An Efficient Synthesis of (+)-*exo*-Brevicomin via Chloroallylboration

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Received August 6, 1998

Introduction

We have recently shown that (*Z*)-(γ-chloroallyl)diisopinocampheylboranes **1a**,**b** (Scheme 1) are readily accessible.[1] The chloroallylboration of **1a** or **1b** with aldehydes provides a highly diastereo- (≥90% de) and enantioselective (90−99% ee) synthesis of chiral *syn*-vinylchlorohydrins and *cis*-vinylepoxides.[1,2] Our interest in chiral pheromone synthesis prompted us to utilize this new strategy for the synthesis of (+)-*exo*-brevicomin, (+)-**2**.

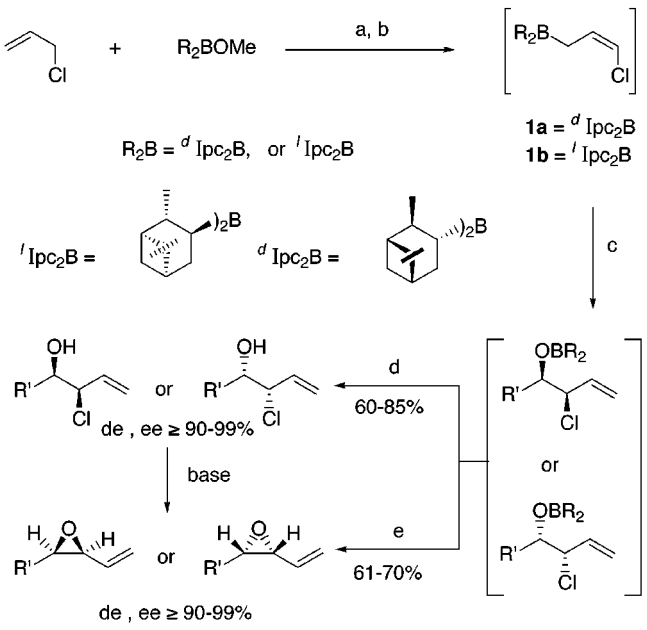
(+)-*exo*-Brevicomin **2** is a component of the attracting pheromone system of several bark beetle species belonging to genera *Dendroctonus* and *Dryocoetes*.[3] Although a number of syntheses of **2** have been reported,[4] many are not satisfactory in terms of process simplicity or enantiomeric and diastereomeric purities of **2**. Herein, we wish to report an efficient synthesis of (+)-**2** starting from *cis*-vinylepoxide **7**, which is obtained via chloroallylboration in 97% ee, 99% de.

Results and Discussion

The synthesis commenced with the preparation of aldehyde **6** according to Scheme 2. Acid-catalyzed protection of 5-chloro-2-pentanone with 2,2-dimethyl-1,3-propanediol gave **4** which was alkylated with the dianion of propargyl alcohol. Lithium metal reduction afforded allylic alcohol **5**,[5] which was transformed, without purification, to aldehyde **6**.

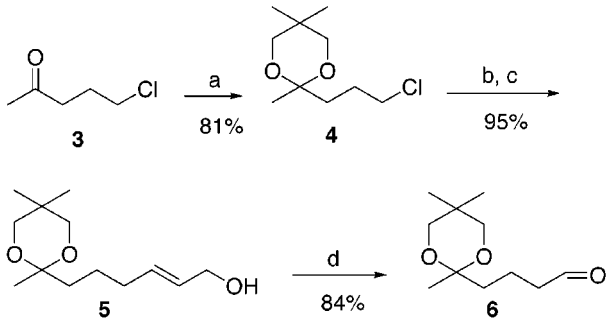
Chloroallylboration was carried out with **1a** and **6** at −95 °C for 4 h (Scheme 1, Scheme 3). The key intermediate, *cis*-vinylepoxide **7**, was prepared in 64% yield with excellent enantiomeric and diastereomeric purities (97% ee, 99% de) by standard oxidation workup. Acid-induced epoxide−carbonyl cyclization was the most common strategy for the synthesis of brevicomins. Cyclization of

Scheme 1[a]



[a] Key: (a) Et_2O, −95 °C, $LiN(c\text{-}Hex)_2$; (b) $BF_3{\cdot}OEt_2$, −95 °C; (c) R′CHO, −95 °C; (d) $HOCH_2CH_2NH_2$; (e) OH^-/H_2O_2.

Scheme 2[a]



[a] Key: (a) 2,2-dimethyl-1,3-propanediol, H^+; (b) propargyl alcohol, $LiNH_2$; (c) Li/NH_3; (d) O_3, then SMe_2.

cis-vinylepoxide **7** in a methanol and water mixture (70:30) with a catalytic amount of *p*-toluenesulfonic acid gave 68% of **8** that had enantiomeric and diastereomeric purities of 88% ee and 90% de, obtained through gas chromatographic analysis performed on a Cyclodex B fused-silica column. Since the starting material **7** had higher enantiomeric and diastereomeric purities, acid-mediated cyclization must be accompanied by some side racemization. Catalytic hydrogenation of **8** furnished 83% of (+)-**2** with undiminished optical and diastereomeric purities.

Palladium-mediated vinylepoxide ring opening with carbon dioxide has been shown to lead to diol with retention of stereochemistry (cis hydroxylation equivalent).[7] Following Trost's strategy,[7a] palladium(0) catalyzed epoxy ring opening of *cis*-vinylepoxide **7** was carried

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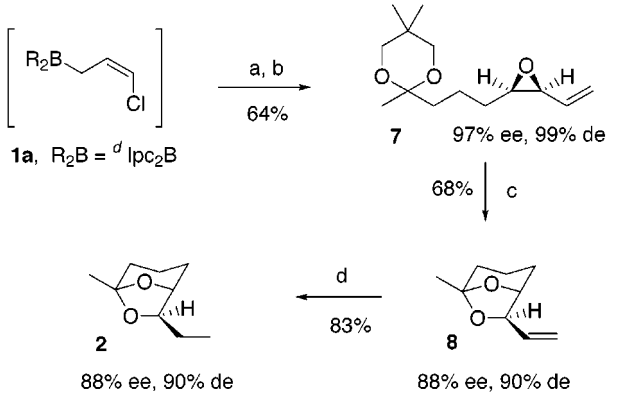
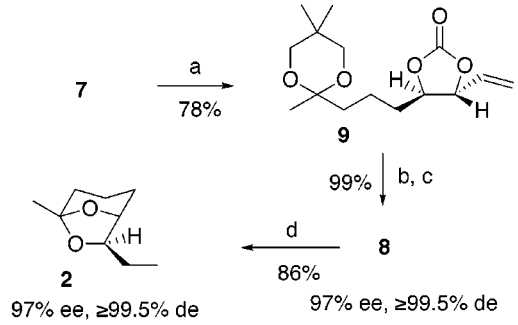
10.1021/jo981604c CCC: $18.00
Published on Web 03/05/1999

Scheme 3[a]



[a] Key: (a) **6**, −95 °C, 4 h. (b) OH^-/H_2O_2. (c) *p*-TsOH, MeOH/H_2. (d) H_2/Pd−C.

Scheme 4[a]



[a] Key: (a) Pd(0), 40 Psi CO_2. (b) 0.5 M NaOH in 50% aqueous dioxane, 15 min. (c) 2 N HCl, 20 min. (d) H_2/Pd−C.

out in a CO_2 atmosphere (40 psi) for 30 min (Scheme 4). Concentration of the reaction mixture *in vacuo* and column chromatography yielded 78% of cyclic carbonate **9** with excellent diastereoselectivity (≥99.5%). Surprisingly, the cyclic carbonate **9** possessed trans stereochemistry, that was assigned on the basis of its clear NMR spectrum (see the Experimental Section). It can be hypothesized that neighboring-group participation of 1,3-dioxane in the epoxy ring opening may be the origin of the unusual trans palladium-mediated opening of *cis*-vinylepoxide.

Various strategies for the cyclization of **9** to form **8** were investigated. Treatment of **9** with dilute acid led to the formation of an unidentified product with high polarity. A two-step approach was more successful in securing the desired product **8**. The one-pot, two-step reaction was carried out by the treatment of the cyclic carbonate **9** with 0.5 M NaOH in dioxane for 15 min, followed by dilution with excess 2 N HCl solution and stirring for another 20 min. This process led to the formation of 99% of **8** with excellent enantiomeric and diastereomeric purities (97% ee, ≥99.5% de).

Palladium catalyzed hydrogenation of **8** gave 86% of (+)-**2** with undiminished enantiomeric and diastereomeric purities.

In summary, *cis*-vinylepoxide **7,** which is readily prepared via chloroallylboration, undergoes acid-induced cyclization to furnish *exo*-brevicomin (+)-**2** in 88% ee and 90% de. Under palladium-mediated epoxy ring opening with carbon dioxide, **7** leads to the formation of cyclic carbonate **9** via an abnormal trans opening. The latter is converted to (+)-**2** with excellent enantiomeric and diastereomeric purities.

Experimental Section

General Chemical Procedures. THF and diethyl ether were distilled from sodium benzophenoneketyl. Dicyclohexylamine [(*c*-Hex)$_2$NH] was freshly distilled from CaH_2 prior to use. Allyl chloride was freshly distilled over P_2O_5 prior to use. The *d*Ipc$_2$BOMe was purchased from Aldrich and used without purification. Moisture- and air-sensitive reactions were conducted under argon in vacuum-dried glassware. A nitrogen glovebag was used to weigh moisture-sensitive compounds. Syringes and cannulas were used to transfer air-sensitive reagents.[8] Unless otherwise stated, standard workup refers to combination of organic extracts, washing with ice-cold brine, drying over anhydrous $MgSO_4$, and concentration *in vacuo*. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. GC analyses were conducted using a 30-m × 0.25-mm i.d. fused-silica column coated with DB-1 with FID.

2,5,5-Trimethyl-2-(3-formylpropyl)-1,3-dioxane (6). 5 was prepared according to the procedure described in ref 5. Ozone was bubbled through a cold solution (−78 °C) of **5** (11.4 g, 100 mmol) in a 1:1 mixture of CH_2Cl_2/MeOH (250 mL) and 10 g of $NaHCO_3$. The reaction was monitored by the appearance of a characteristic blue color. Then, excess ozone was removed by a stream of nitrogen. This was followed by the addition of dimethyl sulfide (50 mL) and, finally, stirring overnight. The reaction mixture was concentrated *in vacuo* to one-third of the volume, diluted with water (200 mL), and then extracted with Et_2O (3 × 100 mL). The combined Et_2O extract was dried over anhyd Na_2SO_4. Column chromatography (7:3 hexane/Et_2O) yielded 8.4 g (84%) of **6** as a colorless liquid. ^{13}C NMR and ^{1}H NMR spectral data are in agreement with reported values.[9]

Chloroallylboration of Aldehyde 6 Using *d*Ipc$_2$BOMe. (4*R*,5*S*)-2,5,5-Trimethyl-2-(*cis*-4,5-epoxy-6-heptenyl)-1,3-dioxane (7). To a stirred and cooled (−95 °C) mixture of *d*Ipc$_2$-BOMe (11.5 mmol) and allyl chloride (15 mmol) in anhyd ether (50 mL) was added a solution of LiN(*c*-Hex)$_2$ (15 mmol) in THF (25 mL). After being stirred for 1 h, BF_3·OEt_2 (30 mmol) was added, followed by aldehyde **6** (11.5 mmol). The reaction was continued at −95 °C for 4 h. All solvents were removed *in vacuo* at room temperature, and the residue was triturated with *n*-pentane (40 mL) and allowed to settle (12 h). The supernatant was transferred to another predried flask through a cannula. The residue was further treated with pentane (2 × 30 mL), and the pentane extracts were combined. Removal of pentane *in vacuo* furnished a semisolid.

Oxidation of Boron Intermediates. The residue obtained was dissolved in THF (20 mL) with stirring and cooled to 0 °C. Then, 3 M NaOH (12 mL) and 30% H_2O_2 (12 mL) were sequentially added. The reaction mixture was allowed to warm to room temperature (14 h). Standard workup followed by flash chromatography yielded a colorless liquid, **7** (1.48 g, 66% yield); $[\alpha]^{23}_D$ +8.34 (*c* = 2.11, Et_2O); ^{13}C NMR ($CDCl_3$) δ 132.6, 120.3, 98.7, 70.4, 58.7, 57.1, 38.1, 29.9, 27.9, 22.8, 22.4, 20.2, 20.0; ^{1}H NMR ($CDCl_3$) δ 5.72 (ddd, *J* = 17.2, 10.4, 7.2 Hz, 1H), 5.47 (ddd, *J* = 17.2, 1, 1 Hz, 1H), 5.34 (ddd, *J* = 10.4, 1, 1 Hz, 1H), 3.56 (d, *J* = 11.6 Hz, 2H), 3.42 (d, *J* = 11.6 Hz, 2H), 3.40 (dd, *J* = 4.8, 7.2 Hz, 1H), 3.08 (m, 1H), 1.52−1.73 (m, 6H), 1.36 (s, 3H), 1.03 (s, 3H), 0.88 (s, 3H); CIMS *m*/*z* (isobutane, rel intensity) 241 (M^+ + 1, 23), 223 (18), 155 (100), 137 (97). Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07. Found: C, 70.01; H, 10.01.

(+)-(1*R*,7*R*)-*exo*-5-Methyl-7-vinyl-6,8-dioxabicyclo[3.2.1]-octane (8). A mixture of **7** (240 mg, 1 mmol), 5 mL of MeOH/H_2O (70:30), and *p*-TsOH (20 mg, 0.1 mmol) was stirred overnight at room temperature. The mixture was then diluted with Et_2O (20 mL) and washed with saturated $NaHCO_3$ solution. The organic layer was dried over anhyd Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography over silica gel gave **8** (96 mg, 68% yield, 90% de, 88% ee) as a volatile

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liquid (GC purity ≥99%): $[\alpha]^{23}_D$ +60.4 (c = 2.10, Et_2O); ^{13}C NMR and ^1H NMR spectral data are in agreement with reported values.[6]

(+)-(1*R*,7*R*)-*exo*-Brevicomin (2). Hydrogenation of **8** (924 mg, 6 mmol) was carried out with 67 mg of Pd/C catalyst (10% on carbon) in ethyl acetate. After being stirred for 2 h, the catalyst was removed by filtration. The filtrate was concentrated *in vacuo* and purified by chromatography followed by distillation to give **2** as a volatile liquid (770 mg, 83% yield, 88% ee, 90% de): $[\alpha]^{23}_D$ +60.8 (c = 2.31, Et_2O) (lit.[4a] $[\alpha]^{23}_D$ +69.7, c = 3.60, Et_2O).

4-(4*R*,5*S*)-[3-(2,5,5-Trimethyl-1,3-dioxan-2-yl)propyl]-5-vinyl-1,3-dioxolan-2-one (9). To a stirred solution of $Pd(OAc)_2$ (5.6 mg, 0.025 mmol) in 1 mL of THF was added triisopropyl phosphite (20 μL, 0.175 mmol), and stirring was continued for 10 min. BuLi (2.5 M in hexane; 20 μL, 0.05 mmol) was added and the mixture stirred for another 30 min. The catalyst solution was poured into a solution of **7** (120 mg, 0.5 mmol) in 2 mL of THF in an autoclave. The mixture was stirred at 5 bar CO_2 at room temperature. After 30 min, the reaction mixture was concentrated *in vacuo* and then chromatographed to give **9** as a light yellow liquid: $[\alpha]^{23}_D$ +18.48 (c = 2.33, Et_2O); ^{13}C NMR ($CDCl_3$) δ 132.2, 121.31, 98.5, 82.5, 81.9, 70.4, 38.9, 33.1, 29.9, 22.8, 22.3, 19.3, 18.7, 15.2; ^1H NMR ($CDCl_3$) δ 5.86 (ddd, J = 17.1, 10.4, 7.2 Hz, 1H), 5.47 (d, J = 17.2 Hz, 1H), 5.34 (d, J = 10.4 Hz, 1H), 4.65 (t, J = 7.2 Hz, 1H), 4.31 (dt, J = 7.2, 4.4 Hz, 1H), 3.58 (d, J = 11.4 Hz, 2H), 3.37 (d, J = 11.4 Hz, 2H), 1.54−1.77 (m, 6H), 1.36 (s, 3H), 1.05 (s, 3H), 0.88 (s, 3H); CIMS m/z (isobutane, rel intensity) 285 (M^+ + 1, 100), 199 (100). Anal. Calcd for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51. Found: C, 63.47; H, 8.61.

(+)-(1*R*,7*R*)-*exo*-5-Methyl-7-vinyl-6,8-dioxabicyclo[3.2.1]-octane (8). A mixture of **9** (85 mg, 0.3 mmol) in 1 mL of 0.5 M NaOH (50% aqueous dioxane) was stirred for 15 min at room temperature. The solution was diluted with 2 N HCl (5 mL) and stirred for another 20 min. Extraction with Et_2O (3 × 20 mL), concentration, and chromatography yielded **8** (46 mg, ≥99% yield) with 97% ee and ≥99.5% de as a volatile liquid (GC purity ≥99%): $[\alpha]^{23}_D$ +87.2 (c = 2.09, Et_2O); ^{13}C NMR and ^1H NMR spectral data are in agreement with reported values.[6]

(+)-(1*R*,7*R*)-*exo*-Brevicomin (2). Hydrogenation of **8** was effected following the same procedure described earlier. (+)-2 was obtained in 86% yield (97% ee, ≥99.5% de): $[\alpha]^{23}_D$ +67.9 (c = 1.41, Et_2O) (lit.[4a] $[\alpha]^{23}_D$ +69.7, c = 3.60, Et_2O).

Acknowledgment. We thank the National Sciences and Engineering Research Council, Canada, for financial support through a research grant to A.C.O.

JO981604C