Asymmetric Syntheses of the Sex Pheromones of Pine Sawflies, Their Homologs and Stereoisomers

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Dedicated to Professor *Dieter Seebach* on the occasion of his 75th birthday

We describe efficient and flexible enantioselective syntheses of the active enantiomers of the pheromones of pine sawflies, including the species *Diprion jingyuanensis*, their homologs and, stereoisomers, as well as those identified from the Chinese species *Diprion jingyuanensis*, *i.e.*, **126**. A total of 48 compounds, including acetates **78**–**101** and propanoates **102**–**125**, have been synthesized. Our general approach towards these compounds originated from the commercially available chirons diethyl (*S*)- and (*R*)-malates, as well as ethyl (*R*)-3-hydroxybutanoate. The *Seebach* asymmetric methylation was employed in a key step to control additional configuration.

Introduction. – Pine sawflies (Hymenoptera: Diprionidae) are common insects found in the coniferous forests of Europe, Asia, and North America. Consisting of more than 120 species, many of them are severe pests on conifers. Since the identification of the acetate **1A** and the propanoate **1P** of 3,7-dimethylpentadecan-2-ol (diprionol; **1**; *Fig.*) as the sex pheromones of *Neodiprion lecontei* (North American species) and *Diprion similes* (European species introduced to North America), respectively [1], intensive studies have been devoted to the pheromones of pine sawflies [2]. While only the free alcohol has been found in the females [3], the males are attracted to the corresponding acetate or propanoate, which leads to the assumption that the alcohol is stored as the sex pheromone precursor and then esterified just before emission [1]. These precursors are basically long-chain 2-alcohols with configurational, chain length, and Me-branching variations. Remarkable impact of chirality and chain length on the behavioral activity was also noted as a common phenomenon in the pheromones [4]. For example, while *Neodiprion* species use (2*S*,3*S*,7*S*)-**1A** (acetate) or **1P** (propionate) as the main pheromones, and (2*S*,3*R*,7*R*)-**1A** or **1P** as a synergist or inhibitor [2], *Diprion similis* contains (2*S*,3*R*,7*R*)-**1P** as the main pheromone [5]. The shorter-chain homolog (2*S*,3*R*,7*R*)-dimethyltridecan-2-ol (**2**) was found in the female European species *Diprion pini* and *Microdiprion pallipes* [6a][6b], and in the Chinese species *Diprion jingyuanensis* as well [6c]. An even shorter homolog, (2*S*,3*R*,9*S*)-3,9-dimethylundecan-2-ol (**3**), was isolated from the

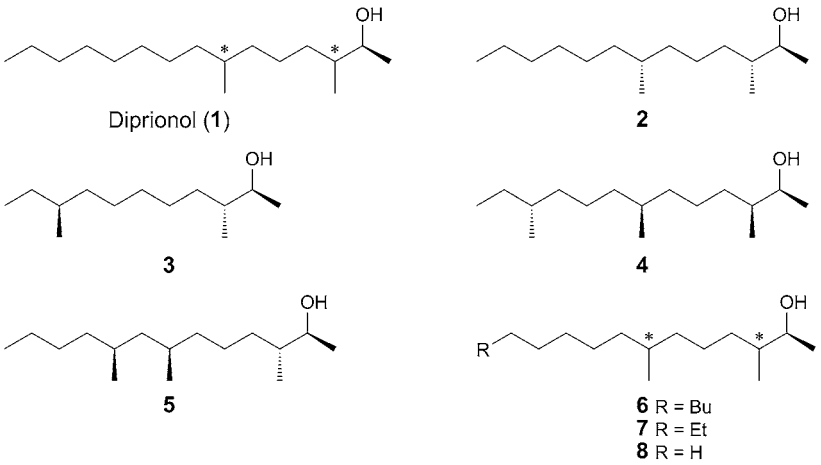


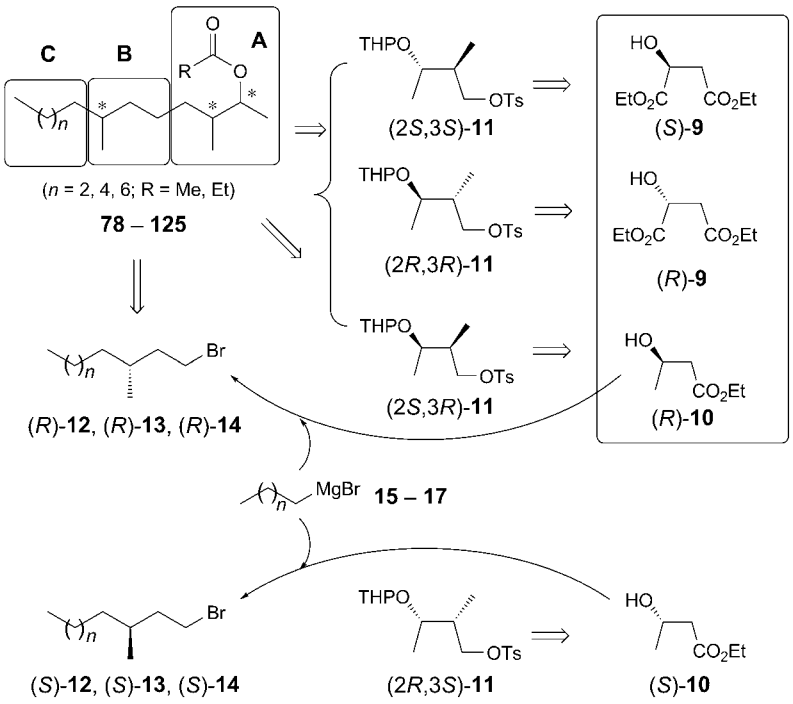
Figure. *Structures of compounds* **1**–**8**. *erythro*-(2*S*,3*S*,7*S*)-**1** and *threo*-(2*S*,3*R*,7*R*)-**1** from *Neodiprion* spp. and *Diprion similis*, *threo*-(2*S*,3*R*,7*R*)-**2** from *Neodiprion pini*, *threo*-(2*S*,3*R*,9*S*)-**3** from *Diprion nipponica*, *threo*-(2*S*,3*S*,7*S*,11*R*)-**4** from *Microdiprion pallipes*, *threo*-(2*S*,3*R*,7*R*,9*S*)-**5** from *Macrodiprion nemoralis*, *threo*-(2*S*,3*R*,7*R*)-**6** and *threo*-(2*S*,3*R*,7*R*)-**7** from *G. pallida* and *N. sertifer*, and **8** from *N. sertifer*.

Japanese pine sawfly *Diprion nipponica* (ROHWER) [7]. The additional Me-branched (2*S*,3*S*,7*S*,11*R*)-3,7,11-trimethyltridecan-2-ol (**4**) was found in *Microdiprion pallipes* (FALLÉN) [8], while (2*S*,3*R*,7*R*,9*S*)-3,7,9-trimethyltridecan-2-ol (**5**) was isolated from the pine sawfly *macrodiprion nemoralis* (Hymenoptera: Diprionidae) [9]. In addition, from female extracts of the pine sawflies *N. sertifer* and *Diprion pini*, 3,7-dimethylhexadecan-2-ol (**6**), 3,7-dimethyltetradecan-2-ol (**7**), and 3,7-dimethyldodecan-2-ol (**8**) were identified as minor pheromone components [6b][10]. Incidentally, Me-branched long-chain 2-alcohol substructure is also present in some bioactive natural products such as cytotoxic butenolides [11].

In view of structural elucidation, identification of active components, and development of selective methods for monitoring and controlling the populations of pine sawflies, the enantioselective synthesis of the sex pheromones of pine sawflies has attracted considerable attention. A number of methods [4–6] have been developed for the asymmetric synthesis of diprionol (**1**) [6][12], its stereoisomers [7][13], and homologs, which are due largely to *Hedenström* and co-workers [3][6a][6b][8][9][10a][10b][12h][13c][13g][13i][13j][14a][14b], *Tai* and co-workers [5][7][12e][13a][13b], and *Mori* and co-workers [4][12b][12c][13d]. In a program aiming at the monitoring of pine sawflies, we needed some homologs and all stereoisomers of pine sawfly pheromones as diprionol esters. Consequently, we undertook the asymmetric syntheses of these compounds as well as the pheromone identified from the Chinese species *Diprion jingyuanensis* [15], and we report the results herein.

Results and Discussion. – Our synthetic plan is outlined in *Scheme 1*, which involves the use of diethyl (*S*)-malate ((*S*)-**9**), diethyl (*R*)-malate ((*R*)-**9**), and ethyl (*R*)-3-

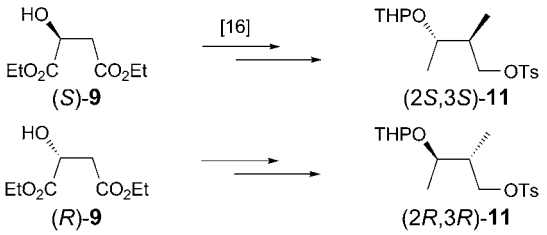
Scheme 1



hydroxybutanoate ((*R*)-**10**) as the chirons for the construction of all stereogenic centers of all target pheromone components, their homologs and stereoisomers **78**–**125**.

erythro-Segment **A**, (2*S*,3*S*)-**11**, was synthesized from diethyl (*S*)-malate according to our previously established method [16], which was based on the *Seebach* asymmetric methylation method [17]. Following the same procedure, (2*R*,3*R*)-**11** was prepared in five steps and 41% overall yield from diethyl (*R*)-malate (*Scheme 2*).

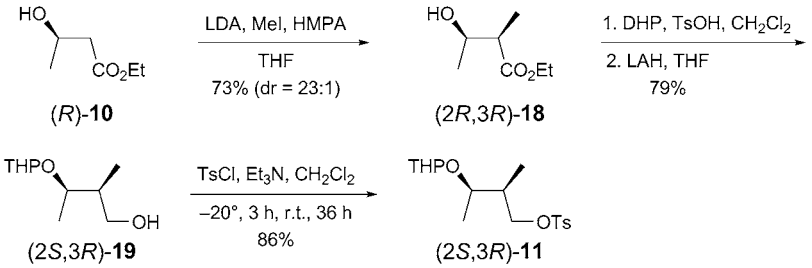
Scheme 2



For the syntheses of *threo*-diastereoisomers (2*S*,3*R*)-**11** and (2*R*,3*S*)-**11**, inexpensive and easily available C_4 building block ethyl (*R*)-hydroxybutanoate ((*R*)-**10**; *Scheme 3*) was used as the only starting enantiomer. Thus, successive treatment of (*R*)-**10** with lithium diisopropylamide (LDA) and MeI gave the desired *C(2)*-methylated product

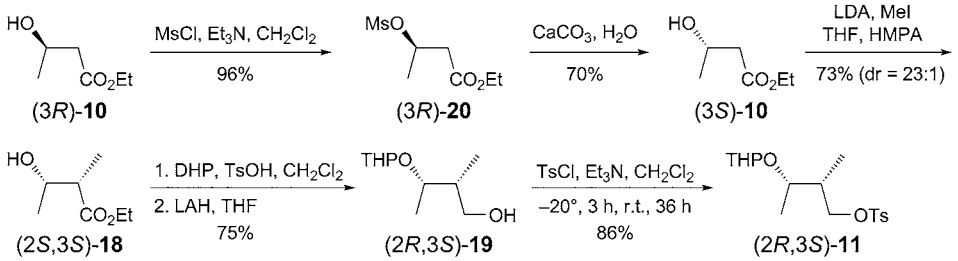
(2*R*,3*R*)-**18** and its diastereoisomer in a 23:1 ratio. The OH group in (2*R*,3*R*)-**18** was protected (3,4-dihydro-2*H*-pyran (DHP), TsOH, CH_2Cl_2), and the resulting tetrahydropyran-2-yl (THP)-protected hydroxy ester was reduced with $LiAlH_4$ (LAH) to give compound (2*S*,3*R*)-**19** in 79% overall yield. Tosylation of (2*S*,3*R*)-**19** (TsCl, Et_3N, CH_2Cl_2, −20°, 3 h; r.t., 36 h) gave (2*S*,3*R*)-**11** in 86% yield (*Scheme 3*).

Scheme 3



To prepare the other enantiomer, (2*R*,3*S*)-**11**, (*R*)-**10** was converted to (*S*)-**10** by a two-step procedure, which involved mesylation (MsCl, Et_3N, CH_2Cl_2, 96%) and a S_N2 reaction ($CaCO_3$, H_2O) [18] leading to an inversion of configuration. Following the procedure described for its enantiomer (*R*)-**10**, (*S*)-**10** was converted to (2*R*,3*S*)-**11** (*via* the intermidates (2*S*,3*S*)-**18** and (2*R*,3*S*)-**19**) in four steps with an overall yield of 50% (*Scheme 4*).

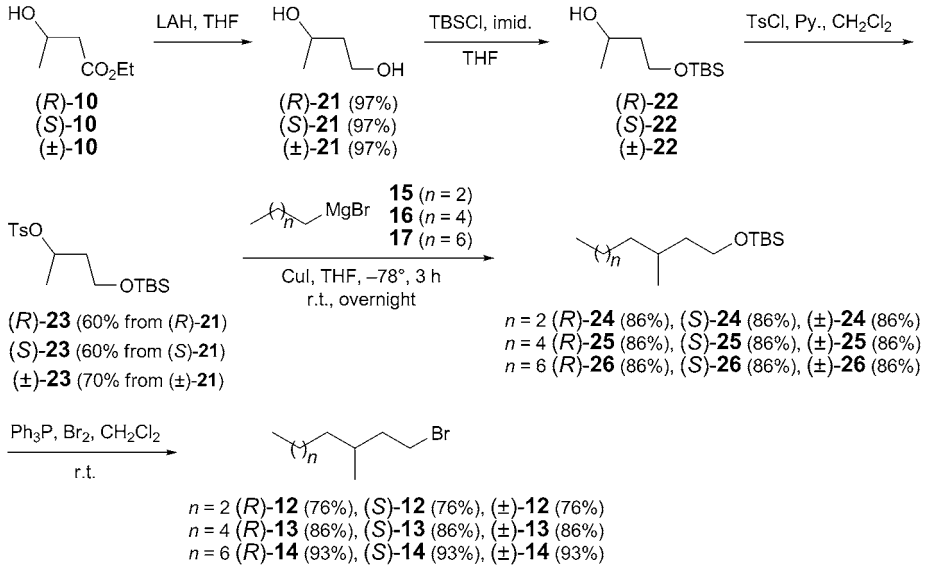
Scheme 4



After securing the synthesis of all four stereoisomers of fragment **A** [14], we next focused on the syntheses of six homologs of **BC** fragments: namely both enantiomers of three **BC** fragments, 1-bromo-3-methylheptane (**12**), 1-bromo-3-methylnonane (**13**), and 1-bromo-3-methylundecane (**14**). Previously, we synthesized **BC** fragments starting from diethyl (*S*)- and (*R*)-malate [16]. As an alternative approach, (*R*)-**10** was used as a chiral starting material for the synthesis of **BC** fragments. Thus, (*R*)-**10** was transformed to toluene-4-sulfonate (*R*)-**23** by reduction with LAH (yield 97%), which, upon chemoselective protection of the primary OH group with ^{t}BuMe$_2$SiCl (TBSCl) (1*H*-imidazole, THF, 24 h), followed by tosylation (TsCl, pyridine (Py), CH_2Cl_2), afforded (*R*)-**23** in 60% yield from (*R*)-**21a**. CuI-Promoted C,C coupling reactions of (*R*)-**23** with butyl, hexyl, and octyl magnesium bromide, gave, *via* the S_N2 reaction, (*R*)-**24**, (*R*)-**25**, and (*R*)-**26** in 86, 86, and 86% yield, respectively. Silyl ethers

(*R*)-**24**, (*R*)-**25**, and (*R*)-**26** were converted to the corresponding bromides (*R*)-**12**, (*R*)-**13**, and (*R*)-**14** (Ph_3P, Br_2, CH_2Cl_2, r.t.) in one pot. The overall yields from (*R*)-**10** (five steps) were 38, 43, and 46%, respectively (*Scheme 5*).

Scheme 5

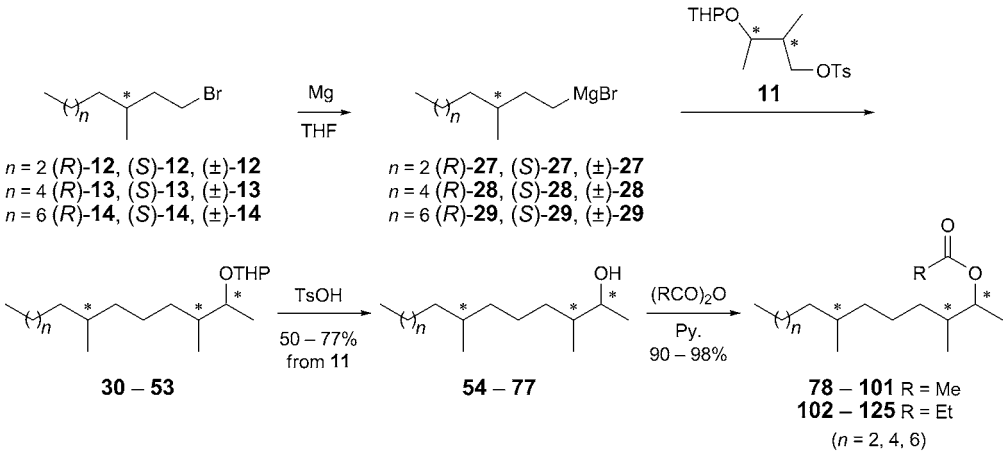


The syntheses of (*S*)-enantiomers of **12**–**14** started with (*S*)-**10**, which was converted to (*S*)-**12**, (*S*)-**13**, and (*S*)-**14**, respectively, according to a similar procedure described for their (*R*)-enantiomers (*Scheme 5*).

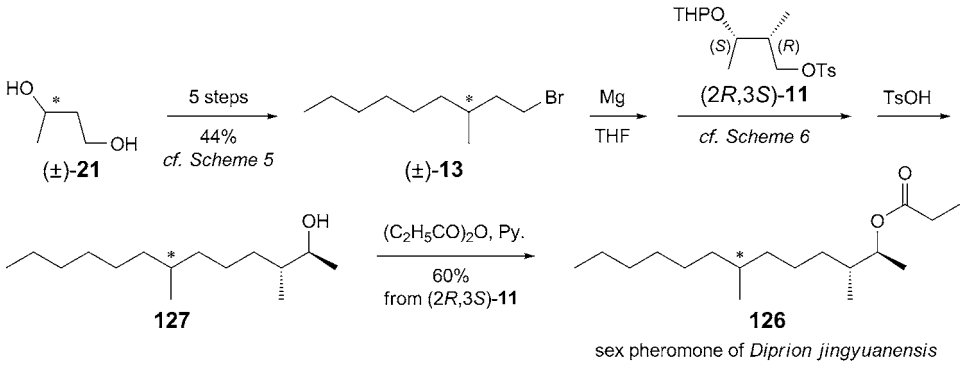
We next turned our attention to the coupling reaction between fragments **A** and **BC**. Thus, Cu-catalyzed coupling of the *Grignard* reagent (*S*)-**27**, prepared *in situ* from bromide (*S*)-**12**, with toluene-4-sulfonate (2*S*,3*S*)-**11**, furnished the desired coupling product **30**. The crude product, without purification, was subjected to acidic conditions to give the alcohol **54** in 50% yield. Following the procedure described for alcohol **54**, alcohols **55**–**77** were obtained in 50–77% yields. The alcohols **54**–**77** were then converted to acetates **78**–**101** and propionates **102**–**125**, respectively, by acylation (*Scheme 6*).

Finally, we set out to synthesize *C(7)*-epimeric mixture of the sex pheromone of *Diprion jingyuanensis* ((2*S*,3*R*,7*R*,*S*)-3,7-dimethylpentadecan-2-yl propanoate; **126**) (*Scheme 7*). The syntheses of the two diastereoisomers, (2*S*,3*R*,7*R*)-**102** and (2*S*,3*R*,7*S*)-**108**, have been described in *Scheme 6*. In light of the finding that both diastereoisomers were the sex pheromonal components of *Diprion jingyuanensis*, it is desirable to adopt a simpler method to prepare the diastereoisomer mixture **126** starting from the racemic butane-1,3-diol ((±)-**21**). To this end, racemic (±)-**13** was synthesized in five steps and 50% overall yield from (±)-**21** (*Scheme 5*). The racemic bromide (±)-**13** was converted to its corresponding *Grignard* reagent (±)-**28** (*Scheme 6*), which was coupled with (2*S*,3*R*)-**11** to yield the desired C-atom skeleton. The coupled product was then converted to **126** *via* successive deprotection and

Scheme 6



Scheme 7



esterification. The overall yield of **126** from (2*S*,3*R*)-**11** was *ca.* 60%, and the purity of the product was >95%.

Conclusions. – In summary, we developed an efficient and flexible methodology for the total syntheses of 48 pheromone related compounds, including active enantiomers of the pheromones of pine sawflies, their homologs, and stereoisomers. The general approach utilizes commercially available chirons diethyl (*S*)- and (*R*)-malate, as well as ethyl (*R*)-3-hydroxybutanoate, to assemble the required stereogenic centers. Sex pheromone identified from the Chinese species *Diprion jingyuanensis*, (2*S*,3*R*,7*R*,*S*)-3,7-dimethylpentadec-2-yl propanoate (**126**), was also synthesized from racemic butane-1,3-diol (**21**) and ethyl (*R*)-3-hydroxybutanoate.

Experimental Part

General. THF was distilled prior to use from sodium benzophenone ketyl under N_2. CH_2Cl_2 was distilled over P_2O_5 under N_2. Silica gel (SiO_2; 300–400 mesh) was used for flash column chromatography

(FC), eluting (unless otherwise stated) with AcOEt/petroleum ether (PE, 60–90°) mixtures. Optical rotations: *Perkin-Elmer 341* automatic polarimeter. IR Spectrum: *Nicolet Avatar 360* FT-IR spectrophotometer; $\tilde{\nu}$ in cm^{-1}. NMR Spectra: *Bruker 400* spectrometer in $CDCl_3$ (^1H: 400 and ^{13}C: 100 MHz); δ in ppm rel. to Me_4Si as internal standard, J in Hz. MS: *Bruker Dalton Esquire 3000 plus* LC/MS apparatus (ESI, direct injection); in m/z. HR-MS: *Shimadzu* LC/MS-IT-TOF apparatus; in m/z.

Synthesis of Sex Pheromone 126 *of Chinese Species* Diprion jingyuanensis. *Ethyl (2*S,*3*S*)-3-Hydroxy-2-methylbutanoate* ((2*S*,3*S*)-**18**). To a soln. of LDA (prepared under N_2 by addition of BuLi (93 ml of 2.5M in hexane, 232.5 mmol) to a soln. of $(i\text{-}Pr)_2NH$ (32.5 ml, 232.5 mmol) in anh. THF (70 ml; at −78° and stirred at 0° for 30 min) was added hydroxy ester (*S*)-**10** (13.99 g, 105.7 mmol) within 10 min at −50°. After stirring for 30 min, MeI (45.01 g, 317.1 mmol) and hexamethylphosphoramide (HMPA) (30 ml, 169.1 mmol) were added. After stirring at −50° for another 10 min and at 0° for 10 min, the reaction was quenched with sat. aq. NH_4Cl soln., and the aq. layer was extracted with AcOEt (3 × 50 ml). The combined org. phases were washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by FC (SiO_2; AcOEt/PE 1:8) to afford (2*S*,3*S*)-**18** (11.4 g, 73%). Colorless oil. $[\alpha]_D^{20} = +19.4$ ($c = 1.0$, $CHCl_3$) ([19a]: $[\alpha]_D^{20} = +14.8$ ($c = 1.83$, $CHCl_3$); [19b]: $[\alpha]_D^{20} = +23.3$ ($c = 1.24$, $CHCl_3$)). IR (film): 3436, 2971, 2930, 1731, 1458, 1375, 1184, 1109, 1042. ^1H-NMR (400 MHz, $CDCl_3$): 1.19 (*d*, *J* = 7.2, 3 H); 1.23 (*d*, *J* = 6.4, 3 H); 1.28 (*t*, *J* = 7.2, 3 H); 2.40–2.42 (*m*, 1 H); 2.81 (*s*, 1 H); 3.90 (*qd*, *J* = 6.4, 6.4, 1 H); 4.1 (*q*, *J* = 7.2, 2 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 14.2; 14.3; 20.9; 47.2; 61.0; 69.8; 177.0. ESI-MS: 169 ($[M + Na]^+$).

*(2*R,*3*S*)-2-Methyl-3-(3,4,5,6-tetrahydro-2*H*-pyran-2-yloxy)butan-1-ol* ((2*R*,3*S*)-**19**) [20]. To a soln. of (2*S*,3*S*)-**18** (8.59 g, 58.8 mmol) and TsOH (cat.) in anh. CH_2Cl_2 (50 ml) was added dropwise dihydropyran (14.8 g, 176.4 mmol) with stirring at r.t. After stirring for 4 h, the mixture was washed successively with sat. aq. $NaHCO_3$ soln. and brine, and dried (anh. Na_2SO_4). After filtering and concentrated under reduced pressure, the crude product was employed for the next step without further purification. To a stirred and ice-cooled suspension of $LiAlH_4$ (4.40 g, 118 mmol) in anh. THF (150 ml) was added dropwise the above-mentioned ester in anh. THF (20 ml). The mixture was stirred overnight at 40°, cooled to r.t., and the reaction was quenched by successive addition of H_2O (4.4 ml), a 10% NaOH aq. soln. (6.6 ml), and H_2O (12 ml). The resulting mixture was filtered through *Celite*. The residue was refluxed for 3 h in EtOH (100 ml), and then filtered through *Celite*. The combined filtrates were concentrated, and the residue purified by FC (AcOEt/PE 1:1) to afford (2*R*,3*S*)-**19** (8.85 g, 75%). Colorless oil. $[\alpha]_D^{20} = +32.4$ ($c = 1.0$, $CHCl_3$). IR (film): 3439, 2941, 1453, 1379, 1116, 1076, 1024. ESI-MS: 188 ($[M + H]^+$), 210 ($[M + Na]^+$).

*(2*R,*3*S*)-2-Methyl-3-(3,4,5,6-tetrahydro-2*H*-pyran-2-yloxy)butyl 4-Methylbenzenesulfonate* ((2*R*,3*S*)-**11**) [7b]. To a soln. of (2*R*,3*S*)-**19** (8.30 g, 44.1 mmol) and 4-(dimethylamino)pyridine (DMAP) in anh. CH_2Cl_2 (2 ml) was added dropwise pyridine (7.1 ml, 88.2 mmol), then a soln. of TsCl (12.6 g, 66.2 mmol) in anh. CH_2Cl_2 was added dropwise on an ice bath. After stirring at r.t. for 16 h, the reaction was quenched by adding H_2O on an ice bath until the solid dissolved. The aq. layer was extracted with CH_2Cl_2 (3 × 20 ml). The combined org. phases were washed with brine (5 ml), dried (anh. Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by FC (AcOEt/PE 1:8) to afford (2*R*,3*S*)-**11** (12.4 g, 86%). Pale yellow oil. $[\alpha]_D^{20} = +14.5$ ($c = 1.1$, $CHCl_3$). IR (film): 2941, 1598, 1495, 1454, 1361, 1033. ESI-MS: 365 ($[M + Na]^+$).

*4-{[(*tert*-Butyl)(dimethyl)silyl]oxy}butan-2-ol* ((±)-**22**) [21]. To an ice-bath cooled soln. of *butane-1,3-diol* ((±)-**21**; 20.4 g, 226 mmol), 1,4-imidazole (37.0 g, 543 mmol), and DMAP (cat.) in anh. THF (300 ml) was added a soln. of $^tBuMe_2SiCl$ (TBSCl; 34.0 g, 226 mmol) in anh. THF (100 ml). The mixture was stirred at r.t. for 24 h and then concentrated under reduced pressure. The resulting mixture was diluted with H_2O (20 ml) and extracted with CH_2Cl_2 (3 × 20 ml). The combined org. phases were washed with brine and dried (Na_2SO_4). After filtration and concentration under reduced pressure, the residue was directly used in next reaction. A sample was purified by FC (AcOEt/PE 1:20) to give (±)-**22**. Colorless oil. IR (film): 3415, 2957, 2930, 2858, 1470, 1256, 1089, 836, 776. ^1H-NMR (400 MHz, $CDCl_3$): 0.07 (*s*, 6 H); 0.89 (*s*, 9 H); 1.20 (*d*, *J* = 6.4, 3 H); 1.58–1.77 (*m*, 2 H); 3.41 (*s*, 1 H); 3.81–3.88 (*m*, 2 H); 4.00–4.20 (*m*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): −5.6; −5.5; 18.1; 23.3; 25.7; 25.8; 40.0; 62.8; 68.3. ESI-MS: 205 ($[M + H]^+$), 227 ($[M + Na]^+$).

*4-{[(*tert*-Butyl)(dimethyl)silyl]oxy}butan-2-yl 4-methylbenzenesulfonate* ((±)-**23**) [22]. To a soln. of crude (±)-**22** and DMAP (cat.) in pyridine (33 ml, 410 mmol) was added slowly TsCl (47.0 g, 246 mmol) at 0°. After stirring overnight at r.t., 1*H*-imidazole (12.0 g, 176 mmol) was added. Then, an aq. HCl soln. (2N, 70 ml) was added, and the mixture was extracted with CH_2Cl_2 (4 × 60 ml). The org. layers were washed successively with a sat. aq. soln. of $NaHCO_3$ (5 ml) and brine (5 ml), dried (anh. Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by FC (AcOEt/PE 1:20) to give (±)-**23** (56.6 g, 70% over two steps). Colorless oil. IR (film): 2954, 2930, 2884, 2851, 1599, 1470, 1360, 1177, 1099. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.05 (*s*, 6 H); 0.86 (*s*, 9 H); 1.24 (*d*, *J* = 6.4, 3 H); 1.70–1.88 (*m*, 2 H); 2.48 (*s*, 3 H); 3.62–3.77 (*m*, 2 H); 4.84–4.92 (*m*, 1 H); 7.37 (*d*, *J* = 8.0, 2 H); 7.83 (*d*, *J* = 8.0, 2 H). ^{13}C-NMR (100 MHz, $CDCl_3$): −5.6; −5.5; 18.1; 21.0; 21.6; 25.8; 25.8; 25.8; 39.5; 58.8; 78.1; 127.7; 129.7; 134.5; 144.4. ESI-MS: 359 ($[M+H]^+$), 381 ($[M+Na]^+$).

*(*tert*-Butyl)(dimethyl)[(3-methylnonyl)oxy]silane* ((±)-**25**). A soln. of hexyl magnesium bromide in THF was prepared from hexyl bromide (40 ml, 371 mmol) and Mg (9.80 g, 408 mmol) in dry THF (146 ml). The soln. was chilled to −78°, to which a soln. of (±)-**23** (18.0 g, 50.2 mmol) in THF (200 ml) and CuI (500 mg) were added. The mixture was gradually warmed to r.t. After stirring overnight at r.t., the mixture was poured into an ice-cooled aq. NH_4Cl soln. (40 ml) and extracted with CH_2Cl_2 (4 × 100 ml). The Et_2O soln. was successively washed with aq. $NaHCO_3$ soln. and brine, dried (anh. Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by FC (PE) to give (±)-**25** (11.8 g, 86%). Colorless oil. IR (film): 2956, 2928, 2857, 1462, 1379, 1254, 1100. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.05 (*s*, 6 H); 0.84–0.91 (*m*, 15 H); 1.09–1.12 (*m*, 1 H); 1.21–1.34 (*m*, 10 H); 1.47–1.58 (*m*, 2 H); 3.58–3.68 (*m*, 2 H). ^{13}C-NMR (100 MHz, $CDCl_3$): −5.3; −5.3; 14.1; 18.3; 19.8; 22.7; 26.0; 26.0; 26.0; 26.9; 29.5; 29.6; 31.9; 37.1; 40.0; 61.6. HR-ESI-MS: 295.2432 ($[M+Na]^+$, $C_{16}H_{36}NaOSi^+$; calc. 295.2432).

1-Bromo-3-methylnonane ((±)-**13**) [23]. To a freshly prepared suspension of Ph_3P/Br_2 in CH_2Cl_2 (180 ml) was added (±)-**25** (10.5 g, 43.1 mmol) in CH_2Cl_2 (50 ml). After stirring at r.t. for 24 h, a sat. aq. soln. of $NaHCO_3$ (20 ml) and a sat. aq. soln. of $Na_2S_2O_4$ (10 ml) were added successively. The mixture was extracted with CH_2Cl_2 (3 × 30 ml). The org. layers were washed with a sat. aq. soln. of $NaHCO_3$ (5 ml) and brine (5 ml), dried (anh. Na_2SO_4), filtered, and concentrated under reduced pressure to get a mash. The mixture was filtered through *Celite* (PE). The org. layer was concentrated under reduced pressure. The residue was purified by FC (PE) to give (±)-**13** (8.2 g, 86%). Colorless oil. IR (film): 2957, 2926, 2856, 1462, 1379, 1254, 1213. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.86–0.93 (*m*, 6 H); 1.10–1.30 (*m*, 10 H); 1.60–1.71 (*m*, 2 H); 1.83–1.92 (*m*, 1 H); 3.37–3.49 (*m*, 2 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 14.1; 19.0; 22.7; 26.8; 29.5; 31.7; 31.9; 32.2; 36.5; 40.1.

(2S,3R,7R,S)-3,7-Dimethyltridecan-2-ol (**127**) [12i]. *Grignard* reagent (±)-**28** was prepared from Mg (962 mg, 40.1 mmol) and (±)-**13** (4.05 g, 18.4 mmol) in THF (18 ml). To a cold soln. (−78°) of the above-mentioned *Grignard* reagent (4.5 ml) was added a soln. of (2*R*,3*S*)-**11** (550 mg, 1.61 mmol) in THF (2 ml) and CuI (cat.). The mixture was allowed to warm up to 0° and kept at this temp. for 3 h. After stirring overnight at r.t., the reaction was quenched with a sat. aq. soln. of NH_4Cl (2 ml) and H_2O (2 ml). The org. layer was separated, and the aq. layer was extracted with Et_2O (3 × 3 ml). The combined org. layers were washed with brine, dried (anh. Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was treated with TsOH (cat.) in MeOH (20 ml) at 50°. After stirring for 1.5 h, the mixture was concentrated under reduced pressure. The residue was purified by FC (SiO_2; AcOEt/PE 1:15) to afford **127** (282 mg, 77%). Colorless oil. $[\alpha]_D^{20} = +13.1$ (*c* = 2.29, hexane). IR (film): 3360, 2959, 2926, 2857, 1587, 1463, 1378, 1096, 1001. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.82–0.92 (*m*, 9 H); 1.02–1.54 (*m*, 22 H); 3.63–3.72 (*m*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 14.1; 14.5; 14.5; 19.3; 19.4; 19.6; 19.8; 22.7; 24.7; 24.7; 27.0; 27.1; 29.7; 32.0; 32.7; 32.8; 32.8; 32.9; 37.0; 37.2; 37.3; 37.4; 40.0; 40.1; 71.8; 71.8. ESI-MS: 251 ($[M+Na]^+$).

(2S,3R,7R,S)-3,7-Dimethyltridecan-2-yl Propanoate (**126**) [12i]. Propanoic anhydride (208 mg, 1.6 mmol) was added to an ice-cooled soln. of **127** (273 mg, 1.2 mmol) in anh. pyridine (0.5 ml). The mixture was left overnight at r.t. and diluted with Et_2O (5 ml). The soln. was washed successively with a 5% aq. soln. of HCl, H_2O, sat. $NaHCO_3$ (aq.), and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by FC (AcOEt/PE 1:30) to give **126** (327 mg, 95%). Colorless oil. $[\alpha]_D^{20} = +4.9$ (*c* = 2.43, hexane). IR (film): 2958, 2927, 2857, 1738, 1463, 1378, 1274, 1193,

1083. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.80–0.93 (*m*, 9 H); 1.00–1.42 (*m*, 23 H); 1.61–1.71 (*m*, 1 H); 2.30 (*q*, *J* = 7.6, 2 H); 4.77–4.87 (*m*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 9.3; 14.1; 14.6; 14.6; 15.8; 15.9; 19.6; 19.7; 22.7; 24.5; 27.0; 27.0; 28.0; 29.7; 32.0; 32.7; 32.7; 32.9; 32.9; 37.0; 37.1; 37.2; 37.3; 74.0; 74.1; 174.1. ESI-MS: 307 ($[M+Na]^+$).

The authors are grateful to the *National Basic Research Program* (*973 Program*) *of China* (Grant No. 2010CB833200), the *NSF of China* (20832005, 21072160), and the *Natural Science Foundation of Fujian Province of China* (No. 2011J01054) for financial support. We are grateful to Prof. Dr. *L.-F. Xie* for valuable discussion.

REFERENCES

[1] D. M. Jewett, F. Matsumura, H. C. Coppel, *Science* **1976**, *192*, 51.

[2] M. R. Wagner, K. F. Raffa, 'Pheromone Biology of Sawflies', in 'Sawfly Life History Adaptations to Woody Plants', Ed. O. Anderbrant, Academic Press, San Diego, 1993, p. 119; M. R. Wagner, K. F. Raffa, in 'Sawfly Life History Adaptations to Woody Plants', Ed. D. R. Smith, Academic Press, San Diego, 1993, p. 3; J. Hardie, A. K. Minks, 'Sawflies and Seed Wasps', in 'Pheromones of Non-Lepidopteran Insects Associated with Agricultural Plants', Ed. O. Anderbrant, CAB International, Wallingford, UK, 1999, p. 199.

[3] A.-B. Wassgren, O. Anderbrant, J. Löfqvist, B. S. Hansson, G. Bergström, E. Hedenström, H.-E. Högberg, *J. Insect Physiol.* **1992**, *38*, 885.

[4] K. Mori, *Biosci. Biotechnol. Biochem.* **1996**, *60*, 1925; K. Mori, *Bioorg. Med. Chem.* **2007**, *15*, 7505.

[5] T. Kikukawa, F. Matsumura, M. Kraemer, H. C. Coppel, A. Tai, *J. Chem. Ecol.* **1982**, *8*, 301.

[6] a) O. Anderbrant, B. S. Hansson, E. Hallberg, C. Geri, M. Varama, E. Hedenström, H.-E. Högberg, J. Fägerhag, H. Edlund, A.-B. Wassgren, G. Bergström, J. Löfqvist, *J. Insect Physiol.* **1995**, *41*, 395; b) G. Bergström, A.-B. Wassgren, O. Anderbrant, J. Fägerhag, H. Edlund, E. Hedenström, H.-E. Högberg, C. Geri, M. A. Auger, M. Varama, B. S. Hansson, J. Löfqvist, *Experientia* **1995**, *51*, 370; c) G.-F. Chen, Z. Zhang, D.-Y. Wei, H.-C. Pan, L.-Y. Huo, *Forest Pest Dis.* **1999**, *1*, 4.

[7] A. Tai, Y. Higashiura, M. Kakizaki, T. Naito, K. Tanaka, M. Fujita, T. Sugimura, H. Hara, N. Hayashi, *Biosci. Biotechnol. Biochem.* **1998**, *62*, 607; A. Tai, E. Syouno, K. Tanaka, M. Fujita, T. Sugimura, Y. Higashiura, M. Kakizaki, H. Hara, T. Naito, *Bull. Chem. Soc. Jpn.* **2002**, *75*, 111.

[8] G. Bergström, A.-B. Wassgren, O. Anderbrant, S. A. Ochieng, F. Östrand, B. S. Hasson, E. Hedenström, H.-E. Högberg, *Naturwissenschaften* **1998**, *85*, 244.

[9] A.-B. Wassgren, G. Bergström, A. Sierpinski, O. Anderbrant, H.-E. Högberg, E. Hedenström, *Naturwissenschaften* **2000**, *87*, 24; F. Östrand, O. Anderbrant, A.-B. Wassgren, G. Bergström, E. Hedenström, H.-E. Högberg, B.-V. Nguyen, M. Larsson, *Chemoecology* **2003**, *13*, 155.

[10] a) E. Hedenström, H.-E. Högberg, A.-B. Wassgren, G. Bergström, J. Löfqvist, B. S. Hansson, O. Anderbrant, *Tetrahedron* **1992**, *48*, 3139; b) E. Hedenström, H. Edlund, A.-B. Wassgren, G. Bergström, O. Anderbrant, F. Östrand, A. Sierpinski, M.-A. Auger-Rozenberg, A. Herz, W. Heitland, M. Varama, *J. Chem. Ecol.* **2006**, *32*, 2525.

[11] V. J. R. V. Mukku, M. Speitling, H. Laatsch, E. Helmke, *J. Nat. Prod.* **2000**, *63*, 1570; K. W. Cho, H.-S. Lee, J.-R. Rho, T. S. Kim, S. J. Mo, J. Shin, *J. Nat. Prod.* **2001**, *64*, 664; D.-H. Li, T.-J. Zhu, H.-B. Liu, Y.-C. Fang, Q.-Q. Gu, W.-M. Zhu, *Arch. Pharm. Res.* **2006**, *29*, 624.

[12] a) G. Mugnusson, *Tetrahedron* **1978**, *34*, 1385; b) K. Mori, S. Tamada, M. Matsui, *Tetrahedron Lett.* **1978**, *19*, 901; c) K. Mori, S. Tamada, *Tetrahedron* **1979**, *35*, 1279; d) S. Byström, H.-E. Högberg, T. Norin, *Tetrahedron* **1981**, *37*, 2249; e) T. Kikukawa, M. Imaida, A. Tai, *Bull. Chem. Soc. Jpn.* **1984**, *57*, 1954; f) T. Itoh, Y. Yonekawa, T. Sato, T. Fujisawa, *Tetrahedron Lett.* **1986**, *27*, 5405; g) M. Larchevêque, C. Sanner, *Tetrahedron* **1988**, *44*, 6407; h) H.-E. Högberg, E. Hedenström, A.-B. Wassgren, M. Hjalmarsson, G. Bergström, J. Löfqvist, T. Norin, *Tetrahedron* **1990**, *46*, 3007; i) A. V. Bekish, K. N. Prokhorevich, O. G. Kulinkovich, *Tetrahedron Lett.* **2004**, *45*, 5253; j) A. V. Bekish, K. N. Prokhorevich, O. G. Kulinkovich, *Eur. J. Org. Chem.* **2006**, 5069; k) Z.-K. Wang, W.-S. Tian, X.-F. Pan, *Acta Chim. Sin.* **2007**, *65*, 705; l) Z.-K. Wang, W.-S. Tian, X.-F. Pan, *Chin. J. Org. Chem.* **2007**, *27*, 866; m) Z.-K. Wang, Q.-H. Xu, W.-S. Tian, X.-F. Pan, *Tetrahedron Lett.* **2007**, *48*, 7549.

[13] a) T. Kikukawa, M. Imaida, A. Tai, *Chem. Lett.* **1982**, 1799; b) A. Tai, T. Sugimura, T. Kikukawa, C. Naito, Y. Nishimoto, N. Morimoto, *Biosci. Biotechnol. Biochem.* **1992**, *56*, 1711; c) S. Karlsson, E. Hedenström, *Acta Chem. Scand.* **1999**, *53*, 620; d) Y. Nakamura, K. Mori, *Eur. J. Org. Chem.* **1999**, 2175; e) J. A. Moreira, A. G. Corrêa, *J. Braz. Chem. Soc.* **2000**, *11*, 614; f) S. Karlsson, H. E. Hogberg, *Synthesis* **2000**, 1863; g) M. Larsson, B.-V. Nguyen, H.-E. Högberg, E. Hedenström, *Eur. J. Org. Chem.* **2001**, 353; h) S. Ebert, N. Krause, *Eur. J. Org. Chem.* **2001**, 3831; i) E. Hedenström, H. Edlund, S. Lund, M. Abersten, D. Persson, *J. Chem. Soc., Perkin Trans. 1* **2002**, 1810; j) Hedenström, E. Andersson, *J. Chem. Ecol.* **2002**, *28*, 1237.

[14] a) E. Hedenström, B.-V. Nguyen, L. A. Silks III, *Tetrahedron: Asymmetry* **2002**, *13*, 835; b) E. Hedenström, H. Edlund, S. Lund, *J. Mol. Catal. B: Enzym.* **2003**, *23*, 53; c) M. Larsson, J. Andersson, R. Liu, H.-E. Högberg, *Tetrahedron: Asymmetry* **2004**, *15*, 2907; d) M. Larsson, E. Galandrin, H.-E. Högberg, *Tetrahedron* **2004**, *60*, 10659.

[15] F. Trand, O. Anderbrant, Q.-H. Zhang, C.-F, Chen, A.-B. Wassgren, G. Bergström, Z. Zhang, E. Hedenström, H.-E. Högberg, 'Scientific Program and Abstracts of First Asia-Pacific Conference on Chemical Ecology', Shanghai, 1999, p. 59; G.-F. Chen, X.-Z. Meng, J. Mei, J.-C. Gao, C.-S. Hou, H.-L. Xiong, C.-R. Shu, *J. Liaoning Forest. Sci. Technol.* **2003**, 22.

[16] P.-Q. Huang, H.-Q. Lan, X. Zheng, Y.-P. Ruan, *J. Org. Chem*. **2004**, *69*, 3964.

[17] D. Seebach, R. Naef, *Helv. Chim. Acta.* **1981**, *64*, 2704; D. Seebach, J. Aebi, D. Wasmuth, *Org. Synth.* **1984**, *63*, 109.

[18] D. Seebach, A. K. Beck, R. Breitschuh, K. Job, *Org. Synth*. **1993**, *71*, 39; A. J. Carnell, R. Head, D. Bassett, M. Schneider, *Tetrahedron: Asymmetry* **2004**, *15*, 821.

[19] a) T. Itoh, T. Sato, T. Fujisawa, *Nippon Kagaku Kaishi* **1987**, *7*, 1414; b) C. Bauder, *Tetrahedron Lett.* **2008**, *49*, 2243.

[20] Q. Wang, J. Ouazzani, N. A. Sasaki, P. Potier, *Eur. J. Org. Chem.* **2002**, 834; W.-M. Dai, L. Shi, Y. Li, *Tetrahedron: Asymmetry* **2008**, *19*, 1549.

[21] G. Hobley, K. Stuttle, M. Wills, *Tetrahedron* **2003**, *59*, 4739.

[22] N. P. Crouch, R. M. Adlington, J. E. Baldwin, M.-H. Lee, C. H. MacKinnon, D. R. Paul, *Tetrahedron* **1997**, *53*, 10827.

[23] E. LeGoff, S. E. Ulrich, D. B. Denney, *J. Am. Chem. Soc.* **1958**, *80*, 622.

Received July 3, 2012