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# Synthesis and Absolute Configuration of (−)-Methyl (*E*)-2,4,5-Tetradecatrienoate, the Sex Attractant of the Male Dried Bean Weevil

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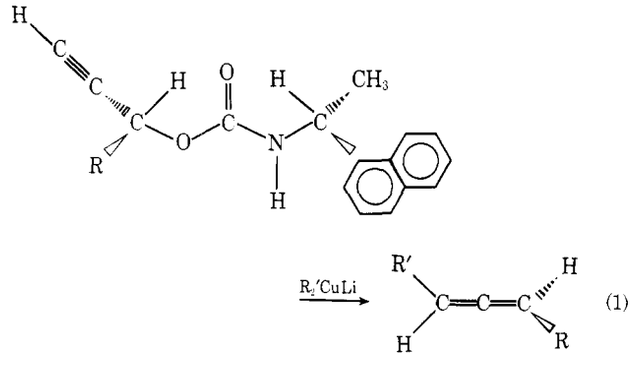
(−)-Methyl (*E*)-2,4,5-tetradecatrienoate [(−)-**1**, $[\alpha]_D$ −98°] was synthesized from β-cyanopropionaldehyde dimethyl acetal. The key intermediates, (*R,R*)- and (*S,R*)-1-ethynyl-3-carbomethoxypropyl *N*-[1-(1-naphthyl)ethyl]-carbamates (**4a,b**) are separable using liquid chromatography. The low temperature reaction of **4b** with lithium di-*n*-octylcuprate affords (*R*)-(−)-methyl 4,5-tetradecadienoate [*R*-(−)-**5**] and this allene was then converted to (*R*)-(−)-**1**. Similarly, (*S*)-(+)-**1** is prepared from **4a**. The synthetic pheromone, (*R*)-(−)-**1**, has 77% the rotatory power of the natural product.

(−)-Methyl (*E*)-2,4,5-tetradecatrienoate [(−)-**1**] has been of synthetic interest since Horler determined it to be a sex attractant produced by the male bean weevil, *Acanthoscelides obtectus*.[1] While several syntheses of the racemic material have been described,[2-6] a synthesis of the chiral pheromone has not been reported nor has the absolute configuration of the natural product been determined. This paper describes the asymmetric synthesis of chiral **1** by a sequence which also enables determination of the absolute configuration of the natural pheromone.

**Synthesis.** We recently reported a simple two-step synthesis of chiral 1,3-dialkyl allenes of moderate to high enantiomeric purity.[7] This sequence involves the reaction of lithium dialkylcuprates with a single diastereomer of the carbamates derived from racemic secondary propargylic alcohols and (*R*)-1-(1-naphthyl)ethyl isocyanate (eq 1). Such carbamates are readily separable by means of liquid chromatography.[7,8] The operational simplicity, known stereochemical pathway, and substantial optical yield of this asymmetric synthesis made it attractive as the key step in the synthesis of (−)-**1**.




(1)

Scheme I outlines the synthesis of **1** from β-cyanopropionaldehyde. Treatment of the aldehyde with ethynylmagnesium bromide afforded racemic alcohol **2** in 72% yield. Cyanocarbamates **3a,b** were isolated as a 1:1 mixture in 90% yield from the reaction of (±)-**2** with (*R*)-1-(1-naphthyl)ethyl isocyanate. Treatment of **3a,b** with methanolic HCl at room temperature for 1 h affords diastereomeric carbamates **4a** and **4b** which are readily separable by liquid chromatography on silica gel. Once separated, these diastereomeric carbamates were treated with di-*n*-octylcuprate to afford chiral allene **5**. The *trans* double bond was introduced by the method of Kocienski et al.[6]

As previously noted,[7] the diastereomers of a propargylic carbamate may afford allenes of different enantiomeric purity and may require different mixing orders of reactants (i.e., normal vs. inverse addition) to optimize the enantiomeric yield. Table I outlines the results of the reaction of di-*n*-octylcuprate with **4a** and **4b** under various conditions. The reaction of **4b** with di-*n*-octylcuprate in diethyl ether using normal addition (adding carbamate to cuprate) afforded (−)-**5**, $[\alpha]_D$ −45° (2.9, hexane), in 62% yield. The pheromone, (−)-**1**, $[\alpha]_D$ −98° (3.9, hexane), was obtained in 83% yield from (−)-**5** and has 77% the rotatory power of the naturally occuring material. Similarly, (+)-**5** (therefore (+)-**1**) was obtained from **4a**. However, maximum enantiomeric yields were obtained from **4a** using inverse addition (cuprate added to carbamate).

**Absolute Configuration of (−)-1.** Introduction of the *trans* double bond in (−)-**5** to afford (−)-**1** does not change the absolute configuration of the allene. Since the stereochemical pathway of the allene forming reaction is known,[7,9] determination of the absolute configuration of **4b** also determines that of (−)-**5** and (−)-**1**. This is straightforward; the absolute configuration of the amine portion of **4b** is known and the realtive configuration (and hence, the absolute configuration) about the carbinyl carbon can be assigned based on NMR spectral differences between **4a** and **4b**.

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Scheme I

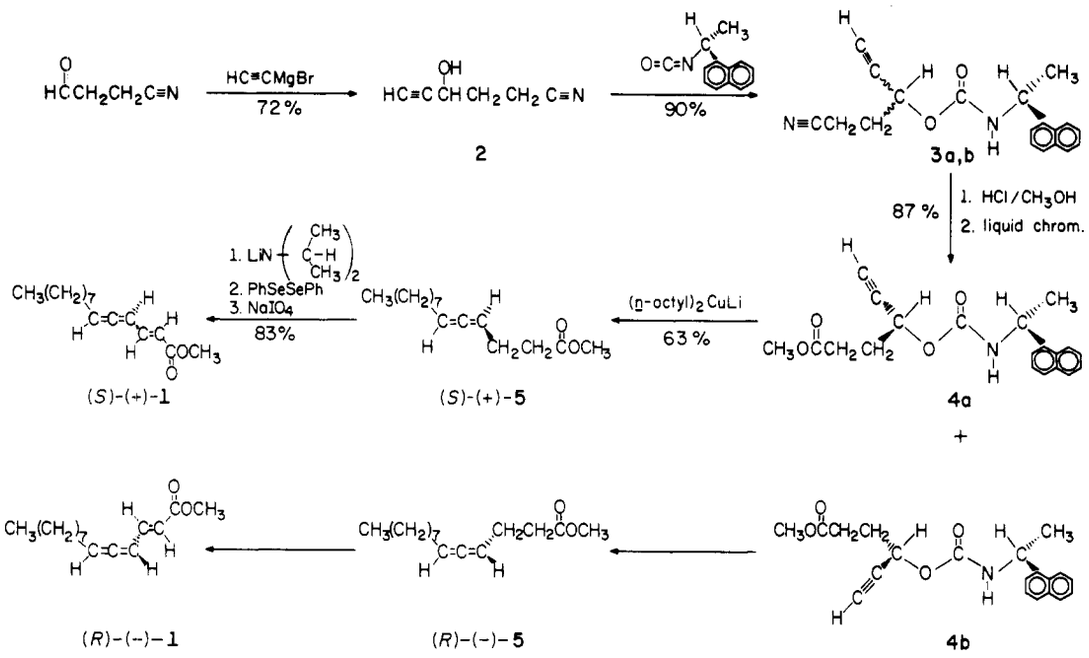

**Table I. The Reaction of Diastereomeric Carbamates 4a and 4b with Di-*n*-octylcuprate for 7 h at −78 °C**

| Carbamate | Solvent | Order of addition | $[\alpha]_D$ of product 5 |
|---|---|---|---|
| **4a** | $Et_2O$ | Normal | +26.7° (4.6, hexane) |
| **4a** | $Et_2O$ | Inverse | +43.5° (5.1, hexane) |
| **4b** | $Et_2O$ | Normal | −45.0° (2.9, hexane) |
| **4b** | $Et_2O$ | Inverse | −30.5° (7.5, hexane) |
| **4b** | THF | Normal | Racemic[a] |
| **4b** | Toluene | Normal | *b* |

[a] Only 20% of the carbamate had undergone reaction under these conditions. [b] Starting material was quantatively recovered after 12 h.

A variety of carbamates derived from secondary alcohols and (*R*)-1-(1-naphthyl)ethyl isocyanate have been shown to preferentially populate conformations similar to those shown in Scheme I for **4a** and **4b**.[8] Owing to the shielding effect of the *cis*-α-naphthyl group, the methoxy resonance of **4a** would be expected to occur upfield of that of **4b.** For the same reason, the ethynyl doublet of **4a** would be expected to occur downfield of that of **4b.** These spectral differences are observed; **4a,** the high $R_f$ diastereomer, is therefore assigned the (*R,R*) configuration; **4b** is assigned the (*S,R*) configuration. This assignment is consistant with NMR spectral differences observed for similar carbamates of configurationally known propargyl alcohols.[8]

Crabbé has shown that (*S*)-(−)-3-hydroxy-1-octyne acetate reacts with lithium dimethylcuprate at −10 °C to afford an (*R*)-allene.[9] Further, it has been demonstrated that acetates, tosylates, and carbamates of (*S*) secondary propargylic alcohols afford (*R*)-allenes when treated with dialkylcuprates and that similarly derivatized (*R*) secondary propargylic alcohols afford (*S*)-allenes.[7] Therefore, carbamate **4b,** having the (*S*) configuration about the carbinyl carbon, affords (*R*)-(−)-**5** when treated with di-*n*-octylcuprate. Hence, the natural product, (−)-**1,** derived from (*R*)-(−)-**5,** has the (*R*) configuration.

**Summary.** Both enantiomers of methyl (*E*)-2,4,5-tetradecatrienoate have been synthesized. The levorotatory isomer has 77% of the rotatory power of the natural product and has been determined to have the (*R*) configuration.

## Experimental Section

Infrared spectra were recorded with a Beckman IR-12 spectrometer, NMR spectra with a Varian EM-390 instrument using $Me_4Si$ as an internal standard, and mass spectra with a Varian CH-5 spectrometer. Melting points are uncorrected.

**β-Cyanopropionaldehyde.** To 500 mL of water was added 65 g (0.50 mol) of β-cyanopropionaldehyde dimethyl acetal[10] and 100 mg of *p*-toluenesulfonic acid. The stirred solution was heated at reflux for 2 h. The water was removed under reduced pressure (bath <50 °C) and the β-cyanopropionaldehyde was distilled under vacuum to afford 40 g (96%): bp 66–68 °C (2 mm); NMR ($CCl_4$) δ 2.6 (m, 2 H), 2.85 (m, 2 H), 9.75 (s, 1 H).

**(±)-5-Cyano-1-pentyn-3-ol (2).** To a stirred solution of ethynylmagnesium bromide[11] (0.15 mol) in 400 mL of dry THF at ambient temperature 8.3 g (0.10 mol) of β-cyanopropionaldehyde in 20 mL of dry THF was added dropwise over a 45-min period. The solution became slightly warm and was stirred for 3 h before the addition of saturated aqueous $NH_4Cl$ (400 mL). The organic phase was separated and the aqueous phase was extracted with three 200-mL portions of $Et_2O$. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated at reduced pressure. The residue was vacuum distilled to afford 7.8 g (72%) of **2:** bp 85 °C (0.05 mm); NMR ($CCl_4$) δ 2.1 (m, 2 H), 2.55 (t, 2 H), 2.67 (d, 1 H), 3.1 (broad s, 1 H), 4.5 (dt, 1 H); IR ($CHCl_3$) 3600, 3460, 3310, 3030, 2260, 2120, 1425, 1235, 1070, 935 $cm^{-1}$; MS (70 eV) *m/e* (rel intensity) 110 [$(M + H)^+$], 55 (100), 54 (34), 41 (11), 39 (14).

**1-Ethynyl-3-cyanopropyl *N*-[1-(1-naphthyl)ethyl]carbamates (3a,b).** A mixture of **2** (5.0 g, 46 mmol), (*R*)-(−)-(1-naphthyl)-ethyl isocyanate (9.06 g, 46 mmol), and *N,N*-dimethylethanolamine (1 wt%) in toluene (200 mL) was heated at reflux for 60 h. The cooled solution was then washed with 1 N HCl (50 mL), saturated $NaHCO_3$ (50 mL), and water (100 mL). The organic layer was dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure to afford a yellow syrup, 12.7 g (90%), of **3a,b** as a 1:1 mixture: NMR ($CCl_4$) δ 1.67 (d, 3 H), 2.1 (m, 2 H), 2.5 (m, 3 H), 5.0–5.8 (m, 3 H), 7.3–8.3 (m, 7 H); IR ($CHCl_3$) 3450, 3310, 3040, 2260, 2130, 1730, 1505, 1450, 1380, 1240, 1060 $cm^{-1}$; MS (70 eV) *m/e* (rel intensity) 360 ($M^+$, 44), 291 (31), 215 (15), 214 (100), 170 (30), 155 (11), 129 (14).

**1-Ethynyl-3-carbomethoxypropyl *N*-[1-(1-Naphthyl)ethyl]carbamates (4a,b).** These methyl esters were prepared from **3a,b** by the method of Betz and Daub.[12] Anhydrous HCl was bubbled into a stirred ice-cooled solution of 12.16 g (40 mmol) of **3a,b** in 100 mL of 1:1 methanol–ether for 1 h. After stirring at 25 °C for 1 h[13] 100 mL

of water was slowly added with cooling and air was bubbled rapidly through the solution for 30 min to remove HCl. The aqueous phase was extracted with ether (200 and 75 mL) and the combined extracts were washed with 10% $NaHCO_3$ and saturated NaCl. After drying ($MgSO_4$), the organic phase was filtered and the solvent was removed under reduced pressure to afford 11.7 g (87%) of **4a,b**. The mixture was then chromatographed on a multigram HPLC system[14] using benzene–ether (15:1) on silica gel. The effluent was monitored at 280 nm.

The first major fraction to be eluted was (*R,R*)-**4a** (5.9 g). Recrystallization from hexane afforded a white solid: mp 104–105 °C; NMR ($CCl_4$) $\delta$ 1.6 (d, 3 H), 2.0 (m, 2 H), 2.3 (d, 1 H), 2.2–2.4 (m, 2 H), 3.50 (s, 3 H), 5.1–5.7 (m, 3 H), 7.2–8.1 (m, 7 H); IR ($CHCl_3$) 3450, 3320, 3020, 2130, 1730, 1510, 1250, 1175, 1065 $cm^{-1}$; MS (70 eV) *m/e* (rel intensity) 339 ($M^+$, 14), 214 (00), 182 (25), 170 (57), 156 (23), 155 (88), 154 (23), 153 (22), 129 (46), 127 (24), 125 (29), 97 (26). Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.92; H, 6.19; N, 3.94.

The second major fraction to be eluted was (*S,R*)-**4b** (5.8 g). Crystallization from hexane afforded a white solid: mp 78.5–80.5 °C; NMR ($CCl_4$) $\delta$ 1.6 (d, 3 H), 2.0 (broad, 2 H), 2.24 (d, 1 H), 2.15–2.6 (broad, 2 H), 3.57 (s, 3 H), 4.9–5.7 (m, 3 H), 7.2–8.1 (m, 7 H); IR ($CHCl_3$) 3460, 3320, 3020, 2130, 1740, 1510, 1250, 1175, 1065 $cm^{-1}$; MS (70 eV) *m/e* (rel intensity) 339 ($M^+$, 9), 214 (98), 197(21), 182 (52), 170 (63), 156 (43), 155 (100), 154 (36), 153 (41), 129 (71), 128 (33), 127 (44), 125 (28), 97 (26). Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.66; H, 6.04; N, 4.37.

**(*R*)-(−)-Methyl 4,5-Tetradecadienoate [(*R*)-(−)-5].** This compound was prepared from the reaction of lithium di-*n*-octylcuprate with **4b** by two procedures.

**Normal Addition.** Carbamate **4b** (1.20 g, 3.5 mmol) in diethyl ether (25 mL) was added dropwise over a 10-min period to a stirred solution of lithium di-*n*-octylcuprate[15] (3.85 mmol) in diethyl ether (40 mL) cooled to −78 °C. After stirring the solution for an additional 7 h at −78 °C, the cooling bath was removed and the reaction mixture was allowed to come to 0 °C. Saturated $NH_4Cl$ (10 mL) was then added and the mixture was stirred for 15 min to allow the copper salts to precipitate. The resulting slurry was filtered and the organic layer was separated, washed with 1 N HCl (10 mL) and saturated $NaHCO_3$ (15 mL), dried ($MgSO_4$), filtered, and concentrated at reduced pressure. Vacuum distillation of the residue afforded 0.52 g (62%) of (*R*)-(−)-**5**, $[\alpha]_D$ −45.0° (2.9, hexane): NMR ($CCl_4$) $\delta$ 0.87 (t, 3 H), 1.25 (broad s, 12 H), 1.9 (m, 2 H), 2.27 (m, 4 H), 3.54 (s, 3 H), 5.0 (m, 2 H); IR ($CHCl_3$) 2940, 1965, 1740 $cm^{-1}$; MS (70 eV) *m/e* (rel intensity) 238 ($M^+$, 21), 140 (92), 98 (37), 85 (40), 83 (85), 81 (61), 80 (100), 79 (40), 71 (61), 67 (33).

**Inverse Addition.** Lithium di-*n*-octylcuprate (3.85 mmol) in diethyl ether (25 mL) cooled to −78 °C was added portionwise over 5 min to a cold (−78 °C) stirred solution of **4b** (1.20 g, 3.5 mmol) in diethyl ether (40 mL). The reaction mixture was stirred for 7 h at −78 °C and worked up as described above to afford 0.54 g (64%) of (*R*)-(−)-**5**, $[\alpha]_D$ −30.5° (7.5, hexane).

**(*S*)-(+)-Methyl 4,5-Tetradecadienoate [(*S*)-(+)-5].** This compound was prepared from the reaction of lithium di-*n*-octylcuprate with **4a** by the procedures described for the preparation of (*R*)-(−)-**5**.

Use of inverse addition afforded (*S*)-(+)-**5** (65%), $[\alpha]_D$ +43.5° (5.1, hexane). Use of normal addition afforded (*S*)-(+)-**5** (61%), $[\alpha]_D$ +26.7° (4.6, hexane).

**(*R*)-(−)-Methyl (*E*)-2,4,5-Tetradecatrienoate [(*R*)-(−)-1].** This compound was prepared from (*R*)-(−)-**5**, $[\alpha]_D$ −45.0°, by the method of Kocienski.[6] Allene (*R*)-(−)-1 was isolated (83%) as a light yellow oil, $[\alpha]_D$ −98.3° (3.8, hexane): NMR ($CCl_4$) $\delta$ 0.87 (t, 3 H), 1.3 (broad s, 12 H), 2.03 (m, 2 H), 3.65 (s, 3 H), 5.3 (m, 1 H), 5.6–5.9 (m, 1 H), 5.72 (d, 1 H), 7.1 (dd, 1 H); IR ($CHCl_3$) 2950, 2880, 1950, 1730, 1635, 1440, 985 $cm^{-1}$; MS (70 eV) *m/e* (rel intensity) 236 ($M^+$, 2),138 (67), 137 (21), 107 (21), 82 (28), 79 (100), 78 (39), 67 (21).

**(*S*)-(+)-Methyl (*E*)-2,4,5-Tetradecatrienoate [(*S*)-(+)-1].** This compound was prepared from (*S*)-(+)-**5**, $[\alpha]_D$ +43.5°, by the method of Kocienski.[6] Allene (*S*)-(+)-1 was isolated as a light yellow oil, $[\alpha]_D$ +94.9° (3.3, hexane).

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**Registry No.**—(*R*)-(−)-**1**, 28066-21-9; (*S*)-(+)-**1**, 65451-10-7; **2**, 65414-51-9; **3a**, 65414-52-0; **3b**, 65414-53-1; **4a**, 65414-54-2; **4b**, 65414-55-3; (*R*)-(−)-**5**, 65451-09-4; (*S*)-(+)-**5**, 65494-90-8; β-cyanopropionaldehyde, 3515-93-3; β-cyanopropionaldehyde dimethyl acetal, 14618-78-1; ethynyl bromide, 593-61-3; *R*-(−)-(1-naphthyl)ethyl isocyanate, 42340-98-7; lithium di-*n*-octylcuprate, 38317-57-6.

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# Total Synthesis of 3-Oxa-4,5,6-trinor-3,7-*inter-m*-phenylene Prostaglandins. 1. Photochemical Approach

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The total syntheses of optically active 3-oxa-4,5,6-trinor-3,7-*inter-m*-phenylene prostaglandins **3**, **28**, **29**, and **30** are described. The synthetic route to these novel and biologically active prostaglandin analogues involved the photochemical cycloaddition of *m*-acetoxybenzaldehyde (**16**) and optically active acetal **5** to give the tricyclic oxetane **17** as the key step. The structure and optical purity of oxetane **17** were supported by model studies and NMR chiral shift reagent studies as well as subsequent transformations to the desired end products.

During the past several years, a number of prostaglandin analogues have been synthesized which have incorporated an aromatic ring at some location in the basic prostaglandin structure. Two such examples are the 17-phenyl-18,19,20-trinor- and the 16-phenoxy-17,18,19,20-tetranor-substituted prostaglandins represented by **1** and **2**, respectively. These

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