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SYNTHESIS OF THE SEX-ATTRACTANT OF PINE SAWFLIES (DIPRION SPECIES); (2S,3R,7R)- AND (2S,3R,7S)-3,7-DIMETHYLPENTADECAN-2-OL

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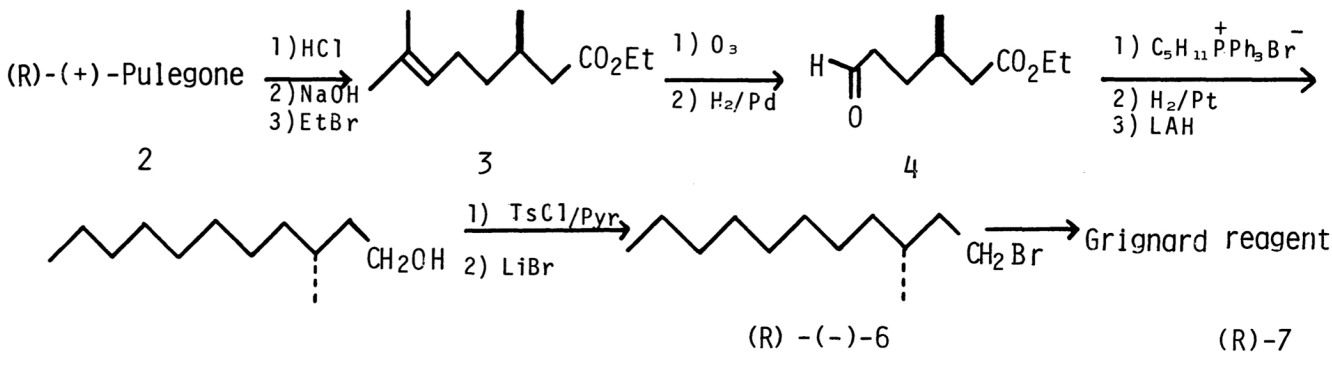
In order to establish the stereochemistry of the sex attractant of *diprion* species of pine sawflies, two candidate epimers, (2S,3R,7R)- and (2S,3R,7S)-3,7-dimethylpentadecan-2-ol were synthesized by the coupling reaction of optically active C_5 and C_{12} units. The C_{12} units, (R)-(-)- and (S)-(+)-1-bromo-2-methylundecane were prepared from (R)-(+)-pulegone. The C_5 unit, (2R,3S)-2-methyl-3-tetrahydropyranoxy-1-tosyloxybutane was derived from (2S,3S)-2-methyl-3-hydroxybutyric acid prepared by the reported procedure.

The sex attractant of several species of pine sawflies was proposed to be acetate or propionate of 3,7-dimethylpentadecan-2-ol (1).[1] Since the compound has three chiral centers in the molecule, it was also expected that stereochemistry as well as ester moiety could bring species recognition among sympatric pine sawflies.

The field assays of acetate and propionate of (2R,3R,7R/S)-(+)-, (2S,3S,7R/S)-(-)-, (2R,3S,7R/S)-(-)- and (2S,3R,7R/S)-(+)-1, synthesized by our group clearly showed that *neodiprion* species responded only to acetate of (2S,3S)-1[2] whereas *diprion* species did only to propionate of (2S,3R)-1.[3] (2S,3S,7S)-, (2S,3S,7R)-, (2R,3R,7R)- and (2R,3R,7S)-1 were synthesized [4)5)] and the major attractant of *neodiprion* was stereochemically established as the acetate of (2S,3S,7S)-1.[6] As for *diprion* species, the stereochemistry of 7-position is still open. This situation prompted us to synthesize (2S,3R,7R)- and (2S,3R,7S)-1.

The synthetic procedures consist of the preparations of optically pure C_{12} unit and C_5 unit and their couplings.

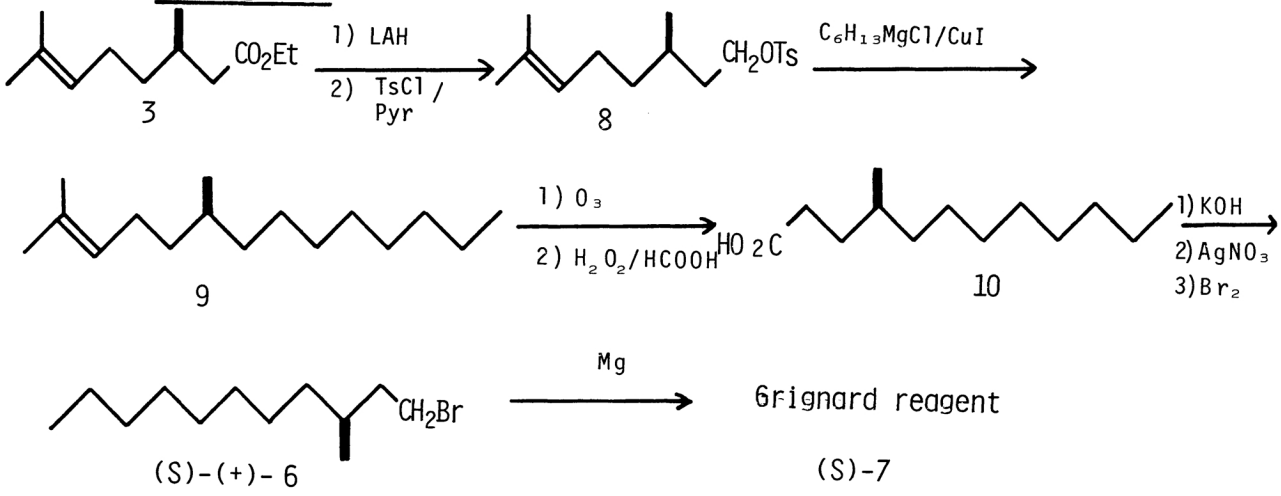
Scheme 1 (R)-C_{12}-unit



Chiral C_{12} units, (R)- and (S)-6, were prepared from (R)-(+)-citronellic acid[7] ($[\alpha]_D^{20}$ + 8.89 (± 0.01°, neat), lit[8] $[\alpha]_D^{25}$ + 8.48 (neat)) derived from (R)-(+)-pulegone (2) ($[\alpha]_D^{20}$ + 21.97 (± 0.01°, neat)) supplied by courtesy of Takasago Perfume Industry Co. The procedure for the preparation of (R)-6 is shown in scheme 1. The ethyl ester(3) of citronellic acid was ozonized in methanol. The hydrogenation of the ozonide over Pd-black gave 4 in quantitative yield based on 3, bp 124 °C/20 mmHg, GLC (2.5% PEG 20M/ 3% $AgNO_3$, 2m x 3mm, 150 °C), a single peak, $[\alpha]_D^{20}$ + 4.01 (±0.04°, c 5.0, methanol), NMR ($CDCl_3$, TMS), δ 9.79 (1H for -CHO, s), IR (neat), 1720 and 1740 cm^{-1} for aldehyde and ester groups. The (R)-(+)-aldehyde (4) was added dropwise to the Wittig reagent prepared from amyltriphenylphosphonium bromide and C_4H_9Li. The reaction mixture was refluxed for 2 hr and filtered on Celite. The filtrate was subjected to chromatography on silica gel (Wakogel C-100) column to give (R)-(+)-ethyl 3-methyl-6-undecenoate in yield of 29.5%, bp 91.5 °C/1.5 mmHg, $[\alpha]_D^{20}$ + 0.24 (± 0.03°, c 5.4, hexane). The hydrogenation of the above ester over PtO_2 gave the saturated ester, which was reduced with $LiAlH_4$ to give the alcohol (5) in quantitative yield, bp 138 °C/15 mmHg, GLC (3% OV-17, 3m x 3mm, 150 °C) a single peak, $[\alpha]_D^{20}$ + 4.80 (±0.03°, c 5.1, hexane), IR (neat), 3300 and 1380 cm^{-1} for the hydroxyl group. The bromination of 5 through tosylate gave (R)-(-)-6 in yield of 70%, bp 99-100°C/5 mmHg, GLC (3% OV-17, 3m x 3mm, 170 °C), 96% purity with 4% unidentified impurity, $[\alpha]_D^{20}$ -4.07 (±0.04°, c 4.9, hexane),[9] lit.[4] $[\alpha]_D^{22}$ - 2.16 (±0.02°, neat). The (R)-(-)-6 was led to the corresponding Grignard reagent in THF-ether (1:2) right before the coupling reaction.

The procedure for the preparation of (S)-6 is shown in scheme 2. The reduction of 3 with $LiAlH_4$ gave the corresponding alcohol, $[\alpha]_D^{20}$ + 5.43 (±0.01°, neat), lit.[8] $[\alpha]_D^{20}$ + 5.37 (neat), which was then converted to tosylate (8).

Scheme 2 (S)-C_{12}-unit

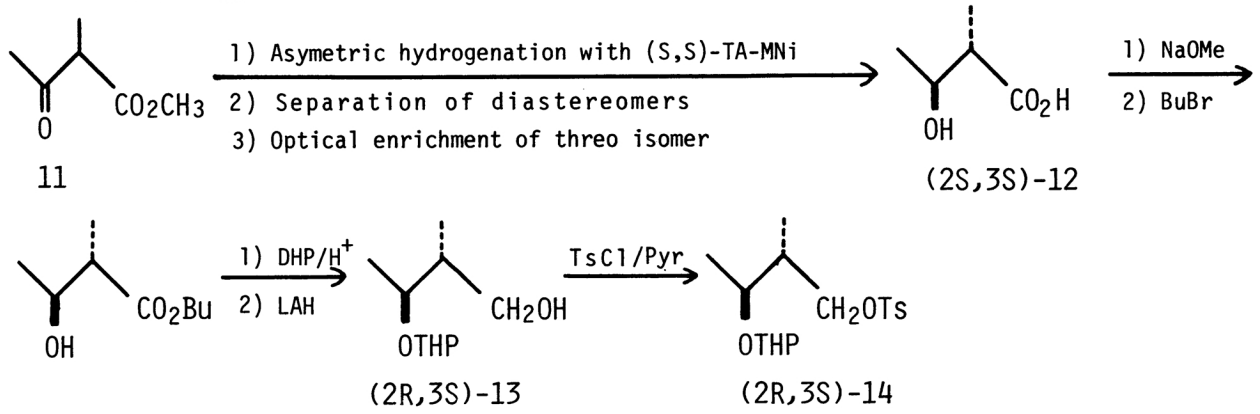


The coupling of 8 with $C_6H_{13}MgCl$ in the presence of CuI gave 80.1% of 9, bp 134-140 °C/13 mmHg, $[\alpha]_D^{20}$ - 1.67 (±0.03°, c 5.5, hexane), lit.[4] $[\alpha]_D^{21.5}$ - 1.26 (± 0.02°, neat). The ozonolysis of 9 in CH_2Cl_2 and oxidative cleavage of the ozonide with H_2O_2/ HCOOH gave 10 in yield of 89.5%, bp 130-134 °C/1.5 mmHg, $[\alpha]_D^{20}$ - 0.60 (±0.03, c 5.3, hexane), IR (neat), 3300-2500 cm^{-1} and 1700 cm^{-1}. The Hunsdiecker reaction[10] of 10 gave 84.6% of (S)-(+)-6, bp 90-93 °C/3 mmHg, GLC (3% OV-17, 3m x 3mm, 170 °C), 95% purity, $[\alpha]_D^{20}$ + 4.04 (±0.04°, c 4.5, hexane),[9] lit.[4] $[\alpha]_D^{21}$ + 2.29 (±0.01° neat). (S)-(+)-6 was led to the corresponding Grignard reagent in THF-ether (1:2) right before

the use for the coupling reaction.

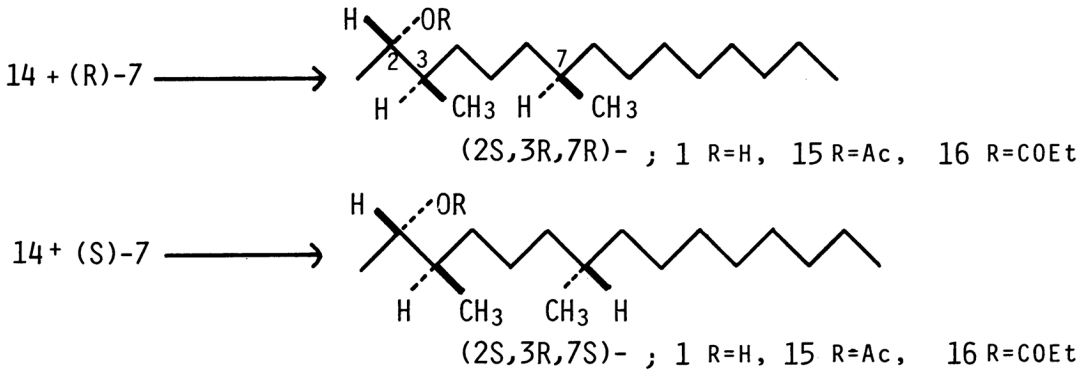
C_5 unit was prepared from methyl 2-methyl-3-oxobutyrate (11) by the method reported before.[11),12)] The hydrogenation of 11 over the nickel catalyst modified with (S,S)-tartaric acid ((S,S)-TA-MNi) gave a mixture of (+)-threo- and (-)-erythro-methyl 3-hydroxy-2-methylbutyrate in a ratio of 35 to 65. The optical purity of each diastereomer was 60%. The separation of diastereomers and the optical enrichment of the threo isomer gave optically pure (2S,3S)-3-hydroxy-2-methylbutyric acid (12) in overall yield of 9% based on 11. The resulting acid (12) was converted to 14 by the conventional methods as shown in scheme 3.

Scheme 3 C_5-unit



The Grignard coupling of 7 and 14 and the following work up were carried out by the published procedure as shown in scheme 4.[13)] The coupling of (R)-(-)-7 and 14 gave (2S,3R,7R)-1 in yield of 84.4% based on 14, bp 116 °C/0.5 mmHg, GLC (3% OV-17, 3m x 3mm, 210°), 96% purity, $[\alpha]_D^{20}$+16.03 (±0.03°, c 5.2, hexane),[9)] IR (neat),[9)] 3370, 1465 and 1380 cm^{-1}, NMR ($CDCl_3$, TMS),[9)] δ 0.85 (9H, m), 1.12 (3H, d, J=6.4 Hz), 1.26 (22H), 3.6 (1H, m). It was showed to be completely free from (2S,3S)-isomer on the capirally GLC[14)] and NMR analyses of this sample.

Scheme 4 C_5-unit + C_{12}-unit



(2S,3R,7S)-1 was prepared by the coupling of (S)-(+)-7 and 14 as mentioned above in yield of 80% based on 14, bp 113-117 °C/0.5 mmHg, $[\alpha]_D^{20}$ + 16.36 (±0.04°, c 3.5, hexane).[9)] The IR,NMR and GLC retention time on the OV-17 column were indistinguishable with those of (2S,3R,7R)-1.

Those compounds were converted to the corresponding acetates (15) and propionates (16). Analyses of (2S,3R,7R)-15, $[\alpha]_D^{20}$ + 6.97 (±0.04°, c 1.7, hexane),[9)] and (2S,3R,

7S)-15, $[\alpha]_D^{20}$ + 6.39 (±0.03°, c 4.9, hexane),[9] gave indistinguishable results with respect to the IR, NMR and GLC on OV-17 column. Furthermore, diastereomeric purity on C-2 and C-3 and enantiomeric purities on C-2 of these compounds were examined by capillary GLC (PEG 20M, 50m x 0.25mm, 140°) and ^{1}H-NMR with chiral shift reagent, respectively. The capillary GLC and ^{1}H-NMR indicated that both (2S,3R,7R)-15 and (2S,3R,7S)-15 were free from (2S,3S, 7R/S)-15. The NMR taken in the presence of chiral shift reagent showed that the samples were optically pure.[15]

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7) Diastereomeric mixture of amide prepared from citronellic acid and racemic α-methyl benzylamine was resolved by GLC (Capillary column OV-101, 50m x 0.25mm,flow rate 0.93 ml/min). Retention times of (R*,S*)- and (R*,R*)-isomer were 69.4 min and 71.4 min respectively at 170 °C. The amide of citronellic acid used in this study with (S)-α-methyl benzylamine ($[\alpha]_D^{20}$-39 (neat), Aldrich Co.) showed essentially a single peak on the GLC under the same condition as above. When the sensitivity of GLC analysis and the purity of the amine used were taken into account, the optical purity of citronellic acid was estimated to be more than 98%.
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14) (2S,3R)-1 and its isomer (2S,3S)-1 can be separated by capillary GLC (PEG 20M, 50m x 0.25mm, 130 °C,flow rate 0.93 ml/min). The retention times of the former and the later were 15.8 min and 15.2 min.
15) C_1-methyl protons of (2S,3R,7R/S)-15 and that of (2R,3S,7R/S)-15 showed different chemical shift in NMR with chiral shift reagent.[3] The difference of chemical shift was 0.05 ppm when NMR spectra were measured with the solution of the sample (8 mg); a mixture of (2S,3R,7R/S)-15 and (2R,3S,7R/S)-15, and $Eu(hfmc)_3$ (10 mg) in $CDCl_3$ (0.4 ml). As for (2S,3R,7R)-15 and (2S,3R,7S)-15, no detectable signals of antipoed were observed.

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