Asymmetric Synthesis of Stegobinone via Boronic Ester Chemistry

Donald S. Matteson,* Hon-Wah Man, and Oliver C. Ho

Contribution from the Department of Chemistry, Washington State University, Pullman, Washington 99164-4630

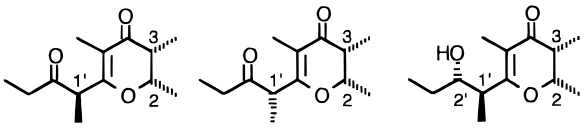
Received February 1, 1996[⊗]

Abstract: Highly stereoselective asymmetric boronic ester chemistry has been used to install all three chiral centers in a convergent synthesis of highly pure stegobinone, the epimerically labile pheromone of the drugstore beetle, *Stegobium paniceum*, and the furniture beetle, *Anobium punctatum*. Asymmetric centers were installed via the reaction of (dichloromethyl)lithium with 1,2-dicyclohexylethane-1,2-diol boronic esters. The synthetic strategy utilizes a common (α-chloroalkyl)boronic ester intermediate as the source of both segments and all of the asymmetry of the target molecule. The two segments are joined by an aldol condensation and converted to stegobiol, a minor component of the *S. paniceum* pheromone and presumably the biogenetic precursor of stegobinone. Stegobiol is stable and easily purified, and is easily converted to pure stegobinone in a single oxidation step.

Introduction

Outstanding stereocontrol has been demonstrated in the chain extension of chiral boronic esters via reaction with (dichloromethyl)lithium.[1,2] Diastereoselection exceeding 500:1 has been achieved for the installation of a pair of adjacent asymmetric centers, and it has been inferred that the enantiomeric purity of the major diastereomer is then within a few parts per million of being equal to that of the chiral director.[2] Such precise stereocontrol is usually not necessary for synthetic purposes, provided that minor amounts of stereoisomers can be removed from the product or are not detrimental to its use. In order to demonstrate the unique utility of this boron chemistry, we sought a synthetic target where such precise stereocontrol would be significant.[3]

(2*S*,3*R*,1′*R*)-Stegobinone (**1**), the epimerically labile pheromone of the drugstore beetle, *Stegobium paniceum*,[4,5] and the furniture beetle, *Anobium punctatum*,[6] has proved to be a particularly elusive synthetic challenge, even though it has a relatively simple structure. Both species are economically important pests.



1 **2** **3**

Pure **1** isolated from *S. paniceum* was crystalline, mp 52.5−53.5 °C.[4] The first synthesis by Hoffmann and co-workers proved which stereoisomer was the natural pheromone, but their product was impure and had only a small fraction of the natural activity.[7] Material synthesized by Mori and Ebata via another route was similarly impure.[8] The 1′-epimer, (2*S*,3*R*,1′*S*)-stegobinone (**2**), is strongly repellent to *S. paniceum* at the level of a few percent,[7] and impure **1** is highly prone to epimerization on standing for a few days.[7,9] Synthetic racemate of **1** was also reported to be repellent.[9]

(2*S*,3*R*,1′*S*,2′*S*)-Stegobiol (**3**) has also been identified as a component of the natural *S. paniceum* pheromone at the 5% level.[10] Natural **3** isolated as an oil by gas chromatography (and not necessarily free from all **1**, *vide infra*) was found to be attractive to *S. paniceum*, though the response of the insects was described as slow.[10] Synthetic **3** has been reported as an oil.[11] A significant synthesis of serricorole, the 2-ethyl homolog of **3**, was reported just prior to our preliminary communication.[12]

Results

General Strategy. Because the natural pheromone of *S. paniceum* contains both stegobinone (**1**) and stegobiol (**3**), a common route to both compounds was sought. The selected synthetic strategy involved initial synthesis and purification of the stable secondary alcohol **3**, which could be oxidized to the labile diketone **1** in diastereomerically and enantiomerically pure form. It was hoped that if **1** was initially free from diastereomers, especially the troublesome isomer **2**, it could be purified rapidly to a stable crystalline solid before significant isomerization took place.

Ultrahigh stereoselection has been observed in reactions of diol boronic esters of C_2 symmetry with (dichloromethyl)lithium followed by nucleophilic substitution of the resulting (α-chloroalkyl)boronic esters.[2] (*R*,*R*)-1,2-Dicyclohexylethane-1,2-diol ["(*R*,*R*)-DICHED"] was chosen for the present work because it is easily prepared by rhodium catalyzed hydrogenation

[⊗] Abstract published in *Advance ACS Abstracts,* May 1, 1996.

(1) (a) Matteson, D. S.; Sadhu, K. M.; Peterson, M. L. *J. Am. Chem. Soc.* **1986**, *108*, 812−819. (b) Matteson, D. S. *Chem. Rev.* **1989**, *89*, 1535−1551. (c) Matteson, D. S.; Kandil, A. A.; Soundararajan, R. *J. Am. Chem. Soc.* **1990**, *112*, 3964−3969.

(2) Tripathy, P. B.; Matteson, D. S. *Synthesis* **1990**, 200−206.

(3) Preliminary communication: Matteson, D. S.; Man, H.-W. *J. Org. Chem.* **1993**, *58*, 6545−6547.

(4) Kuwahara, Y.; Fukami, H.; Howard, R.; Ishii, S.; Matsumura, F.; Burkholder, W. E. *Tetrahedron* **1978**, *34*, 1769−1774.

(5) Burkholder, W. E.; Wang, Y. Personal communication, 1994.

(6) White, P. R.; Birch, M. C. *J. Chem. Ecol.* **1987**, *13*, 1695−1706.

(7) (a) Hoffmann, R. W.; Ladner, W.; Steinbach, K.; Massa, W.; Schmidt, R.; Snatzke, G. *Chem. Ber.* **1981**, *114*, 2786−2801. (b) Hoffmann, R. W.; Ladner, W. *Tetrahedron Lett.* **1979**, 4653−4656.

(8) Mori, K.; Ebata, T. *Tetrahedron* **1986**, *42*, 4413−4420.

(9) Kodama, H.; Mochizuki, K.; Kohno, M.; Ohnishi, A.; Kuwahara, Y. *J. Chem. Ecol.* **1987**, *13*, 1859−1869

(10) Kodama, H.; Ono, M.; Kohno, M.; Ohnishi, A. *J. Chem. Ecol.* **1987**, *13*, 1871−1879.

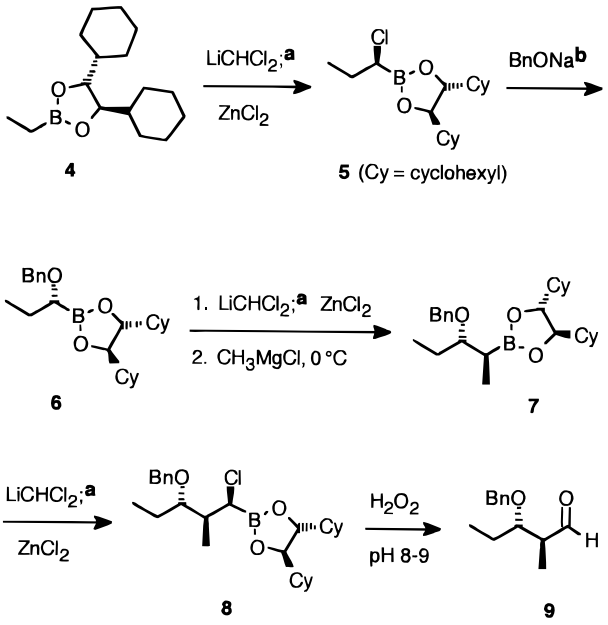
(11) Mori, K.; Ebata, T. *Tetrahedron* **1986**, *42*, 4685−4689.

(12) (a) Oppolzer, W.; Rodriguez, I. *Helv. Chim. Acta* **1993**, *76*, 1275−1281; (b) Oppolzer, W.; Rodriguez, I. *Helv. Chim. Acta* **1993**, *76*, 1282−1291.

S0002-7863(96)00345-9 CCC: $12.00

of (*R,R*)-1,2-diphenylethane-1,2-diol,[13,15] which in turn is available in large quantities from the catalytic asymmetric dihydroxylation of *trans*-stilbene.[14] 1,2-Diphenylethane-1,2-diol as chiral director has not yielded satisfactory diastereoselection.[16] The highest stereoselectivity measured rigorously has been achieved with another chiral director of C_2 symmetry, 2,5-dimethyl-3,4-hexanediol, which requires a more laborious preparation than DICHED.[2]

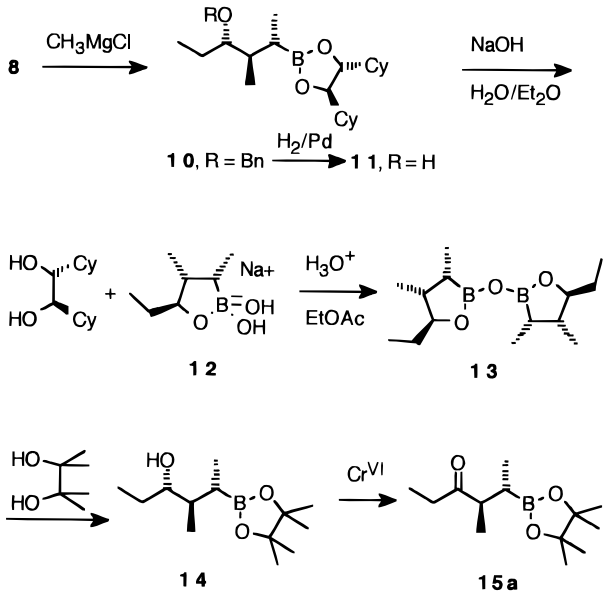
Preferred Route. The synthetic route utilizes chloro boronic ester **8** as a common intermediate for making both segments of stegobiol (**3**). From a practical standpoint, it is significant that DICHED ethylboronate (**4**) can be purified by vacuum distillation, and none of the intermediates **5**−**8** have to be purified beyond removal of solvents or inorganic salts before proceeding to the next step. Intermediate chloro boronic ester **8** contains all of the stereocenters of stegobiol. The first true purification is distillation of aldehyde **9**, which constitutes one of the two segments to be joined.



(**a**) Generated in situ from CH_2Cl_2 + LDA at −40 °C.
(**b**) In DMSO/THF.

Enolic epimerization of aldehyde **9** (∼10% on silica, ∼50% on alumina) made purification by chromatography impossible. When generated from chloro boronic ester **8** with proper pH control and freshly distilled, aldehyde **9** contained ∼0.5−1% epimer as judged from ^{1}H-NMR data. The relevant NMR curves have been published previously.[3] Although this falls far short of the diastereomeric purity achieved with compounds that are not stereolabile,[2] it has proved sufficient for our purposes.

The second segment is the keto boronic ester **15a**. Its synthesis from chloro boronic ester **8** began with methylation to **10**, followed by debenzylation to γ-hydroxy boronic ester **11**. Basic hydrolysis of **11** separated the ether soluble DICHED and impurities and yielded an aqueous solution of the oxaborolane salt **12**. Acidification of **12** yielded the oxaborolane in its dimeric anhydride form **13**, which with an equivalent amount of pinacol resulted in an equilibrium mixture containing **14** together with unchanged **13**, pinacol, and according to mass spectral analysis, the species $C_{20}H_{40}O_4B_2$ [**13** + pinacol − H_2O].[17] The mixture was oxidized by pyridinium dichromate to the stable keto boronic ester **15a**. It is again significant from a practical standpoint that none of the intermediates between **4** and **15a** require more than partial purification. Most of the impurities are extracted by ether from the aqueous solution of **12**, and **15a** is obtained sufficiently pure for further use with no purification except removal of solvent under vacuum.



For connection to **9**, **15a** must be converted to a suitable enolate. Of several boron enolates tested, the most satisfactory proved to be **16a**, which was prepared from **15a** and 9-borabicyclo[3.3.1]nonane 9-triflate at −78 °C. Dialkylboron halides required higher temperatures and did not lead to efficient enolate formation. This is the only step in the reaction sequence that has not been satisfactorily achieved at −40 °C or above. The initially formed aldol **17a** was not isolated but oxidized to the corresponding ketone **18a**, which on peroxidic deboronation followed by acidification yielded *O*-benzylstegobiol (**19**).

O-Benzylstegobiol (**19**) is easily purified by chromatography. Cleavage of the benzyl group by catalytic hydrogenation over palladium resulted in a few percent of hydrogenation of the carbon−carbon double bond, and a surprisingly mild alternative cleavage with ∼25% methanesulfonic acid in chloroform at 25 °C is recommended for the conversion to stegobiol (**3**). It is

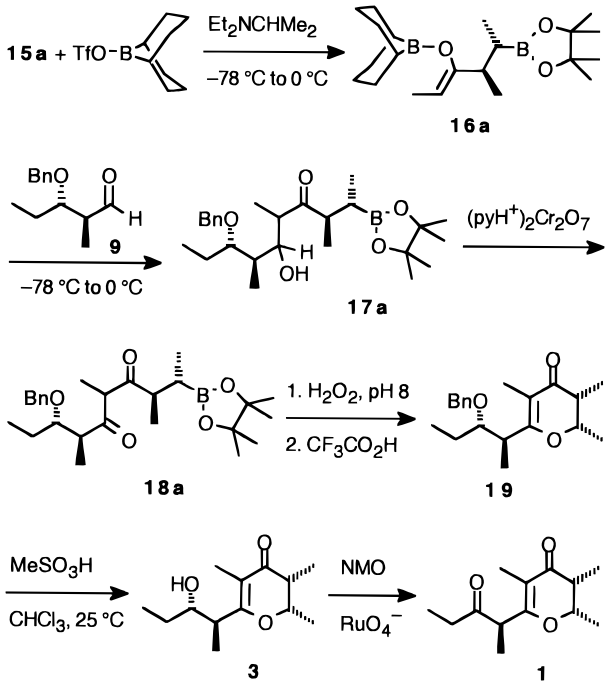
(13) Hoffmann, R. W.; Ditrich, K.; Köster, G.; Stürmer, R. *Chem. Ber.* **1989**, *122*, 1783−1789.

(14) (a) Jacobsen, E. N.; Markó, I.; Mungall, W. S.; Schröder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968−1970. (b) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M., Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768−2771. (c) Wang, Z.-M.; Sharpless, K. B. *J. Org. Chem.* **1994**, *59*, 8302−8303. (d) A potassium osmate sample consisting of larger crystals, black in appearance, failed to dissolve under the conditions described in (c), and hydroxylation failed. Addition of the osmate as a 1% aqueous solution over a period of ∼15 min resulted in satisfactory hydroxylation of the stilbene in ∼24 h. We thank Rajendra Prasad Singh for these observations.

(15) (*R,R*)-1,2-Diphenyl-1,2-ethanediol (50 g) was dissolved in ethyl acetate and washed with aqueous sulfuric acid to remove traces of alkaloidal catalyst poison and then concentrated and hydrogenated at 1 atm over 5% Rh/Al_2O_3 (2 g) in methanol (600 mL) containing 1% water and 1% acetic acid over a period of 2−4 weeks. We thank Dr. G. D. Schaumberg, Sonoma State University, for developing the hydrogenation conditions. Improved hydrogenation conditions currently under development by W. C. Hiscox will be reported elsewhere.

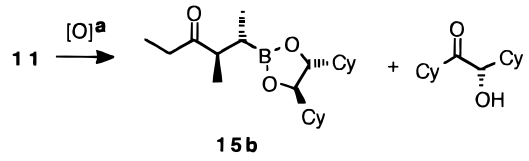
(16) This finding has been replicated in our laboratory by G. D. Schaumberg.

(17) Plausible structures include $[C_7H_{14}O]B-O-CMe_2CMe_2-O-B[OC_7H_{14}]$, where $[C_7H_{14}O]B-$ represents an oxaborolane unit, or $[C_7H_{14}O]B-OCHEtCHMeCHMeB[O_2C_2Me_4]$, an oxaborolane−hydroxy boronic ester−pinacol linkage. Either of these would equilibrate rapidly with pinacol, water, **13**, and **14**.



important that **3** be purified by chromatography before oxidation to stegobinone (**1**) with *N*-methylmorpholine *N*-oxide catalyzed by tetrapropylammonium perruthenate.[18] Stegobinone (**1**) prepared in this manner readily crystallizes after rapid chromatography over a short silica column and concentration of the solution, and recrystallization from pentane effectively removes the small amounts of impurities that remain.

Alternative Routes. Leaving the relatively fragile carbon—boron bond of γ-benzyloxy boronic ester **10** in place in subsequent intermediates, after it is no longer needed for construction of asymmetric carbons, carries the obvious liability of potential side reactions, especially during oxidative procedures. These problems were indeed encountered in a closely related route tested earlier. Oxidation of γ-hydroxy boronic ester **11** to the corresponding ketone **15b** with pyridinium

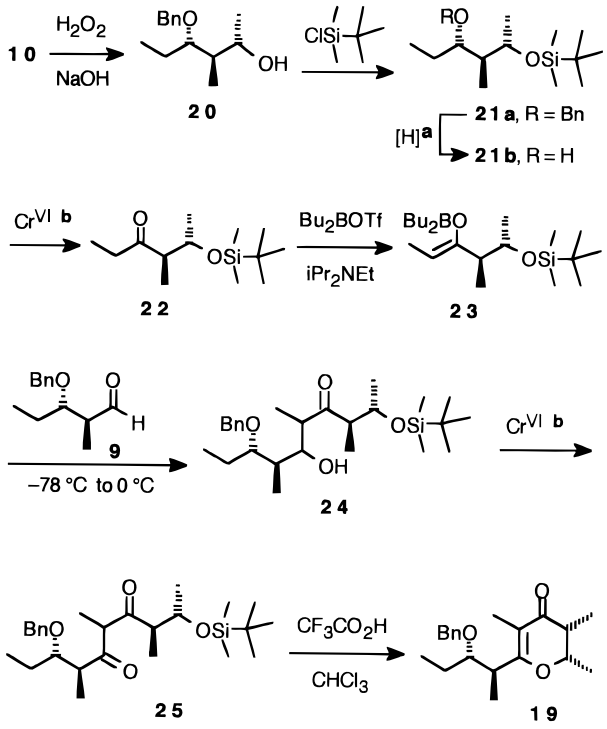


(**a**) $(pyH)_2Cr_2O_7$ or NMO/$(Pr_4N)RuO_4$ or ClCOCOCl/ DMSO /Et_3N

dichromate, *N*-methylmorpholine *N*-oxide, and tetrapropylammonium perruthenate, or Swern's method, was accompanied by significant competing oxidation of the chiral director DICHED. NMR evidence indicated that 1,2-dicyclohexyl-2-hydroxyethanone was the major byproduct.

Even with the loss, the overall yield of **15b** from **4** was 38%. However, after aldol condensation of the dibutylboron enolate from **15b** with aldehyde **9**, the resulting alcohol intermediate **17b** (DICHED analog of **17a**, not illustrated) had to be similarly oxidized to **18b**, and a second round of DICHED oxidation occurred.

Oxidation of the boronic ester function of **10** with hydrogen peroxide to the hydroxyl function of **20** successfully avoided the problem of DICHED oxidation, at the cost of some lengthening of the synthesis. Silylation of **20** to **21a** was straightforward, but if sufficient care was not taken to remove all traces of acid from **21a** before reductive debenzylation to **21b**, a significant amount of desilylation to useless 3-methyl-2,4-hexanediol was observed. The remainder of the route to *O*-benzylstegobiol (**19**) was straightforward.



(**a**) Cyclohexene/$Pd(OH)_2$, $CaCO_3$, EtOH.
(**b**) $(pyH)_2Cr_2O_7$, CH_2Cl_2, molecular sieves, 3 h.

Before finding the successful procedures described above, we attempted a route via an intermediate of the type used by Mori and Ebata,[8] a 3-methyl-4-(ketohexyl) 2-methyl-3-(silylyloxy)pentanoate. We were unable in several attempts to close the six-membered ring via ketone enolate attack at the ester carbonyl group under conditions similar to those described by Mori and Ebata,[8] and Oppolzer's method[12] had not yet been reported. This work will be reported elsewhere.

Discussion

Properties of Stegobinone and Stegobiol. Tests carried out by Burkholder and Wang have shown that pure synthetic stegobinone (**1**) is highly attractive to *S. paniceum*.[5] Crystalline **1** is stable indefinitely at −10 °C and for several months at room temperature. A sample stored at room temperature for more than a year became visibly gummy, acquired a different and stronger odor, and showed a few percent of epimer **2** by ^{1}H NMR analysis.

Ours was the first reported crystalline sample of stegobiol (**3**). Crystallization is difficult to initiate in spite of the melting point of 74 °C, and we have been unsuccessful in attempts to purify **3** by recrystallization. Although oily **3** isolated from the insects has been reported to be an attractant,[10] pure synthetic **3** has been found to have no detectable attractant activity.[5] The presence of 5% **3** in the natural pheromone is sufficient to assure the presence of a liquid phase and consequent significant epimerization of attractant **1** to repellent **2** over the course of a few hours.

(18) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625.
(19) (a) Paterson, I.; Lister, M. A.; McClure, C. K. *Tetrahedron Lett.* **1986**, *27*. 4787−4790. (b) Paterson, I.; McClure, C. K. *Tetrahedron Lett.* **1987**, *28*. 1229−1232.

Comparison of Synthetic Routes. It is evident that high enantioselectivity and diastereoselectivity were important to the success of our synthesis of stegobinone (**1**). The problems with the previous syntheses[7,8] appeared to result from the presence of diastereomeric or enantiomeric impurities coupled with the strong tendency of **1** to epimerize during attempted purification. Recrystallization of **1** from pentane is successful only if **1** is already pure enough to crystallize easily.

The boronic ester chemistry utilized for establishment of the asymmetry is the same for all of the synthetic routes described. Somewhat higher yields of (2*S*,3*S*)-2-methyl-3-(benzyloxy)-pentanal (**9**) were obtained when the chain extensions were carried out with preformed (dichloromethyl)lithium [65% based on DICHED ethylboronate (**4**)] than when the in situ dichloromethane/LDA method was used (55%). In view of the possible variations in purity of small lots of LDA or butyllithium from commercial sources[20] and the generally comparable yields seen in previous work with the two procedures,[1] this difference is not necessarily real, and even if it is, it is offset by the practical consideration that generation of preformed (dichloromethyl)lithium requires cooling to −100 °C, but the in situ method is successful at −40 °C and is easy to scale up.

In spite of the detour via oxaborolane **13**, the yield of ketone intermediate **15a** (39% from **4** via the in situ method) appears to be higher than that of the alternate route intermediate **15b** (38% from **4** via the higher yielding preformed (dichloromethyl)lithium). The major advantage of the route via **15a** is that the chiral director DICHED is recovered at the earliest possible point in the procedure and without oxidative loss. (DICHED is also readily recoverable from the byproduct boronic ester fractions, as well as from the preparation of **9**, in the general manner previously described for 1,2-diisopropylethane-1,2-diol.[21]) It is also helpful that purification of the sodium salt **12** by aqueous extraction and acid regeneration of **13** gets rid of the various minor boronic ester and other organic impurities, because only the γ-hydroxy boronic ester hydrolyzes to any significant extent and is extracted into the aqueous phase. The overall yield of stegobinone (**1**) from DICHED ethylboronate (**4**) was ∼12.5%.[22]

Ketone **22** described in our preliminary communication[3] has been obtained in up to 29% yield from **4**, via preformed (dichloromethyl)lithium. It appears that the aldol condensation of **22** and subsequent steps are more efficient than those of **15a**, and the net yield of stegobinone from **4** was the same within experimental error.[22] Considering the problems we had with acid sensitivity of the silyl protecting group of **21a**, we consider the route via **15a** to be more dependable.

(20) During our first successful synthesis of stegobinone, ∼5% of contaminants having butoxy in place of benzyloxy persisted from **6** on throughout the synthesis until debenzylation of **19** to **3** provided a readily purifiable intermediate. It is unclear whether the butoxide source was oxidized butyllithium or dibutyl ethylboronate not separated from **4** by distillation. A recent simple preparation of dimethyl ethylboronate from ethylene, boron trichloride, triethylsilane, and methanol (Soundararajan, R.; Matteson, D. S. *Organometallics* **1995**, *14*, 4157−4166) presumably makes the use of dibutyl ethylboronate for this purpose obsolete, though the preparation **4** from this source has not yet been tested. Commercial LDA does not contain lithium butoxide.

(21) Matteson, D. S.; Tripathy, P. B.; Sarkar, A.; Sadhu, K. M. *J. Am. Chem. Soc*. **1989**, *111*, 4399−4402.

(22) To produce 1 mol of **9** required 1.82 mol of **4**, and 1 mol of **15a** required 2.56 mol of **4**. From 1 mol each of **9** and **15a**, the yield of *O*-benzylstegobiol (**19**) would be 0.367 mol, and conversion to stegobinone (**1**) was 75%. Thus, the overall yield of **1** from **4** was 12.5%. The route via **22** was estimated to be ∼14%, but this required the higher yielding preformed $LiCHCl_2$, and includes a higher but small-scale yield of **1** from **19**, ∼80%, only observed once.

Experimental Section

General Data. NMR spectra were recorded on a Bruker 300 MHz or Varian VXR-500s spectrometer. Melting points were determined in open-ended capillaries using a Thomas-Hoover melting point apparatus and are uncorrected. Tetrahydrofuran, 1,2-dimethoxyethane, and diethyl ether were distilled from benzophenone ketyl under argon prior to use. Sure Seal bottles of dimethyl sulfoxide, dimethylformamide, Grignard reagents, and lithium diisopropylamide solutions were purchased from the Aldrich Chemical Co. Other chemicals were reagent grade. Flash chromatography was performed on Merck silica gel 60, 230−400 mesh. Elemental analyses were preformed by Desert Analytics, Tucson, AZ.

[4*R*-(4α,5*β*)]-4,5-Dicyclohexyl-2-ethyl-1,3,2-dioxaborolane (4). Method A: From Dibutyl Ethylboronate and DICHED.[20] (1*R*,2*R*)-1,2-Dicyclohexylethane-1,2-diol (*R*,*R*-DICHED) (46 g, 203 mmol) was added to a solution of dibutyl ethylboronate (37.9 g, 203 mmol) in hexanes (500 mL) at room temperature. The solution was stirred for 1 h. Distillation yielded **4**: 52.5 g, 98%; bp 85−87 °C (1 Torr); 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.90−1.28 and 1.50−1.77 (m, 22), 0.78 (q, J = 8.1 Hz, 2), 0.96 (t, J = 7.3 Hz, 3), 3.81−3.83 (m, 2); 75 MHz ^{13}C NMR ($CDCl_3$) δ 2.51 (br), 7.91, 25.88, 26.01, 26.44, 27.29, 28.27, 42.99, 83.18; HRMS calcd for $C_{16}H_{29}BO_2$ (M^+) 264.2261, found 264.2253. Anal. Calcd for $C_{16}H_{29}BO_2$: C, 72.73; H, 11.06; B, 4.09. Found: C, 72.86; H, 10.86; B, 4.31.

Method B: From DICHED, Triisopropyl Borate, and Ethylmagnesium Chloride. [*R*-(*R**,*R**)]-1,2-Dicyclohexylethane-1,2-diol (67.54 g, 298 mmol) was dried by addition of cyclohexane (500 mL) and distillation of the cyclohexane−water azeotrope. The residue was treated with THF (200 mL) and triisopropyl borate (61.8 g, 328 mmol) at room temperature. THF and 2-propanol were distilled under vacuum. THF (200 mL) was again added, the solution was cooled to −78 °C, and ethylmagnesium chloride (150 mL, 2 M, 300 mmol) was added dropwise. The solution was allowed to warm to room temperature and kept for 12 h. Hydrochloric acid (1 M, ∼20 mL) was added in small portions to the mixture until the initial exothermic reaction and effervescence subsided. (A small amount of unchanged Grignard reagent may have been destroyed by this procedure.) The mixture was concentrated under vacuum and then treated with diethyl ether (600 mL) and hydrochloric acid (1 M, 200 mL). The ether solution was washed with water (200 mL) and dried over magnesium sulfate. Distillation yielded **4**; 59.4 g, 75%; bp 125−130 °C (0.5 Torr).

[4*R*-[2(*R),4α,5*β*]]-4,5-Dicyclohexyl-2-[1-(phenylmethoxy)propyl]-1,3,2-dioxaborolane (6).** To a solution of [4*R*-(4α,5*β*)]-4,5-dicyclohexyl-2-ethyl-1,3,2-dioxaborolane (**4**) (54 g, 204 mmol) and dichloromethane (52 g, 610 mmol) in THF (300 mL) was added LDA (120 mL, 2 M, 240 mmol) at −40 °C via cannula. After 10 min, zinc chloride (55.5 g, 408 mmol), which had been fused before use, was added to the solution. After 30 min, the ice bath was removed. The solution was allowed to warm to room temperature and kept for 2 h to form [4*R*-(2*S**,4α,5*β*)]-2-(1-chloropropyl)-4,5-dicyclohexyl-1,3,2-dioxaborolane (**5**). NMR analysis of a sample of **5** obtained by concentration of the crude solution showed that the reaction was complete.[23] The solution of crude **5** was concentrated under vacuum to remove excess dichloromethane. THF (300 mL) was added to the mixture, which was then added dropwise via additional funnel to a solution of sodium benzyl oxide in THF and DMSO at 0 °C. [The sodium benzyl oxide solution was prepared as follows. To a solution of benzyl alcohol (26 g, 240 mmol) in 100 mL of THF and 300 mL of DMSO was added sodium hydride (9 g, 225 mmol) (60% dispersion in mineral oil) at room temperature, and the mixture was stirred overnight.] The solution was allowed to warm to room temperature and stirred for 48 h. The solvent was distilled at 1 atm. Hexanes (1000 milliliters) and aqueous ammonium chloride (500 mL) were added to the mixture. Sufficient hydrochloric acid (a few mL) was added to ensure that the solution was acidic to avoid any possible hydrolysis.

(23) A sample of **5** obtained by concentration of the crude solution obtained from a run in which preformed (dichloromethyl)lithium was used (no LDA, see the supporting information) showed the following: 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.9−1.4 and 1.55−1.98 (m, 24), 1.02 (t, J = 7.3 Hz, 3), 3.40 (dd J = 6.3 and 8.0 Hz, 1), 3.92−3.96 (m, 2); 75 MHz ^{13}C NMR ($CDCl_3$) δ 11.92, 25.70, 25.90, 26.33, 27.18, 27.53, 28.11, 42.81, 45 (br), 84.00; HRMS calcd for $C_{17}H_{30}O_2BCl$ (M^+) 312.2027, found 312.2048.

The organic solution was washed with water (6 × 200 mL) and brine (100 mL). Concentration in a rotary evaporator gave crude [4*R*-[2(*R**),4α,5*β*]]-4,5-dicyclohexyl-2-[1-(phenylmethoxy)propyl]-1,3,2-dioxaborolane (**6**) (75 g), which was used in the next step without further purification. An analytical sample of **6** was obtained by chromatography with considerable loss due to decomposition on the column: 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.90−1.42 and 1.58−1.84 (m, 24), 1.01 (t, J = 7.3 Hz, 3), 3.24 (t, J = 6.7 Hz, 1), 3.91−3.96 (m, 2), 4.53 (AB, J = 12 Hz, 1), 4.61 (AB, J = 12 Hz, 1), 7.22−7.41 (m, 5); 75 MHz ^{13}C NMR ($CDCl_3$) δ 10.87, 24.33, 25.77, 25.89, 26.31, 27.24, 28.14, 42.81, 69 (br), 71.87, 83.43, 127.11, 127.66, 128.02, 139.12; HRMS calcd for $C_{24}H_{37}O_3B$ (M^+) 384.2836, found 384.2802. Anal. Calcd for $C_{24}H_{37}BO_3$: C, 74.00; H, 9.70. Found: C, 74.78; H, 9.40.

[4*R*-[2(1*S,2*S**),4α,5*β*]]-4,5-Dicyclohexyl-2-[1-methyl-2-(phenylmethoxy)butyl]-1,3,2-dioxaborolane (7).** To a solution of [4*R*-(2*R**,4α,5*β*)]-4,5-dicyclohexyl-2-[1-(phenylmethoxy)propyl]-1,3,2-dioxaborolane (**6**) (75 g) and dichloromethane (52 g, 610 mmol) in THF (300 mL) was added LDA (120 mL, 2 M, 240 mmol) at −40 °C via cannula. After 10 min, zinc chloride (69.36 g, 510 mmol), which was fused before use, was added to the solution. The resulting solution of [4*R*-[2(1*S**,2*S**)4α,5*β*]]-2-(1-chloro-2-(phenylmethoxy)butyl]-4,5-dicyclohexyl-1,3,2-dioxaborolane was allowed to warm to room temperature and kept for 2 h. The solution was cooled to 0 °C, and methylmagnesium chloride (204 mL, 2.5 M, 510 mmol) was added dropwise. The solution was allowed to warm to room temperature and kept for 36 h. Aqueous ammonium chloride (20 mL) was added to the mixture. Some gas (methane) was liberated. The solvent was removed by vacuum distillation. Pentane (1000 mL) and aqueous ammonium chloride (500 mL) were added to the mixture. The organic solution was washed with ammonium chloride (300 mL) followed by water (3 × 300 mL) and dried over magnesium sulfate. Removal of the solvent by vacuum distillation yielded a mixture containing a small amount of [4*R*-(4α,5*β*)]-4,5-dicyclohexyl-2-methyl-1,3,2-dioxaborolane with the major product [4*R*-[2(1*S**,2*S**)4α,5*β*]]-2-[1-methyl-2-(phenylmethoxy)butyl]-4,5-dicyclohexyl-1,3,2-dioxaborolane (**7**) (70.5 g). The crude material was used in the next step without further purification. A partially purified analytical sample was obtained by flash chromatography on silica with 1:30 ether/hexane: 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.92−1.38 and 1.48−1.82 (m, 25), 0.93 (t, J = 7.4 Hz, 3), 0.99 (d, J = 7.47 Hz, 3), 3.49 (ddd, J = 4.5, 5.7, 6.8 Hz, 1), 3.80−3.85 (m, 2), 4.48 (AB, J = 12 Hz, 1), 4.54 (AB, J = 12 Hz, 1), 7.24−7.37 (m, 5); 75 MHz ^{13}C NMR ($CDCl_3$) δ 9.86, 10.65, 20 (br), 24.61, 25.86, 25.98, 26.44, 27.52, 28.29, 42.99, 70.72, 82.84, 83.25, 127.03, 127.35, 128.11, 139.46. The analysis was not satisfactory. Anal. Calcd for $C_{26}H_{41}BO_3$: C, 75.72; H, 10.02; B, 2.62. Found: C, 72.44; H, 9.72; B, 2.63.

[4*R*-[2(1*S,2*S**),4α,5*β*]]-2-[1-Chloro-2-(phenylmethoxy)butyl]-4,5-dicyclohexyl-1,3,2-dioxaborolane.** A small sample of this compound (chloro boronic ester intermediate between **6** and **7**) was concentrated for NMR and mass spectral analysis: 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.85−1.76 (m, 24), 0.96 (t, J = 7.4 Hz, 3), 3.64−3.72 (m, 2), 3.93−3.96 (m, 2), 4.62 (AB, J = 11.4 Hz, 1), 4.69 (AB, J = 11.4 Hz, 1), 7.23−7.40 (m, 5); 125 MHz ^{13}C NMR ($CDCl_3$) δ 9.86, 24.78, 25.75, 25.87, 26.32, 27.34, 28.15, 42.78, 45 (br), 72.40, 81.77, 84.15, 127.36, 127.48, 128.18, 138.59; HRMS calcd for $C_{25}H_{38}O_3BCl$ (M^+) 432.2602, found 432.2641.

[4*R*-[2(1*S,2*S**,3*S**),4α,5*β*]]-2-[1-Chloro-2-methyl-3-(phenylmethoxy)pentyl]-4,5-dicyclohexyl-1,3,2-dioxaborolane (8).** A solution of crude [4*R*-[2(1*S**,2*S**),4α,5*β*]]-4,5-dicyclohexyl-2-[1-methyl-2-(phenylmethoxy)butyl]-1,3,2-dioxaborolane (**7**) (23.5 g), and dichloromethane (17 g, 200 mmol) in THF (100 mL) was treated with LDA (40 mL, 2 M, 80 mmol) at −40 °C via cannula. After 10 min, zinc chloride (23.3 g, 171 mmol), which was fused before use, was added to the solution. The solution was allowed to warm to room temperature and kept for 18 h. The solvent was distilled. The mixture was treated with hexanes (200 mL) and aqueous ammonium chloride (100 mL). The organic solution was washed with ammonium chloride (100 mL) and dried over magnesium sulfate. The solution was filtered through a short pad of magnesium sulfate to remove zinc chloride. The magnesium sulfate pad was washed with 10% ether in pentane for complete product recovery. Concentration in a rotary evaporator gave a mixture containing [4*R*-[2(1*S**,2*S*,3*S**)4α,5*β*]-2-[1-chloro-2-methyl-3-(phenylmethoxy)pentyl]-4,5-dicyclohexyl-1,3,2-dioxaborolane (**8**) (22 g), which was used in the next steps without further purification: 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.84−1.82 (m, 24), 0.93 (t, J = 7.4 Hz, 3,), 1.01 (d, J = 6.7 Hz, 3) 2.15−2.25 (m, 1), 3.36−3.42 (m, 1), 3.88−3.93 (m, 2), 4.00 (d, J = 4.4 Hz), 4.56 (br s, 2), 7.25−7.41 (m, 5); 75 MHz ^{13}C NMR ($CDCl_3$) δ 8.29, 13.30, 22.49, 25.82, 25.92, 26.39, 27.48, 28.28, 38.73, 42.85, 47 (br), 71.72, 80.08, 84.16, 127.48, 127.92, 128.31, 138.78; HRMS calcd for $C_{27}H_{42}O_3BCl$ (M^+) 460.2915, found 460.2875.

[*S*-(*R,*R**)]-2-Methyl-3-(phenylmethoxy)pentanal (9).** To a solution of crude [4*R*-[2(1*S**,2*S**,3*S**),4α,5*β*]]-2-[1-chloro-2-methyl-3-(phenylmethoxy)pentyl]-4,5-dicyclohexyl-1,3,2-dioxaborolane (**8**) (33 g) in 300 mL of THF and 150 mL of phosphate buffer (pH 8) was added hydrogen peroxide (30 mL, 30%) at 0 °C. After the addition of hydrogen peroxide, sodium carbonate (20 g, 188 mmol) was added to keep the pH at 8−9. After 0.5 h, the cold bath was removed. The pH of the aqueous solution was checked frequently. Acid is produced in the reaction, and if the pH falls below 8, the oxidation stops. Sodium carbonate was added as necessary to keep the pH at 8−9, and the reaction was complete within 3 h. Sodium iodide (3 g, 20 mmol) was added at 0 °C. The iodine was reduced by sodium thiosulfate (24.8 g, 100 mmol). The THF solution was separated from aqueous solution. The aqueous layer was extracted with ether (2 × 600 mL). The combined organic layer was washed with sodium thiosulfate solution (10%, 100 mL) and dried over magnesium sulfate. Vacuum distillation of the solvent gave a residue of [4*R*-(4α,5*β*)]-4,5-dicyclohexyl-2-hydroxy-1,3,2-dioxaborolane and [*S*-(*R**,*R**)]-2-methyl-3-(phenylmethoxy)pentanal (**9**). Bulb to bulb distillation of the residue yielded **9** containing a small amount of benzyl alcohol: 8.1 g [55.3% overall yield via method B from [4*R*-(4α,5*β*)]-4,5-dicyclohexyl-2-ethyl-1,3,2-dioxaborolane (**4**); via method A on one-fourth the described scale, 65.4% of **9** was obtained, based on **4**],; bp 94−95 °C (0.4 Torr); 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.97 (t, J = 7.4 Hz, 3), 1.08 (d, J = 7 Hz, 3), 1.55−1.8 (m, 2), 2.69 (dp, J = 2.3, 7 Hz, 1), 3.64−3.69 (m, 1), 4.48 (AB, J = 11.5 Hz, 1), 4.59 (AB, J = 11.5 Hz, 1), 7.25−7.35 (m, 5), 9.75 (d, J = 2.3 Hz, 1);.75 MHz ^{13}C NMR ($CDCl_3$) δ 8.80, 10.09, 23.37, 48.90, 71.50, 80.39, 127.66, 127.69, 128.36, 138.16, 204.69; HRMS calcd for $C_{13}H_{18}O_2$ (M^+) 206.1307, found 206.1317. Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69 ; H, 8.80. Found: C, 75.17; H, 8.84. The amount of epimer in **9** prepared in this manner was estimated by ^{1}H NMR to be 0.5−1.0%.[3]

Epimer of 9: [*R*-(*R,*S**)]-2-Methyl-3-(phenylmethoxy)pentanal.** Chromatography of samples of **9** on silica or alumina resulted in ∼10% and ∼50% (*R**,*S**)-epimer formation, respectively, based on additional absorptions in the ^{1}H NMR; 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.96 (t, J = 7 Hz, 3), 1.14 (d, J = 7 Hz, 3), 1.55−1.8 (m, 2), 2.59 (ddq, J = 1.0, 3.9, 7.0 Hz, 1), 3.77 (dt, J = 3.9, 6.6 Hz, 1), 4.52 (AB, J = 11.5 Hz, 1), 4.54 (AB, J = 11.5 Hz, 1), 7.25−7.35 (m, 5), 9.75 (d, J = 1.1 Hz); 75 MHz ^{13}C NMR ($CDCl_3$) δ 8.01, 10.20, 24.33, 49.26, 71.67, 79.80, 127.66, 127.69, 128.36, 138.16, 204.74.

[4*R*-[2(1*S,2*R**,3*S**),4α,5*β*]]-4,5-Dicyclohexyl-2-[1,2-dimethyl-3-(phenylmethoxy)pentyl]-1,3,2-dioxaborolane (10).** Crude [4*R*-[2(1*S**,2*S**),4α,5*β*]]-4,5-dicyclohexyl-2-[1-methyl-2-(phenylmethoxy)-butyl]-1,3,2-dioxaborolane (**7**) (47 g) was converted to [4*R*-[2(1*S**,2*S**,3*S**),4α,5*β*]]-2-[1-chloro-2-methyl-3-(phenylmethoxy)pentyl]-4,5-dicyclohexyl-1,3,2-dioxaborolane (**8**) by the method described above. After the reaction mixture had been treated with zinc chloride and kept at 25 °C for 18 h, the solution was cooled to 0 °C and methylmagnesium chloride (136 mL, 2.5 M, 340 mmol) was added dropwise. The solution was allowed to warm to room temperature and kept for 36 h. Aqueous ammonium chloride (20 mL) was added to the mixture. Some gas (methane) was liberated. The solvent was removed by vacuum distillation. To the mixture were added pentane (800 mL) and saturated aqueous ammonium chloride (400 mL). The organic solution was washed with ammonium chloride solution (300 mL) followed by 1 M hydrochloric acid (2 × 300 mL) and brine (400 mL) and dried over magnesium sulfate. Concentration in a rotary evaporator gave an oil (52 g) containing [4*R*-[2(1*S**,2*R**,3*S**),4α,5*β*]]-4,5-dicyclohexyl-2-[1,2-dimethyl-3-(phenylmethoxy)pentyl]-1,3,2-dioxaborolane (**10**) and [4*R*-(4α,5*β*)]-4,5-dicyclohexyl-2-methyl-1,3,2-dioxaborolane. The crude **10** was stirred with Raney nickel (15 g) in ethyl acetate (400 mL) to remove traces of DMSO before it was used in the next step. A sample of crude **10** was purified with flash column

chromatography (silica, 2% ether/hexanes): 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.88−1.85 (m, 26), 0.89 (d, J = 6.9 Hz, 3), 0.92 (t, J = 7.3 Hz, 3), 0.99 (d, J = 7.5 Hz, 3), 3.38 (dt, J = 3.6, 6.8 Hz, 1), 3.76−3.81 (m, 2), 4.47 (AB, J = 11.6 Hz), 4.57 (AB, J = 11.6 Hz), 7.22−7.39 (m, 5); 75 MHz ^{13}C NMR ($CDCl_3$) δ 9.51, 14.02, 14.39, 18 (br), 22.23, 25.88, 25.98, 26.46, 27.67, 28.49, 38.45, 43.04, 71.36, 82.93, 83.21, 127.19, 127.69, 128.17, 139.46; HRMS calcd for $C_{28}H_{45}O_3B$ (M^+) 440.3462, found 440.3492. Anal. Calcd for $C_{28}H_{45}BO_3$: C, 76.35; H, 10.30; B, 2.45. Found: C, 76.49; H, 10.33; B, 2.58.

[4*R*-[2(1*S,2*R**,3*S**),4α,5*β*]]-4,5-Dicyclohexyl-2-(3-hydroxy-1,2-dimethylpentyl)-1,3,2-dioxaborolane (11).** A solution of crude [4*R*-[2(1*S**,2*R**,3*S**),4α,5*β*]]-4,5-dicyclohexyl-2-[1,2-dimethyl-3-(phenylmethoxy)pentyl]-1,3,2-dioxaborolane (**10**) (52 g) in ethyl acetate (400 mL) was stirred with palladium on charcoal catalyst (8 g, 10%) under 1 atm of hydrogen until TLC or GC analysis showed no **10** remaining. The mixture was filtered through a pad of Celite. Concentration in a rotary evaporator gave a mixture of impurities [4*R*-(4α,5*β*)]-4,5-dicyclohexyl-2-(1-methylethyl)-1,3,2-dioxaborolane and [4*R*-(4α,5*β*)]-4,5-dicyclohexyl-2-methyl-1,3,2-dioxaborolane, together with the major product [4*R*-[2(1*S**,2*R**,3*S**),4α,5*β*]]-4,5-dicyclohexyl-2-(3-hydroxy-1,2-dimethylpentyl)-1,3,2-dioxaborolane (**11**) (39.8 g), which was used in the next step without further purification: 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.85−1.81 (m, 35), 2.10−2.25 (br, 1 H), 3.29−3.36 (m, 1), 3.80−3.84 (m, 2); 75 MHz ^{13}C NMR ($CDCl_3$) δ 10.37, 13.12, 15.43, 25.87, 25.97, 26.43, 27.61, 27.77, 28.42, 41.63, 42.90, 76.58, 83.36; HRMS calcd for $C_{21}H_{37}O_2B$ ($M^+ - H_2O$) 332.2886, found 332.2903.

[3*S*-[2(3'R*,4'S*,5'R*),3α,4*β*,5*β*)]]-2,2′-Oxybis(5-ethyl-3,4-dimethyl-1,2-oxaborolane) (13). A solution of crude [4*R*-[2(1*S**,2*R**,3*S**),4α,5*β*]]-4,5-dicyclohexyl-2-(3-hydroxy-1,2-dimethylpentyl)-1,3,2-dioxaborolane (**11**) (39.8 g) in diethyl ether (400 mL) was stirred with sodium hydroxide (1 M, 400 mL) at room temperature for 8 h. At this point the ratio of free (*R*,*R*)-1,2-dicyclohexyl-1,2-ethanediol to unhydrolyzed [4*R*-[2(1*S**,2*R**,3*S**),4α,5*β*]]-4,5-dicyclohexyl-2-(3-hydroxy-1,2-dimethylpentyl)-1,3,2-dioxaborolane (**11**) in the ether phase was 4:1 as determined by GC and proton NMR analysis. The 1,2-dicyclohexylethanediol was removed by separating the organic layer and evaporating diethyl ether. The oily residue was redissolved in diethyl ether (300 mL) and returned to the sodium hydroxide aqueous layer for another 8 h until GC or NMR showed no **11** left. The sodium hydroxide aqueous layer, which presumably contained sodium [3*S*-(3α,4α,5*β*)]-2,2-dihydroxy-3,4-dimethyl-5-ethyl-1,2-oxaborolate[24] (**12**), was acidified with hydrochloric acid to pH ∼2−3. The solution was extracted with ethyl acetate (2 × 400 mL) and dried over magnesium sulfate. Concentration in a rotary evaporator gave pure [3*S*-[2(3'*R**,4'*S**,5'*R**),-(3α,4*β*,5*β*)]-2,2′-oxybis(5-ethyl-3,4-dimethyl-1,2-oxaborolane) (**13**): 8.5 g [47% overall yield from [4*R*-(4α,5*β*)-4,5-dicyclohexyl-2-ethyl-1,3,2-dioxaborolane (**4**)]; ^{1}H NMR ($CDCl_3$) δ 0.91 (d, J = 7.9 Hz, 3), 0.93 (d, J = 7.0 Hz, 3), 0.98 (t, J = 7.3 Hz, 3), 1.40 (m, 2), 1.61 (m, 1), 1.98 (m, 1), 3.76 (dt, J = 4.1, 7.3 Hz, 1); 75 MHz ^{13}C NMR ($CDCl_3$) δ 8.18, 10.25, 13.89, 20.55 (br), 27.88, 40.43, 86.78; HRMS calcd for $C_{14}H_{28}B_2O_3$ (M^+) 266.2225, found 266.2196.

[*R*-(*R,*S**)]-2-(1,2-Dimethyl-3-oxopentyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (15a).** A solution of [*S*-(3α,4α,5*β*)]-2,2′-oxybis(3,4-dimethyl-5-ethyl-1,2-oxaborolane) (**13**) (8.5 g, 31.9 mmol) and pinacol (11.3 g, 95.8 mmol) in diethyl ether (150 mL) was stirred at room temperature for 1 h. Concentration in a rotary evaporator gave a mixture of four different compounds, presumably including [1*S*-(1*R**,2*S**,3*R**)]-2-(3-hydroxy-1,2-dimethylpentyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**14**). One of the constituents had the composition (**13** + pinacol − H_2O) [HRMS calcd for $C_{20}H_{40}B_2O_4$ (M^+) 366.3113, found 366.3088]. A solution of the foregoing mixture and pyridinium dichromate (108 g) in dichloromethane (300 mL) was stirred with molecular sieves (40 g) at room temperature for 3 h. Celite (30 g) and silica gel (30 g) were added to the mixture, and stirring was continued for 30 min. The mixture was filtered though a short pad of Florisil. The solid was washed with ethyl acetate (2 × 200 mL) and then concentrated in a rotary evaporator and purified by redissolving in pentane (300 mL) and washing with water (2 × 200 mL). The pentane solution was dried over magnesium sulfate. Concentration in a rotary evaporator gave [*R*-(*R**,*S**)]-2-(1,2-dimethyl-3-oxopentyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**15a**) as an oil: 13 g, 54 mmol [39.7% overall yield from [4*R*-(4α,5*β*)-4,5-dicyclohexyl-2-ethyl-1,3,2-dioxaborolane (**4**)]; ^{1}H NMR ($CDCl_3$) δ 0.90 (d, J = 7.3, 3 Hz, 3), 1.03 (t, J = 7.2 Hz, 3), 1.11 (d, J = 7.0 Hz, 3, 1.24 (s, 12), 2.3−2.5 (m, 3), 2.62 (dq, J = 7.1, 7.2 Hz, 1); 75 MHz ^{13}C NMR ($CDCl_3$) δ 7.69, 13.07, 16.01, 24.64, 24.73, 34.35, 48.63, 82.97, 215.53; HRMS calcd for $C_{13}H_{25}BO_3$ (M^+) 240.1897, found 240.1874. Anal. Calcd for $C_{13}H_{25}BO_3$: C, 65.02; H 10.49 B, 4.50. Found: C, 64.83; H, 10.20, B, 4.16.

***O*-Benzylstegobiol {[2*S*-[2α,3α,6(1*R**,2*R**)]]-2,3-Dihydro-2,3,5-trimethyl-6-[1-methyl-2-(phenylmethoxy)butyl]-4*H*-pyran-4-one} (19) via 9-Borabicyclo[3.3.1]nonane 9-Triflate and 15a.** A solution of [*R*-(*R**,*S**)]-2-(1,2-dimethyl-3-oxopentyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**15a**) (4.25 g, 17.7 mmol) in dichloromethane (60 mL) was added dropwise at −78 °C to a mixture of 9-borabicyclo[3.3.1]-nonane-9-triflate (0.5 M, 53 mL, 26.5 mmol; ^{11}B NMR δ 64.7 (br) and *N*,*N*-diisopropylethylamine (5.3 mL, 30 mmol) in dichloromethane (60 mL). The ^{11}B NMR spectrum of the 9-borabicyclononane 9-triflate and *N*,*N*-diisopropylethylamine mixture showed a broad peak at −0.4 ppm. The reaction mixture was stirred at −78 °C for 2 h. A sample was withdrawn at this time, and the ^{11}B NMR spectrum was taken at −20 °C. There were three major peaks at δ 0.9, 33.9, and 58.7. The peak at δ 0.9 disappeared after 4 h at 0 °C. After the initial period at −78 °C, the reaction mixture, which presumably contained [*R*-(*R**,*S**)]-2-[1,2-dimethyl-3-[(9-borabicyclo[3.3.1]non-9-yl)oxy]-3-pentenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**16a**), was placed in an ice−water bath for 24 h. The mixture was cooled to −78 °C, and a solution of aldehyde **9** (3.65 g, 17.7 mmol) in 20 mL of dichloromethane was added via syringe. The solution was allowed to warm to 0 °C and kept for 24 h. Ether (200 mL), 2-aminoethanol (1 g), and aqueous ammonium chloride (100 mL) were added to the mixture. The aqueous layer was extracted with ether (3 × 100 mL). The combined organic layer was washed with brine (100 mL) and dried over magnesium sulfate. Concentration in a rotary evaporator yielded a product (12.64 g) containing keto boronic ester **15a**, aldehyde **9**, and aldol condensation product [1*S*-[1*R**,2*S**,4(*R** and/or *S**),5(*R** and/or *S**),6*S**,7*R**]]-2-[5-hydroxy-1,2,4,6-tetramethyl-3-oxo-7-(phenylmethoxy)nonyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**17a**). The solution of the crude mixture in dichloromethane (120 mL) was stirred with pyridinium dichromate (39.9 g, 106 mmol) and molecular sieves (4 Å, 16 g) at room temperature for 12 h. Celite was added to the mixture and stirring was continued for 30 min. The mixture was filtered through a short pad of Florisil. The solid was washed with ethyl acetate (200 mL). Concentration in a rotary evaporator gave a mixture of keto boronate **14**, aldehyde **9**, and [1*S*-[1*R**,2*S**,4(*R** and/or *S**),6*R**,7*R**]]-4,4,5,5-tetramethyl-2-[1,2,4,6-tetramethyl-3,5-dioxo-7-(phenylmethoxy)nonyl]-1,3,2-dioxaborolane (**18a**) (9.26 g). To a solution of the above mixture in 140 mL of THF and 70 mL of phosphate buffer (pH 8) was added hydrogen peroxide (6.8 mL, 30%) at 0 °C. After 0.5 h, the cold bath was removed. After 3 h at room temperature, the solution was treated with sodium iodide and sodium thiosulfate. The THF solution was separated from the aqueous solution. The aqueous layer was extracted with ether (2 × 200 mL). The combined organic layer was washed with sodium thiosulfate solution (10%, 300 mL) and dried over magnesium sulfate. Concentration in a rotary evaporator gave a mixture of deboronated product (7 g). A solution of the above mixture in chloroform (32 mL) was stirred with trifluoroacetic acid (10.7 mL) at room temperature. The reaction was complete by ^{1}H NMR analysis after 50 min. Ether (200 mL) was added to the solution. The solution was washed with sodium bicarbonate (saturated 100 mL) and dried over magnesium sulfate. Concentration in a rotary evaporator and separation of product by flash column chromatography (silica, 20% ether/hexanes) gave *O*-benzylstegobiol (**19**): 2.06 g, 6.5 mmol (36.7% from **15a**); solidifies in the freezer but melts below 20 °C; 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.97 (t, J = 7.4 Hz, 3), 1.01 (d, J = 7.3 Hz, 3), 1.06 (d, J = 7 Hz, 3), 1.25 (d, J = 6.6 Hz, 3), 1.43−1.59 (m, 1), 1.7−1.8 (m, 1), 1.77 (s, 3), 2.25 (dq, J = 3.4, 7.3 Hz, 1), 3.02 (dq, J = 7, 8.8 Hz, 1), 3.56 (ddd, J = 3.5, 6.2, 8.8 Hz, 1), 4.25 (dq, J = 3.4, 6.6 Hz, 1), 4.41 (AB, J = 11.5 Hz, 1), 4.52 (AB, J = 11.5 Hz, 1), 7.25−7.38 (m, 5); ^{13}C NMR δ 8.47, 9.11, 9.45, 13.69, 16.05, 23.31, 39.28, 43.66, 71.85, 76.03, 80.92, 108.58, 127.45, 127.50, 128.29,

(24) *Chemical Abstracts* name: sodium [*T*-4-[3*S*-(3*R**,4*S**,5*R**)]]-dihydroxy[4-methyl-3-hexanolato(2−)-*C*^{5},*O*^{3}]borate(1−).

138.67, 173.69, 197.58;[25] HRMS calcd for $C_{20}H_{28}O_3$ (M^+) 316.2038, found 316.1999. Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.39; H, 8.89.

[2*S*-[2α,3*β*,6(1*R,2*R**)]]-2,3-Dihydro-6-[1-methyl-2-(phenylmethoxy)butyl]-2,3,5-trimethyl-4*H*-pyran-4-one (3-Epimer of *O*-Benzylstegobiol).** When 9-bromo-9-borabicyclo[3.3.1]nonane was used as the enolization reagent, the 3-epimer was found in the aldol reaction mixture and was separated by flash column chromatography (silica, 20% ether/hexanes): 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.96 (t, J = 7.4 Hz, 3), 1.06 (d, J = 7.0 Hz, 6), 1.34 (d, J = 6.3 Hz, 3), 1.43−1.59 (m, 1), 1.7−1.8 (m, 1), 1.77 (s, 3), 2.25 (m, 1), 3.03 (dq, J = 7, 8.55 Hz, 1), 3.54 (ddd, J = 3.5, 6.3, 8.55 Hz, 1), 3.79 (dq, J = 6.3, 12.36 Hz, 1), 4.41 (AB, J = 11.5 Hz, 1), 4.51 (AB, J = 11.5 Hz, 1), 7.25−7.38 (m, 5); 75 MHz ^{13}C NMR ($CDCl_3$) δ 8.53, 9.28, 10.79, 13.46, 19.18, 23.20, 39.20, 44.74, 71.74, 78.88, 80.97, 109.50, 127.45, 127.54, 128.28, 138.70, 173.39, 195.29; HRMS calcd for $C_{20}H_{28}O_3$ (M^+) 316.2038, found 316.2011.

[2*S*-[2α,3α,6(1*R,2*R**)]]-2,3-Dihydro-6-[2-hydroxy-1-methylbutyl]-2,3,5-trimethyl-4*H*-pyran-4-one (Stegobiol) (3). Method A: With Palladium Hydroxide.** *O*-Benzylstegobiol (**19**) (1.1 g, 3.48 mmol) and 20% palladium hydroxide on charcoal (30 mg) in ethanol (8 mL) and cyclohexene (4 mL) were stirred under reflux for 12 h. The mixture was filtered through a pad of Celite, concentrated in a rotary evaporator, and purified by flash column chromatography (silica, 40% ethyl acetate/hexanes) to yield (2*S*,3*R*,1′*S*,2′*S*)-stegobiol (**3**) (0.7 g, 86%). Stegobiol (**3**) was crystallized after complete removal of solvent: mp 73−74.2 °C (sealed tube, uncorrected); $[\alpha]^{25}_D$ −118.7° (±7°) (c = 0.107, $CHCl_3$) [lit.[10] $[\alpha]^{23}_D$ −98.3° (c = 0.06, $CHCl_3$); lit.[11] −110° (±6°) (c = 0.42, $CHCl_3$)]; 500 MHz ^{1}H NMR ($CDCl_3$) δ 0.99 (t, J = 7.3 Hz, 3), 1.02 (d, J = 7.3 Hz, 3), 1.16 (d, J = 7.1 Hz, 3), 1.31 (d, J = 6.6 Hz, 3), 1.36−1.44 (m, 1), 1.52−1.60 (m, 1), 1.73 (s, 3), 1.93 (br s, 1), 2.36 (dq, J = 3.4, 7.3 Hz, 1), 2.84 (dq, J = 6.6, 7.1 Hz, 1), 3.56 (ddd, J = 3.7, 6.4, 8.6 Hz, 1), 4.48 (dq, J = 3.7, 6.6 Hz, 1) [lit.[4] ^{1}H NMR δ 1.00 (t), 1.04 (d), 1.18 (d, J = 7.1 Hz), 1.33 (d), 1.42 (m), 1.60 (ddq, J = 14.0, 7.4 Hz), 1.75 (s), 2.38 (dq, J = 7.3 Hz), 2.86 (dq, J = 6.8 Hz), 3.58 (ddd, J = 3.8, 8.5 Hz), 4.49 (dq, J = 3.4, 6.6 Hz)]; 75 MHz ^{13}C NMR ($CDCl_3$) δ 9.22, 9.43, 10.08, 14.72, 15.89, 28.25, 40.85, 43.67, 75.32, 76.60, 109.29, 172.76, 197.1; HRMS calcd for $C_{13}H_{22}O_3$ (M^+) 226.1569, found 226.1557. From the ^{1}H NMR, no 1′-epimer was observed, even though the ^{13}C-satellite was observed. Since we had no reference NMR spectrum of the 2-epimer, we cannot rule out the presence of some 2-epimer. Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C 68.90; H, 9.66.

Method B: With Methanesulfonic Acid. A mixture of *O*-benzylstegobiol (**19**) (1.71 g, 5.41 mmol) and methanesulfonic acid (13.6 mL) in chloroform (30 mL) was stirred for 1 h. The solution was poured onto ice (45 mL). Ethyl acetate (150 mL) was added. The organic layer was washed with sodium bicarbonate (saturated, 30 mL) and brine (30 mL) and dried over $MgSO_4$. Removal of solvent and separation of product by flash column chromatography (silica, 25% ethyl acetate/hexanes) yielded (2*S*,3*R*,1′*S*,2′*S*)-stegobiol (**3**) (1.03 g, 84%).

[2*S*-[2α,3α,6(1*S,2*R**)]]-2,3-Dihydro-6-[2-hydroxy-1-methylbutyl]-2,3,5-trimethyl-4*H*-pyran-4-one ((1′)-Epimer of Stegobiol).** When an impure sample of the aldehyde **9** was used, chromatography yielded an impure sample of the 1′-epimer of stegobiol: 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.97 (t, J = 7.4 Hz, 3), 1.04 (d, J = 7.3 Hz, 3), 1.18 (d, J = 6.9 Hz, 3), 1.32 (d, J = 6.6 Hz, 3), 1.4−1.5 (m, 1), 1.73 (s, 3), 2.32 (dq, J = 3.4, 7.3 Hz, 1), 2.77 (dq, J = 5.9, 6.9 Hz, 1), 3.66−3.72 (m, 1), 4.42 (dq, J = 3.4, 6.6 Hz, 1).

[2*S*-[2α,3α,6(1*S)]]-2,3-Dihydro-6-[1-methyl-2-oxobutyl]-2,3,5-trimethyl-4*H*-pyran-4-one (Stegobinone) (1).** A mixture of stegobiol (**3**) (0.70 g, 3 mmol), tetrapropylammonium perruthenate (TPAP) (120 mg, 0.34 mmol), *N*-methylmorpholine *N*-oxide (0.76 g, 6.5 mmol), and molecular sieves (8 g) in 40 mL of dichloromethane was stirred at room temperature for 1 h. The mixture was separated by flash chromatography on a short column of silica with 4:1 dichloromethane/ether to yield (2*S*,3*R*,1′*R*)-stegobinone (**1**) as an oil, which crystallized after removal of solvent under vacuum and chilling to −20 °C (0.65 g, 2.66 mmol, 89%), mp 45−48 °C. Recrystallization from pentane removed the ∼2% of unknown impurity indicated by a ^{1}H-NMR multiplet at δ 4.55 and yielded pure stegobinone (**1**): mp 51.5−52.5 °C (uncorrected) (lit.[4] mp 52.5−53.5 °C); 500 MHz ^{1}H NMR ($CDCl_3$) δ 1.03 (d, J = 7.3), 1.05 (t, J = 7.3), 1.28 (d, J = 6.6), 1.30 (d, J = 7.0), 1.788 (s), 2.32−2.55 (m), 3.63 (q, J = 7.0), 4.45 (dq, J = 3.54, 6.6) [lit.[8] 500 MHz ^{1}H NMR ($CDCl_3$) δ 1.04 (d, J = 7), 1.06 (t, J = 7), 1.29 (d, J = 7), 1.31 (d, J = 7), 1.79 (s), 2.3−2.5 (m), 3.62 (q), 4.55 (dq, J = 3.5, 7)]; 75 MHz ^{13}C NMR ($CDCl_3$) δ 7.87, 9.37, 9.40, 12.77, 15.68, 33.87, 43.66, 49.15, 77.17, 109.41, 168.99, 197.13, 207.60 [lit.[4,7] 25 MHz ^{13}C NMR similar (±0.1 δ)]. Pure stegobinone stored in the freezer for 9 months showed no measurable amount (<1%) of epimer by 500 MHz ^{1}H NMR. After storage for ∼1 year at 20−25 °C, the crystals became visibly contaminated with liquid, the odor changed perceptibly, and the ^{1}H NMR indicated several percent of the 1′-epimer.

Epimerization of Stegobinone (1) to (2*S*,3*R*,1′*S*)-*epi*-Stegobinone (2). An NMR sample of stegobinone (**1**) in $CDCl_3$ treated with triethylamine showed a few percent of *epi*-stegobinone (**2**) after 1 day and a ∼1:1 mixture of **1** and **2** after 3 months. Data for **2**: 500 MHz ^{1}H NMR ($CDCl_3$) δ 1.05 (d, J = 7.3 Hz), 1.07 (t, J = 7.3 Hz), 1.29 (d, J = 6.9 Hz), 1.30 (d, J = 6.6 Hz), 1.80 (s), 2.3−2.6 (m), 3.65 (q, J = 6.9 Hz), 4.43 (dq, $J = 3.4_d, 6.6_q$ Hz) [lit.[26] 500 MHz ^{1}H NMR ($CDCl_3$) δ 1.05 (d, J = 7.3 Hz, 3), 1.07 (t, J = 7.3 Hz, 3), 1.29 (d, J = 7.1 Hz, 3), 1.30 (d, J = 6.7 Hz, 3), 1.80 (s, 3), 2.31−2.56 (m, 3), 3.65 (q, J = 7.1 Hz, 3), 4.43 (dq, J = 3.4, 6.7 Hz, 1)].

Acknowledgment. This work was supported by NSF Grants CHE-8922672 and CHE-9303074 and a grant from the Washington Technology Center. Support of the WSU NMR Center by NIH Grant RR 0631401, NSF Grant CHE-9115282, and Battelle Pacific Northwest Laboratories Contract No. 12-097718-A-L2 is also gratefully acknowledged.

Supporting Information Available: Text describing the experimental details for alternative preparations of compounds **6**, **7**, **8**, **10**, and **19**, for preparations of **15b**, and for the alternative route to **19** via **20**−**25** (13 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

JA960345A

(25) In an early run, a sample of **19** known to contain (1′*R*)-epimer showed additional peaks in the 75 MHz ^{13}C NMR at δ 8.88, 9.32, 14.95, 16.24, 24.71, 40.05, 43.80, 72.52, 77.04, 81.78, 108.40, 127.57, 127.71, 128.34, and 173.30.

(26) Ebata, T.; Mori, K. *Agric. Biol. Chem.* **1990**, *54*, 527−530.