

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

by Jian-Feng Zheng^a), Hong-Qiao Lan^a), Rui-Feng Yang^a), Qi-Long Peng^a), Zhen-Hua Xiao^a), Shi-Chuan Tuo^a), Kong-Zhen Hu^a), Yong-Gang Xiang^a), Zhen Wei^a), Zhen Zhang^b), and Pei-Qiang Huang^{*a})

^a) Department of Chemistry and Fujian Provincial Key Laboratory of Chemical Biology, College of Chemistry and Chemical Engineering, Xiamen University, Xiamen 361005, P.R. China
(e-mail: pqhuang@xmu.edu.cn)

^b) The Research Institute of Forest Ecology, Environment and Protection, Chinese Academy of Forestry, Key Laboratory of Forest Protection of State Forestry Administration, Beijing 100091, P.R. China

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 similis* (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

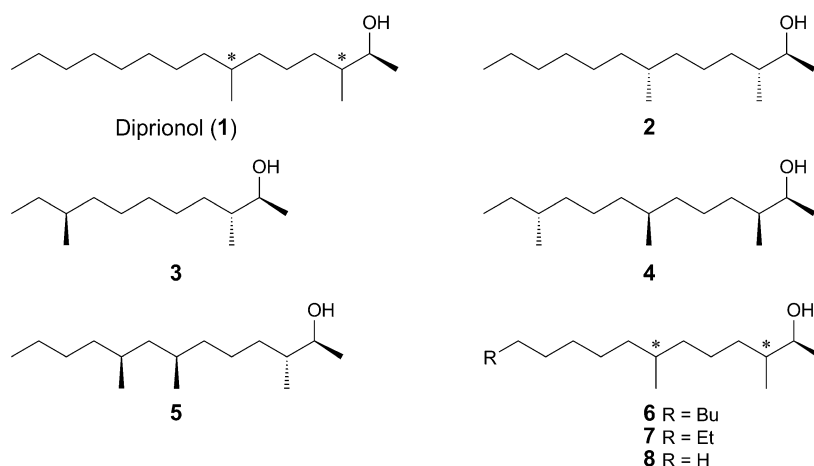


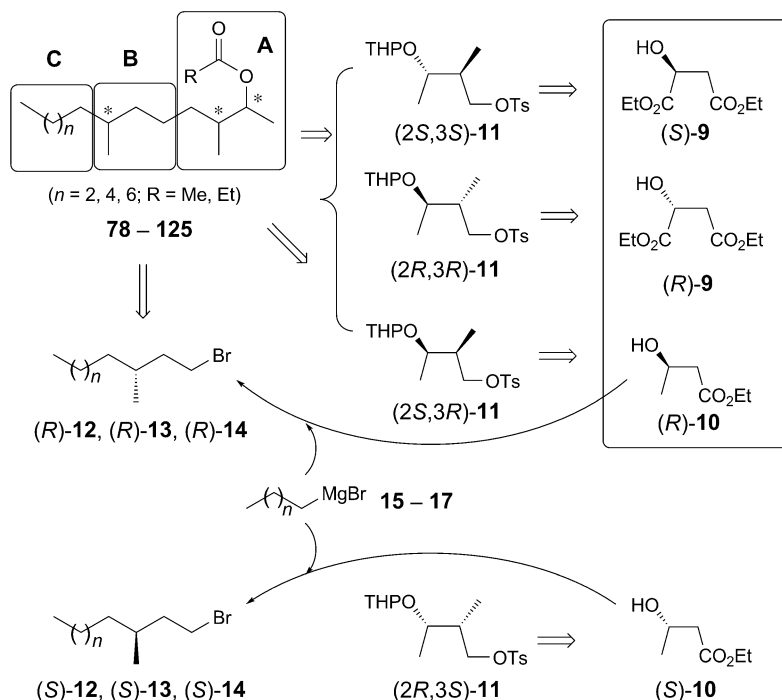
Figure. Structures of compounds **1–8**. *erythro*-(2*S*,3*S*,7*S*)-**1** and *threo*-(2*S*,3*R*,7*R*)-**1** from *Neodiprion* spp. and *Diprion similis*, *threo*-(2*S*,3*R*,7*R*)-**2** from *Neodiprion pini*, *threo*-(2*S*,3*R*,9*S*)-**3** from *Diprion nipponica*, *threo*-(2*S*,3*S*,7*S*,11*R*)-**4** from *Microdiprion pallipes*, *threo*-(2*S*,3*R*,7*R*,9*S*)-**5** from *Macrodipteron 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 *macrodipteron 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-

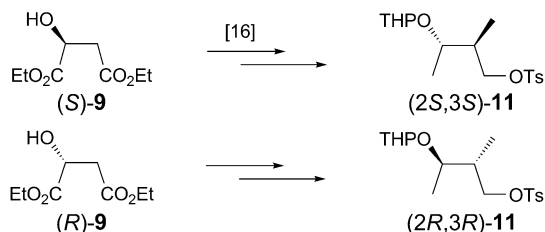
Scheme 1



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).

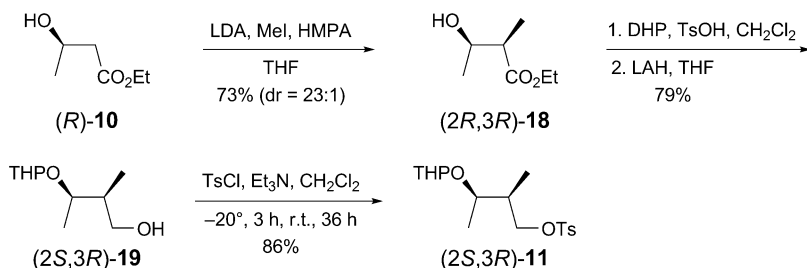
Scheme 2



For the syntheses of *threo*-diastereoisomers (2*S*,3*R*)-**11** and (2*R*,3*S*)-**11**, inexpensive and easily available C₄ 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

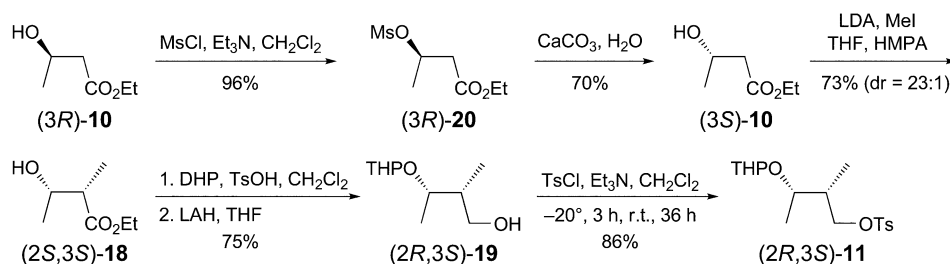
(2*R*,3*R*)-**18** and its diastereoisomer in a 23 : 1 ratio. The OH group in (2*R*,3*R*)-**18** was protected (3,4-dihydro-2*H*-pyran (DHP), TsOH, CH₂Cl₂), and the resulting tetrahydropyran-2-yl (THP)-protected hydroxy ester was reduced with LiAlH₄ (LAH) to give compound (2*S*,3*R*)-**19** in 79% overall yield. Tosylation of (2*S*,3*R*)-**19** (TsCl, Et₃N, CH₂Cl₂, –20°, 3 h; r.t., 36 h) gave (2*S*,3*R*)-**11** in 86% yield (Scheme 3).

Scheme 3



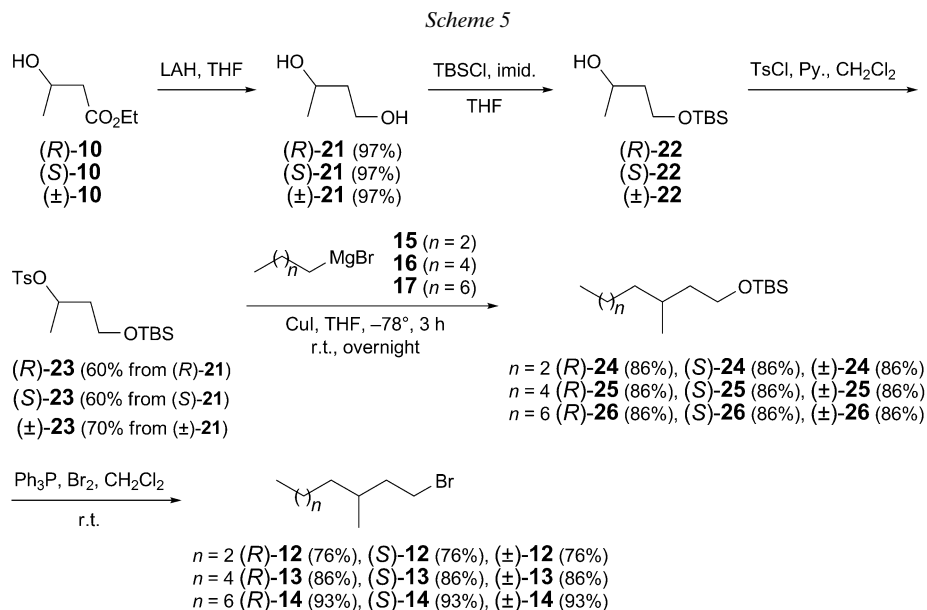
To prepare the other enantiomer, (2*R*,3*S*)-**11**, (*R*)-**10** was converted to (*S*)-**10** by a two-step procedure, which involved mesylation (MsCl, Et₃N, CH₂Cl₂, 96%) and a S_N2 reaction (CaCO₃, H₂O) [18] leading to an inversion of configuration. Following the procedure described for its enantiomer (*R*)-**10**, (*S*)-**10** was converted to (2*R*,3*S*)-**11** (via the intermediates (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 ^tBuMe₂SiCl (TBSCl) (1*H*-imidazole, THF, 24 h), followed by tosylation (TsCl, pyridine (Py), CH₂Cl₂), 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*).

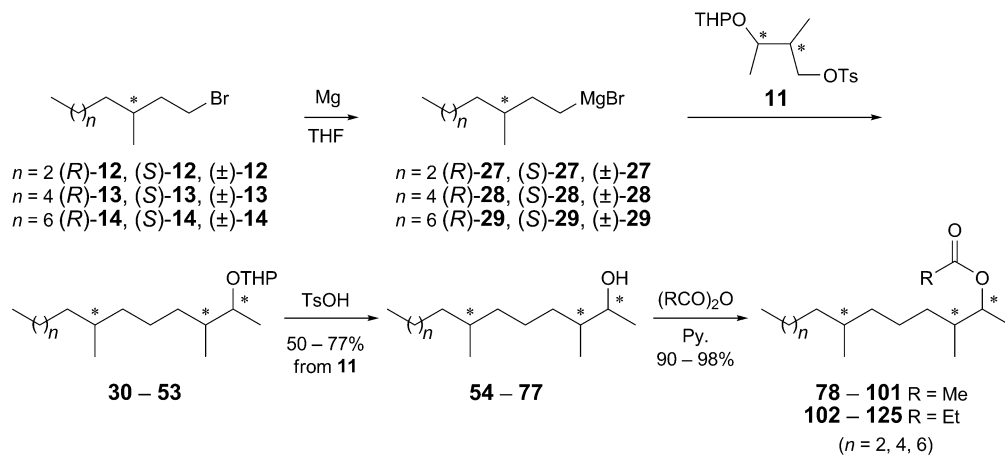


The syntheses of (*S*)-enantiomers of **12–14** started with (*S*)-**10**, which was converted to (*S*)-**12**, (*S*)-**13**, and (*S*)-**14**, respectively, according to a similar procedure described for their (*R*)-enantiomers (*Scheme 5*).

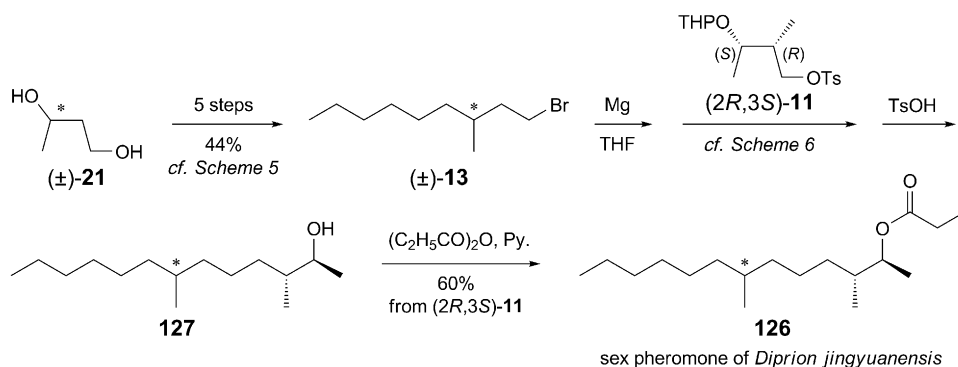
We next turned our attention to the coupling reaction between fragments **A** and **BC**. Thus, Cu-catalyzed coupling of the *Grignard* reagent (*S*)-**27**, prepared *in situ* from bromide (*S*)-**12**, with toluene-4-sulfonate (2*S*,3*S*)-**11**, furnished the desired coupling product **30**. The crude 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 (($\pm$)-**21**). To this end, racemic ($\pm$)-**13** was synthesized in five steps and 50% overall yield from ($\pm$)-**21** (*Scheme 5*). The racemic bromide ($\pm$)-**13** was converted to its corresponding *Grignard* reagent ($\pm$)-**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 (*2S,3R*)-**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 chiral diols, 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*, (*2S,3R,7R,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 N₂. CH₂Cl₂ was distilled over P₂O₅ under N₂. Silica gel (SiO₂; 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-Pr) $_2$ NH (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 ($[M + \text{Na}]^+$).

(2*R*,3*S*)-2-Methyl-3-(3,4,5,6-tetrahydro-2H-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 ($[M + \text{H}]^+$), 210 ($[M + \text{Na}]^+$).

(2*R*,3*S*)-2-Methyl-3-(3,4,5,6-tetrahydro-2H-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 ($[M + \text{Na}]^+$).

4-[(tert-Butyl)(dimethylsilyl)oxy]butan-2-ol (($\pm$)-**22**) [21]. To an ice-bath cooled soln. of butane-1,3-diol (($\pm$)-**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 $t\text{-BuMe}_2\text{SiCl}$ (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 ($\pm$)-**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 ($[M + \text{H}]^+$), 227 ($[M + \text{Na}]^+$).

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. (2*N*, 70 ml) was added, and the mixture was extracted with CH₂Cl₂ (4 × 60 ml). The org. layers were washed successively with a sat. aq. soln. of NaHCO₃ (5 ml) and brine (5 ml), dried (anh. Na₂SO₄), 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. ¹H-NMR (400 MHz, CDCl₃): 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). ¹³C-NMR (100 MHz, CDCl₃): –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. NH₄Cl soln. (40 ml) and extracted with CH₂Cl₂ (4 × 100 ml). The Et₂O soln. was successively washed with aq. NaHCO₃ soln. and brine, dried (anh. Na₂SO₄), 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. ¹H-NMR (400 MHz, CDCl₃): 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). ¹³C-NMR (100 MHz, CDCl₃): –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]⁺, C₁₆H₃₆NaOSi⁺; calc. 295.2432).

1-Bromo-3-methylnonane ((±)-**13**) [23]. To a freshly prepared suspension of Ph₃P/Br₂ in CH₂Cl₂ (180 ml) was added (±)-**25** (10.5 g, 43.1 mmol) in CH₂Cl₂ (50 ml). After stirring at r.t. for 24 h, a sat. aq. soln. of NaHCO₃ (20 ml) and a sat. aq. soln. of Na₂S₂O₄ (10 ml) were added successively. The mixture was extracted with CH₂Cl₂ (3 × 30 ml). The org. layers were washed with a sat. aq. soln. of NaHCO₃ (5 ml) and brine (5 ml), dried (anh. Na₂SO₄), 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. ¹H-NMR (400 MHz, CDCl₃): 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). ¹³C-NMR (100 MHz, CDCl₃): 14.1; 19.0; 22.7; 26.8; 29.5; 31.7; 31.9; 32.2; 36.5; 40.1.

(2*S*,3*R*,7*R*,*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 NH₄Cl (2 ml) and H₂O (2 ml). The org. layer was separated, and the aq. layer was extracted with Et₂O (3 × 3 ml). The combined org. layers were washed with brine, dried (anh. Na₂SO₄), 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 (SiO₂; AcOEt/PE 1:15) to afford **127** (282 mg, 77%). Colorless oil. [α]_D²⁰ = +13.1 (*c* = 2.29, hexane). IR (film): 3360, 2959, 2926, 2857, 1587, 1463, 1378, 1096, 1001. ¹H-NMR (400 MHz, CDCl₃): 0.82–0.92 (*m*, 9 H); 1.02–1.54 (*m*, 22 H); 3.63–3.72 (*m*, 1 H). ¹³C-NMR (100 MHz, CDCl₃): 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]⁺).

(2*S*,3*R*,7*R*,*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 Et₂O (5 ml). The soln. was washed successively with a 5% aq. soln. of HCl, H₂O, sat. NaHCO₃ (aq.), and brine, dried (MgSO₄), filtered, and concentrated under reduced pressure. The residue was purified by FC (AcOEt/PE 1:30) to give **126** (327 mg, 95%). Colorless oil. [α]_D²⁰ = +4.9 (*c* = 2.43, hexane). IR (film): 2958, 2927, 2857, 1738, 1463, 1378, 1274, 1193,

1083. ¹H-NMR (400 MHz, CDCl₃): 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). ¹³C-NMR (100 MHz, CDCl₃): 9.3; 14.1; 14.6; 14.6; 15.8; 15.9; 19.6; 19.7; 22.7; 24.5; 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]⁺).

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