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SYNTHESIS OF BOTH THE ENANTIOMERS OF DIHYDROACTINIDIOLIDE, A PHEROMONE COMPONENT OF THE RED IMPORTED FIRE ANT†

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Abstract -- Both the enantiomers of dihydroactinidiolide (4,4,7a-trimethyl-2-oxo-2,4,5,6,7,7a-hexahydrobenzofuran) were synthesized in 15 steps from (S)-3-hydroxy-2,2-dimethylcyclohexanone.

The red imported fire ant (Solenopsis invicta Buren) is a widely distributed pest of the southern United States. Attempts to control the insect with conventional pesticides have not been successful so far. There exists a queen recognition pheromone for S. invicta which attracts worker-ants and causes them to move inanimated objects treated with queeen extracts into their nests as if they were real queens. The chemicals responsible for the behaviors were isolated by Rocca et al.[1] They were **A**, **B**, and **C**, and each 5~25μg of these compounds were isolated from 18,000 fire ant queens. **A** and (±)-**B** were synthesized by Rocca et al.[1,2] As a part of our project to clarify the stereochemistry-pheromone activity relationship, we carried out the synthesis of the enantiomers of **B** and **C**. Herein we describe the synthesis of the enantiomers (**1** and **1'**) of dihydroactinidiolide **C**.

Dihydroactinidiolide **1** was first isolated by Sakan et al. from leaves of Actinidia polygama Miq.[3,4] It was later obtained from various plant sources, such as tea[5-8] and tobacco.[9,10] Since the first synthesis of (±)-**1** by Sakan et al.,[3,4] many different syntheses of (±)-**1** were recorded.[10-22]

As early as in 1969, Ribi and Eugster achieved a synthesis of (3aR,7aS)-(+)-tetrahydroactinidiolide **2** from (R)-(+)-α-cyclogeranic acid, establishing the stereochemistry of (+)-**2**.[23] Subsequently in 1972, the absolute configuration of (-)-dihydroactinidiolide **1'** was assigned by Isoe et al. as R by synthesizing it from natural zeaxanthin.[24] This was followed by a synthesis of optically pure (R)-(-)-**1'** from (4R,6R)-4-hydroxy-2,2,6-trimethylcyclohexanone by Kienzle et al.[25] Conversion of (-)-azafrin Me ester, a carotenoid, to both the enantiomers of **1** was also reported.[26] (The amount of the enantiomers of **1** secured by this conversion was so small that only their CD data were reported with no $[\alpha]_D$ values.[26]) Very recently Fujisawa and his co-workers achieved a synthesis of (-)-**1'**,

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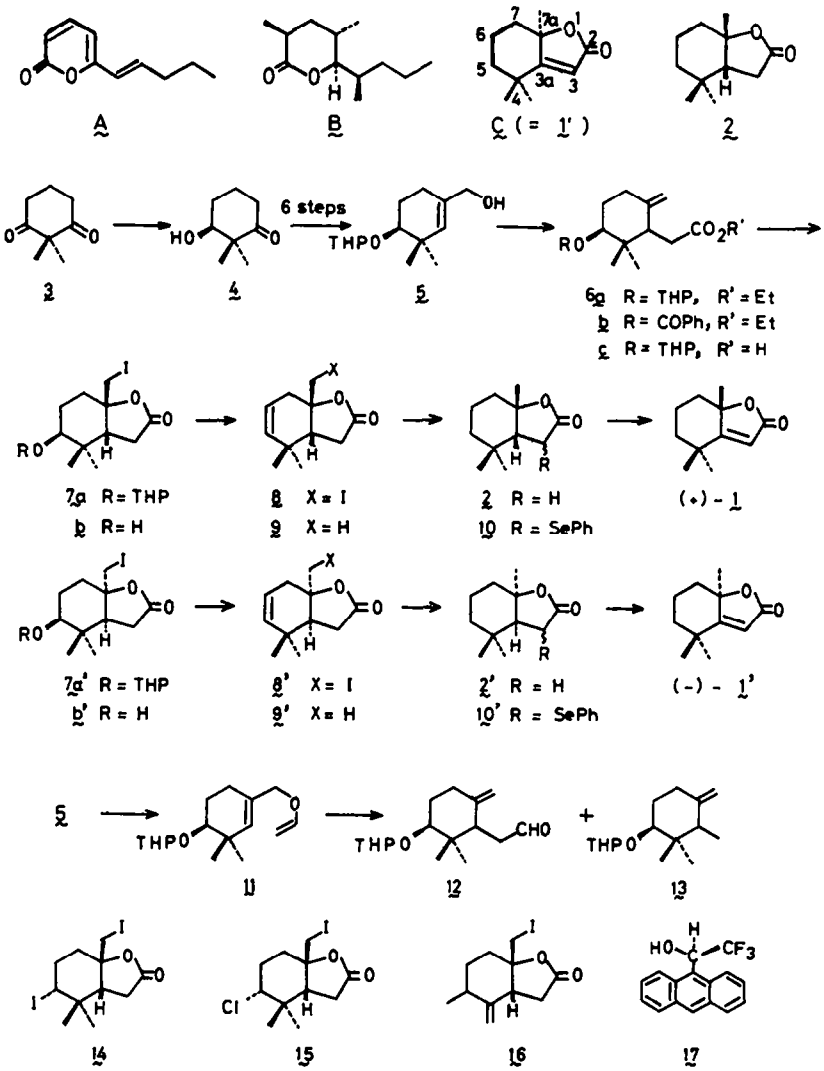
starting from cyclohexane-1,2-dione and employing (S)-prolinol Me ether as a chiral auxiliary.[27]

We chose (S)-3-hydroxy-2,2-dimethylcyclohexanone **4** as our starting material for the synthesis of both (R)-**1'** and (S)-**1**. The ketol **4** was readily obtainable by the yeast reduction of a prochiral diketone **3**, and previously had been converted to an alcohol **5** in six steps in 49 % overall yield.[28] The remaining two-carbon side chain was attached to the molecule by employing the Claisen-type rearrangement. Our first attempt was to thermolyze the vinyl ether **11**, which was prepared in 72 % yield from **5** and $EtOCH{=}CH_2$ in the presence of $Hg(OAc)_2$.[29,30] The Claisen rearrangement of **11** at 180~190°,[30,31] however, gave only 22 % yield of the desired **12** together with an unwanted by-product **13**. (18 % yield). We then turned our attention to the orthoester Claisen rearrangement.[32] Thus a soln of **5** in freshly distilled $MeC(OEt)_3$ containing a trace amount of $EtCO_2H$ was heated at 140° under conditions for distillative removal of EtOH to furnish **6a** in 96 % yield. The stereocontrolling effect of the preexisting chiral center of **5** was so small that the rearrangement proceeded non-stereoselectively, and the product **6a** was a mixture of diastereomers due to the stereoisomerism at the newly generated chiral center at C-1 of **6a**.



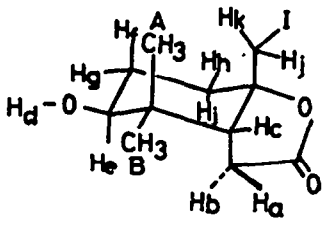
The ratio of the two diastereomers was determined as 64:36 by the HPLC analysis of **6b**. At this stage no stereochemical assignment was made for the two diastereomers, although the assignment was later possible. The lack of stereoselectivity in the course of the ortho-ester Claisen rearrangement was welcome, because the synthesis of both **1** and **1'** became possible starting from the single chiral source **4**.

The diastereomeric mixture of **6a** was then hydrolyzed with KOH, and the resulting diastereomeric mixture of the corresponding unsaturated acids **6c** was submitted to iodo-lactonization reaction with I_2-KI and $NaHCO_3$ in a two-phase mixture of refluxing ether and water to give a mixture of **7a** and **7a'**. Removal of the THP protective group of **7a** and **7a'** with p-TsOH in MeOH yielded a mixture of **7b** and **7b'**. Fortunately these two were completely separable by SiO_2 chromatography. The more polar lactone **7b**, m.p. 136~136.5°; $[\alpha]_D^{22}$ +35.5° ($CHCl_3$), was obtained in 49 % yield from **6a**, and the less polar lactone **7b'**, m.p. 134.5~135.0°; $[\alpha]_D^{22}$ -11.1° ($CHCl_3$), was obtained in 30 % yield from **6a**.

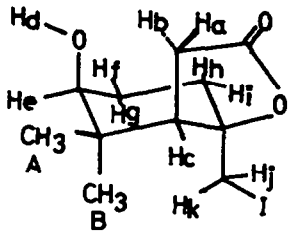
The assignment of the structures **7b** and **7b'** for the lactone isomers was based on the careful examination of their 400 MHz ^1H NMR spectra as shown in Table 1. The signals due to the CHOH proton (**He**) of the more polar lactone **7b** appeared as ddd (J=4,5, 4.7 and 10.5 Hz). The CHOH proton (**He**) must be an ax H considering its J-value as large as 10.5 Hz, and therefore the more polar **7b** has its OH group in eq orientation. As to the less polar lactone **7b'**, its **He** signal again appeared as ddd but with a smaller J-value of 3.5 Hz. Therefore **He** must be in eq orientation with an ax OH group attached to C-5 of **7b'**. The configuration at C-3a of **7b** was deduced as follows. A small coupling (J_{ch}=2 Hz) between **Hc** and **Hh** of **7b** revealed a coplaner zig-zag configurational relationship between **Hc** and **Hh**.[33] This so-called "W-configuration" between **Hc** and **Hh** indicated the ax nature of the $-CH_2CO-$ group at C-3. The C-O bond at C-7a must be eq to make the lactone formation possible. Therefore the structure **7b** was assigned to the more polar lactone. This assignment was later verified by converting **7b** to (3a*R*,7a*S*)-(+)-tetrahydroactinidiolide **2**[23] and (*S*)-(+)-dihydroactinidiolide **1**. In the case of the less polar lactone **7b'**, a long-range coupling due to the "W-configuration" between **Hc** and **Hi** was clearly observable in the signals due to **Hi** (J_{ic}=1.2 Hz), although it was impossible to observe the same small splitting in the signals due to **Hc**. The structure **7b'** assigned to the less polar lactone was also confirmed by its conversion to (-)-**2'** and (-)-**1'**. The ratio of the isolated yield of **7b** to that of **7b'** was 1.6~1.8:1.

The remaining task was the conversion of **7b** and **7b'** to **1** and **1'**, respectively. Our first attempt was to prepare **14** from **7b**. Hydrogenolytic removal of I from **14** was expected to give **2**. However, **14** could not be prepared from **7b** presumably due to the steric hindrance at C-5 caused by the two Me groups at C-4. Our next attempt was to dehydrate **7b** to give **8**. In a similar system, CF_3SO_2Cl (TfCl) and 4-(*N*,*N*-dimethylamino)pyridine (DMAP) in CH_2Cl_2 was known to cause dehydration.[34] The reaction was best carried out by treating a soln of **7b** and DMAP (5 equiv) in dry CH_2Cl_2 with TfCl (2~3 equiv) under ice-cooling to give a mixture of products. This was separated by SiO_2 chromatography. The major product obtained in 78 % yield was the desired olefinic lactone **8**. Two by-products were obtained in small amounts (6.0 % of **15** and 6.4 % of **16**), of which structures were deduced from their IR and NMR spectra coupled with elemental analyses. Hydrogenation of **8** with either Raney Ni W-7 or Pd-C as a catalyst did not give useful results. We therefore decided to carry out the stepwise reduction of **8** to **2** *via* **9**. Treatment of **8** with $(n\text{-}Bu)_3SnH$ in C_6H_6 removed I to furnish **9** almost quantitatively. Hydrogenation of **9** to **2** was accomplished in 80 % yield under high pressure using Adams's PtO_2 in AcOH. The resulting *cis*-tetrahydroactinidiolide **2**, m.p. 74~75°, was dextrorotatory: $[\alpha]_D^{24}$ +63.5° ($CHCl_3$) [lit.[23] $[\alpha]_D^{22}$ +62.5° ($CHCl_3$)]. Its (3a*R*,7a*S*)-stereochemistry as depicted in **2** was thus confirmed on the basis of the work of Ribi and Eugster.[23] Conversion of **2** to the target molecule **1** was executed by employing organoselenium chemistry as had been reported by Hoye and Kurth for

Table 1. 400 MHz ^{1}H NMR spectral data of the lactone isomers **7b** and **7b'** (Solvent: $CDCl_3$)



7b



7b'

Assignment	**7b** Chemical shifts (δ) and coupling constants (Hz)	**7b'** Chemical shifts (δ) and coupling constants (Hz)
CH_3A	1.06 (3H, s)	1.02 (3H, s)
CH_3B	1.04 (3H, s)	1.11 (3H, s)
Ha	2.62 (d, J_{ac}=7.5)	3.32 (dd, J=11, 16.5)
Hb	2.61 (d, J_{bc}=12)	2.56 (dd, J=8.5, 16.5)
Hc	2.69 (ddd, J=2, 7.5, 12)	2.49 (dd, J=8.5, 11)
Hd	1.43 (d, J_{de}=4.7)	1.59 (d, J_{de}=3.5)
He	3.68 (ddd, J=4.5, 4.7, 10.5)	3.58 (ddd, J=3.5, 3.5, 3.5)
Hf	1.56 (dddd, J=4, 10.5, 12, 14)	1.78 (ddd, J=3.5, 4, 7)
Hg	1.80 (dddd, J=4.5, 4.5, 4.5, 14)	1.79 (ddd, J=3.5, 4, 10.5)
Hh	2.24 (dddd, J=2.4, 4.5, 15)	2.28 (ddd, J=7, 10.5, 14.5)
Hi	1.93 (ddd, J=4.5, 12, 15)	2.00 (dddd, J=1.2, 4, 4, 14.5)
Hj	3.58 (d, J=11.5)	3.55 (d, J=11.5)
Hk	3.64 (d, J=11.5)	3.68 (d, J=11.5)

the synthesis of (±)-**1** from (±)-**2**,[21] except that we used PhSeBr instead of Ph_2Se_2 for the selenylation reaction. Treatment of **2** with LiN(i-Pr)$_2$ (LDA) and PhSeBr in THF-HMPA gave **10**, which was oxidized with H_2O_2 to give in 46 % yield (S)-(+)-dihydroactinidiolide **1**, m.p. 67~68°; $[\alpha]_D^{23}$ +120.9° ($CHCl_3$). Its IR and NMR data were in complete accord with the published data of dihydroactinidiolide.[3-10] The overall yield of (+)-**1** was 5.7 % in 15 steps from **4**.

(R)-(-)-Dihydroactinidiolide **1'** was similarly synthesized from **7b'**. In this case, dehydration of **7b'** with TfCl-DMAP in CH_2Cl_2 was very smooth owing to the ax nature of the OH group of **7b'**. The desired **8'** was the only isolable product obtained in 94 % yield. Reduction of **8'** to **9'** was follwed by hydrogenation to give (3aS,7aR)-(-)-tetrahydroactinidiolide **2'**, m.p. 80~81°; $[\alpha]_D^{24}$ -66.1° ($CHCl_3$), in 79 % yield from **8'**. Finally introduction of a double bond to **2'** via **10'** afforded in 64 % yield (R)-(-)-dihydroactinidiolide **1'**, m.p. 70~71°; $[\alpha]_D^{24}$ -121.0° ($CHCl_3$) [lit.[24] $[\alpha]_D^{15}$ -86.3° ($CHCl_3$); Lit.[25] m.p. 69~71°; $[\alpha]_D^{20}$ -119.9° ($CHCl_3$); lit.[27] $[\alpha]_D$ -85.8° ($CHCl_3$)]. The overall yield of (-)-**1** was 5.8 % from **4** in 15 steps.

The optical purities of our **1** and **1'** were checked by the method of Pirkle et al.[35] The NMR nonequivalence induced by a chiral solvating reagent (R)-(-)-2,2,2-trifluoro-1-(9-anthryl)ethanol **17** upon its addition to **1** or **1'** was carefully examined. The NMR nonequivalence of the olefinic proton of C-3 of (S)-**1** and that of (R)-**1'** was sufficiently large (Δδ=0.04 p.p.m.) as to enable us to estimate the optical purities of our **1** and **1'** to be

both ca. 100 % e.e.

In conclusion, we synthesized the optically pure enantiomers of dihydroactinidiolide in amounts sufficient for biological study. Comparison of both the m.p.'s and the $[\alpha]_D$ values of our 1 [m.p. 67~68°; $[\alpha]_D^{24}$ +120.9° ($CHCl_3$)] and 1' [m.p. 70~71°; $[\alpha]_D^{23}$ -121.0° ($CHCl_3$)] with those reported for the naturally occurring ones [m.p. 40~41°; $[\alpha]_D^{15}$ +7.1° (from Actinidia polygama)[3,4] or m.p. 43.5~44°; $[\alpha]_D^{25}$ -36.5° (EtOH) (from Manila cigar leaves)[9] suggests that the samples of dihydroactinidiolide isolated from plant sources must be a mixture of the two enantiomers. It is obscure whether this was caused by racemization in the course of its isolation and purification or this reflected racemization in the course of its formation from carotenoid precursors in plants. The pheromone activity of 1 and 1' on the red imported fire ant will be reported in due course.

EXPERIMENTAL

All b.pe and m.pe were uncorrected. IR spectra were measured as films for oils or as KBr discs for solids on a Jasco IRA-102 spectrometer. NMR spectra were recorded with TMS as an internal standard at 60 MHz on a Hitachi R-24A spectrometer or at 100 MHz on a JEOL JMN FX-100 spectrometer or at 400 MHz on a JEOL JMN FX-400 spectrometer. Optical rotations were measured on a Jasco DIP 140 polarimeter. Mass spectra were recorded on a JEOL DX-300 spectrometer at 70 eV. Fuji Davison BW-820 MH was used for SiO_2 column chromatography.

(4S)-3,3-Dimethyl-4-tetrahydropyranyloxy-1-vinyloxymethyl-1-cyclohexene **11**. A suspension of (4S)-3,3-Dimethyl-4-tetrahydropyranyloxy-1-hydroxymethyl-1-cyclohexene **5** (0.20 g, 0.83 mmol, prepared from (S)-2,2-dimethyl-3-hydroxycyclohexanone of 98.3 % e.e.[28]) and $Hg(OAc)_2$ (0.044 g, 0.14 mmol) in $EtOCH=CH_2$ (10 ml) was stirred and heated under reflux for 2 days under Ar. After cooling, sat $NaHCO_3$ soln was added to the mixture, and the mixture was extracted with ether (20 ml x 2). The ether layer was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (10 g). Elution with n-hexane-EtOAc (10:1) gave 0.158 g of **11** (72.3 %). This was distilled to give 0.113 g of pure **11**, b.p. 120~130°/0.25 Torr; n_D^{22} 1.4822; $[\alpha]_D^{22}$ -3.07°(c=0.99, $CHCl_3$); vmax 1640 (s), 1615 (s), 1200 (s), 1060 (s), 1035 (s) cm^{-1}; δ ($CDCl_3$) 0.99, 1.02, 1.11 (total 6H, each s), 1.25~2.31 (10H, m), 3.26~3.80 (3H, m), 4.00 (1H, dd, J=2 Hz, 7 Hz), 4.08 (2H, s), 4.24 (1H, dd, J=2 Hz, 14 Hz), 4.72 (1H, m), 5.43 (1H, br s), 6.52 (1H, dd, J=7 Hz, 14 Hz). (Found: C, 72.01; H, 9.85. Calc for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84 %).

(1RS,3S)-2,2-Dimethyl-6-methylene-3-tetrahydropyranyloxycyclohexylacetaldehyde **12** and (1S,3RS)-2,2,3-trimethyl-4-methylene-1-tetrahydropyranyloxycyclohexane **13**. **11** (0.096 g, 0.36 mmol) was heated for 2 h at 180~190° under Ar. This was chromatographed over SiO_2 (2 g). Elution with n-hexane-ether (10:1) gave **13** (0.015 g, 18 %), vmax 3100 (w), 1645 (w), 1025 (s) cm^{-1}; δ ($CDCl_3$) 0.6~1.2 (9H, m), 1.2~2.5 (11H, m), 3.2~4.1 (3H, m), 4.5~4.9 (3H, m); MS m/z 238 (M^+), 137 (M^+-101). Elution with n-hexane-ether (8:1) gave **12** (0.021 g, 22 %), vmax 3100 (w), 2725 (w), 1730 (s), 1650 (w), 1025 (s), 900 (m) cm^{-1}; δ ($CDCl_3$) 0.81, 0.87, 0.98, 1.08 (total 6H, each s), 1.30~2.70 (13H, m), 3.11~4.10 (3H, m), 4.47~4.88 (3H, m), 9.74 (1H, t, J=3 Hz); MS m/z 266 (M^+), 164 (M^+-102), 121 (M^+-145).

Ethyl [(1RS,3S)-2,2-dimethyl-6-methylene-3-tetrahydropyranyloxycyclohexyl]acetate **6a**. A soln containing **5** (9.45 g, 39.3 mmol) and $EtCO_2H$ (0.187 g, 2.50 mmol) in freshly distillled $MeC(OEt)_3$ (51.0 g, 314 mmol) was stirred at 140° for 6 h under the conditions for distillative removal of EtOH. Then the mixture was concentrated to remove $MeC(OEt)_3$. After cooling, the residue was diluted with ether. The ether soln was washed with sat $NaHCO_3$ soln and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (200 g). Elution with n-hexane-EtOAc (20:1) gave **6a** (11.7 g, 37.7 mmol, 96 %) as a mixture of (1S,3S)-**6a** and (1R,3S)-**6a**, n_D^{22} 1.4774; $[\alpha]_D^{22}$ +25.5°(c=0.81, $CHCl_3$); vmax 3100 (w), 1740 (s), 1650 (m), 1030 (s), 890 (m) cm^{-1}; δ ($CDCl_3$) 0.73~1.08 (6H, m), 1.23 (3H, t, J=7 Hz), 1.36~2.78 (13H, m), 3.18~4.20 (3H, m), 4.10 (2H, q, J=7 Hz), 4.48~4.86 (3H, m). (Found: C, 69.31; H, 9.72. Calc for $C_{18}H_{30}O_4$: C, 69.64; H, 9.74 %). The ratio of (1S,3S)-**6a** and (1R,3S)-**6a** was determined to be 64:36 by the HPLC analysis of corresponding 3-benzoyloxy derivatives **6b**; HPLC (Column, NUCLEOSIL® 50-5, 25 cm x 4.6 mm ϕ; Solvent, n-hexane-THF-MeOH (6000:100:1), Press. 15kg/cm^2; Detected at 254 nm) Rt 44.6 min [(1S,3S)-**6b**, 64 %], 47.6 min [(1R,3S)-**6b**, 36 %].

(1'RS,3'S)-2',2'-Dimethyl-6'-methylene-3'-tetrahydropyranyloxycyclohexylacetic acid **6c**. **6a** (11.7 g, 37.7 mmol) was dissolved in 2.5 % KOH-EtOH soln (120 ml) and the mixture was heated under reflux for 2 h. The mixture was concentrated in vacuo to remove EtOH. The residue was diluted with water, acidified with N-HCl (pH 4) and extracted with ether (x2). The ether soln was washed with brine, dried ($MgSO_4$) and concentrated in vacuo to give crude **6c** (10.6 g), vmax 3100 (br.s), 1725 (s), 1025 (s) cm^{-1}. This was employed for the next step without further purification.

(3aRS,5S,7aRS)-4,4-Dimethyl-7a-iodomethyl-2-oxo-3-tetrahydropyranyloxyoctahydrobenzofuran **7a** + **7a'**. 0.5 M $NaHCO_3$ soln (120 ml) was added to a soln of **6c** (10.6 g, 37.7 mmol) in ether (120 ml). The mixture was stirred at room temp for 20 min. To the refluxing mixture was gradually added a soln of KI (37.8 g) and I_2 (19.2 g) in water (150 ml). The mixture was stirred overnight under reflux. After cooling, the mixture was washed with $Na_2S_2O_3$ soln, sat $NaHCO_3$ soln and brine, dried ($MgSO_4$) and concentrated in vacuo to give crude **7a** + **7a'** (14.5 g, 35.5 mmol). vmax 1780 (s), 1460 (s), 1160 (s), 1030 (s) cm^{-1}; δ ($CDCl_3$) 0.83~1.20 (6H, m), 1.30~2.45 (11H, m), 2.60 (2H, s), 3.21~4.11 (5H, m), 4.66 (1H, m). This was employed for the

next step without further purification.

(3aR,5S,7aS)-4,4-Dimethyl-3-hydroxy-7a-iodomethyl-2-oxo-octahydrobenzofuran **7b**, and (3aS,5S,7aR)-**7b'**. The crude **7a** + **7a'** (14.5 g, 35.5 mmol) was dissolved in 0.5 % p-TsOH-MeOH (150 ml) and the mixture was stirred at room temp for 8 h. The mixture was concentrated in vacuo to remove MeOH. The residue was diluted with EtOAc. The EtOAc soln was washed with sat $NaHCO_3$ soln and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (150 g). Elution with n-hexane-EtOAc (7:3) gave **7b'** (3.60 g, 11.1 mmol, 30 % from **6a**). This was recrystallized from n-hexane-EtOAc to give **7b'** (3.23 g), m.p. 134.5~135.0°; $[\alpha]_D^{22}$ -11.1°(c=0.075, $CHCl_3$); νmax (KBr) 3490 (s, sh), 1755 (vs), 1180 (s), 1155 (m), 1140 (s), 1020 (m), 1000 (m), 980 (s), 960 (s) cm^{-1}. For 400 MHz ^1H NMR spectrum of **7b'**, see Table 1. (Found: C, 40.79; H, 4.99. Calc for $C_{11}H_{17}O_3I$: C, 40.75; H, 5.28 %). Elution with n-hexane-EtOAc (1:1) gave crystalline (3aR,5S,7aS)-**7b** (6.00 g, 18.5 mmol, 49 % from **6a**). This was recrystallized from ether to give **7b** (4.22 g), m.p. 136.0~136.5°; $[\alpha]_D^{22}$ +35.5°(c=0.095, $CHCl_3$); νmax (KBr) 3450 (m, br), 1780 (vs, sh), 1165 (s), 1055 (s), 1000 (m), 965 (m) cm^{-1}. For 400 MHz ^1H NMR spectrum of **7b**, see Table 1. (Found: C, 40.48; H, 5.11. Calc for $C_{11}H_{17}O_3I$: C, 40.75; H, 5.28 %).

(3aR,7aS)-4,4-Dimethyl-7a-iodomethyl-2-oxo-2,3,3a,4,7,7a-hexahydrobenzofuran **8**, (3aR,4RS,7aS)-7a-iodomethyl-5-methyl-4-methylene-2-oxo-octahydrobenzofuran **16** and (3aR,5R,7aS)-5-chloro-4,4-dimethyl-7a-iodomethyl-2-oxo-octahydrobenzofuran **15**. TfCl (4.50 g, 26.7 mmol) was added dropwise to the stirred soln of **7b** (4.00 g, 12.3 mmol) and DMAP (7.50 g, 61.5 mmol) in dry CH_2Cl_2 (80 ml) at 5~15° under Ar. The mixture was stirred for 10 min at 5° and for 1 h at room temp. Water was added to the mixture. After stirring for 30 min, the mixture was washed with water and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (150 g). The first fraction eluted with n-hexane-EtOAc (40:1) gave **16** (0.240 g, 6.4 %). $n_D^{23.5}$ 1.5578; $[\alpha]_D^{23.5}$ +16.0°(c=0.82, $CHCl_3$); νmax 3100 (w), 3050 (w), 1780 (s), 1645 (m) cm^{-1}; δ ($CDCl_3$) 1.25 (3H, d, J=7 Hz), 1.00~3.30 (8H, m), 3.35 (1H, d, J=12 Hz), 3.55 (1H, d, J=12 Hz), 5.00 (2H, br.s). (Found: C, 43.42; H, 4.87. Calc for $C_{11}H_{15}O_2I$: C, 43.15; H, 4.94 %). The second fraction eluted with n-hexane-EtOAc (40:1) gave **8** (2.94 g, 78 %), n_D^{22} 1.5542; $[\alpha]_D^{22}$ +124.8°(c=1.56, $CHCl_3$); νmax 3050 (m), 1780 (s), 1660 (w) cm^{-1}; δ ($CDCl_3$) 1.05 (3H, s), 1.10 (3H, s), 2.58 (5H, m), 3.38 (1H, d, J=12 Hz), 3.68 (1H, d, J=12 Hz), 5.65 (2H, br.s). (Found: C, 43.02; H, 4.94. Calc for $C_{11}H_{15}O_2I$: C, 43.15; H, 4.94 %). The third fraction eluted with n-hexane-EtOAc (40:1) gave crystalline **15** (0.253 g, 6.0 %), m.p. 127.0~127.5°; $[\alpha]_D^{24}$ -19.2°(c=1.57, $CHCl_3$); νmax (KBr) 3010 (s), 3000 (s), 2960 (s), 2920 (s), 1780 (vs), 1190 (s), 1000 (s), 965 (s) cm^{-1}; δ (100 MHz, $CDCl_3$) 1.16 (3H, s), 1.18 (3H, s), 1.93~3.41 (7H, m), 3.49 (1H, d, J=12 Hz), 3.64 (1H, d, J=12 Hz), 3.99 (1H, dd, J=4 Hz, 4 Hz). (Found: C, 38.50; H, 4.74. Calc for $C_{11}H_{16}O_2ClI$: C, 38.56; H, 4.71 %).

(3aR,7aS)-2-Oxo-4,4,7a-trimethyl-2,3,3a,4,7,7a-hexahydrobenzofuran **9**. $(n\text{-}Bu)_3SnH$ (5.60 g, 19.2 mmol) was added dropwise to a stirred and ice-cooled soln of **8** (2.90 g, 9.47 mmol) in dry C_6H_6 (7.5 ml) under Ar. The mixture was stirred overnight at room temp and then chromatographed over SiO_2 (130 g). Elution with n-hexane-EtOAc (10:1) gave **9** (1.70 g, 99.6 %). An analytical sample of **9** was obtained by distillation, b.p. 100~110° (bath temp)/0.2 Torr; $n_D^{23.5}$ 1.4815; $[\alpha]_D^{23.5}$ +170.0°(c=1.09, $CHCl_3$); νmax 3060 (m), 1780 (s), 1660 (w), 1385 (m), 1230 (m), 1180 (m), 1095 (m), 950 (m), 725 (m) cm^{-1}; δ ($CDCl_3$) 1.02 (3H, s), 1.10 (3H, s), 1.55 (3H, s), 2.00~2.85 (5H, m), 5.60 (2H, m). GLC (column, OV-1, 1 m x 2 mm at 140°; carrier gas, N_2, 1.3 kg/cm^2) Rt 2.33 min (100 %); (Found: C, 73.06; H, 8.92. Calc for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95 %).

(3aR,7aS)-2-Oxo-4,4,7a-trimethyloctahydrobenzofuran **2**. PtO_2 (0.10 g) was added to a soln of **9** (1.00 g, 5.55 mmol) in AcOH (60 ml) and the mixture was stirred under H_2 (30 atm) for 23 h. Subsequently the catalyst was filtered off and the filtrate was concentrated in vacuo. The residue was diluted with EtOAc. The EtOAc soln was washed with sat $NaHCO_3$ soln, water and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (10 g). Elution with n-hexane-EtOAc (10:1) gave crystalline (3aR,7aS)-**2** (0.910 g, 80 %). This was recrystallized from n-hexane to give (3aR,7aS)-**2** (0.669 g), m.p. 74~75°; $[\alpha]_D^{24}$ +63.5°(c=0.95, $CHCl_3$); νmax (KBr) 1770 (s), 1265 (s), 1100 (s), 945 (s) cm^{-1}; δ (400 MHz, $CDCl_3$) 0.91 (3H, s), 1.05 (3H, s), 1.53 (3H, s), 1.28~1.65 (5H, m), 1.86 (1H, br d, J=12.5 Hz), 2.07 (1H, dd, J=8.7 Hz, 12.5 Hz), 2.43 (1H, dd, J=8.7 Hz, 15.4 Hz), 2.51 (1H, dd, J=12.5 Hz, 15.4 Hz). GLC (column, OV-101, 50 m x 0.25 mm at 200°; carrier gas, N_2, 1.2 kg/cm^2) Rt 22.13 min (98 %); (Found: C, 72.40; H, 9.74. Calc for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95 %).

(3aR,7aS)-2-Oxo-3-phenylselenyl-4,4,7a-trimethyloctahydrobenzofuran **10**. A soln of LDA was prepared by the addition of n-BuLi in n-hexane (1.52 N, 2.2 ml) to a stirred and cooled soln of $(i\text{-}Pr)_2NH$ (0.45 g, 4.4 mmol) in dry THF (8 ml) at -70~-55° under Ar. After the addition, the mixture was stirred for 10 min at -10°. It was then cooled to -70°. A soln of (3aR,7aS)-**2** (0.40 g, 2.20 mmol) in dry THF (8 ml) was added slowly to the stirred soln during 1 h. After the addition, the mixture was stirred for 30 min at -70°. HMPA (0.7 ml) was added to the mixture. Subsequently a soln of PhSeBr in dry THF (3.5 M, 1.6 ml) prepared by the addition of Br_2 (0.45 ml, 8.8 mmol) to a stirred soln of PhSeSePh (2.75 g, 8.8 mmol) in dry THF (5 ml) at room temp was added rapidly to the mixture. After the addition, the reaction temp was gradually raised to room temp. Then N-HCl soln (5 ml) was added to the mixture and the mixture was diluted with ether. The ether soln was washed with water and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (20 g). Elution with n-hexane-EtOAc (20:1) gave (3aR,7aS)-**10** (0.70 g), νmax 3080 (m), 1765 (s), 1580 (m), 1480 (m), 1440 (m), 1380 (m), 1100 (s), 960 (m), 785 (s), 740 (s), 690 (s) cm^{-1}; δ ($CDCl_3$) 1.00 (3H, s), 1.19 (3H, s), 1.32 (3H, s), 0.80~2.40 (6H, m), 1.92 (1H, d, J=10 Hz), 3.62 (1H, d, J=10 Hz), 7.10~7.52 (3H, m), 7.52~7.80 (2H, m). This was employed for the next step without further purification.

(S)-(+)-2-Oxo-4,4,7a-trimethyl-2,4,5,6,6,7a-hexahydrobenzofuran [(+)-Dihydroactinidiolide] **1**. 35 % H_2O_2 soln (0.8 ml, 9.15 mmol) was added to a stirred and ice-cooled soln of (3aR,7aS)-**10** (0.62 g) and AcOH (1 drop) in THF (10 ml). The mixture was stirred for 1 h at 5°. A small amount of Pt black was added to the mixture to decompose excess H_2O_2. Sat $NaHCO_3$ soln was added to the mixture and the mixture was stirred for 30 min at room temp. The mixture was diluted with ether. The ether soln was washed with sat $NaHCO_3$ soln, water and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (20 g). Elution with n-hexane-EtOAc (20:1) gave (S)-(+)-**1** (0.120 g, 48 % from **2**), m.p. 67~68°; $[\alpha]_D^{23}$ +120.9°(c=1.00, $CHCl_3$); νmax (KBr) 3040 (m), 3020 (m), 2980 (s), 2960 (s), 2880 (s), 1750 (vs, br), 1635 (s), 1465

(s), 1390 (m), 1375 (s), 1370 (s), 1330 (m) 1300 (w), 1265 (vs), 1230 (s), 1195 (s), 1185 (s), 1155 (s), 1125 (s), 1070 (w), 1035 (s), 1015 (w), 995 (s), 985 (s), 960 (vs), 950 (s), 915 (s), 885 (s), 860 (vs), 790 (w), 730 (s), 685 (s), 660 (w) cm^{-1}; δ (400 MHz, $CDCl_3$) 1.22 (3H, s), 1.28 (3H, s), 1.28 (1H, ddd, J=5 Hz, 12.5 Hz, 12.5 Hz), 1.46 (1H, ddd, J=5 Hz, 12.5 Hz, 12.5 Hz), 1.55 (3H, s), 1.62~1.81 (3H, m), 2.24 (1H, ddd, J=2.5 Hz, 5 Hz, 12.5 Hz), 5.65 (1H, s); GLC (column, PEG-20M, 50 m x 0.25 mm at 200°; carrier gas, N_2, 1 kg/cm^2), Rt 12.29 min (98.4 %); (Found: C, 73.60; H, 9.01. Calc for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95 %).

(3aS,7aR)-4,4-Dimethyl-7a-iodomethyl-2-oxo-2,3,3a,4,7,7a-hexahydrobenzofuran (3aS,7aR)- 8'. In the same manner as described for the preparation of (3aR,7aS)-8, 3.99 g of 7b' yielded 3.54 g (94 %) of (3aS,7aR)-8', n_D^{23} 1.5535; $[\alpha]_D^{23}$ -130.7° (c=1.58, $CHCl_3$); (Found: C, 43.09; H, 4.94. Calc for $C_{11}H_{15}O_2I$: C, 43.15; H, 4.94 %). Its IR and NMR spectra were identical with those of (3aR,7aS)-(+)-8.

(3aS,7aR)-2-Oxo-4,4,7a-trimethyl-2,3,3a,4,7,7a-hexahydrobenzofuran (3aS,7aR)-(-)-9'. In the same manner as described for preparation of (3aR,7aS)-9, 3.30 g of (3aS,7aR)-8' yielded 1.69 g (87 %) of (3aS,7aR)-(-)-9'. An analytical sample of (3aS,7aR)-9' was obtained by distillation, b.p. 100~105° (bath temp)/0.2 Torr; n_D^{24} 1.4812; $[\alpha]_D^{24}$ -183.2°(c=1.02, $CHCl_3$); GLC (column, OV-1, 1 m x 2 mm at 132°; carrier gas, N_2, 1.2 kg/cm^2) Rt 4.03 min (100 %). (Found: C, 73.12; H, 8.80. Calc for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95 %). Its IR and NMR spectra were identical with those of (3aR,7aS)-(+)-9.

(3aS,7aR)-2-Oxo-4,4,7a-trimethyloctahydrobenzofuran (3aS,7aR)-(-)-2'. In the same manner as described for the preparation of (3aR,7aS)-(+)-2, 1.20 g of (3aS,7aR)-(-)-9' yielded 1.10 g (91 %) of (3aS,7aR)-(-)-2'. This was recrystallized from n-hexane to give (3aS,7aR)-(-)-2' (0.960 g), m.p. 80~81°; $[\alpha]_D^{24}$ -66.1°(c=0.97, $CHCl_3$); GLC (column, OV-101, 50 m x 0.25 mm at 200°; carrier gas, N_2, 1.2 kg/cm^2) Rt 22.15 min (99.6 %). (Found: C, 72.74; H, 9.90. Calc for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95 %). Its IR and NMR spectra were identical with those of (3aR,7aS)-(+)-2.

(3aS,7aR)-2-Oxo-3-phenylselenyl-4,4,7a-trimethyloctahydrobenzofuran (3aS, 7aR)-10'. In the same manner as described for the preparation of (3aR, 7aS)-10, 0.40 g of (3aS, 7aR)-2' yielded 0.60g of (3aS,7aR)-10'. Its IR and NMR spectra were identical with those of (3aR,7aS)-10. This was employed for the next step without further purification.

(R)-(-)-2-Oxo-4,4,7a-trimethyl-2,4,5,6,6,7a-hexahydrobenzofuran [(-)-Dihydroactinidiolide] 1'. In the same manner as described for the preparation of (S)-(+)-1, 0.55 g of (3aS,7aR)-10' yielded 0.23 g [64 % from (3aS,7aR)-2'] of (R)-(-)-1'. This was recrystallized from n-pentane to give (R)-(-)-1' (0.19 g), m.p. 70~71°; $[\alpha]_D^{24}$ -121.0°(c=1.05, $CHCl_3$); GLC (column, PEG-20M, 50 m x 0.25 mm at 200°; carrier gas, N_2, 1 kg/cm^2), Rt 13.72 min (98.9 %). (Found: C, 73.39; H, 8.93. Calc for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95 %). Its IR and NMR spectra were identical with those of (S)-(+)-1.

Determination of the optical purities of (S)-(+)-1 and (R)-(-)-1'. The optical purities of (S)-(+)-1 and (R)-(-)-1' were estimated by 400 MHz ^1H-NMR in the presence of chiral solvating reagent 17[35]; δ [10 mg of (S)-(+)-1 and 46 mg of 17 in $CDCl_3$ (0.3 ml)] 5.31 (s, vinylic H); [10 mg of (R)-(-)-1' and 46 mg of 17 in $CDCl_3$ (0.3 ml)] 5.36 (s, vinylic H). The optical purities of (S)-(+)-1 and (R)-(-)-1' were therefore both 100 % e.e.

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