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A facile asymmetric synthesis of (+)-eldanolide

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Abstract—The monoterpenoid pheromone (+)-eldanolide, a long range sex attractant, has been synthesized in four steps from the chiral 2,3-epoxy alcohol **4** in 36% overall yield. Our synthetic strategy features the formation of a 1,3-diol by regio- and stereoselective ring opening of 2,3-epoxy alcohol **4**, an intermediate easily available from Sharpless asymmetric epoxidation. Other key steps include one carbon elongation, saponification, and lactonization. The present work constitutes a general method for the rapid synthesis of a number of related γ-lactone natural products.

1. Introduction

The naturally occurring compound (+)-eldanolide **1** (Fig. 1) was isolated as a long range sex attractant from the male wing glands of African sugarcane stem borer *Eldana sacharina* (Wlk.) in 1981.[1,2] Due to its attractive biological activities, the monoterpenoid pheromone has aroused enormous attention (Fig. 1) from the synthetic community since the assignment of its absolute configuration.[3,4] Most of the known synthetic approaches required enantiomerically pure natural products as the starting materials and involved quite lengthy reaction sequences. Therefore, more efficient strategies for the assembly of eldanolide are still desirable. Herein, we report our synthesis of (+)-eldanolide **1** featuring a Sharpless asymmetric epoxidation[5] (SAE) followed by regio- and stereoselective ring opening of the resultant 2,3-epoxy alcohol. The latter is a powerful and practical strategy for the construction of chiral, substituted 1,3- or 1,2-diol units with a predictable stereochemical outcome.[6]

2. Results and discussion

Our asymmetric synthesis of (+)-eldanolide **1** is outlined in Scheme 1. Copper(I) iodide-catalyzed alkylation of the dianion of propargyl alcohol (generated with ethylmagnesium bromide in THF at 0 °C) with prenyl bromide led to enynol **2**[7] in 93% yield, via a remarkable sp–sp^3 coupling. Reduction with $LiAlH_4$ in refluxing THF resulted in the formation of dienol **3**[8] in good yield (89%). Treatment of *trans*-allylic alcohol **3** with (−)-DIPT, $Ti(OPr^i)_4$, TBHP, and 4 Å molecular sieves (powdered) in CH_2Cl_2 (−30 °C, N_2, 3 h) afforded 2,3-epoxy alcohol **4** in 75% yield {93.6% ee;[10] $[\alpha]_D^{27} = +19.15$ (*c* 2.25, $CHCl_3$); lit.[9] $[\alpha]_D^{20} = +16.3$ (*c* 1.9, $CHCl_3$)} by following a standard Sharpless asymmetric epoxidation protocol.[5] The subsequent ring opening of **4** with Me_2CuLi in ether at 0 °C produced an inseparable mixture of 1,3-diol **5** and 1,2-diol **5′** in a combined yield of 84%. The ratio of **5**/**5′** was found to be approximately 2:1, based on the line integrals of the ^1H NMR spectrum. Exposure of the mixture of **5**/**5′** to $NaIO_4$ in acetone and water at room temperature cleanly provided pure **5** (56% from **4**) through destroying **5′** via vicinal diol cleavage, which set the stage for homologation at C-1.[11] Selective tosylation of diol **5** at the primary hydroxyl (TsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C to room temperature)

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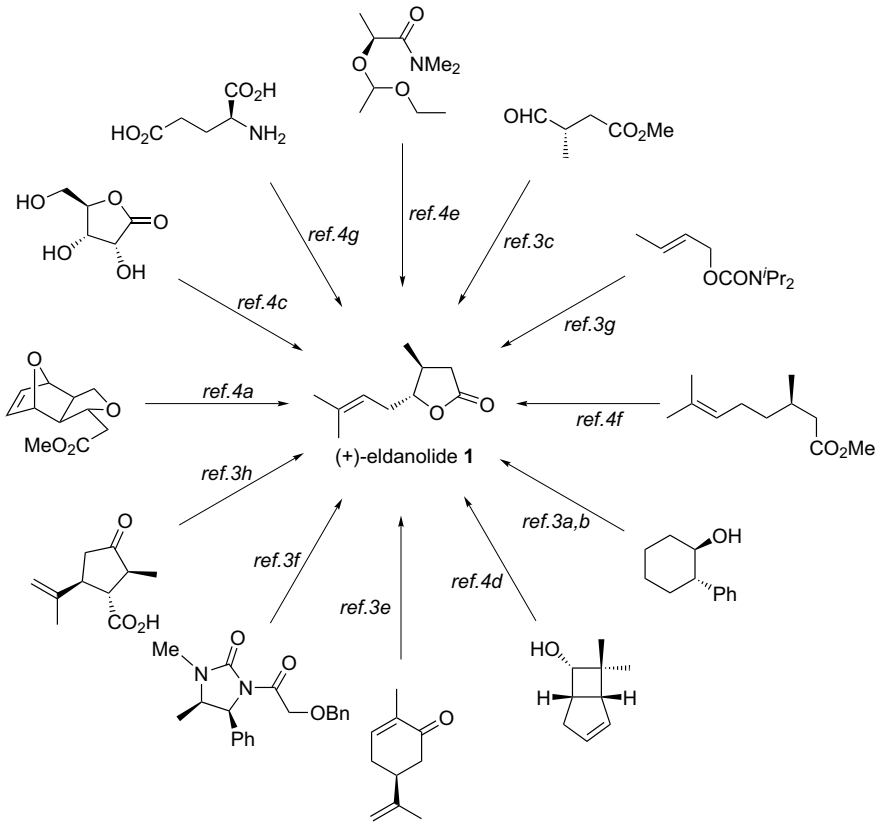
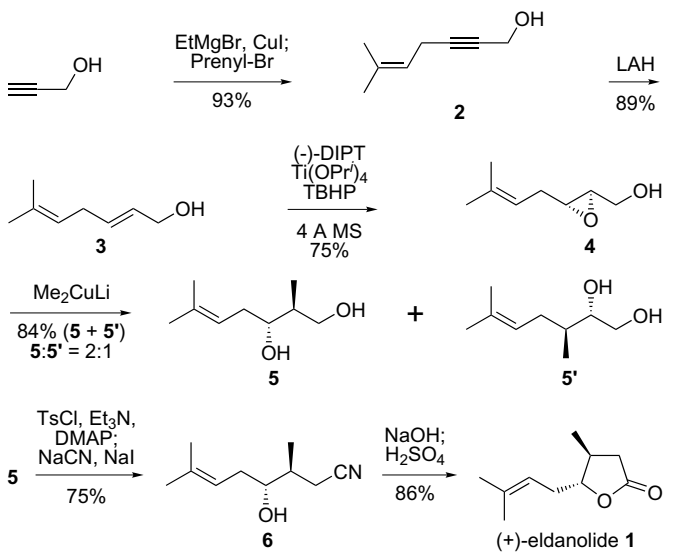


Figure 1. Some representative synthesis of (+)-eldanolide (**1**) recorded in the literature.



Scheme 1. Synthesis of (+)-eldanolide (**1**).

gave a monotosylate, which was subjected to a typical S_N2 displacement (NaCN, NaI, DMSO, 60 °C) to furnish nitrile **6** in good overall yield (75% for the two steps). Finally, saponification (NaOH, EtOH, H_2O, reflux) followed by lactonization in an acidic media (0.7 M H_2SO_4, THF, pH 2–3, room temperature) in a one-pot fashion[12] smoothly converted **6** into (+)-eldanolide (**1**) {$[\alpha]_D^{20} = +48.2$ (*c* 1.15, MeOH); lit.[4e] $[\alpha]_D^{20} = +51.5$ (*c* 1.15, MeOH)} in 86% yield. The ^1H and ^{13}C NMR spectroscopic data of **1** were in full agreement with those reported in the literature.[1,2]

3. Conclusion

In conclusion, we have accomplished a concise, asymmetric synthesis of the monoterpenoid pheromone (+)-eldanolide in four steps from the chiral 2,3-epoxy alcohol **4** in 36% overall yield or in seven steps from propargyl alcohol in 22% overall yield. Our synthetic strategy features the formation of a 1,3-diol by the regio- and stereoselective ring opening of 2,3-epoxy alcohol **4**, an intermediate easily available from a Sharpless asymmetric epoxidation. Other key steps include one carbon elongation, saponification, and lactonization. The present work constitutes a general method for the rapid synthesis of a number of related γ-lactone natural products.

4. Experimental

4.1. General

Melting points are uncorrected. All solvents were obtained from commercial sources and dried/purified before use. NMR spectra were recorded in $CDCl_3$ (^1H at 300 MHz and ^{13}C at 75 MHz) using TMS as the internal standard. Analytical samples were obtained by chromatography on silica gel using EtOAc/hexane as the eluent.

4.2. 6-Methylhept-5-en-2-yn-1-ol 2

To a solution of propargyl alcohol (2.9 mL, 38 mmol) in THF (100 mL) was added EtMgBr (in Et_2O, 1.14 M, 66 mL, 75 mmol) dropwise at 0 °C over 1 h. After 30 min, CuI (714 mg, 3.75 mmol) was added in one portion at 0 °C. After a further 30 min, a solution of prenyl bromide (4.4 mL, 37 mmol) in THF (120 mL) was added dropwise at 0 °C. The reaction mixture was stirred overnight (the internal temperature changed from 0 °C to rt), quenched with saturated aqueous NH_4Cl solution (60 mL), extracted with ether (50 mL × 3), dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed (SiO_2, EtOAc/hexane, 1:15) to give **2** (4.35 g, 93%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.63 (3H, s), 1.71 (3H, s), 2.14 (1H, br s), 2.92 (2H, d, $J = 6.0$ Hz), 4.25 (2H, t, $J = 2.4$ Hz), 5.15–5.28 (1H, m).

4.3. (2*E*)-6-Methylhepta-2,5-dien-1-ol 3

A solution of **2** (7.58 g, 61.1 mmol) in THF was added dropwise to the suspension of LAH (3.48 g, 91.6 mmol) in anhydrous THF (100 mL) at 0 °C. The reaction mixture was heated at reflux for 8 h, cooled to rt, quenched with 1 M HCl, and extracted with ether (50 mL × 3). The combined organic layers were washed successively with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed (SiO_2, EtOAc/hexane, 1:15–1:10) to give **3** (6.89 g, 89%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.62 (3H, s), 1.72 (3H, s), 2.68–2.79 (2H, m), 4.09 (2H, d, $J = 2.7$ Hz), 5.10–5.20 (1H, m), 5.64–5.68 (2H, m).

4.4. (2*R*,3*R*)-2,3-Epoxy-6-methylhept-5-en-1-ol 4

To a cooled (−30 °C) suspension of activated, powdered 4 Å MS (5.21 g) in CH_2Cl_2 (100 mL) were added (−)-DIPT (0.26 mL, 1.23 mmol), $Ti(OPr^i)_4$ (0.33 mL, 1.11 mmol), and TBHP (4.4 M, 2.8 mL, 12 mmol). After 20 min, a solution of alcohol **3** (1.55 g, 12.3 mmol) in CH_2Cl_2 (90 mL) was added at −30 °C over 20 min. The resulting mixture was stirred at that temperature for 3 h, quenched with a cooled solution of ferrous sulfate and tartaric acid (stoichiometric amount) in de-ionized water, stirred vigorously for 30 min, and extracted with ether (50 mL × 3). The combined organic layers were treated with a pre-cooled (0 °C) solution of 30% NaOH (w/v) in brine and stirred for 1 h at rt. The two layers were separated and the aqueous layer was extracted with ether (30 mL × 3). The combined ether layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed (SiO_2, EtOAc/hexane, 1:15) to give **4** (1.31 g, 75%) as a colorless oil: $[\alpha]_D^{27} = +19.15$ (*c* 2.25, $CHCl_3$) {lit.[9] $[\alpha]_D^{20} = +16.3$ (*c* 1.9, $CHCl_3$)}; ^{1}H NMR ($CDCl_3$) δ 1.62 (3H, s), 1.71 (3H, s), 2.19–2.41 (2H, m), 2.64 (1H, br s), 2.93–2.99 (2H, m), 3.57–3.64 (1H, m), 3.86–3.97 (1H, m), 5.10–5.17 (1H, m).

4.5. (2*S*,3*R*)-2,6-Dimethylhept-5-en-1,3-diol 5

To a suspension of CuI (1.33 g, 6.98 mmol) in anhydrous ether (8 mL), MeLi (in ether, 1.04 M, 14.0 mL, 14.6 mmol) was added dropwise while keeping the internal temperature at 0 °C. When the initial yellowish slurry turned slowly into a green solution, a solution of **4** (497 mg, 3.50 mmol) in ether (5 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 1 h and turned yellowish again. Saturated aqueous NH_4Cl solution and aqueous $NH_3{\cdot}H_2O$ solution (25%) were added sequentially, and the slurry turned into gray and finally blue. After the solid mass was filtered off, the filtrate was diluted with water and extracted with EtOAc (40 mL × 4). The combined organic layers were washed with water and brine successively, dried over Na_2SO_4, filtered, and concentrated. The residue was chromatographed (SiO_2, EtOAc/hexane, 1:10–1:6) to give a inseparable mixture of (2*S*,3*R*)-2,6-dimethylhept-5-en-1,3-diol **5** and (2*S*,3*S*)-3,6-dimethylhept-5-en-1,2-diol **5′** (**5**+**5′**: 464 mg, 84%; **5**/**5′** = ca. 2:1, deduced from the line integrals of ^{1}H NMR spectrum). The mixture of **5**/**5′** was diluted with acetone (24 mL) and H_2O (30 mL), and $NaIO_4$ (1.27 g, 5.94 mmol) was added in portion. After 2 h the resulting mixture was diluted with saturated aqueous Na_2SO_3 solution and extracted with ether. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was chromatographed (SiO_2, EtOAc/hexane, 1:10–1:6) to give **5** (309 mg, 56%) as a colorless oil: $[\alpha]_D^{20} = +20.6$ (*c* 1.2, EtOH); IR (film) ν_{max} 3361, 2966, 2917, 1738, 1454, 1377, 1030 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.90 (3H, d, $J = 7.0$ Hz), 1.66 (3H, s), 1.76 (3H, s), 2.15–2.35 (2H, m), 2.76 (1H, br s), 3.38 (1H, br s), 3.50–3.62 (1H, m), 3.65 (1H, dd, $J = 7.4$, 3.5 Hz), 3.73 (1H, dd, $J = 10.9$, 3.5 Hz), 5.13–5.23 (1H, m); ^{13}C NMR ($CDCl_3$) δ 13.9, 18.1, 26.0, 34.1, 39.5, 67.6, 77.2, 119.9, 135.4. ESI-MS *m*/*z* 181 (M+Na), 159 (M+H). ESI-HRMS calcd for $C_9H_{18}NaO_2$ (M+Na): 181.1197. Found: 181.1199.

4.6. (3*S*,4*R*)-3,7-Dimethyl-4-hydroxy-6-octenenitrile 6

To a mixture of TsCl (115 mg, 0.603 mmol), DMAP (4 mg, 0.03 mmol) and Et_3N (0.14 mL, 0.98 mmol) in CH_2Cl_2 (3 mL) was added dropwise a solution of **5** (65 mg, 0.41 mmol) in CH_2Cl_2 (3 mL) at 0 °C. The reaction mixture was warmed to rt, stirred at rt for 3 h, diluted with CH_2Cl_2, washed successively with water and brine, dried (Na_2SO_4), filtered, and concentrated. The residue was chromatographed (SiO_2, EtOAc/hexane, 1:12–1:10) to give the monotosylate (109 mg, 85%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 0.96 (3H, d, $J = 7.0$ Hz), 1.62 (3H, s), 1.73 (3H, s), 1.81–1.92 (1H, m), 2.03–2.27 (2H, m), 2.45 (3H, s), 3.40–3.51 (1H, m), 4.08–4.13 (2H, m), 5.11–5.12 (1H, m), 7.35 (2H, d, $J = 8.1$ Hz), 7.80 (2H, d, $J = 8.1$ Hz).

To a solution of the above monotosylate (96 mg, 0.31 mmol) in DMSO (1 mL) was added NaI (7 mg, 0.05 mmol) and NaCN (152 mg, 3.10 mmol). The reaction mixture was heated at 60 °C for 4 h, cooled to rt, diluted with water (10 mL), and extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was chromatographed (SiO_2, EtOAc/hexane, 1:6) to give **6** (45 mg, 88%) as a colorless oil: $[\alpha]_D^{20} = -5.4$ (*c* 1.2, EtOH) IR (film) ν_{max} 3488, 2968, 2910, 2248, 1454, 1425, 1384, 1100, 1049 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.09 (3H, d, $J = 6.9$ Hz), 1.63 (3H, s),

1.73 (3H, s), 1.80–1.93 (1H, m), 1.94–1.98 (1H, m), 2.06–2.19 (1H, m), 2.20–2.31 (1H, m), 2.39–2.60 (2H, m), 3.34–3.44 (1H, m), 5.08–5.18 (1H, m); ^{13}C NMR ($CDCl_3$) δ 16.2, 17.9, 20.7, 25.9, 33.3, 35.6, 73.6, 118.9, 119.2, 136.6. ESI-MS *m*/*z* 168 (M+H), 190 (M+Na). ESI-HRMS calcd for $C_{10}H_{17}NNaO$ (M+Na) 190.1203. Found: 190.1202.

4.7. (+)-Eldanolide 1

An aqueous solution of NaOH (2.0 M, 0.45 mL, 0.90 mmol) was added to a solution of **8** (53 mg, 0.32 mmol) in EtOH (2.5 mL). The reaction mixture was refluxed overnight, cooled to rt, concentrated by removing EtOH under reduced pressure, diluted with THF (5 mL), made acidic (pH 2–3) with aqueous H_2SO_4 (0.7 M), and extracted with Et_2O. The combined organic layers were washed successively with water, saturated aqueous $NaHCO_3$ solution and brine, dried Na_2SO_4, filtered, and concentrated. The residue was chromatographed (SiO_2, EtOAc/hexane, 1:12) to afford **1** (46 mg, 86%) as a colorless oil: $[\alpha]_D^{20} = +48.2$ (*c* 1.15, MeOH) {lit.[4e] $[\alpha]_D^{20} = +51.5$ (*c* 1.15, MeOH)}; IR (film) ν_{max} 2967, 2930, 1781, 1214, 1157, 1031, 1004 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.08 (3H, d, $J = 6.2$ Hz), 1.59 (3H, s), 1.67 (3H, s), 2.07–2.28 (2H, m), 2.28–2.43 (2H, m), 2.63 (1H, dd, $J = 16.2$, 7.5 Hz), 3.97–4.08 (1H, m), 5.07–5.20 (1H, m); ^{13}C NMR ($CDCl_3$) δ 17.5, 17.8, 25.6, 31.9, 34.9, 36.9, 86.9, 117.8, 135.2, 176.4. ESI-MS *m*/*z* 169 (M+H), 191 (M+Na). ESI-HRMS calcd for $C_{10}H_{16}NaO_2$ (M+Na): 191.1044. Found: 191.1043.

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10. (a) The ee value of **4** was assumed to be the same as that of its corresponding *O*-benzoate **7**, determined to be 93.6% by HPLC analysis: Chiral Delta-S column (250 × 4.6 mm), UV detector 254 nm, eluent hexanes/2-propanol (100:1), flow rate 0.8 mL/min. Benzoate **7** was prepared in 85% yield by treating **4** with BzCl, Et_3N, and DMAP in CH_2Cl_2 at 0 °C.[10b] Compound **7**: ^{1}H NMR ($CDCl_3$) δ 1.63 (s, 3H), 1.72 (s, 3H), 2.27–2.45 (m, 2H), 2.95–2.99 (m, 1H), 3.11–3.15 (m, 1H), 4.17 (dd, $J = 12.6$, 6.6 Hz, 1H), 4.64 (dd, $J = 12.3$, 3.3 Hz, 1H), 5.16 (t, $J = 8.7$ Hz, 1H), 7.44 (t, $J = 7.8$ Hz, 2H), 7.57 (t, $J = 6.9$ Hz, 1H), 8.06 (d, $J = 7.2$ Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 17.9, 25.7, 30.1, 55.0, 56.0, 65.2, 117.7, 128.4, 129.8, 129.8, 133.2, 135.3, 166.3. Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 72.92; H, 7.36. Racemic **4** was prepared in 90% yield by epoxidation of **3** with $VO(acac)_2$ and TBHP in refluxing benzene.[10c] (b) Watanabe, H.; Bando, M.; Kido, M.; Kitahara, T. *Tetrahedron* **1999**, *55*, 9755–9776; (c) Ziegler, F. E.; Wang, Y. *Tetrahedron Lett.* **1996**, *37*, 6299–6302.
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