A Sex Pheromone Isolated from *Macrocentrus grandii*: Absolute Stereochemistry Determination and Implications

Injae Shin, Hui-qiang Zhou, Nanette Loida S. Que, and Hung-wen Liu*

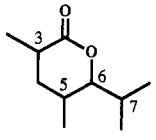
Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455

Paul D. Swedenborg and Richard L. Jones

Department of Entomology, University of Minnesota, St. Paul, Minnesota 55108

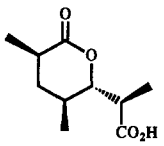
Received November 12, 1992 (Revised Manuscript Received February 26, 1993)

One of nature's designs to control the European corn borer (*Ostrinia nubilalis*) population involves deployment of its natural enemy, the larval parasitoid *Macrocentrus grandii*.[1] In light of the increasing emphasis toward more ecologically sound methods of solving agricultural problems,[2] an approach analogous to that employed by nature in containing the population, and hence, the damage inflicted by the corn borer, is quite appealing.[3] This particular strategy hinges on enhancing the fluctuating *M. grandii* population, and toward this objective, an exploration of the insect's courtship behavior, as well as the chemical nature of their sex pheromones, could be beneficial. Recently, a tetrahydropyranone derivative, (3*S**,5*R**,6*S**)-3,5-dimethyl-6-isopropyl-2,4,5,6-tetrahydropyran-2-one (**1**), had been isolated and identified as



1

(3*R*,5*S*,6*R*) or (3*S*,5*R*,6*S*)



2

(3*R*,5*S*,6*S*)

the third and most interesting component of the *M. grandii* sex pheromone.[4] Of particular interest is the structural similarity of the isolated tetrahydropyranone from this insect with the Prelog–Djerassi lactonic acid **2**, a well-known oxidative degradation product of a number of microbial macrolide antibiotics.[5] In order to confirm the identity of this natural product, as well as to establish its absolute stereochemistry, the two possible enantiomers (**1a** and **1b**) of this pheromone component, based on the relative stereochemistry, were prepared.

Retrosynthetical examination of potential routes to the target molecules led to the recognition of the potential of the meso compound **3** as a common precursor for both enantiomers. The essence of the synthesis resides on whether asymmetric hydroboration of **6** was performed prior to or after the removal of the chiral auxiliary, thus affording enantiomers **8** and **10** whose enantiotopic hydroxyl groups are differentially protected. As shown in Scheme I, preparation of the key intermediate **6** as a single diastereomer, initiated by acylation of the lithium anion of oxazolidinone **4**[6] and alkylation of the resulting product **5**, was effected by Evan's procedure.[7] While reductive removal of the oxazolidinone followed by hydroxyl protection and then olefin hydroboration gave **8** in 40% overall yield, reversal of the reaction sequence conveniently led to the other enantiomer **10**. Although a 6:1 diastereoselectivity was found for the hydroboration of **6**,[8] owing to the little steric bias imposed by the appendant methyl substituent at the adjacent chiral center, only a 2:1 diastereofacial selectivity was observed upon hydroboration of **7**. After the minor contaminant was removed by flash chromatography (0–5% EtOAc in hexane) in both cases, the configuration of the newly generated chiral center in **8** and **9** was assigned based on a transition-state model,[9] and the enantiomeric purity of both samples was confirmed by NMR analysis of the corresponding Mosher esters.[10] The fact that nearly identical rotation with opposite signs was observed for **8** and **10** further established their enantiomeric relationship. Conversion to the aldehyde **11** was achieved using the Parikh modification of the Moffatt oxidation (95%),[11] which was subsequently alkylated in the presence of methylaluminum bis(2,4,6-tri-*tert*-butylphenoxide) (MAT), the Yamamoto reagent.[12] Unfortunately, instead of the expected and desired product **12a**, a Meerwein–Pondorf–Verley-type reduction occurred to give back **8** as the sole product.[13] Thus, an alternate strategy was adapted involving a simple Grignard reaction using isopropylmagnesium chloride as the nucleophile (92%), PCC oxidation (95%), and stereoselective reduction

(1) (a) Chiang, H. C.; Palmer, D. F. *J. Minnesota Acad. Sci.* **1978**, *44*, 15. (b) Lewis, L. C. *Iowa State J. Res.* **1982**, *56*, 429. (c) Ding, D.; Swedenborg, P. D.; Jones, R. L. *Ann. Entomol. Soc. Am.* **1989**, *82*, 232. Other examples, see: (d) Lewis, W. J.; Snow, J. W.; Jones, R. L. *J. Econ. Entomol.* **1971**, *64*, 1417. (e) Robacker, D. C.; Weaver, K. M.; Hendry, L. B. *J. Chem. Ecol.* **1976**, *2*, 39. (f) Takahashi, S.; Sugai, T. *Entomol. Gen.* **1982**, *7*, 287.

(2) (a) Greany, P. D.; Vinson, S. B.; Lewis, W. J. *BioScience* **1984**, *34*, 690. (b) Tumlinson, J. H. *J. Chem. Ecol.* **1988**, *14*, 2109.

(3) (a) Winnie, W. V.; Chiang, H. C. *Entomophaga* **1984**, *27*, 183. (b) Andreadis, T. G. *J. Invert. Path.* **1980**, *5*, 229. (c) Burbutis, P. P.; Erwin, N.; Ertle, L. R. *Environ. Entomol.* **1981**, *10*, 779. (d) Andreadis, T. G. *J. Econ. Entomol.* **1982**, *75*, 626.

(4) Compound **1** elicits upwind anemotaxis in the males and exhibits synergism with two other pheromone constituents, (*Z*,*Z*)-9,13-heptacosadiene and (*Z*)-4-tridecenal (Swedenborg, P. D.; Jones, R. L. *J. Chem. Ecol.* **1992**, *18*, 1913. Swedenborg, P. D.; Jones, R. L.; Liu, H.-w.; Krick, T. P. *J. Chem. Ecol.* **1993**, *19*, 485).

(5) (a) Djerassi, C.; Zderic, J. A. *J. Am. Chem. Soc.* **1956**, *78*, 6390. (b) Anliker, R.; Dvornik, D.; Gubler, K.; Heusser, H.; Prelog, V. *Helv. Chim. Acta* **1956**, *39*, 1785. (c) Rickards, R. W.; Smith, R. M. *Tetrahedron Lett.* **1970**, 1025. (d) Manwaring, D. G.; Rickards, R. W.; Smith, R. M. *Tetrahedron Lett.* **1970**, 1029. (e) Martin, S. F.; Guinn, D. E. *Synthesis* **1991**, 245.

(6) Correa, A.; Denis, J. N.; Greene, A. E. *Synth. Commun.* **1991**, *21*, 1.

(7) (a) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737. (b) Evans, D. A.; Bartroli, J. *Tetrahedron Lett.* **1982**, 807. (c) Evans, D. E.; Mathre, D. J. *J. Org. Chem.* **1985**, *50*, 1830. (d) Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001. (e) Evans, D. A.; Polniaszek, R. P.; DeVries, K. M.; Guinn, D. E.; Mathre, D. J. *J. Am. Chem. Soc.* **1991**, *113*, 7613.

(8) An 85:15 diastereofacial selectivity was found for the hydroboration of a similar system.[7b]

(9) Evans, D. A.; Bartroli, J.; Godel, T. *Tetrahedron Lett.* **1982**, 4577.

(10) (a) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543. (b) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. (c) Yasuhara, F.; Yamaguchi, S. *Tetrahedron Lett.* **1977**, 4085. (d) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.

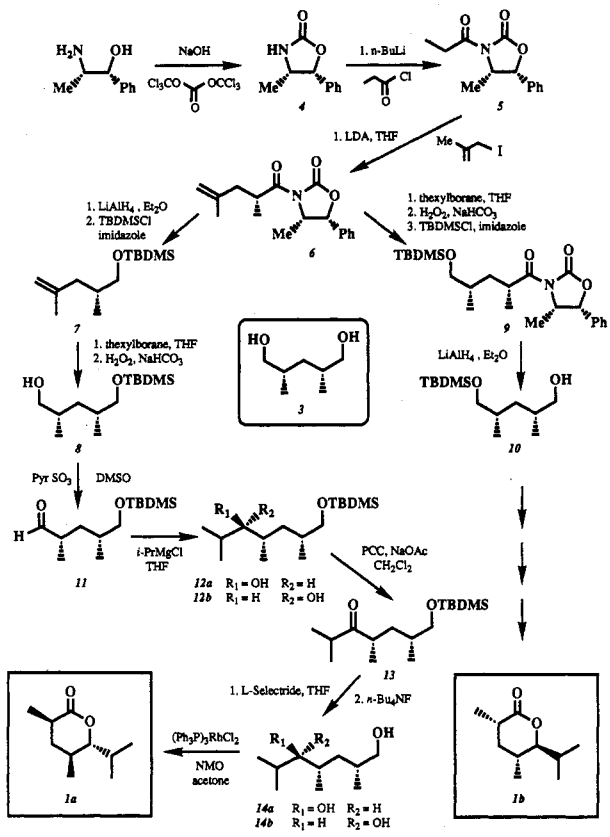
(11) Parikh, J. R.; Doering, W. von E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.

(12) Maruoka, K.; Itoh, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1985**, *107*, 4573.

(13) It had been reported that reduction could occur if the nucleophile is a *sec*-alkyl or *tert*-alkylmagnesium halide.[12]

0022-3263/93/1958-2923$04.00/0

Scheme I



with L-Selectride (Aldrich) (95%).[14] Since alkylation of **11** follows Cram addition, the desired **12a** was obtained in a 1:4.6 ratio along with **12b** as expected. The last two steps in the aforementioned sequence were intended to reverse the product ratio. In cognizance of the general Cram selectivity of L-Selectride on the reduction of α-chiral ketones, it was hoped that this reducing agent would stereoselectively favor the formation of the desired **12a**. However, due to the large steric interaction between the isopropyl group and the methyl group in **13**, this reduction still yielded the undesired isomer as the major product, albeit the Cram product was generated in a better ratio than was previously obtained (1:1.8 versus 1:4.6). After deprotection (quantitative), **14a** was separated from **14b** and was finally converted to target molecule **1a** by oxidative lactonization (99%).[7b,15] The overall yield starting from **4** was 4.8%. Analogous steps were carried out for the preparation of **1b**. The spectral properties of **1a** and **1b** were identical in all respects with those of the natural product.[4]

Upon completion of the wind tunnel and field tests, the stereospecificity in the recognition of this pheromone component became apparent when only enantiomer **1b**, individually and in combination with another pheromone component, (*Z*)-4-tridecenal, elicited the expected behaviors from the male insects characteristic of those observed with the natural pheromone.[16] These results unequivocally reveal the absolute configuration of this natural component as (3*S*,5*R*,6*S*)-3,5-dimethyl-6-isopropyl-3,4,5,6-tetrahydropyran-2-one.[17] This constitutes only the second example of the isolation, identification, synthesis, and field bioassay of a parasitoid's sex pheromone.[18]

With the understanding of the chemical nature of this pheromone as a whole and with further studies, its potential in pest control may be realized.

Experimental Section

Melting points are uncorrected. The NMR spectra were recorded on a 300- or a 200-MHz spectrometer. *J* values are given in Hz. The NMR assignments labeled with an asterisk (*) may be interchangeable. Flash chromatography was performed in columns of various diameters with J. T. Baker (230–400 mesh) silica gel by elution with the solvents reported. Analytical thin-layer chromatography (TLC) was carried out on Merck silica gel 60 G-254 plates (25 mm). TLC spots were visualized either with UV light or by dipping the plates into the staining solutions of vanillin/ethanol/sulfuric acid (1:98:1) or phosphomolybdic acid (7% ethanolic solution) and then heating them. The drying agent used in the routine workup was anhydrous magnesium sulfate. Solvents, unless otherwise specified, were reagent grade and distilled once prior to use. It should be pointed out that no attempt was made to optimize the stereoselectivity and chemical yield of each step.

(2*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]-2,4-dimethylpent-4-ene (7). To a well-stirred suspension of 2.23 g (58.8 mmol) of lithium aluminum hydride in 120 mL of ether at 0 °C was added dropwise a solution of 16.9 g (58.9 mmol) of imide **6**[7b] in 25 mL of ether. The ice bath was removed, and the solution was allowed to warm to room temperature. After being stirred for 30 min, the reaction was quenched by sequential addition of 2.2 mL of water, 2.2 mL of 15% aqueous NaOH, and 6.6 mL of water. The mixture was filtered, and the filtrate was washed with brine, dried, filtered, and concentrated in vacuo. The alcohol product, (2*R*)-2,4-dimethylpent-4-en-1-ol, was isolated in 70% (4.7 g) yield by distillation under reduced pressure (60 °C, 20 mmHg): ^{1}H NMR ($CDCl_3$) δ 4.73 (1 H; d; *J* = 1.3; 5-H), 4.69 (1 H; d; *J* = 1.3; 5-H), 3.53–3.37 (2 H; m; 1-H's), 2.19–2.06 (1 H; m; 3-H), 1.88–1.79 (2 H; m; 2-H and 3-H), 1.71 (3 H; s; 4-Me), 0.88 (3 H; d; *J* = 6.3; 2-Me); ^{13}C NMR ($CDCl_3$) δ 144.2 (C-4), 111.4 (C-5), 68.0 (C-1), 42.0 (C-3), 33.3 (C-2), 21.9 (4-Me), 16.3 (2-Me).

To a solution of 1.72 g (15.09 mmol) of (2*R*)-2,4-dimethylpent-4-en-1-ol and 1.23 g (18.1 mmol) of imidazole in 40 mL of methylene chloride was added 2.7 g (18.1 mmol) of *tert*-butyldimethylsilyl chloride at 0 °C. While stirring, the reaction mixture was allowed to warm to room temperature. After the mixture was stirred overnight, water was added to quench the reaction, and the resulting mixture was extracted with methylene chloride (25 mL × 3), dried, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (5% ethyl acetate in hexane) to afford 3.27 g (95%) of product **7**: ^{1}H NMR ($CDCl_3$) δ 4.73 (1 H; bs; 5-H), 4.65 (1 H; bs; 5-H), 3.46–3.34 (2 H; m; 1-H's), 2.15 (1 H; dd; *J* = 12.4, 4.5; 3-H), 1.79–1.69 (2 H; m; 2- and 3-H's), 1.71 (3 H; s; 4-Me), 0.89 (9 H; s; *tert*-butyl), 0.84 (3 H; d, *J* = 6.3; 2-Me), 0.03 (6 H; s; Si-Me's); ^{13}C NMR ($CDCl_3$) δ 144.5 (C-4), 111.4 (C-5), 68.1 (C-1), 42.0 (C-3), 33.7 (C-2), 25.9 (4-Me), 22.3 (C(*Me*)$_3$), 18.3 (*C*(Me)$_3$), 16.5 (2-Me), -5.4 (Si-Me's); high-resolution FAB-MS calcd for $C_{13}H_{29}OSi$ $(M+1)^+$ 229.1988, found 229.1979.

(2*R*,4*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-2,4-dimethylpentan-5-ol (8). A solution of thexylborane was generated by dropwise addition of 5.5 mL (5.5 mmol) of 1 M solution of

(14) Midland, M. M.; Kown, Y. C. *J. Am. Chem. Soc.* **1983**, *105*, 3725.
(15) Sharpless, K. B.; Akashi, K.; Oshima, K. *Tetrahedron Lett.* **1976**, 2503.

(16) Wind tunnel bioassays demonstrated that enantiomer **1b** elicited flight initiation, upwind anemotaxis, and casting in male wasps comparable to female-derived lactone. Response to the **1a** enantiomer averaged 14% of the response to the **1b** enantiomer. Field studies demonstrated the **1b** enantiomer trapped male wasps ($\bar{X}$ = 32.8) comparable to female-derived lactone ($\bar{X}$ = 27.2) and when either lactone was combined with (*Z*)-4-tridecenal the response was synergistic ($\bar{X}$ = 136.2 and $\bar{X}$ = 143.0, respectively).
(17) An analogous compound, invictolide, has been isolated from fire ant queens (*Solenopsis invicta*) (Rocca, J. R.; Tumlinson, J. H.; Glancey, B. M.; Lofgren, C. S. *Tetrahedron Lett.* **1983**, 1893; Mori, K. *Tetrahedron* **1989**, *45*, 3233).
(18) The first example was the characterization of (*Z*)-9-hexadecenoate as a sex pheromone of *Syndipnus rubiginosus*, a sawfly parasitoid (Eller, F. J.; Bartelt, R. J.; Jones, R. L.; Kulman, H. M. *J. Chem. Ecol.* **1984**, *10*, 291. Morse, B. W.; Kulman, H. M. *Environ. Entomol.* **1985**, *14*, 131).

tetramethylethylene in THF to 5.5 mL (5.5 mmol) of 1 M solution of borane in THF at −15 °C. After being stirred for 4 h at −15 °C, this cold thexylborane solution was added to a separate flask containing 500 mg (2.19 mmol) of the silylated olefin 7 in 5 mL of THF at −15 °C. The reaction was allowed to proceed at −15 °C for 5 h. It was then quenched by sequential addition of 8 mL of 5% aqueous $NaHCO_3$, 90 mL of methanol, and 8 mL of 30% aqueous H_2O_2. After the solution was stirred at 0 °C for 1 h, the volatiles were removed in vacuo, and the residue was extracted with methylene chloride (20 mL × 3). The combined organic extracts were dried, filtered, and concentrated in vacuo. The residue, a mixture (2:1) of alcohol 8 and its 4-epimer, was purified by flash chromatography (ethyl acetate in hexane, 0–10% gradient) to give 327 mg of the desired product 8. The total yield of 8 and its 4-epimer was 91%. Compound 8: $[\alpha]_D$ −1.2° ($CHCl_3$, *c* 1.4); ^1H NMR ($CDCl_3$) δ 3.51–3.32 (4 H; m; 1-H's and 5-H's), 1.74–1.62 (3 H; m; 2-, 3-, and 4-H's), 1.42 (1 H; m; 3-H), 0.92 (3 H; d; *J* = 6.7; 4-Me)*, 0.88 (9 H; s; *tert*-butyl), 0.87 (3 H; d; *J* = 6.3; 2-Me)*, 0.02 (6 H; s; Si-Me's); ^{13}C NMR ($CDCl_3$) δ 68.3, 68.2 (C-1 and C-5), 37.3, 33.3 (C-2 and C-4)*, 33.2 (C-3)*, 25.9 (C(*Me*)$_3$), 18.3 (*C*(Me)$_3$), 17.8, 17.7 (2-Me and 4-Me), −5.4 (Si-Me's); high-resolution FAB-MS calcd for $C_{13}H_{31}O_2Si$ (M + 1)$^+$ 247.2093, found 247.2088.

The alcohol product yielded from the asymmetric hydroboration reaction was also converted to the corresponding Mosher ester which was then subjected to NMR analysis to determine its enantiomeric purity. The Mosher ester was obtained by the incubation of the parent alcohol (30 mg, 98 μmol) with DMAP (50 mg, 41 mmol), triethylamine (30 μL, 0.11 mmol), and (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetic chloride (42 μL, 0.11 mmol) at room temperature overnight. The desired product was isolated by flash chromatography (12% ethyl acetate in hexane) in 59% yield: ^1H NMR ($CDCl_3$) δ 7.51–7.38 (5 H; m; Ar H's), 4.26 (1 H; dd; *J* = 10.7, 4.8; 1-H), 3.99 (1 H; dd; *J* = 10.7, 7.0; 1-H), 3.54 (3 H; s; OMe), 3.39 (1 H; dd; *J* = 9.7, 5.5; 5-H), 3.30 (1 H; dd, *J* = 9.7, 6.3; 5-H), 1.96 (1 H; m; 2-H)*, 1.66 (1 H; m; 4-H)*, 1.37 and 0.93 (1 H each; m; 3'-Hs), 0.92 (3 H; d, *J* = 6.7; 4-Me), 0.87 (3 H; buried; 2-Me), 0.86 (9 H; s; *tert*-butyl), 0.01 (6 H; s; SiMe's). The methoxyl signal remained as a singlet upon successive addition of chiral shifting reagent.

(4*S*,5*R*)-3-[(2'*R*,4'*S*)-1'-Oxo-2',4'-dimethyl-5'-[(*tert*-butyldimethylsilyl)oxy]pentyl]-4-methyl-5-phenyl-2-oxazolidinone (9). To a chilled (−15 °C) thexylborane solution (0.5 M), which was generated by mixing dropwise 16.8 mL of 1 M tetramethylethylene in THF with 16.8 mL of 1 M borane in THF at −20 °C for 5 h, was added 1.2 g (4.2 mmol) of 6 in 10 mL of THF, and the resulting mixture was stirred for 36 h at −15 °C. The reaction was quenched by sequential addition of 10 mL of 5% $NaHCO_3$, 30 mL of methanol, and 10 mL of 30% H_2O_2 at 0 °C. After being stirred at 0 °C for 1 h, the volatiles were removed under reduced pressure, and the residue was extracted three times with 30 mL of ether. The ether layer was washed with brine, dried, and filtered. After solvent was removed in vacuo, the crude product which contained the (2'*R*,4'*S*) and (2'*R*,4'*R*) isomers in 6:1 ratio was purified by flash chromatography (15% ethyl acetate in hexane) to give the desired alcohol in 63% yield: ^1H NMR ($CDCl_3$) δ 7.46–7.26 (5 H; m; Ar H's), 5.66 (1 H; d; *J* = 7.2; 5-H), 4.78 (1 H; dq; *J* = 7.2, 6.6; 4-H), 3.81 (1 H; m; 2'-H), 3.59 (1 H; dd; *J* = 11.3, 4.5; 5'-H), 3.46 (1 H; dd; *J* = 11.3, 4.5; 5'-H), 2.24 (1 H; s; OH), 1.97–1.83, 1.74–1.62, 1.26–1.10 (1 H each; m; 3'-H's and 4'-H), 1.19 (3 H; d; *J* = 6.7; 2'-Me), 0.97 (3 H; d, *J* = 6.7; 4'-Me), 0.87 (3 H; d, *J* = 6.6; 4-Me); ^{13}C NMR ($CDCl_3$) δ 176.6 (C-1'), 152.6 (C-2), 132.9, 128.5, 128.4, 125.3, (Ar C's), 78.6 (C-5), 65.9 (C-5'), 54.7 (C-4), 36.6 (C-2')*, 35.4 (C-4)*, 33.0 (C-3')*, 17.4 (4'-Me), 16.6 (2'-Me), 14.2 (4-Me).

To a solution of 900 mg (2.95 mmol) of the above alcohol and 401 mg (5.9 mmol) of imidazole in 20 mL of methylene chloride was added 888 mg (5.9 mmol) of *tert*-butyldimethylsilyl chloride at 0 °C. The mixture was stirred at room temperature overnight. After solvent was removed, the residue was purified by flash chromatography (10% ethyl acetate in hexane) to give compound 9 (1.21 g) in 98% yield: ^1H NMR ($CDCl_3$) δ 7.47–7.25 (5 H; m; Ar H's), 5.65 (1 H; d; *J* = 7.3; 5-H), 4.77 (1 H; dq; *J* = 7.3; 6.6; 4-H), 4.01–3.92 (1 H; m; 2'-H), 3.52 (1 H; dd; *J* = 10.0, 5.3; 5'-H), 3.33 (1 H; dd; *J* = 10.0, 6.8; 5'-H), 1.87, 1.66–1.59, 1.24–1.11 (1 H each; m; 3'-H's and 4'-H)*, 1.20 (3 H; d; *J* = 6.0; 2'-Me), 0.90 (3 H; d; *J* = 6.7; 4'-Me), 0.88 (9 H; s; *tert*-butyl), 0.86 (3 H; d; *J* = 6.6; 4-Me), 0.03 (6 H; s; Si-Me's); ^{13}C NMR ($CDCl_3$) δ 177.2 (C-1'), 152.7 (C-2), 133.5, 128.7, 125.7 (Ar C's), 78.6 (C-5), 68.1 (C-5'), 54.8 (C-4), 37.5 (C-2')*, 35.2 (C-4')*, 33.7 (C-3')*, 25.9 (C(*Me*)$_3$), 18.3 (*C*(Me)$_3$), 18.2 (4'-Me), 17.3 (2'-Me), 14.6 (4-Me), −5.4 (SiMe's); high-resolution FAB-MS calcd for $C_{23}H_{38}NO_4Si$ (M + 1)$^+$ 420.2570, found 420.2566.

The alcohol product yielded from the asymmetric hydroboration reaction was also converted to the corresponding Mosher ester by the aforementioned procedure and then subjected to NMR analysis to determine its enantiomeric purity: ^1H NMR ($CDCl_3$) δ 7.51–7.25 (10 H; m; Ar H's), 5.65 (1 H; d; *J* = 7.3; 5-H), 4.76 (1 H; dq; *J* = 7.3, 6.6; 4-H), 4.31 (1 H; dd; *J* = 10.7, 6.8; 5'-H), 4.07 (1 H; dd; *J* = 10.7, 6.2; 5'-H), 3.55 (3 H; s; OMe), 3.33 (1 H; m; 2'-H), 1.90 (2 H; m) and 1.24 (1 H; m), 3'-H's and 4'-H, 1.19 (3 H; d; *J* = 6.8; 4'-Me), 0.94 (3 H; d; *J* = 6.3; 2'-Me), 0.86 (3 H; d; *J* = 6.6; 4-Me). The methoxyl signal remained as a singlet upon successive addition of chiral shifting reagent.

(2*S*,4*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]-2,4-dimethylpentan-5-ol (10). To a well-stirred suspension of 127 mg (3.34 mmol) of lithium aluminum hydride in 10 mL of ether at 0 °C was added a solution of 1.4 g (3.34 mmol) of compound 9 in 20 mL of ether in dropwise fashion. After being stirred at 0 °C for 1.5 h, the reaction was quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted three times with ether, and the combined organic extracts were washed with brine, dried, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (15% ethyl acetate in hexane) to give 10 (757 mg) in 92% yield: $[\alpha]_D$ +1.3° ($CHCl_3$, *c* 1.4); ^1H NMR ($CDCl_3$) δ 3.52–3.33 (4 H; m; 1-H's and 5-H's), 1.76–1.63 (2 H; m), 1.54 (1 H; m), and 1.41 (1 H; m), 2-, 3-, and 4-H's, 0.92 (3 H; d; *J* = 6.7; 4-Me)*, 0.88 (9 H; s; *tert*-butyl), 0.87 (3 H; d; *J* = 6.3; 2-Me)*, 0.03 (6 H; s; SiMe's); ^{13}C NMR ($CDCl_3$) δ 68.2 (C-1 and C-5), 37.3, 33.3 (C-2 and C-4)*, 26.0 (C(*Me*)$_3$), 18.4 (*C*(Me)$_3$), 17.9, 17.7 (2-Me and 4-Me), −5.4 (Si-Me's); high-resolution FAB-MS calcd for $C_{13}H_{31}O_2Si$ (M + 1)$^+$ 247.2093, found 247.2089.

(2*S*,4*R*)-5-[(*tert*-Butyldimethylsilyl)oxy]-2,4-dimethylpentanal (11). To a solution of 780 mg (3.17 mmol) of alcohol 8 and 3.1 mL (22.2 mmol) of triethylamine in 9 mL of DMSO at 25 °C was slowly added a solution 1.51 g (9.51 mmol) of pyridine sulfur trioxide complex in 6 mL of DMSO. After being stirred for 30 min, the reaction was quenched by partitioning between 30 mL of ether and 20 mL of water. The aqueous layer was discarded, and the cloudy ethereal layer was washed twice with 5 mL of saturated aqueous cupric sulfate and once with 5 mL of water, dried, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (5% ethyl acetate in hexane) to give 780 mg (95%) of 11: ^1H NMR ($CDCl_3$) δ 9.55 (1 H; d; *J* = 2.5; C*H*O), 3.40 (2 H; d; *J* = 3.4; 5-H's), 2.48–2.40, 1.92–1.82, 1.82–1.61, 1.24–1.13 (1 H each; m; 2-, 3-, 4-H's), 1.12 (3 H; d; *J* = 6.7; 2-Me), 1.06 (3 H; d; *J* = 6.3; 4-Me), 0.89 (9 H; s; *tert*-butyl), 0.01 (6 H; s; SiMe's); ^{13}C NMR ($CDCl_3$) δ 205.5 (C-1), 67.9 (C-5), 44.3 (C-2), 34.7, 33.5 (C-3 and C-4), 25.9 (C(*Me*)$_3$), 18.3 (*C*(Me)$_3$), 17.2 (2-Me)*, 14.3 (4-Me)*, −5.4 (Si-Me's); high-resolution FAB-MS calcd for $C_{13}H_{29}O_2Si$ (M + 1)$^+$ 245.1937, found 245.1931.

(3*R*,4*S*,6*R*)-7-[(*tert*-Butyldimethylsilyl)oxy]-2,4,6-trimethylheptan-3-ol (12a) and (3*S*,4*S*,6*R*)-7-[(*tert*-Butyldimethylsilyl)oxy]-2,4,6-trimethylheptan-3-ol (12b). To a solution of 1.6 mL (3.2 mmol) of 2 M isopropylmagnesium chloride in 10 mL of dry THF was added 384 mg (1.6 mmol) of aldehyde 11 in 3 mL of THF at room temperature. After 1 h at room temperature, the reaction was quenched with saturated ammonium chloride. The resulting mixture was extracted with ether (10 mL × 2), dried, filtered, and concentrated in vacuo. After the solvent was removed, the residue was purified by flash chromatography (10% ethyl acetate in hexane) to give **12a** and **12b** as a 1:4.6 mixture in 92% yield: ^1H NMR ($CDCl_3$) of **12a**/**12b** δ 3.47–3.34 (2 H; m; 7-H's), 3.07 (0.8 H; dd; *J* = 8.0; 3.5; 3-H of 12b), 3.04 (0.2 H; dd; *J* = 5.7, 5.7; 3-H of **12a**), 1.76–1.67 (3 H; m; 2-, 4-, and 6-H's), 0.96 (3 H; d, *J* = 6.6; Me), 0.93–0.81 (11 H; m; 5-H's and Me's), 0.88 (9 H; s; *tert*-butyl), 0.04 (6 H; s; SiMe's); ^{13}C NMR ($CDCl_3$) of **12b** δ 79.3 (C-3), 68.2 (C-7), 37.8, 32.8, 32.2, 30.9, 26.0, 19.3, 19.1, 18.4, 16.9, 13.5, −5.4; high-resolution FAB-MS calcd for $C_{16}H_{37}O_2Si$ (M + 1)$^+$ 289.2563, found 289.2560.

Synthesis of the desired alcohol **12a** was also attempted by a similar approach with the addition of MAT (methylaluminum bis(tri-*tert*-butylphenoxide)) which was prepared *in situ* from trimethylaluminum (3 equiv) and tri-*tert*-butylphenol (6 equiv) in methylene chloride at room temperature (1 h). This reagent was first cooled to −78 °C, and to this chilled mixture was added 150 mg (0.62 mmol) of aldehyde **11** followed by 0.93 mL (3 equiv) of 2 M isopropylmagnesium chloride. The solution was maintained at −78 °C for 1.5 h and then quenched with 1 N HCl. The organic layer was separated, washed with brine, dried, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (10% ethyl acetate in hexane) to afford 197 mg (81%) of the reduced alcohol **8**. No coupled adduct **12** was detected.

(4*S*,6*R*)-7-[(*tert*-Butyldimethylsilyl)oxy]-2,4,6-trimethylheptan-3-one (13). To a stirred solution containing 200 mg (0.69 mmol) of mixed alcohol **12a/12b** (1:4.6), 57 mg (0.69 mmol) of sodium acetate, and 30 mg of powdered 4-Å molecular sieves in 10 mL of methylene chloride was added 449 mg (3 equiv) of pyridinium chlorochromate in one portion. After being stirred at room temperature for 1 h, the dark brown reaction mixture was filtered through a pad of silica gel and the filtrate was concentrated in vacuo. The desired product (189 mg) was isolated in 95% yield by flash chromatography (5% ethyl acetate in hexane): ^{1}H NMR ($CDCl_3$) δ 3.42 (1 H; dd; J = 9.8, 5.3; 7-H), 3.35 (1 H; dd; J = 9.8, 6.0; 7-H), 2.77 (1 H; heptet; J = 6.9; 2-H), 2.72 (1 H; m; 4-H), 1.79–1.69, 1.55–1.49, 1.00–0.94 (2 H; m; 5-H's and 6-H), 1.06 (3 H; d; J = 6.9; 2-Me), 1.04 (3 H; d; J = 6.6; 4-Me), 1.04 (3 H; d; J = 6.9; 2-Me), 0.88 (3 H; d; J = 6.7; 6-Me), 0.87 (9 H; s; *tert*-butyl), 0.05 (6 H; s; SiMe's); ^{13}C NMR ($CDCl_3$) δ 218.4 (C-3), 67.9 (C-7), 42.2 (C-2)*, 39.4 (C-4)*, 36.9 (C-6), 33.5 (C-5), 25.9 (C(*Me*)$_3$), 18.5 (Me), 18.4 (Me), 18.3 (*C*(Me)$_3$), 17.4 (Me), 17.3 (Me), −5.4 (Si-Me's); high-resolution FAB-MS calcd for $C_{16}H_{35}O_2Si$ $(M + 1)^+$ 287.2406, found 287.2411.

(2*R*,4*S*,5*R*)-2,4,6-Trimethylheptane-1,5-diol (14a) and (2*R*,4*S*,5*S*)-2,4,6-Trimethylheptane-1,5-diol (14b). To a solution of 165 mg (0.58 mmol) of ketone **13** in 2 mL of THF was added 1.74 mL (1.74 mmol) of 1 M L-Selectride in THF at −78 °C. The mixture was allowed to stand at −25 °C overnight. The reaction was quenched by sequential addition of 5 mL of 5% $NaHCO_3$, 15 mL of methanol, and 3 mL of 30% aqueous H_2O_2. After the solution was stirred at 0 °C for 1 h, the volatiles were removed under reduced pressure, and the residue extracted with methylene chloride (10 mL × 3). The combined extracts were dried, filtered, and concentrated in vacuo, and the residue was purified by flash chromatography (10% ethyl acetate in hexane) to give 158 mg (95%) of a mixture of (2*R*,4*S*,5*R*)- and (2*R*,4*S*,5*S*)-1-[(*tert*-butyldimethylsilyl)oxy]-2,4,6-trimethylheptan-5-ol (1:1.8). This reaction was repeated twice to collect more material.

To a THF solution (6 mL) of silyl ether (200 mg, 0.69 mmol) was added 2.0 mL (2.0 mmol) of 1 M tetrabutylammonium fluoride in THF. After being refluxed for 40 min, the reaction was quenched with saturated ammonium chloride, and the aqueous layer was extracted with ether (15 mL × 3). The combined organic layers were washed with brine, dried, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (20% ethyl acetate in hexane) to give 40 mg of the desired product **14a** and 76.8 mg of the diastereomer **14b**. Compound **14a**: ^{1}H NMR ($CDCl_3$) δ 3.48 (2 H; d; J = 4.6; 1-H's), 3.04 (1 H; dd; J = 6.9, 4.6; 5-H), 2.47–1.82 (2 H; bs; OH's), 1.81–1.59 (4 H; m; 2-, 3-, 4-, 6-H's)*, 1.32–1.24 (1 H; m; 3-H)*, 0.95 (3 H; d; J = 6.4; Me), 0.91 (3 H; d; J = 6.9; Me), 0.87 (3 H; d; J = 6.7; Me), 0.85 (3 H; d; J = 6.7; Me); ^{13}C NMR ($CDCl_3$) δ 81.7 (C-5), 66.9 (C-1), 36.2, 33.6, 33.4, 29.9 (C-2, 3, 4, 6)*, 20.1 (Me), 18.8 (Me), 17.4 (Me), 15.7 (Me); high-resolution FAB-MS calcd for $C_{10}H_{23}O_2$ $(M + 1)^+$ 175.1698, found 175.1695.

(3*R*,5*S*,6*R*)-3,5-Dimethyl-6-isopropyl-3,4,5,6-tetrahydropyran-2-one (1a) and (3*S*,5*R*,6*S*)-3,5-Dimethyl-6-isopropyl-3,4,5,6-tetrahydropyran-2-one (1b). To a solution of 30 mg (0.17 mmol) of diol **14a** in 2.5 mL of dry acetone was added 15 mg (15 μmol) of tris(triphenylphosphine)ruthenium(II) chloride and 70 mg (0.6 mmol) of *N*-methylmorpholine *N*-oxide. The mixture was stirred at room temperature for 5 h. After removal of solvent under reduced pressure, the residue was dissolved in 5 mL of methylene chloride and washed twice with 5 mL of 1 N HCl, once with 5 mL of water, dried, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (5% ethyl acetate in hexane) to give 29 mg (99%) of the final product **1a**. Compound **1b** was prepared from the corresponding diol by the same procedure in quantitative yield. Spectral data of **1a** and **1b**: ^{1}H NMR ($CDCl_3$) δ 3.81 (1 H; dd; J = 10.1, 2.0; 6-H), 2.47 (1 H; quartet of doublets; J = 11.5, 7.0, 6.0; 3-H), 1.90 (1 H; septet of doublets; J = 7.0, 7.0, 2.0; 7-H), 1.90–1.83 (2 H; m; 4-H, 5-H), 1.30 (1 H; ddd; J = 12.5, 11.5, 11.5; 4-H), 1.23 (3 H; d; J = 7.0; 3-Me), 1.03 (3 H; d; J = 7.0; 7-Me), 0.93 (3 H; d; J = 6.5; 5-Me), 0.87 (3 H; d; J = 7.0; 7-Me); ^{13}C NMR ($CDCl_3$) δ 174.9 (C-2), 91.0 (C-6), 37.7 (C-4), 36.3, 31.2, 29.4, 19.9 (Me), 17.3 (Me), 14.2 (Me); high-resolution FAB-MS calcd for $C_{10}H_{19}O_2$ $(M + 1)^+$ 171.1385, found 171.1380. Compound **1a**: $[\alpha]_D$ +24.0° ($CHCl_3$, *c* 0.5). Compound **1b**: $[\alpha]_D$ −25.0° ($CHCl_3$, *c* 0.2).

Acknowledgment. This work was supported in part by funding from National Institutes of Health (GM 35906 and 40541 to H.-w.L.) and the Minnesota Agricultural Experiment Station (to R.L.J.). H.-w.L. also thanks the National Institutes of Health for a Research Career Development Award (GM 00559).

Supplementary Material Available: NMR spectra (28 pages). This material is contained on libraries in microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.