Total Synthesis of (−)-Chiloscyphone, Sesquiterpenoid Isolated from the Liverwort. Absolute Configuration of (−)-Chiloscyphone and (+)-Chiloscypholone

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The absolute configurations of (−)-chiloscyphone and (+)-chiloscypholone isolated from the liverwort *Chiloscyphus polyanthos* and *C. pallescens* respectively, have been determined by the total synthesis of the optically active compound. The 1,4-addition of vinylmagnesium bromide to 3,4-dimethyl-2-cyclohexenone in the presence of copper(I) bromide-dimethyl sulfide complex and the subsequent aldol condensation of the keto-aldehyde derived in several steps afforded the hydrindenone derivative. The key intermediate alcohol has been resolved by the use of (1S)-(−)-camphanic chloride. The optically active hydroxy ester has been converted to (−)-chiloscyphone.

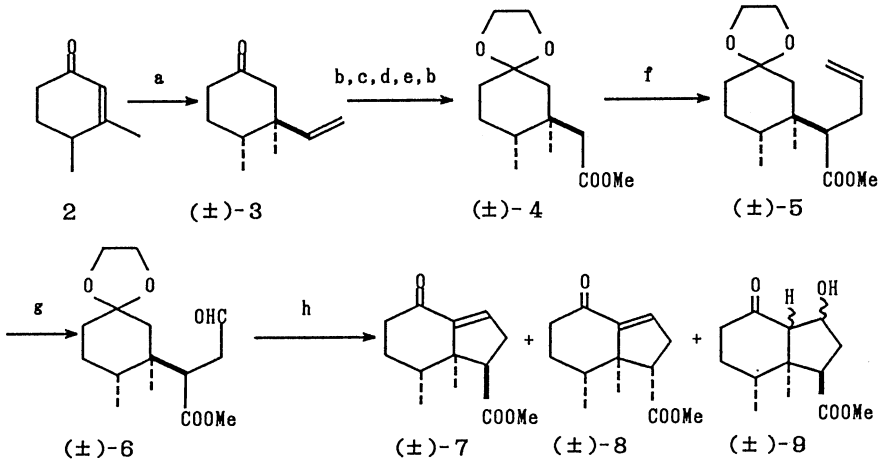
Most liverworts produce various kinds of terpenoids and/or aromatic substances.[1] Some of the chemical constituents have the opposite sign of rotation of those found in higher plants. For example, spathulenol has the opposite sign of rotation, while caryophyllene and caryophyllene oxide have the same sign of rotation as those found in the higher plants.[1] Further example shows an interesting feature of these problems. (−)-Frullanolide has been isolated from the liverwort *Frullania tamarisci* and the absolute configuration assigned, while the one from the quite similar species *Frullania dilatata* showed the opposite sign of rotation.[1] It is, thus, very interesting and also important to study the absolute configuration of terpenoids found in the liverworts.

(−)-Chiloscyphone (**1**) was first isolated from the liverwort *Chiloscyphus polyanthos* by Matsuo[2] and later the structure was revised by Connolly and his associates in 1982.[3] (+)-Chiloscypholone was also found by them in *C. pallescens* at the same time.[3] However, its absolute configuration has not been determined.[4]

We planned the total synthesis of the optically active substances through intramolecular aldol condensation and the resolution of the key intermediate alcohol by esterification with (1S)-(−)-camphanic chloride. We now report on the detail of our successful total synthesis of (−)-chiloscypone.[5]

Results and Discussion

Synthesis of Racemic Chiloscyphone ((±)-1). The *cis*-dimethyl arrangement was accomplished by 1,4-addition[6] of vinylmagnesium bromide to 3,4-dimethyl-2-cyclohexen-1-one (**2**) in the presence of $CuBr \cdot SMe_2$. Acetal ester **4** was derived from 3,4-dimethyl-3-vlnylcyclohexan-1-one (**3**)[6] in five steps conversion. Alkylation (LDA/allyl bromide) of **4** into **5** and ozonolysis (CH_2Cl_2/−78 °C) followed by Zn/AcOH treatment afforded acetal aldehyde **6** in good yield.[7] When **6** was subjected to acidic conditions (TsOH/acetone-H_2O), three products (**7**, **8**, and **9**) were isolated in 35, 23, and 22% yield, respectively (Scheme 1). Compound **7** showed the presence of the



(a)CH_2=$CHMgBr/CuBr \cdot Me_2S$/THF; (b)$HOCH_2CH_2OH$/TsOH; (c)$BH_3 \cdot$ THF; H_2O_2/OH^-; (d)Jones; (e)CH_2N_2; (f)LDA/CH_2=$CHCH_2Br$; (g)O_3/Zn-AcOH; (h) TsOH/H_2O-acetone

Scheme 1.[a]

β proton of the α,β-unsaturated ketone system [δ=6.54 (dd, J=3.3 and 2.1 Hz)], two methyl groups [δ=1.03 (d, J=6.8 Hz) and 1.08 (s)] and methoxycarbonyl group [δ=3.67 (s)] in its ^{1}H NMR spectrum. The spectral data of compound **8** also suggested a similar structure to **7**, indicating that these two are isomers in each other concerning the 6-position. When the methyl group at either C-4[8] or C-5 of **7** was irradiated, NOE into H-6 was observed. While irradiation at H-6 of **8** caused NOE into H-4. These experiments indicated the orientation of the methoxycarbonyl group as depicted in Fig. 1. The third compound **9** [IR 3450 cm^{-1}, δ=9.83 (s)] was obviously hydrogen bonded hydroxy ketone. Since **9** was converted to **7** under the same acidic conditions described above, the orientation of the methoxycarbonyl group was determined to be trans to both methyl groups.

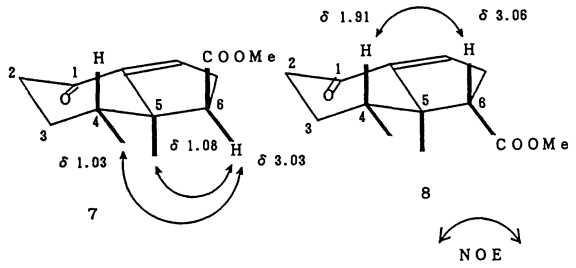
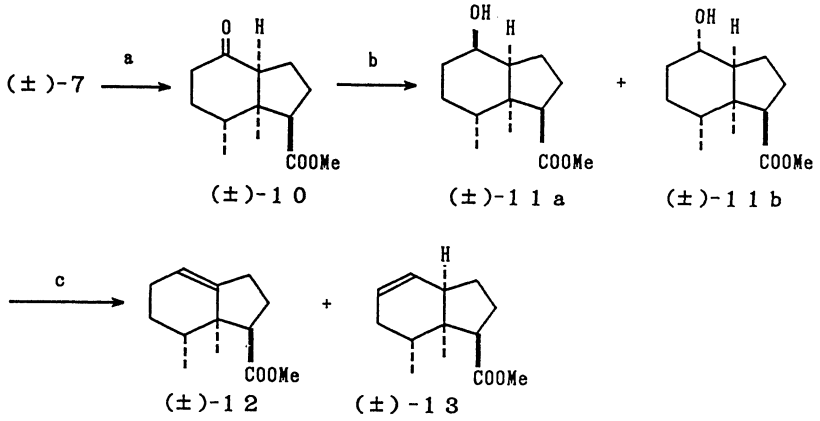


Fig. 1. The stereochemistry of methyl ester **7** and **8**.

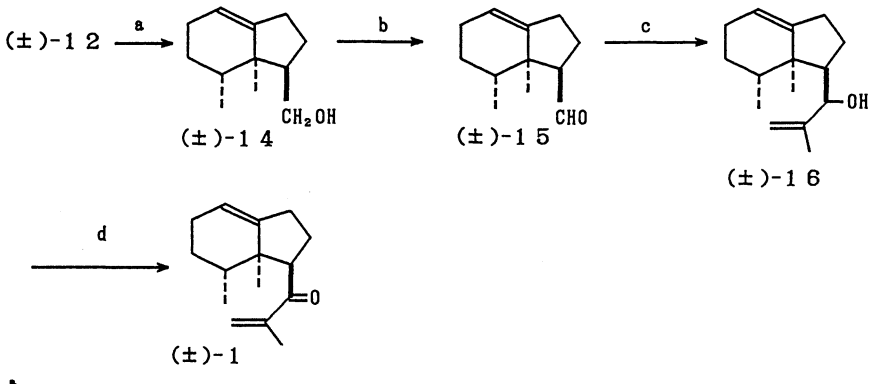
The conversion of enone **7** to olefin **12** was accomplished in three steps (Scheme 2). Hydrogenation of enone **7** (H_2/Pd-C), to give dihydro ketone **10**, followed by $NaBH_4$ reductlon afforded two isomeric alcohols **11**, which were dehydrated ($POCl_3$/Py) to give a mixture of trisubstituted olefin **12** [δ=5.39 (1H, m)] and disubstituted olefin **13** [δ=5.61 (2H, m)]. This mixture was separated by $AgNO_3$ impregnated silica-gel column chromatography. The olefln **12** was reduced ($LiAlH_4$), oxidized (Swern oxidation), alkylated [CH_2=C(Me)MgBr], and oxidized (Jones oxidation) to afford (±)-**1** (Scheme 3). The spectral data of synthetic (±)-**1** were identical with those reported in the literature.[2]

Synthesis of (−)-Chiloscyphone ((−)-1). The ketone **10** was reduced with $NaBH_4$ to afford two isomeric alcohols (**11a** and **11b**). After separation by silica-gel column chromatography, each alcohol was esterified with (1*S*)-(−)-camphanic chloride (DMAP/CH_2Cl_2-Py) to form a mixture of diastereoisomers (**17**—**20**)



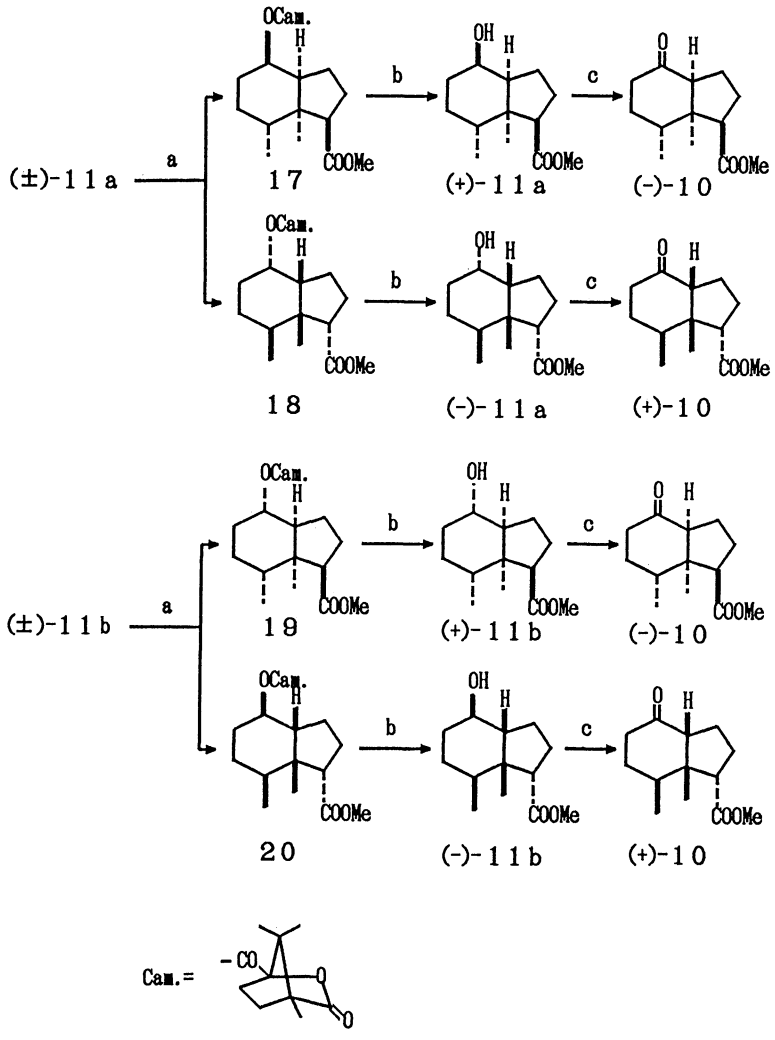
(a)H_2/Pd-C; (b)$NaBH_4$/MeOH; (c)$POCl_3$/Py/100°

Scheme 2.[a]



(a)$LiAlH_4$; (b)Swern; (c)CH_2=C(Me)MgBr; (d)Jones

Scheme 3.[a]



(a)(1S)-(-)-camphanic chloride/CH_2Cl_2-Py/DMAP; (b)KOH/MeOH; (c)Jones

Scheme 4.[a)]

(Scheme 4). Separation of these isomers was achieved by HPLC (JASCO TRI ROTAR-V, KNAUER RI detector, NUCLEOSIL 50-5 10X250; hexane-EtOAc 9:1) to give **17**, **18**, **19**, and **20**. These camphanic esters were hydrolyzed (KOH/MeOH/rt/5h) to afford (+)-**11a**, (−)-**11a**, (+)-**11b**, and (−)-**11b**. Ketones **10** derived from these alcohols showed antipodal CD curves. Namely (+)-**11a** and (+)-**11b** gave (−)-**10**, and (−)-**11a** and (−)-**11b** afforded (+)-**10**.

cis-Hydrindanones have two conformations in general.[9)] In this case, however, the steroid form is energetically less stable than the non-steroid form due to quasi-axial orientation of the methoxycarbonyl group.[9)] While in the non-steroid form this interaction is released to be more stable. Actually, NOE's between 5-Me and H-I0, 5-Me and H-3β, and 5-Me and 4-Me were observed,[8)] while the one between 4-Me and H-10 did not appear.[10)] From the back octant for the non-steroid (+)-**10** shown in Fig. 2. the (+)-Cotton effect is expected. The CD spectrum of (+)-**10** exhibited $\Delta\varepsilon_{289nm}$+0.60 (Fig. 2), indicating the absolute

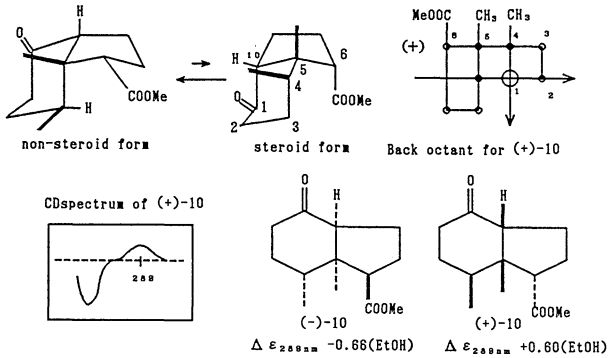


Fig. 2. Conformation and back octant for **10**.

configuration as depicted in the formula.

The alcohol (+)-**11a** was dehydrated ($POCl_3$/Py/100 °C) to give only a trisubstituted olefin (+)-**12**, which was converted to (−)-**1** ($[\alpha]_D^{19}$−15.1° (*c* 0.4, $CHCl_3$) [lit.[3)] −24.4° (*c* 0.76, $CHCl_3$)] in four steps (vide supra). The spectral data of the product were completely identical with those of (±)-**1** and also the reported

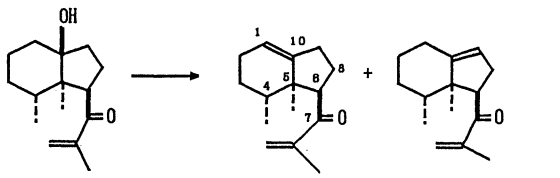
data.[2,3] The value of the optical rotation was somewhat smaller than that of the natural product. This is presumably due to the only minute quantity of the product obtained (see Experimental Section). The purity of (+)-**11a** was rechecked by HPLC showing the corresponding MTPA ester to be >95% pure.

Synthesis of (+)-Chiloscyphone ((+)-1). To consolidate the above result further, we synthesized (+)-**1** starting from (−)-**11a** by the same route. The synthetic (+)-**1** showed $[\alpha]_D^{19}$+24.2° (*c* 1.2, $CHCl_3$), the absolute value of which was in a good accordance with that reported.[3]

Conclusions

These results clearly show that the natural (−)-chiloscyphone must be the one depicted in the formula.

Since (+)-chiloscypholone (**21**) was converted to (−)-**1**,[3] the absolute configuration of **21** was also determined as depicted in Scheme 5.



Scheme 5.[3]

Experimental

General. IR spectra were recorded on a Shimadzu IR-27G (solution or film) spectrophotometer. Low and high resolution MS spectra were taken with a Shimadzu LKB-9000B or JEOL JMS HX 100 spectrometer. ^{1}H NMR spectra were measured on a JEOL JNM GX 400 (400 MHz) or JNM FX 90Q (90 MHz) spectrometer with TMS as internal standard. ^{13}C NMR spectra were taken on a JNM FX 90Q spectrometer. All the NMR spectra were measured in $CDCl_3$. Specific rotations and circular dichroism spectra were recorded on a JASCO DIP-140 polarimeter and a JASCO J-500 spectrophotometer, respectively.

A JASCO Tri Rotar-V was used for HPLC, and KNAUER RI detector and JASCO UVIDEC-100-V were used for the detector. The column was Chemcopak NUCLEOSIL 50-5, 10×250 mm and the solvent system hexane : EtOAc=9 : 1 was used. Kieselgel 60 (70—230 mesh, Merck) was used for column chromatography and Kieselgel 60F_{254} (0.25 mm and 0.50 mm thick) was used for thin layer chromatography.

Ether, THF, and benzene were distilled from Na wire; pyridine was dried over KOH, and dichloromethane was stored over molecular sieves 3A.

Methyl (1*S,2*R**)-1,2-dimethyl-5-oxocyclohexylacetate Ethylene Acetal (4).** Copper (I) bromide-dimethyl sulfide complex (170 mg) was dissolved in dry THF (50 ml) and kept at −30 °C. A THF solution of vinylmagnesium bromide (0.98 mol, 124 ml) was added at the same temperature. To this mixture was added a THF solution of 3,4-dimethyl-2-cyclohexenone (**2**, 10 g). The temperature was kept at −30 °C for 1 h before quenching with saturated aqueous ammonium chloride. The mixture was extracted with ether and the extract was washed with brine. The ethereal solution was dried over magnesium sulfate and evaporated in vacuo to afford a residue, which was distilled under reduced pressure to give (3*R**,4*R**)-3,4-dimethyl-3-vinylcyclohexanone (**3**, 8.2 g, 67%), bp 60—64 °C (400 Pa) [lit.[6] 51—54 °C (40 Pa)]. A solution of **3** (45 g) in benzene (400 ml) was treated with *p*-toluenesulfonic acid (4.5 g) and ethylene glycol (20 ml) with the aid of the Dean-Stark water separator under reflux for 12 h. Usual work up afforded (3*R**,4*R**)-3,4-dimethyl-3-vinylcyclohexanone ethylene acetal (40.7 g, 70%), ^{1}H NMR δ=0.78 (3H, d, *J*=6.0 Hz), 1.01 (3H, s), 3.91 (4H, br s), 4.8—5.0, 5.5—5.9 (3H, m); EIMS *m/z* 196 (M^+), 181, 139, 125, 99 (base), 86. To a solution of (3*R**,4*R**)-3,4-dimethyl-3-vinylcyclohexanone ethylene acetal (4.5 g) in dry THF (5 ml) was added BH_3-THF (1 M, 23 ml) at room temperature and the solution was stirred for 1.5 h. Water (1 ml), 3 M NaOH solution (10 ml, 1 M=1 mol dm^{-3}), 30% H_2O_2 (10 ml) were added successively to keep the temperature between 30 °C and 50 °C. Usual work up gave (3*R**,4*R**)-3,4-dimethyl-3-(2-hydroxyethyl)cyclohexanone ethylene acetal (4.5 g, 92%), IR (film) 3400 cm^{-1}; ^{1}H NMR δ=0.87 (3H, d, *J*=7.7 Hz), 0.91 (3H, s), 3.91 (4H, s), 3.79 (2H, t, *J*=4.4 Hz); ^{13}C NMR δ=15.0, 19.3, 27.9, 34.3, 36.0, 38.1, 44.3, 44.9, 58.3, 63.2, 64.0, 109.1; EIMS *m/z* 214 (M^+), 197, 157, 113, 99 (base), 86. A solution of (3*R**,4*R**)-3,4-dimethyl-3-(2-hydroxyethyl)cyclohexanone ethylene acetal (10 g) in acetone was treated with Jones reagent (10 ml) at 0 °C for 1 h. Usual work up afforded a residue, which was treated with diazomethane without purification. The methyl ester in benzene (200 ml) was refluxed with ethylene glycol (2.6 ml) and *p*-toluenesulfonic acid (1 g) with the aid of the Dean-Stark water separator for 6 h. Usual work up and chromatographic purification (silica gel, hexane-EtOAc gradient) gave **4** (8.7 g, 77%). HRMS Found: *m/z* 242.1522 (M^+). Calcd for $C_{13}H_{22}O_4$: M, 242.1518. IR (film) 1730 cm^{-1}; ^{1}H NMR δ=0.88 (3H, d, *J*=6.1 Hz), 0.99 (3H, s), 1.55 (4H, m), 1.69 (2H, br s), 2.29 (2H, br s), 3.64 (3H, s), 3.91 (4H, s); ^{13}C NMR δ=14.9, 19.3, 27.8, 34.0, 37.0, 37.5, 43.7, 46.1, 50.6, 63.2, 64.0, 108.7, 171.9; EIMS *m/z* 242 (M^+), 185, 99 (base), 86, 55.

Methyl 2-[(1*R,2*R**)-1,2-Dimethyl-5-oxocyclohexyl]-4-pentenoate Ethylene Acetal (5)** To an LDA solution prepared from diisopropylamine (9.1 ml, 65.1 mmol), *n*-BuLi (40 ml, 64 mmol), and dry THF (40 ml) was added HMPA (0.2 ml, 1.1 mmol) at −78 °C. A solution of **4** (7.2 g, 29.7 mmol) in dry THF (10 ml) was added during 15 min. In 1 h, allyl bromide (3.1 ml, 35.8 mmol) in dry THF (10 ml) was added slowly. The mixture was stirred for 2 h at room temperature before work up. Purification by column chromatography of silica gel (hexane-EtOAc gradient) gave **5** (6.3 g, 75%).[7] HRMS Found: *m/z* 282.1828 (M^+). Calcd for $C_{16}H_{26}O_4$: M, 282.1831. IR (film) 1725 cm^{-1}; ^{1}H NMR δ=0.91 (3H, d, *J*=5.1 Hz), 1.00 (3H, s), 3.63 (3H, s), 3.91 (4H, s), 5.03—5.66 (3H, m); ^{13}C NMR δ=15.3, 18.4, 28.7, 31.4, 34.9, 37.6, 39.8, 50.7, 53.0, 55.3, 63.4, 64.3, 109.4, 116.2, 136.2, 174.4; EIMS *m/z* 282 (M^+), 251, 225, 169, 125, 113, 99 (base), 55, 41.

Methyl 2-[(1*R,2*R**)-5,5-Ethylenedioxy-1,2-dimethylclohexyl]-4-oxobutanoate Ethylene Acetal (6).** Ozone was

passed through a solution of **5** (728 mg) in dichloromethane (20 ml) for 1.5 h at −78 °C. Zinc dust (100 mg) and acetic acid (8 ml) were added. Usual work up afforded **6** (676 mg, 92%).[7] HRMS Found: *m/z* 284.1626 (M^+). Calcd for $C_{15}H_{24}O_5$: M, 284.1624. IR (film) 1720 cm^{-1}; ^1H NMR δ=0.95 (3H, s), 0.97 (3H, d, *J*=6.1 Hz), 3.68 (3H, s), 3.91 (4H, s), 9.76 (1H, s); ^{13}C NMR δ=15.4, 18.5, 28.5, 34.5, 36.9, 40.2, 41.9, 47.5, 51.4, 63.4, 64.4, 109.1, 173.9, 200.5; EIMS *m/z* 284 (M^+), 256, 227, 209, 195, 169 (base), 125, 99.

Aldol Condensation of Methyl 2-[(1*R,2*R**)-5,5-Ethylenedioxy-1,2-dimethylcyclohexyl]-4-oxobutanoate Ethylene Acetal (6).** A mixture of **6** (633 mg), TsOH (140 mg), acetone (30 ml), and water (5 ml) was heated at reflux for 12 h. Usual work up and column chromatography of silica gel (hexane-EtOAc gradient) afforded methyl (1*R**,2*R**,9*R**)-1,2-dimethyl-5-oxobicyclo[4.3.0]non-6-ene-9-carboxylate (**7**, 175 mg, 35%), methyl (1*R**,2*R**,9*R**)-1,2-dimethyl-5-oxobicyclo[4.3.0]non-6-ene-9-carboxylate (**8**, 112 mg, 23%), and methyl (1*ξ*,5*R**,6*R**,7*R**,9*ξ*)-5,6-dimethyl-9-hydroxy-2-oxobicyclo[4.3.0]nonane-7-carboxylate (**9**, 107 mg, 22%). **7**: HRMS Found: *m/z* 222.1261 (M^+). Calcd for $C_{13}H_{18}O_3$: M, 222.1256. IR (film) 1730, 1680, and 1620 cm^{-1}; ^1H NMR δ=1.03 (3H, d, *J*=6.8 Hz), 1.08 (3H, s), 3.03 (1H, d, *J*=7.1 Hz), 3.67 (3H, s), 6.54 (1H, dd, *J*=3.3 and 2.1 Hz); ^{13}C NMR δ=16.1, 19.6, 28.8, 33.5, 34.7, 39.6, 50.9, 54.0, 54.8, 135.4, 147.2, 174.2, 198.3; EIMS *m/z* 222 (M^+), 207, 191, 175, 163 (base). **8**: HRMS Found: *m/z* 222.1261 (M^+). Calcd for $C_{13}H_{18}O_3$: M, 222.1256. IR (film) 1725, 1685, and 1620 cm^{-1}; ^1H NMR δ=0.95 (3H, s), 1.08 (3H, d, *J*=6.6 Hz), 1.91 (1H, m), 3.06 (1H, t, *J*=9.2 Hz),3.71 (3H, s), 6.39 (1H, dd, *J*=3.4 and 2.2 Hz); ^{13}C NMR δ=14.0, 15.5, 29.1, 34.0, 39.5, 42.0, 51.2, 53.0, 55.7,133.3, 148.4, 173.5, 199.0; EIMS *m/z* 222 (M^+) 207, 191, 175, 163 (base). **9**: IR (film) 3450 and 1720 cm^{-1}; ^1H NMR δ=0.94 (3H, d, *J*=7.0 Hz), 1.25 (3H, s), 3.35 (1H, s), 3.70 (3H, s), 9.84 (1H, s); ^{13}C NMR δ=15.7, 24.9, 27.0, 32.8, 36.5, 45.2, 45.5, 51.5, 51.7, 57.5, 80.6, 172.7, 203.4; EIMS *m/z* 240 (M^+), 209, 194, 151, 135, 125 (base), 116.

Methyl (1*S,5*R**,6*S**,7*R**)-5,6-Dimethyl-2-oxobicyclo[4.3.0]nonane-7-carboxylate (10).** A solution of **7** (129 mg) in ethyl acetate (5 ml) was hydrogenated in the presence of 10% Pd-C (25 mg) for 1 h. Filtration and evaporation of the solvent afforded **10** (109 mg). HRMS Found: *m/z* 224.1409 (M^+). Calcd for $C_{13}H_{20}O_3$: M, 224.1412. IR (film) 1725 and 1705 cm^{-1}; ^1H NMR δ=0.80 (3H, d, *J*=6.2 Hz), 1.15 (3H, s), 3.66 (3H, s); ^{13}C NMR δ=16.4, 20.6, 25.7, 26.2, 31.0, 31.0, 37.3, 51.2, 52.9, 55.1, 62.1, 174.1, 213.0; EIMS *m/z* 224 (M^+), 192, 169, 147, 129, 109, 81, 55 (base), 41.

Sodium Borohydride Reduction of 10. A solution of **10** (150 mg) in methanol (8 ml) was treated with sodium borohydride (25 mg) at 0 °C for 1 h. Usual work up afforded a mixture (150 mg) of methyl (1*S**,2*R**,5*R**,6*S**,7*R**)-5,6-dimethyl-2-hydroxybicyclo[4.3.0]nonane-7-carboxylate (**11a**) and methyl (1*S**,2*S**,5*R**,6*S**,7*R**)-5,6-dimethyl-2-hydroxybicyclo[4.3.0]nonane-7-carboxylate (**11b**). The mixture was separated by column chromatography of silica gel (hexane-EtOAc gradient) to afford **11a** (69 mg, 46%) and **11b** (74 mg, 49%). **11a**: HRMS Found: *m/z* 226.1564 (M^+). Calcd for $C_{13}H_{22}O_3$: M, 226.1569. IR (film) 3380 and 1720 cm^{-1}; ^1H NMR δ=0.60 (3H, d, *J*=6.2 Hz), 1.12 (3H, s), 3.66 (3H, s), 3.88 (1H, m); ^{13}C NMR δ=16.7, 19.2, 20.4, 23.5, 29.0, 29.0, 31.2, 49.4, 51.3, 54.8, 55.6, 69.0, 174.9; EIMS *m/z* 226 (M^+), 208, 193, 176, 161, 149, 133, 107 (base). **11b**: HRMS Found: *m/z* 226.1569 (M^+). Calcd for $C_{13}H_{22}O_3$: M, 226.1569. IR (film) 3400 and 1717 cm^{-1}; ^1H NMR δ=0.67 (3H, d, *J*=5.7 Hz), 1.26 (3H, s), 3.66 (3H, s), 3.92 (1H, m); ^{13}C NMR δ=17.4, 21.5, 24.3, 25.9, 25.9, 28.2, 30.0, 47.6, 51.2, 54.7, 55.8, 69.2, 175.2; EIMS *m/z* 226 (M^+), 208, 195, 176, 161, 149, 134, 122, 107 (base).

(±)-Chiloscyphone ((±-1). A solution of the mixture of **11a** and **11b** (91.1 mg) in dry pyridine (5 ml) was treated with phosphoryl chloride (0.5 ml) at 100 °C under argon for 2 h. Usual work up and column chromatography of silica gel impregnated with silver nitrate (15% $AgNO_3$-SiO_2, benzene) afforded methyl(5*R**,6*R**,7*R**)-5,6-dimethylbicyclo[4.3.0]-non-1-ene-7-carboxylate (**12**, 37.4 mg, 45%), ^1H NMR δ=0.94 (3H, s), 0.97 (3H, d, *J*=6.4 Hz), 3.61 (3H, s), 5.31 (1H, m), and methyl(1*S**,5*R**,6*S**,7*R**)-5,6-dimethylbicyclo[4.3.0]non-2-ene-7-carboxylate (**13**, 24.5 mg, 29%); ^1H NMR δ=0.74 (3H, d, *J*=6.4 Hz), 1.10 (3H, s), 3.67 (3H, s), 5.58 (2H, m). An ethereal solution of **12** (37.4 mg) was treated with lithium aluminum hydride (10 mg) at room temperature for 0.5 h. Usual work up gave [(5*R**,6*R**,7*R**)-5,6-dimethylbicyclo-[4.3.0]non-1-en-7-yl]methanol (**14**, 30.1 mg, 93%), ^1H NMR δ=0.90 (3H, s), 0.94 (3H, d, *J*=6.4 Hz), 5.34 (1H, m). Swern oxidation of **14** (30.1 mg) by using oxalyl chloride (0.016 ml), DMSO (0.026 ml), and triethylamine (0.12 ml) afforded (5*R**,6*R**,7*R**)-5,6-dimethylblcyclo[4.3.0]non-1-ene-7-carbaldehyde (**15**, 28.2 mg, 95%), ^1H NMR δ=0.96 (3H, s), 0.99 (3H, d, *J*=6.4 Hz), 5.44 (1H, m), 9.46 (1H, d, *J*=5.3 Hz). A solution of **15** (28.2 mg) in dry THF was added into Grignard reagent prepared from 2-bromopropene (0.1 ml) in dry THF (0.2 ml) at 0 °C for 15 min. Usual work up and column chromatography (hexane-EtOAc gradient) afforded 1-[(5*R**,6*R**,7*R**)-5,6-dimethylbicyclo[4.3.0]non-1-en-7-yl]-2-methyl-2-propen-1-ol (**16**, 30.4 mg, 87%), ^1H NMR δ=0.95 (3H, s), 0.98 (3H, d, *J*=6.6 Hz), 1.67 (3H, s), 4.28 (1H, m), 4.90 (2H, m), 5.40 (1H, m). A solution of **16** (30.4 mg) in acetone (4 ml) was treated with Jones reagent (0.5 ml) at 0 °C for 10 min. Usual work up and preparative TLC purification (hexane-EtOAc 9 : 1) gave (±)-chiloscyphone (**1**, 4.2 mg, 14%). IR (film) 1665 and 1625 cm^{-1}; ^1H NMR δ=0.85 (3H, d, *J*=6.4 Hz), 0.98 (3H, s), 1.85 (3H, s), 3.58 (1H, d, *J*=7.3 Hz), 5.42 (1H, br s), 5.74 (1H, s), 5.94 (1H, s); ^{13}C NMR δ=17.5, 17.8, 20.7, 25.5, 26.2, 27.1, 29.2, 33.1, 49.8, 52.8, 117.3, 123.5, 146.2, 146.5, 206.5; EIMS *m/z* 218 (M^+), 203, 175, 149, 147, 122, 107, 91, 79, 69, 41 (base). The spectral data were identical with those reported in the literature.[2]

Esterification of Methyl (1*S,2*R**,5*R**,6*S**,7*R**)-5,6-Dimethyl-2-hydroxybicyclo[4.3.0]nonane-7-carboxylate (11a) with (1*S*)-(−)-Camphanic chloride.** A mixture of **11a** (150 mg), (1*S*)-(−)-camphanic chloride (400 mg), DMAP (60 mg), dry pyridine (0.5 ml), and dry dichloromethane (5 ml) was stirred overnight at room temperature. Water was added and the mixture was extracted with ether. The ethereal solution was washed with 1 M HCl, 5% aqueous $NaHCO_3$, and brine, dried over anhydrous magnesium sulfate, and evaporated to give a residue. The residue was separated with HPLC (Chemcopak, NUCLEOSIL 50-5, 10×250 mm; hexane-EtOAc 9:1) to afford methyl (1*S*,2*R*,5*R*,6*S*,7*R*)-5,6-dimethyl-2-camphanoyloxybicyclo[4.3.0]nonane-7-carboxylate (**17**, 96 mg, 35.5%) and methyl (1*R*,2*S*,5*S*,6*R*,7*S*)-5,6-dimethyl-2-camphanoyloxybicyclo[4.3.0]nonane-7-carboxylate (**18**, 95 mg, 35.4%). **17**: Anal. Found: C, 67.60; H, 8.48%. Calcd for $C_{23}H_{34}O_6$: C, 67.95; H, 8.43%. HRMS Found: *m/z* 406.2355 (M^+). Calcd for $C_{23}H_{34}O_6$: M, 406.2355. $[\alpha]_D^{19}$ −7.8° (*c* 5.1, $CHCl_3$), IR ($CHCl_3$) 1780 and

1720 cm^{-1}; ^{1}H NMR δ=0.63 (3H, d, J=5.9 Hz), 0.95 (3H, s), 1.04 (3H, s), 1.11 (3H, s), 1.19 (3H, s), 3.67 (3H, s), 5.13 (1H, m); ^{13}C NMR δ=9.6, 16.5, 16.7, 19.1, 21.3, 23.5, 25.5, 28.9, 28.9, 30.5, 30.6, 49.7, 51.3, 53.8, 54.7, 55.3, 55.3, 74.0, 91.0, 166.7, 174.4, 178.1; EIMS m/z 406 (M^+), 375, 208, 193, 149 (base), 122, 107. **18**: Anal. Found: C, 67.69; H, 8.54%. Calcd for $C_{23}H_{34}O_6$: C, 67.95; H, 8.43%. HRMS Found: m/z 406.2349 (M^+). Calcd for $C_{23}H_{34}O_6$: M, 406.2355. $[\alpha]_D^{19}$ −1.4° (c 4.9, $CHCl_3$); IR ($CHCl_3$) 1780 and 1715 cm^{-1}; ^{1}H NMR δ=0.63 (3H, d, J=6.2 Hz), 0.95 (3H, s), 1.04 (3H, s), 1.11 (3H, s), 1.19 (3H, s), 3.67 (3H, s), 5.22 (1H, m); ^{13}C NMR δ=9.6, 16.5, 16.6, 16.8, 19.1, 21.3, 23.4, 25.6, 29.9, 29.9, 30.6, 30.6, 49.7, 51.3, 53.8, 54.7, 55.3, 55.3, 73.8, 91.0, 166.6, 174.3, 177.9; EIMS m/z 406 (M^+), 375, 208, 193, 149 (base), 122, 107.

Esterification of Methyl (1*S,2*S**,5*R**,6*S**,7*R**)-5,6-Dimethyl-2-hydroxybicyclo[4.3.0]nonane-7-carboxylate (11b) with (1*S*)-(−)-Camphanic Chloride.** A solution of **11b** (112 mg) in dichloromethane (5 ml) was treated as above with (1*S*)-(−)-camphanic chloride (300 mg), DMAP (50 mg), dry pyridine (0.5 ml) at room temperature for 18 h. Usual work up and HPLC separation afforded methyl (1*S*,2*S*,5*R*,6*S*,7*R*)-5,6-dimethy-2-camphanoyloxybicyclo[4.3.0]nonane-7-carboxylate (**19**, 101 mg, 50%) and methyl (1*R*,2*R*,5*S*,6*R*,7*S*)-5,6-dimethy-2-camphanoyloxybicyclo[4.3.0]nonane-7-carboxylate (**20**, 85 mg, 42%). **19**: HRMS Found: m/z 406.2355 (M^+). Calcd for $C_{23}H_{34}O_6$: M, 406.2355. $[\alpha]_D^{19}$ +21.6° (c 5.0, $CHCl_3$); IR ($CHCl_3$) 1780 and 1717 cm^{-1}; ^{1}H NMR δ=0.68 (3H, d, J=5.9 Hz), 0.97 (3H, s), 1.08 (3H, s), 1.12 (3H, s), 1.22 (3H, s), 3.66 (3H, s), 5.18 (1H, m); ^{13}C NMR δ=9.6, 16.8, 16.8,17.2, 20.8, 24.0, 25.3, 25.5, 26.5, 29.0, 29.6, 30.5,47.4, 51.3, 51.6, 53.9, 54.7, 55.5, 73.5, 91.0, 166.6, 174.6, 178.0; EIMS m/z 406 (M^+), 376, 208, 177, 149 (base), 122, 107. **20**: Anal Found: C, 67.68; H, 8.48%. Calcd for $C_{23}H_{34}O_6$: C, 67.95; H, 8.43%. HRMS Found m/z 406.2349 (M^+). Calcd for $C_{23}H_{34}O_6$: M, 406.2355. $[\alpha]_D^{19}$ −26.6° (c4.0, $CHCl_3$); IR ($CHCl_3$) 1778 and 1715 cm^{-1}; ^{1}H NMR δ=0.68 (3H, d, J=5.7 Hz), 0.98 (3H, s), 1.07 (3H, s), 1.12 (3H, s), 1.24 (3H, s), 3.67 (3H, s), 5.13 (1H, m); ^{13}C NMR δ=9.7, 16.7, 17.2, 20.9, 24.0, 25.4, 25.4, 26.4, 28.9, 29.6, 30.5, 47.5, 51.3, 51.4, 54.0, 54.7, 55.6, 73.5, 91.0, 166.8, 174.7, 178.2; EIMS m/z 406 (M^+), 376, 208, 149 (base), 122, 107.

Hydrolysis of Methyl (1*S*,2*R*,5*R*,6*S*,7*R*)-5,6-Dimethyl-2-camphanoyloxybicyclo[4.3.0]nonane-7-carboxylate (17). Ester **17** (54.8 mg) was treated with KOH (150 mg) in methanol (2 ml) at room temperature for 12 h. Usual work up afforded methyl (1*S*,2*R*,5*R*,6*S*,7*R*)-5,6-dimethyl-2-hydroxybicyclo[4.3.0]nonane-7-carboxylate ((+)-**11a**, 28.8 mg, 94%). HRMS Found m/z 226.1571 (M^+). Calcd for $C_{13}H_{22}O_3$: M, 226.1569. $[\alpha]_D^{18}$ +9.5° (c 4.9, $CHCl_3$); IR (film) 3380 and 1720 cm^{-1}; ^{1}H NMR δ=0.61 (3H, d, J=6.2 Hz), 1.13 (3H, s), 3.66 (3H, s), 3.89 (1H, m); ^{13}C NMR δ=16.6, 19.3, 20.4, 23.5, 29.0, 29.0, 31.2, 49.5, 51.3, 54.8, 55.6, 69.1, 174.9; EIMS m/z 226 (M^+), 208, 193, 176, 148, 122, 107 (base).

Hydrolysis of Methyl (1*R*,2*S*,5*S*,6*R*,7*S*)-5,6-Dimethyl-2-camphanoyloxybicyclo[4.3.0]nonane-7-carboxylate (18). Ester **18** (43.2 mg) was treated as above to give methyl-(1*R*,2*S*,5*S*,6*R*,7*S*)-5,6-dimethyl-2-hydroxybicyclo[4.3.0]-nonane-7-carboxylate ((−)-**11a**. 23.2 mg, 97%). HRMS Found: m/z 226.1586 (M^+). Calcd for $C_{13}H_{22}O_3$: 226.1569. $[\alpha]_D^{18}$ −7.2°(c 3.4, $CHCl_3$); IR (film) 3380 and 1720 cm^{-1}; ^{1}H NMR δ=0.61 (3H, d, J=6.2 Hz), 1.13 (3H, s), 3.66 (3H, s), 3.89 (1H, m); ^{13}C NMR δ=16.6, 19.3, 20.3, 23.5, 29.0, 29.0, 31.2, 49.5, 51.3, 54.8, 55.6, 69.2, 174.9; EIMS m/z 226 (M^+), 208, 193, 176, 149, 122, 107 (base).

Hydrolysis of Methyl (1*S*,2*S*,5*R*,6*S*,7*R*)-5.6-dimethyl-2-camphanoyloxybicyclo[4.3.0]nonane-7-carboxylate (19). Ester **19** (45.1 mg) was treated as above to afford methyl-(1*S*,2*S*,5*R*,6*S*,7*R*)-5,6-dimethyl-2-hydroxybicyclo-[4.3.0]nonane-7-carboxylate ((+)-**11b**, 23.3 mg, 93%). HRMS Found: m/z 226.1570 (M^+). Calcd for $C_{13}H_{22}O_3$: M, 226.1569. $[\alpha]_D^{18}$ +29.3° (c 5.7, $CHCl_3$); IR (film) 3440 and 1720 cm^{-1} ^{1}H NMR δ=0.68 (3H, d, J=5.7 Hz), 1.26 (3H, s), 3.66 (3H, s), 3.95 (1H, m); ^{13}C NMR δ=17.4, 21.5, 24.5, 26.0, 26.0, 28.3, 30.0, 47.7, 51.3, 54.7, 55.9, 69.3, 175.2; EIMS m/z 226 (M^+), 208, 195, 176, 161, 149, 122, 107 (base).

Hydrolysis of Methyl (1*R*,2*R*,5*S*,6*R*,7*S*)-5,6-Dimethyl-2-camphanoyloxybicyclo[4.3.0]nonane-7-carboxylate (20). Ester **20** (38.5 mg) was treated as above to afford methyl-(1*R*,2*R*,5*S*,6*R*,7*S*)-5,6-dimethyl-2-hydroxyblcyclo[4.3.0]-nonane-7-carboxylate ((−)-**11b**, 19.6 mg, 92%). HRMS Found: m/z 226.1570 (M^+). Calcd for $C_{13}H_{22}O_3$: M, 226.1569. $[\alpha]_D^{18}$ −32.6° (c 4.8, $CHCl_3$); IR (film) 3440 and 1715 cm^{-1}; ^{1}H NMR δ=0.68 (3H, d, J=5.7 Hz), 1.26 (3H, s), 3.66 (3H, s), 3.95 (1H, m); ^{13}C NMR δ=17.4, 21.5, 24.2, 26.0, 26.0, 28.3, 30.0, 47.7, 51.3, 54.7, 55.9, 69.4, 175.2; EIMS m/z 226 (M^+), 208, 195, 176, 161, 149, 122, 107 (base).

Oxidation of (+)-11a. Alcohol (+)-**11a** (29.8 mg) was treated with Jones reagent (0.5 ml) in acetone (5 ml) at 0 °C for 10 min. Usual work up afforded methyl(1*S*,5*R*,6*S*,7*R*)-5,6-dimethyl-2-oxobicyclo[4.3.0]nonane-7-carboxylate ((−)-**10**, 28.6 mg, 96%). HRMS Found: m/z 224.1408 (M^+). Calcd for $C_{13}H_{20}O_3$: M, 224.1412. $[\alpha]_D^{18}$ −25.0° (c 2.3, EtOH) ; IR (film) 1720 and 1700 cm^{-1}; ^{1}H NMR δ=0.80 (3H, d, J=6.2 Hz), 1.15 (3H, s), 3.66 (3H, s); EIMS m/z 224 (M^+), 192, 164, 147 (base), 136, 124, 109; CD (c 0.10, EtOH, 21 °C) $[\theta]_{289}$−2176.

Oxidation of (−)-11a. Alcohol (−)-**11a** (27.1 mg) was treated with Jones reagent as above to afford (+)-**10** (22.5mg, 83%). HRMS Found: m/z 224.1410 (M^+). Calcd for $C_{13}H_{20}O_3$: M, 224.1412. $[\alpha]_D^{18}$ +29.8° (c 1.9, $CHCl_3$); IR (film) 1720 and 1700 cm^{-1}; ^{1}H NMR δ=0.80 (3H, d, J=6.2 Hz), 1.15 (3H, s), and 3.66 (3H, s); EIMS m/z 224 (M^+), 192, 164, 147 (base), 136, 124, 109; CD (c 0.086, EtOH, 21 °C) $[\theta]_{289}$+1984.

Oxidation of (+)-11b. Alcohol (+)-**11b** (57 mg) was treated as above to afford ((−)-**10** (50.2 mg, 88%), $[\alpha]_D^{19}$ −20.3° (c 2.5, EtOH).

Oxidation of (−)-11b. Alcohol (−)-**11b** (48 mg) was treated as above to give (+)-**10** (40 mg, 83%), $[\alpha]_D^{19}$ +27.6° (c 1.6, EtOH).

Dehydration of (+)-11a. To a solution of alcohol (+)-**11a** (30 mg) in dry pyridlne (5 ml) was added phosphoryl chloride (0.02 ml) and the mixture was heated at 100 °C for 2 h. Usual work up gave (+)-**12** (10 mg, 36%). HRMS Found: m/z 208.1465 (M^+). Calcd for $C_{13}H_{20}O_2$: M, 208.1464. $[\alpha]_D^{19}$ +4.4° (c 0.99, $CHCl_3$); IR (film) 1725 cm^{-1}; ^{1}H NMR δ=0.95 (3H, s), 0.97 (3H, d, J=6.5 Hz), 3.61 (3H, s), 5.39 (1H, m); ^{13}C NMR δ=17.0, 20.3, 24.8, 25.5, 27.1, 28.8, 34.8, 48.8, 50.9, 54.2, 117.7, 145.9, 176.0; EIMS m/z 208 (M^+), 193, 176, 149, 133, 107 (base).

Reduction of (+)-12. Olefin (+)-**12** (10 mg) was reduced with lithium aluminum hydride (5 mg) as before to afford (−)-**14** (8.5 mg, 98%). HRMS Found: m/z 180.1512 (M^+). Calcd for $C_{12}H_{20}O$: M, 180.1514. $[\alpha]_D^{19}$ −8.0° (c 0.87, $CHCl_3$); IR (film) 3420 cm^{-1}; ^{1}H NMR δ=0.90 (3H, s), 0.94 (3H, d, J=6.4 Hz), 5.34 (1H, m); ^{13}C NMR δ=17.0, 20.3, 23.3,

25.8, 26.7, 27.8, 32.7, 46.1, 49.4, 63.9, 117.4, 147.6; EIMS *m/z* 180 (M^+), 149 (base), 147, 107.

(−)-Chiloscyphone ((−)-(1)). Oxidation of (−)-**14** (8.5 mg) by oxalyl chloride (0.005 ml), DMSO (0.007 ml), and triethylamine (0.04 ml) in dry dichloromethane (1 ml)as before to afford (5*R*,6*R*,7*R*)-5,6-dimethylbicyclo[4.3.0]non-1-ene-7-carbaldehyde (**15**, 7.9 mg, 92%), IR (film) 1715 cm^{-1}; ^1H NMR δ=0.96 (3H, s), 0.99 (3H, d, *J*=6.4 Hz), 5.44 (1H, m), 9.46 (1H, d, *J*=5.3 Hz). Aldehyde **15** (7.9 mg) was treated with 2-propenylmagnesium bromide as before to afford 1-[(5*R*,6*R*,7*R*)-5,6-dimethylbicyclo[4.3.0]non-1-en-7-yl]-2-methyl-2-propen-1-ol (**16**, 8 mg, 82%). Alcohol **16** (8.0 mg) was treated withJones reagent (0.5 ml) as before to give (−)-**1** (4.1 mg, 52%) after column chromatographic purification (hexane-EtOAc gradient), $[\alpha]_D^{19}$ −15.1° (*c* 0.4, $CHCl_3$) [lit.[3] −24.4° (*c* 0.76, $CHCl_3$)].

(+)-Chiloscyphone ((+)-1). Alcohol (−)-**11a** (27.7 mg) in dry pyridine (3 ml) was treated with $POCl_3$ (0.05 ml) at 100 °C for 2 h. Usual work up gave (−)-**12** (14.6 mg), $[\alpha]_D^{19}$ −7.4° (c 1.6, $CHCl_3$). Reduction of (−)-**12** with $LiAlH_4$ (8 mg) in ether (3 ml) afforded (+)-**14** (11.9 mg), $[\alpha]_D^{19}$ +4.5° (*c* 0.6, $CHCl_3$). Swern oxidation of (+)-**14** afforded **15** (11.4 mg), which was treated with 2-propenylmagnesium bromide to yield **16** (11.0 mg). Jones oxidation of **16** (8 mg) produced (+)-**1** (2.5 mg) after preparative TLC (hexane-EtOAc 9:1), $[\alpha]_D^{19}$ +24.2° (*c* 1.2, $CHCl_3$) [lit.[3] −24.4° (*c* 0.76, $CHCl_3$)].

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