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

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Abstract -- Both the enantiomers of invictolide [3,5-dimethyl-6-(1'-methylbutyl)-tetrahydro-2H-pyran-2-one] were synthesized in 17 steps from propargyl alcohol.

Invictolide **1** (=**C**) is one of the three lactones (**A**, **B** and **C**) isolated from the red imported fire ant (Solenopsis invicta Buren) as the queen recognition pheromone.[1,2] The lactone **A** is an achiral compound, and was synthesized by Rocca et al.[1] As to dihydroactinidiolide **B**, we recently reported a synthesis of the both of its enantiomers.[3] Invictolide **1** possesses four chiral centers. Its relative stereochemistry was shown to be 3R*,5R*,6S*,1'R* as depicted in **1** by Rocca's synthesis of (±)-**1**.[2] Since then, three additional syntheses of (±)-**1** were announced as preliminary communications.[4~6] Ziegler's success in synthesizing (3S,5S,6R,1'S)-(+)-invictolide **1'** made its bioassay possible.[7] The fact that (+)-**1'** was biologically inactive while (±)-**1** was active suggested the absolute configuration of natural invictolide to be 3R,5R,6S,1'R as depicted in **1**. Herein we report in detail our own approach to the synthesis of invictolide enantiomers, which culminated in the preparation of both (-)-**1** and (+)-**1'** as crystals.

Our synthesis of invictolide was linear and straightforward as shown in the Scheme, and employed the Sharpless asymmetric epoxidation (**4** → **5a**),[8] cleavage of an epoxide with Me_3Al (**5a** → **6a**),[9~11] methylation of the dianion derived from a β-hydroxy ester (**10** → **11a**)[12], and the Evans asymmetric alkylation (**13** → **14** → **15**),[13] respectively, for the introduction of the four chiral centers in the desired stereochemical sense.

The first phase of our work was the preparation of a diol **6a**. This diol **6a** as well as an epoxide **8** were previously prepared by us employing enzymatic resolution of an amino acid as the key-step.[14] An alternative synthesis of (-)-invictolide **1** by this approach will be reported separately.[15] To improve the poor overall yield of (-)-**1** by the enzymatic route,[15] we decided to use another procedure for the preparation of **6a**. What we employed was the modification of our previous procedure based on the Sharpless asymmetric epoxidation.[16] Alkylation of **2** with n-PrBr and $LiNH_2$ in NH_3 yielded **3** in 84 % yield.[16] This was hydrogenated over Pd-$BaSO_4$ poisoned with quinoline to give **4** with >99 % chemical purity as checked by GLC.[16] Asymmetric epoxidation of **4** using (-)-diisopropyl tartrate and t-BuOOH furnished **5a** in 56 % yield, whose enantiomeric purity was estimated to be 81 % e.e. by the HPLC analysis of the corresponding (S)-α-methoxy-α-trifluoromethylphenyl-

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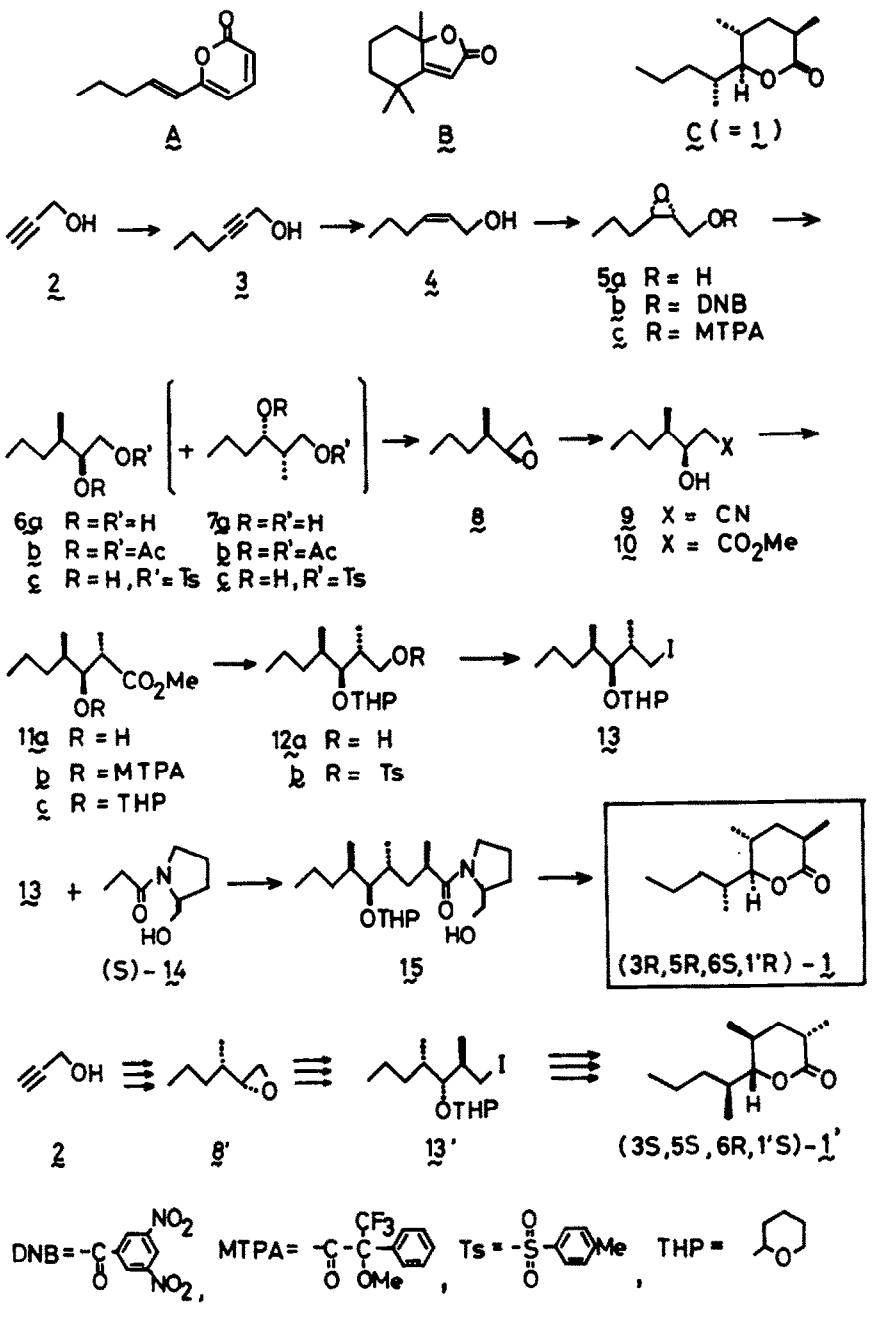

acetate (MTPA ester) **5c**.[17] To enhance the enantiomeric purity of **5c**, it was converted to the corresponding crystalline 3,5-dinitrobenzoate (DNB ester) **5b**. After several recrystallizations, pure **5b**, m.p. 53~54°, was obtained in 37 % recovery. Saponification of pure **5b** gave back pure (2R,3S)-**5a**, which was shown to be of 99.4 % e.e as checked by the HPLC analysis of its (R)-MTPA ester **5c**. Treatment of the epoxy alcohol **5a** in n-pentane with ca. 4 eq of Me_3Al and ca. 0.25 eq of n-BuLi furnished a mixture of the desired **6a** and undesired **7a**. The composition of the mixture was shown to be **6a**:**7a** = 86:14 by analyzing (GLC) the mixture after acetylation to the corresponding mixture of **6b** and **7b**. The mixture of **6a** and **7a** was tosylated, and the product was chromatographed over SiO_2 giving the pure monotosylate **6c** in 72 % yield from the mixture of **6a** and **7a**. Treatment of **6c**

with NaOMe in MeOH furnished the (2S,3R)-epoxide **8** in 77 % yield. The overall yield of **8** from **2** was 5.8 % in 8 steps. By the previous method,[14,15] the overall yield of **8** was 1.0 % in 7 steps from 2-methylpentanal, the commercially available starting material. The present route to **8** was thus more efficient than the previous one.

The second stage of our work was the introduction of the third chiral center. Cleavage of the epoxide **8** with excess NaCN in hot 40 % EtOH gave **9**, which was hydrolyzed concomitantly giving a β-hydroxy acid.[18] The acid was immediately methylated with CH_2N_2, and the product was purified by SiO_2 chromatography to give **10** in 79 % yield. Methylation of the dianion derived from **10** with MeI according to Fráter[12] furnished **11a** in 49 % yield after chromatographic purification. The methylation proceeded with high diastereoselectivity giving a mixture of **11a** and its syn-isomer in a ratio of 88:12 as analyzed by GLC. The chemical and enantiomeric purities of **11a** were 95 % and 100 %, respectively, as checked by the GLC analysis of **11a** and the HPLC analysis of **11b**. Conversion of **11a** to the alkylating agent **13** was straightforward. After protecting the OH group of **11a** as a THP ether, the resulting **11c** was reduced with LAH to give **12a**. Tosylation of **12a** to **12b** was followed by treatment of **12b** with NaI in DMF in the presence of $NaHCO_3$ to afford **13** in rather low yield of 33 %.

The final phase of our work was to introduce the remaining fourth chiral center. Alkylation of the dianion derived from (S)-prolinol propanamide **14**[13,19] with **13** was best carried out by using an excess of **14** (ca. 10 eq) and by cooling the reaction mixture at -100° for 4 h and then at -80° for 2 days to give **15** in 82 % yield. Acid hydrolysis of **15** resulted in concomitant lactonization to give **1** in 80 % yield after column chromatography. (3R,5R,6S,1'R)-Invictolide **1** was recrystallized from n-hexane to give pure (-)-**1** as needles, m.p. 28.0~28.5°, $[\alpha]_D^{25}$ -101° ($CHCl_3$).

In the same manner, (3S,5S,6R,1'S)-(+)-invictolide **1'**, m.p. 28.5~29.0°, $[\alpha]_D^{25}$ +101° ($CHCl_3$) [lit.[7] $[\alpha]_D^{25}$ +77.4° ($CDCl_3$)], was synthesized. In this case, the asymmetric epoxidation was carried out with (+)-diisopropyl tartrate as the chiral auxiliary, and for the Evans asymmetric alkylation (R)-**14'** was employed. Our synthetic enantiomers of invictolide showed the ^1H NMR spectrum identical to the authentic spectrum kindly provided by Dr. J. H. Tumlinson (measured as a C_6H_6 soln) and Prof. F. E. Ziegler (measured as a $CDCl_3$ soln).

In conclusion, both the bioactive (-)-invictolide **1** and inactive (+)-**1'** were synthesized in 17 steps from propargyl alcohol **2** in 0.7 % and 0.2 % overall yield, respectively. In the course of our work, a synthesis of (+)-Prelog-Djerassi lactone was reported in which Tsai and Midland also employed the Evans asymmetric alkylation as the key-step.[20] Bioassay of our synthetic enantiomers (**1** and **1'**) against both the red and the black species of fire ants is now under way by Drs. B. M. Glancey and J. H. Tumlinson at Insect Attractants, Behavior and Basic Biology Research Laboratory, U. S. A., and will be reported in due course.

EXPERIMENTAL

All b.ps and m.ps were uncorrected. IR spectra were measured as films for oils or as nujol mulls for solids unless otherwise stated on a Jasco IRA-102 spectrometer. ^1H NMR spectra were recorded with TMS as an internal standard at 60 MHz on a Hitachi R-24A spectrometer or at 400 MHz on a JEOL JNM GX-400 spectrometer. Optical rotations were measured on a Jasco DIP 140 polarimeter. Merck Kieselgel 60 (particle size 0.063~0.200 mm) or Fuji-Davison BW-820 MH were used for SiO_2 column chromatography. HPLC analyses were performed on Nucleosil® 50-5 (25 cm x 4.6 mm) as a column by the detection at 254 nm.

2-Hexyn-1-ol **3**. To a suspension of $LiNH_2$ (from 19.8 g, 2.85 mol of Li) in liq NH_3 (1200 ml) was added **2** (69.5 g, 1.24 mol) at -30°. After 1 h of stirring, a soln of n-PrBr (83.0 g, 0.675 mol) in dry THF (200 ml) was added to the suspension at -30°. The mixture was stirred under reflux for 2 h. The mixture was left to stand overnight at room temp and the NH_3 was allowed to evaporate. The residue was diluted with sat NH_4Cl aq soln and extracted with ether. The combined ether soln was washed with brine and dried ($MgSO_4$). Filtration and concentration of the filtrate in vacuo was followed by distillation to give 65.5 g (84 %) of **3** as a pale yellow oil, b.p. 76~85°/32 Torr; νmax 3350 (s), 2980 (s), 2960 (s), 2890 (s), 2300 (w), 2240 (w), 1460 (m), 1435 (m), 1385 (m), 1360 (m), 1340 (m), 1330 (m), 1280 (w), 1230 (w), 1140 (s), 1075 (w),

1035 (s), 1010 (s) cm^{-1}; δ ($CDCl_3$) 0.98 (3H, t, J=7 Hz), 1.32 (2H, tq, J=6, 7 Hz), 2.18 (2H, m), 2.45 (1H, s), 4.25 (2H, t, J=2 Hz).

(Z)-2-Hexen-1-ol **4**. To a suspension of Pd-$BaSO_4$ (6 g) in n-hexane (700 ml) was added 3 (60.0 g, 0.612 mol) and quinoline (120 drops). The mixture was shaken under H_2 (1 atm) for 4 h. Subsequently the catalyst was filtered off, and the filtrate was washed with dil HCl aq soln and brine, dried ($MgSO_4$) and concentrated under atmospheric press. The residue was distilled to give 50.2 g (82 %) of **4** as a colorless oil, b.p. 79~80°/45 Torr; νmax 3330 (s), 3030 (m), 2975 (s), 2940 (s), 2880 (s), 1660 (w), 1460 (m), 1380 (w), 1045 (s), 1010 (s) cm^{-1}; δ ($CDCl_3$) 0.90 (3H, t, J=7 Hz), 1.20~1.60 (2H, m), 2.05 (2H, dt, J=6, 6 Hz), 2.40 (1H, s), 4.15 (2H, d, J=5 Hz), 5.40~5.80 (2H, m); GLC (Column, OV-101, 50 m x 0.25 mm at 70°; Carrier gas, N_2, 0.7 kg/cm^2): Rt 24.3 min (100 %).

2,3-Epoxy-1-hexanol **5a**. a) (2R,3S)-Isomer. A mixture of $Ti(OPr^i)_4$ (125 g, 440 mmol) and D-(-)-diisopropyl tartarate (103 g, 484 mmol) in dry CH_2Cl_2 (3200 ml) was stirred at -20° for 5 min under Ar. To the mixture was added **4** (40.0 g, 400 mmol), followed by the addition of t-BuOOH in CH_2Cl_2 (4.50 M, 196 ml, 880 mmol). The mixture was left to stand for 3 days at -20°. In order to decompose the excess amount of t-BuOOH, Me_2S (150 ml, 2.05 mol) was added to the mixture, and the mixture was stirred at -20° for 30 min. The mixture was poured into pre-cooled (-20°) acetone (4800 ml containing 80 ml of water) and stirred at room temp overnight. Filtration and concentration of the filtrate in vacuo gave 165 g of an oily material, which was purified by column chromatography (SiO_2, CH_2Cl_2) to give 26 g (56 %) of (2R,3S)-**5a** as a pale yellow oil. An analytical sample was obtained by distillation, b.p. 105~107°/27 Torr; n_D^{22} 1.4322; $[\alpha]_D^{23.5}$ +4.91° (c=2.02, $CHCl_3$); GLC (Column, OV-101, 50 m x 0.25 mm at 100°; Carrier gas, N_2, 0.8 kg/cm^2): Rt 9.9 min (100 %); νmax 3420 (s), 2975 (s), 2950 (s), 2880 (s), 1460 (s), 1430 (m), 1380 (m), 1265 (w), 1230 (w), 1145 (w), 1105 (m), 1040 (s), 905 (m), 860 (m), 830 (m), 765 (m) cm^{-1}; δ ($CDCl_3$) 0.95 (3H, t, J=6 Hz), 1.20~1.80 (4H, m), 2.75~3.45 (3H, m), 3.50~4.10 (2H, m). The optical purity of (2R,3S)-**5a** was determined by HPLC analyses of the corresponding (S)-MTPA ester **5c**: [Solvent: n-hexane:1,2-dichloroethane (DCE)=5:2, 60 kg/cm^2, 1.5 ml/min] Rt (2R,3S,S)-isomer 35.5 min (90.2 %), (2S,3R,S)-isomer 38.1 min (9.8 %), the optical purity was calculated to be 80.4 % e.e.

b) (2S,3R)-Isomer. In the same manner as described above, the above mentioned mixture of $Ti(OPr^i)_4$ (65.4 g, 230 mmol), L-(+)-DIPT (59.3 g, 253 mmol), **4** (23.0 g, 230 mmol) and t-BuOOH in CH_2Cl_2 (4.40 M, 104 ml, 460 mmol) was left to stand for 7 days at -20° to give 15 g (57 %) of (2S,3R)-**5a'**, b.p. 103.5~104.5°/19 Torr; $n_D^{23.5}$ 1.4322; $[\alpha]_D^{22}$ -12.0° (c=2.78, $CHCl_3$); GLC (Column, OV-101, 50 m x 0.25 mm at 100°; Carrier gas, N_2, 1.2 kg/cm^2): Rt by-product 13.6 min (11.2 %), (2S,3R)-**5a'** 15.9 min (88.8 %). The optical purity of (2S,3R)-**5a'** was determined by HPLC analyses of the corresponding (R)-MTPA ester: [Solvent: n-hexane:DCE=3:1, 100 kg/cm^2, 2.0 ml/min] Rt (2S,3R,R)-isomer 49.5 min (93.7 %), (2R,3S,R)-isomer 54.5 min (6.3 %). The optical purity was calculated to be 87.4 % e.e.

2',3'-Epoxyhexyl 3,5-dinitrobenzoate **5b**. a) (2'R,3'S)-Isomer. Asymmetric epoxidation of **4** gave (2R,3S)-**5a** of 80.4 % e.e. Its enantiomeric excess was enhanced by recrystallizing **5b**. To a soln of (2R,3S)-**5a** (42.0 g, 362 mmol) in dry ether (1000 ml) were added pyridine (400 ml) and 3,5-dinitrobenzoyl chloride (109 g, 472 mmol) at 0~5°. The stirring was continued for 20 min at 0~5°. The mixture was then poured into ice-water. The ether layer was separated and the aq layer was extracted with ether. The combined organic layer was washed with water, sat $CuSO_4$ aq soln, water and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue (115 g) was recrystallized from n-hexane:benzene (6:1) to give 41.0 g (37 % recovery) of (2'R,3'S)-**5b**, m.p. 53.0~54.0°; $[\alpha]_D^{24.5}$ +28.1° (c=0.780, $CHCl_3$); νmax 3120 (w), 2930 (s), 2860 (s), 1725 (s), 1630 (w), 1600 (w), 1550 (s), 1460 (s), 1400 (w), 1375 (m), 1345 (s), 1295 (m), 1265 (w), 1175 (w), 1090 (w), 1080 (m), 975 (m), 935 (m), 920 (m), 880 (w), 840 (m), 815 (w), 770 (m), 735 (m), 720 (s) cm^{-1}; δ ($CDCl_3$) 1.05 (3H, m), 1.30~1.85 (4H, m), 2.90~3.50 (2H, m), 4.15~4.95 (2H, m), 9.26 (3H, br.s). (Found: C, 50.02; H, 4.62; N, 9.03. Calc for $C_{13}H_{14}O_7N_2$: C, 50.32; H, 4.55; N, 9.03 %).

b) (2'S,3'R)-Isomer. In the same manner as described above, (2S,3R)-**5a'** (21.0 g, 181 mmol) yielded 17.5 g (30 %) of (2'S,3'R)-**5b'**, m.p. 53.0~54.0°; $[\alpha]_D^{20}$ -28.5° (c=0.580, $CHCl_3$); (Found: C, 50.33; H, 4.61; N, 8.83. Calc for $C_{13}H_{14}O_7N_2$: C, 50.32; H, 4.55; N, 9.03 %).

2,3-Epoxy-1-hexanol **5a**. a) (2R,3S)-Isomer. *N* KOH aq soln (131 ml) was added dropwise to a stirred and cooled soln of (2'R,3'S)-**5b** (40.7 g, 131 mmol) in THF-MeOH (1:1, 800 ml) at 0°. The mixture was stirred for 15 min at 0° and then poured into sat $NaHCO_3$ soln. The aq layer was extracted with ether. The combined organic layer was dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2. Elution with n-hexane:EtOAc (4:1) gave (2R,3S)-**5a** (13.8 g, 91 %). An analytical sample was obtained by distillation, b.p. 103~104°/20 Torr; $[\alpha]_D^{27}$ +5.69° (c=1.41, $CHCl_3$); GLC (Column, OV-101, 50 m x 0.25 mm at 100°; Carrier gas, N_2, 0.8 kg/cm^2): Rt (2R,3S)-**5a** 10.1 min (100 %). The optical purity of (2R,3S)-**5a** was determined by HPLC analyses of the corresponding (R)-MTPA ester **5c**: [Solvent: n-hexane:DCE=5:2, 40 kg/cm^2, 1.0 ml/min] Rt (2S,3R,R)-isomer 55.8 min (0.3 %), (2R,3S,R)-isomer 59.2 min (99.7 %). The optical purity was calculated to be 99.4 % e.e.

b) (2S,3R)-Isomer. In the same manner as described above, (2'S,3'R)-**5b'** (17.4 g, 56.1 mmol) yielded 6.50 g (99 %) of (2S,3R)-**5a**, b.p. 98~99°/21 Torr; $[\alpha]_D^{22}$ -5.73° (c=1.50, $CHCl_3$); GLC (Column, OV-101, 50 m x 0.25 mm at 100°; Carrier gas, N_2, 1.2 kg/cm^2): Rt impurity 13.1 min (0.9 %), (2S,3R)-**5a'** 14.6 min (99.1 %). Optical purity of (2S,3R)-**5a'** was determined to be 97.6 % e.e. in the same manner as described above.

3-Methyl-1,2-hexanediol **6a**. a) (2S,3R)-Isomer. A soln of Me_3Al (10 % in n-hexane, 154 ml, 210 mmol) was added to a stirred and cooled (dry ice-acetone) suspension of (2R,3S)-**5a** (11.5 g, 99.1 mmol) in dry n-pentane (220 ml) at -40~-50° under Ar. A soln of n-BuLi in n-hexane (1.72 M, 14.0 ml, 24.8 mmol) was added to the mixture at -50°. The mixture was allowed to warm to room temp and stirred for 2 days. The mixture was cooled to -50° and 2N HCl aq soln (240 ml) was added carefully. The organic layer was separated and the aq layer was extracted with ether. The combined organic layer was washed with sat $NaHCO_3$ aq soln and brine and then dried ($MgSO_4$). Filtration and concentration of the filtrate in vacuo gave 13.3 g of an oily material, which was submitted to column chromatography (SiO_2, n-hexane:EtOAc) to give 11.3 g (86 %) of (2S,3R)-**6a**, νmax 3350 (s), 2975 (s), 2950 (s), 2880 (s), 1460 (s), 1380 (m), 1140 (m), 1060 (s), 1030 (s) cm^{-1}; δ ($CDCl_3$) 0.60~1.10 (6H, m), 1.10~1.80 (5H, m), 3.12 (2H, s), 3.50 (3H, br.s). The ratio of regioisomers was determined by GLC analysis of diacetyl derivatives (**6b** + **7b**). GLC (Column, OV-101, 50 m x 0.25 mm at 160°; Carrier gas, N_2, 1.0 kg/cm^2): Rt **6b** 39.8 min (86 %), **7b** 40.9 min (14 %). This was employed for the next step without further purification.

b) (2R,3S)-Isomer. In the same manner as described above, (2S,3R)-**5a'** (5.09 g, 43.9 mmol) yielded 4.33 g (75 %) of (2R,3S)-**6a'**. This was employed for the next step without further purificatin.

3-Methyl-1-tosyloxy-2-hexanol **6c**. a) (2S,3R)-Isomer. p-TsCl (21.0 g, 111 mmol) was added to a soln of (2S,3R)-**6a** (11.3 g, 85.6 mmol) and 4-(N,N-dimethylamino)pyridine (2.00 g, 17.1 mmol) in dry pyridine (100 ml) with stirring and ice-cooling. The stirring was continued for 3 h at 0°. The mixture was then poured into ice-water and extracted with ether. The ether soln was washed with dil HCl aq soln, sat $NaHCO_3$ aq soln and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was submitted to column chromatography (SiO_2, n-hexane:ether) to give 17.5 g (72 % from the mixture of **6a** and **7a**) of (2S,3R)-**6c**, νmax 3425 (m), 2980 (s), 2950 (s), 2900 (s), 1600 (m), 1500 (w), 1460 (m), 1360 (s), 1190 (s), 1180 (s), 1100

(s), 970 (s), 820 (m), 660 (s) cm^{-1}. This was employed for the next step without further purification.

b) (2R,3S)-Isomer. In the same manner as described above, (2R,3S)-**6a'** (4.20 g, 31.8 mmol) yielded 6.50 g (72 % from the mixture of **6a'** and **7a'**) of (2R,3S)-**6c'**. This was employed for the next step without further purification.

1,2-Epoxy-3-methylhexane **8**. a) (2S,3R)-Isomer. A soln of (2S,3R)-**6c** (17.5 g, 6.2 mmol) in dry MeOH (40 ml) was added to a stirred and ice-cooled soln of NaOMe (24.2 g of 28 % MeOH soln, 125 mmol) in dry MeOH (40 ml). The mixture was stirred for 1 h at 0°, poured into ice-water and extracted with n-pentane. The n-pentane soln was washed with water and brine, dried (K_2CO_3) and concentrated under atm press with a Vigreaux column. The residue was distilled to give 5.00 g (72 %) of (2S,3R)-**8**, b.p. 110~115°; n_D^{24} 1.4060; $[\alpha]_D^{24}$ -4.00° (c=0.915, ether); [lit $[\alpha]_D^{23}$ -4.2° (c=0.867, ether)[14]]; νmax 3050 (m), 2960 (s), 2930 (s), 2880 (s), 1485 (m), 1470 (s), 1460 (s), 1380 (s), 1260 (m) cm^{-1}; δ ($CDCl_3$) 0.60~1.70 (11H, m), 2.10~2.75 (3H, m). (Found: C, 73.51; H, 12.14. Calc for $C_7H_{14}O$: C, 73.63; H, 12.36 %).

b) (2R,3S)-Isomer. In the same manner as described above, (2R,3S)-**6c'** (6.50 g, 22.7 mmol) yielded 1.99 g (77 %) of (2R,3S)-**8'**, b.p. 110~115°; n_D^{24} 1.4122; $[\alpha]_D^{22}$ +3.41° (c=0.750, ether); [lit $[\alpha]_D^{22}$ +4.2° (c=1.122, ether)[14]]; (Found: C, 73.68; H, 12.21. Calc for $C_7H_{14}O$: C, 73.63; H, 12.36 %). The IR and NMR spectra were identical with those of (2S,3R)-**8**.

Methyl 3-hydroxy-4-methylheptanoate **10**. a) (3S,4R)-Isomer. A soln of (2S,3R)-**8** (4.90 g, 43.0 mmol) in 40 % EtOH aq soln (20 ml) was added to a soln of NaCN (6.30 g, 129 mmol) in 40 % EtOH aq soln (50 ml). The mixture was heated under reflux with stirring for 7 h. Then EtOH was removed in vacuo. The residue was acidified to pH 4 with N HCl aq soln. It was then extracted with CH_2Cl_2 and the organic layer was dried (Na_2SO_4) and concentrated in vacuo to give an oily material (ca 6.2 g). This was methylated with ethereal CH_2N_2 to give crude (3S,4R)-**10**. This was submitted to column chromatography (SiO_2, n-hexane:ether) to give 5.90 g (79 %) of (3S,4R)-**10**. An analytical sample was obtained by distillation, b.p. 71~75°/0.5 Torr; n_D^{25} 1.4323; $[\alpha]_D^{25}$ +40.0° (c=0.820, $CHCl_3$); GLC (Column, OV-101, 50 m x 0.25 mm at 150°; Carrier gas, N_2, 0.8 kg/cm^2): Rt 38.8 min (100 %); νmax 3360 (m), 2980 (s), 2950 (s), 2890 (s), 1735 (s), 1440 (s), 1170 (s), 1040 (m), 985 (m) cm^{-1}; δ ($CDCl_3$) 0.65~1.05 (6H, m), 1.05~1.70 (5H, m), 2.45 (2H, d, J=6 Hz), 2.72 (1H, m), 3.68 (3H, s), 3.80 (1H, m). (Found: C, 61.93; H, 10.43. Calc for $C_9H_{18}O_3$: C, 62.04; H, 10.41 %).

b) (3R,4S)-Isomer. In the same manner as described above, (2R,3S)-**8'** (1.90 g, 16.7 mmol) yielded 1.25 g (43 %) of (3R,4S)-**10'**, b.p. 77~79°/1.5 Torr; n_D^{25} 1.4326; $[\alpha]_D^{22}$ -41.5° (c=1.70, $CHCl_3$); GLC (Column, OV-101, 50 m x 0.25 mm at 120°; Carrier gas, N_2, 1.1 kg/cm^2): Rt 23.2 min (100 %); (Found: C, 61.83; H, 10.27. Calc for $C_9H_{18}O_3$: C, 62.04; H, 10.41 %). The IR and NMR spectra were identical with those of (3S,4R)-**10**.

Methyl 2,4-dimethyl-3-hydroxyheptanoate **11a**. a) (2S,3S,4R)-Isomer. A soln of LDA was prepared from i-Pr_2NH (4.7 ml, 33 mmol) and n-BuLi (1.56 N in n-hexane, 14.2 ml, 22.1 mmol) in dry THF (100 ml) under Ar at -10~0°. To this mixture was added dropwise a soln of (3S,4R)-**10** (1.28 g, 7.36 mmol) in dry THF (13 ml) with stirring and cooling at -70~-60°. The temp was raised to -15°. Then the mixture was stirred at -15° for 30 min. After the addition of HMPA (5.93 g, 33.6 mmol), the mixture was cooled to -60°. To this mixture was added a soln of MeI (2.62 g, 18.4 mmol) in dry THF (13 ml) at -65~-60°. The temp was gradually raised to -20° over 2 h. Then the mixture was left to stand for 2 days at -20°. Sat NH_4Cl aq soln (60 ml) was added to the reaction mixture at -20° and it was extracted with ether. The ether soln was washed with brine, dried ($MgSO_4$) and concentrated in vacuo to give an oily material, GLC (Column, OV-101, 50 m x 0.25 mm at 150°; Carrier gas, N_2 1.2 kg/cm^2): Rt (3S,4R)-**10** 28.0 min (5.7 %), impurity 32.0 min (2.6 %), (2S,3S,4R)-**11a** 32.8 min (80.6 %), syn-isomer 33.8 min (11.1 %). This was submitted to column chromatography (230~400 mesh SiO_2, n-hexane:ether) to give 0.67 g (49 %) of (2S,3S,4R)-**11a**. An analytical sample was obtained by distillation, b.p. 65°/0.32 Torr; n_D^{23} 1.4326; $[\alpha]_D^{24}$ +15.4° (c=1.13, $CHCl_3$); GLC (Column, OV-101, 50 m x 0.25 mm at 120°; Carrier gas, N_2, 1.1 kg/cm^2): Rt impurity 24.6 min (4.1 %), (2S,3S,4R)-**11a** 25.2 min (95.3 %), syn-isomer 26.0 min (0.6 %); νmax 3520 (m), 2960 (s), 2930 (s), 2880 (m), 1725 (s), 1460 (s), 1200 (s), 1170 (s), 740 (s) cm^{-1}; δ ($CDCl_3$) 0.65~1.80 (14H, m), 2.30~2.80 (2H, m), 3.35~3.90 (1H, m), 3.68 (3H, s). (Found: C, 63.54; H, 10.74. Calc for $C_{10}H_{20}O_3$: C, 63.79; H, 10.71 %). The optical purity of (2S,3S,4R)-**11a** was determined by HPLC analyses of the corresponding (R)-MTPA ester. [Solvent: n-hexane:THF=30:1, 1.0 ml/min] Rt 22.1 min (single peak). Therefore the optical purity was determined to be ~100 % e.e.

b) (2R,3R,4S)-Isomer. In the same manner as described above, (3R,4S)-**10'** (0.50 g, 2.87 mmol) yielded 0.30 g (56 %) of (2R,3R,4S)-**11a'**, b.p. 75°/1.5 Torr; n_D^{23} 1.4340; $[\alpha]_D^{23}$ -15.1° (c=0.470, $CHCl_3$); GLC (Column, OV-101, 50 m x 0.25 mm at 120°; Carrier gas, N_2, 1.1 kg/cm^2): Rt (3R,4S,)-**10'** 23.0 min (0.7 %), impurity 26.4 min (0.7 %), (2R,3R,4S)-**11a'** 27.2 min (97.2 %), syn-isomer 28.2 min (1.4 %); Optical purity of (2R,3R,4S)-**11a'**=97.2 % e.e. (determined by HPLC analysis of the corresponding (R)-MTPA ester); The IR and NMR spectra were identical with those of (2S,3S,4R)-**11a**. (Found: C, 63.32; H, 10.68. Calc for $C_{10}H_{20}O_3$: C, 63.79; H, 10.71 %).

Methyl 2,4-dimethyl-3-tetrahydropyranyloxyheptanoate **11c**. a) (2S,3S,4R)-Isomer. Dihydopyran (0.616 g, 7.30 mmol) and PPTS (0.116 g, 0.460 mmol) were added to a soln of (2S,3S,4R)-**11a** (0.810 g, 4.30 mmol) in dry CH_2Cl_2 (16 ml). The mixture was stirred at room temp for 16 h. The mixture was diluted with CH_2Cl_2 and washed with sat $NaHCO_3$ aq soln and brine, dried (Na_2SO_4) and concentrated in vacuo to give 1.35 g (quantitative) of (2S,3S,4R)-**11c**, νmax 2960 (s), 2890 (s), 1745 (s), 1460 (m), 1380 (m), 1260 (m), 1205 (m), 1170 (m), 1130 (m), 1080 (m), 1030 (s), 990 (m), 970 (m) cm^{-1}. This was employed for the next step without further purification.

b) (2R,3R,4S)-Isomer. In the same manner as described above, (2R,3R,4S)-**11a'** (0.350 g, 1.86 mmol) yielded 0.540 g (quantitative) of crude (2R,3R,4S)-**11c'**. This was employed for the next step without further purification.

2,4-Dimethyl-3-tetrahydropyranyloxy-1-heptanol **12a**. a) (2R,3S,4R)-Isomer. A soln of (2S,3S,4R)-**11c** (1.35 g, crude) in dry ether (4 ml) was added dropwise to a stirred and ice-cooled suspension of LAH (0.330 g, 8.60 mmol) in dry ether (8 ml). The mixture was stirred for 40 min at room temp. Then the excess LAH was destroyed by the addition of water (0.40 ml), 15 % NaOH aq soln (0.30 ml) and water (1.2 ml). The mixture was filtered and the filter cake was washed with ether. The combined organic soln was concentrated in vacuo. The residue was submitted to column chromatography (SiO_2, n-hexane:ether) to give 1.04 g (99 %) of (2R,3S,4R)-**12a**, $[\alpha]_D^{25}$ +15.5° (c=1.50, $CHCl_3$); νmax 3450 (m), 2950 (s), 2880 (s), 1460 (m), 1380 (m), 1135 (s), 1075 (s), 1030 (s), 980 (m) cm^{-1}; δ ($CDCl_3$) 0.60~1.10 (9H, m), 1.10~2.10 (12H, m), 3.10~4.20 (6H, m), 4.50 (1H, m). This was employed for the next step without further purification.

b) (2S,3R,4S)-Isomer. In the same manner as described above, (2R,3R,4S)-**11c'** (0.54 g, crude) yielded 0.45 g (99 %) of (2S,3R,4S)-**12a'**, $[\alpha]_D^{23}$ -13.8° (c=1.00, $CHCl_3$). The IR and NMR spectra were identical with those of (2R,3S,4R)-**12a**. This was employed for the next step without further purification.

2,4-Dimethyl-3-tetrahydropyranyloxyheptyl toesylate **12b**. a) (2S,3S,4R)-Isomer. p-TsCl (1.20 g, 6.20 mmol) was added to a soln of (2R,3S,4R)-**12a** (1.00 g, 4.10 mmol) in dry pyridine (10 ml) with stirring and ice-cooling. The stirring was continued overnight at 0~5°. The mixture was then poured into ice-water and extracted with ether. The ehter soln was washed with water, sat $CuSO_4$ aq soln and sat $NaHCO_3$ aq soln, dried ($MgSO_4$) and concentrated in vacuo to give 1.54 g (97 %) of (2S,3S,4R)-**12b**, νmax 2950 (s), 2880 (m), 1600 (m), 1460 (m), 1360 (s), 1190 (s), 1180 (s), 1125 (m), 1100 (m), 1080 (m), 1030 (s), 960 (s), 840 (m), 810 (m) cm^{-1}. This was employed for the next step without further purification.

b) (2R,3R,4S)-Isomer. In the same manner as described above, (2S,3R,4S)-**12a'** (0.43 g, 1.76 mmol) yielded 0.620 g (91

%) of (2R,3R,4S)-**12b'**. Its IR spectrum was identical with that of (2S,3S,4R)-**12b**. This was employed for the next step without further purifiction.

2,4-Dimethyl-3-tetrahydropyranyloxyheptyl iodide **13**. a) (2S,3S,4R)-Isomer. A mixture of crude (2S,3S,4R)-**12b** (1.54 g), NaI (1.20 g, 8.00 mmol) and $NaHCO_3$ (1.68 g, 20.0 mmol) in dry DMF (15 ml) was stirred overnight at 50-60°. The mixture was poured into water and extracted with benzene. The benzene soln was washed with water and brine, dried (Na_2SO_4) and concentrated in vacuo to give an oily material. This was submitted to column chromatography (SiO_2, n-hexane:ether) to give 0.472 g (33 %) of (2S,3S,4R)-**13**, n_D^{23} 1.4926; $[\alpha]_D^{25}$ +47.0° (c=1.58, $CHCl_3$); νmax 2960 (s), 2880 (s), 1460 (m), 1380 (m), 1365 (m), 1200 (m), 1130 (s), 1080 (s), 1040 (s), 990 (m), 960 (m), 905 (m), 870 (m), 810 (w), 740 (w) cm^{-1}; δ ($CDCl_3$) 0.70~1.15 (9H, m), 1.15~2.00 (12H, m), 3.20~4.10 (5H, m), 4.30~4.70 (1H, m). This was dried before use for the next step by azeotropic removal of water with dry benzene.

b) (2R,3R,4S)-Isomer. In the same manner as described above, (2R,3R,4S)-**12b'** (0.620 g) yielded 0.315 g (51 %) of (2R,3R,4S)-**13'**, n_D^{23} 1.4806; $[\alpha]_D^{23}$ -36.3° (c=1.39, $CHCl_3$). The IR and NMR spectra were identical with those of (2S,3S,4R)-**13**.

1-(5'-Tetrahydropyranyloxy-2',4',6'-trimethylnonanoyl)-2-hydroxymethylpyrrolidine **15**. a) (2S,2'R,4'R,5'S,6'R)-Isomer. A soln of LDA was prepared from i-Pr_2NH (2.55 ml, 18.1 mmol) and n-BuLi (1.57 N in n-hexane, 5.8 ml, 9.04 mmol) in dry THF (32 ml) under Ar at -10°. Then a soln of (S)-**14** (0.710 g, 4.52 mmol) in dry THF (5 ml) was added dropwise to the mixture. The stirring was continued for 1 h at room temp. HMPA (1.6 ml) was added to the mixture and it was cooled to -100°. To this stirred mixture was added a soln of (2S,3S,4R)-**13** (0.160 g, 0.450 mmol) in dry THF (5 ml) at -100~-95°. The mixture was stirred at this temp for 5 h and then the mixture was left to stand at -80° for 2 days. Water was added to the mixture at -80°. The mixture was then warmed up to room temp. This ewas extracted with ether. The ether soln was washed with water and brine, dried ($MgSO_4$) and concentrated in vacuo to give an oily material. This was chromatographed over SiO_2. Elution with CH_2Cl_2 yielded 0.142 g (82 %) of (2S,2'R,4'R,5'S,6'R)-**15**, νmax 3400 (m), 2960 (s), 2880 (s), 1620 (s), 1460 (s), 1430 (s), 1130 (m), 1080 (s), 1030 (s) cm^{-1}; δ ($CDCl_3$) 0.60~2.20 (31H, m), 2.50~2.90 (1H, m), 3.15~4.60 (9H, m). This was employed for the next step without further purificatin.

b) (2R,2'S,4'S,5'R,6'S)-Isomer. In the same manner as described above, (2R,3R,4S)-**13'** (0.179 g, 0.506 mmol) and (R)-**14'** (0.199 g, 1.27 mmol) yielded 0.029 g (34 % based on the recovery) of (2R,2'S,4'S,5'R,6'S)-**15'**. The IR and NMR spectra were identical with those of (2S,2'R,4'R,5'S,6'R)-**15**. This was employed for the next step without further purification.

Tetrahydro-3,5-dimethyl-6-(1'-methylbutyl)-2H-pyran-2-one (Invictolide) **1**. a) (3R,5R,6S,1'R)-(-)-Isomer. A mixture of (2S,2'R,4'R,5'S,6'R)-**15** (0.140 g, 0.360 mmol) and N HCl aq soln (3 ml) was stirred and heated under reflux for 2 h. After cooling, the mixture was extracted with $CHCl_3$. The $CHCl_3$ soln was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography (n-hexane:ether) to give 57.3 mg (80 %) of (-)-invictolide. This was recrystallized from n-hexane to give colorless needles, m.p. 28.0~28.5°; $[\alpha]_D^{25}$ -101° (c=0.450, $CHCl_3$); GLC (Column, OV-101, 50 m x 0.25 mm at 190°; Carrier gas, N_2, 1.6 kg/cm^2): Rt impurity 22.3 and 25.2 min (4.0 %), (-)-invictolide 22.8 min (96.0 %); νmax (CS_2) 2970 (s), 2945 (s), 2880 (m), 1750 (s), 1382 (m), 1360 (w), 1232 (w), 1192 (s), 1170 (m), 1150 (w), 1125 (m), 1095 (m), 1025 (m), 990 (m) cm^{-1}; ; νmax ($CHCl_3$) 2990 (s), 2960 (s), 2895 (m), 1730 (s), 1460 (m), 1385 (m), 1360 (w), 1200 (s), 1150 (w), 1100 (m), 1025 (w), 980 (m), 720 (m) cm^{-1}; δ (C_6D_6) 0.456 (3H, d, J=6.8 Hz), 0.814 (3H, d, J=6.5 Hz), 0.870 (3H, t, J=7.2 Hz), 0.989 (1H, ddd, J=7, 8, 13.5 Hz), 1.068 (3H, d, J=7 Hz), 1.096~1.300 (3H, m), 1.318~1.443 (3H, m), 1.508 (1H, dddq, J=7.5, 7.5, 10, 7 Hz), 2.040 (1H, ddq, J=8, 9, 7 Hz), 3.442 (1H, dd, J=0.8, 10 Hz); δ ($CDCl_3$) 0.900 (3H, t, J=6.8 Hz), 0.912 (3H, d, J=7 Hz), 0.972 (3H, d, J=6.8 Hz), 1.221 (3H, d, J=7 Hz), 1.23~1.50 (5H, m), 1.668 (1H, ddd, J=8, 8, 8 Hz), 1.707 (1H, dtq, J=2, 7, 7 Hz), 1.988 (1H, dddq, J=8, 8, 10, 6.5 Hz), 2.641 (1H, ddq, J=8, 8, 7 Hz), 3.902 (1H, dd, J=2, 10 Hz). These NMR spectral data were in good accord with those sent to us by Dr. Tumlinson and Prof. Ziegler. (Found: C, 72.40; H, 10.96. Calc for $C_{12}H_{22}O_2$: C, 72.68; H, 11.19 %).

b) (3S,5S,6R,1'S)-(+)-Isomer. In the same manner as described above, (2R,2'S,4'S,5'R,6'S)-**15'** (0.040 g, 0.104 mmol) yielded 13.3 mg (65 %) of (+)-invictolide, m.p. 28.5~29.0°; $[\alpha]_D^{22}$ +101° (c=0.615, $CHCl_3$); GLC (Column, OV-101, 50 m x 0.25 mm at 150°°; Carrier gas, N_2, 1.0 kg/cm^2): Rt impurity 31.4 min (3.0 %), (+)-invictolide 32.3 min (97.0 %); The IR and NMR spectra were identical with those of (-)-invictolide. (Found: C, 72.28; H, 11.15. Calc for $C_{12}H_{22}O_2$: C, 72.68; H, 11.19 %).

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