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Note

Asymmetric synthesis of the Japanese beetle pheromone via boronic esters

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Abstract

The pheromone of the Japanese beetle, [*R*-(*Z*)]-5-(1-decenyl)dihydro-2(3*H*)-furanone (**7**), has been synthesized efficiently in high enantiomeric purity via 1,2-dicyclohexyl-1,2-ethanediol boronic esters. The synthetic route involves reaction of an α-chloro boronic ester with an alkynyllithium, and provides the first successful example of this substitution process in an asymmetric synthesis.

Keywords: Boronic ester; Asymmetric; Propargylborane; Pheromone

The enantiomeric purity of japonilure (**7**), the pheromone of the Japanese beetle *Popillia japonica*, must be very high in order for the material to be attractive to the insects [1]. The (*S*)-enantiomer ***ent*-7** is the similarly enantiospecific pheromone of the Osaka beetle *Anomala osakana*, which shares a common habitat with the Japanese beetle [2]. In each of these two species of scarab beetle, a single binding protein binds both enantiomers, and enantiospecific neurons distinguish the attractive enantiomer from the repellent one [3]. Other species of scarab beetle respond to mixtures of **7** and buibuilactone, which is similar to **7** but has 1-octenyl in place of 1-decenyl, and are unaffected by the enantiomers [4].

Japonilure seemed a suitable synthetic target for our asymmetric boronic ester chemistry [5], which has previously produced single isomers of liquid products directly in 99.9% stereopurity [6]. The most practical previous syntheses [7,8] involved asymmetric reduction of an acetylenic ketone precursor. Subsequent further enantiomeric purification was accomplished by recrystallizing a salt of the opened lactone. Other syntheses have involved derivation from a natural chiron such as glutamic acid [1] or a pentose [9], or resolution by enzymatic [10] or chemical [11] means. This brief review is not exhaustive.

The 3-borylpropionate **1** has been prepared from pinacol (iodomethyl)boronate and *tert*-butyl lithioacetate [12]. The more conveniently available (bromomethyl)boronate [13] proved satisfactory in the present work. Conversion of **1** to asymmetric boronic ester **2** was accomplished by treatment with (*R*,*R*)-1,2-dicyclohexyl-1,2-ethanediol [(*R*)-DICHED] [14]. Reaction of **2** with (dichloromethyl)lithium followed by zinc chloride [5] resulted in chain extension to chloro boronic ester **3**. Treatment of **3** with lithio-1-decyne yielded propargylic boronic ester **4**. Oxidation of **4** with alkaline hydrogen peroxide yielded *tert*-butyl (*R*)-4-hydroxy-5-tetradecynoate **5**. Lactonization of **5** with *p*-toluenesulfonic acid yielded the known (*R*)-5-(1-decynyl)dihydro-2(3*H*)-furanone (**6**) [7,8], which was hydrogenated over Lindlar's catalyst according to the literature method [7,8] to form japonilure (**7**).

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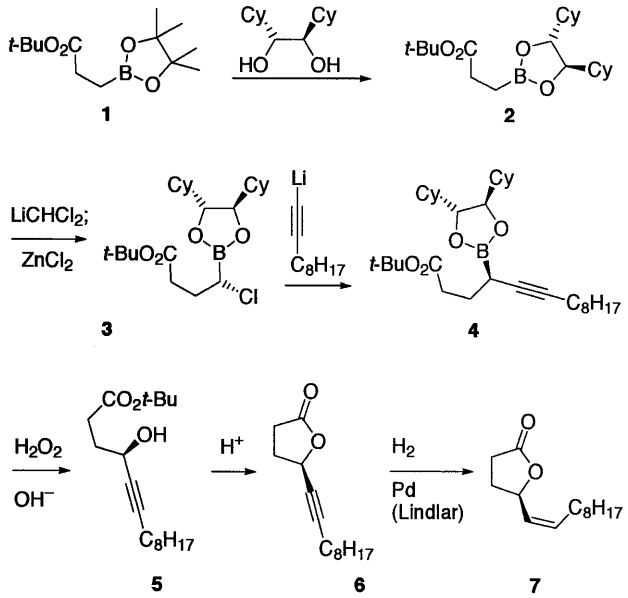

This synthesis illustrates the efficiency and predictability of asymmetric synthesis with α-halo boronic ester intermediates [5]. The yield of propargylic alcohol ester **5** from **1** was 66%, and the yield of distilled known lactone **6** was 45% based on **1**.

The reaction of (halomethyl)boronic esters with alkynyllithiums to produce propargylboronic esters has been reported by Brown et al. [15]. An unsuccessful attempt to synthesize an asymmetric propargylic alcohol from the (cyclohexyl)(chloro)methylboronic ester of dicyclohexylidenemannitol and 1-pentynyllithium resulted instead in apparent rearrangement of the boronic ester intermediate to the allenylboronic ester, which was oxidized to 1-cyclohexyl-3-hexenone [16]. The procedure reported by Li and Kabalka did not include a step to remove the zinc chloride from the α-chloro boronic ester before the pentynyllithium was introduced. Our procedure included thorough separation of the chloro boronic ester **3** from the zinc chloride promoter used in its preparation. We do not know whether this was the critical difference.

Although our preparation of **4** was efficient, it might be noted that reaction of (dichloromethyl)lithium with an acetylenic boronic ester, which requires an inherently slower borate rearrangement, has not been accomplished.

The oily precursor boronic esters **3** and **4** were not chromatographed and therefore contained small amounts ($\sim 5\%$) of unchanged precursors and other impurities. Consequently, the ^{1}H- and ^{13}C-NMR spectra of these compounds are inconclusive with regard to the possible presence of a very small amount of diastereomer. There was no evidence of any contamination of **4** by an allenic isomer, and chromatographed **5** did not contain any detectable α,β-unsaturated ketone. The magnitude of rotation of **7** produced by our synthesis, $[\alpha]_D^{24}$ −71.4°, is within experimental error of the best previously reported values, $[\alpha]_D$ −70° to −71° [1b,7,8,9,11,17], with one anomalous value at −73.9° [10b].

1. Experimental

1.1. General

The usual procedures for handling reactive organometallic reagents were followed, including the use of an inert atmosphere (argon) and THF (tetrahydrofuran) that had been rigorously dried over sodium benzophenone ketyl.

1.2. 2-[2-[[(1,1-Dimethylethyl)oxy]carbonyl]ethyl]-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane (*1*)

Lithium diisopropylamide (150 ml of 1.5 M, 225 mmol) was added dropwise in 30 min to a stirred solution of pinacol (bromomethyl)boronate (45.3 g, 205 mmol) and *tert*-butyl acetate (29.7 g, 256 mmol) in tetrahydrofuran (400 ml) at −78°C under argon. The solution was allowed to warm slowly overnight to room temperature, then quenched with water. The mixture was extracted with pentane (400 ml). The organic phase was washed with water (4 × 250 ml), separated, dried over anhydrous magnesium sulfate, filtered, concentrated under vacuum, and distilled, b.p. 90°C (0.5 torr) (48.3 g, 92%); 300 MHz ^{1}H-NMR ($CDCl_3$) δ 0.94 (t, 2), 1.21 (s, 12), 1.41 (s, 9), 2.32 (t, 2); 75 MHz ^{13}C-NMR ($CDCl_3$) δ 6.2 (br), 24.9, 28.2, 30.2, 79.6, 82.9, 173.9. HRMS: Calc. for $C_{13}H_{25}BO_4$ (M-55) 201.1298; Found 201.1300.

1.3. (4R,5R)-2-[2-[(1,1-Dimethylethyl)oxy]carbonyl]-ethyl]-4,5-dicyclohexyl-1,3,2-dioxaborolane (*2*)

The pinacol ester **1** (37.3 g, 146 mmol) in diethyl ether (400 ml) was treated with (*R*,*R*)-1,2-dicyclohexyl-1,2-ethanediol [(*R*)–DICHED] (35 g, 155 mmol). The solution was stirred overnight, then extracted with water (6 × 150 ml) to remove pinacol. The organic phase was dried over anhydrous magnesium sulfate, then concentrated to precipitate excess DICHED. The slurry was washed with pentane (250 ml), and the pentane solution was concentrated under vacuum to yield **2** (50.0 g, 94%); 300 MHz ^{1}H-NMR ($CDCl_3$) δ 0.8–1.39 (m, 12), 1.40 (s, 9), 1.41–1.82 (m, 10), 2.32 (t, 2), 3.79 (m, 2); 75 MHz ^{13}C-NMR ($CDCl_3$) δ 5.9 (br), 25.9, 26.0, 26.5, 27.5, 28.1, 28.4, 30.1, 43.0, 79.7, 83.4, 173.7. HRMS: Calc. for $C_{21}H_{37}BO_4$ (M-55) 309.2237; Found (EI) 309.2219.

1.4. [2(1′S),4R,5R]-2-[3-[[(1,1-Dimethylethyl)oxy]-carbonyl]-1-chloropropyl]-1,3,2-dioxaborolane (*3*)

(Dichloromethyl)lithium was prepared as previously described by the addition of butyllithium (133 mmol) to a solution of dichloromethane (234 mmol) in THF (1 l)

stirred at −100°C [5a]. A solution of **2** (42.2 g, 116 mmol) in tetrahydrofuran (300 ml) was added. The mixture was allowed to warm to −78°C. Anhydrous zinc chloride in diethyl ether (208 ml, 1 M) was added and the solution was kept for 20 h at 20–25°C, then poured into pentane (1 l). The organic phase was washed with water (4 × 200 ml) and concentrated under vacuum. The residue was dissolved in pentane (400 ml), washed with water (3 × 200 ml), dried over magnesium sulfate, filtered, and concentrated to yield **3** (38.0 g, 79%); 300 MHz ^{1}H-NMR ($CDCl_3$) δ 0.85–1.85 (m, 22), 1.42 (s, 9), 1.98–2.25 (m, 2), 2.30–2.52 (m, 2), 3.49 (m, 1), 3.92 (m, 2).

*1.5. [2(1′R),4R,5R]-2-[3-[[(1,1-Dimethylethyl)-oxy]carbonyl]-1-(1-decynyl)propyl]-4,5-dicyclohexyl-1,3,2-dioxaborolane (**4**)*

Lithium diisopropylamide (68 ml, 1.5 M, 102 mmol) was added dropwise to a stirred solution of 1-decyne (15.3 g, 111 mmol) in THF (250 ml) at −78°C. After an additional 15 min at −78°C, the resulting solution of 1-lithiodecyne was transferred via cannula to a stirred solution of chloro boronic ester **3** (38.0 g, 92.0 mmol) in THF (250 ml). The mixture was allowed to warm to 20–25°C and stirred for 18 h. Pentane (500 ml) was added. The organic phase was washed with water (3 × 250 ml), dried over magnesium sulfate, and concentrated under vacuum (1 torr) to yield a residue of **4** (45.8 g, 97%); 300 MHz ^{1}H-NMR ($CDCl_3$) δ 0.86 (t, 3), 0.88–1.91 (m, ~37), 1.42 (s, 9), 2.11 (t, 2), 2.2–2.5 (m, 2), 3.87 (m, 2). This material was used directly in the next step.

*1.6. (R)-[1,1-Dimethylethyl 4-hydroxy-5-tetradecynoate] (**5**)*

Hydrogen peroxide (20 ml, 30%) and sodium hydroxide solution (200 ml, 1 M) were added to a stirred solution of decynyl boronic ester **4** (45.8 g, 89 mmol) in diethyl ether (500 ml) in a flask equipped with a reflux condenser. Stirring at 25°C was continued for 2 h. The ether phase was separated and concentrated under vacuum. The resulting slurry was treated with pentane (500 ml) to complete the precipitation of DICHED, which was filtered and washed with an additional 250 ml of pentane. The combined pentane solution was concentrated under vacuum to clear, colorless liquid **5** (23.6 g, 89%). A portion was chromatographed on silica with 20% ethyl acetate in pentane; 300 MHz ^{1}H-NMR ($CDCl_3$) δ 0.75 (t, 3), 1.10–1.31 (m, 10), 1.34 (s, 9), 1.37 (t, 2), 1.81 (m, 2), 2.04 (dd, 2), 2.30 (m, 2), 3.11 (br s, 1), 4.30 (m, 1); 75 MHz ^{13}C-NMR ($CDCl_3$) δ 13.9, 18.5, 22.3, 27.6, 28.1, 29.0, 29.3, 30.6, 31.2, 32.9, 64.1, 80.2, 80.4, 85.4, 173.0. HRMS: Calc. for $C_{14}H_{23}O_2$ [M–(55 + 18)] 223.1698; Found (EI) 223.1683.

*1.7. [(R)-5-(1-Decynyl)dihydro-2(3H)-furanone (**6**)*

(*R*)-[1,1-Dimethylethyl 4-hydroxy-5-tetradecynoate] (**5**) (4.50 g, 1.52 mmol) and *p*-toluenesulfonic acid (0.061 g, 0.03 mmol) were dissolved in dichloromethane (5 ml). When the solution became homogeneous, the solvent was distilled and the resulting red liquid was heated at 100°C under vacuum for 2 h. The product was distilled bulb-to-bulb (130°C, 1 torr), 2.36 g (69%). The material was chromatographed on silica gel, (20% ethyl acetate in pentane); 300 MHz ^{1}H-NMR ($CDCl_3$) δ 0.79–0.85 (t, 3), 1.16–1.34 (m, 10), 1.40–1.48 (m, 2), 2.14–2.25 (m, 3), 2.40–2.49 (m, 2), 2.54–2.64 (m, 1), 5.07 (m, 1); 75 MHz ^{13}C-NMR ($CDCl_3$) δ 14.0, 18.6, 22.6, 27.9, 28.2, 28.7, 29.0, 29.1, 30.1, 31.7, 69.7, 76.4, 88.7, 176.3.

*1.8. [R-(Z)]-5-(1-Decenyl)dihydro-2(3H)-furanone (**7**)*

Hydrogenation of lactone **6** (0.860 g) was carried out at 1 atm for 1 h at 0°C over Lindlar catalyst (5% palladium on calcium carbonate poisoned with lead acetate, 200 mg, plus quinoline, 8 drops) in pentane (50 ml) according to the procedure of Senda and Mori [8]; yield of **7** 0.854 g; after chromatography on silica (10% ethyl acetate in pentane) 0.554 g (65%); 300 MHz ^{1}H-NMR ($CDCl_3$) δ 0.83 (t, 3), 1.19–1.31 (m, 10), 1.32–1.42 (m, 2), 1.88–2.00 (m, 1), 2.00–2.17 (m, 2), 2.30–2.40 (m, 1), 2.48–2.60 (m, 2), 5.19–5.27 (m, 1), 5.39–5.47 (m, 1), 5.60–5.69 (m, 1); 75 MHz ^{13}C-NMR ($CDCl_3$) δ 14.1, 22.6, 27.8, 29.0, 29.1, 29.2, 29.3, 29.36, 29.37, 31.8, 76.4, 127.1, 135.8, 177.2; $[\alpha]_D^{24}$ −71.4° ($c = 1.00$, $CHCl_3$) [lit. $[\alpha]_D^{25}$ −70.0° ($c = 5.0$, $CHCl_3$) [1b], $[\alpha]_D^{21}$ −70.4° ($c = 1.082$, $CHCl_3$) [8], $[\alpha]_D^{26}$ −69.93° ($c = 9.84$, $CHCl_3$) [7], $[\alpha]_D^{26}$ −71.0° (c = 5.387, $CHCl_3$ [9a], $[\alpha]_D^{22}$ −70.4° ($c = 0.4$, $CHCl_3$) [9b], $[\alpha]_D^{25}$ −70.0° ($c = 6.4$, $CHCl_3$) [11], $[\alpha]_D^{25}$ −70.82° ($c = 0.19$, $CHCl_3$) [15]; the only value beyond −71°: $[\alpha]_D^{25}$ −73.9° (c = 1.004, $CHCl_3$) [10b].

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