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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 7549–7551

Stereoselective synthesis of (2*S*,3*S*,7*S*)-3,7-dimethylpentadec-2-yl acetate and propionate, the sex pheromones of pine sawflies

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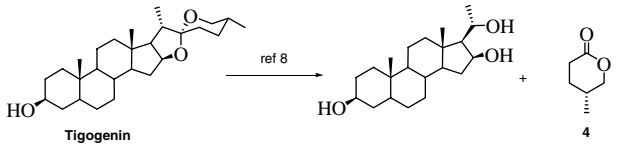
Received 17 April 2007; revised 19 June 2007; accepted 22 June 2007
Available online 24 June 2007

Abstract—The stereoselective synthesis of (2*S*,3*S*,7*S*)-3,7-dimethylpentadec-2-yl acetate (**2**) and propionate (**3**) was accomplished by utilizing the cheap and easily available chiron (*R*)-4-methyl-δ-valerolactone (**4**). The key steps were chelation-controlled addition of Gilmann reagent to chiral β-alkoxy aldehyde **12** and the Cu(I)-catalyzed coupling of Grignard reagent with bromoester **5** in the presence of NMP.

Pine sawflies (Hymenoptera: *Diprionidae*) are widely distributed in the coniferous forests of Northern Europe, Asia and North America. Considering they are severe pests on conifers, the identification and synthesis of the pheromones of this and related species are essential for the development of selective monitoring and control of the populations of these insects. Because of the pioneering work of Coppel, Jewett and co-workers,[1,2] the major pheromone components of several species of pine sawflies were found to be esters of 3,7-dimethyl-2-pentadecanol **1**. Acetate **2** is the most active in the *Neodiprion* species, whereas propionate **3** is preferred by the *Diprion* species.[2,3] Further researches showed that the esters of (2*S*,3*S*,7*S*)-alcohol **1** were the most active for all *Neodiprion* species.[4] Up to date, a number of methods[5–7] have been developed for the syntheses of stereoisomers of compound **1**. Compared with the existing syntheses of those pheromones, the present route seems more practical and economical.

As a result of our group's efforts in resource chemistry (the organic synthetic chemistry based on the rational utilization of resource compounds), we can produce (*R*)-4-methyl-δ-valerolactone (**4**) in kilograms scales via a green method (Scheme 1).[8] In connection with our work in using the cheap and easily available lactone **4** as a chiron for the asymmetric syntheses of natural products,[9] we report here a new route to the esters of (2*S*,3*S*,7*S*)-alcohol **1**.



Scheme 1.

Our retrosynthetic analysis is shown in Scheme 2. The chelation-controlled addition to aldehyde and the coupling of Grignard reagent with bromide were the key steps in this synthesis.

The asymmetric synthesis started with lactone **4**. On the treatment of HBr gas in MeOH,[10] lactone **4** was converted to bromoester **5**. In the presence of NMP, Cu(I)-catalyzed coupling[11] of Grignard reagent with bromoester was achieved in high chemoselectivity and yield. After reduction with $LiAlH_4$, the alcohol was oxidized by Swern protocol[12] to provide aldehyde **7**. By a $TiCl_4$-mediated aldol condensation[13] of the known *N*-propionyl-oxazolidinone[14] with the aldehyde, the desired compound **9** was achieved. Protection of the

Keywords: Sex pheromones; Pine sawflies; Chiron; Resource chemistry; Chelation-controlled.
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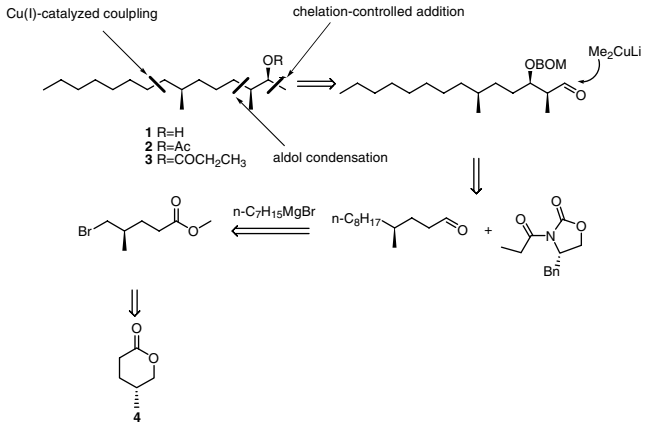
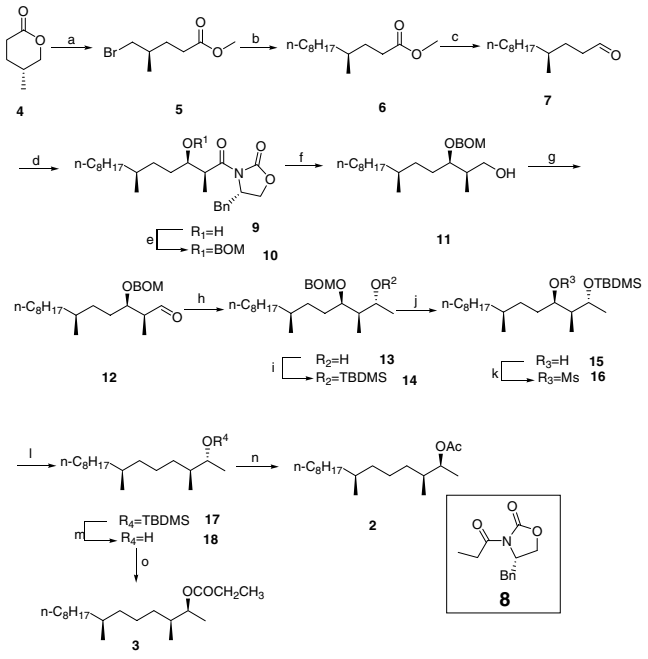
0040-4039/$ - see front matter © 2007 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2007.06.123



Scheme 2. Retrosynthetic analysis of **1**.

secondary alcohol group of resulting alcohol **9** with BOMCl, followed by reduction cleavage of the chiral auxiliary with $NaBH_4$ in a THF/H_2O mixture,[15] provided primary alcohol **11**. After an IBX oxidation,[16] aldehyde **12** was treated with Gilmann reagent to give the chelation-controlled adduct **13** as a single isomer.[17] TBDMS protection of **13**, followed by debenzyloxymethylation, gave alcohol **15**. The secondary alcohol of compound **15** was removed via reduction of its mesylate **16** with $NaBH_4$ in NMP.[18] Deprotection of TBDMS followed by Mitsunobu reaction[19] afforded sex pheromones **2**[20] and **3**[21] (see Scheme 3).



Scheme 3. Reagents and conditions: (a) dry HBr, MeOH, rt, 56%; (b) 4 equiv NMP, 3% Li_2CuCl_4, $CH_3(CH_2)_5CH_2MgBr$, THF, rt, 92%; (c) (1) $LiAlH_4$, Et_2O, −78 °C , 90%; (2) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C to 0 °C, 85%; (d) **8**, $TiCl_4$, *i*Pr_2NEt, NMP, CH_2Cl_2, 0 °C, 82%; (e) BOMCl, *i*Pr_2NEt, TBAI, CH_2Cl_2, 0 °C to rt, 80%; (f) $NaBH_4$, THF/H_2O (v/v,1:2.5), 0 °C to rt, 87%; (g) IBX, DMSO, rt 88%; (h) Me_2CuLi, Et_2O, −78 °C, 76%; (i) TBDMSCl, imidazole, DMF, rt 95%; (j) H_2, 10% Pd–C, EtOAc/MeOH (v/v,3:1), rt 90%; (k) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 96%; (l) $NaBH_4$, HMPA, 80 °C, 78%; (m) HF (40%), CH_3CN, rt, 94%; (n) DEAD, Ph_3P, pyridine, AcOH, THF, −45 °C to 0 °C, 80%; (o) DEAD, Ph_3P, pyridine, CH_3CH_2COOH, THF, −45 °C to 0 °C, 77%.

In conclusion, starting from (*R*)-4-methyl-δ-valerolactone (**4**), which was regarded as industrial waste in the past, an efficient synthesis of the active enantiomers of the pheromones of pine sawflies has been achieved. The key steps of this synthesis include the highly diastereoselective addition to chiral β-alkoxy aldehyde, and the Cu(I)-catalyzed coupling of Grignard reagent with bromoester.

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20. (2*S*,3*S*,7*S*)-3,7-Dimethylpentadec-2-yl acetate (**2**): $[\alpha]_D^{25}$ −5.6 (*c* 0.18, hexane); IR(film): 2963, 2928, 2857, 1741, 1465, 1374, 1261 1246, 1098, 1020, 803 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 4.70–4.83 (m, 1H), 2.03 (s, 3H), 0.95–1.60 (m, 22H), 1.16 (d, $J = 6.3$ Hz, 3H), 0.76–0.84 (m, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 170.8, 74.137.6, 37.3, 37.0, 32.8, 32.8, 31.9, 30.0, 29.7, 29.4, 27.0, 24.5, 22.7, 21.3, 19.7, 17.0, 14.8, 14.1; MS EI *m*/*z* (%): 239 (M^+−59, 1), 154(1), 140(3), 125(4), 111(3), 97(5), 87(29), 72(35), 57(23), 43(100).
21. (2*S*,3*S*,7*S*)-3,7-Dimethylpentadec-2-yl propionate (**3**): $[\alpha]_D^{25}$ −5.8 (*c* 0.35, hexane); IR(film): 2962, 2928, 2856, 1739, 1464, 1378, 1261 1193, 1084, 1019, 805 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 4.78–4.87 (m, 1H), 2.30 (q, $J = 7.5$ Hz, 2H), 1.16 (d, $J = 6.6$ Hz, 3H), 1.14 (t, $J = 7.6$ Hz, 3H), 0.99–1.60 (m, 22H), 0.93–0.76 (m, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 174.1, 73.8, 37.7, 37.3, 37.0, 32.9, 32.7, 31.9, 30.0, 29.7, 29.4, 28.0, 27.1, 24.5, 22.7, 19.7, 17.0, 14.8, 14.1, 9.3; MS EI *m*/*z* (%): 238 (M^+−74, 2), 155(1), 139(3), 125(4), 111(3), 101(20), 86(21), 69(15), 57(100).