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TERPENES IN ORGANIC SYNTHESIS.

8.* SYNTHESIS OF OPTICALLY ACTIVE (2R/S, 3S, 7R/S)-(−)-DIPRIONYL ACETATE FROM (S)-(+)-3,7-DIMETHYL-1,6-OCTADIENE

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Coniferous sawflies of the *Diprion* and *Neodiprion* species (*Hymenoptera; Diprionidae*) damage pine forests, causing defoliation of the crowns and weakening the trees. Several syntheses have been described (for the most recent, see [2]) of racemic mixtures of all possible stereoisomers of 2-acetoxy-3,7-dimethylpentadecane (I), the sex attractant of sawflies, which is suitable for reducing sawfly populations in forests. Optically active forms of (I) have also been obtained which are configurationally homogeneous at C^2 and C^3 [3, 4], or at all three chiral centers of the pheromone [5-7]. Tests on various *Diprion* and *Neodiprion* species have shown that of the eight possible stereoisomers of (I), attractant activity is shown only by the (2S, 3S, 7S)-enantiomer (Ia) [3, 8, 9]. The (2S, 3S, 7S)-enantiomer (Ib) is synergistic with this [9], the remaining six enantiomers being inactive [3, 8, 9]. We here describe the synthesis of (2R/S, 3S, 7R/S)-diprionyl acetate (Ic), i.e., a four-component mixture of (Ia), (Ib) and the inactive (2R, 3S, 7S)- and (2R, 3S, 7R)-enantiomers, from the available (S)-(+)-3,7-dimethyl-1,6-octadiene (II).

The monoepoxide obtained from (II) was treated without purification with Et_2NLi in a mixture of ether and heptane at the boil for 10 h, to give 78% [calculated on (II)] of (3R/S, 6S)-2,6-dimethyl-1,7-octadien-3-ol (III), which was readily converted into the acetate (IV) on treatment with acetic anhydride and triethylamine in the presence of catalytic amounts of 4-dimethylaminopyridine (DMAP). Reaction of (IV) with the organocuprate reagent obtained from $n\text{-}C_7H_{15}Br$ by successive treatment with magnesium and CuI in dry THF (−10 to 20°C, 6 h)

*For previous communication, see [1].

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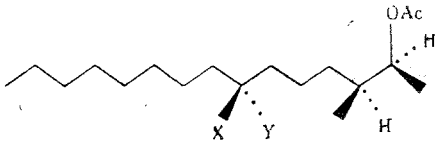
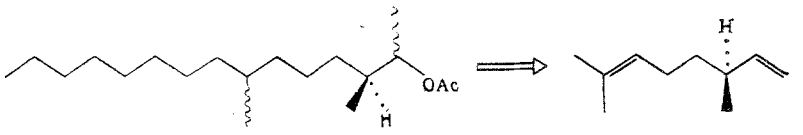


(Ia,b)



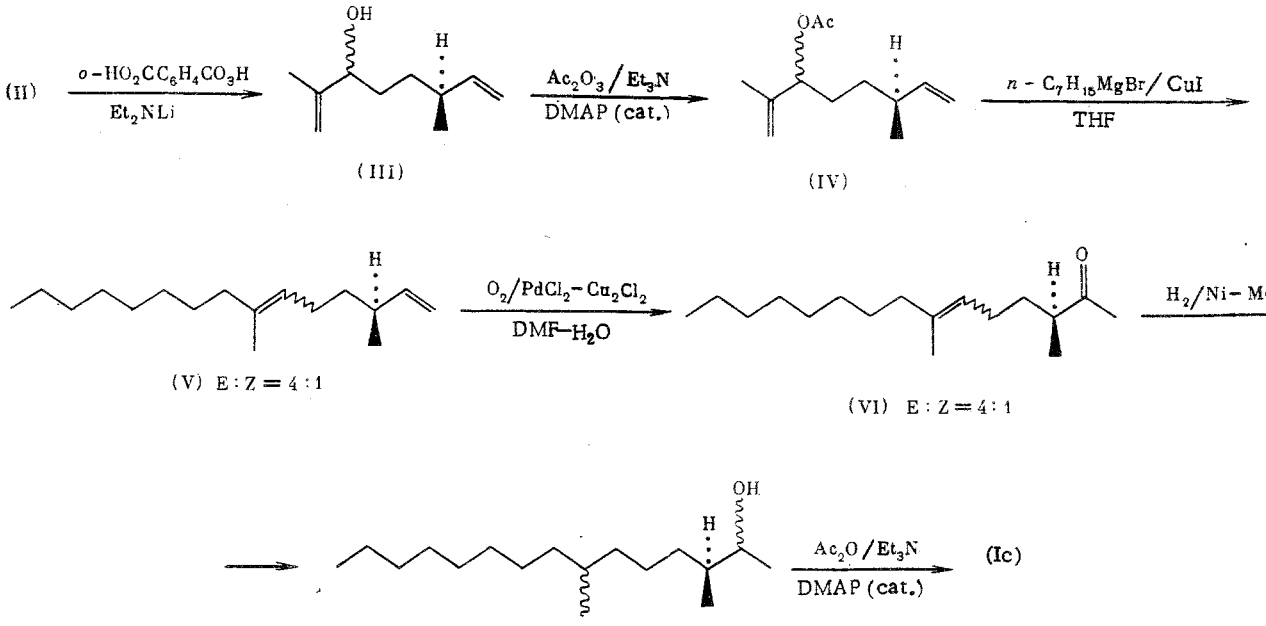
(Ic) (II)

X = Me, Y = H(Ia); X = H, Y = Me(Ib).

afforded 84% of (3S, 6E/Z)-3,7-dimethyl-1,6-pentadecadiene (V), thus completing assembly of the carbon skeleton of (I).

The terminal double bond in the diolefin (V) on Walker–Tsudzi oxidation was converted into the unsaturated ketone (VI) in 70% yield, exhaustive hydrogenation of which over skeletal nickel in methanol (23°C, 5 atm. H_2, 7 h) gave (2R/S, 3S, 7R/S)-3,7-dimethyl-2-pentadecanol (VII) in 96% yield. Acetylation of (VII) under the conditions used for the synthesis of (IV) afforded the required product (Ic) in 92% yield. The overal yield of (Ic) from II) in seven steps was 36%. The sign of the optical rotation of (Ic) was the same as that of the natural attractant (Ia) and its synergist (Ib).

This synthetic method is not stereospecific with respect to the chiral centers at C^2 and C^7, since on hydrogenation of the unsaturated ketone (VI) the (2S, 3S)-erythro-isomers (Ia) and (Ib) are formed together with the inactive (2R, 3S)-threo-isomers, as shown by capillary GLC of the alcohol (VII) and the PMR spectra of (VII) and (Ic) (see Experimental). This drawback is to some extent compensated for by the simplicity, small number of steps, and the completeness of the utilization of the chiral precursor (II), which is wholly incorporated into (I).



EXPERIMENTAL

All boiling points are uncorrected. The purity of the products was checked by TLC on Silufol plates, and by GLC on a capillary column (30 m × 0.3 mm) with 0.15% OU-101 (column A) or XE-60 (column B) as the stationary phase (Biokhrom-1 instrument). PMR spectra were obtained in deuterochloroform on a Bruker WH-250 (250 MHz) instrument, and IR spectra in CCl_4 on a UR-20 instrument. The $[\alpha]_D$ values were measured in chloroform on an AI-EPO polarimeter.

Alcohol (III). To a solution of a 23 g of technical dihydromyrcene in 25 ml of ether, containing according to GLC ~0.10 mole of pure (S)-(+)-diolefin (II), was added dropwise with stirring at 0°C 100 ml of a 1.0 M solution of monoperphthalic acid in ether. The mixture was kept for 24 h at 20°C, the phthalic acid which separated was filtered off, the filtrate washed with 10% aqueous $NaHCO_3$, water, and saturated aqueous sodium chloride, and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue [(II) monoepoxide] dissolved in 60 ml of dry ether and treated dropwise with stirring with a solution of Et_2NLi (from 220 ml of a 0.9 M solution of n-C_4H_9Li in hexane and 14 g of diethylamine in 10 ml of dry ether). The mixture was boiled for 10 h, cooled, decomposed with water, the organic layer separated, and the aqueous layer extracted with ether. The combined organic solutions were washed with 10% hydrochloric acid, 10% sodium bicarbonate, water, and saturated aqueous sodium chloride, dried over magnesium sulfate, and evaporated under reduced pressure. Distillation of the residue gave the pure alcohol (III), bp 56°C (2 mm), $n_D^{23.5}$ 1.4539, $[\alpha]_D^{24}$ +3.5° (c 10), τ_R 13.6 min (column A, 80°C, helium pressure 2.4 atm). Yield 12 g (78%). IR spectrum (ν, cm^{-1}): 3360, 3080, 2970, 2880, 1640, 1460, 1380, 1320, 1060, 1030, 1000, 910. PMR spectrum (δ, ppm, J, Hz): 0.96 d (3H, CH_3–C^6, J = 7), 1.00-1.60 m (4H, CH_2CH_2), 1.66 s (3H, CH_3–C^3), 2.09 m (1H, H–C^6), 2.37 s (1H, OH), 3.97 t (1H, H–C^9, J = 6), 4.75-5.0 m (4H, H_2–C^1 and H_2–C^8), 6.63 m (1H, H–C^7). Found, %: C 77.51; H 11.38. $C_{10}H_{18}O$. Calculated, %: C 77.86; H 11.76.

(3R/S, 6S)-3-Acetoxy-2,6-dimethyl-1,7-octadiene (IV). To a mixture of 6.2 g (40 mmoles) of (III), 4.8 g of acetic anhydride, and 18 ml of triethylamine in 60 ml of dry dichloromethane was added 0.1 g of DMAP, and the mixture kept for 48 h at 20-25°C. It was then decomposed with water and extracted with ether. The organic layer was washed with saturated aqueous solutions of $CuSO_4$, $NaHCO_3$, and NaCl, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was filtered through a thin layer of silica gel, and distilled in vacuo to give the acetate (IV), bp 54°C (1.5 mm), n_D^{24} 1.4402, $[\alpha]_D^{24}$ +2.6°C (c 6), τ_R 24.6 min (column A, 80°C, helium pressure 2.4 atm). Yield 7.1 g (90%). IR spectrum (ν, cm^{-1}): 3085, 2965, 2940, 2880, 1740, 1640, 1460, 1375, 1240, 1060, 1023, 912. PMR spectrum (δ, ppm, J, Hz): 0.98 d (3H, CH_3–C^6, J = 7), 1.1-1.75 m (4H, CH_2CH_2), 1.70 s (3H, CH_3-C^2), 2.06 s (3H, CH_3CO), 2.10 m (1H, H-C^6), 4.85-5.00 m (4H, H_2–C^1 and H_2–C^8), 5.14 t (1H, H–C^3, J = 6,5), 5.65 m (1H, H–C^7). Found, %: C 73.49; H 10.25. $C_{12}H_{20}O_2$. Calculated, %: C 73.43; H 10.27.

Diolefin (V). To a Grignard reagent [from 5.4 g (30 mmoles) n-$C_7H_{15}Br$ and 0.75 g (31 mg·atom) Mg in 24 ml abs. TGF] stirred at −10°C under argon, was added 1.9 g (10 mmoles) (IV) in 8 ml TGF; this was stirred at for 2 h at −10°C and for 4 h at 20°C after which the mixture was treated with saturated aqueous NH_4Cl and extracted with ether. The extract was washed with 10% $NaHCO_3$, H_2O and saturated aqueous NaCl, dried over $MgSO_4$ and evaporated. By distillation of the residue in vacuo, (V) was obtained in the form of a mixture of 6E- and 6Z-isomers (4:1), bp 115-120°C (1.5 mm), n_D^{23} 1.4415, τ_R 12.6 min (Z-isomer) and 14.6 min (E-isomer) (column A, 150°C, helium pressure 2.5 atm). Yield 2.0 g (84%). IR spectrum (ν, cm^{-1}): 3080, 2960, 2930, 2860, 1640, 1470, 1380, 1080, 1000, 910, 730. PMR spectrum (δ, ppm, J, Hz): 0.90 t (3H, H_3–C^{15}, J = 6.5), 1.01 d (3H, CH_3–C^3, J = 6.5), 1.28 br. s (14H, CH_2), 1.59 s and 1.68 s (3H, CH_3–C^7, ratio of intensities ~4:1), 1.97 m (4H, H_2–C^5 and H_2–C^8), 2.14 m (1H, H–C^3), 4.95 m and 5.70 m (3H, multiplet for the grouping CH_2=CH–), 5.11 t (1H, H–C^6, J = 6).

(3S)-3,7-Dimethyl-6-pentadecen-2-one (VI). A mixture of 0.96 g (4 mmoles) of (V), 1.6 g of Cu_2Cl_2, and 0.32 g of $PdCl_2$ in 24 ml of DMF and 2 ml of water was stirred in an atmosphere of oxygen for 24 h at 20-25°C, then extracted with 100 ml of dichloromethane. The extract was washed with 10% hydrocloric acid (3 × 40 ml) and water, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was dissolved in 10 ml of hexane, filtered through a funnel with ~1 g of silica gel, and the hexane removed under reduced pressure to give a colorless liquid (VI), ratio of 6E- to 6Z-isomers 4:1, n_D^{24} 1.4451, $[\alpha]_D^{23}$ +2.6° (c 2.5), τ_R 27.6 min (Z-isomer) and 31.0 min (E-isomer) (column A, 150°C, helium pressure

2.4 atm). Yield 0.78 g (70%). IR spectrum (ν, cm^{-1}): 2960, 2930, 2860, 1715, 1460, 1380, 1360, 1160, 1120, 1075, 955. PMR spectrum (δ, ppm, J, Hz): 0.87 t (3H, H_3–C^{15}, J = 6.5), 1.07 d (3H, CH_3–C^3, J = 6.5), 1.0-1.8 m (14H, CH_2), 1.55 s and 1.65 s (3H, CH_3–C^7), 1.95 m (4H, H_2–C^5 and H_2–C^8), 2.10 s (3H, CH_3CO), 2.50 m (1H, H–C^3), 5.05 t (1H, H–C^6, J = 6). Found, %: C 80.45; H 12.91. $C_{17}H_{32}O$. Calculated, %: C 80.88; H 12.78.

Alcohol (VII). A solution of 0.75 g of (VI) in 10 ml of methanol was hydrogenated in a rocking autoclave in the presence of 0.15 g of skeletal nickel at 23°C and a hydrogen pressure of 5 atm until take-up of hydrogen ceased (7 h). The mixture was filtered, and the filtrate evaporated under reduced pressure to give the alcohol (VII) as a colorless, oily liquid, n_D^{24} 1.4501 and $[\alpha]_D^{24}$ −3.7° (c 1.5), which on GLC on column A behaved as a homogeneous compound, τ_R 41.6 min (150°C, helium pressure 2.4 atm), but on column B as a mixture of erythro- and threo-isomers in a ratio of ~1:1 (τ_R 24.1 and 24.6 min, 170°C, helium pressure 1.3 atm). Yield 0.73 g (96%). IR spectrum (ν, cm^{-1}): 3340, 2960, 2930, 2860, 1460, 1380, 1300, 1160, 1100, 1060, 1000, 920, 885, 720. PMR spectrum (δ, ppm; J, Hz): 0.85 t (3H, H_3–C^{15}, J = 6.5), 0.87 d (3H, CH_3–C^7, J = 6.5), 0.89 d (3H, CH_3–C^3, J = 6.5), 1.11 d (1.5 H, erythro-CH_3–C^2, J = 6.5), 1.14 d (1.5H, threo-CH_3–C^2, J = 6.5), 1.26 br. s (22H, CH_2 and CH), 1.57 s (1H, OH), 3.67 m (1H, H–C^2). Found, %: C 79.67; H 14.11. $C_{17}H_{36}O$. Calculated, %: C 79.61; H 14.15.

(2R/S, 3S, 7R/S)-2-Acetoxy-3,7-dimethylpentadecane (Ic). To a mixture of 0.14 g (0.5 mmole) of (VII), 0.12 ml of acetic anhydride, and 0.5 ml of triethylamine in 4 ml of dry dichloromethane was added 3 mg of DMAP (catalyst). The mixture was kept for 30 h at 20-25°C, diluted with water and extracted with ether (3 × 20 ml). The organic layer was extracted with saturated aqueous solutions of $CuSO_4$ and NaCl, dried over magnesium sulfate, and evaporated under reduced pressure. The residue was dissolved in 5 ml of hexane and filtered through a funnel with 0.3 g of neutral alumina (activity grade II/III). Removal of the hexane gave (2R/S, 3S, 7R/S)-diprionyl acetate (Ic) as a colorless, oily liquid, n_D^{24} 1.4389, $[\alpha]_D^{24}$ −3.3° (c 2.5), τ_R 17.7 min (column A, 180°C, helium pressure 2.4 atm) GLC of the mixture on a capillary column (OV-275, 180°C) failed to separate the erythro- and threo-isomers. Yield 0.15 g (92%). IR spectrum (ν, cm^{-1}): 2960, 2940, 2860, 1740, 1460, 1380, 1260, 1160, 1110, 1080, 1050, 1020, 960, 850, 730. PMR spectrum (δ, ppm, J, Hz): 0.85 t (3H, H_3–C^{15}, J = 7), 0.87 d (3H, CH_3–C^7, J = 7), 0.89 d (3H, CH_3–C^3, J = 7), 1.14 d and 1.16 d (total 3H, CH_3–C^2, erythro/threo = 1:1, J = 7), 0.90-1.70 m (22H, CH_2 and CH), 2.02 s (3H, CH_3CO), 482 m (1H, H–C^2). Found, %: C 76.18; H 12.95. $C_{19}H_{38}O_2$. Calculated, %: C 76.45; H 12.83. The IR and PMR spectra of (Ic) were identical with those given in the literature [2-7]. The pure (2S, 3S, 7S)-enantiomer (Ia) has $[\alpha]_D$ −5.76° [3], and the pure (2S, 3S, 7R)-enantiomer (Ib), $[\alpha]_D$ −6.18° [3]. The amounts of these components present in the sample of (Ic) were close to 50%, in accordance with the GLC analysis of the alcohol (VII) on column B, and the PMR spectra of the alcohol (VII) and the product (Ic).

CONCLUSIONS

A seven-stage synthesis has given optically active (2R/S, 3S, 7R/S)-2-acetoxy-3,7-dimethylpentadecane from the readily available (S)-(+)-3,7-dimethyl-1,6-octadiene, in an overall yield of 36%. The synthetic route utilizes all ten carbon atoms of the starting chiral diene.

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