Stereocontrolled Synthesis of the Sex Pheromones of the Green Stink Bug

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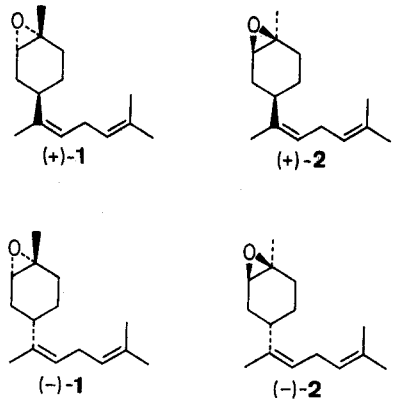
The four diastereoisomeric 3',4'-epoxides of (*Z*)-α-bisabolene, (+)-**1**, (+)-**2**, (−)-**1** and (+)-**2**, have been synthesized by stereocontrolled sequences. Comparisons with natural materials collected from the stink bug *Nezara viridula* revealed that the pheromone blend of this species contains (+)-**1** or (−)-**2** as major epoxide and (+)-**2** or (−)-**1** as minor epoxide in varying ratios depending on the geographical site of collection.

Stink bugs (Heteroptera: Pentatomidae) are major cosmopolitan pests that feed on a variety of crops. Their euryphytophagous behavior has made their control extremely difficult.[1] Recently the attractant pheromone of the southern green stink bug *Nezara viridula* has been isolated from bugs collected in the southern United States. The pheromone liberated by males of the *Nezara* species attracts conspecific females, other males, late stage larvae and the parasitoid *Trichopoda pennipes* (Diptera: Tachinidae). This pheromone blend typically consists of (*Z*)-α-bisabolene[1-methyl-4-(1,5-dimethyl-(*Z*)-1,4-hexadienyl)cyclohexene] (17%), *trans*- and *cis*-3',4'-epoxides of (*Z*)-α-bisabolene (44% and 15%, respectively), (*E*)-nerolidol (1.4%) and *n*-nonadecane (7.4%), although significant variations in the pheromone strain composition have been reported.[2-4]

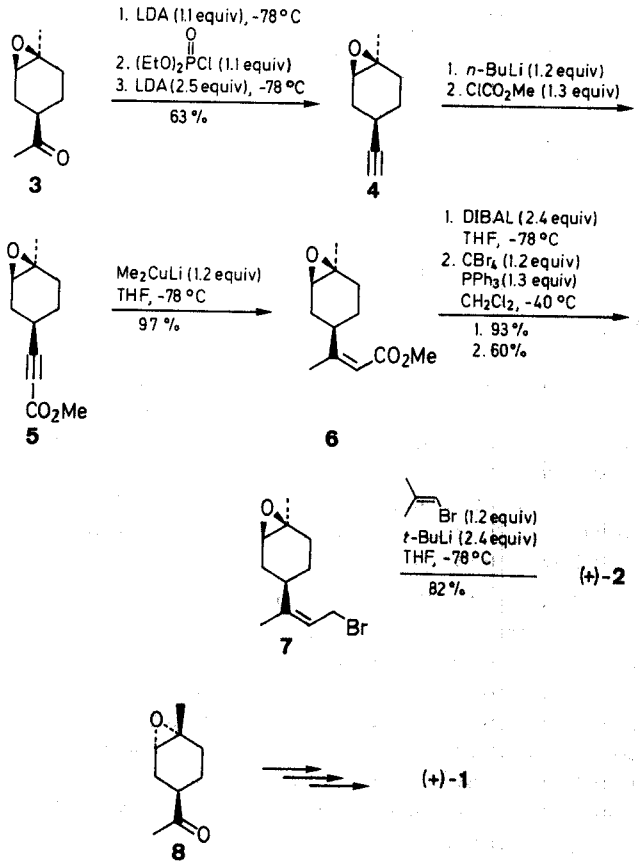
In view of the importance of these pheromones in understanding the behavior of stink bugs and eventually controlling them, the synthesis of the four isomeric 3',4'-epoxides of (*Z*)-α-bisabolene (Scheme **A**) was deemed important. In this communication stereocontrolled syntheses of these epoxide isomers [(+)-**1**, (−)-**1**, (+)-**2**, (−)-**2**] are described.



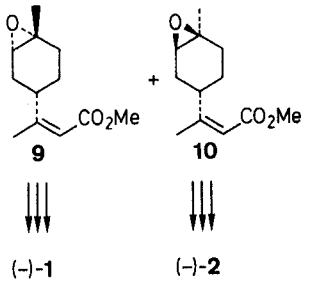
Scheme **A**

Previous studies in the area encountered difficulties in controlling the double bond geometry in constructing the bisabolene skeleton.[4,5] In designing our synthesis, we therefore, focused our attention on stereochemically controlling this construction and achieving an efficient route to these systems amenable to large scale operations.

Scheme **B** presents the synthesis of the bisabolene epoxide (+)-**2**, which exemplifies the chemistry involved in the construction of all four isomers. R-(+)-limonene oxide, commercially available as a 1:1 mixture of α- and β-epoxides[6] was ozonized at −78°C, and the ozonide so formed decomposed with triphenylphosphine leading to ketones **3** and **8** in 92% total yield.[7] These diastereomeric ketones were chromatographically separated (flash column, silica gel, 5→40% ether in petroleum ether; **3**: $R_f = 0.25$; **8**: $R_f = 0.20$, silica gel, 30% ether in petroleum ether), and identified by comparing their ^{1}H-NMR data to those previously reported.[7] Each isomer was processed separately through the rest of the sequence, although it was later discovered that separation of diastereoisomers could be better achieved at the stage of **6** (*vide infra*). Thus, ketone **3** was converted to the terminal acetylene **4** (63%) via the corresponding vinyl phosphate by the method of Negishi[8] and then to the acetylenic ester **5** (95%) by standard chemistry. Stereospecific delivery of the requisite methyl group to substrate **5** was secured employing dimethyllithium cuprate addition to the acetylenic ester leading exclusively to the (*Z*)-olefin **6** (97% yield). The assignment of geometry of the double bond in **6** was based on the expected mode of addition[9] and was confirmed by NOE studies (irradiation of the olefinic signal, $\delta = 5.62$, produced 5.7% enhancement of the vinyl methyl resonance, $\delta = 1.78$). Reduction of the ester functionality in **6** in THF at −78°C produced cleanly (93%) the corresponding alcohol, which was converted to bromide **7** (60%) by treatment with carbon tetrabromide/triphenylphosphine. Finally, coupling of **7** with 1-lithio-2-methylpropene generated from the corresponding vinyl bromide and *tert*-butyllithium by exchange at −78°C[10] resulted in the formation of *endo*-epoxide (+)-**2** in 82% yield (see the Table for physical data). This epoxide (and its isomers) proved to be rather sensitive to acid, but was quite stable in benzene or hexane solutions at −20°C for several weeks. Diastereoisomeric ketone **8** was similarly converted to (+)-**1** (see the Table for physical data).



Scheme **B**



Scheme C

The synthesis of (−)-**1** and (−)-**2** (see the Table for physical properties) proceeded from *S*-(−)-limonene oxide (mixture of epoxides)[6] along similar lines except that the separation of diastereoisomers was carried out at the stage of α,β-unsaturated esters **9, 10** (Scheme C) which, as mentioned above, proved easier to separate chromatographically than the ketones generated by ozonolysis of limonene oxides.

^{1}H-NMR, ^{13}C-NMR, mass spectra, and GC co-injections with naturally derived material showed that the major component of the pheromone of *Nezara vividula* from the Southern United States is the *exo*-epoxide (+)-**1** or (−)-**2** and the minor component its *endo*-isomer (+)-**2** or (−)-**1**. Gram quantities of all four compounds have been synthesized by this route and are awaiting field tests. These tests are expected to determine the active enantiomers and whether these pests can be controlled by appropriate use of the synthetic pheromones.

NMR spectra were recorded on an IBM AF-250 or Bruker AM-500 instrument. IR spectra were recorded on a Perkin-Elmer Model 781 infrared spectrophotometer. High resolution mass spectra (HRMS) were recorded on a VG 7070 HS mass spectrometer under chemical ionization (CI) conditions. All reactions were monitored by TLC carried out on 0.25-mm E. Merck silica gel plates (60F-254) using UV light and 7% ethanolic phosphomolybdic acid and heat as developing agent. E. Merck silica gel (60, particle size 0.050–0.062 mm) was used for flash column chromatography. All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise noted. Yields refer to chromatographically and spectroscopically (^{1}H-NMR) homogeneous materials, unless otherwise stated. All new compounds gave satisfactory spectral and analytical data.

(+)-(1*S*,2*R*-4*R*)-*endo*-1,2-Epoxy-4-ethynyl-1-methylcyclohexane (4):
Lithium diisopropylamide (LDA) is prepared by standard conditions anhydrous THF (14.5 mL), diisopropylamine (2.2 mL), a 1.5 M solution of *n*-BuLi in hexanes (10.5 mL), 0 °C, 0.5 h) and cooled to −78 °C under an argon atmosphere. The methyl ketone **4** (2.61 g, 15.9 mmol) in THF solution (5 mL) is slowly (5 min) added, and stirring is continued at −78 °C for 1 h. Diethyl chlorophosphate (2.3 mL, 15.9 mmol) is then slowly added via syringe, and the reaction mixture is allowed to reach room temperature over a period of 3.5 h. The resulting brown solution is slowly added via cannula over a 3 h period to a solution of LDA [prepared by standard conditions at 0 °C in anhydrous THF (39 mL) from diisopropylamine (5.5 mL) and a 1.5 M solution of *n*-BuLi in hexanes (26 mL)] at −78 °C. The reaction mixture is then allowed to reach room temperature over a period of 3.5 h and quenched with sat. aq. NH_4Cl (50 mL). Extraction with hexane (3 × 50 mL) followed by washing of the combined organic phase with 1 N aq. HCl (3 × 20 mL), sat. aq. $NaHCO_3$ (30 mL), and brine (20 mL) gave a solution of the products. Drying ($MgSO_4$), concentration, and flash column chromatography (silica gel, 5% ether in petroleum ether, bp 40–60 °C) gave pure acetylene **4** having a light sweet, piney odor as a colorless, volatile oil; yield: 1.15 g (60%); R_f 0.11 (silica gel, 2.5% ether in petroleum ether, bp 40–60 °C); $[\alpha]_D^{25}$ +142.20° (*c* = 1.68, CH_2Cl_2).

IR (neat): ν = 2922 (s), 2850 (m), 2110 (w), 1433 (m), 1210 (m), 1020 (m) cm^{-1}.

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.31 (s, 3 H); 1.63 (m, 3 H); 1.96 (m, 2 H); 2.06 (d, 1 H, *J* = 2.3 Hz); 2.23 (m, 2 H); 2.93 (d, 1 H, *J* = 4.9 Hz).

MS: *m/z* (%) = 137 (M^+ + H, 100), 121 (52), 107 (61).

HRMS calc. for $C_9H_{13}O$ (M^+ + H): 137.0966, found: 137.0972.

Methyl (+)-(*Z*)-(1′*R*,3′*R*,4′*S*)-*endo*-3-(3′,4′-Epoxy-4′-methylcyclohexyl)-2-butynoate (5):
Acetylene **4** (16.8 g, 123 mmol) is methoxycarbonylated according to Ref. 11 to give butynoate **5**; yield: 22.7 g (95%).

Methyl (+)-(*Z*)-(1′*R*,3′*R*,4′*S*)-*endo*-3-(3′,4′-Epoxy-4′-methylcyclohexyl)-2-butenoate (6):
Copper(I) iodide (720 mg, 3.78 mmol) is placed in a 50 mL, flame-dried flask equipped with a stirring bar and a 3-way stopcock under argon. Anhydrous THF (18 mL) is added, and the resultant mixture is cooled to 0 °C and stirred while a 1.5 M solution of MeLi in ether (5.4 mL, 7.54 mmol) is slowly added via syringe. After stirring at 0 °C for 15 min, the clear solution is cooled to −78 °C, and the acetylenic ester **5** (699 mg, 3.60 mmol) in THF (5 mL) is added dropwise with stirring. The reaction mixture is stirred at −78 °C for 3 h before quenching with excess MeOH (2 mL). The mixture is allowed to reach room temperature and then poured into a sat. aq. NH_4Cl solution (50 mL) in a separatory funnel. Shaking until the solution turns blue followed by extraction with CH_2Cl_2 (3 × 25 mL), drying ($MgSO_4$), and concentration gives the crude product as a yellow oil. Flash column chromatography (silica gel, 20% ether in petroleum ether, bp 40–60) gave pure α,β-unsaturated ester **6** as a colorless oil; yield: 739 mg (97%); R_f 0.38 (silica gel, 30% ether in petroleum ether, bp 40–60 °C); $[\alpha]_D^{25}$ +39.27° (*c* = 6.02, CH_2Cl_2).

Table. Selected Physical Data of (+)-**1**, (+)-**2**, (−)-**1**, and (−)-**2**

Compound	$[\alpha]_D^{25}$	*c*[a]	^{1}H-NMR[b] δ, *J*(Hz)	^{13}C-NMR[c] δ	HRMS[d] *m/z* (M^+ + H)
(+)-**1**	+19.36°	10.2	1.28 (m, 1H, CH_2); 1.32 (s, 3H, H-7′); 1.58 (s, 3H, CH_3); 1.62 (s, 3H, H-1); 1.68–1.72 (m, 5H, CH_3, CH_2); 1.89 (m, 3H, CH_2); 2.67 (m, 3H, H-4, 1′); 3.05 (s, 1H, H-3′); 5.07 (m, 2H, H-3,5)	138.66, 132.34, 125.51, 124.30, 61.80, 58.04, 31.11, 30.91, 30.22, 27.38, 27.20, 26.67, 25.55, 20.19, 18.69	221.1913
(−)-**1**	−19.97°	15.7	same as above		221.1915
(+)-**2**	+34.42°	2.73	1.17 (m, 1H, CH_2); 1.34 (s, 3H, H-7′); 1.48 (m, 1H, CH_2); 1.57 (d, *J* = 1.3, 3H, CH_3); 1.63 (s, 3H, H-1); 1.69 (m, 4H, CH_3, CH_2); 1.78 (m, 2H, CH_2); 2.03 (m, 1-H, CH_2); 2.42 (m, 1H, H-1′); 2.67 (bt, 2H, H-4); 3.00 (m, 1H, H-3′); 5.07 (m, 2H, H-3,5)	138.04, 131.43, 123.80, 123.32, 59.43, 59.37, 34.47, 30.68, 28.38, 26.36, 25.68, 23.77, 23.18, 19.04, 17.68	221.1918
(−)-**2**	−34.67°	15.3	same as above		221.1888

[a] Grams per 100 mL CH_2Cl_2.
[b] 250 MHz, $CDCl_3$, TMS.
[c] 125 MHz, $CDCl_3$.
[d] High resolution mass spectrometry, CI; calc. for $C_{15}H_{25}O$ (M^+ + H): 221.1905.

IR (neat): ν = 2948 (s), 1718 (s), 1640 (s), 1435 (s), 1383 (s), 1153 (s) cm^{-1}.

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.32 (s, 3 H, C(O)CH_3); 1.5 (m, 1 H, CH_2); 1.64 (m, 1 H, CH_2); 1.74 (m, 1 H, CH_2); 1.78 (d, 3 H, J = 1.4 Hz, CH_3C=C); 2.03 (m, 2 H, CH_2); 3.00 (d, 1 H, J = 5.2 Hz, CH–O); 3.61 (m, 1 H, CH); 3.67 (s, 3 H, OCH_3); 5.62 (d, 1 H, J = 0.9 Hz, CH=C).

MS: m/z (%) = 211 (M^+ + H, 41), 193 (100, 179 (73), 161 (33).

HRMS (calc. for $C_{12}H_{19}O_3$(M^+ + H): 211.1334, found: 211.1352.

(+)-(*Z*)-(1′*R*,3′*R*,4′*S*)-*endo*-1-Bromo-3-(3′,4′-epoxy-4′-methylcyclohexyl)-2-butene (7):

Ester **6** (2.13 g, 10.1 mmol) is reduced[12] with DIBAL (2.4 equiv) in THF (67 mL) at −78 °C to give the corresponding primary alcohol; yield: 1.72 g (93 %).

This alcohol (88.9 g, 0.488 mmol) is brominated[13] with CBr_4 (1.2 equiv) and PPh_3 (1.3 equiv) in CH_2Cl_2 (2.4 mL) at −40 °C to give bromide **7**; yield: 75.6 mg (60 %).

(*Z*)-(1′*R*,3′*R*,4′*S*)-(+)-2-(3′,4′-Epoxy-4′-methylcyclohexyl)-6-methylhepta-2,5-diene[(+)-2]:

A flame-dried 10 mL flask equipped with a magnetic stirring bar and a 3-way stopcock is charged with anhydrous THF (1.0 mL) and a 2.0 M solution of *t*-BuLi in pentane (0.33 mL, 0.66 mmol) and cooled to −78 °C under argon. 1-Bromo-2-methylpropene (34 mg, 45 µl, 0.33 mmol) is added, and the reaction mixture is stirred at that temperature for 2.5 h. To the resulting yellow solution of the vinyl anion, the allylic bromide **7** (74.3 mg, 0.303 mmol) in anhydrous THF (0.5 mL) is added at −78 °C, and the reaction mixture is allowed to stir at that temperature for 10 min before quenching with water (200 mL) warming to room temperature followed by dilution with hexanes (15 mL), water (2 × 5 mL) and brine (5 mL) gave a solution which was dried ($MgSO_4$) and concentrated. Flash column chromatography (silica, 5 % ether in petroleum ether) gave pure epoxide (+)-**2** as a colorless oil (yield: 54.1 mg (81 %).

IR (neat): ν = 2983 (s), 2918 (s), 1451 (m), 1430 (m), 1380 (m), 1210 (w), 1109 (w) cm^{-1}.

MS: m/z (%) = 221 (M^+ + H, 12), 203 (24), 165 (60), 147 (65), 135 (70), 121 (85), 109 (100).

HRMS calc. for $C_{15}H_{25}O$ (M^+ + H): 221.1905, found: 221.1918.

For further physical data see the Table.

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