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Transformation of esters into allyl halides via substituted cyclopropanols. Application in the synthesis of (2*S*,3*R*,7*R*/*S*)-3,7-dimethyltridec-2-yl acetate and propionate, sex attractants of pine sawfly *Diprion pini*

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Abstract—A convenient new approach to the synthesis of the acetate and the propionate of (2*S*,3*R*,7*R*/*S*)-3,7-dimethyltridecan-2-ol, sex attractants of *Diprion pini* L., using the cyclopropanation of the ethoxycarbonyl group in *O*-THP protected ethyl (*S*)-lactate with ethylmagnesium bromide in the presence of titanium(IV) isopropoxide followed by C-2–C-3 cyclopropane ring opening as the key steps has been performed.

Pine sawfly *Diprion pini* L. is a widely spread severe pest on conifers, the sex pheromone of which has been identified as the acetate (**1-COMe**) and the propionate (**1-COEt**) of (2*S*,3*R*,7*R*)-3,7-dimethyltridecan-2-ol **1**.[1] Enantiomerically pure (2*S*,3*R*,7*R*)-3,7-dimethyltridecan-2-ol **1** was synthesized starting from (3*R*,4*R*)-3,4-dimethyl-γ-butyrolactone, which was obtained in 10 steps from (2*R*,3*R*)-tartaric acid.[1] (2*S*,3*R*,7*R*/*S*)-3,7-Dimethyltridecan-2-ol **1** is also of practical interest, because esters of (2*S*,3*R*,7*S*)-3,7-dimethyltridecan-2-ol **1** do not inhibit the biological activity of the natural pheromone.[2] Recently, Hedenstrom et al. have performed a synthesis of (2*S*,3*R*,7*R*/*S*)-3,7-dimethyltridecan-2-ol **1** using stereoselective enzymatic acylation of racemic *threo*-3,7-dimethyltridecan-2-ol **1** to create the required stereochemistry at C-2 and C-3 carbon atoms.[3] In the present work a new convenient approach to the synthesis of **1** starting from ethyl (*S*)-lactate has been performed.

For the preparation of organic compounds with methyl or methylene substituents, it is sometimes convenient to use a three-membered ring cleavage in an appropriate cyclopropanol precursor.[4] Thus, C-1–C-3 bond cleavages in the three-membered cycle of 1,2-disubstituted cyclopropanols leading to the corresponding α-methyl ketones, were successfully used in short syntheses of racemic pheromones of the German cockroach *Blattella germanica* and mixobacterium *Stigmatella aurantiaca*.[5,6] In the present work, to create the methyl-branched skeleton of (2*S*,3*R*,7*R*/*S*)-3,7-dimethyltridecan-2-ol **1**, we have used an alternative approach based on the transformation of mesylates of cyclopropanols into 2-substituted allyl halides accompanied by C-2–C-3 bond cleavage of a three-membered ring.[7]

To obtain the key (2*S*)-3-(bromomethyl)but-3-en-2-ol **2** we used ethyl (*S*)-lactate **3**, which was transformed into the corresponding THP derivative **4** (Scheme 1). The ester **4** was reacted with ethylmagnesium bromide in the presence of Ti(O*i*-Pr)$_4$[8] to form cyclopropanol **5** in a high yield.[9] The latter was transformed into mesylate **6** by a standard procedure. When treated with $MgBr_2$, the crude mesylate **6** underwent cationic cyclopropyl–allyl isomerization with C-2–C-3 bond cleavage of the cyclopropane ring.[7] This reaction was performed in a diethyl ether/chloroform mixture, and was accompanied by removal of the THP protecting group[10] to form (2*S*)-3-(bromomethyl)but-3-en-2-ol **2**.[11,12] Protection of the hydroxy group in the latter and subsequent reaction of **7** with 3-methylnonylmagnesium bromide[13] catalyzed by copper(I) iodide led to allylic alcohol derivative **8** in 91%

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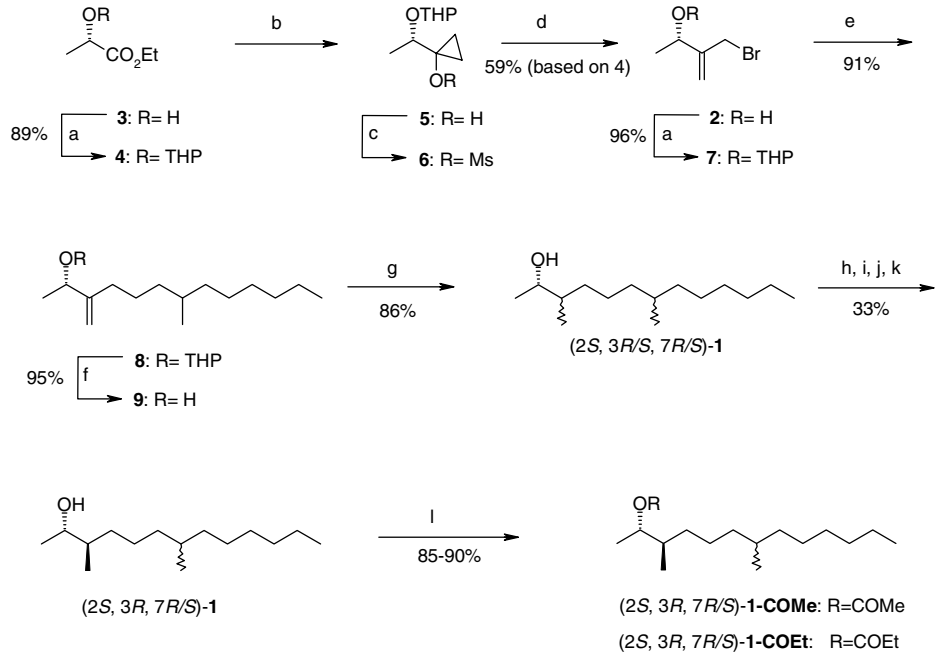

Scheme 1. Reagents and conditions: (a) DHP, PPTS (5 mol%), CH_2Cl_2; (b) EtMgBr, Ti(O*i*-Pr)$_4$, Et_2O/THF; (c) MsCl, Et_3N, Et_2O; (d) $MgBr_2$, $CHCl_3/Et_2O$; (e) 3-methylnonylmagnesium bromide, CuI (5 mol%); (f) MeOH, PPTS (5 mol%.); (g) $NaBH_4$, $NiCl_2{\cdot}6H_2O$, MeOH; (h) phthalic anhydride, Et_3N, C_6H_6; (i) (*S*)-(−)-1-phenylethylamine, acetone; (j) four recrystallizations from acetone; (k) KOH, MeOH; (l) CH_3COCl or C_2H_5COCl, Et_3N, Et_2O.

yield.[14] Removal of the THP group in **8** by acid-catalyzed methanolysis gave alcohol **9**.[15] Based on ^{1}H NMR spectra of the (+)- and (−)-MTPA-esters[16] of **9**, we found that the stereoisomeric purity of **9** at C-2 was more than 98%.[17] Smooth reduction of double bond in **9**, which led to a mixture of *erythro*- and *threo*-diastereomeric alcohols **1** in a nearly equimolar ratio (GLC analysis) in 86% total yield, was performed by the action of $NaBH_4$ in the presence of $NiCl_2{\cdot}6H_2O$ in methanol.[18,19]

Separation of (2*S*,3*R*/*S*,7*R*/*S*)-3,7-dimethyltridecan-2-ol **1** into (2*S*,3*R*,7*R*/*S*)- and (2*S*,3*S*,7*R*/*S*)-diastereomers was performed by its transformation into acid phthalate esters by reaction with phthalic anhydride[20] followed by salt formation with (*S*)-(−)-1-phenylethylamine in acetone. The (*S*)-(−)-1-phenylethylamine salt was recrystallized four times from acetone and then hydrolyzed by potassium hydroxide to give (2*S*,3*R*,7*R*/*S*)-dimethyltridecan-2-ol **1**, which contained 4% of diastereomeric (2*S*,3*S*,7*R*/*S*)-dimethyltridecan-2-ol **1** in 66% of the theoretical yield.[21] ^{1}H and ^{13}C NMR spectral data of (2*S*,3*R*,7*R*/*S*)-3,7-dimethyltridecan-2-ol **1**, as well as ^{1}H NMR spectral data of its acetate (**1-COMe**) and propionate (**1-COEt**) were in accordance with the data reported in the literature.[1,2]

Acknowledgements

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References and notes

1. Bergstrom, G.; Wassegren, A.-B.; Anderbrant, O.; Fagerhag, J.; Edlund, H.; Hedenstrom, E.; Hogberg, H.-E.; Geri, C.; Auger, M. A.; Varama, M.; Hansson, B. S.; Lofqvist, J. *Experientia* **1995**, *51*, 370–380.
2. Anderbrant, O.; Hansson, B. S.; Hallberg, E.; Geri, C.; Varama, M.; Hedenstrom, E.; Hogberg, H.-E.; Fagerhag, J.; Edlund, H.; Wassgren, A.-B.; Bergstrom, G.; Lofqvist, J. *J. Insect Physiol.* **1995**, *41*, 395–401.
3. Hedenstrom, E.; Edlund, H.; Lund, S.; Abersten, M.; Persson, D. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1810–1817.
4. (a) Kulinkovich, O. G. *Chem. Rev.* **2003**, *103*, 2597–2632; (b) Gibson, D. H.; De Puy, C. H. *Chem. Rev.* **1974**, *74*, 605–623.
5. Epstein, O. L.; Kulinkovich, O. G. *Tetrahedron Lett.* **1998**, *39*, 1823–1826.
6. Epstein, O. L.; Kulinkovich, O. G. *Tetrahedron Lett.* **2001**, *42*, 3757–3758.
7. Kozyrkov, Yu. Yu.; Kulinkovich, O. G. *Synlett* **2002**, *3*, 443–446.
8. (a) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A.; Prityts kaya, T. S. *Zh. Org. Khim.* **1989**, *25*, 2244–2245; (b) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A. *Synthesis* **1991**, 234.
9. Esposito, A.; Taddei, M. *J. Org. Chem.* **2000**, *65*, 9245–9248.
10. For deprotection of tetrahydropyranyl ethers with magnesium bromide see: Sunggak, K.; Park, J. H. *Tetrahedron Lett.* **1987**, *28*, 439–440.
11. Using ether as the only solvent in this transformation resulted in a low conversion of **6** to a mixture of **2** and **7**.
12. THP protected ethyl (*S*)-lactate (13.10 g, 64.9 mmol) **4** was converted into mesylate **6** via cyclopropanol **5** according to published procedures[9] without purification of **5**. A solution of $MgBr_2$, prepared from magnesium (5.52 g, 227 mmol) and 1,2-dibromoethane (42.70 g, 227 mmol) in

diethyl ether (170 mL), was added in one portion to a solution of crude mesylate **6** in chloroform (170 mL). The reaction mixture was refluxed for 3 h under an argon atmosphere. After cooling in ice, the reaction mixture was treated with water (200 mL). The organic layer was separated, and the aqueous layer was extracted with dichloromethane (5×40 mL). The combined organic extracts were dried over Na_2SO_4, concentrated under reduced pressure and distilled under reduced pressure, giving 12.58 g of a fraction which boiled at 70–120 °C (6 mm). 2-Substituted allyl bromide **2** (6.31 g, 59%) was isolated by column chromatography on silica gel (eluent: cyclohexane/ethyl acetate). ^{1}NMR (400 MHz, $CDCl_3$): δ 5.28–5.31 (m, 2H), 4.54 (q, $J = 6.5$ Hz, 1H), 4.11 (d, $J = 10.2$ Hz, 1H), 3.99 (d, $J = 10.2$ Hz, 1H), 1.87 (br s, 1H), 1.37 (d, $J = 6.5$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 149.0, 115.1, 68.1, 32.8, 22.1.

13. Kletzke, P. G. *J. Org. Chem.* **1964**, *29*, 1363–1366.
14. Copper(I) iodide (0.19 g, 1.0 mmol) was added in one portion to a solution of 3-methylnonylmagnesium bromide (prepared from 1-bromo-3-methylnonane (8.90 g, 40.3 mmol) and magnesium (0.82 g, 33.7 mmol) in diethyl ether (40 mL)) cooled to −20 °C. After stirring for 3–5 min, allyl bromide **7** (4.90 g, 19.7 mmol) in THF (15 mL) was added drop wise to the reaction mixture over 5 min and stirring was continued at −20 °C for 30 min and then 4 h at room temperature. The reaction mixture was quenched with 25 mL of saturated aqueous solution of NH_4Cl. The organic layer was separated, and the aqueous layer was extracted with diethyl ether (4×15 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Compound **8** (5.55 g, 91%) was isolated by column chromatography on silica gel (eluent: cyclohexane/ethyl acetate).
15. NMR (400 MHz, $CDCl_3$): δ 5.02–5.04 (m, 1H), 4.79–4.82 (m, 1H), 4.25 (q, $J = 6.5$ Hz, 1H), 1.92–2.12 (m, 2H), 1.56 (br s, 1H), 1.04–1.52 (m, 18H), 1.29 (d, $J = 6.5$ Hz), 0.88 (t, $J = 6.6$ Hz, 3H), 0.85 (d, $J = 6.3$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.5, 107.9, 70.9, 70.9, 37.0, 37.0, 36.9, 36.9, 32.6, 32.0, 31.9, 29.6, 27.0, 25.4, 25.4, 22.7, 22.1, 19.6, 19.6, 14.1.
16. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543–2549.
17. The signals of the protons of the methoxy groups at 3.53 and 3.58 ppm were used to determine stereoisomeric purity.
18. Toshio, S.; Kenryo, N.; Shuichi, S. *Chem. Pharm. Bull.* **1971**, *19*, 817–820.
19. $NaBH_4$ (0.50 g, 13.2 mmol) was added in small portions to a solution of allylic alcohol **9** (1.50 g, 6.64 mmol) and $NiCl_2 \cdot 6H_2O$ (0.39 g, 6.64 mmol) in methanol (30 mL) at −20 °C over 5 min. The reaction mixture was stirred at −20 °C for 15 min and then for 1 h at room temperature. After solvent removal under reduced pressure, the residue was diluted with diethyl ether and washed with brine. The organic layer was separated, and the aqueous layer was extracted with diethyl ether (4×5 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. Compound **1** (1.30 g, 86%) was isolated by column chromatography on silica gel (eluent: cyclohexane/ethyl acetate). ^{1}NMR (400 MHz, $CDCl_3$): δ 3.61–3.73 (m, 1H), 2.00 (br s, 1H), 1.00–1.54 (m, 21H), 1.15 (d, $J = 6.3$ Hz), 1.12 (d, $J = 6.3$ Hz), 0.80–0.90 (m, 9H).
20. Kantor, S. W.; Hauser, Ch. R. *J. Am. Chem. Soc.* **1953**, *75*, 1744.
21. Ratio of diastereomeric alcohols **1** was found on the basis of it ^{1}H NMR spectrum.[1,2]