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SYNTHESIS OF BOTH THE ENANTIOMERS OF 4-DODECANOLIDE, THE PHEROMONE OF THE ROVE BEETLE

S.Chattopadhyay, V.R.Mamdapur* and M.S.Chadha

Bio-Organic Division, B.A.R.C., Bombay-400 085, India.

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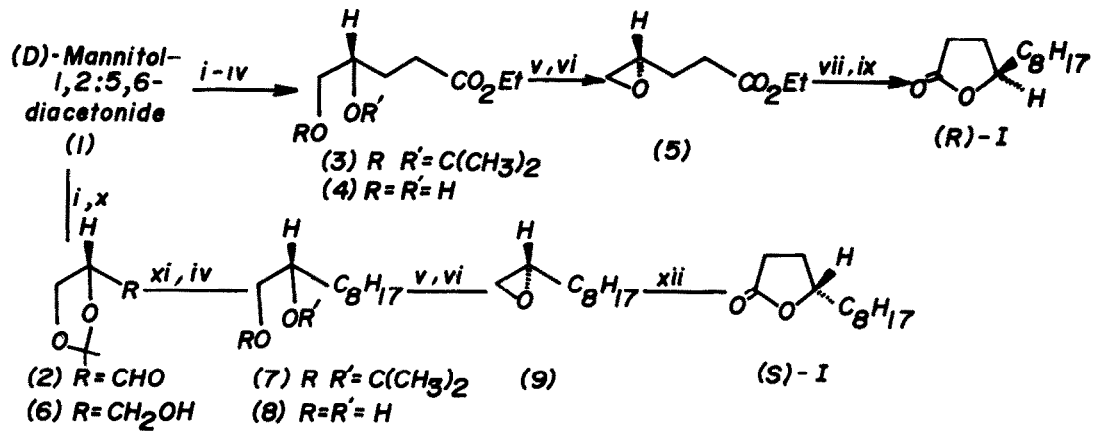
Abstract: A simple and efficient synthesis of the target pheromone in its enantiomeric forms has been formulated using easily accessible (R)-2,3-isopropanedioxyglyceraldehyde (2) as the single starting chiron.

Compounds with chiral lactone function occupy important positions both as target bioactive molecules and useful synthons in total synthesis and hence attracted the attention of synthetic organic chemists. One such γ-lactone, 4-dodecanolide(I) constitutes[1] the active defensive principle of the rove beetles, Bledious mandibularis and B. spectabilis and is also found in fruits[2] and butterfats[3]. Its absolute configuration is still obscure. The existing syntheses[4] of I involved use of difficultly accessible reagents or stringent reaction conditions. Hence we felt the need to develop a simple and efficient synthesis of optically pure (R) and (S)-I in sufficient quantity using chiron approach. Incidentally this is the first synthesis of I employing chiral pool.

The chiron(2), obtained[5-7] in high optical purity from naturally available (D)-mannitol-1,2:5,6-bisacetonide(1), offers sufficient flexibility to allow useful synthetic manoeuvers because of its highly functionalised small C-skeleton. The above feature along with the required chiral carbinol centre present in it prompted us to use the aldehyde (2) in the present synthesis. The salient features of the route were sequential introduction of the required alkyl chain and the acetate equivalents at both the reactive terminals of 2 to furnish (R)- and (S)-I respectively (SCHEME).

For the synthesis of (R)-I, the chiron (2) was subjected[8] to in situ Wittig-Horner olefination with triethyl phosphonoacetate to furnish an intermediate α,β-unsaturated ester in excellent yield. Its catalytic hydrogenation over 10% Pd-C afforded the ketalester (3). Acidic hydrolysis of its ketal

function, selective monotosylation of the resultant diol (4) and subsequent base treatment led to the desired epoxide (5). Regioselective coupling at the epoxy site of 5 with lithium diheptylcuprate yielded a C_{12}-hydroxy ester which was converted to (R)-I by alkaline hydrolysis and subsequent acidification.



(i) $NaIO_4/NaHCO_3$, (ii) $(EtO)_2P(O)CH_2CO_2Et/Na_2CO_3$, (iii) H_2/10% Pd-C/EtOH, (iv) eq. HCl/THF, (v) p-TsCl/Py, (vi) NaOMe/$CHCl_3$, (vii) $(C_7H_{15})_2CuLi$/ether/-78° (viii) NaOH/EtOH/aq. (ix) H, (x) $NaBH_4$/MeOH, (xi) $C_7H_{15}MgBr/CuBr.Me_2S$ (xii) $NaCH(COOEt)_2$/dimethylacetamide/ $MgCl_2$, $6H_2O$/Δ

SCHEME– I

For the synthesis of its antipode, 2 was reduced with sodium borohydride to obtain the alcohol(6). Its tosylation and subsequent coupling with heptylmagnesium bromide in the presence of CuBr,Me_2S[9] produced the ketal (7) in good yield. This was converted to the epoxide (9) via the diol (8) as described for 5. This epoxide (9) on reaction with sodium diethyl malonate in dimethylacetamide followed by in situ decarbethoxylation with $MgCl_2 . 6H_2O$[10] directly afforded (S)-I by simultaneous lactonisation.

Recently Hirth et al[11] have determined the optical purity of (S)-3 and measured its $[\alpha]_D$-value. Based on those data, the optical purity of 3 prepared by us was assessed to be ≈98%. Later during the course of the synthesis we have neither altered its chirality nor have we used any racemising reaction conditions, hence our synthetic pheromones should also be of same optical purity. This has also been substantiated by comparison of their $[\alpha]_D$

-values with those reported[11] for enatiomerically pure samples.

EXPERIMENTAL:

All b.ps and m.ps are uncorrected. IR spectra were recorded on a Perkin-Elmer model 783 spectrophotometer. PMR spectra were scanned on a Varian 80 FT 80 MHz instrument in $CDCl_3$ solvent using TMS as the internal standard. Optical rotations were measured on a Perkin-Elmer 243 polarimeter. The purities of the liquid samples were checked by GLC analysis on a Shimadzu GC-7A chromatogram using a 3% OV-17 on Gas-chrome Q (80-100) column.

Ethyl(S)-4,5-isopropanedioxypentanoate (3): Following reported[8] procedure, 1 (5.0g, 0.019mol) was converted to an intermediate α,β-unsaturated ester using $NaIO_4$ (4.9g, 0.023mol) and triethyl phosphonoacetate (8.4ml, 0.042mol). Yield 6.5g (84%); b.p.78-84°/10mm, (lit[8]. 80-90°/13mm); IR (film): 1715, 1640 and 970 cm^{-1}.

The above ester (6.0g, 0.03mol) was catalytically hydrogenated over 10% Pd-C in ethanol (60ml) to furnish 3. Yield 5.4g (90%); b.p. 90-92°/10mm, (lit[8]. 100-10°/13mm); $[\alpha]_D^{22}$ -4.63° (c 2.38,MeOH), (lit[8]. $[\alpha]_D^{18}$ -4.75° (c 2.02, MeOH); IR (film): 1740 cm^{-1}; PMR : δ 1.25 (t,3H,J=6Hz,$-CO_2CH_2CH_3$), 1.37 & 1.43 (two s,3H each,$-C(CH_3)_2$), 1.5-1.9 (m,2H) 2.3-2.6 (m,2H,$-CH_2CO_2Et$), 3.50 (d,2H,J=7Hz,$-CH_2O-$), 3.6-4.2 (m containing a q at δ 4.12,J=6Hz,3H, -CHO-, $-CO_2CH_2CH_3$). Anal. calcd. for $C_{10}H_{18}O_4$: C, 59.41; H, 8.91. Found C, 59.22; H, 9.12.

Ethyl(S)-4,5-dihydroxypentanoate (4): A solution of the ester (3) (4.5g, 0.022mol) in THF (30ml) containing aqueous HCl (10ml, 2M) was stirred at ambient temperature. After completion of the reaction, the acid was carefully neutralised with $NaHCO_3$ (S) at 0°, most of the solvent was removed under vaccuo and the residue extracted with ethyl acetate. Usual isolation furnished 4 which was found to be sufficiently pure (cf. TLC and spectral data) and hence used as such in the next step. Yield 2.7g (76%); IR (film): 3350, 1740 and 1060 cm^{-1}; PMR : δ 1.36 (t,3H,J=6Hz,$-CO_2CH_2CH_3$), 1.6-2.4 (m,4H) 2.62 (bs,2H,D_2O exchangeable,2x-OH), 3.68 (d,2H,J=7Hz,$-CH_2OH$), 4.0-4.3 (m containing a q at δ 4.12,J=6Hz,3H,$-CH(OH)-$,$-CO_2CH_2CH_3$).

Ethyl(S)-4,5-epoxypentanoate (5): To a magnetically stirred and cooled (0°) solution of 4 (2.5g, 0.015mol) in $CHCl_3$ (20ml) containing pyridine (1.5ml, 0.019mol) was added a solution of p-TsCl (2.9g, 0.015mol) in $CHCl_3$ (10ml).

The mixture was stirred at the same temperature for 1 hr and kept overnight -10°. It was then poured in ice-cold water, the organic layer separated and washed successively with 2N aqueous HCl, water, 10% aqueous $NaHCO_3$, water and brine. After drying, the solvent was removed to afford the monotosylate which was purified by "flash-chromatography" over neutral alumina (grade II). Yield 3.6g (76%); IR (film): 3450, 1740, 1640, 1480, 1180, 880 and 820 cm^{-1}.

To a solution of NaOMe in absolute EtOH (20ml) [prepared from Na-metal (0.27g, 0.012g.atom)] was added a solution of the monotosylate (3.6g, 0.011mol) in $CHCl_3$ (15ml) at 0°. Immediately a heavy precipitate settled. After stirring for 0.5 hr, it was carefully neutralised with CO_2 (S), poured into water and extracted with $CHCl_3$. Usual isolation led to 5. Yield 1.31g (80%); $[\alpha]_D^{21}$ -17.6° (c 6.8,$CHCl_3$); IR (film): 1740 and 1120 cm^{-1}; PMR : δ 1.36(t,3H,J=6Hz,$-CO_2CH_2CH_3$), 1.6-1.8 (m,2H), 2.1-2.4 (m,5H,$-CH_2CO_2Et$, ) 4.08 (q,J=6Hz,2H,$-CO_2CH_2CH_3$). Anal. calcd. for $C_7H_{12}O_3$: C, 58.33; H, 8.33. Found C, 58.14; H, 8.56.

(R)-γ-Dodecanolide (I): A solution of heptyl lithium in anhydrous ether (50ml) [prepared from Li-metal (0.84g, 0.12mol) and n-bromoheptane (8.9g, 0.05mol)] was dropwise added to a well cooled (-40°) and stirred suspension of CuI (4.76g, 0.025mol) in ether (10ml). After ≈15min. all the CuI had dissolved producing a grey solution of the corresponding lithium dialkylcuprate. Then it was cooled further to -78° (dry ice-acetone bath) and a solution of 5 (1.2g, 0.008mol) in ether (10ml) was injected into it. It was stirred for 2 hr at -78°, 1 hr at -40° and 2 hr at ambient temperature. The reaction was quenched with aqueous NH_4Cl at 0°, the ethereal layer separated, washed with water, brine and dried. After removal of solvent, the residue was taken in alcoholic KOH solution (30ml,2M) and stirred for 4 hr. The reaction mixture was extracted with ethyl acetate, the aqueous layer separated, carefully acidified with conc. HCl under ice-cold condition and reextracted with ether. The ether extract was with washed water, brine and dried. Removal of solvent followed by column chromatography over silica gel furnished pure (R)-I. Yield 0.96g (60%); b.p 133-36°/0.3mm, (lit[4]. b.p. 125°/0.55m); $[\alpha]_D^{23}$ +37.9° (c 1.24, MeOH), (lit[4]. $[\alpha]_D^{20}$ +39.0° (c 1.03, MeOH); IR (film): 1790 cm^{-1}; PMR: δ 0.86 (t,3H,J=7Hz,CH_3-), 1.31 (bs,16H,8x-CH_2-), 2.1-2.6 (m,2H, $-CH_2CO_2$-), 4.2-4.6 (m,1H). Anal.calcd. for $C_{12}H_{22}O_2$: C, 72.73; H, 11.11. Found, C, 72.54; H, 11.34.

(S)-2,3-Isopropanedioxyglycerol (6): Following reported procedure[6,7], 1 (10.0g, 0.038mol) was converted to 6 via the aldehyde (2). Yield 3.7g (73%); b.p. 86-88°/10mm, (lit[11] b.p. 82°/13.0mm); $[\alpha]_D^{22}$ +14.83° (neat), (lit[11]. $[\alpha]_D^{20}$ +15.14° (neat)); IR (film): 3420 and 1020 cm^{-1}; PMR: δ 1.38 & 1.40 (two s,each 3H,$-C(CH_3)_2$), 2.64 (bs,1H,D_2O exchangeable,-OH), 3.4-3.8 (m,5H). Anal.calcd. for $C_{10}H_{22}O_2$: C, 68.97; H, 12.64. Found C, 68.72; H, 12.88.

(S)-1,2-Isopropanedioxydecane (7): The compound 6 (2.0g, 0.015mol) was tosylated with p-TsCl (3.5g, 0.018mol) in presence of pyridine (1.5ml, 0.018mol) in $CHCl_3$ (30ml). The tosylate was purified by rapid column chromatography (neutral alumina, grade II, 0-20% EtOAc in hexane). Yield 3.47g (81%); IR (film): 1640, 1180, 1020 and 880 cm^{-1}.

Then a Grignard reagent was prepared from n-bromoheptane (3.2g, 0.018mol) and magnesium turnings (0.52g, 0.022mol) in anhydrous THF (30ml). It was cooled to -40°, CuBr.Me_2S (2 mol%) was introduced in it followed by slow addition of a solution of the above tosylate (3.47g, 0.012mol) in THF (20ml) at the same temperature. It was stirred at -40°, 2 hr at 0° and kept overnight at room temperature. Usual workup and isolation afforded an yellow oil which after column chromatography (neutral alumina, grade II, 0-10% ether in hexane as eluent) yielded pure 7. Yield 1.85g (72%); PMR: δ 0.86 (t,3H,J=6Hz,CH_3-), 1.24 (bs,14H,7x-CH_2-), 1.38 and 1.40 (two s,each 3H,. -$C(CH_3)_2$), 3.5-3.9 (m,3H,-CH_2O-,-CHO-). Anal.Calcd. for $C_{13}H_{26}O_2$: C, 72.90; H, 12.15. Found, C, 72.77; H, 12.01.

(S)-1,2-Dihydroxydecane (8): Following the procedure already described, the acetonide(7) (1.8g, 0.008mol) was hydrolysed with aqueous HCl to furnish the diol as a viscous liquid which was crystallised from ether-hexane as a white solid. Yield 1.35g (92%) m.p. 48-50°, (lit[12]. m.p. 53-54°); $[\alpha]_D^{22}$ -12.2° (c 0.586,MeOH), (lit[12]. $[\alpha]_D^{22}$ -11.9° (c 0.431,MeOH); IR (film): 3440 and 1060 cm^{-1}; PMR:δ 0.86 (t,3H,J=6Hz,-CH_3), 1.22 (bs,14H,7x-CH_2-), 3.55 (d,2H,J=6Hz,. -CH_2OH), 3.8-4.1 (m,1H,-CH(OH)-), 4.16 (bs,2H,D_2O exchangeable,2x-OH).

(S)-1,2-Epoxydecane (9): Following the procedure already described, the diol 8 (2.6g, 0.015mol) was converted to 9 (1.46g) in 63% yield. b.p. 80-84°/50mm, (lit[4]. 111-12°/34mm); $[\alpha]_D^{23}$ -14.7° (c 1.44, ether), (lit[4]. $[\alpha]_D^{17}$ -14.1° (c 1.11, ether); PMR: δ 0.86 (t,3H,J=6Hz,CH_3-), 1.32 (bs,14H,7x-CH_2-), 2.2-2.5 (m,3H,-  -CH_2).

(S)-γ-Dodecanolide (I): To a well stirred suspension of NaH (1.3g, 0.027mol,

50% suspension in oil) in dimethylacetamide (40ml) was added a solution of diethyl malonate (4.32g, 0.027mol) in the same solvent. Stirring was continued for 0.5 hr followed by addition of 9 (1.4g, 0.009mol) in dimethylacetamide (10ml). The reaction mixture was refluxed for 3 hr. Then, $MgCl_2.6H_2O$ (1.8g, 0.009mol) was added into it and the reaction mixture heated to 140° for 20 hr. It was cooled to room temperature, poured in ice-water and the aqueous layer was extracted with ether. The organic extract was washed with water, brine and dried. Removal of solvent and subsequent column chromatography of the residue over silica gel (0-15% EtOAc in hexane) furnished pure (S)-I. The spectral data of (S)-I were identical to those of its antipode. Yield 1.1g (62%); b.p. 130-32°/0.3mm, (lit[4]. b.p. 111°/0.25mm); $[\alpha]_D^{23}$ -37.0° (c 1.18, MeOH), (lit[4].$[\alpha]_D^{18}$ -37.8° (c 1.04, MeOH). Anal.Calcd. for $C_{12}H_{22}O_2$: C, 72.73; H, 11.11. Found, C, 72.96; H, 11.01.

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