Pheromone Synthesis, CXCVII[+]

Synthesis of the Enantiomers of 2-*sec*-Butyl-4,5-dihydrothiazole and (1*R*,5*S*,7*R*)-3,4-Dehydro-*exo*-brevicomin, Pheromone Components of the Male Mouse, *Mus musculus*

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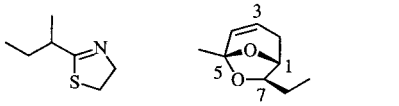
Two components [2-*sec*-butyl-4,5-dihydrothiazole (**1**) and 3,4-dehydro-*exo*-brevicomin (**2**)] of a male-produced pheromone of the mouse *Mus musculus* have been synthesized in optically active forms. The enantiomers of **1** were obtained with an enantiomeric purity of ca. 92% *ee* and were found to be readily racemizable. Asymmetric dihydroxylation was employed as the key reaction (**15**→**16**) allowing the preparation of (1*R*,5*S*,7*R*)-**2** with ca. 94% *ee*.

Introduction

In 1984, 2-*sec*-butyl-4,5-dihydrothiazole (**1**) and 3,4-dehydro-*exo*-brevicomin (**2**) were isolated by Novotny and co-workers from the urine of the male mouse *Mus musculus* as pheromone components.[1] They act, synergistically, in promoting intermale aggression, sex attraction, and estrus synchronization in female mice.[2] The pheromone binding proteins in male mouse urine, which selectively bind **1** and **2**, were isolated in 1992 by Cavaggioni and co-workers,[3] and further studied by Beynon's group.[4] Novotny et al. subsequently determined the absolute configuration of the naturally occurring **2** as 1*R*,5*S*,7*R* by GC comparison with synthetic enantiomers.[2] In the case of **1**, however, they were unable to prepare enantiomers due to their facile racemization. Moreover, conditions could not be found under which their enantiomeric purity could be determined.[2]

We describe herein a synthesis of the enantiomers (ca. 92% *ee*) of **1** and a method for the analytical separation, as well as a new synthesis of (1*R*,5*S*,7*R*)-**2** (ca. 94% *ee*).



2-*sec*-Butyl-4,5-dihydrothiazole (**1**) (1*R*,5*S*,7*R*)-3,4-Dehydro-*exo*-brevicomin (**2**)

Scheme 1. Structures of the pheromone components of the house mouse, *Mus musculus*

Results and Discussion

Synthesis of the Enantiomers of 2-*sec*-Butyl-4,5-dihydrothiazole (1)

Most of the existing methods for the construction of a dihydrothiazole ring are not sufficiently mild to avoid racemization of the enantiomers of **1** at the asymmetric center α to the 2-position of the heterocycle. Indeed, in their attempts to prepare (*S*)-**1**, Novotny et al. obtained (±)-**1** as the product.[2] The only report on the synthesis of optically active **1** has been that by Masaki et al. in 1988.[5] They prepared both (*R*)- and (*S*)-**1** by condensation of (*R*)- and (*S*)-2-methylbutanenitrile with cysteamine. The enantiomeric purity of their enantiomers of **1** was, however, somewhat obscure, because there was no good analytical method available at that time. In 1996, Busacca et al. published a new method for the construction of 2-substituted dihydrothiazoles involving the addition of esters to a complex generated from triisobutylaluminum and cysteamine hydrochloride.[6] This procedure seemed to be sufficiently mild to enable us to carry out syntheses of (*R*)- and (*S*)-**1**.

Scheme 2 shows our synthesis of (*S*)-**1**. Commercially available (*S*)-2-methyl-1-butanol (**3**, 99.9% *ee*[7]) was oxidized to give (*S*)-**4**, which was esterified with diazomethane. The resulting ester (*S*)-**5** (98.8% *ee* by GC analysis) was then treated with a complex generated by the addition of triisobutylaluminum to a suspension of cysteamine hydrochloride (**6**) in toluene, according to Busacca et al.[6] After refluxing for 2 h, the reaction mixture was worked-up to give (*S*)-**1**, $[\alpha]_D^{22} = +21.6$ ($CHCl_3$), in 41% yield. The overall yield was 22% based on (*S*)-**3** (3 steps). The enantiomers of **1** were separable by HPLC using a combination of Chiralcel-OD® and OD-H® columns. The (*S*)-**1** obtained was of 92.6% *ee*. Masaki's reported specific rotation of (*S*)-**1** was $[\alpha]_D^{20} = +15.8$ ($CHCl_3$). On this basis, Masaki's (*S*)-**1** must have had an enantiomeric purity of 68% *ee*.

Because (*R*)-**3** is not commercially available, it was prepared as shown in Scheme 3, and then converted to (*R*)-**1**. The starting (*R*)-3-*tert*-butyloxycarbonyl-2-methylpropanoic acid (**7**, >99.6% *ee*) has recently become commercially available from Mitsubishi Rayon Co.[8][9] and we were

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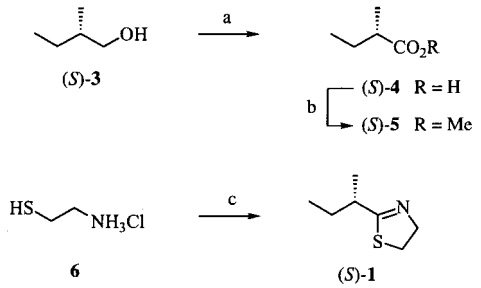
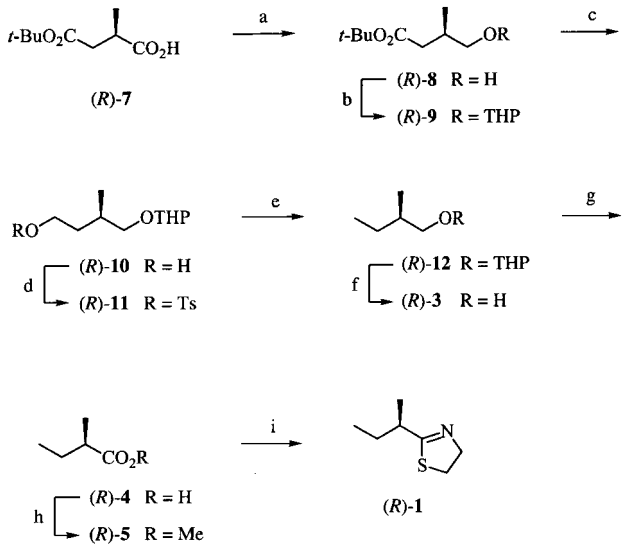


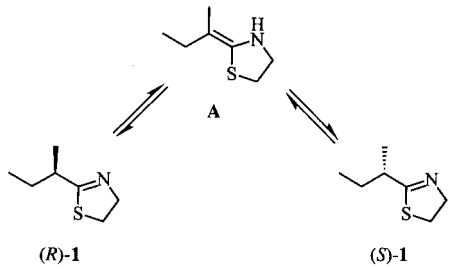
Scheme 2. Synthesis of (*S*)-**1**; reagents: (a) Jones' CrO_3, Me_2CO (85%). – (b) CH_2N_2, Et_2O (80%). – (c) 1.5 equiv. $(iBu)_3Al$, toluene, (*S*)-**5**, reflux, 2 h (41%)

kindly provided with a sample. Reduction of (*R*)-**7** with borane–dimethyl sulfide complex furnished the hydroxy ester (*R*)-**8**. The corresponding tetrahydropyranyl (THP) ether (*R*)-**9** was reduced with lithium aluminum hydride to give the alcohol (*R*)-**10**. Tosylation of (*R*)-**10** afforded the tosylate (*R*)-**11**, which was reduced with lithium aluminum hydride to yield (*R*)-**12**.[10] Deprotection of (*R*)-**12** provided the desired intermediate, (*R*)-2-methyl-1-butanol (**3**)[10][11] in 48% overall yield based on (*R*)-**7** (6 steps). The alcohol (*R*)-**3** was converted to the final product (*R*)-**1**, $[\alpha]_D^{22} = -21.3$ ($CHCl_3$), via (*R*)-**4** and (*R*)-**5**, in 20% overall yield based on (*R*)-**3** (3 steps). The enantiomeric purity of (*R*)-**1** was estimated as 91.6% *ee* by HPLC analysis. Masaki's (*R*)-**1**,[5] with $[\alpha]_D^{20} = -14.9$ ($CHCl_3$), must therefore have been of 64% *ee*.



Scheme 3. Synthesis of (*R*)-**1**; reagents: (a) $BH_3 \cdot SMe_2$, THF (97%). – (b) DHP, *p*TsOH, CH_2Cl_2 (99%). – (c) $LiAlH_4$, Et_2O (93%). – (d) *p*TsCl, C_5H_5N (97%). – (e) $LiAlH_4$, Et_2O (98%). – (f) *p*TsOH, MeOH (57%). – (g) Jones' CrO_3, Me_2CO (75%). – (h) CH_2N_2, Et_2O (76%). – (i) **6**, 1.5 equiv. $(iBu)_3Al$, toluene, reflux, 2 h (35%)

We made several attempts to improve the enantiomeric purities of the final products (*R*)- and (*S*)-**1**. When the solvent used for the ring-formation reaction was changed from toluene to benzene, the *ee* of the final product dropped to 77% *ee*. Addition of triethylamine to the reaction mixture, so as to liberate cysteamine from its hydrochloride, was drastically detrimental and led to (*S*)-**1** of 24% *ee*. Chromatographic purification of (*S*)-**1** (92% *ee*) on silica gel caused partial racemization to give (*S*)-**1** with an *ee* of as low as 36%. Slow partial racemization of (*S*)-**1** (92% *ee*) was also observed with alumina resulting in (*S*)-**1** of 51% *ee*. We therefore purified our optically active **1** as rapidly as possible by chromatography on alumina. Racemization of **1** is thought to take place by an acid- or base-catalyzed process via **A**, as shown in Scheme 4. In short, we were unable to secure the pure enantiomers of **1**. Our products were about 92% enantiomerically pure.



Scheme 4. Mechanism of racemization of the enantiomers of **1**

In view of the optical instability of the enantiomers of **1**, it was necessary to ascertain the appropriate storage conditions under which they could be kept without racemization. The results are summarized in Table 1. It is clear that storage at a low temperature (–78°C) or as a dilute solution [5% (*w/v*)] is preferable. A neat sample of (*S*)-**1** underwent considerable racemization within 5 days at room temperature. The enantiomers of **1** were sent to Prof. A. Cavaggioni in Italy for biological evaluation.

Synthesis of (1*R*,5*S*,7*R*)-3,4-Dehydro-*exo*-brevicomin (2)

There are three existing syntheses of the enantiomers of **2**.[12][13][14] Two of them employ the enantiomers of tartaric acid as starting materials,[12][13] while the third involves Sharpless asymmetric epoxidation as the key step.[14] Because the absolute configuration of the naturally occurring **2** was shown to be 1*R*,5*S*,7*R*,[2] its new synthesis was planned to employ Sharpless asymmetric dihydroxylation[15] for the installation of the asymmetric centers at C-1 and C-7, and then to follow the latter part of our 1986 synthesis of (1*R*,5*S*,7*R*)-**2**, exploiting organoselenium chemistry for the introduction of the double bond at C-3.[12]

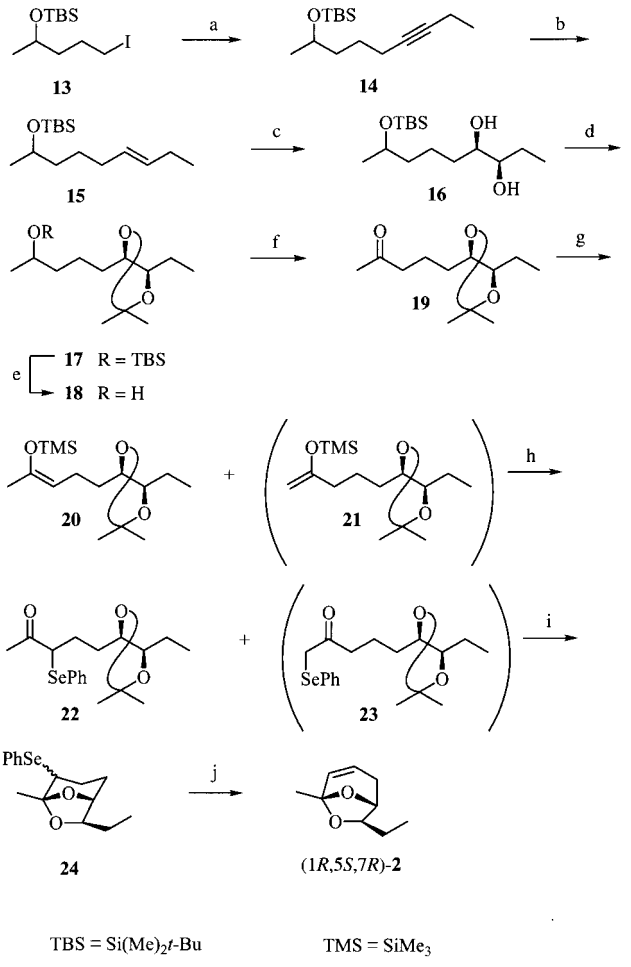
Scheme 5 summarizes our synthesis of (1*R*,5*S*,7*R*)-**2**. Our starting material was the known iodide **13**.[16] Alkylation of but-1-yne with **13** yielded **14**, which was reduced with sodium in liquid ammonia to give the (*E*)-alkene **15**. Asymmetric dihydroxylation of **15** was achieved by treating it with osmium tetroxide-based oxidant in the presence of 1,4-bis(9-*O*-dihydroquinidine)phthalazine [$(DHQD)_2PHAL$] under the so-called AD-mix β® conditions[15] to give, in 97% yield, (2*RS*,6*R*,7*R*)-**16** with ca. 93% *ee* at C-6 and C-7, as determined by GC analysis on Chirasil-DEX-CB®. The diol system of **16** was then protected as acetonide, and the resulting acetonide *tert*-butyldimethylsilyl (TBS) ether

Table 1. Decrease in the enantiomeric purity of **1** under different storage conditions

	State of the sample of (*S*)-**1**	Storage temperature	Duration of storage	Decrease in the *ee* of (*S*)-**1**[a]
a	neat	room temp.	5 days	6.7% (82.4→75.7)
b	neat	−78°C	5 days	0.4% (82.4 → 82.0)
c	50% (*w*/*v*) in hexane	room temp.	5 days	3.3% (82.4 → 79.1)
d	10% (*w*/*v*) in hexane	room temp.	9 days	1.7% (92.7 → 91.0)
e	5% (*w*/*v*) in hexane	room temp.	9 days	0.6% (92.7 → 92.1)

[a] The enantiomeric excess (*ee*) was determined by HPLC analysis [Chiralcel-OD® + Chiralcel-OD-H® (two combined columns), hexane/*i*PrOH, 150:1, 5°C, 0.5 mL/min, detection at 254 nm]

17 was desilylated to furnish **18**. Oxidation of **18** with pyridinium chlorochromate (PCC) afforded the ketone **19**, $[\alpha]_D^{20}$ = +21.1 ($CHCl_3$), the spectral properties of which matched those of our previously reported sample of **19**, $[\alpha]_D^{24}$ = +22.5 ($CHCl_3$), prepared from D-(−)-tartaric acid.[12] Conversion of **19** to (1*R*,5*S*,7*R*)-**2** was achieved via **20**, **22**, and **24** to give 2, $[\alpha]_D^{20}$ = −84.1 ($CHCl_3$), ca. 94% *ee*, as estimated by GC analysis, in 27% overall yield based on **13** (10 steps).



Scheme 5. Synthesis of (1*R*,5*S*,7*R*)-**2**; reagents: (a) *n*BuLi, but-1-yne, THF/HMPA (92%). − (b) Na, NH_3 (88%). − (c) $(DHQD)_2PHAL$, $K_2OsO_2(OH)_4$, $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$, *t*BuOH/H_2O (97%). − (d) *p*TsOH, $Me_2C(OMe)_2$, Me_2CO (99%). − (e) $(nBu)_4NF$, THF (93%). − (f) PCC, NaOAc, CH_2Cl_2 (92%). − (g) TMSCl, Et_3N, DMF (92%, **20**:**21** = 4:1). − (h) PhSeCl, C_5H_5N, CH_2Cl_2 (66%). − (i) *p*TsOH, Et_2O/H_2O (95%). − (j) *m*CPBA, $NaHCO_3$, CH_2Cl_2 (70%).

In conclusion, both enantiomers of 2-*sec*-butyl-4,5-dihydrothiazole (**1**) and those of (1*R*,5*S*,7*R*)-3,4-dehydro-*exo*-brevicomin (**2**) have been synthesized, which might be useful in further studies of the biological role of these compounds in chemical communication among mice.

Experimental Section

General: Boiling points: uncorrected values. − IR: Jasco A-102 and Perkin−Elmer 1640. − ^{1}H NMR: Jeol JNM-EX 90A (90 MHz), Jeol JNM-LA400 (400 MHz), and Jeol JNM-LA500 (500 MHz, TMS at δ = 0.00 or $CHCl_3$ at δ = 7.26 as internal standard). − ^{13}C NMR: Jeol JNM-LA400 (100 MHz) and Jeol JNM-LA500 (126 MHz, TMS at δ = 0.00 as internal standard). − Optical rotation: Jasco DIP-1000. − MS: Jeol JMS-SX102A. − Column chromatography: Merck Kieselgel 60 Art 1.07734 and Merck aluminium oxide 90 active basic Art 1.01076. − TLC: 0.25 mm Merck silica gel plates (60F-254).

(*S*)-2-Methylbutanoic Acid [(*S*)-4]: To a stirred and cooled solution of (*S*)-**3** (20.6 g, 233 mmol) in acetone (200 mL), Jones' CrO_3 reagent (2.69 M, 110 mL, 296 mmol) was added dropwise at 0°C and the mixture was stirred for 2 h at room temperature. The reaction was then quenched by the addition of 2-propanol and the mixture was concentrated in vacuo. The residue was diluted with water and extracted with diethyl ether. The organic phase was washed with dilute HCl and brine, dried with $MgSO_4$, and concentrated. The residue was distilled to give 20.1 g (85%) of (*S*)-**4** as a colorless oil; b.p. 76−78°C/13 Torr. − n_D^{24} = 1.4049. − $[\alpha]_D^{19}$ = +19.8 (*c* = 1.15, $CHCl_3$) {ref.[17] n_D^{25} = 1.4043, $[\alpha]_D^{25}$ = +19.14}. − IR (film): $\tilde{\nu}$ = 3200−2575 cm^{-1} (bs, O−H), 1710 (bs, C=O), 1465 (s), 1420 (s), 1230 (s), 1090 (m), 1015 (m), 945 (s), 780 (m). − ^{1}H NMR (90 MHz, $CDCl_3$): δ = 0.94 (t, *J* = 7.4 Hz, 3 H, 4-H_3), 1.18 (d, *J* = 6.8 Hz, 3 H, 2-H_3), 1.30−1.89 (m, 2 H, 3-H_2), 2.21−2.53 (sextet, *J* = 6.9 Hz, 1 H, 2-H), 8.25−9.80 (br. s, 1 H, CO_2H).

Methyl (*S*)-2-Methylbutanoate [(*S*)-5]: To a solution of (*S*)-**4** (9.51 g, 102 mmol) in diethyl ether (20 mL) at 0°C, a solution of diazomethane (194 mmol) in diethyl ether (110 mL) was added and the mixture was stirred at room temperature for 1 h. The reaction was then quenched with acetic acid. The mixture was poured into saturated aqueous $NaHCO_3$ and extracted with diethyl ether. The organic phase was washed with brine, dried with $MgSO_4$, and concentrated. The residue was distilled to give 2.67 g (76%) of (*S*)-**5** as a colorless oil; b.p. 77−78°C/196 Torr. − n_D^{24} = 1.3910. − $[\alpha]_D^{19}$ = +23.1 (*c* = 1.11, $CHCl_3$) {ref.[18] $[\alpha]_D^{27}$ = +21.1 (*c* = 1.7, MeOH)}. − IR (film): $\tilde{\nu}$ = 1740 cm^{-1} (s, C=O), 1460 (s), 1435 (m), 1260 (m), 1200 (s), 1155 (m, C−O), 1090 (m), 1020 (m), 985 (m), 870 (m), 800 (m), 755 (m). − ^{1}H NMR (90 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.3 Hz, 3 H, 4-H_3), 1.14 (d, *J* = 7.1 Hz, 3 H, 2-CH_3), 1.26−1.95 (m, 2 H, 3-H_2), 2.17−2.59 (sextet, *J* = 6.9 Hz, 1 H, 2-H), 3.67 (s, 3 H, OCH_3). − HRMS ($C_6H_{12}O_2$): calcd.

116.0837; found 116.0836. − GC [column: Chirasil-DEX®-CB, 0.25 mm × 25 m, 50 + 1.0°C/min; carrier gas: He, pressure 150 kPa]: t_R = 6.68 min [(*R*)-**5**, 0.6%], 6.95 [(*S*)-**5**, 99.4%]. The enantiomeric purity of (*S*)-**5** was 98.8% *ee*.

(*S*)-2-*sec*-Butyl-4,5-dihydrothiazole [(*S*)-1]: To a suspension of 2-aminoethanethiol (cysteamine) hydrochloride (0.68 g, 6.0 mmol) in dry toluene (25 mL) under argon, a solution of $(i\text{Bu})_3\text{Al}$ (1.0 M in toluene, 15 mL, 15 mmol) was added dropwise at room temperature. The solution was refluxed for 30 min., then (*S*)-**5** (0.66 g, 5.7 mmol) was added dropwise. After stirring for 2 h under reflux, the mixture was diluted with 25 mL of toluene, cooled to room temperature, and quenched with MeOH (4 mL). The mixture was stirred at room temperature for 15 min., and then a saturated aqueous solution of Rochelle's salt (20 mL), saturated aqueous $NaHCO_3$ (20 mL), and brine (20 mL) were successively added. Diethyl ether (50 mL) was then added and the mixture was stirred vigorously for 15 min. The organic phase was then separated and the aqueous phase was extracted with further diethyl ether. The combined organic phases were dried with $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on alumina (activity grade I, 20 g, pentane/diethyl ether, 5:1) and distilled to give 331 mg (41%) of (*S*)-**1** as a colorless oil; b.p. 61−63°C/8 Torr. − n_D^{23} = 1.4948. − $[\alpha]_D^{22}$ = +21.6 (*c* = 1.04, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 2975 cm^{-1} (s, C−H), 2950 (s, C−H), 2900 (s, C−H), 2875 (s, C−H), 1630 (s, C=N), 1460 (s), 1380 (m), 1330 (w), 1310 (w), 1260 (w), 1200 (m), 1155 (m), 1060 (m), 1020 (m), 985 (s), 960 (m), 925 (s), 850 (w), 840 (m), 820 (w), 795 (m), 705 (w). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (t, *J* = 7.3 Hz, 3 H, 3′-H_3), 1.19 (d, *J* = 6.8 Hz, 3 H, 1′-CH_3), 1.45−1.74 (m, 2 H, 2′-H_2), 2.48−2.72 (m, 1 H, 1′-H), 3.24 (t, *J* = 8.3 Hz, 2 H, 4-H_2), 4.21 (ddt, *J* = 8.3, 0.7, 0.7 Hz, 2 H, 5-H_a). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.7 (C-3′), 18.7 (C-1′), 28.5 (C-5), 33.0 (C-2′), 40.8 (C-1′), 64.3 (C-4), 176.8 (C-2). − HRMS ($C_7H_{13}NS$): calcd. 143.0766; found 143.0762. Due to the high volatility of (*S*)-**1**, correct combustion analytical data could not be obtained. − HPLC [column: Chiralcel-OD® + Chiralcel-OD-H®, 2 × 4.6 mm × 25 cm (2 combined columns); solvent: hexane/*i*PrOH, 150:1, flow rate: 0.5 mL/min; detection: 254 nm], t_R = 25.7 min [(*R*)-**1**, 3.7%], 27.0 [(*S*)-**1**, 96.3%]. The enantiomeric purity of (*S*)-**1** was 92.6% *ee*.

***tert*-Butyl (*R*)-4-Hydroxy-3-methylbutanoate (8):** To a solution of **7** (7.00 g, 37.2 mmol) in dry THF (50 mL), borane−dimethyl sulfide complex (2.0 M in THF, 20 mL, 40 mmol) was added dropwise at room temperature. After stirring for 24 h, this mixture was quenched with water at 0°C and neutralized with K_2CO_3. The mixture was extracted with diethyl ether, and the organic phase was washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was distilled to give 6.28 g (97%) of **8** as a colorless oil. This was employed in the next step without further purification; b.p. 72−74°C/1.4 Torr. − n_D^{26} = 1.4280. − $[\alpha]_D^{25}$ = +4.99 (*c* = 1.03, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 3435 cm^{-1} (s, O−H), 1730 (s, C=O), 1365 (s), 1255 (m, *t*Bu), 1160 (s, C−O), 1040 (s), 995 (m), 965 (m), 840 (m). − ^{1}H NMR (90 MHz, $CDCl_3$): δ = 0.96 (d, *J* = 6.5 Hz, 3 H, 3-CH_3), 1.45 [s, 9 H, $C(CH_3)_3$], 1.62 (s, 1 H, OH), 1.72−2.51 (m, 3 H, 2-H_2, 3-H), 3.41−3.65 (m, 2 H, 4-H_2).

***tert*-Butyl (*R*)-3-Methyl-4-tetrahydropyranyloxybutanoate (9):** To a solution of **8** (5.67 g, 32.6 mmol) in dry CH_2Cl_2 (100 mL), 3,4-dihydro-2*H*-pyran (DHP, 4.0 mL, 44.2 mmol) and *p*-toluenesulfonic acid monohydrate (0.04 g) were added at room temperature. After stirring for 4 h, the mixture was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic phase was washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (100 g, hexane/ethyl acetate, 10:1) and distilled to give 8.31 g (99%) of **9** as a colorless oil; b.p. 95−97°C/1.0 Torr. − n_D^{25} = 1.4420. − $[\alpha]_D^{24}$ = +4.48 (*c* = 1.02, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 1730 cm^{-1} (s, C=O), 1365 (s), 1255 (m, *t*Bu), 1160 (s, C−O), 1035 (s, C−O), 980 (m), 905 (m), 870 (m). − ^{1}H NMR (90 MHz, $CDCl_3$): δ = 0.98 (d, *J* = 6.2 Hz, 3 H, 3-CH_3), 1.40−2.58 (m, 9 H, 3-H, 2-, 2′-, 3′-, 4′-H_2), 1.45 [s, 9 H, $C(CH_3)_3$], 3.16−3.97 (m, 4 H, 4-, 5′-H_2), 4.57 (br. s, 1 H, 1′-H). − $C_{14}H_{26}O_4$ (258.4): calcd. C 65.09, H 10.14; found C 65.11, H 10.15.

(*R*)-3-Methyl-4-tetrahydropyranyloxy-1-butanol (10): To a suspension of $LiAlH_4$ (0.56 g, 14.8 mmol) in dry diethyl ether (40 mL), a solution of **9** (3.80 g, 14.7 mmol) in dry diethyl ether (40 mL) was added at 0°C and the mixture was stirred at room temperature for 4 h. The mixture was then quenched with water (0.6 mL), 15% aqueous NaOH (0.6 mL), and further water (1.8 mL) at 0°C. After stirring for 30 min., the suspension was filtered through a bed of Celite. The filtrate was dried with K_2CO_3 and concentrated in vacuo. The residue was chromatographed on silica gel (50 g, hexane/ethyl acetate, 10:1) and distilled to give 2.58 g (93%) of **10** as a colorless oil; b.p. 97−99°C/1.1 Torr. − n_D^{25} = 1.4552. − $[\alpha]_D^{26}$ = +7.89 (*c* = 1.03, $CHCl_3$). − IR(film): $\tilde{\nu}$ = 3420 cm^{-1} (s, O−H), 1200 (s, C−O), 1120 (s, C−O), 1030 (s, C−O), 975 (m), 900 (m), 835 (m), 810 (m). − ^{1}H NMR (90 MHz, $CDCl_3$): δ = 0.95 (d, *J* = 6.6 Hz, 3 H, 3-CH_3), 1.25−2.08 (m, 9 H, 3-H, 2-, 2′-, 3′-, 4′-H_2), 2.27−2.47 (pseudo t, 1 H, OH), 3.19 (dd, *J* = 9.5, 7.1 Hz, 1 H, 4-H_a), 3.28 (dd, *J* = 9.5, 4.7 Hz, 1 H, 4-H_b), 3.39−4.03 (m, 4 H, 1-, 5′-H_2), 4.59 (br. s, 1 H, 1′-H). − $C_{10}H_{20}O_3$ (188.3): calcd. C 63.80, H 10.71; found C 63.55, H 10.84.

(*R*)-3-Methyl-4-tetrahydropyranyloxybutyl Tosylate (11): To a solution of **10** (12.5 g, 66.3 mmol) in dry pyridine (70 mL), *p*-toluenesulfonyl chloride (10.3 g, 93.7 mmol) was added at 0°C. After stirring at 0°C for 18 h, the mixture was diluted with water and extracted with diethyl ether. The organic phase was washed with saturated aqueous $CuSO_4$, water, saturated aqueous $NaHCO_3$ and brine, dried with K_2CO_3, and concentrated in vacuo to give 21.1 g (97%) of crude **11**. This was employed in the next step without further purification. − IR (film): $\tilde{\nu}$ = 1600 cm^{-1} (m, C=C), 1500 (m), 1360 (s, SO_2), 1180 (s, SO_2), 1120 (m, C−O), 1100 (m, C−O), 1040 (s, C−O), 950 (s), 820 (s), 770 (s), 665 (s). − ^{1}H NMR (90 MHz, $CDCl_3$): δ = 0.88 (d, *J* = 6.2 Hz, 3 H, 3-CH_3), 1.20−2.11 (m, 9 H, 3-H, 2-, 2′-, 3′-, 4′-H_2), 2.45 (s, 3 H, *p*-CH_3), 2.98−3.92 (m, 4 H, 4-, 5′-H_2), 4.12 (t, *J* = 6.4 Hz, 2 H, 1-H_2), 4.50 (br. s, 1 H, 1′-H), 7.34 (d, *J* = 8.1 Hz, 2 H, Ph), 7.80 (d, *J* = 8.1 Hz, 2 H, Ph).

(*R*)-2-Methyl-1-tetrahydropyranyloxybutane (12): To a suspension of $LiAlH_4$ (3.47 g, 91.4 mmol) in dry diethyl ether (150 mL), a solution of **11** (21.0 g, 64.4 mmol) in dry diethyl ether (30 mL) was added at 0°C and the mixture was stirred at room temperature for 4 h. The mixture was then quenched with water (3.5 mL), 15% aqueous NaOH (3.5 mL), and further water (10.5 mL) at 0°C. After stirring for 30 min., the suspension was filtered through a bed of Celite. The filtrate was dried with K_2CO_3 and concentrated in vacuo. The residue was chromatographed on silica gel (100 g, hexane/ethyl acetate, 20:1) and distilled to give 10.9 g (98%) of **12** as a colorless oil; b.p. 74−76°C/10 Torr. − n_D^{24} = 1.4346. − $[\alpha]_D^{20}$ = −2.53 (*c* = 1.15, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 1465 cm^{-1} (m), 1380 (m), 1355 (m), 1205 (s), 1135 (s, C−O), 1085 (s, C−O), 1070 (s, C−O), 1040 (s, C−O), 980 (m), 910 (m), 875 (m), 820 (m). − ^{1}H NMR (90 MHz, $CDCl_3$): δ = 0.82−0.96 (m, 6 H, 2-CH_3, 4-H_3), 1.01−1.89 (m, 9 H, 2-H, 3-, 2′-, 3′-, 4′-H_2), 3.06−4.00 (m, 4 H, 1-, 5′-H_2), 4.56 (br. s, 1 H, 1′-H). These data are in good accord with those in ref.[10]

(*R*)-2-Methyl-1-butanol [(*R*)-3]: To a solution of **12** (2.56 g, 14.9 mmol) in MeOH (60 mL) was added *p*-toluenesulfonic acid

monohydrate (0.01 g) and the mixture was stirred for 3 h under reflux. After neutralization with K_2CO_3, the mixture was poured into brine and extracted with diethyl ether. The organic phase was washed with brine, dried with $MgSO_4$, and concentrated. The residue was chromatographed on silica gel (20 g, pentane/diethyl ether, 5:1) and distilled to give 0.74 g (57%) of (*R*)-**3** as a colorless oil; b.p. 127−128°C. − n_D^{23} = 1.4103. − $[\alpha]_D^{20}$ = +6.32 (*c* = 1.08, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 3350 cm^{-1} (s, O−H), 1045 (s, C−O), 1015 (m), 760 (m). − ^{1}H NMR (90 MHz, $CDCl_3$): δ = 0.85−0.97 (m, 3 H, 4-H_3), 0.91 (d, *J* = 6.2 Hz, 3 H, 2-CH_3), 1.07−1.67 (m, 4 H, 2-H, 3-H_2, OH), 3.47 (dd, *J* = 5.8, 2.4 Hz, 2 H, 1-H_2). These data are in good accord with those in ref.[11]

(*R*)-2-Methylbutanoic Acid [(*R*)-4]: In the same manner as described above, (*R*)-**3** (3.71 g, 42.2 mmol) was converted to (*R*)-**4** (3.21 g, 75%), b.p. 83−85°C/18 Torr. − n_D^{24} = 1.4047. − $[\alpha]_D^{24}$ = −19.9 (*c* = 1.18, $CHCl_3$) {ref.[17] n_D^{25} = 1.4049, $[\alpha]_D^{25}$ = −19.8}. − Its IR and ^{1}H-NMR spectra were identical to those of the (*S*) isomer.

Methyl (*R*)-2-Methylbutanoate [(*R*)-5]: In the same manner as described above, (*R*)-**4** (3.11 g, 30.5 mmol) was converted to (*R*)-**5** (2.67 g, 76%), b.p. 68−72°C/170 Torr. − n_D^{23} = 1.3935. − $[\alpha]_D^{20}$ = −23.2 (*c* = 1.10, $CHCl_3$). − Its IR and ^{1}H-NMR spectra were identical to those of the (*S*) isomer. − HRMS ($C_6H_{12}O_2$): calcd. 116.0837; found 116.0826. − GC [under the same conditions as for the analysis of (*S*)-**5**]: t_R = 6.68 min [(*R*)-**5**, 100%]. The enantiomeric purity of (*R*)-**5** was ca. 100% *ee*.

(*R*)-2-*sec*-Butyl-4,5-dihydrothiazole [(*R*)-1]: In the same manner as described above, (*R*)-**5** (0.66 g, 5.71 mmol) was converted to (*R*)-**1** (282 mg, 35%), b.p. 69−71°C/11 Torr. − n_D^{24} = 1.4952. − $[\alpha]_D^{22}$ = −21.3 (*c* = 1.01, $CHCl_3$). − Its IR, ^{1}H-, and ^{13}C-NMR spectra were identical to those of the (*S*) isomer. − HRMS ($C_7H_{13}NS$): calcd. 143.0766; found 143.0764. Due to the high volatility of (*R*)-**1**, correct combustion analytical data could not be obtained. − HPLC [under the same conditions as for the analysis of (*S*)-**1**]: t_R = 26.4 min [(*R*)-**1**, 95.8%], 27.6 [(*S*)-**1**, 4.2%]. The enantiomeric purity of (*R*)-**1** was 91.6% *ee*.

8-(*tert*-Butyldimethylsilyloxy)non-3-yne (14): To a solution of but-1-yne (18.3 g, 339 mmol) in dry THF (400 mL) at −78°C under argon, *n*BuLi in hexane (3.02 M, 40 mL, 121 mmol) was added dropwise. The mixture was allowed to warm to −15°C and stirring was continued at this temperature. After 2 h, hexamethylphosphoric triamide (HMPA, 40 mL) was added at −20°C and the resulting mixture was stirred for 10 min. A solution of **13** (31.4 g, 95.7 mmol) in dry THF (40 mL) and HMPA (40 mL) was then added at −30°C and the mixture was left to stir overnight at room temperature. Saturated aqueous NH_4Cl solution and diethyl ether were then added and the organic phase was separated. The combined organic phases were washed with water, saturated aqueous $NaHCO_3$ solution and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (300 g, hexane/ethyl acetate, 150:1) to give 22.4 g (92%) of **14** as a colorless oil. An analytical sample was purified by distillation; b.p. 78−81°C/1.1 Torr. − n_D^{24} = 1.4424. − IR (film): $\tilde{\nu}$ = 2975 cm^{-1} (s, C−H), 1260 (s, Si−CH_3), 1130 (s, C−O), 1095 (s, Si−O), 840 (s) 770 (s). − ^{1}H NMR (90 MHz, $CDCl_3$): δ = 0.05 [s, 6 H, $Si(CH_3)_2$], 0.89 [s, 9 H, $SiC(CH_3)_3$], 1.11 (t, *J* = 7.3 Hz, 3 H, 1-H_3) 1.12 (d, *J* = 6.0 Hz, 3 H, 9-H_3), 1.38−1.62 (m, 4 H, 6-, 7-H_2), 1.99−2.37 (m, 4 H, 2-, 5-H_2), 3.64−3.98 (m, 1 H, 8-H). − $C_{15}H_{30}OSi$ (254.5): calcd. C 70.80, H 11.88; found C 70.78, H 11.85.

***trans*-8-(*tert*-Butyldimethylsilyloxy)non-3-ene (15):** Under argon atmosphere, sodium (4.70 g, 204 mmol) was added to ammonia (200 mL) at −60°C. After stirring for 1 h at −65°C, a solution of **14** (17.6 g, 69.2 mmol) in dry THF (60 mL) was added dropwise. After stirring for 3 h, the reaction was quenched with NH_4Cl (12.4 g). Stirring was continued overnight at room temperature. The mixture was then concentrated in vacuo, diluted with water, and extracted with diethyl ether. The organic phase was washed with saturated aqueous $NaHCO_3$ and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was distilled to give 15.6 g (88%) of **15** as a colorless oil; b.p. 77−80°C/1.7 Torr. − n_D^{24} = 1.4371. − IR (film): $\tilde{\nu}$ = 1250 cm^{-1} (s, Si−CH_3), 1140 (s, C−O), 1095 (s, Si−O), 970 (m), 840 (s), 770 (s). − ^{1}H NMR (90 MHz, $CDCl_3$): δ = 0.05 [s, 6 H, $Si(CH_3)_2$], 0.89 [s, 9 H, $SiC(CH_3)_3$], 0.96 (t, *J* = 7.1 Hz, 3 H, 1-H_3), 1.11 (d, *J* = 6.2 Hz, 3 H, 9-H_3), 1.22−1.61 (m, 4 H, 6-, 7-H_2), 1.84−2.19 (m, 4 H, 2-, 5-H_2), 3.60−3.97 (m, 1 H, 8-H), 5.35−5.46 (m, 2 H, 3-, 4-H). − $C_{15}H_{32}OSi$ (256.5): calcd. C 70.24, H 12.58; found C 69.84, H 12.79.

(2*RS*,6*R*,7*R*)-2-(*tert*-Butyldimethylsilyloxy)-6,7-dihydroxynonane (16): To a mixture of water (300 mL) and 2-methylpropan-2-ol (270 mL) at room temperature were added potassium hexacyanoferrate(III) (58.8 g, 178 mmol), K_2CO_3 (24.7 g, 179 mmol), potassium osmate dihydrate (0.0875 g, 0.237 mmol), the AD ligand [$(DHQD)_2PHAL$, 0.464 g, 0.596 mmol], and methanesulfonamide (5.70 g, 59.9 mmol). The mixture was stirred for 90 min., and then cooled to 0°C. A solution of **15** (15.4 g, 60.0 mmol) in 2-methylpropan-2-ol (30 mL) was added and the resulting mixture was stirred for 40 h at 0°C. The reaction was subsequently quenched by the addition of sodium sulfite heptahydrate (90.0 g, 357 mmol) at 0°C. The mixture was then allowed to warm to room temperature, stirred for 2 h, saturated with NaCl, and extracted with ethyl acetate. The organic phase was washed with 2 M aqueous KOH, dried with anhydrous magnesium sulfate, and concentrated in vacuo. The residue was chromatographed on silica gel (200 g, hexane/ethyl acetate, 10:1) to give 16.8 g (97%) of **16** as a colorless oil; n_D^{24} = 1.4515. − $[\alpha]_D^{20}$ = +13.3 (*c* = 1.10, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 3400 cm^{-1} (s, O−H), 1255 (s, Si−CH_3), 1135 (s, C−O), 840 (s), 805 (m), 775 (s). − ^{1}H NMR (90 MHz, $CDCl_3$): δ = 0.05 [s, 6 H, $Si(CH_3)_2$], 0.89 [s, 9 H, $SiC(CH_3)_3$], 0.98 (t, *J* = 7.1 Hz, 3 H, 9-H_3), 1.12 (d, *J* = 6.2 Hz, 3 H, 1-H_3), 1.20−1.72 (m, 6 H, 3-, 4-, 8-H_2), 1.95−2.09 (m, 2 H, OH), 3.21−3.60 (m, 2 H, 5-, 6-H), 3.62−3.97 (m, 1 H, 2-H). − $C_{15}H_{34}O_3Si$ (290.520): calcd. C 62.02, H 11.80; found C 61.94, H 11.62. − GC [Chirasil-DEX-CB®, 0.25 mm × 25 m, 160 + 0.4°C/min; carrier gas: He, pressure 120 kPa]: t_R = 28.87 min [one isomer of (2*RS*,6*S*,7)-**16**, 1.8%], 29.23 [the other isomer of (2*RS*,6*S*,7*S*)-**16**, 1.9%], 29.59 [(2*RS*,6*R*,7*R*)-**16**, 96.3%]. The enantiomeric purity of (6*R*,7*R*)-**16** was 93% *ee*.

(4*R*,5*R*)-5-Ethyl-2,2-dimethyl-4-(4-*tert*-butyldimethylsilyloxypentyl)-1,3-dioxolane (17): To a solution of **16** (15.5 g, 53.4 mmol) in acetone (200 mL) at room temperature were added 2,2-dimethoxypropane (7.30 mL, 59.4 mmol) and *p*-toluenesulfonic acid monohydrate (0.04 g) and the resulting mixture was stirred for 7 h. K_2CO_3 (0.50 g, 3.62 mmol) was then added and stirring was continued for a further 30 min. The mixture was then concentrated in vacuo, poured into saturated aqueous $NaHCO_3$ solution, and extracted with diethyl ether. The organic phase was washed with brine, dried with K_2CO_3, and concentrated in vacuo. The residue was chromatographed on silica gel (300 g, hexane/ethyl acetate, 100:1) to give 17.4 g (97%) of **17** as a colorless oil; n_D^{24} = 1.4357. − $[\alpha]_D^{20}$ = +15.5 (*c* = 1.14, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 1260 cm^{-1} (s, Si−CH_3), 1140 (m), 1105 (s, C−O), 880 (m), 840 (s), 775 (s). − ^{1}H NMR (90 MHz, $CDCl_3$): δ = 0.04 [s, 6 H, $Si(CH_3)_2$], 0.88 [s,

9 H, $SiC(CH_3)_3$], 0.88−1.08 (m, 3 H, 2′′-H_3), 1.12 (d, J = 6.2 Hz, 3 H, 5′-H_3), 1.20−1.77 (m, 8 H, 1′-, 2′-, 3′-, 1′′-H_2), 1.38 [s, 6 H, 2-$(CH_3)_2$], 3.40−4.04 (m, 3 H, 4-, 5-, 4′-H). − $C_{18}H_{38}O_3Si$ (330.6): calcd. C 65.40, H 11.59; found C 65.20, H 11.34.

(4*R*,5*R*)-5-Ethyl-2,2-dimethyl-4-(4-hydroxypentyl)-1,3-dioxolane (18): To a solution of **17** (15.2 g, 45.9 mmol) in THF (250 mL) at room temperature was added Bu_4NF (1.0 M solution in THF, 92 mL, 92 mmol). After stirring at room temperature for 12 h, the mixture was poured into water and extracted with diethyl ether. The organic phase was washed with saturated aqueous $NaHCO_3$ solution and brine, dried with K_2CO_3, and concentrated in vacuo. The residue was chromatographed on silica gel (100 g, hexane/ethyl acetate, 3:1) and distilled to give 9.18 g (93%) of **18** as a colorless oil; b.p. 92−93°C/1.4 Torr. − n_D^{24} = 1.4424. − $[\alpha]_D^{21}$ = +25.7 (c = 1.10, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 3450 cm^{-1} (s, O−H), 1240 (s), 1100 (s, C−O), 880 (S). − ^1H NMR (90 MHz, $CDCl_3$): δ = 0.99 (t, J = 7.3 Hz, 3 H, 2′′-H_3), 1.20 (d, J = 6.2 Hz, 3 H, 5′-H_3), 1.36−1.72 (m, 9 H, 1′-, 2′-, 3′-, 1′′-H_2, OH), 1.38 [s, 6 H, 2-$(CH_3)_2$], 3.43−4.02 (m, 3 H, 4-, 5-H, 4′-H). − $C_{12}H_{24}O_3$ (216.3): calcd. C 66.63, H 11.18; found C 66.49, H 11.10.

(4*R*,5*R*)-4-Ethyl-2,2-dimethyl-5-(4-oxopentyl)-1,3-dioxolane (19): To a suspension of PCC (4.90 g, 22.7 mmol) and sodium acetate (0.10 g, 1.23 mmol) in CH_2Cl_2 (80 mL) was added a solution of **18** (2.40 g, 11.1 mmol) in CH_2Cl_2 (20 mL) at 0°C. After stirring at room temperature for 12 h, the suspension was diluted with diethyl ether and filtered through silica gel. The filtrate was concentrated in vacuo and the residue was chromatographed on silica gel (30 g, hexane/ethyl acetate, 75:1) and distilled to give 2.18 g (92%) of **19** as a colorless oil; b.p. 80−81°C/1.3 Torr. − n_D^{25} = 1.4364. − $[\alpha]_D^{20}$ = +21.1 (c = 1.14, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 1720 cm^{-1} (s, C=O), 1170 (s, C−O), 1100 (s), 880 (m). − ^1H NMR (90 MHz, $CDCl_3$): δ = 0.99 (t, J = 7.4 Hz, 3 H, 2′-H_3), 1.15−1.90 (m, 6 H, 1′′-, 2′′-, 1′-H_2), 1.37 [s, 6 H, 2-$(CH_3)_2$], 2.14 (s, 3 H, 5′′-H_3), 2.41 (t, J = 6.6 Hz, 2 H, 4′′-H_2), 3.42−3.71 (m, 2 H, 4-, 5-H).

(4*R*,5*R*)-4-Ethyl-2,2-dimethyl-5-(4-trimethylsilyloxy-3-pentenyl)-1,3-dioxolane (20): To a solution of TMSCl (9.0 mL, 70.9 mmol) and Et_3N (20 mL, 143 mmol) in dry DMF (80 mL) at 45°C was added **19** (5.03 g, 23.5 mmol) and the mixture was heated at 130°C. After 24 h, 72 h, and 120 h, further aliquots of TMSCl (9.0 mL, 70.9 mmol) and Et_3N (20 mL, 143 mmol) were added and heating was continued for 48 h with stirring. After cooling, the mixture was diluted with *n*-pentane and washed with cold saturated aqueous $NaHCO_3$ (twice). The organic phase was rapidly washed with cold aqueous 1 N HCl and cold saturated aqueous $NaHCO_3$, dried with $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (100 g, hexane/ethyl acetate, 50:1) to give 6.16 g (92%) of a mixture of silyl enol ethers **20** and **21** (ca. 20% by 500 MHz ^1H NMR). This was employed in the next step without further purification. An analytical sample was purified by distillation; b.p. 103−104°C/3.9 Torr. − n_D^{24} = 1.4385. − $[\alpha]_D^{21}$ = +21.4 (c = 1.34, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 1680 cm^{-1} (s, C=C), 1250 (s, Si−Me), 1180 (s, C−O), 1100 (s), 845 (s), 760 (s), 690 (m). − ^1H NMR (90 MHz, $CDCl_3$): δ = 0.19 [s, 9 H, $Si(CH_3)_3$], 0.99 (t, J = 7.4 Hz, 3 H, 2′-H_3), 1.21−1.64 (m, 4 H, 1′′-, 1′-H_2), 1.38 [s, 6 H, 2-$(CH_3)_2$], 1.74−1.77 (m, 3 H, 5′′-H_3), 1.88−2.27 (m, 2 H, 2′′-H_2), 3.42−3.78 (m, 2 H, 4-, 5-H), 4.44 (t, J = 8.9 Hz), 4.64 (t, J = 9.8 Hz, total 1H, 3′′-H)

(4*R*,5*R*,3′*RS*)-4-Ethyl-2,2-dimethyl-5-(4-oxo-3-phenylselenopentyl)-1,3-dioxolane (22): Under argon atmosphere, to a solution of PhSeCl (4.08 g, 21.3 mmol) in dry CH_2Cl_2 (250 mL) at 0°C was added pyridine (1.8 mL, 22.3 mmol). After stirring for 30 min., a solution of **20** contaminated with **21** (5.51 g, 19.3 mmol) in CH_2Cl_2 (50 mL) was added to the mixture at the same temperature. After stirring at 0°C for 2 h, the mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $CuSO_4$ solution, water, saturated aqueous $NaHCO_3$ solution and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (150 g, benzene/diethyl ether, 15:1) to give 4.70 g (66%) of **22** as a colorless oil and 1.61 g of **23** as a yellow oil. **22**: n_D^{24} = 1.5238. − $[\alpha]_D^{21}$ = +47.4 (c = 1.19, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 3075 cm^{-1} (m, C−H), 3000 (s), 2950 (s), 2875 (s), 1705 (s, C=O), 1580 (m, C=C), 1480 (m, C=C), 1440 (m), 1380 (s), 1370 (s), 1240 (s), 1175 (s, C−O), 1105 (s), 1000 (s), 875 (m), 740 (s), 695 (m). − ^1H NMR (90 MHz, $CDCl_3$): δ = 0.90−1.07 (t, J = 7 Hz, 3 H, 2′-H_3), 1.15−1.90 (m, 6 H, 1′′-, 2′′-, 1′-H_2), 1.37 [s, 6 H, 2-$(CH_3)_2$], 2.14 (s, 3 H, 5′′-H_3), 3.42−3.71 (m, 3 H, 4-, 5-, 3′′-H), 7.21−7.58 (m, 5 H, Ph).

(2*R*,4*RS*,6*S*,7*R*)-*exo*-7-Ethyl-5-methyl-4-phenylseleno-6,8-dioxabicyclo[3.2.1]octane (24): To a solution of **22** (3.10 g, 8.40 mmol) in diethyl ether (30 mL), *p*-toluenesulfonic acid monohydrate (1.52 g) and 12 drops of water were added at room temperature. After stirring for 3 h at room temperature, the mixture was diluted with diethyl ether, washed with saturated aqueous $NaHCO_3$, water and brine, dried with K_2CO_3, and concentrated in vacuo to give 2.48 g (95%) of **24**. This was employed in the next step without further purification; n_D^{24} = 1.5182. − $[\alpha]_D^{20}$ = +89.0 (c = 1.14, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 3075 cm^{-1} (m, C−H), 1580 (s, C=C), 1480 (s), 1455 (s), 1380 (s), 1330 (m), 1310 (m), 1235 (s), 1185 (s), 1175 (s, C−O), 1125 (s), 1000 (s), 970 (s), 930 (m), 860 (s), 740 (s), 695 (m). − ^1H NMR (90 MHz, $CDCl_3$): δ = 0.90 (t, J = 7 Hz, 3 H, 9-H_3), 1.36−2.63 (m, 6 H, 1′′-, 2′′-, 1′-H_2), 1.56, 1.71 (each s, total 3 H, 5-CH_3), 3.22−3.32 (m, 1 H, 4-H), 3.84−4.02 (m, 1 H, 7-H), 4.18 (br. s, 1 H, 1-H), 7.21−7.58 (m, 5 H, Ph).

(2*R*,5*S*,7*R*)-3,4-Dehydro-*exo*-brevicomin {*exo*-7-Ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]oct-3-ene} (2): To a solution of **24** (2.45 g, 7.88 mmol) in dry CH_2Cl_2 (70 mL) at −78°C, $NaHCO_3$ (1.66 g, 19.8 mmol) and a solution of *m*CPBA (70% purity, 2.18 g, 8.84 mmol) in dry CH_2Cl_2 (20 mL) were added dropwise. After stirring at this temperature for 10 min., the reaction was quenched with 10% aqueous sodium sulfite solution. The mixture was washed with saturated aqueous $NaHCO_3$ (twice) and brine, dried with $MgSO_4$, and concentrated. The residue was distilled to give 847 mg (70%) of **2** as a colorless oil; b.p. 94−96°C/51 Torr. − $[\alpha]_D^{20}$ = −84.1 (c = 1.14, $CHCl_3$) {ref.[12] $[\alpha]_D^{24}$ = −90.5 (c = 0.95, $CHCl_3$)}. − n_D^{24} = 1.4499. − IR (film): $\tilde{\nu}$ = 3060 cm^{-1} (s, C−H), 2975 (s), 2950 (s), 2900 (s), 2850 (s), 1640 (m, C=C), 1460 (m), 1425 (m), 1395 (s), 1380 (s), 1345 (w), 1320 (m), 1255 (s), 1200 (s), 1185 (m, C−O), 1150 (m), 1130 (w), 1115 (m), 1095 (m), 1065 (w), 1045 (s), 1025 (m), 1020 (s), 1005 (m), 970 (s), 925 (m), 905 (s), 890 (w), 860 (s), 845 (m), 780 (m), 760 (m), 715 (s). − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.94 (t, J = 7.4 Hz, 3 H, 9-H_3), 1.55 (s, 3 H, 5-CH_3), 1.55−1.64 (m, 2 H, 8-H_2), 1.85 (dddd, J = 18.0, 4.3, 1.8, 0.9 Hz, 1 H, 2-H_a), 2.65 (dddd, J = 18.0, 4.3, 2.2, 2.2 Hz, 1 H, 2-H_b), 3.79 (td, J = 6.4, 1.8 Hz, 1 H, 7-H), 4.24 (dddd, J = 4.2, 1.8, 1.8, 0.9 Hz, 1 H, 6-H), 5.71 (dddd, J = 9.5, 4.3, 2.2, 1.8 Hz, 1 H, 4-H), 5.82 (ddd, J = 9.5, 2.3, 1.8 Hz, 1 H, 3-H). − ^{13}C NMR (125 MHz, $CDCl_3$): δ = 9.8 (C-9), 22.1 (C-8), 27.5 (C-1′), 32.1 (C-2), 77.1 (C-1), 82.0 (C-7), 102.5 (C-5), 124.3 (C-4), 132.0 (C-3). − HRMS ($C_9H_{14}O_2$): calcd. 154.0994; found 154.0987. − No correct combustion analytical data could be obtained due to the high volatility of **2**. − GC [column: Chirasil-DEX-CB®, 0.25 mm × 25 m, 90 + 0.4°C/min); carrier gas: He, pressure 150 kPa]: t_R = 11.68 min

[(2*R*,5*S*,7*R*)-**2**, 97.1%], 14.28 [(2*S*,5*R*,7*S*)-**2**, 2.9%]. The enantiomeric purity of (2*R*,5*S*,7*R*)-**2** was 94.2% *ee*.

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