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TETRAHEDRON

A Convenient Synthesis of (2*S*,3*R*,6*S*,7*Z*)- and (2*R*,3*S*,6*S*,7*Z*)-2,3-Epoxy-7,10-bisaboladiene, the Sex Pheromones of the Southern Green Stink Bug (*Nezara viridula*)

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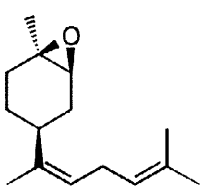
Abstract: (2*S*,3*R*,6*S*,7*Z*)-2,3-Epoxy-7,10-bisaboladiene, a sex pheromone component of the southern green stink bug, *Nezara viridula* (L.), was synthesized stereoselectively in four steps (19% overall yield) from (*S*)-4-methyl-3-cyclohexene-1-carboxylic acid. This epoxy bisaboladiene was converted in three more steps (64% yield) to its (2*R*,3*S*,6*S*,7*Z*)-isomer, another sex pheromone component of the southern green stink bug, by inverting the configuration of the epoxide ring.

Keywords: Pheromones; Terpenes and terpenoids; Sulfur compounds; Olefination.

INTRODUCTION

The southern green stink bug, *Nezara viridula* (L.), is one of the most notorious agricultural pests inhabiting most of the tropical and temperate regions of the world. This insect causes significant damage to production of a wide variety of grain, vegetable, and fruit crops in both quantity and quality. It has been reported that the sex pheromone released by males of *Nezara viridula* consists typically of five components: (2*S*,3*R*,6*S*,7*Z*)-2,3-epoxy-7,10-bisaboladiene **1**, its (2*R*,3*S*)-diastereomer **2**, (*Z*)-α-bisabolene, *n*-nonadecane, and (*E*)-nerolidol.[1-3] Interestingly, the ratio of these components varies depending on the habitats of populations of *N. viridula*.[2,3] It is also known that the pheromonal activity is elicited mainly by the *cis*- and *trans*-(*Z*)-α-bisabolene oxide, **1** and **2**, respectively.[3] From the standpoint of the pest management by environmentally sound methods, the bisabolene oxides, **1** and **2**, have been attracting the interest of organic chemists, and five synthetic works



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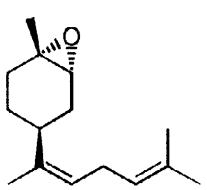

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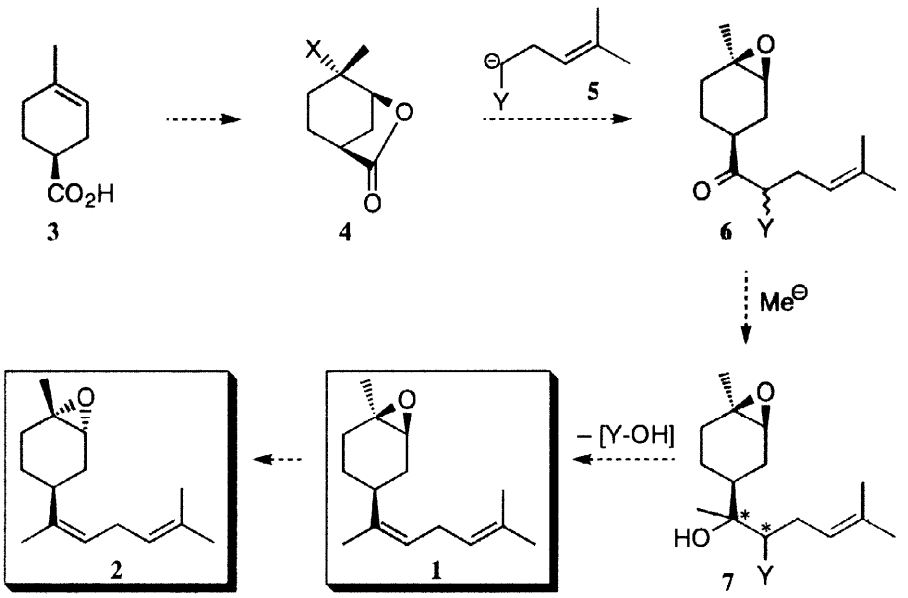


Scheme 1. Synthetic Plan for **1** and **2**.

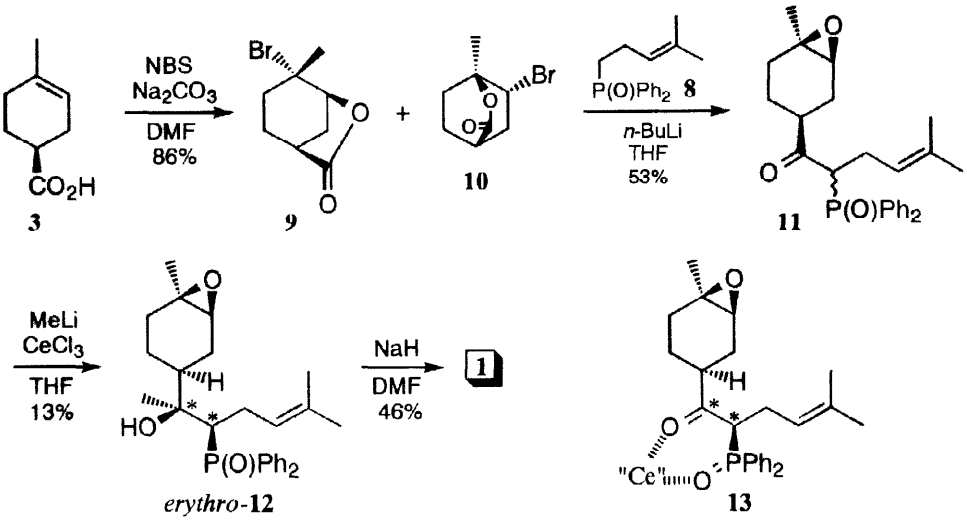
have been reported to date.[1,3-6] The previous syntheses, however, seemed to leave some room for improvement in convenience and/or stereoselectivity, which prompted us to develop a more expeditious and stereoselective synthetic route to **1** and **2**. In our previous communication,[7] we reported a four-step enantioselective synthesis of **1**. In this paper, we describe the details of our previous synthesis and the conversion of **1** to another sex pheromone component **2**.

Our synthetic plan for **1** and **2** starting from (*S*)-4-methyl-3-cyclohexene-1-carboxylic acid **3** is shown in Scheme 1. The acid **3** is known to be readily available in large quantity *via* Helmchen's asymmetric Diels-Alder reaction.[8] We envisioned that halolactonization of **3** would produce **4**. This lactone **4** would be convertible in a single step to epoxy ketone **6** through the lactone ring opening with a carbanion (**5**) stabilized by a substituent Y and concomitant epoxide ring formation *via* the resulting vicinal halo alkoxide. The substituent Y incorporated in the side chain part of the ketone **6** would serve to induce a diastereoselective addition of methyl anion to **6** leading to alcohol **7** with a predictable relative stereochemistry between Y and OH. Finally, a stereospecific elimination of Y-OH would produce **1**. The configuration of the epoxide ring of **1** would be invertible through a three-step sequence consisting of *trans*-diaxial epoxide ring opening with an appropriate oxygen nucleophile such as acetate anion, conversion of the resulting tertiary hydroxyl group into a leaving group, and finally regeneration of the epoxide ring with the opposite configuration. As described below, we were able to accomplish the synthesis of **1** and **2** along this simple synthetic plan.

RESULTS AND DISCUSSION

Synthesis of 1.

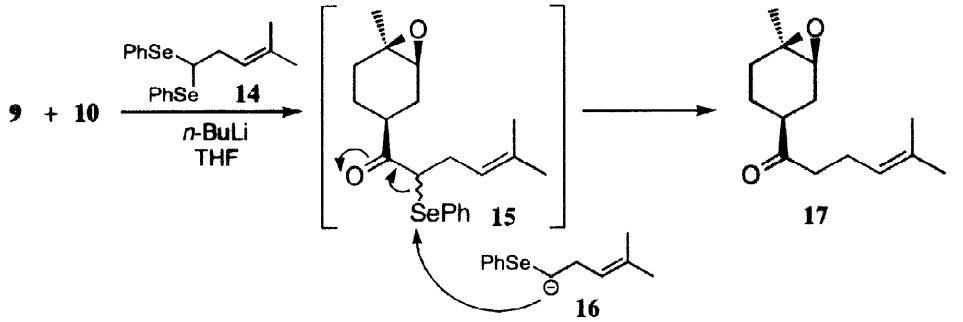
Our first approach to **1** using homoprenyldiphenylphosphine oxide **8**[9] as a building block for the side chain moiety is shown in Scheme 2. Bromolactonization of **3** was effected by treating **3** with *N*-bromosuccinimide and



Scheme 2

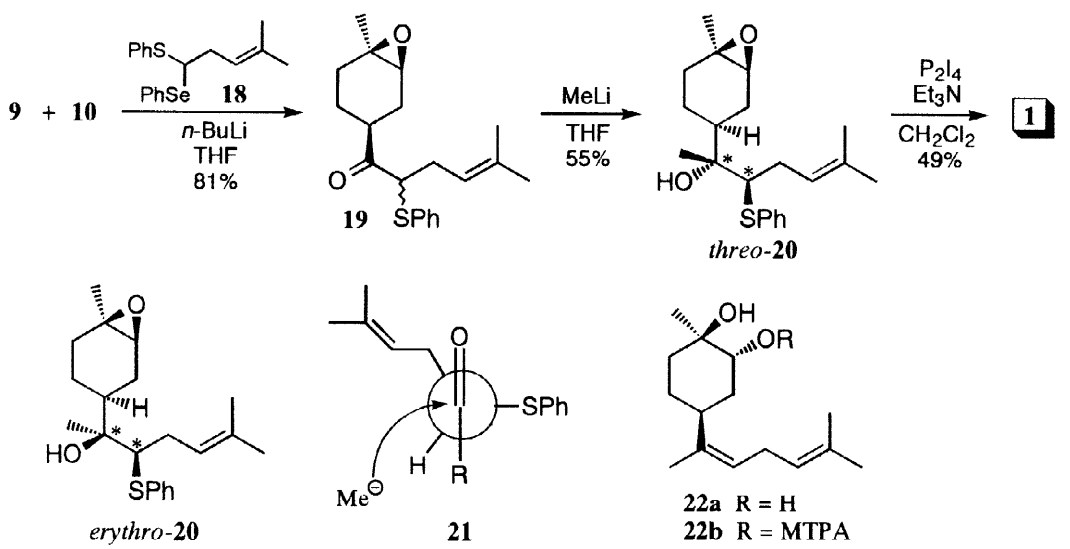
sodium carbonate in DMF to give γ-lactone **9** and δ-lactone **10** in a ratio of 1 : 1.3 in 86% combined yield. These lactones were separable by silica gel column chromatography, but were used as a mixture for the next step, since both of them were considered to lead to the same intermediate **11** by the following reaction. Thus, the mixture of **9** and **10** was allowed to react with 1-diphenylphosphinyl-4-methyl-3-pentenyllithium generated by the reaction of **8** with butyllithium[9,10] to give, as expected, epoxy ketone **11** in 53% yield as a 3 : 4 mixture of diastereomers at the diphenylphosphinyl-substituted position. Next, we attempted the diastereoface-selective addition of CH_3CeCl_2, prepared from methyllithium and $CeCl_3$,[11,12] to the carbonyl of **11** hoping that the cerium cation would form a cyclic intermediate as depicted in **13** by chelation with the oxygen atoms of the carbonyl and diphenylphosphinyl substituent, and then the methyl anion would approach to the carbonyl from the less hindered α-side of **13** to afford *erythro*-**12**.[13] However, the reaction resulted in the recovery of a substantial amount (>50%) of **11**, yielding *erythro*-**12** and the corresponding *threo*-**12** in only 13% and 19% yields, respectively, even when 10 eq. of the reagent was employed. The recovery of **11** was not entirely unexpected because the doubly activated hydrogen α to both of the carbonyl and the posphinyl substituent was considered to enolize very easily. In addtion, the observed poor stereoselectivity in this reaction might be consistent with experimental results observed previously in the Luche reduction[14] of similar α-phosphinyl ketones,[13] in which α-phosphinyl ketones possessing a primary alkyl substituent at the α-position showed only a little *erythro*-selectivity when reduced with $NaBH_4$-$CeCl_3$ in contrast to the high *erythro*-selectivity observed in the reduction of those having a secondary α-alkyl substituent (isopropyl or cyclohexyl). Other methyl donors including MeLi, MeMgCl, MeMgCl-$CeCl_3$,[15] MeMnCl,[16] Me_3Al,[16] $MeTiCl_3$,[16,17] $LiAlMe_4$,[18] Li_2ZnMe_4,[18] and $MeZn(O\text{-}n\text{-}Bu)_3$[19,20] were also tried, but in all these cases no detectable amount of *erythro*-**12** was obtained, only the recovery of **11** or the epoxide ring opening being observed. The *erythro*-phosphinyl alcohol (*erhythro*-**12**), obtained as mentioned above, could be converted in a moderate yield to **1** by treating with sodium hydride in DMF *via* stereospecific *syn*-elimination of diphenylphosphinic acid according to the literature protocol.[10]

In order to suppress the enolization in the conversion of **6** into **7** (Scheme 1), we next chose **14** (Scheme 3) instead of **8** as the side chain moiety, because the α-hydrogen of the product expected from the reaction of the mixture of **9** and **10** with the anion derived from **14** (i.e. α-phenylseleno ketone **15**) should be more resistant



Scheme 3

to such enolization as observed in **11**. In this attempt, however, the addition of 1-phenylseleno-4-methyl-3-pentenyllithium (**16**) generated by treatment of **14** with butyllithium[21,22] to the mixture of **9** and **10** did not give the desired product **15**, but afforded **17**. The latter (**17**) was presumed to be produced from **15** *via* reductive elimination caused by the attack of the carbanion **16** to the selenium atom of **15** as shown in Scheme 3. This presumption made us envisage **19** (Scheme 4) as a promising intermediate, which had a carbon-sulfur bond instead of a carbon-selenium bond in **15** and could be more resistant to such a bond cleavage reaction as observed in **15**. Thus, the mixture of **9** and **10** was treated with 1-phenylthio-4-methyl-3-pentenyllithium prepared by reaction of **18** with butyllithium[23,24] to give successfully the desired intermediate **19** in 81% yield as an inseparable 1 : 1.2 diastereomeric mixture. The addition of methyllithium to **19** gave *threo*-**20** in 55% yield, along with *erythro*-**20** and the starting ketone **19** in 9% and 12% yields, respectively. The *threo*-selectivity (*threo*-**20** : *erythro*-**20** = ca. 6 : 1) obseved in this addition reaction could be explained by considering the Felkin-Anh transition state as depicted in **21**. The recovery of the substrate **19** seems to be ascribable again to its enolization, since **19** was recovered even when a large excess of methyllithium was used. Quite fortunately, each compound produced in this addition reaction could be isolated by a simple silica gel column chromatography, and

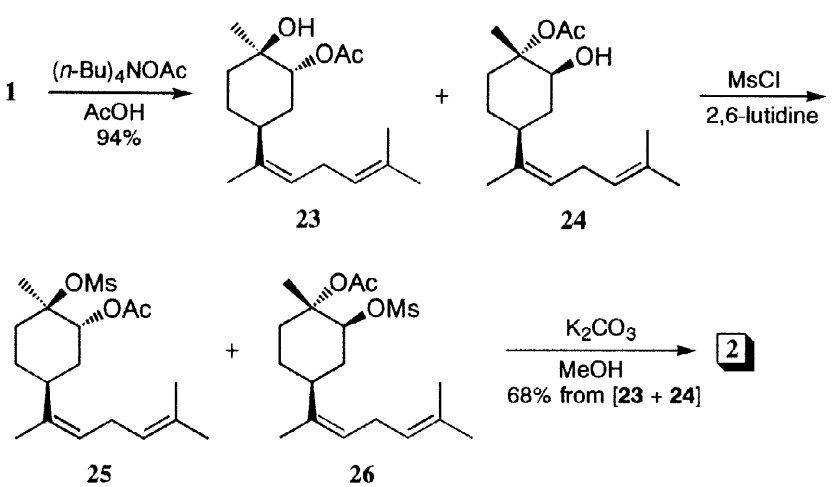


Scheme 4

threo-**20** was obtained in 55 % isolated yield, as mentioned above (the *Rf* values of *threo*-**20** and *erythro*-**20**: 0.67 and 0.56, respectively; dichloromethane/ethyl acetate = 4 : 1, Merck silica gel 60 F_{254} 5715-1M). Finally, the *threo*-phenylthio alcohol (*threo*-**20**) was subjected to a stereospecific *anti*-elimination developed by Krief *et al.*[25] to give **1** in 49% yield, $[\alpha]_D^{22}$ –27.0° (c = 1.2, CH_2Cl_2), along with some uncharacterized by-products.[26] Other elimination conditions such as $SOCl_2$-Et_3N-CH_2Cl_2,[25] MsCl-Et_3N-CH_2Cl_2, and $C_5H_4(F)NEt{\cdot}BF_4$-LiI-acetone[27] were not successful in the present case. The ^1H and ^{13}C NMR spectra of **1** were identical to those previously reported.[1,4] The optical purity of **1** was determined to be 99% by ^1H NMR analysis of **22b** which was obtained by the *trans*-diaxial epoxide ring opening of **1** with dil. H_2SO_4-DMSO followed by esterification of the resulting diol **22a**[28] with (*R*)-MTPACl in pyridine.

Conversion of the cis-epoxide 1 to the corresponding trans-epoxide 2.

According to the aforementioned synthetic plan, **1** was subjected to the epoxide ring opening reaction (Scheme 5). Among several conditions tried including NaOAc-AcOH, HCO_2H, TFA, H_2SO_4-DMSO-H_2O,[29] and KOH-H_2O-DMSO,[29] the best result was obtained when **1** was treated with tetrabutylammonium acetate in acetic acid at 50 °C for 7.5 hours. Under these conditions, β-acetoxy alcohol **23**, the expected *trans*-diaxial opening product, and its regioisomer **24** were obtained in 94% combined yield in a ratio of 7 : 1. Although these two isomers were separable by preparative TLC, they were submitted to the next reaction as a mixture, since both of them should lead to **2** by the following sequence of reactions. Mesylation of the mixture of alcohols, **23** and **24**, was first tried using methanesulfonyl chloride and triethylamine in dichloromethane.[30] Judging from the TLC monitoring of the process, the mesylation of **24** into **26** was rapid and clean. On the other hand, the reaction of **23** was very sluggish and the resulting mesylate **25** gradually changed into the corresponding *exo*-methylene compound *via* the elimination of methanesulfonic acid before the completion of the mesylation reaction. When the reaction was carried out in the presence of pyridine instead of triethylamine, the elimination leading to the olefinic compound was not significant, but the reaction did not go to completion even after 24 hours. After several other attempts, we could finally find that the mesylation of **23** led cleanly to the completion of reaction within 3 hours at 0 °C without significant side reactions when pyridine was substituted by 2,6-lutidine. The resulting mixture of **25** and **26** was then treated with potassium carbonate in methanol to give **2** as



Scheme 5

a single stereoisomer in 68% yield from the mixture of **23** and **24**. The ^1H and ^{13}C NMR spectra of **2** were identical to those reported in the literature.[1,4,6]

CONCLUSION

A convenient stereoselective synthesis of **1** was accomplished in 19% overall yield starting from readily available (*S*)-4-methyl-3-cyclohexene-1-carboxylic acid. The synthesis consisted of only four steps: 1) bromolactonization; 2) introduction of the side chain moiety involving the lactone ring opening accompanied by epoxide ring formation; 3) *threo*-selective addition of methyl anion; and 4) stereospecific *anti*-elimination. The configuration of the epoxide ring of **1**, which is *cis* to the side chain, was inverted in three steps to afford the *trans*-epoxide **2** in 64% overall yield.

EXPERIMENTAL

All mps and bps are not corrected. IR spectra were measured as films for oils or KBr discs for solids on a Jasco FT/IR-5000 specrometer. ^1H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded with TMS as an internal standard in $CDCl_3$ on a JEOL JNM-A500 spectrometer unless otherwise stated. High resolution mass specta (70 eV) were measured on a Shimadzu GCMS 9020-DF spectrometer. Optical rotations were measured with a Jasco DIP-370 polarimeter. Tetrahydrofuran was purified by distilling from benzophenone ketyl. Dichloromethane was purified by drying with P_2O_5 followed by distillation from CaH_2. Merck Kieselgel 60 Art 7734 was used for silica gel column chromatography unless otherwise stated.

(1S,4S,5S)-4-Bromo-4-methyl-6-oxabicyclo[3.2.1]octan-7-one (**9**) and *(1R,4S,6R)-6-bromo-1-methyl-2-oxabicyclo[2.2.2]octan-3-one* (**10**). To a stirred mixture of **3** [1.44 g, 10.3 mmol; $[\alpha]_D^{22}$ -105° (*c* = 4.00, 95% EtOH), lit.[8] $[\alpha]_D^{20}$ -107° (*c* = 4, 95% EtOH)] and sodium carbonate (1.20 g, 11.3 mmol) in DMF (21 ml) was added dropwise a solution of *N*-bromosuccinimide (2.00 g, 11.3 mmol) in DMF (11 ml). After stirring in the dark for 16 h at room temperature, the reaction mixture was diluted with ether (20 ml) and quenched with sodium hydrogensulfite (2.36 g, 22.6 mmol). The mixture was poured into brine and extracted with ether. The ethereal solution was washed successively with water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over silica gel (25 g, hexane/ethyl acetate = 8:1) to give 1.93 g (86%) of a 1:1.3 mixture of **9** and **10** as a colorless solid. Further chromatographic purification enabled us to isolate both **9** and **10**. Compound **9**: mp 69.0-71.5 °C; $[\alpha]_D^{22}$-11.6° (*c* = 1.00, CH_2Cl_2); ν_{max} 1775 (s), 1154 (m), 1077 (m), 988 (m), 899 (m); δ 1.87 (3H, s), 1.87-1.96 (2H, m), 2.02 (1H, ddd, *J* = 16.0, 12.0, 7.0 Hz), 2.26 (1H, br dd, *J* = 16.0, 5.0 Hz), 2.38 (1H, dtd, *J* = 12.5, 6.0, 2.5 Hz), 2.65-2.68 (1H, m), 2.76 (1H, d, *J* = 12.5 Hz), 4.60 (1H, d, *J* = 6.0 Hz); HRMS m/z (M^+) 217.9983 (calcd for $C_8H_{11}O_2{}^{79}Br$, 217.9942) and 219.9944 (calcd for $C_8H_{11}O_2{}^{81}Br$, 219.9922). Compound **10**: mp 83.0-85.5 °C; $[\alpha]_D^{22}$ -78.5° (*c* = 1.00, CH_2Cl_2); ν_{max} 1760 (s), 1265 (m), 1220 (m), 1052 (m), 1019 (m); δ 1.52 (3H, s), 1.78-1.84 (1H, m), 1.95-2.00 (2H, m), 2.22 (1H, ddd, *J* = 14.5, 5.0, 2.5 Hz), 2.40-2.47 (1H, m), 2.62 (1H, br qui, *J* = ca. 3.0 Hz), 2.68-2.75 (1H, m), 4.05 (1H, ddd, *J* = 10.5, 5.0, 2.5 Hz); HRMS m/z (M^+) 217.9978 (calcd for $C_8H_{11}O_2{}^{79}Br$, 217.9942) and 219.9872 (calcd for $C_8H_{11}O_2{}^{81}Br$, 219.9922).

5,5-Bis(phenylseleno)-2-methyl-2-pentene (**14**). To a stirred solution of lithium diisopropylamide in THF, prepared by the addition of butyllithium (1.6 M in hexane, 18.6 ml, 30.3 mmol) to a solution of diisopropylamine (4.24 ml, 30.3 mmol) in THF (50 ml), was added dropwise a solution of bis(phenylseleno)methane[20] (8.22 g, 25.2 mmol) in THF (40 ml) at 0 °C. After 1 h, a solution of 4-bromo-2-methyl-2-butene (3.05 ml, 26.5 mmol) in THF (15 ml) was added. The reaction mixture was stirred for 10 min, and then poured into brine. The mixture was extracted with ether and the ethereal solution was washed successively with water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over silica gel (170 g, hexane) to give 9.93 g (99%) of **14**: ν_{max} 3058 (w), 1578 (m), 1477 (s), 1437 (s), 1023 (m), 739 (vs), 690 (vs); δ 1.48 (3H, br s), 1.69 (3H, br s), 2.66 (2H, br dd, *J* = 6.5, 7.0 Hz), 4.48 (1H, t, *J* = 6.5 Hz), 5.26-5.31 (1H, tm, *J* = 7.0 Hz), 7.27-7.30 (6H, m), 7.57-7.59 (4H, m); HRMS m/z (M^+ - C_6H_5SeH) 238.0258 (calcd for $C_{12}H_{14}Se$, 238.0260).

2-Methyl-5-phenylseleno-5-phenylthio-2-pentene (**18**). To a stirred solution of **14** (2.00 g, 5.08 mmol) in THF (30 ml) was added dropwise a solution of butyllithium (1.60 M in hexane, 3.80 ml, 6.09 mmol) at -78 °C. After 1h, a solution of diphenyl disulfide (1.33 g, 6.09 mmol) in THF (6.7 ml) was added and the mixture was stirred for an additional 1 h at -78 °C. The mixture was allowed to warm gradually to room temperature and then poured into brine. The mixture was extracted with ether and the ethereal solution was washed successively with water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over silica gel (50 g, hexane) to give 1.61 g (92%) of **18**: ν_{max} 3060 (w), 1580 (m), 1477 (s), 1437 (s), 1379 (w), 1023 (m), 739 (vs), 690 (vs); δ 1.51 (3H, br s), 1.71 (3H, br s), 2.55-2.67 (2H, m), 4.45 (1H, t, *J* = 6.5 Hz), 5.28-5.33 (1H, tm, *J* = 7.0 Hz), 7.26-7.31 (6H, m), 7.42-7.46 (2H, m), 7.57-7.60 (2H, m); HRMS m/z (M^+ - C_6H_5Se) 191.0891 (calcd for $C_{12}H_{15}S$, 191.0894).

(1'S,3'S,4'R)-1-(3',4'-Epoxy-4'-methylcyclohexyl)-5-methyl-2-phenylthio-4-hexen-1-one (**19**). To a stirred solution of **18** (4.16 g, 9.69 mmol) in THF (62 ml) was added dropwise a solution of butyllithium in hexane (1.64 M, 6.5 ml, 9.69 mmol) at -78 °C. After 30 min, a solution of the mixture of **9** and **10**, prepared as described above, (1.93 g, 8.81 mmol) in THF (9.7 ml) was added dropwise. The mixture was stirred for 30 min at -78 °C and then allowed to warm gradually to room temperature. The reaction mixture was poured into sat. NH_4Cl aq. and extracted with ether. The ethereal solution was washed successively with water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over silica gel (96 g, hexane/ethyl acetate = 14:1) to give 2.37 g (81%) of **19** as a 1:1.2 diastereomeric mixture at C-2: $[\alpha]_D^{22}$ -72.7° (as a 1:1.24 mixture, *c* = 1.00, CH_2Cl_2); ν_{max} 3060 (w), 2975 (m), 2922 (s), 1707 (vs), 1439 (s), 1379 (m), 839 (m), 746 (m), 692 (m); δ 1.31 (1.35H, s), 1.32 (1.65H, s), 1.35 (0.55H, td, *J* = 12.0, 4.0 Hz), 1.42-1.48 (1H, m), 1.52 (0.45H, td, *J* = 12.0, 4.0 Hz), 1.57 (1.65H, s), 1.58 (1.35H, s), 1.61-1.67 (1H, m), 1.67 (1.65H, br s), 1.68 (1.35H, br s), 1.85 (0.45H, dd, *J* = 12.0, 15.5 Hz), 1.94-2.07 (2H, m), 2.19 (0.55H, dd, *J* = 12.0, 15.5 Hz), 2.31-2.40 (1H, m), 2.44-2.54 (1H, m), 2.56-2.64 (1H, m), 2.96 (0.45H, d, *J* = 5.0 Hz), 2.99 (0.55H, d, *J* = 5.0 Hz), 3.64 (0.55H, dd, *J* = 8.0, 7.0 Hz), 3.68 (0.45H, dd, *J* = 8.0, 7.0 Hz), 5.03-5.10 (1H, m), 7.27-7.32 (3H, m), 7.34-7.37 (2H, m); HRMS m/z (M^+ - C_6H_5S) 221.1546 (calcd for $C_{14}H_{21}O_2$, 221.1541).

(2R,3R*,1'S,3'S,4'R)-2-(3',4'-Epoxy-4'-methylcyclohexyl)-6-methyl-3-phenylthio-5-hepten-2-ol* (*threo*-**20**). To a stirred solution of **19** (0.792 g, 2.40 mmol) in THF (62 ml) was added dropwise a solution of

methyllithium in ether (1.02 M, 7.05 ml, 7.20 mmol) at -78 °C. The mixture was stirred at -78 °C for 1.5 h and then at -50 °C for 1.5 h. The mixture was poured into sat. NH_4Cl aq. and extracted with ether. The ethereal solution was washed successively with water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over silica gel (Katayama Chemical Silica gel 60 K230 W, 230-400 mesh, benzene/ethyl acetate = 35:1) to give 0.459 g (55%) of *threo*-**20** as a 1:1.2 diastereomeric mixture (*Rf* = ca. 0.67, Merck Silica gel 60 F_{254} 5715-1M, CH_2Cl_2/ethyl acetate = 4:1), along with 0.075 g (9%) of the corresponding *erythro*-isomers (*Rf* = ca. 0.56, Merck Silica gel 60 F_{254} 5715-1M, CH_2Cl_2/ethyl acetate = 4:1). The mixture of *threo*-isomers showed the following spectral data: ν_{max} 3462 (m), 3060 (w), 2968 (s), 2920 (s), 1582 (m), 1481 (m), 1439 (s), 1379 (s), 1340 (m), 1139 (m), 1023 (m), 859 (m), 746 (s), 692 (m); HRMS m/z (M^+ - C_6H_5SH) 236.1771 (calcd for $C_{15}H_{24}O_2$, 236.1775). Each of the two *threo*-isomers could be isolated by preparative TLC (Merck Silica gel 60F_{254} 5744) and showed the following NMR signals. One 2,3-*threo*-isomer (the major isomer): δ 1.14 (3H, s), 1.27 (3H, s), 1.26-1.36 (3H, m), 1.62-1.69 (1H, m), 1.64 (3H, br s), 1.68 (3H, br s), 1.85-1.97 (3H, m), 2.21-2.29 (1H, m), 2.40-2.46 (1H, m), 2.48 (1H, s, OH), 2.97 (1H, d, *J* = 5.0 Hz), 3.25 (1H, dd, *J* = 11.0, 3.0 Hz), 5.25-5.30 (1H, m), 7.19-7.23 (1H, m), 7.25-7.29 (2H, m), 7.42-7.45 (2H, m). The other *threo*-isomer (the minor isomer): δ 1.13 (3H, s), 1.29 (3H, s), 1.34 (1H, td, J = 12.0, 4.0 Hz), 1.45-1.51 (1H, m), 1.57-1.71 (2H, m), 1.61 (3H, br s), 1.67 (3H, br s), 1.79 (1H, dd, *J* = 15.0, 11.5 Hz), 1.83-1.90 (1H, m), 2.03 (1H, br dt, *J* = 14.5, 3.0 Hz), 2.21-2.29 (1H, m), 2.38 (1H, s, OH), 2.38-2.45 (1H, m), 2.88 (1H, d, *J* = 5.0 Hz), 3.26 (1H, dd, *J* = 9.5, 3.5 Hz), 5.29-5.34 (1H, m), 7.18-7.22 (1H, m), 7.24-7.28 (2H, m), 7.42-7.46 (2H, m).

(2S,3R,6S,7Z)-2,3-Epoxy-7,10-bisaboladiene (**1**). To a stirred suspension of diphosphorus tetraiodide (2.17 g, 3.82 mmol) in dichloromethane (28 ml) was added dropwise a solution of *threo*-**20** (1.20 g, 3.47 mmol) and triethylamine (2.13 ml, 17.34 mmol) at about -10 °C. After 4 h, the reaction was quenched with a mixture of 5% aq. Na_2CO_3 and 5% aq. $Na_2S_2O_3$ at ca. -20 °C, and the resulting mixture was filtered through a Celite pad. The filtrate was extracted with ether and the ethereal solution was washed successively with water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over silica gel (Katayama Chemical Silica gel 60 K230 W, 35 g, benzene/ethyl acetate = 3:2) to give 0.374 g (49%) of **1**: $[\alpha]_D^{22}$ -27.0° (*c* = 1.60, CH_2Cl_2); ν_{max} 2970 (s), 2920 (s), 2860 (m), 1450 (m), 1435 (m), 1379 (m), 1212 (w), 1120 (w), 1110 (w), 1020 (w), 1000 (w), 839 (m), 750 (w), 669 (w); ^1H NMR (CD_2Cl_2) δ 1.11-1.17 (1H, m), 1.29 (3H, s), 1.45 (1H, qd, *J* = 13.0, 4.5 Hz), 1.55 (3H, q, *J* = ca. 1.2 Hz), 1.62 (3H, br s), 1.68 (3H, d, *J* = ca. 1.2 Hz), 1.68-1.75 (2H, m), 1.76-1.82 (1H, m), 1.98 (1H, br ddd, *J* = 14.5, 4.0, 2.0 Hz), 2.41 (1H, tdd, *J* = 12.0, 6.5, 2.5 Hz), 2.62-2.72 (2H, m), 2.94 (1H, d, *J* = 5.0 Hz), 5.04-5.08 (2H, m); ^{13}C NMR ($CDCl_3$) δ 17.7, 19.0, 23.2, 23.8, 25.7, 26.3, 28.4, 30.7, 34.5, 57.4, 59.4, 123.4, 123.8, 131.4, 138.1; HRMS m/z (M^+) 220.1847 (calcd for $C_{15}H_{24}O$, 220.1826).

Determination of the enantiomeric excess of 1. To a stirred solution of **1** (0.030 g, 0.14 mmol) in DMSO-water (3 : 1, 3 ml) was added conc. H_2SO_4 (16 μl). After 7 h, the reaction mixture was quenched with sat. $NaHCO_3$ aq. and extracted with dichloromethane. The extract was washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. Preparative thin layer chromatography (Merck Silica gel 60F_{254} 13895) of the residue afforded 13.6 mg of **22a**.[28] This diol (2 mg) was converted into **22b** by treating with (*R*)-MTPACl (5 μl) and pyridine (10 μl) in dichloromethane (50 μl). In the same manner, (±)-**1** was also converted to a diastereomeric

mixture of the corresponding MTPA esters. The ^{1}H NMR spectrum of the mixture of MTPA esters derived from (±)-**1** showed two methoxy signals with almost equal intensity at δ 3.56 and δ 3.51, while the ratio of the methoxy signals of **22b** derived from **1** was 99.5 : 0.5. Therefore the enantiomeric excess of **1** was estimated to be 99%.

(2R,3R,6S,7Z)-2-Acetoxy-3-hydroxy-7,10-bisaboladiene (**23**) *and (2S,3S,6S,7Z)-3-acetoxy-2-hydroxy-7,10-bisaboladiene* (**24**). A solution of anhydrous tetrabutylammonium acetate (0.547 g, 1.81 mmol) in acetic acid (4 ml) was mixed with **1** (0.406 g, 1.81 mmol) and the mixture was stirred for 7.5 h at 50 °C. The mixture was poured into sat. $NaHCO_3$ aq. and extracted with ether. The ethereal solution was washed successively with water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over silica gel (12 g, hexane/ethyl acetate = 7:2) to give 0.479 g (94%) of a 7:1 mixture of **23** and **24**: $[\alpha]_D^{22}$ -77.6° (as a 7:1 mixture, c = 1.25, CH_2Cl_2); ν_{max} 3460 (m), 1721 (s), 1437 (m), 1377 (s), 1241 (s), 1205 (m), 1033 (s); HRMS m/z (M^+) 280.2039 (calcd for $C_{17}H_{28}O_3$, 280.2037). Both **23** and **24** could be isolated by preparative TLC and showed the following NMR signals. Compound **23**: δ 1.19 (3H, s), 1.24 (1H, s, OH), 1.31-1.35 (1H, m), 1.46-1.61 (2H, m), 1.62 (3H, d, J = ca. 1.2 Hz), 1.63 (3H, br s), 1.69 (3H, br s), 1.69-1.80 (2H, m), 1.99 (1H, ddd, J = 15.0, 13.0, 3.0 Hz), 2.08 (3H, s), 2.67 (2H, br t, J = 7.5 Hz), 2.74 (1H, tt, J = 12.5, 3.5 Hz), 4.80 (1H, br s), 5.07 (1H, tm, J = 7.5 Hz), 5.10 (1H, tm, J = 7.5 Hz). Compound **24**: δ 1.37-1.51 (3H, m), 1.51 (3H, br s), 1.62 (3H, d, J = ca. 1.2 Hz), 1.63 (3H, br s), 1.60-1.67 (1H, m), 1.69 (3H, br s), 1.72-1.77 (1H, m), 2.06 (3H, s), 2.30 (1H, dt, J = 13.0, 3.0 Hz), 2.56-2.63 (1H, m), 2.68 (2H, br t, J = 7.5 Hz), 3.85 (1H, dd, J = 12.0, 5.0 Hz), 3.89 (1H, br s, OH), 5.06 (1H, tm, J = 7.5 Hz), 5.12 (1H, tm, J = 7.5 Hz).

(2R,3R,6S,7Z)-2-Acetoxy-3-methanesulfonyloxy-7,10-bisaboladiene (**25**) *and (2S,3S,6S,7Z)-3-acetoxy-2-methanesulfonyloxy-7,10-bisaboladiene* (**26**). To a stirred solution of the 7:1 mixture of **23** and **24** (0.461 g, 1.65 mmol) in 2,6-lutidine (1.15 ml, 9.87 mmol) was added methanesulfonyl chloride (1.15 ml, 14.8 mmol) at 0 °C. After 3 h, the reaction mixture was poured into brine and extracted with ether. The ethereal solution was washed successively with $CuSO_4$ aq., NH_3 aq., water and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 0.563 g of a mixture of **25** and **26**: ν_{max} 3025 (w), 2940 (m), 1746 (s), 1439 (m), 1375 (m), 1344 (s), 1236 (s), 1178 (s), 1164 (s), 1031 (m), 975 (m), 899 (s). Because of their instability to silica gel column chromatography, this mixture was used for the next step without further purification.

(2R,3S,6S,7Z)-2,3-Epoxy-7,10-bisaboladiene (**2**). Potassium carbonate (0.652 g, 1.59 mmol) was added to a solution of the mixture of **25** and **26** (0.563 g, 1.65 mmol) in methanol (17.0 ml). The mixture was stirred for 3 h at room temperature and then poured into brine. The mixture was extracted with ether and the ethereal solution was washed successively with water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over silica gel (Katayama Chemical Silica gel 60 K230 W, 33 g, benzene/hexane = 2:3) to give 0.236 g (68% from the mixture of **23** and **24**) of **2**: $[\alpha]_D^{22}$ --16.8° (c = 1.04, CH_2Cl_2); ν_{max} 2970 (s), 2932 (s), 2862 (m), 1439 (m), 1379 (m), 1357 (w), 1181 (w), 1120 (w), 1035 (w), 1013 (w), 953 (w), 905 (w), 843 (m), 758 (m), 677 (w); ^{1}H NMR (CD_2Cl_2) δ 1.21-1.33 (2H, m), 1.27 (3H, s), 1.57 (3H, q, J = ca. 1.2 Hz), 1.62 (3H, br s), 1.67 (3H, br d, J = ca. 1.2 Hz), 1.72 (1H, ddd, J = 14.5, 13.0, 2.0 Hz), 1.84-1.89 (3H, m), 2.63 (1H, tt, J = 12.0, 4.0 Hz), 2.66 (2H, br t, J = 7.5 Hz), 3.00 (1H, t, J = 2.0 Hz), 5.05 (1H, tm, J = 7.5 Hz), 5.07 (1H, tm, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 17.7, 19.2, 24.6, 25.7, 26.2, 26.4, 29.2, 29.9,

30.1, 57.1, 60.8, 123.3, 124.5, 131.4, 137.7; HRMS m/z (M^+) 220.1823 (calcd for $C_{15}H_{24}O$, 220.1826).

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