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STEREOSELECTIVE SYNTHESIS OF OPTICALLY ACTIVE DISPARLURE, THE PHEROMONE OF THE GYPSY MOTH (*PORTHETRIA DISPAR* L.)

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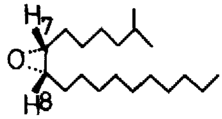
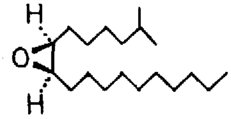
Disparlure (*cis*-7,8-epoxy-2-methyloctadecane) is the sex pheromone produced by the female gypsy moth, *Porthetria dispar* L.[1] Although several syntheses of its racemate have been reported,[2] there exist only one synthesis of the optically active forms (1 and 2) of disparlure.[3] However, the synthesis was not stereoselective and the final product was contaminated with at least 5.8% of its enantiomer.[3]

As a part of our efforts to synthesize optically active insect pheromones, we undertook a synthesis of optically active disparlure. This work resulted in the preparation of optically pure (>98%) disparlure enantiomers in quantities (>1g) sufficient for wind tunnel bioassays, EAG and field tests.[4]

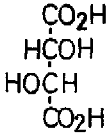
The (2*S*:3*S*)-*threo* configuration of L-(+)-tartaric acid (3) was particularly favorable for its use in disparlure synthesis. The elongation of the carbon chain and discrimination of the two hydroxyl groups were the major problems in the present synthesis. These were solved in the following manner. L-(+)-Tartaric acid (3) was converted to the known tosylate (4) as described previously.[5] This was treated with i-Am$_2$CuLi in ether (-78°, 2h; -78∼-30°)[6] to give a dimethoxy ester (5) in 65% yield, bp 107°/0.75mm, n_D^{24} 1.4327; $[\alpha]_D^{26}$ -15.8° (c=4.5, CHCl$_3$)[7]. Demethylation of 5 with excess BCl$_3$ in CH$_2$Cl$_2$ (-60°∼-20°, 2h; quenching with MeOH at -50°) gave a hydroxylactone (6) in 56.5% yield after recrystallization from i-Pr$_2$O-hexane, mp 53∼54°, $[\alpha]_D^{23}$ -56.7° (c=2.0, CHCl$_3$). This lactonization discriminated the γ-hydroxyl group from the β. The corresponding tetrahydropyranyl (THP) ether (7) was reduced with i-Bu$_2$AlH(THF-PhMe 1:1,-50°,1h)



1
(7R:8S)



2
(7S:8R)



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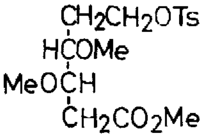

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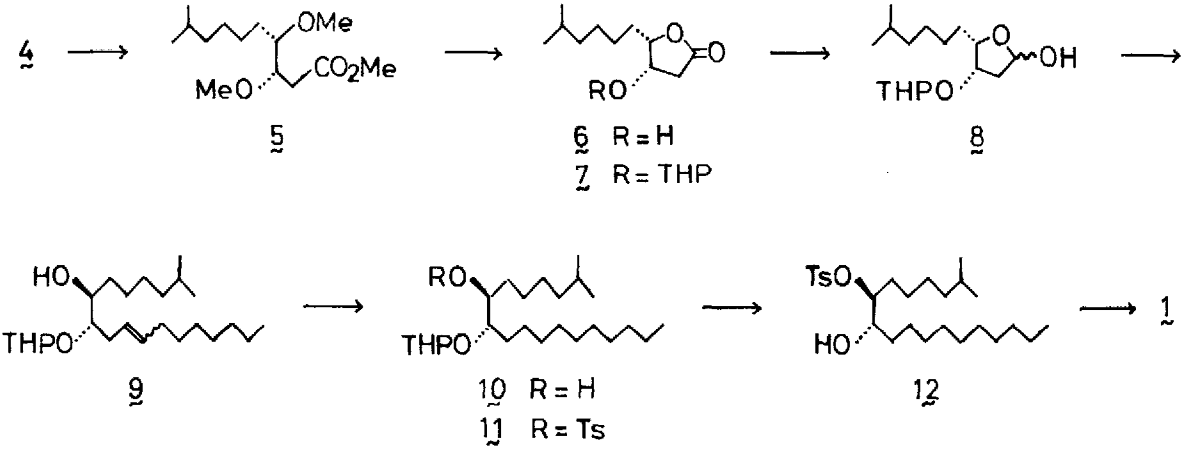

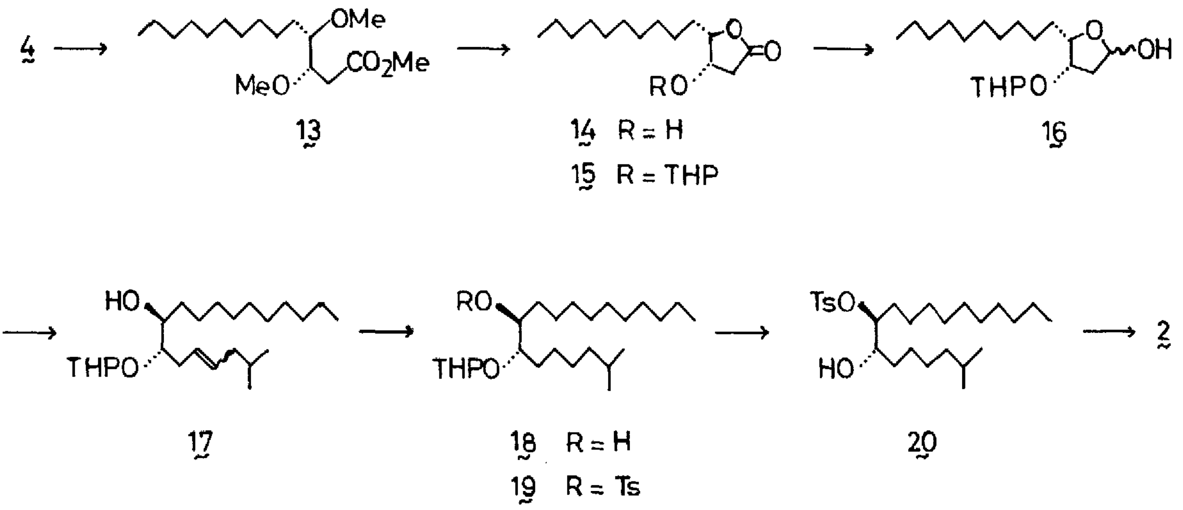

to give a lactol 8 in a quantitative yield, $[\alpha]_D^{23}$-25.9° (c=2.6, $CHCl_3$). This was treated with a phosphorane derived from *n*-$C_8H_{17}PPh_3Br$ and *n*-BuLi in THF (room temp, overnight) to yield a mixture of geometric isomers of the olefin 9 in 69% yield. Hydrogenation of 9 over Pd-C (EtOH) gave 10 in 90% yield,$[\alpha]_D^{23}$ -25.2° (c=2.1, $CHCl_3$). This was tosylated (TsCl/C_5H_5N, 2 days at room temp) to give 11 in 78% yield, $[\alpha]_D^{23}$-31.3° (c=2.2, $CHCl_3$). Removal of the THP protecting group of 11 (TsOH/MeOH, room temp, overnight) gave a crystalline tosyloxy alcohol (12) in 67% yield after recrystallization from hexane. Further recrystallization gave pure 12, mp 42-43°,$[\alpha]_D^{23}$-13.1° (c=4.1, $CHCl_3$). (7*R*:8*S*)-(+)-Disparlure (1) was obtained in 85% yield (1.43g) by the ring closure of 12 with 0.25N-KOH-MeOH (0~5°, 1h), bp 134~135°/0.55mm, n_D^{23}1.4450; $[\alpha]_D^{23}$+0.8°±0.1° (c=6.0, CCl_4); ν_{max} (film) 2965 (sh.), 2930 (vs), 2870 (vs), 1475 (s), 1398 (m), 1378 (m), 1280 (w), 1180 (w), 1020 (w), 940 (w), 920(w), 880(w), 840(sh.), 830 (w), 810(sh.), 760(w), 730(w)cm^{-1}; δ(CCl_4, 100MHz) 0.87 (6H, d, J=6Hz), 0.88 (3H, t, J=6Hz), 1.0~2.0 (27H), 2.67 (2H, br. s), *Anal*. Found: C, 80.86; H, 13.44%. These spectral data were identical with those of (±)-disparlure.

(-)-Disparlure was prepared in a similar manner by changing the order of the introduction of the alkyl groups. Thus the tosylate (4) was treated with $(n\text{-}C_8H_{17})_2CuLi$ to give 13 (73.5%), bp 126-127°/0.5mm, n_D^{23} 1.4390; $[\alpha]_D^{23}$ -15.2° (c=2.2, $CHCl_3$). Its demethylation with BCl_3 gave a crystalline hydroxylactone 14 (44%) after recrystallization from Et_2O-*i*-Pr_2O, mp 80.5~81°,$[\alpha]_D^{24}$ -48.0° (c=2.0, $CHCl_3$). The corresponding THP ether 15 was reduced with *i*-Bu_2AlH to give a lactol 16 (94%), $[\alpha]_D^{23}$ -54.7° (c=2.4, $CHCl_3$). The Wittig reaction between 16 and isoamylene triphenylphosphorane in THF gave 17 (90%). This was hydrogenated to 18 (90%), $[\alpha]_D^{23}$ -47.0° (c=2.2, $CHCl_3$). The corresponding tosylate (19) was treated with TsOH-MeOH to give a crystalline tosyloxy alcohol (20) in 76% yield after recrystallization from hexane. Further recrystallization gave pure 20, mp 48.5~49.0°,$[\alpha]_D^{23}$ -14.3° (c=2.0, $CHCl_3$). (7*S*:8*R*)-(-)-Disparlure (2) was obtained by the ring closure (KOH/MeOH) of 20 in 90% yield (1.01g), bp 134~135°/0.55mm, n_D^{23} 1.4450; $[\alpha]_D^{23}$-0.6°±0.1° (c=6.0, CCl_4). The spectral data were identical with those of (±)- and (+)-disparlures. GLC analysis

(Carbowax 20M, 20m x 0.28 mm i.d., 170°) revealed our **1** and **2** to be of 99.3 and 98.6% purities, respectively. Their retention times were identical with that of the racemate.

Since the crystalline nature of **12** and **20** enabled their purifications by repeated recrystallization, the optical purities of our disparlure enantiomers were considered to be high. This was supported by the NMR analysis of (*S*)-(-)-MTPA (α-methoxy-α-trifluoromethylphenylacetic acid) ester[8] of **20**. The optical purity of **20** was thought to be > 98%. Details will be described in the forthcoming full paper which will appear in *Agr. Biol. Chem.*

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3. S. Iwaki, S. Marumo, T. Saito, M. Yamada, K. Katagiri, *J. Am. Chem. Soc.*, **96**, 7842 (1974).
4. The biological studies are under way in Prof. W.L. Roelofs' and Prof. J.P. Vité's laboratories. Prof. Vité's field test in Germany revealed the high attractancy of (+)-disparlure, while very few gypsy moths were attracted by the (-)-isomer. Offered in a higher proportion than the antipode, (-)-disparlure drastically lowered the moths'response. (J.P. Vité, D. Klimetzek, G. Loskant, R. Hedden and K. Mori, *Naturwissenschaften*, in press.)
5. K. Mori, *Tetrahedron*, **30**, 4223 (1974).
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7. Satisfactory spectral and analytical data were obtained for all the compounds described in this paper.
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