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Total synthesis of (±)-heliannuol C and E via aromatic Claisen rearrangement

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Abstract—The total synthesis of heliannuol C and E from a common intermediate are described. Key steps in the synthesis include a regioselective aromatic Claisen rearrangement to install the (1-vinyl)-4-methyl-3-pentenyl substituent and regioselective biomimetic 7-*endo* and 6-*exo* phenol epoxide cyclizations to form the cyclic ether moieties.

Although the term allelopathy was first used in 1937, the chemical interaction between plants has been known for thousands of years.[1] Allelochemicals that suppress or eliminate competing plant species near the source plant have received special attention due to the agricultural potential of these compounds as selective natural herbicides.[2] The heliannuols (**1**–**12**, Fig. 1) are a promising group of phenolic allelochemicals isolated from *Helianthus annuus* that exhibit activity against dicotyledon plant species.[3] Heliannuols A (**1**) and C (**3**) are the most active members of the family, with effective concentrations as low as 10^{-9} M for germination inhibition of lettuce and cress, while heliannuol E (**5**) exhibits weaker activity.[3b,4] The unusual structures and agricultural potential of the heliannuols have attracted significant attention from the synthetic community.[5] Herein we report the total synthesis of (±)-heliannuol C (**3**) and (±)-heliannuol E (**5**).[6]

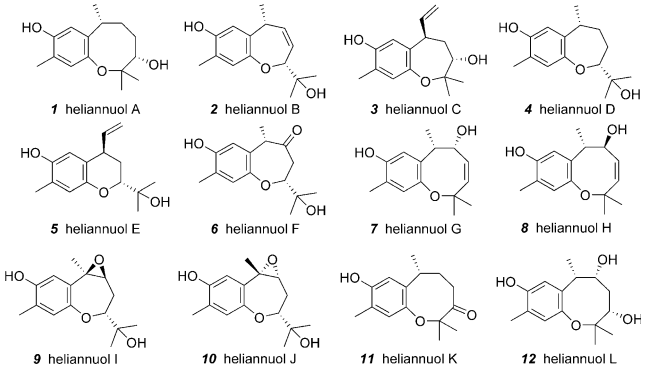

Figure 1. Structures of the heliannuols.

We envisioned preparing both heliannuol C (**3**) and E (**5**) via biomimetic phenol–epoxide cyclizations.[3b] A 7-*endo*-cyclization of the phenol onto the more substituted position of the appropriate diastereomer of epoxide **13** would lead to **3** (Fig. 2). Similarly, heliannuol E (**5**) would be made via 6-*exo*-cyclization of the phenol group to the less substituted epoxide position of **13**.[5a–c,h] Epoxide **13** would be prepared by selective epoxidation of diene **14**, which in turn would be prepared via Claisen rearrangement of aryl allyl ether **15**.

Mitsunobu etherification[7] of 4-methoxy-3-methylphenol (**16**)[8] with *E* -6-methyl-2,5-heptadien-1-ol (**17**)[9] afforded

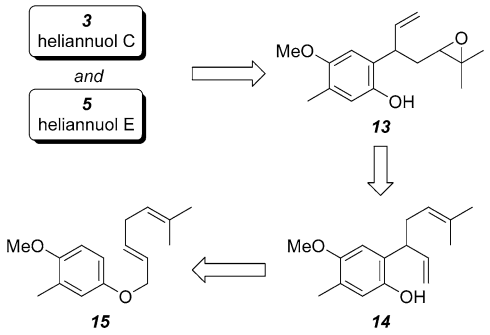

Figure 2. Retrosynthesis of heliannuols C and E.

Keywords: Allelopathy; Biomimetic reactions; Epoxides; Herbicides; Oxygen heterocycles.
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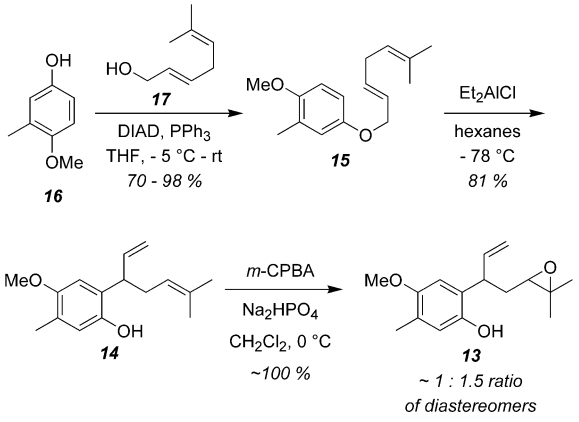
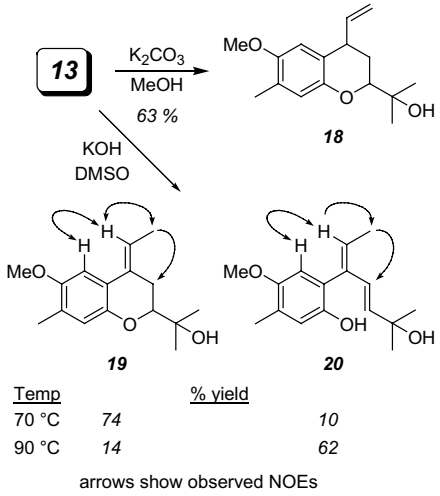


Scheme 1. Preparation of cyclization precursor **13**.

diene ether **15**,[10,11] in good to excellent yield (Scheme 1). Claisen rearrangement of **15** produced diene phenol **14**[12] as a single regioisomer in good yield when the reaction was done at low temperature. Adding *m*-CPBA in small portions to a cold, buffered solution of **14** selectively oxidized the more substituted olefin to yield diastereomeric epoxides **13** in quantitative yield.[13,5a] Unfortunately we were not able to easily separate the diastereomers at this stage and the diastereomeric mixture was used directly in the subsequent cyclization reactions.

The conditions used previously for a 7-*exo*-cyclization in our synthesis of heliannuol D[5a] resulted in a 6-*exo*-cyclization to produce **18** when the reaction was done on a small scale, but when the reaction was repeated with more material, the pendant olefin migrated into conjugation with the aromatic ring[14] to form mixtures of **19** and **20** (Scheme 2).[15] The ring-opened compound **20** was the major product at higher temperatures. Using a weaker base in the reaction[5c] resulted in a relatively clean 6-*exo*-cyclization that provided chromane derivative **18**[16] in good yield, but the diastereomers remained inseparable at this stage. Cleavage of the methyl ether group in **18** proved to be a difficult transformation. Many commonly employed demethylation procedures



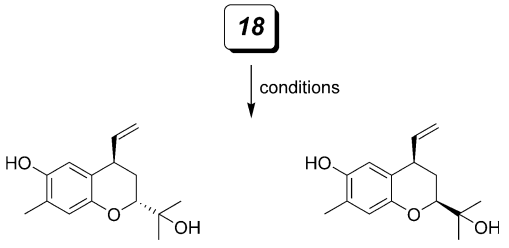
Scheme 2. Base-promoted reactions of epoxide **13**.

(BBr_3,[17] NaSEt,[18] NaSPh[19]) all failed in this case, resulting in complex mixtures of compounds formed by decomposition of the starting material. Treatment of **18** with excess neat MeMgI at high temperatures,[20] however, afforded heliannuol E (**5**) and its diastereomer **21** in 41% combined yield after purification (Table 1, entry 1). The highly basic nature of this method, however, led to the formation of side products containing an isomerized olefin (cf. **19** and **20** above).

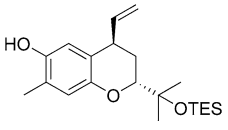
Reaction of **18** with triethylsilane in the presence of a catalytic amount of $B(C_6F_5)_3$ at room temperature followed by treatment of the reaction mixture with TBAF[21] provided **5** and **21**[22] in a much improved 74% combined yield (Table 1, entry 2). A considerable amount of tertiary triethylsilyl ether **22** was also obtained, even after prolonged exposure to TBAF in THF, but it was found that treatment of **22** with HF/CH_3CN yielded (±)-heliannuol E (**5**). Using HF/CH_3CN instead of TBAF in the deprotection of **18** resulted in exclusive formation of **5** and **21**, but in lower overall yield (Table 1, entry 3). The IR, ^1H, and ^{13}C NMR spectral data of **5** were in complete agreement with those reported for the natural product[3c,23] and in previous syntheses.[5c,f,g,m]

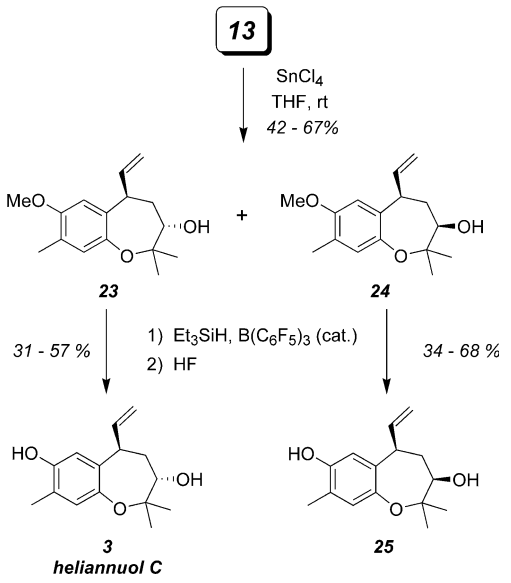
Treatment of epoxide **13** with $SnCl_4$ resulted in a regioselective 7-*endo*-cyclization[24] to form the separable benzoxepanes **23** and **24** (Scheme 3).[25] Deprotection of the methyl ether group in **23** using the triethylsilane/catalytic $B(C_6F_5)_3$ system employed above[21] provided (±)-heliannuol C (**3**). The yield of **3** was slightly lower when HF/CH_3CN was used in the final step of the deprotection (31–36%) as compared to HF–pyridine (53–57%). Subjecting **24** to the same ether cleavage protocol afforded *epi*-heliannuol C (**25**)[26] in similar yields.

Table 1. Deprotection of **18**; synthesis of (±)-heliannuol E



Entry	Conditions	%Yield	
		5	**21**
1	CH_3MgI (15 equiv), 170–190 °C	12	29
2	(i) Et_3SiH, $B(C_6F_5)_3$ (cat), CH_2Cl_2 (ii) TBAF, THF, room temp	37	37
3	(i) Et_3SiH, $B(C_6F_5)_3$ (cat), CH_2Cl_2 (ii) HF, CH_3CN	20	19





Scheme 3. Synthesis of (±)-heliannuol C (**3**) and its epimer **25**.

The room temperature ^{13}C NMR spectra of benzoxepane compounds **3** and **23**–**25** contain three very broad, almost indiscernible resonances corresponding to the benzylic methine and the geminal methyl groups. These signals sharpen somewhat at elevated temperature, indicating a conformational exchange process occurring in solution on an intermediate time scale.[27] Thorough comparison of NMR spectral data from natural (−)-heliannuol C with those obtained from our synthetic (±)-**3**, however, showed that the samples were identical.[28]

In summary, the aromatic Claisen rearrangement of diene **15** results in rapid construction of the heliannuol C/E skeleton. (±)-Heliannuol E (**5**) was prepared in 9% yield and (±)-heliannuol C (**3**) in 15% yield over seven linear steps each from 2-methylanisole.

Acknowledgements

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10. All new compounds exhibited IR, ^1H, and ^{13}C NMR spectra in agreement with the assigned structures.
11. Ether **15**: ^1H NMR: (300 MHz, $CDCl_3$) δ 6.72 (m, 3H), 5.76 (m, 2H), 5.16 (t of septets, $J = 7.0$, 1.5 Hz, 1H), 4.40 (m, 2H), 3.78 (s, 3H), 2.77 (br t, $J = 6.2$ Hz, 2H), 2.19 (s, 3H), 1.71 (s, 3H), and 1.62 (s, 3H); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 152.4, 152.0, 133.7, 133.0, 127.7, 125.1, 121.3, 118.0, 111.8, 110.7, 69.3, 55.8, 31.0, 25.7, 17.7, and 16.4. Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 78.26; H, 8.85.
12. Phenol **14**: ^1H NMR: (300 MHz, $CDCl_3$) δ 6.62 (s, 1H), 6.58 (s, 1H), 6.03 (ddd, $J = 17.0$, 10.6, 6.4 Hz, 1H), 5.13 (m, 3H), 4.62 (s, 1H), 3.77 (s, 3H), 3.51 (br q, $J = 6.5$ Hz, 1H), 2.44 (m, 2H), 2.16 (s, 3H), 1.67 (d, $J = 1.0$ Hz, 3H), and 1.59 (br s, 3H); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 151.9, 146.9, 140.9, 133.0, 127.0, 125.6, 122.2, 118.8, 114.8, 110.9, 56.1, 43.8, 32.2, 25.7, 17.9, and 15.7. Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 78.08; H, 9.11.

13. Epoxide **13**: ^{1}H NMR: (300 MHz, $CDCl_3$) δ (mixture of diastereomers) 6.64 (s, 0.5H), 6.61 (s, 0.5H), 6.60 (s, 0.5H), 6.58 (s, 0.5H), 6.09 (m, 1H), 5.19 (m, 2H), 4.94 (s, 0.5H), 4.79 (s, 0.5H), 3.78 (s,1.5H), 3.77 (s, 1.5H), 3.73 (m, obs, 1H), 2.80 (t, J = 6.2 Hz, 0.5H), 2.73 (t, J = 6.2 Hz, 0.5H), 2.16 (s, 1.5H), 2.15 (s, 1.5H), 1.99 (m, 2H), 1.29 (s, 1.5H), 1.28 (s, 1.5H), 1.21 (s, 1.5H), and 1.12 (s, 1.5H); ^{13}C NMR: (75 MHz, $CDCl_3$) δ (mixture of diastereomers) 151.52, 151.46, 147.2, 147.0, 140.6, 140.1, 126.9, 126.4, 125.6, 25.5, 118.6, 118.5, 114.8, 114.4, 110.9, 110.4, 63.6, 63.4, 59.7, 9.6, 56.0 (2C), 40.9, 40.5, 33.1, 32.9, 24.7, 24.6, 18.7, 18.5, and 15.7 (2C).
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15. Compound **19**: ^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.91 (s, 1H), 6.67 (s, 1H), 6.07 (qd, J = 7.3, 1.5 Hz, 1H), 3.79 (s, 3H), 3.68 (dd, J = 12.7, 2.4 Hz, 1H), 2.80 (dd, J = 15.1, 2.0 Hz, 1H), 2.45 (s, 1H), 2.26 (dddq, J = 15.1, 12.7, 2.4, 1.5 Hz, 1H), 2.16 (s, 3H), 1.79 (dd, J = 7.3, 1.5 Hz, 3H), 1.34 (s, 3H), and 1.30 (s, 3H); ^{13}C NMR: (125 MHz, $CDCl_3$) δ 152.2 (C), 147.7 (C), 129.2 (C), 127.6 (C), 120.1 (C), 119.2 (CH), 116.0 (CH), 104.0 (CH), 81.9 (CH), 71.7 (C), 55.7 (CH_3), 25.9 (CH_3), 25.5 (CH_2), 24.5 (CH_3), 15.9 (CH_3), and 13.2 (CH_3). Compound **20**: mp = 106–109 °C; ^{1}H NMR: (300 MHz, $CDCl_3$) δ 6.82 (d, J = 15.6 Hz, 1H), 6.72 (s, 1H), 6.51 (s, 1H), 5.69 (br q, J = 7.1 Hz, 1H), 5.63 (d, J = 15.6 Hz, 1H), 4.70 (br s, 1H), 3.76 (s, 3H), 2.21 (s, 3H), 1.95 (d, J = 7.1 Hz, 3H), and 1.33 (s, 6H); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 151.5, 146.2, 141.5, 135.1, 129.8, 127.1, 125.0, 121.2, 117.7, 112.3, 71.1, 55.9, 29.9 (2C), 16.0, and 13.8; Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.52; H, 8.68.
16. Compound **18**: ^{1}H NMR: (300 MHz, $CDCl_3$) δ (mixture of diastereomers) 6.67 (s, 0.5H), 6.65 (s, 0.5H), 6.57 (s, 0.5H), 6.48 (s, 0.5H), 5.99 (ddd, J = 17.0, 10.0, 6.3 Hz, 0.5H), 5.70 (ddd, J = 17.0, 10.0, 9.1 Hz, 0.5H), 5.26 (ddd, J = 17.0, 1.7, 0.6 Hz, 0.5H), 5.19 (dd, J = 10.0, 1.7 Hz, 0.5H), 5.10 (dt, J = 10.0, 1.5 Hz, 0.5H), 4.91 (dt, J = 17.0, 1.5 Hz, 0.5H), 3.79 (dd, J = 11.5, 1.5 Hz, 0.5H), 3.74 (dd, J = 11.4, 2.4 Hz, 0.5H), 3.746 (s, 1.5 H), 3.737 (s, 1.5H), 3.50 (br m, 1H), 2.4 (br s, 1H), 2.16 (s, 1.5H), 2.15 (s, 1.5H), 2.03 (ddd, J = 13.2, 5.9, 1.5 Hz, 0.5H), 1.89 (m, 1H), 1.65 (ddd, J = 13.2, 11.8, 11.8 Hz, 0.5H), 1.30 (s, 1.5H), 1.29 (s, 1.5H), 1.26 (s, 1.5H), and 1.24 (s, 1.5H); ^{13}C NMR: (75 MHz, $CDCl_3$) δ (mixture of diastereomers) 151.7, 151.6, 148.0, 147.7, 142.3, 140.9, 126.7, 126.6, 121.1, 119.7, 118.7, 118.6, 116.6, 115.8, 111.5, 110.1, 81.4 (2C), 71.7 (2C), 55.8 (2C), 41.2, 38.2, 30.1, 27.5, 25.8, 25.7, 24.4, 24.3, 15.9, and 15.8.
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22. Compound **21**: ^{1}H NMR: (300 MHz, $CDCl_3$) δ 6.62 (s, 1H), 6.54 (s, 1H), 5.66 (dt, J = 17.0, 10.0 Hz, 1H), 5.23 (ddd, J = 17.0, 1.7, 0.6, Hz, 1H), 5.10 (dd, J = 10.0, 1.7 Hz, 1H), 4.40 (br s, 1H), 3.79 (dd, J = 11.5, 1.5 Hz, 1H), 3.47 (br m, 1H), 2.4 (br s, 1H), 2.18 (s, 3H), 2.02 (ddd, J = 13.2, 5.9, 1.5 Hz, 1H), 1.65 (ddd, J = 13.2, 11.7, 11.7 Hz, 1H), 1.31 (s, 3H), and 1.26 (s, 3H); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 147.9, 147.5, 140.7, 123.9, 122.1, 118.5, 116.7, 114.5, 81.5, 71.9, 41.0, 30.0, 25.8, 24.2, and 15.6.
23. Our pure (±)-**5** is a solid (mp = 104–106 °C) whereas natural (−)-5 is reported to be an oil. See Refs. 3c,5c.
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25. Compound **23**: ^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.72 (s, 1H), 6.53 (s, 1H), 6.13 (ddd, J = 17.2, 10.2, 7.3 Hz, 1H), 5.11 (br d, J = 10.2 Hz, 1H), 5.01 (br d, J = 17.2 Hz, 1H), 3.81 (m, 1H), 3.78 (s, 3H), 3.60 (br m, 1H), 2.14 (s, 3H), 2.02 (ddd, J = 13.8, 7.7, 3.3 Hz, 1H), 1.95 (ddd, J = 13.8, 9.0, 3.3 Hz, 1H), 1.30 (s, 3H), and 1.15 (s, 3H); ^{13}C NMR: (125 MHz, $CDCl_3$, 45 °C) δ 153.9 (C), 147.3 (C), 139.7 (CH), 133.8 (C), 126.3 (CH), 125.2 (C), 115.2 (CH_2), 110.1 (CH), 79.7 (C), 74.6 (CH), 55.6 (CH_3), 42.8 (CH), 36.1 (CH_2), 26.7 (CH_3), 21.1 (CH_3), and 15.7 (CH_3). Compound **24**: ^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.75 (s, 1H), 6.25 (s, 1H), 6.21 (ddd, J = 17.1, 10.3, 6.8 Hz, 1H), 5.15 (br d, J = 10.3 Hz, 1H), 4.96 (br d, J = 17.1 Hz, 1H), 3.77 (s, 3H), 3.76 (m, 1H), 3.54 (br t, J = 6.5 Hz, 1H), 2.15 (s, 3H), 2.08 (dt, J = 13.8, 3.5 Hz, 1H), 1.93 (m, 1H), 1.31 (s, 3H), and 1.13 (s, 3H); ^{13}C NMR: (125 MHz, $CDCl_3$, 45 °C) δ 153.9 (C), 147.5 (C), 141.0 (CH), 133.5 (C), 126.3 (CH), 125.2 (C), 114.9 (CH_2), 109.9 (CH), 79.3 (C), 78.1 (CH), 55.6 (CH_3), 43.2 (CH), 35.8 (CH_2), 26.4 (CH_3), 21.6 (CH_3), and 15.9 (CH_3).
26. Compound **25**: ^{1}H NMR: (500 MHz, CD_3OD) δ 6.62 (s, 1H), 6.52 (s, 1H), 6.10 (ddd, J = 17.1, 10.0, 8.5 Hz, 1H), 5.17 (dd, J = 10.0, 1.5 Hz, 1H), 5.12 (d, J = 17.1 Hz, 1H), 4.65 (br s, 1H), 3.66 (dd, J = 11.1, 3.5 Hz, 1H), 3.42 (br t, J = 9.6 Hz, 1H), 2.10 (s, 3H), 1.93 (ddd, J = 13.5, 3.5, 2.5 Hz, 1H), 1.64 (dt, J = 13.5, 11.1 Hz, 1H), 1.42 (s, 3H), and 0.89 (s, 3H); ^{13}C NMR: (125 MHz, CD_3 OD, 50 °C) δ 152.7 (C), 147.7 (C), 142.3 (CH), 136.6 (C), 127.2 (CH), 123.8 (C), 115.2 (CH_2), 114.2 (CH), 81.0 (C), 78.9 (CH), 43.0 (CH), 38.5 (CH_2), 29.0 (CH_3), 19.0 (CH_3), and 15.9 (CH_3).
27. The corresponding resonances in the ^{1}H NMR spectra of **3** and **23**–**25** are only slightly broadened. Neither Macías (Ref. 3b) nor Shishido (Ref. 5n) comment on this phenomenon, but Macías' ^{13}C NMR spectrum of (−)-**3** exhibits the same broadening observed by us.
28. Our pure (±)-**3** is a solid (mp = 184–188 °C) and is only sparingly soluble in $CDCl_3$, in contrast to the properties reported by Macías for natural (−)-heliannuol C. See Ref. 3b.