Efficient and Convenient Syntheses of (*R*)-(−)-Cryptone and (*S*)-(−)-4-Isopropenyl-2-cyclohexen-1-one

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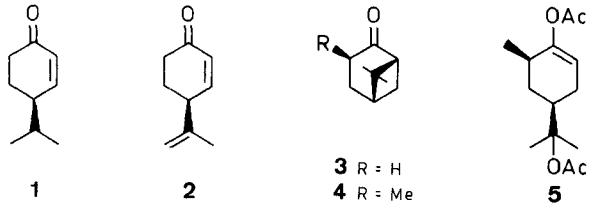
Starting with (+)-nopinone (**3**); (R)-(−)-cryptone (**1**) and (S)-(−)-4-isopropenyl-2-cyclohexen-1-one (**2**) were synthesized in five steps and 42% overall yield, and four steps and 49% overall yield, respectively.

2-Cyclohexen-1-ones are useful compounds in organic synthesis, e.g. they serve not only as dienophiles in the Diels–Alder reaction for the construction of 1-decalones, but also as acceptors in conjugate addition reactions for the synthesis of 3-substituted cyclohexanones.

In connection with our program dealing with the asymmetric synthesis of natural products, substantial quantities of (*R*)-(−)-4-isopropyl-2-cyclohexen-1-one (cryptone, **1**) and (*S*)-(−)-4-isopropenyl-2-cyclohexen-1-one (**2**) were required as chiral starting materials. Although the C_9-monoterpenoid, cryptone (**1**), is obtainable in both (+)- and (−)-forms from a few plants, especially from the Eucalyptus species,[1] it is commercially available only in the racemic form. Preparation of (+)-enantiomer **1** was recently reported by two groups; conversion of racemic **1** into the (+)-enantiomer **1** by Schreiber,[2] and asymmetric synthesis from 4-isopropylcyclohexanone by Koga,[3] whereas for (−)-enantiomer of **1**, few efficient and practical preparations have been reported.[4] On the other hand, a search of the literature for the substrate (−)-**2** revealed only one synthetic route by Stevens and Albizati,[5] wherein **2** was prepared, during the synthetic approach to the amphilectane diterpenes, from (*S*)-(−)-perilly alcohol in five steps and 40% overall yield. The synthesis of (+)-enantiomer of **2** from (*S*)-2-cyclohexen-1-ol was recently reported by Fujisawa.[6]

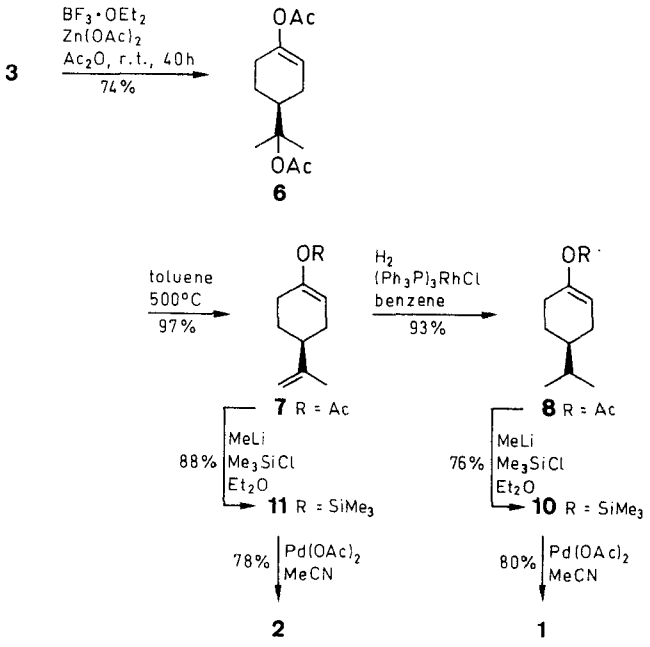


1 **2** **3** R = H, **4** R = Me **5**

In continuation of our work on the synthesis of natural products starting with (+)-nopinone (**3**), readily obtainable in large quantities by ozonolysis of (−)-β-pinene,[7] we wish to report here the convenient and efficient preparation of (−)-**1** and (−)-**2** from **3**.[8]

It was reported that (+)-nopinone (**3**) was converted into racemic cryptone (**1**) on treatment with ethylaluminum dichloride[9] or fluorosulfonic acid.[10] Our synthetic plan is based on the regioselective cyclobutane cleavage in the nopinone skeleton without loss of optical purity. We have confirmed that the combined reagent, diethyl ether–boron trifluoride complex/zinc acetate in acetic anhydride, effected the regioselective cyclobutane cleavage of (+)-*cis*-3-methylnopinone (4) with little loss of optical integrity followed by acetylation to produce the optically pure diacetate **5** in high yield.[11]

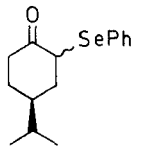
Thus, (+)-nopinone (**3**) was submitted to the diethyl ether–boron trifluoride complex-promoted cyclobutane cleavage, giving the diacetate **6** in 74% yield (Scheme 1). Pyrolysis of the latter at 500 °C proceeded smoothly and cleanly to afford the isopropenyl enol acetate **7** as the only product. Regioselective hydrogenation of **7** was carried out under the homogeneous conditions employing tris(triphenylphosphine)rhodium(I) chloride at atmospheric pressure to give the isopropyl enol acetate **8** in high yield.



Scheme 1

An enol acetate function is synthetically equivalent to an enolate anion, and would play an important role in regioselective introduction of a double bond. Regioselective enone formation by aid of the enol acetate function in **8** was first examined with two-step sequence consisting of phenylselenenylation followed by selenoxide fragmentation.[12] The lithium enolate generated from **8** with methyllithium (2 equiv) was treated with benzeneselenenyl chloride in diethyl ether at −78 °C to produce diastereomeric α-phenylselenocyclohexanone **9** in 78% yield. However, the attempted syn elimination of the selenoxide derived from **9** (15% aqueous hydrogen peroxide/pyridine/dichloromethane, 0 °C) resulted in a disappointingly low yield (20–30%) of (−)-cryptone (**1**).

This drawback was efficiently overcome by employing Saegusa's method.[13] The enol acetate **8** was converted regioselectively into the enol silyl ether **10** by treatment



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with methyllithium at −78 °C followed by addition of chlorotrimethylsilane. Palladium-catalyzed dehydrosilylation of **10** proceeded smoothly to give the desired (−)-cryptone **(1)**, $[\alpha]_D^{20}$ −85.2° (c = 3.88, EtOH), in 61% and 42% overall yield from **8** and **3**, respectively. GC analysis employing SUMICHIRAL OA-700 column showed an enantiomeric excess (ee), of 86.2% for the synthetic **1**, indicating that the present chemical transformation of (+)-nopinone **(3)**, 92% ee into (−)-**1** was carried out with almost little loss of optical integrity. For the optical rotation, (−)-cryptone **(1)** obtained from the natural source was reported to show $[\alpha]_D^{20}$ −119.3° (c = 2.0, EtOH),[14] whereas (−)-**1** derived from optical purification via (−)-cryptol showed $[\alpha]_D^{20}$ −91.7° (c = 2.2, EtOH).[15]

For the preparation of (*S*)-(−)-4-isopropenyl-2-cyclohexen-1-one **(2)**, the isopropenyl enol acetate **7** was used as a common chiral source. Transformation of **7** into **2** was accomplished by the use of two-step sequence of reactions described above; conversion of **7** into the corresponding silyl enol ether **11** with methyllithium and chlorotrimethylsilane followed by palladium-catalyzed dehydrosilylation provided **2**, $[\alpha]_D^{19}$ −161.9° (c = 1.5, MeOH), [Lit.[5] $[\alpha]_D^{22}$ −153.8° (MeOH)] in 49% overall yield from **3**. Though the dienone **2** is unstable on heating and gave a mixture of double bond-isomerization products on distillation, the compound **2** obtained here by chromatographic purification was proved to be homogeneous enough to use as a chiral building block[16] by ^{1}H NMR and HPLC analyses.

The synthetic procedures described here are practically useful for the laboratory scale preparation of (−)-**1** and (−)-**2** because of simplicity and good overall yield.

(*S*)-(−)-β-Pinene was purchased from Aldrich Chemical Co. All reactions were carried out under dry N_2 or Ar atmosphere, unless otherwise stated. Na_2SO_4 was used for drying of extracts. Column chromatography was performed on 70–230 mesh silica gel (Merck). Solvents for elution are given in parentheses. IR spectra were obtained with a JASCO A-3 spectrophotometer. ^{1}H NMR spectra were recorded on a JEOL FX90 spectrometer. Observed rotations at the Na-D line were obtained with a JASCO DIP-181 Polarimeter.

(+)-Nopinone **(3)**, $[\alpha]_D^{23}$ +36.9° (c = 4.2, MeOH, 92% optical purity)[17] was prepared by the ozonolysis of (*S*)-(−)-β-pinene according to the published procedure.[7]

(*S*)-(−)-1-Acetoxy-4-(1-acetoxy-1-methylethyl)-1-cyclohexene (6):
$BF_3 \cdot OEt_2$ (0.21 mL, 1.79 mmol) was added to a stirred suspension of (+)-nopinone (**3**; 2.48 g, 17.93 mmol) and $Zn(OAc)_2$ (3.28 g, 17.93 mmol) in AcOH (15 mL). The resulting mixture was stirred at r.t. for 40 h, and poured into water (40 mL). After stirring vigorously for 1 h, the product was extracted with Et_2O (4 × 40 mL). The combined extracts were washed successively with sat. $NaHCO_3$ (3 × 20 mL), water (50 mL) and brine (50 mL), and dried. Evaporation at reduced pressure followed by purification of the residue by column chromatography on silica gel (hexane/Et_2O, 9 : 1) gave **6** as an oil; yield: 3.18 g, (74%); $[\alpha]_D^{14}$ −49.5° (c = 2.0, $CHCl_3$).

$C_{13}H_{20}O_4$ (240.3) calc. C 64.98 H 8.39 found 64.81 8.30

IR (film): ν = 1760, 1730, 1260, 1220, 1120 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.42, 1.44 [2s, 3H each, $C(CH_3)_2$], 1.4–2.4 (m, 7H, H-3-6), 1.96, 2.12 (2s, 3H, each 2 $COCH_3$), 5.45 (br s, 1H, =CH).

(*S*)-(−)-1-Acetoxy-4-isopropenyl-1-cyclohexene (7):
A solution of **6** (3.0 g) in toluene (20 mL) was passed dropwise through a quartz tube (21 × 1.5 cm) packed with quartz beads at 500 °C with the aid of N_2 stream, and the vapor was condensed in an ice trap. The condensate was washed with water (5 mL) and brine (5 mL), dried, and then concentrated. The oily residue was passed through a short silica gel column (hexane/Et_2O, 9 : 1) to give **7** as an oil; yield: 2.15 g (97%); $[\alpha]_D^{21}$ −57.4° (c = 5.30, $CHCl_3$).

$C_{11}H_{16}O_2$ (180.2) calc. C 73.30 H 8.95 found 73.05 8.73

IR (film): ν = 3050, 1760, 1610, 1220, 890 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.75 (s, 3H, $=CCH_3$), 2.12 (s, 3H, $COCH_3$), 1.5–2.5 (m, H-3-6), 4.75, (s, 2H, $=CH_2$), 5.37 (br s, 1H, =CH).

(*S*)-(−)-1-Acetoxy-4-isopropyl-1-cyclohexene (8):
Compound **7** (1.08 g, 6.00 mmol) and $(Ph_3P)_3RhCl$ (280 mg, 0.3 mmol) were dissolved in degassed benzene (15 mL), and the resulting solution was hydrogenated at atmospheric pressure for 15 h. The solvent was removed at reduced pressure and the product was taken up in hexane (hexane/Et_2O, 4 : 1). The combined extracts (50 mL) were filtered through a short silica gel column. Evaporation followed by distillation of the residue gave **8** as an oil; yield: 1.00 g, (93%); bp 100 °C/2 Torr (bath temperature); $[\alpha]_D^{14}$ −59.2° (c = 1.52, $CHCl_3$).

$C_{11}H_{18}O_2$ (182.3) calc. C 72.49 H 9.96 found 72.28 9.78

IR (film): ν = 3050, 1760, 1695, 1610, 1220, 1120, 910 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.88 [d, 6H, J = 6 Hz, $CH(CH_3)_2$], 2.10 (s, 3H, $COCH_3$), 1.2–2.5 [m, 8H, $CH(CH_3)_2$ + H-3-6], 5.3 (br m, 1H, =CH).

(*R*)-(−)-Cryptone (1):
To a stirred solution of 0.98 M MeLi in Et_2O (6.7 mL, 6.60 mmol) and Et_2O (10 mL) was added dropwise at −78 °C a solution of **8** (562 mg, 3.08 mmol) in Et_2O (5 mL). After stirring for 20 min, a solution of $ClSiMe_3$ (0.85 mL, 6.78 mmol) followed by Et_3N (1 mL) and HMPA (0.6 mL) was added to the reaction mixture, and stirring was continued for an additional 4 h at the range of −78 to −30 °C. Pentane (15 mL) was added, and the solid was filtered. The filtrate was washed successively with cold 5% HCl (7 mL), 5% $NaHCO_3$ (2 × 5 mL), and brine (10 mL), and dried. Evaporation followed by distillation of the oily residue gave the silyl enol ether **10** as an oil; yield: 495 mg (76%); bp 95 °C/2 Torr (bath temperature).

10:

^{1}H NMR ($CDCl_3$): δ = 0.15 [s, 9H, $Si(CH_3)_3$], 0.90 [d, 6H, J = 6 Hz, $CH(CH_3)_2$], 1.2–2.6 [m, 8H, $CH(CH_3)_2$ + H-3-6], 4.85 (br s, 1H, =CH).

A mixture of **10** (495 mg, 2.34 mmol) and $Pd(OAc)_2$ (525 mg, 2.34 mmol) in MeCN (10 mL) was stirred at r.t. for 7 h. Concentration at reduced pressure followed by purification of the residue by chromatography on silica gel (hexane/Et_2O, 9 : 1) gave **1** as an oil; yield: 258 mg (80%); bp 95 °C/2 Torr (bath temperature). Determination of enantiomeric purity of the synthetic **1** by GC analyses was performed, after setting up the chromatographic conditions by use of (±)-**1**, on a Shimadzu GC-14A equipped with flame ionization detectors and a SUMICHIRAL OA-700 column (0.25 mm i.d. × 25 m, FS)[18] at 50 °C with a flow rate of 1.0 mL/min, indicating a 93.1 : 6.9 ratio of *R*-(−)-**1** (t_R 65.0 min) and *S*-(+)-**1** (t_R 66.2 min); $[\alpha]_D^{20}$ −85.2° (c = 3.88, EtOH) {Lit.[14] $[\alpha]_D^{20}$ −119.3° (c = 2, EtOH), Lit.[15] $[\alpha]_D^{20}$ −91.7° (c = 2.2, EtOH)}. Spectral data are identical with those reported for (+)-**1**.[5]

(−)-2:

IR (film): ν = 3030, 1680, 1610, 830 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.95, 0.97 [2d, 3H, J = 7 Hz, each, $CH(CH_3)_2$], 1.4–2.6 [m, 6H, H-4-6 + $CH(CH_3)_2$], 6.0 (dd, 1H, J = 10.1, 2.7 Hz, $COCH{=}CH$), 6.85 (ddd, 1H, J = 10.1, 2.5, 1 Hz, $COCH{=}CH$).

(4*S*)-(−)-4-Isopropenyl-2-cyclohexen-1-one (2):
According to the procedure described for the preparation of **1**, **7** (540 mg, 3.0 mmol) was treated with 1.06 M MeLi in Et_2O (6.1 mL, 6.48 mmol) at −78 °C followed by addition of a mixture of $ClSiMe_3$ (0.84 mL, 6.6 mmol), Et_3N (1.0 mL) and HMPA (0.7 mL). After stirring for 5 h at −78 to 30 °C, workup afforded the enol silyl ether **11** as an oil; yield: 554 mg (88%).

11:

^1H NMR ($CDCl_3$): δ = 0.17 [s, 9H, $Si(CH_3)_3$], 1.75 (s with fine splittings, 3H, $=CCH_3$), 1.2–2.3 (m, 7H, H-3-6), 4.70 (s, 2H, $=CH_2$), 4.89 (br s, 1H, =CH).

A mixture of **11** (500 mg, 2.38 mmol) and $Pd(OAc)_2$ (534 mg, 2.38 mmol) in MeCN (10 mL) was stirred for 7 h. Workup followed by purification by chromatography on silica gel (hexane/Et_2O, 9 : 1) gave **2** as an oil; yield: 252 mg, (78%); $[\alpha]_D^{20}$ −161.9° (c = 1.5, MeOH). The IR and ^1H NMR data are identical with those reported for (±)-**2**.[5]

(−)-2:

$C_9H_{12}O$	calc.	C 79.37	H 8.88
(136.2)	found	79.54	8.74

IR (film): ν = 3040, 1685, 1610, 900, 850, 735 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.79 (s, 3H, $=CCH_3$), 1.9–2.6 (m, 2H, H-4,5), 3.0 (br m, 2H, $COCH_2$), 4.75 (br s, 1H, $=CHH$), 4.90 (t, 1H, J = 1 Hz, $=CHH$), 6.05 (dd, 1H, J = 14, 2 Hz, $COCH{=}CH$), 6.85 (dd with fine splittings, 1H, J = 14, 5 Hz, $COCH{=}CH$).

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