Enantiodivergent Preparation of Optically Pure Tricyclic Cyclohexanoids via Lipase-Mediated Asymmetrization of a *meso*-Symmetric Starting Material

Minoru Moriya, Takashi Kamikubo, Kunio Ogasawara*
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980-77, Japan
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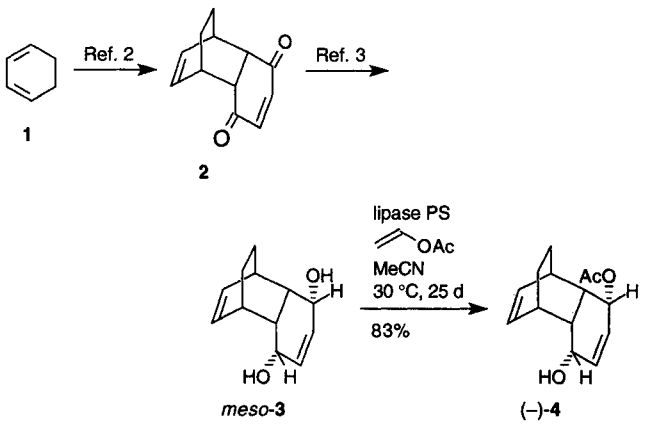
Two potentially useful, optically pure, tricyclohexanoids having 1,4-ethanohydronaphthalen-5-one system have been prepared in an enantiodivergent way from a single chiral tricyclic cyclohexanoid precursor obtained by lipase-mediated asymmetrization of a *meso*-symmetric starting material.

A good number of useful cyclohexanoid and condensed cyclohexanoid compounds are known in the literature, however, it would be synthetically useful if highly functionalized cyclohexanoid chiral building blocks were available. We wish to report here the preparation of two potentially useful optically active condensed cyclohexanoids having 1,4-ethanohydronaphthalen-5-one system in an enantiodivergent way from a single chiral tricyclic cyclohexanoid precursor obtained by lipase-mediated asymmetrization of a *meso*-symmetric condensed 2-cyclohexene-1,4-diol.[1]

Diels–Alder reaction of 1,3-cyclohexadiene **(1)** and benzoquinone in benzene at 50 °C afforded the tricyclic adduct **2** as a single product.[2] The adduct **2** was then reduced with diisobutylaluminium hydride to give stereoselectively the *endo*-diol[3] **3** in an excellent overall yield. Treatment of this *meso*-symmetric diol **3** with three equivalents of vinyl acetate in acetonitrile in the presence of lipase PS[1] (Amano, *Pseudomonas* sp.) furnished the optically active mono-acetate **4** in 83 % yield after stirring for 25 days at 30 °C (Scheme 1). Optical purity of the product could not be determined at this stage, but it could be presumed to be optically pure by the following transformation.



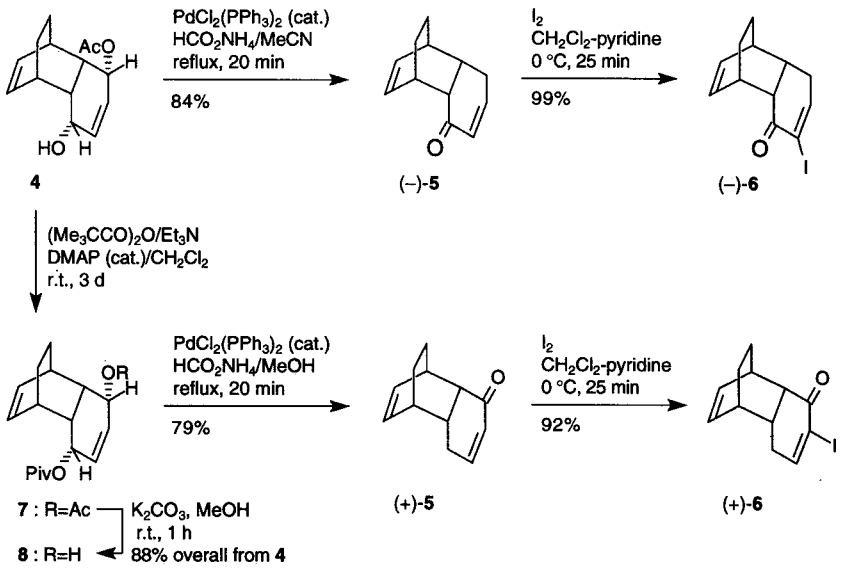
Scheme 1

Thus, the acetate **4**, on reflux with a catalytic amount of dichlorobis(triphenylphosphine)palladium(II) and ammonium formate in acetonitrile,[1,4] afforded the (–)-enone (–)-**5** in 84 % yield in one step after 20 minutes which was shown to be > 99 % ee by HPLC equipped with a chiral column. This palladium-mediated transformation had been encountered unexpectedly[1] and could not be well-explained,[4] but it could be nicely applicable to transform the pivalate **8** into the enantiomeric (+)-enone (+)-**5**.

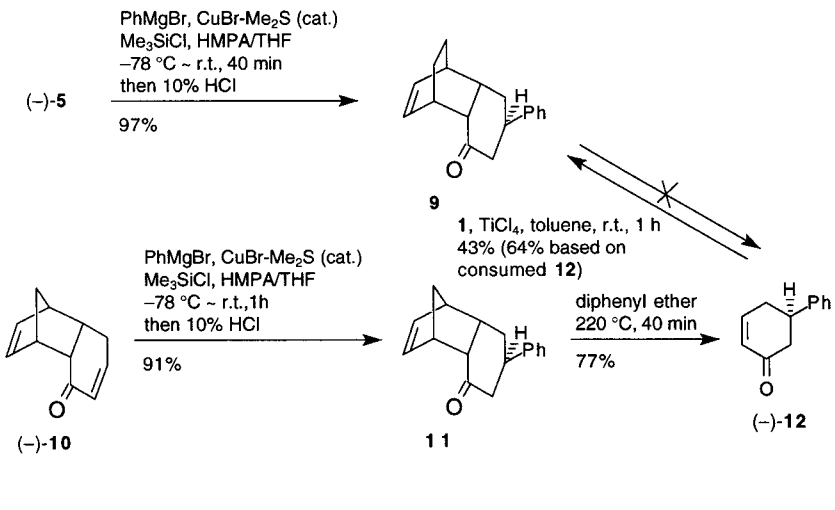
The acetate **4** was first treated with pivalic anhydride in the presence of triethylamine and 4-(*N,N*-dimethylamino)pyridine to give the diester **7** which then was stirred with potassium carbonate in methanol to afford the pivalate ester **8**, a virtual enantiomer of the acetate **4** in 88 % overall yield by selective removal of the acetyl group. Upon the same palladium-mediated treatment the pivalate **8** gave the (+)-enone (+)-**5** in 79 % yield which was shown to be optically pure (> 99 % ee) by HPLC analysis.

To functionalize the enone double bond, **5** was treated with iodine in the presence of pyridine[5] in which the reaction was found to occur only at the enone double bond to furnish the α-iodoenone **6** in an excellent yield in each enantiomer without affecting the other double bond in the molecule (Scheme 2).

Having established the enantiodivergent preparation of two tricyclic cyclohexanoid ketones **5** and **6** in optically pure forms via the common chiral intermediate **4**, we next determined the absolute configuration of these tricyclic products by correlating the optically active **5** to a known compound. We first attempted to transform the optically pure enone **5** into optically active 5-phenyl-2-cyclohexenone **(12)** whose stereochemistry has been established.[6] To this end, (–)-**5** was treated with phenylmagnesium bromide in the presence of copper(I) bromide–dimethyl sulfide complex and trimethylsilyl chloride[7] in tetrahydrofuran containing hexamethylphosphoric triamide (HMPA) to give the 1,4-adduct **9** in 97 % yield as a single product after hydrolytic workup. Stereospecific convex-face addition of the phenyl group was confirmed by a NOE experiment (500 MHz) which showed a significant interaction between the olefinic proton at C_2 center and the benzylic α-proton at C_7 center as expected from the result observed with the 1,4-methano analogue[8] **10**. The adduct **9**, however, was found to be stable under the thermolytic conditions and failed to give the anticipated (–)-5-phenyl-2-cyclohexenone (–)-**12** by retro-Diels–Alder cleavage. The known tricyclic enone (–)-**10**, the 1,4-methano analogue of (–)-**5**, was therefore treated with phenylmagnesium bromide under the same conditions above to give the *exo*-adduct **11** in 91 % yield as a single product. Upon thermolysis in diphenyl ether at 220 °C, **11** afforded the expected (–)-enone **12** in 77 % yield by retro-Diels–Alder cleavage. Then, **12** was reacted with 1,3-cyclohexadiene **(1)** in toluene at room temperature in the presence of titanium(IV) chloride to carry out the Diels–Alder reaction which afforded stereoselectively the adduct (–)-**9** in 43 % yield (64 %



Scheme 2



Scheme 3

yield based on the consumed **12**) accompanied by the unreacted enone (−)-**12** in 32% yield (Scheme 3). Since the Diels–Alder adduct and the above 1,4-adduct obtained from the (−)-enone (−)-**5** were identical in all respects, the stereochemistry of (−)-**5** as well as other optically active cyclohexanoid products have been determined as shown.

Utilization of the optically pure tricyclic cyclohexanoids thus obtained for the enantiocontrolled construction of natural products are in progress.

Melting points are uncorrected. IR specta were recorded on a JASCO-IR 700 spectrometer. ^{1}H NMR spectra were recorded on Hitachi R-3000 (300 MHz) and JEOL-JNM-GX500 (500 MHz) spectrometers. Mass spectra were measured on a JEOL JMS-DX303 instrument. Optical purities were determined on a Gilson Model-307 instrument equipped with a chiral column. Optical rotations were measured with a JASCO-DIP-370 digital polarimeter. All reactions were carried out under Ar. For all new compounds satisfactory microanalyses obtained: C ± 0.14, H ± 0.12.

(−)-(1*S*,4*R*,4a*S*,5*R*,8*S*,8a*S*)-5-Acetoxy-1,4,4a,5,8,8a-hexahydro-8-hydroxy-*endo*-1,4-ethanonaphthalene (4):

A suspension of the diol **3** (200 mg, 1.04 mmol), vinyl acetate (0.30 mL, 3.3 mmol) and Lipase PS on Celite (Amano, *Pseudomonas* sp., 90 mg) in MeCN (5 mL) was stirred at 30 °C for 25 d. The reaction mixture, after being filtered through a Celite pad, was evaporated under reduced pressure and chromatographed on silica gel (15 g, eluent, EtOAc/hexane, 1:4); yield: 202 mg (83%); colorless crystals; mp 37.5–38.0 °C; $[\alpha]_D^{30}$ −76.5 (c = 1.02, $CHCl_3$).

IR (Film): ν = 3442, 1737 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.16–1.70 (4H, m), 1.90 (1H, s, exchangeable with D_2O), 2.03 (3H, s), 2.26 (2H, ddd, J = 7.1, 5.4, 1.7 Hz), 2.42–2.79 (2H, m), 4.14 (1H, quint, J = 5.4 Hz), 5.39 (1H, t, J = 5.4 Hz), 5.96–6.48 (4H, m).

MS: m/z = 234 (M^+), 80 (100%).

HRMS (Calc. for $C_{14}H_{18}O_3$): m/z = 234.1256, Found: 234.1240.

(−)-(1*R*,4*S*,4a*S*,8a*S*)-1,4,4a,8a-Tetrahydro-*endo*-1,4-ethanonaphthalen-5(8*H*)-one [(−)-5] from the Acetate 4:

A mixture of **4** (100 mg, 0.427 mmol), $PdCl_2(PPh_3)_2$ (3 mg, 0.004 mol), and ammonium formate (41 mg, 0.65 mmol) in MeCN (2 mL) was refluxed for 20 min. After dilution with Et_2O, the mix-

ture was washed with 5% $NaHCO_3$, brine, dried ($MgSO_4$), and evaporated under reduced pressure. The residue was chromatographed on silica gel (7 g, eluent: Et_2O/hexane, 1:6) to give (−)-enone (−)-**5**; yield: 62 mg (84%); colorless crystals; mp 46.5–47.5 °C; $[\alpha]_D^{32}$ −147.0 ($c = 0.41$, $CHCl_3$); optical purity > 99% ee by HPLC (CHIRALCEL OB, eluent: *i*-PrOH/hexane, 5:95).

IR (Nujol): $\nu = 1650\ cm^{-1}$.

^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.11–1.69$ (4H, m), 1.73–2.26 (1H, m), 2.27–2.67 (4H, m), 3.09 (1H, br s), 5.79 (1H, ddd, $J = 10.2, 2.5, 1.7$ Hz), 6.03–6.35 (2H, m), 6.56–6.78 (1H, m).

MS: $m/z = 174$ (M^+), 80 (100%).

HRMS (Calc. for $C_{12}H_{14}O$): $m/z = 174.1045$. Found: 174.1059.

(−)-(1*R*,4*S*,4a*S*,8a*S*)-1,4,4a,8a-Tetrahydro-*endo*-6-iodo-1,4-ethanonaphthalen-5(8*H*)-one [(−)-6]:
To a stirred solution of (−)-**5** (86.4 mg, 0.497 mmol) in CH_2Cl_2 (4 mL) and pyridine (0.8 mL) was added iodine (252.6 mg, 0.995 mmol) at 0 °C and the mixture was stirred at the same temperature for 25 min. The mixture, after being diluted with CH_2Cl_2, was washed with 5% $NaHCO_3$, 10% $Na_2S_2O_3$, brine, dried ($MgSO_4$), and evaporated under reduced pressure. The residue was chromatographed on silica gel (16 g, eluent: Et_2O/hexane, 1:3) to give (−)-iodide (−)-**6**; yield: 147 mg (99%); colorless needles; mp 111–112 °C (hexane); $[\alpha]_D^{32}$ −20.2° ($c = 0.94$, $CHCl_3$).

IR (Nujol): $\nu = 1662\ cm^{-1}$.

^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.24–1.40$ (2H, m), 1.52–1.71 (2H, m), 2.16 (1H, ddd, $J = 18.7, 6.6, 4.0$ Hz), 2.50–2.81 (4H, m), 3.20–3.22 (1H, m), 6.20–6.32 (2H, m), 7.45 (1H, dd, $J = 5.5, 4.0$ Hz).

^{13}C NMR (75 MHz), $CDCl_3$): $\delta = 24.594, 25.158, 33.640, 36.050, 36.797, 50.282, 100.912, 133.878, 134.854, 157.126, 36.797, 50.282, 100.912, 133.878, 134.854, 157.126, 193.020$.

MS: $m/z = 300$ (M^+), 80 (100%).

HRMS (Calc. for $C_{12}H_{13}IO$): $m/z = 300.0001$, Found: 300.0011.

(+)-(1*R*,4*S*,4a*R*,5*S*,8*R*,8a*R*)-1,4,4a,5,8,8a-Hexahydro-8-hydroxy-5-pivaloyloxy-*endo*-1,4-ethanonaphthalene (8):
A solution of the acetate **4** (146 mg, 0.624 mmol), Et_3N (0.35 mL, 2.5 mmol), 4-(*N*,*N*-dimethylamino)pyridine (5 mg, 0.04 mmol), and pivalic anhydride (0.38 mmol, 1.9 mmol) in CH_2Cl_2 (1 mL) was stirred at r.t. for 3 d. The reaction was diluted with CH_2Cl_2 and washed with brine, 5% $NaHCO_3$, brine, dried ($MgSO_4$), and evaporated under reduced pressure. The residue was chromatographed on silica gel (15 g, elution with 1:10 v/v Et_2O/hexane) to give the diester **7** which was used immediately for the next reaction.

The diester **7** was then stirred with K_2CO_3 (50 mg, 0.36 mmol) in MeOH (3 mL) for 1 h at r.t. and the mixture, after evaporation under reduced pressure, was extracted with CH_2Cl_2. The extract was washed with brine, dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed on silica gel (10 g, eluent: Et_2O/hexane, 1:3) to give pivalate **8**; yield: 152 mg (88% overall from **4**); colorless crystals; mp 72–73 °C; $[\alpha]_D^{30}$ +99.3 ($c = 1.06$, $CHCl_3$).

IR (Nujol): $\nu = 1731, 1695\ cm^{-1}$.

^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.17$ (9H, s), 1.17–1.55 (4H, m), 1.62 (1H, s), 2.04–2.78 (4H, m), 4.13 (1H, quint, $J = 5.6$ Hz), 5.29 (1H, t, $J = 5.4$ Hz), 6.00–6.46 (4H, m).

MS: $m/z = 276$ (M^+), 80 (100%).

HRMS (Calc. for $C_{17}H_{24}O_3$): $m/z = 276.1725$, Found: 276.1725.

(+)-(1*S*,4*R*,4a*R*,8a*R*)-1,4,4a,8a-Tetrahydro-*endo*-1,4-ethanonaphthalen-5(8*H*)-one [(+)-5] from the Pivalate 8:
A mixture of **8** (99 mg, 0.359 mmol), $PdCl_2(PPh_3)_2$ (2.5 mg, 0.0035 mmol), and ammonium formate (34 mg, 0.54 mmol) in MeCN (3 mL) was refluxed for 20 min. After dilution with Et_2O, the mixture was washed with 5% $NaHCO_3$, brine, dried ($MgSO_4$), and evaporated under reduced pressure. The residue was chromatographed on silica gel (7 g, eluent: Et_2O/hexane, 1:6) to give (+)-enone (+)-**5** yield: 49 mg (79%); colorless crystals; mp 46–47 °C; $[\alpha]_D^{31}$ +144.6 ($c = 0.42$, $CHCl_3$); optical purity > 99% ee by HPLC (CHIRALCEL OB, elution with 5:95 v/v *i*-PrOH/hexane). Spectral data were identical with those of (−)-**5**.

(+)-(1*S*,4*R*,4a*R*,8a*R*)-1,4,4a,8a-Tetrahydro-*endo*-6-iodo-1,4-ethanonaphthalen-5(8*H*)-one [(+)-6]:
To a stirred solution of (+)-**5** (45.5 mg, 0.261 mmol) in CH_2Cl_2 (2.5 mL) and pyridine (0.5 mL) was added I_2 (134.1 mg, 0.53 mmol) at 0 °C and the mixture was stirred at the same temperature for 25 min. The mixture was worked up as for the (−)-enantiomer (−)-**5** to give (+)-**6**; yield: 71.5 mg (92%); colorless needles; mp 112–113 °C; $[\alpha]_D$ +20.4° ($c = 0.86$, $CHCl_3$). Spectral data were identical with those of (−)-**6**.

(−)-(1*R*,4*S*,4a*R*,8a*S*)-1,4,4a,5,6,7,8,8a-Octahydro-1,4-ethano-7-phenylnaphthalen-5-one [(−)-9] from the (−)-Enone (−)-5:
To a stirred solution of (−)-enone (−)-**5** (100 mg, 0.56 mmol), CuBr–SMe_2 (6 mg, 0.03 mmol), and HMPA (0.20 mL, 1.15 mmol) in THF (3 mL) was added $ClSiMe_3$ (0.14 mL, 1.1 mmol), followed by PhMgBr (1.6 M in THF, 0.7 mL, 1.12 mmol) at −78 °C and the mixture was stirred at the same temperature for 40 min. The reaction was quenched by addition of 10% HCl and extracted with Et_2O. The extract was washed with 5% $NaHCO_3$, brine, dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed on silica gel (7 g, eluent: Et_2O/hexane, 1:15) to give ketone (−)-**9**; yield: 140 mg (97%); colorless oil; $[\alpha]_D^{26}$ −129.5 ($c = 0.94$, $CHCl_3$).

IR (Film): $\nu = 1698\ cm^{-1}$.

^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.17–1.35$ (2H, m), 1.47–1.56 (2H, m), 1.60 (1H, ddd, $J = 13.2$, 8.4, 3.7 Hz), 2.04 (1H, dt, $J = 13.5$, 6.6 Hz), 2.27 (1H, q, $J = 8.7$ Hz), 2.38–2.44 (1H, m), 2.44–2.52 (2H, m), 2.57 (1H, dd, $J = 17.9, 6.6$ Hz), 3.15–3.20 (1H, m), 3.26 (1H, qd, $J = 7.0, 4.0$ Hz), 6.22–6.33 (2H, m), 7.16–7.26 (3H, m), 7.28–7.36 (2H, m).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 24.014, 26.622, 33.243, 37.102, 37.133, 37.774, 45.126, 52.061, 126.311, 126.800, 128.615, 134.015, 134.122, 144.693, 213.278$.

MS: $m/z = 252$ (M^+), 171 (100%).

HRMS (Calc. for $C_{18}H_{20}O$): $m/z = 252.1514$, Found: 252.1540.

(−)-(1*R*,4*S*,4a*R*,8a*S*)-1,4,4a,5,6,7,8,8a-Octahydro-*endo*-1,4-methano-7-phenylnaphthalen-5-one [(−)-11]:
To a stirred solution of (−)-enone (−)-**10** (1.04 g, 6.5 mmol), CuBr–SMe_2 (67 mg, 0.32 mmol), and HMPA (2.26 mL, 13.0 mmol) in THF (20 mL) was added $ClSiMe_3$ (1.65 mL, 13.0 mmol), followed by PhMgBr (1.6 M in THF, 8.1 mL, 13.0 mmol) at −78 °C and the mixture was stirred at the same temperature for 1 h. The reaction was quenched by addition of 10% HCl and extracted with Et_2O. The extract was washed with 5% $NaHCO_3$, brine, dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed on silica gel (40 g, eluent: Et_2O/hexane, 1:15) to give (−)-ketone (−)-**11**; yield: 1.41 g (91%); colorless oil; $[\alpha]_D^{31}$ −162.9 ($c = 1.2$, $CHCl_3$) [Lit.[1] value for (+)-**11**: $[\alpha]_D^{21}$ +131.0 ($c = 1.05$, $CHCl_3$)]. Spectral data were identical with those reported for (+)-**11**.

(−)-(*R*)-5-Phenyl-2-cyclohexen-1-one [(−)-12]:
A solution of the ketone (−)-**11** (537 mg, 2.26 mmol) in diphenyl ether (6 mL) was heated at 220 °C for 40 min. After cooling, the mixture was chromatographed on silica gel (20 g, eluent: EtOAc/hexane, 1:15) to give enone (−)-**12**; yield: 300 mg (77%); pale yellow crystals; mp 56–57 °C (Lit.[1] mp 60 °C); $[\alpha]_D^{26}$ −43.0 ($c = 1.25$, $CHCl_3$) [Lit.[1] $[\alpha]_D^{25}$ +44.4 ($c = 1.13$, $CHCl_3$)]. Spectral data were identical with those reported for (+)-**12**.[1]

(−)-(1*R*,4*S*,4a*R*,8a*S*)-1,4,4a,5,6,7,8,8a-Octahydro-1,4-ethano-7-phenylnaphthalen-5-one [(−)-9] from the (−)-Enone (−)-12:
To a stirred solution of the (−)-enone (−)-**12** (100 mg, 0.58 mmol) in toluene (5 mL) was added $TiCl_4$ (0.07 mL, 0.63 mmol) at r.t. and, after 1 h at the same temperature, 1,3-cyclohexadiene (0.17 mL, 1.80 mmol) was added and the mixture was stirred at the same temperature for 5 h. The reaction was quenched by addition of 5% NaOH and extracted with CH_2Cl_2. The extract was washed with brine, dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed on silica gel (10 g, eluent: Et_2O/hexane, 1:15) to give

the (−)-ketone (−)-**9** (63 mg, 43%: 64% based on consumed **12**) as a colorless oil and the starting material (−)-**12** (32 mg, 32%).

The (−)-ketone (−)-**9**, $[\alpha]_D^{26}$ −122.5 (c = 0.89, $CHCl_3$), was identical in all respects with that obtained from (−)-**5**.

We would like to express our gratitude to Professor Seiichi Takano for kind encouragement and to the Japan Society for the Promotion of Science for Japanese Junior Scientists for a fellowship (to M.M.).

(1) An enantiodivergent route to some 1,4-methanohydronaphthalenes has been reported: Takano, S.; Higashi, Y.; Kamikubo, T.; Moriya, M.; Ogasawara, K. *Synthesis* **1993**, 948.

(2) Diels, O.; Alder, K. *Ber. Dtsch. Chem. Ges.* **1929**, *62*, 2337.

(3) Craze, G.-A.; Watt, I. *J. Chem. Soc., Perkin Trans. 1* **1981**, 175.

(4) Takano, S.; Moriya, M.; Kamikubo, T.; Hiroya, K. Ogasawara, K. *Tetrahedron Lett.* **1993**, *34*, 8485.

(5) Johnson, C.R.; Adams, P.A.; Braun, M.P.; Senanayake, C.B.W.; Wovkulich, P.M.; Uskokovic, M.R. *Tetrahedron Lett.* **1992**, *33*, 1917.

(6) Asaoka, M.; Nishimura, K.; Takei, H. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 407.

(7) Horiguchi, Y.; Matsuzawa, S.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 4025.

(8) Takano, S.; Moriya, M.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1993**, 614.
Takano, S.; Higashi, Y.; Kamikubo, T.; Moriya, M.; Ogasawara, K. ibid. **1993**, 788.
Takano, S.; Moriya, M.; Ogasawara, K. *Synlett* **1993**, 601.