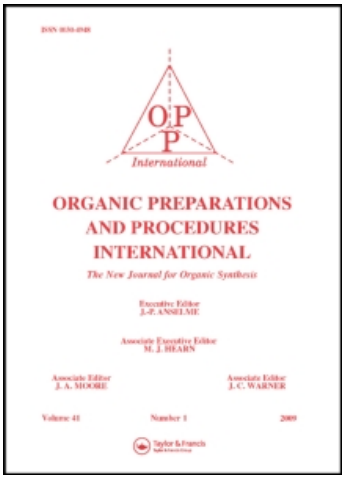

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ENANTIOSELECTIVE SYNTHESIS OF (4R)-4-NONANOLIDE AND (5R)-5-DECANOLIDE FROM A COMMON INTERMEDIATE†

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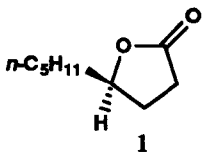
There are many reports on the synthesis of γ- and δ-lactones since they are widely distributed in nature. Some of these lactones are important as insect pheromones and aroma compounds.[1] We now report the enantioselective synthesis of (4R)-4-nonanolide (**1**), an attractant for rice weevil[1a] and of (5R)-5-decanolide (**2**) from a common intermediate, (+)-(2R,3R)-epoxy alcohol (**3**) (Schemes 1 and 2).

The (+) epoxy alcohol (**3**) was prepared through the Sharpless asymmetric epoxidation[2] of E-2 octenol (**4**). Based on the fact that Sharpless' epoxidation makes available a wide variety of either the (2R,3R) or (2S,3S)-α,β-epoxy alcohol in high optical purity, the present work makes it possible to prepare either the R or S enantiomer of a γ-lactone and also either R or S enantiomer of a δ-lactone starting from an appropriate allylic alcohol.



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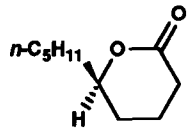

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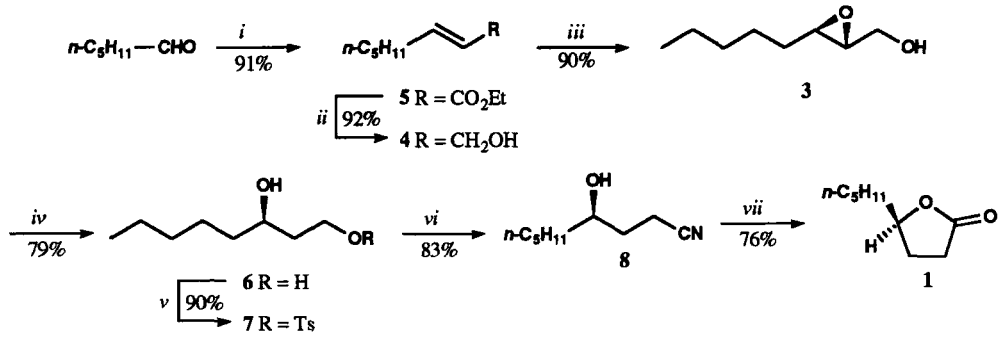
3

Allyl alcohol **4** was prepared from *n*-hexanal (Scheme 1). Sharpless' asymmetric epoxidation of **4** furnished (2R,3R)-epoxy alcohol **3** having 90% e.e.[3] Red-Al reduction[4] of **3** proceeded regioselectively to furnish the 1,3-diol (**6**). The primary hydroxyl group of **6** was selectively tosylated and the one-carbon homologation effected through reaction of the tosylate (**7**) with sodium cyanide. Hydrolysis of the nitrile **8** and subsequent acidification of the resulting γ-hydroxy acid furnished the γ-lactone (+)-(**1**).[5]

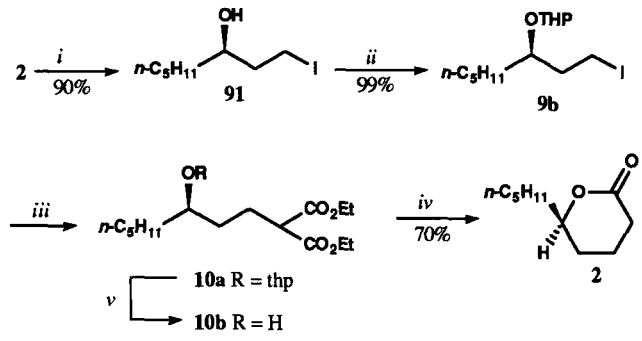
Tosylate **7**, an intermediate of the synthesis of the lactone **1** was also used for the synthesis of the (+)δ-lactone **2** (Scheme 2). It was converted to the iodo compound **9a**, whose hydroxyl group was blocked to give **9b**. Two carbon homologation was carried out on the iodide **9b** by reaction with diethyl malonate in the presence of a base; removal of blocking group furnished the hydroxy ester **10b** which was saponified. Subsequent acidification furnished the (+)δ-lactone **2**.[6]

Scheme 1



i) $(EtO)_2P(O)CH_2CO_2Et$, NaH, ether, rt, 10 hrs; *ii)* DIBAL-H, CH_2Cl_2, 30 min at 0°, 1 hr at 25° ; *iii)* (-)DIPT, $Ti(OiPr)_4$, TBHP, CH_2Cl_2; *iv)* Red-Al, THF; *v)* Tosyl chloride, CH_2Cl_2, NEt_3, DMAP *vi)* NaCN, DMF, NaI; *vii)* NaOH, EtOH, water; then H^+, H_2O

Scheme 2



i) NaI, DMF; *ii)* dihydropyran, pyridinium *p*-toluenesulfonate, CH_2Cl_2 *iii)* $CH_2(CO_2Et)_2$, NaH, DMF; *iv)* NaOH, EtOH, water; then H^+, H_2O *v)* pyridinium *p*-toluenesulfonate, EtOH

EXPERIMENTAL SECTION

The (-)-diisopropyl D-tartrate employed for this study was purchased from E. Merck Company (Schuchardt, Munich) and shows [α] = -16° (neat). Silica gel (60-120 mesh) was used for column chromatography. IR spectra were recorded on a Perkin Elmer 683 spectrometer. ^1H NMR and ^{13}C NMR were determined on a Varian FT-200 spectrometer (200 MHz) using TMS as internal standard and optical rotations were measured on a Jasco DIP 360 digital polarimeter at 25°. The GC analysis were carried out on a Hewlett Packard 5890 unit with 5% SE 30 on CHW column (8'x1/8" i.d.) and FID detector. Temp. of injector: 300°; temp. of detector: 300°; temp. of oven: 200° for 1 min, then 30°/min to 300°. Carrier: N_2; 42 psi.

(2R,3R)-2,3-Epoxyoctan-1-ol (3). Method A.- The ester **5** was prepared in 91% yield starting from 1-hexanal employing the Horner-Emmons reaction and its ^1H NMR spectrum[7] showed that it did not contain the Z-isomer. DIBAL-H reduction of **5** furnished in 92% yield (E)-2-octen-1-ol (**4**). A flask

containing dry CH_2Cl_2 (100 mL) under N_2 was cooled to -23°. To this were added the following reagents sequentially with stirring: i) titanium isopropoxide (9.096 g, 0.032 mole), ii) (-)-diisopropyl D-tartrate (7.496 g, 0.032 mole) and after a gap of 15 min., iii) allylic alcohol (**4**) (4.045 g, 0.032 mole) dissolved in dry CH_2Cl_2 (10 mL) and after a gap of 10 min., iv) anhydrous *tert*-butyl hydroperoxide (5.768 g, 0.064 mole) dissolved in isooctane (10 mL). The reaction mixture was stirred at -23° for 1 hr and kept at -20° for 18 hrs. The product obtained after work-up according to a reported procedure[8] was chromatographed. Elution with 1:9 mixture of ethyl acetate-hexane furnished the epoxy alcohol **3** (4.105 g, 90% yield) which solidified on refrigeration, mp. 31-32°, lit.[9] mp. 34-35°, $[\alpha]_D$ +32° (c, 1.3, $CHCl_3$). This sample showed 90% e.e.[3] ^1H NMR ($CDCl_3$): δ 0.90 (t, J = 7Hz, 3H), 1.2-1.7 (m, 8H), 2.80-2.95 (m, 2H), 3.58 (m, 1H) and 3.87 (m, 1H).

Method B.- This procedure is based on the work of Hanson *et al.*[10] A mixture of powdered molecular sieves 4Å (0.102 g, E. Merck) and 10 mL of dichloromethane was cooled to -10°. (-)Diisopropyl D-tartrate (0.071 g, 0.3 mmole), titanium isopropoxide (0.056 g, 0.2 mmole) and *tert*-butyl hydroperoxide (0.718 g, 8 mmoles) in isooctane were added sequentially. After 20 min the mixture was cooled to -20° and (E)-2-octen-1-ol (**4**) (0.510 g, 4 mmoles) dissolved in dry CH_2Cl_2 (2 mL) was added dropwise with stirring. After 3 hrs of stirring at -20° the reaction mixture was brought to 0° and quenched with water. The product obtained after workup was purified by chromatography; elution with 1:9 mixture of ethyl acetate-hexane furnished the epoxy alcohol **3** (0.492 g, 86% yield), mp. 33-34°, $[\alpha]_D$ +33° (c, 1.5, $CHCl_3$). The sample showed 92% e.e. After two recrystallizations from *n*-hexane the e.e. was raised to >96%.

(R)-1,3-Octanediol (6).- A mixture of (+)**3** having 90% e.e. (3.45 g, 0.024 mole) in THF (80 mL) and sodium bis (2-methoxyethoxy) aluminium hydride (Red-Al) (14.11 mL, 3.4 M) in toluene was stirred at -20° under N_2 for 4 hrs and at 25° for 2 hrs. The product obtained after work-up was chromatographed. Elution with 1:4 mixture of ethyl acetate-hexane afforded the diol (**6**) (2.75 g, 79% yield); $[\alpha]_D$ +2° (c, 2.07, $CHCl_3$); purity: 97%; GC = t_{ret}: 3.43 min. (**6**). ^1H NMR ($CDCl_3$): δ 0.87 (t, J = 7Hz, 3H), 1.28-1.72 (m, 10H), 2.8 (s, 2H, disappears after D_2O exchange), 3.85 (m, 3H).

Anal. Calcd. for $C_8H_{18}O_2$: C, 65.71; H, 12.41. Found.: C, 65.98; H, 12.25

(R)-3-Hydroxyoctanyl Tosylate (7).- Tosylation of **6** (2.21 g, 0.015 mole) with tosyl chloride (3.47 g, 0.018 mole), triethylamine (3.83 g, 0.038 mole) and 4-dimethylaminopyridine (0.050 g) in (CH_2Cl_2 (40 mL) was carried out at 0° for 50 hrs. The resulting tosylate was chromatographed using 1:99 mixture of ethyl acetate-hexane as eluent to furnish **7** (4.10 g, 90% yield). ^1H NMR ($CDCl_3$): δ 0.90 (t, J = 7Hz, 3H), 2.46 (s, 3H), 3.17 (m, 1H), 4.05-4.35 (m, 2H). 7.36 (d, J = 10Hz, 2H), 7.80 (d, J = 10Hz, 2H).

Anal. Calcd. for $C_{15}H_{24}SO_4$: C, 59.98; H, 8.05. Found: C, 59.71; H, 7.92

(R)-3-Hydroxyoctyl Cyanide (8).- A mixture of the tosylate **7** (1.20 g, 4.01 mmoles), N,N'-dimethylformamide (12 mL), NaCN (0.393 g, 8.02 mmoles) dissolved in water (2 mL) and NaI (1.32 g, 8.81 mmoles) was heated at 110° for 3 hrs. The product obtained after work-up was chromatographed. Elution with 1:9 mixture of ethyl acetate-hexane gave the hydroxy nitrile **8** (0.516 g, 83% yield). IR (film): 3380, 2230 cm^{-1}. ^1H NMR($CDCl_3$): δ 0.90 (t, J = 7Hz, 3H), 1.10-2.00 (m,

1H), 2.50 (t, J = 7Hz, 2H), 3.70 (m, 1H).

Anal. Calcd. for $C_9H_{17}NO$: C, 69.63; H, 11.04. Found: C, 69.54; H, 10.89

(4R)-4-Nonanolide (1).- A mixture of nitrile **8** (0.509 g, 3.28 mmoles), ethanol (5 mL) and NaOH (1.31 g, 33.0 mmoles) dissolved in water (1 mL) was heated under reflux for 8 hrs diluted with water (10 mL) and most of the ethanol was removed under vacuum. The residue was acidified with HCl and extracted with ethyl acetate (10 mL x 3). The product obtained after work-up was purified by chromatography using 1:9 mixture of ethyl acetate-hexane as eluent to afford the γ-lactone **1**[11] (0.389 g, 76% yield), $[\alpha]_D$ +42° (c, 1.0, MeOH), lit.[5b] $[\alpha]_D$ +47.2° (1.0, MeOH). The identity of **1** was established by comparing its GC, IR and ^1H NMR with those of an authentic sample of racemic γ-nonanolide; purity: 98%; GC = t_{ret}: 6.34 min (**1**). IR (film): 1770 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.88 (t, J = 7Hz, 3H), 1.10-2.55 (m, 12H), 4.42 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 13.6, 22.2, 24.6, 27.7, 28.9, 31.2, 35.2, 81.1, 177.7.

Anal. Calcd. for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.47; H, 10.19

(R)-3-Hydroxy-1-iodooctane (9a).- A mixture of tosylate **7** (1.80 g, 6.0 mmoles), NaI (2.25 g, 15 mmoles) and dry DMF (10 mL) was stirred at 50-60° for 5 hrs. The product obtained after work-up was chromatographed. Elution with 1:99 mixture of ethyl acetate-hexane afforded the iodo compound **9a** (1.381 g, 90% yield), $[\alpha]_D$ -28° (c, 1.28, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.92 (t, J = 6Hz, 3H), 1.10-2.10 (m, 10H), 3.31 (t, J = 7Hz, 2H), 3.70 (m, 1H).

Anal. Calcd. for $C_8H_{17}IO$: C, 37.51; H, 6.69. Found:C, 37.43; H, 6.48

1-Iodo-3-octyl 2-tetrahydropyranyl Ether (9b).- The iodo compound **9a** (1.301 g, 5.08 mmoles) was reacted with dihydropyran in the presence of pyridinium *p*-toluenesulfonate to furnish the ether **9b** (1.718 g, 99% yield).

Anal. Calcd. for $C_{13}H_{25}IO_2$: C, 45.89; H , 7.40. Found: C, 45.75; H, 7.32

Ethyl 2-Ethoxycarbonyl-5-hydroxydecanoate (10b).- Diethyl malonate (1.214 g, 7.57 mmoles) in DMF (5 mL) was added slowly to a stirred suspension of NaH (0.182 g, 7.58 mmoles) in dry benzene (8 mL) and dry DMF (10 mL) under N_2. After 30 min the iodo compound **9b** (1.718 g, 5.05 mmoles) in DMF (5 mL) was added. The reaction mixture was heated at 100° for 8 hrs. Workup furnished a mixture of **10a** and diethyl malonate; the THP blocking group in **10a** was removed by treatment with pyridinium *p*-toluenesulfonate in ethanol at 55° for 4 hrs and the product after work-up was chromatographed. The fraction eluted with 1:9 mixture of ethyl acetate-hexane furnished the hydroxy ester **10b** (1.189 g, 82% yield for the two step conversion of **9b**→**10a**→**10b**), $[\alpha]_D$ -4° (c, 2.56, $CHCl_3$); purity: 99%; GC: t_{ret}: 5.25 min (**10b**). ^1H NMR ($CDCl_3$): δ 0.90 (t, J = 7Hz, 3H), 1.28 (t, J = 7Hz, 6H), 3.36 (t, J = 7 Hz, 1H), 3.62 (m, 1H), 4.20 (q, J = 7Hz, 4H).

Anal. Calcd. for $C_{15}H_{28}O_5$: C, 62.47; H, 9.79. Found: C, 62.21; H, 9.58

(+)-(R)-5-Decanolide (2).- A mixture of hydroxy ester **10b** (1.09 g, 3.78 mmoles), NaOH (1.515 g, 37 mmoles) and methanol (10 mL) was heated under reflux for 2 hrs cooled to rt, diluted with water and acidified. The product obtained after work-up was chromatographed. Elution with 1:9 mixture of ethyl acetate-hexane gave the δ-lactone **2** (0.450 g, 70% yield), $[\alpha]_D$ +48° (c, 1.0, MeOH), lit.[1a] $[\alpha]_D$

+55.6° (MeOH); purity: 95%; GC: t_{ret}: 7.82 min (**2**). IR (film): 1720 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.90 (t, *J* = 7Hz, 3H), 1.20-2.70 (m, 14H), 4.30 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 13.9, 18.4, 22.5, 24.6, *27.7*, 29.4, 31.5, 35.7, 80.6 and 172.0.

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66. Found: C, 70.78; H, 10.51

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