High-Precision Asymmetric Synthesis of Stegobiol and Stegobinone via Boronic Esters

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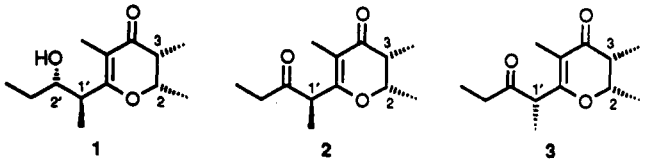
Summary: Highly stereoselective boronic ester chemistry has been used to synthesize the drugstore beetle pheromones stegobiol and stegobinone. The convergent route utilizes a single intermediate containing all of the stereogenic centers for both segments of the pheromones, requires only one chromatographic separation, and is the first synthesis to provide pure, crystalline samples.

(2*S*,3*R*,1′*S*,2′*S*)-Stegobiol (**1**) and (2*S*,3*R*,1′*R*)-stegobinone (**2**) are pheromones of the drugstore beetle *Stegobium paniceum* (Anobiidae),[1,2] an economically important pest of stored foodstuffs, and **2** is also the attractant of the furniture beetle, *Anobium punctatum*, a wood-eating pest.[3] Stegobinone (**2**) has proved a particularly elusive synthetic target because it readily epimerizes, the 1′-epimer (**3**) is repellent to *S. paniceum*, and previous partially crystalline[4] or oily[5] synthetic **2**, which contained some **3** and other diastereomers, was unstable to prolonged storage. Synthetic racemate of **2** was also repellent, and samples of **2** at room temperature lost attractiveness in 2 weeks.[6]

The asymmetric chain extension of alkylboronic esters,[7] which with chiral directors of C_2 symmetry has yielded diastereoselectivities >1000:1,[8] is the key to the first pure, crystalline synthetic (2*R*,3*R*,1′*S*,2′*S*)-stegobiol (**1**) (mp 73–74 °C (lit.[2,9] oil) and (2*R*,3*R*,1′*R*)-stegobinone (**2**) (mp 51.5–52.5 °C; from natural source[2] mp 52.5–53.5 °C). Both the flexibility of the method and the precise stereocontrol, even though only ~100:1 at the critical labile stereogenic C(1′), were significant factors in the success of this approach. The only necessary chromatography in the entire synthetic sequence is for the final purification of **1**.



1 **2** **3**

Key intermediate chloro boronic ester **8** incorporates all of the stereogenic carbons of both intermediates **9** and **12**, which are converted to **1** via convergent aldol condensation.[10] Chiral boronic ester **4** was prepared from dibutyl ethylboronate and (1*R*,2*R*)-1,2-dicyclohexylethanediol,[11] available from Sharpless dihydroxylation of *trans*-stilbene[12] and hydrogenation over rhodium.[11,13] Previously described procedures[7] were used for the reaction of **4** with (dichloromethyl)lithium to form chain-extended chloro boronic ester **5** and for the reaction of **5** with lithium benzyl oxide to form **6**. Similar reaction of **6** with (dichloromethyl)lithium followed by reaction of the chloro boronic ester (not illustrated) with methylmagnesium bromide yielded **7**. A third chain extension, **7** with (dichloromethyl)lithium, yielded key intermediate **8**.

Deboronation of **8** to aldehyde **9** with hydrogen peroxide proved efficient at pH 9, in contrast to some previous oxidations of α-chloro boronic esters.[14] Chromatography on silica partially epimerized **9**, but bulb to bulb distillation yielded **9** containing 0.5–1% (2*R**,3*S**)-epimer by ^{1}H-NMR analysis, bp 94–95 °C (0.4 Torr), 65% from **4** without purification of any intermediate, except to obtain analytical samples.[10]

A second portion of **8** was treated with methylmagnesium bromide to furnish **10**, which was deboronated with alkaline hydrogen peroxide to **11a**, which was distilled, *tert*-butyldimethylsilylated to **11b**, debenzylated to **11c**, and finally oxidized with pyridinium dichromate to **12**, bp 41 °C (2 Torr), 28% based on **4**. Ketone **12** is the second piece needed for the aldol condensation. In order to achieve debenzylation of **11b** without desilylation, it was necessary to use palladium hydroxide and calcium carbonate to suppress traces of acid from the silylation step.

Conversion of **12** to dibutylboron enolate **13** and reaction with aldehyde **9** was carried out by a literature method

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(10) The following were characterized by 300-MHz ^{1}H-NMR and 75-MHz ^{13}C-NMR, plus analysis or high-resolution mass spectra if indicated: [4*R*-(4α,5β)]-4,5-dicyclohexyl-2-ethyl-1,3,2-dioxaborolane (**4**), HRMS ($C_{16}H_{29}BO_2$), C, H, B; **5**, HRMS ($C_{17}H_{30}O_2BCl$); [4*R*-[2(*R**),4α,5β]]-2-[1-(phenylmethoxy)propyl]-4,5-dicyclohexyl-1,3,2-dioxaborolane (**6**), HRMS ($C_{24}H_{37}BO_3$) C calcd 74.00, found 74.78, H; [4*R*-[2(1*S**,2*S**),4α,5β]]-2-[1-chloro-2-(phenylmethoxy)butyl]-4,5-dicyclohexyl-1,3,2-dioxaborolane (intermediate between **6** and **7**), HRMS ($C_{25}H_{38}BClO_3$), **7**; [4*R*-(2(1*S**,2*S**,3*S**),4α,5β]]-2-[1-chloro-2-methyl-3-(phenylmethoxy)pentyl]-4,5-dicyclohexyl-1,3,2-dioxaborolane (**8**), HRMS ($C_{27}H_{42}BClO_3$); **9** HRMS ($C_{13}H_{18}O_2$); **10**, HRMS ($C_{28}H_{45}BO_3$), C, H, B; **11a** ($C_{14}H_{22}O_2$), C, H; **11b**, HRMS-CI ($C_{20}H_{37}O_2Si$, M$^+$ + 1); **12**, reported previously;[5] **14**, HRMS-CI ($C_{26}H_{47}O_4Si$, M$^+$ + 1); **15**, HRMS-CI ($C_{26}H_{45}O_4Si$, M$^+$ + 1); *O*-benzylstegobiol (**16**), HRMS ($C_{20}H_{28}O_3$, M$^+$), calcd C, 75.91, H, 8.92, found C, 75.39, H, 8.89; **1**, $C_{13}H_{22}O_3$ calcd C, 68.99, H, 9.80, found C, 68.90; H, 9.66; **2**.

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(13) (a) (*R*,*R*)-1,2-Diphenyl-1,2-ethanediol (50 g) was 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 a few days. Diphenylethanediol should be washed with aqueous sulfuric acid to remove traces of alkaloidal catalyst poison before hydrogenation. One batch from the new procedure[12b] appeared to contain a catalyst poison that could not be removed, another did not. We thank Dr. G. D. Schaumberg, Sonoma State University, for developing the hydrogenation conditions. (b) Diphenylethanediol is not a satisfactory chiral director,[11] a finding that has been replicated by G. D. Schaumberg.
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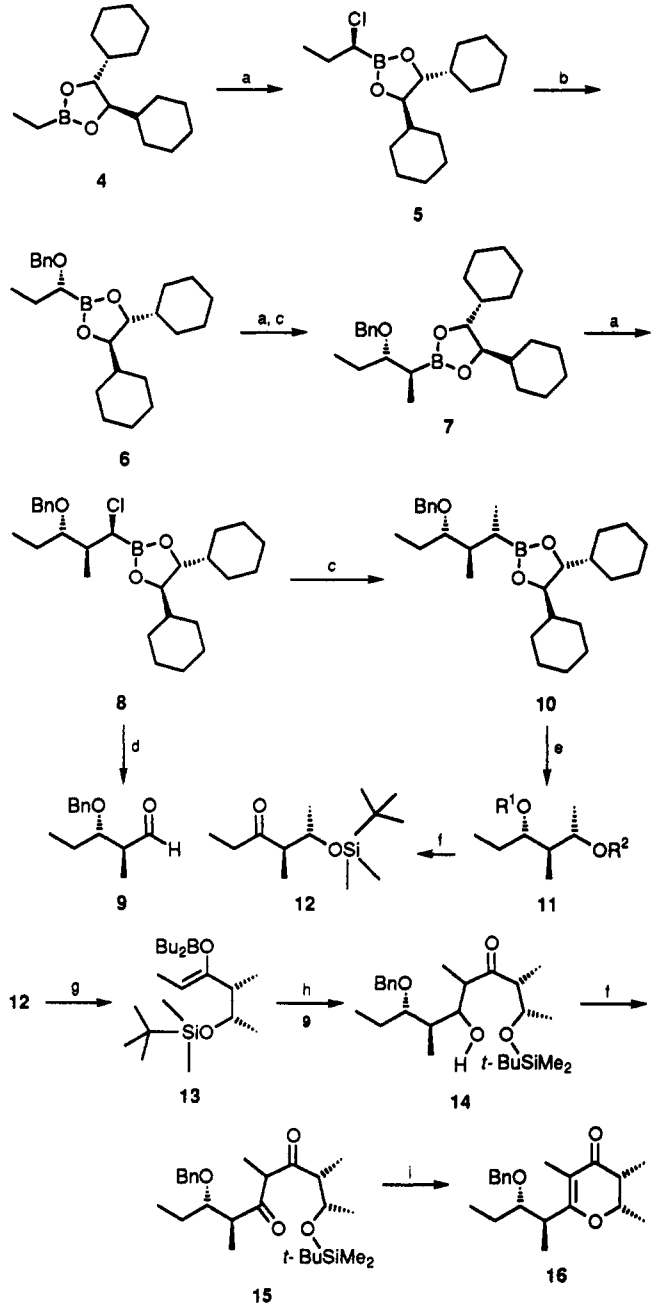
Scheme I[a]



[a] (a) $LiCHCl_2$ (−100 °C); $ZnCl_2$ (−100 → +25 °C, 8–16 h);[7] (b) BnOLi, THF, −78 °C, DMSO (4 equiv), 25 °C 18 h; (c) CH_3MgBr, −78 → 25 °C, 24 h; (d) H_2O_2, 2:1 THF/H_2O, pH 8–9; (e) H_2O_2, NaOH → **11a**, R^1 = Bn, R^2 = H; $ClSiMe_2CMe_3$ → **11b**, R^1 = Bn, R^2 = $SiMe_2(t\text{-Bu})$; cyclohexene/$Pd(OH)_2$, $CaCO_3$, EtOH → **11c**, R^1 = H, R^2 = $SiMe_2(t\text{-Bu})$; (f) $(pyH)_2Cr_2O_7$, CH_2Cl_2, molecular sieves, 3 h; (g) Bu_2BOTf, *i*-Pr_2NEt, −78 °C, 0.5 h; 0 °C, 4 h;[15] (h) −78 → 0 °C, 15 h; (i) 25% CF_3COOH in $CHCl_3$, 25 °C, 30 min.

suitable for the structure types.[15] Aldol product **14** was oxidized with pyridinium dichromate to diketone **15**, which readily ring closed with trifluoroacetic acid in chloroform to form *O*-benzylstegobiol (**16**), 43% based on **12** that had not been chromatographed. In most runs, **16** was chromatographed, but crystallizable stegobiol has been obtained without this step.

Debenzylation of **16** to stegobiol (**1**) was readily accomplished with palladium hydroxide and cyclohexene in ethanol. The 0.5–1% of (1′*R*)-epimer was removed only by chromatography of stegobiol (**1**) [mp 73–74.2 °C (sealed tube, uncorrected); $[\alpha]^{25}_D$ ~118.7° (±7°) (*c* = 0.107, $CHCl_3$) (lit.[2] $[\alpha]^{23}_D$ −98.3° (*c* = 0.06, $CHCl_3$); lit.[9] $[\alpha]^{23}_D$ ~110° (±6°) (*c* = 0.42, $CHCl_3$))], which failed to crystallize until this and other minor impurities were reduced to very low levels as shown by ^{1}H-NMR analysis.

Oxidation of pure **1** with *N*-methylmorpholine *N*-oxide/tetrapropylammonium perruthenate[16] yielded stegobinone

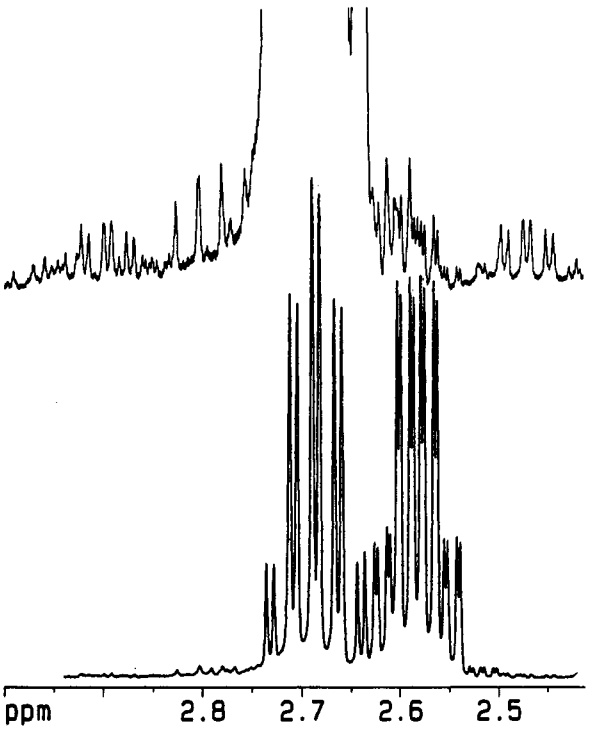


Figure 1. Portion of the 300-MHz ^{1}H-NMR spectrum of [*S*-(2*R**,3*R**)]-2-methyl-3-(phenylmethoxy)pentanal (**9**). (a) Upper curve: magnified, showing ~0.5% [*R*-(2*R**,3*S**)]-epimer at δ 2.58, flanked by ^{13}C satellites of **9**, J_{CH} = 127 Hz. The taller of the impurity peaks near δ 2.6 correspond to (2*R**,3*R**)-3-butoxy-2-methylpentanal and those near δ 2.8 to (2*R**,3*R**)-2-methyl-3-(phenylmethoxy)pentanoic acid. (b) Lower curve: a ~1:1 mixture of **9** and its (2*R**,3*S**)-epimer.

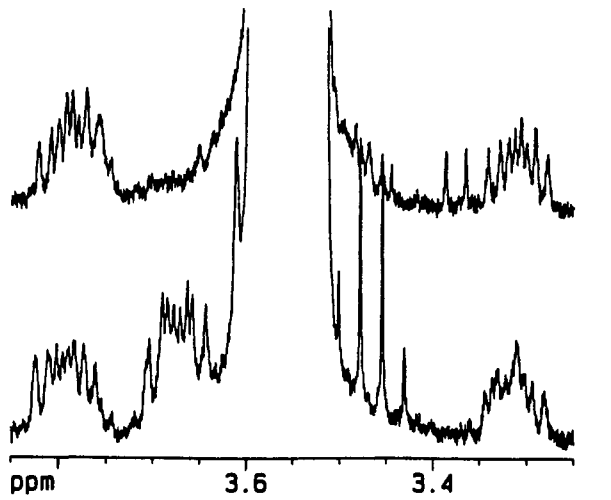


Figure 2. Magnified portion of the 300-MHz ^{1}H-NMR spectrum of purified stegobiol (**1**), showing ^{13}C-satellites, *J* = 144 Hz. (a) Upper curve: without detectable *epi*-stegobiol. (b) Lower curve: with ~1% added *epi*-stegobiol, evident at δ 3.67, and accidental diethyl ether, δ 3.47 (q).

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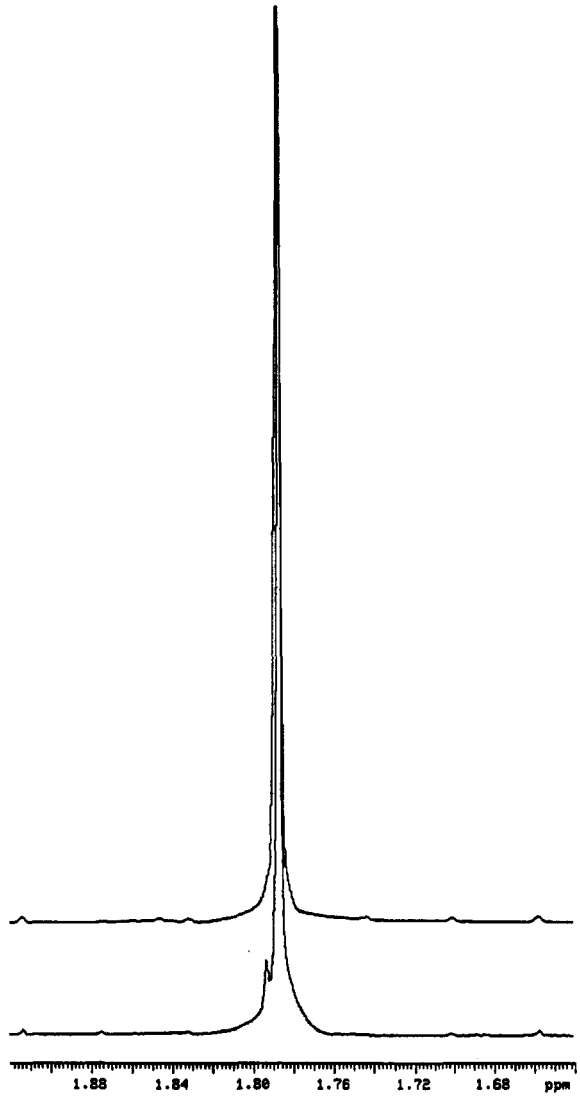

Figure 3. A magnified portion of the 500-MHz ^{1}H-NMR spectrum of stegobinone (**2**) with ^{13}C satellites, J = 128 Hz. (a) Upper curve: after 9 months in crystalline state at −15 °C. (b) Lower curve: stegobinone (**2**) containing ~5% (1′*S*)-epimer (**3**), which appears as a small peak at δ 1.795.

(**2**), which crystallized on evaporation of the solvent and was purified by washing with cold pentane (90%),[17] mp 51.5–52.5 °C (uncorr) (lit.[1] mp 52.5–53.5 °C). Crystalline **2** stored 9 months at −15 °C did not contain sufficient epimer **3** for detection (<1%) by 500-MHz ^{1}H NMR. Because the NMR spectra of **2** and **3** differ only slightly,[5,18] a sample containing some **3** for direct comparison was produced by adding triethylamine to the $CDCl_3$ solution of stegobinone and storing overnight.

The great flexibility and efficiency of the boronic ester chemistry was an important factor in the success of this synthesis. Before finding the successful strategy, we used boronic ester chemistry for preparation of the carboxylic ester intermediate used by Mori and Ebata.[5,9] Attempted improvement of the poor yield and purity of **1**[9] or **2**[5] by this route failed in our laboratory. However, Oppolzer and Rodriguez have recently achieved the synthesis of serricorole, the homologue of **1** bearing an ethyl group at C(2), by this route,[19] using titanium tetrachloride to catalyze ring closure. We have also successfully explored an alternative in which the boronic ester group of **10** was left in place until after conversion to a ketone, aldol condensation, and oxidation to the analogue of **15** having the boronic ester group in place of the silyloxy. Lithium enolates have been used in place of boron enolate **13**. These alternatives led to less satisfactory results and will be described in detail later.

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Supplementary Material Available: Experimental procedures and characterization data for all new compounds (12 pages). This material is contained in libraries on 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.

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