid for Scientific Research on Priority Areas (Multiplex Organic Systems) from the Ministry of Education, Science and Culture, Japan.

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