Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron Letters

Tetrahedron Letters 47 (2006) 4019–4021

The synthesis of heliannuol C, an allelochemical from *Helianthus annuus*

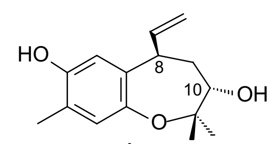
Bidyut Biswas, Prabir K. Sen and Ramanathapuram V. Venkateswaran*

Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Kolkata 700 032, India

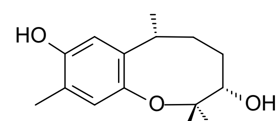
Received 26 January 2006; revised 30 March 2006; accepted 5 April 2006
Available online 2 May 2006

Abstract—The synthesis of the allelochemical heliannuol C **1** is described by employing a Bargellini condensation and a Claisen rearrangement to install the *gem*-dimethyl and vinyl functionalities, respectively. A Dieckmann cyclisation of diester **11** enabled the generation of the benzoxepane ring system enshrined in **1**.

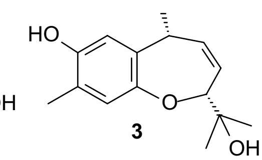
Heliannuol C **1**, a novel allelopathic sesquiterpene, was isolated from the cultiver sunflowers *Helianthus annuus*.[1] Although Macias et al. established the gross structure and relative stereochemistry of **1**, the absolute stereochemistry as (8*R*,10*S*) was assigned by Shishido et al. by synthesis.[2] Sesquiterpene **1**, along with its congeners heliannuols A–B and D–E **2**–**5**, have been implicated in the powerful allelopathic activity displayed by these sunflowers.[1] Subsequently, many oxidised variants of these compounds have been isolated from these flowers.[1e,f] Their unique structural features, combined with their potential agricultural importance as natural and eco-friendly herbicide models, have rendered them attractive targets for synthesis.[3] We initiated a comprehensive programme directed to the synthesis of these compounds and have reported the synthesis of heliannuols A and D.[4] Both heliannuols C **1** and D **4** possess a benzoxepane ring system. Our previous synthesis of **4** had relied on the regioselective oxidative ring opening of a benzobicyclo[3.2.1]octanone, and a ring-closing metathesis, to develop this ring system.[4b,c] Herein, we disclose the synthesis of **1** by employing a Claisen rearrangement and Bargellini condensation to install the vinyl and *gem*-dimethyl groups, respectively, and a Dieckmann cyclisation to generate the benzoxepane ring system.



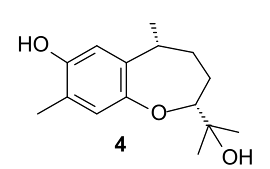
1



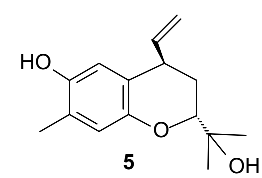
2



3



4



5

The synthesis began with 6-methoxy-7-methylcoumarin **7**, obtained from methylation of the corresponding 6-hydroxycoumarin **6**[5] with methyl iodide under standard conditions. Low temperature reduction of this coumarin with LAH in ether at −40 °C furnished the unsaturated diol **8**, in 70% yield, contaminated with benzoxepane ring system the saturated diol in varying proportions (20–25%). Chromatographic separation yielded the desired unsaturated diol **8** in 50% yield as a colourless solid, mp 88–89 °C.[6] Diol **8** underwent a selective Bargellini condensation[7] with acetone and chloroform

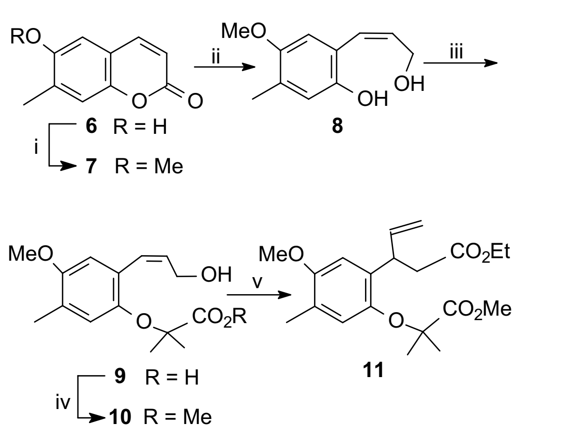
Keywords: Allelochemical; Heliannuol C; Bargellini condensation; Claisen orthoester rearrangement; Benzoxepane ring system.
* Corresponding author. Fax: +91 33 24732805; e-mail: ocrvv@iacs.res.in

0040-4039/$ - see front matter
doi:10.1016/j.tetlet.2006.04.011

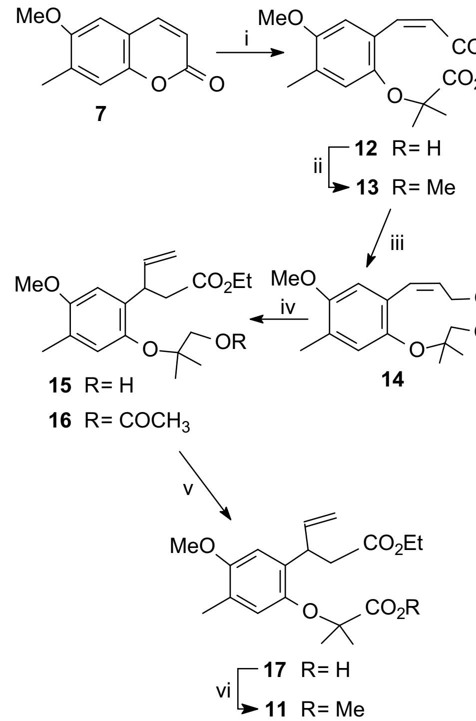
in the presence of powdered sodium hydroxide to afford the *gem*-dimethyl group incorporated carboxylic acid **9** in 65% yield, which was converted to methyl ester **10**[6] by reaction with diazomethane. This allylic alcohol ester **10** was subjected to a Claisen orthoester rearrangement by refluxing with triethyl orthoacetate in the presence of a catalytic amount of propionic acid to afford the diester **11**[6] in 70% yield, thereby installing the crucial vinyl group (Scheme 1).

An alternative, better yielding, method involved the direct Bargellini condensation of coumarin **7**. We recently reported such direct condensations with coumarins to furnish, in good yields, *o*-carboxyvinylphenoxy isobutyric acids.[8] Following on from this, when coumarin **7** was reacted with acetone and chloroform in the presence of sodium hydroxide, it furnished the expected diacid **12** in 75% yield, which was quantitatively converted to dimethyl ester **13**[6] with diazomethane. Reduction of this diester with LAH in ether at −20 °C delivered diol **14**[6] in excellent yield (90%). The differential reactivity of diol **14** was suitably exploited to install the vinyl moiety employing the Claisen orthoester rearrangement as before. In the event, refluxing a mixture of diol **14** in triethyl orthoacetate containing a catalytic amount of propionic acid furnished the rearranged ester–alcohol **15**[6] in 75% yield. In some runs, acetate **16** was also obtained as a separable minor component. Mild base treatment of this acetate readily converted it into alcohol **15**. Oxidation of ester–alcohol **15** with Jones' reagent at room temperature produced the carboxylic acid **17**, which was esterified with diazomethane to furnish diester **11** (Scheme 2). Although this synthesis involved an additional oxidative step, the cleaner reaction products and better overall yield made this approach more suitable for large scale operations as against the former approach, which necessitated a separation in the first step of the reduction process.

Diester **11** now set the stage for the generation of the benzoxepane ring system through an intramolecular cyclisation. Treatment of this diester with LDA in



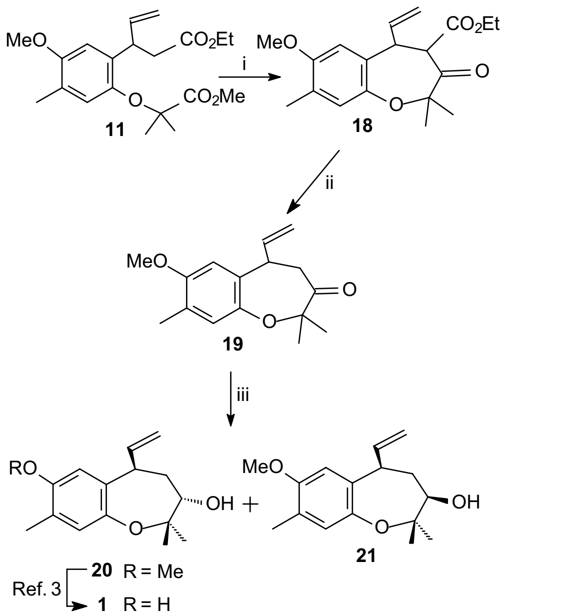
Scheme 1. Reagents and conditions: (i) K_2CO_3, acetone, MeI, reflux, 8 h, 99%; (ii) LAH, Et_2O, −40 °C, 2 h, 50%; (iii) NaOH, acetone, $CHCl_3$, reflux, 6 h, 65%; (iv) CH_2N_2, Et_2O, 1 h, 0 °C, 98%; (v) $CH_3C(OEt)_3$, C_2H_5COOH, reflux, 8 h, 70%.



Scheme 2. Reagents and conditions: (i) NaOH, acetone, $CHCl_3$, reflux, 6 h, 75%; (ii) CH_2N_2, Et_2O, 0 °C, 98%; (iii) LAH, Et_2O, −20 °C, 4 h, 90%; (iv) $CH_3C(OEt)_3$, C_2H_5COOH, reflux, 5 h, 75%; (v) Jones' oxidation, 70%; (vi) CH_2N_2, Et_2O, 0 °C, 1 h, 99%.

THF achieved the expected cyclisation to deliver the β-ketoester **18**, which was subjected to de-ethoxycarbonylation by heating in dimethyl sulfoxide with lithium chloride and water to furnish benzoxepanone **19**[6] incorporating all the structural features as present in **1** in an overall yield of 61% from **11**. Reduction of this ketone with sodium borohydride in methanol afforded, in 98% yield, a mixture of *O*-methyl heliannuol C **20** and its epimer **21** in a ratio of 1:3 (Scheme 3). Preparative thin layer chromatography allowed an efficient separation of the components and the spectral data (^{1}H NMR and ^{13}C NMR) of **20** fully matched those reported previously.[3] Since **20** has been demethylated to heliannuol C **1**, the present work concluded the synthesis of this allelochemical. The low yield of the desired product in the reduction step prompted further experiments. Initial efforts towards inversion of the hydroxy group in the undesired epimer **21** through a Mitsunobu reaction were not encouraging. Alternatively, **21** was oxidised back to ketone **19** in near quantitative yield employing Jones' reagent and the ketone reduced with sodium borohydride to yield a mixture of **20** and **21**. This sequence of oxidation and reduction was repeated and after four such runs, the combined yield of the desired alcohol **20** was improved to 62–65%.

In summary, we have developed the synthesis of heliannuol C **1** employing a Claisen orthoester rearrangement and a Dieckmann cyclisation to construct the benzoxepane core of **1**, which demonstrates another application of the Bargellini condensation of coumarins.



Scheme 3. Reagents and conditions: (i) LDA, THF, −10 to 0 °C, then rt, 12 h, 72%; (ii) LiCl, DMSO, H_2O, 160 °C, 5 h, 85%; (iii) $NaBH_4$, MeOH, 0 °C, 0.5 h, 98%.

Acknowledgements

We sincerely thank Professor J. R. Vyvyan, Department of Chemistry, Western Washington University, Bellingham WA, for providing us with copies of the spectra (^{1}H NMR and ^{13}C NMR) of their synthetic *O*-methyl heliannuol C and its epimer. We also gratefully acknowledge financial support from the Department of Science and Technology, Government of India, New Delhi.

References and notes

1. (a) Macias, F. A.; Varela, R. M.; Torres, A.; Molinillo, J. M. G.; Fronczek, F. R. *Tetrahedron Lett.* **1993**, *34*, 1999–2002; (b) Macias, F. A.; Molinillo, J. M. G.; Varela, R. M.; Torres, A.; Fronczek, F. R. *J. Org. Chem.* **1994**, *59*, 8261–8266; (c) Macias, F. A.; Varela, R. M.; Torres, A.; Molinillo, J. M. G. *Tetrahedron Lett.* **1999**, *40*, 4725–4728; (d) Macias, F. A.; Varela, R. M.; Torres, A.; Molinillo, J. M. G. *J. Nat. Prod.* **1999**, *62*, 1636–1639; (e) Macias, F. A.; Varela, R. M.; Torres, A.; Molinillo, J. M. G. *J. Chem. Ecol.* **2000**, *26*, 2173–2186; (f) Macias, F. A.; Torres, A.; Galindo, J. L. G.; Varela, R. M.; Alvarez, J. A.; Molinillo, J. M. G. *Phytochemistry* **2002**, *61*, 687–692.
2. Kamei, T.; Shindo, M.; Shishido, K. *Tetrahedron Lett.* **2003**, *44*, 8505–8507.
3. Vyvyan, J. R.; Oaksmith, J. M.; Parks, B. W.; Peterson, E. M. *Tetrahedron Lett.* **2005**, *46*, 2457–2460, and references cited therein.
4. (a) Tuhina, K.; Bhowmik, D. R.; Venkateswaran, R. V. *Chem. Commun.* **2002**, 634–635; (b) Sabui, S. K.; Venkateswaran, R. V. *Tetrahedron Lett.* **2004**, *45*, 983–985; (c) Sabui, S. K.; Venkateswaran, R. V. *Tetrahedron Lett.* **2004**, *45*, 2047–2048.
5. Sethna, S.; Phadke, R. In *The Pechmann Reaction*, Blatt, A. H., Cope, A. C., McGrew, F. C., Niemann, C., Snyder, H. R., Eds.; Org. React.; 1953; Vol. VII, p 46.
6. All new compounds reported here gave analytical and spectral data consistent with the assigned structures. Selected spectral data: For **8**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.18 (s, 3H), 3.76 (s, 3H), 4.23 (d, $J = 7.1$ Hz, 2H), 5.99–6.07 (m, 1H), 6.52 (s, 1H), 6.55 (d, $J = 11.4$, 1H), 6.69 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 16.2, 56.0, 58.7, 112.4, 117.9, 121.3, 125.4, 126.5, 131.4, 148.6, 150.1; HRMS (ES +ve) calcd for $C_{11}H_{14}O_3Na$ $[M+Na]^+$ 217.0841, found 217.0841. For **10**: IR (neat) 1738, 3450 (br) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48 (s, 6H), 2.16 (s, 3H), 3.78 (s, 3H), 3.79 (s, 3H), 4.25 (d, $J = 7.2$ Hz, 2H), 5.85–5.94 (m, 1H), 6.59 (s, 1H), 6.64 (d, $J = 11.7$ Hz, 1H), 6.66 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.2, 25.0, 25.1, 52.5, 55.6, 59.9, 80.4, 111.5, 122.3, 122.9, 126.5, 127.9, 130.6, 145.6, 153.1, 174.9. For **11**: IR (neat) 1735 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (t, $J = 7.2$ Hz, 3H), 1.53 (s, 3H), 1.56 (s, 3H), 2.11 (s, 3H), 2.69 (d, $J = 7.5$ Hz, 2H), 3.76 (s, 3H), 3.79 (s, 3H), 4.10 (q, $J = 7.2$ Hz, 2H), 4.25–4.28 (m, 1H), 5.05–5.12 (m, 2H), 5.95–6.06 (m, 1H), 6.49 (s, 1H), 6.59 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 16.0, 25.0, 25.5, 39.2, 39.4, 52.3, 55.6, 60.2, 79.2, 110.0, 114.7, 120.2, 125.0, 131.7, 139.6, 145.9, 152.7, 172.0, 175.3; HRMS (ES +ve) calcd for $C_{20}H_{29}O_6$ $[M+H]^+$ 365.1965, found 365.1959. For **13**: IR (neat) 1716, 1738 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.51 (s, 6H), 2.16 (s, 3H), 3.69 (s, 3H), 3.78 (s, 3H), 3.79 (s, 3H), 5.92 (d, $J = 12.7$ Hz, 1H), 6.61 (s, 1H), 7.19 (d, $J = 12.7$ Hz, 1H), 7.32 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.4, 25.0, 25.0, 51.1, 52.2, 55.4, 80.2, 111.8, 118.3, 121.2, 125.9, 128.9, 139.4, 146.8, 152.3, 166.6, 174.6. For **14**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (s, 6H), 2.18 (s, 3H), 3.53 (s, 2H), 3.78 (s, 3H), 4.18 (d, $J = 6.9$ Hz, 2H), 5.89–5.92 (m, 1H), 6.56 (s, 1H), 6.57 (d, $J = 9.9$ Hz, 1H), 6.81 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.9, 22.9, 22.9, 55.4, 59.6, 70.0, 81.7, 111.1, 126.0, 126.3, 128.2, 129.2, 131.0, 144.9, 153.4; HRMS (ES +ve) calcd for $C_{15}H_{22}O_4Na$ $[M+Na]^+$ 289.1416, found 289.1416. For **15**: IR (neat) 1735, 3450 (br) cm^{-1} ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (t, $J = 7.2$ Hz, 3H), 1.27 (s, 3H), 1.34 (s, 3H), 2.16 (s, 3H), 2.59 (dd, A of ABX, $J_{AB} = 14.4$ Hz, $J_{AX} = 6.5$ Hz, 1H), 2.65 (dd, B of ABX, $J_{BA} = 14.4$ Hz, $J_{BX} = 8.5$ Hz, 1H), 3.57 (dd, $J = 11.5$, 4.8 Hz, 1H), 3.70 (d, $J = 11.5$ Hz, 1H), 3.77 (s, 3H), 4.11 (q, $J = 7.2$ Hz, 2H), 4.35–4.42 (m, X of ABX, 1H), 5.08–5.15 (m, 2H), 5.93–6.05 (m, 1H), 6.58 (s, 1H), 6.83 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 15.9, 22.3, 23.8, 38.5, 39.8, 55.4, 60.5, 70.8, 80.8, 109.1, 114.8, 124.2, 125.0, 133.6, 139.4, 145.4, 153.3, 172.6; HRMS (ES +ve) calcd for $C_{19}H_{28}O_5Na$ $[M+Na]^+$ 359.1835, found 359.1834. For **19**: IR (neat) 1720 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (s, 3H), 1.40 (s, 3H), 2.14 (s, 3H), 2.85 (dd, $J = 10.8$, 5.8 Hz, 1H), 3.42 (t, $J = 10.8$ Hz, 1H), 3.63–3.75 (m, 1H), 3.75 (s, 3H), 5.08 (d, $J = 10.0$ Hz, 1H), 5.13 (d, $J = 17.0$ Hz, 1H), 5.83–5.95 (m, 1H), 6.50 (s, 1H), 6.74 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.7, 22.6, 25.1, 42.7, 43.9, 55.5, 87.9, 111.9, 114.9, 126.4, 126.6, 129.0, 141.3, 146.7, 154.4, 214.1; HRMS (ES +ve) calcd for $C_{16}H_{21}O_3$ $[M+H]^+$ 261.1491, found 261.1485.
7. Bargellini, G. *Gazz. Chim. Ital.* **1906**, *36*, 329–339.
8. Sen, P. K.; Biswas, B.; Venkateswaran, R. V. *Tetrahedron Lett.* **2005**, *46*, 8741–8743.