Pergamon

Tetrahedron Letters, Vol. 35, No. 37, pp. 6847-6850, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01480-9

Total Synthesis of (±)-Heliannuol A

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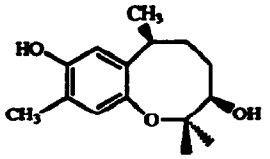
Abstract: (±) - Heliannuol A has been synthesized via *intramolecular* Julia coupling and *intramolecular* sulfone ester cyclization.

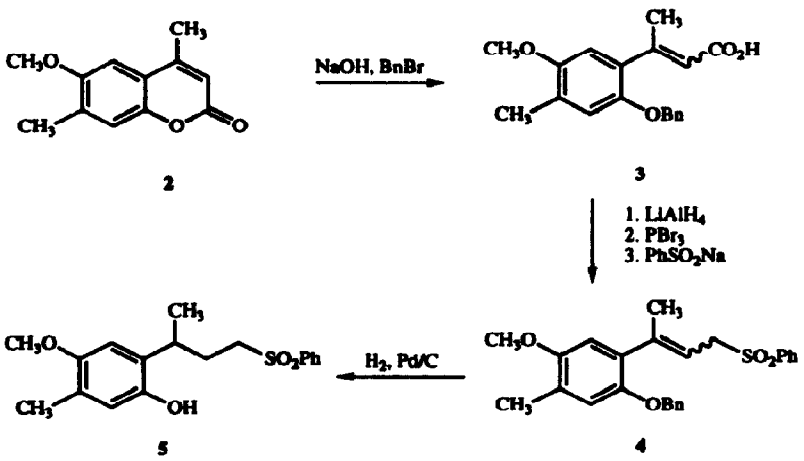
Heliannuol A (1), a bicyclic sesquiterpene of previously unknown carbon skeleton, was recently isolated from the extracts of cultivated sunflowers (*Helianthus annuus* L. var. SH-222).[1] Its structure and absolute configuration were deduced from extensive NMR studies as well as X-ray crystallography. Heliannuol A is believed to be involved in the allelopathic action of sunflowers.[2,3] It is speculated that its biosynthesis may proceed through a bisabolene-type precursor.[1,4]

In continuation of our interest in medium ring cyclization we now report the first total synthesis of (±)-heliannuol A (1) using a route that involves pivotal eight-membered ring construction via *intramolecular* sulfone ester[5] as well as sulfone aldehyde cyclization. The ring closure process affords products with complete stereocontrol.



1

Starting with coumarin 2,[6] ring opening of the lactone (NaOH, BnBr, reflux, 5.5 h) yielded acid 3[7] in 65% yield (Scheme 1). Reduction of the acid ($LiAlH_4$, THF, 0°C, then reflux 3.5 h) and conversion of the resulting alcohol to unsaturated sulfone 4[8] (PBr_3, Et_2O, 0°C, then $PhSO_2Na$, DMF, 25°C, 15 h) proceeded in excellent overall yield (85%). Hydrogenation of 4 (H_2, Pd/C, EtOAc) resulted in both the reduction of the double bond and removal of the benzyl protecting group to afford racemic 5[9] in quantitative yield.



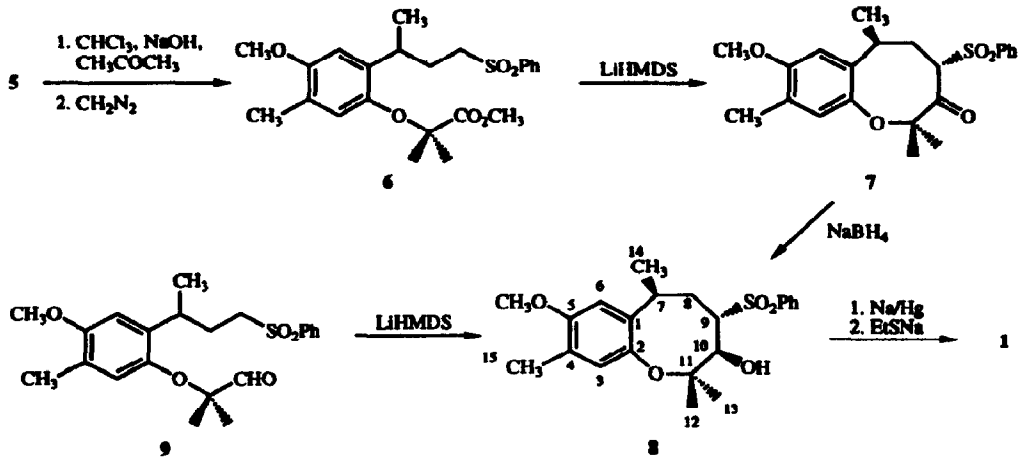
Scheme 1

Incorporation of the *gem*-dimethyl side chain was accomplished by reacting **5** with a mixture of chloroform and powdered sodium hydroxide in refluxing acetone according to Bargellini.[10] Subsequent treatment of the crude acid with diazomethane gave ester **6**[11] (70% overall) (Scheme 2).

The critical ring closure was readily achieved by slow addition of 2.2 equiv. of lithium bis (trimethylsilyl) amide (LiHMDS, 1.0 *M* in THF) to a solution of **6** ($5 \cdot 10^{-3}$ *M* in THF) at 0°C followed by stirring at this temperature for 1.5 h.[5] After extractive isolation and filtration through a plug of silica gel, ketosulfone **7**[12] was obtained in 87% yield as a colourless solid. Reduction of **7** ($NaBH_4$, MeOH, 0°C, 1.5 h) occurred with complete stereocontrol to furnish **8**[13] as the sole product (83% yield). Extensive ^1H NMR decoupling and NOE studies at 235K rigorously established the stereochemistry at C-7, C-9, and C-10[14]. Alternatively, **8** can be prepared via *intramolecular* Julia coupling of aldehyde **9**[15] with 2.0 equiv. of LiHMDS ($5 \cdot 10^{-3}$ *M* in THF, 0°C, 0.5 h) although in only 59% unoptimized yield. To our knowledge this is the first application of the Julia coupling in eight-membered ring construction.[16]

Finally, (±)-heliannuol A (**1**) was obtained via desulfonation (5% Na/Hg, MeOH, 0°C then room temperature, 16 h, 45% yield) and demethylation (EtSNa, DMF, 150°C, 16 h, 70% yield). ^1H and ^{13}C NMR, IR, and MS data of synthetic (±)-**1** were in complete agreement with a sample of natural heliannuol A kindly provided by Professor Macías.

In summary, *intramolecular* Julia coupling as well as sulfone ester cyclization provide efficient access for a stereocontrolled construction of the heliannuol nucleus. Further studies in other ring systems are underway.



Scheme 2

Acknowledgement: We wish to thank NSERC for an undergraduate research award to SL and Professor Macías for a sample of natural heliannuol A.

REFERENCES AND NOTES:

1. Macías, F.A.; Varela, R.M.; Torres, A.; Molinillo, J.M.G.; Fronczek, F.R. *Tetrahedron Lett.* **1993**, *34*, 1999.

2. Varela, R.M. "Allelopathic Studies on Cultivar Sunflowers". Master's dissertation, University of Cádiz , Spain, **1992**.

3. For interesting reviews of the science of allelopathy, see:
   (a) Putnam, A.R.; Tang, C.S. "The Science of Allelopathy", **1986**, John Wiley and Sons, New York.
   (b) Einhellig, F.A. *Anan. Chem. Soc., ACS Symposium Series* **1985**, *276*, 109.

4. Spring, O.; Rodon, U.; Macías, F.A. *Phytochemistry* **1992**, *31*, 1541.

5. (a) Grimm, E.L.; Coutu, M.L.; Trimble, L.A. *Tetrahedron Lett.* **1993**, *34*, 7017.
   (b) Grimm, E.L.; Levac, S.; Coutu, M.L. *Tetrahedron Lett.* **1994**, 0000.
   (c) For other *intramolecular* acylation reactions, see: Gopalan, A.S.; Jacobs, H.K. *J. Org. Chem.* **1994**, *59*, 2014 and references cited therein.

6. Kaufman, K.D.; Kelly, R.C.; Eaton, D.C. *J. Org. Chem.* **1967**, *32*, 504.

7. 3: yellow solid, mp 109-112°C; ^{1}H NMR (400 MHz, acetone-d_6) δ 7.50 - 7.25 (m, 5H), 6.99 (s, 0.3H), 6.89 (s, 0.7H), 6.78 (s, 0.3H), 6.66 (s, 0.7H), 5.96 (s, 0.7H), 5.94 (s, 0.3H), 3.83 (s, 0.9H), 3.76 (s, 2.1H), 2.49 (s, 0.7H), 2.18 (s, 0.7H), 2.16 (s, 2.1H), 2.15 (s, 2.1H); IR (KBr) υ 3200-2800, 1690, 1635, 1610 cm^{-1}; MS (CI, CH_4) *m/z* 312 (M^+), 295 ($M+H-H_2O)^+$; anal. calcd for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45; found: C, 73.00; H, 6.53.

8. 4: *Z*-isomer: colourless crystals, mp 89-91°C; ^{1}H NMR (400 MHz, acetone-d_6) δ 7.81 (d, 2H), 7.70 (t, 1H), 7.59 (t, 2H), 7.41-7.28 (m, 5H), 6.91 (s, 1H), 6.46 (s, 1H), 5.53 (t, 1H, *J*=7.5 Hz), 4.97 (s, 2H), 3.74 (d, 2H, *J*=7.7 Hz), 3.72 (s, 3H), 2.15 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 152.75, 149.64, 144.30, 140.74, 138.69, 134.33, 129.97, 129.16, 128.85, 128.41, 128.22, 127.81, 127.21, 117.56, 114.88, 112.44, 71.77, 57.87, 56.17, 25.13, 16.31; IR (KBr) υ 2920, 1645, 1580 cm^{-1}; MS (CI, CH_4) *m/z* 423 $(M+H)^+$; anal. calcd for $C_{25}H_{26}O_4S$: C, 71.06; H, 6.20; found: C, 71.26; H, 6.18;
   4: *E*-isomer: colourless crystals, mp 100-104°C; ^{1}H NMR (400 MHz, acetone-d_6) δ 7.95 (d, 2H), 7.64 (t, 1H), 7.59 (t, 2H), 7.43-7.30 (m, 5H), 6.88 (s, 1H), 6.54 (s, 1H), 5.42 (t, 1H, *J*=8.0 Hz), 5.01 (s, 2H), 4.09 (d, 2H, *J*=8.0 Hz), 3.79 (s, 3H), 2.14

(s, 3H), 1.76 (s, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 152.70, 149.98, 145.10, 140.42, 138.66, 134.39, 132.50, 129.94, 129.25, 129.20, 128.45, 128.39, 127.05, 117.38, 116.45, 112.27, 71.83, 56.48, 56.15, 17.68, 16.19; IR (KBr) υ 2910, 1645, 1580 cm^{-1}; MS (CI, CH_4) *m/z* 423 $(M+H)^+$; anal. calcd for $C_{25}H_{26}O_4S$: C, 71.06; H, 6.20; found: C, 71.24; H, 6.21.

9. **5**: colourless crystals, mp 115-116°C; ^{1}H NMR (200 MHz, acetone-d_6) δ 7.88 (d, 2H), 7.72 (t, 1H), 7.62 (t, 2H), 6.61 (s, 2H), 3.69 (s, 3H), 3.24-3.10 (m, 2H), 3.03-2.90 (m, 1H), 2.05 (s, 3H), 2.0-1.86 (m, 2H), 1.21 (d, 3H, *J*=6.9 Hz); ^{13}C NMR (100 MHz, acetone-d_6) δ 152.30, 148.68, 140.73, 134.31, 130.10, 129.45, 128.73, 125.46, 118.69, 110.17, 56.13, 55.15, 33.80, 32.59, 20.87, 15.87; IR (KBr) υ 3670-3140, 2950, 2925, 1600, 1580 cm^{-1}; MS (CI, CH_4) *m/z* 363 $(M+C_2H_5)^+$, 335 $(M+H)^+$; anal. calcd for $C_{18}H_{22}O_4S$: C, 64.65; H, 6.63; found: C, 64.65; H, 6.54.

10. Bargellini, G. *Gazz. Chim. Ital.* **1906**, *36*, 337; see also: Corey, E.J.; Barcza, S.; Klotmann, G. *J. Am. Chem. Soc.* **1969**, *91*, 4782.

11. **6**: yellow oil; ^{1}H NMR (400 MHz, acetone-d_6) δ 7.89 (d, 2H), 7.72 (t, 1H), 7.63 (t, 2H), 6.69 (s, 1H), 6.50 (s, 1H), 3.72 (s, 3H), 3.30-3.15 (m, 2H), 3.05-2.95 (m, 1H), 2.08 (s, 3H), 1.94 (apparent q, 2H, *J*=7.7 Hz), 1.49 (s, 3H), 1.47 (s, 3H), 1.23 (d, 3H, *J*=7.0 Hz); ^{13}C NMR (100 MHz, acetone-d_6) δ 175.22, 153.76, 147.03, 140.64, 134.88, 134.37, 130.15, 128.79, 125.01, 120.41, 109.80, 79.66, 55.90, 55.12, 52.59, 32.69, 30.89, 25.85, 25.40, 20.98, 16.25; IR (NaCl) υ 2945, 1735, 1580, 1500 cm^{-1}; MS (CI, CH_4) *m/z* 463 $(M+C_2H_5)^+$, 435 $(M+H)^+$.

12. **7**: This compound exists as two major conformers at 235K; colourless crystals, mp 135-137°C; ^{1}H NMR (500 MHz, acetone-d_6, 235K) δ 7.92 (d, 1H), 7.86 - 7.75 (m, 2H), 7.70 - 7.44 (m, 2H), 6.89 (s, 1H), 6.76 (s, 0.5H), 6.60 (s, 0.5H), 5.28 (dd, 0.5H, *J*=11.8, 1.5 Hz), 3.90 (dd, 0.5 H, *J*=12.3, 4.6 Hz), 3.82 (s, 1.5 H), 3.69 (s, 1.5 H), 3.09 (dd, 0.5H, *J*=4.4, 3.1 Hz), 2.91 (dd, 0.5 H, *J*=12.7, 5.0 Hz), 2.39 (ddd, 0.5H, *J*=13.6, 5.0, 1.5 Hz), 2.09 (s, 1.5H), 2.06 (hidden m, 0.5H), 2.01 (s, 1.5 Hz), 1.89 (mc, 0.5H), 1.80 (ddd, 0.5H, *J*=12.3, 4.4, 4.4 Hz), 1.50 (s, 1.5H), 1.34 (s, 1.5H), 1.33 (d, 3H, *J*=7.0 Hz), 1.32 (s, 3H), 1.21 (s, 1.5H), 1.13 (s, 1.5H); ^{13}C NMR (125 MHz, acetone-d_6, 235K) δ 205.69, 201.94, 156.30, 155.38, 146.38, 145.69, 138.52, 138.42, 136.47 (2), 135.44, 135.29, 130.92, 130.81, 130.10, 130.04, 127.89 (2), 125.70, 125.48, 113.13, 107.35, 86.80, 85.57, 68.90, 65.80, 55.77, 55.61, 39.25 (2), 36.65, 36.27, 25.25, 24.36, 21.47, 21.19, 19.09, 18.41, 16.45, 16.15; IR (KBr) υ 2940, 1720, 1500, 1400 cm^{-1}; MS (CI, CH_4) *m/z* 403 $(M+H)^+$; anal. calcd for $C_{22}H_{26}O_5S$: C, 65.65; H, 6.51; found: C, 65.43; H, 6.48.

13. **8**: colourless crystals, mp 151-153°C; ^{1}H NMR (500 MHz, acetone-d_6, 235K) δ 7.83 (d, 2H), 7.65 (t, 1H), 7.55 (t, 2H), 6.72 (s, 1H), 6.69 (s, 1H), 4.35 (d, 1H, *J*=6.7 Hz), 4.17 (dd, 1H, *J*=10.7, 6.7 Hz), 3.82 (s, 3H), 3.76 (ddd, 1H, *J*=10.6, 4.3, 3.3 Hz), 3.29 (m, 1H), 3.13 (ddd, 1H, *J*=15.2, 12.9, 4.6 Hz), 2.52 (ddd, 1H, *J*=15.1, 3.6, 3.6 Hz), 2.07 (s, 3H), 1.20 (s, 3H), 1.19 (s, 3H), 1.17 (d, 3H, *J*=6.8 Hz); ^{13}C NMR (125 MHz, acetone-d_6, 235K) δ 154.69, 144.62, 144.13, 138.53, 133.16, 129.06, 128.62, 128.43, 124.16, 111.96, 81.46, 69.82, 68.36, 55.38, 36.36, 31.42, 27.86, 25.48, 21.05, 15.99. IR (KBr) υ 3510, 2970, 1590 cm^{-1}; MS (CI, CH_4) *m/z* 404 (M^+); anal. calcd for $C_{22}H_{28}O_5S$: C, 65.32; H, 6.98; found: C, 65.09; H, 6.73.

14. Key NOE's were observed between 10-OH and 14-CH_3, 10-OH and 9-H, 10-H and 7-H.

15. The aldehyde was prepared from **6** via reduction/oxidation (DIBAL/PCC).

16. Intramolecular Julia condensations have been reported for the tetronolide and dolabellane ring systems:
    (a) Yoshii, E.; Takeda, K.; Urahata, M.; Takayanagi, H.; Ogura, H. *J. Org. Chem.* **1986**, *51*, 4735.
    (b) Takeda, K.; Yano, S.-g.; Yoshii, E. *Tetrahedron Lett.* **1988**, *29*, 6951.
    (c) Takeda, K.; Kawanishi, E.; Nakamura, H.; Yoshii, E. *Tetrahedron Lett.* **1991**, *32*, 4925.
    (d) Williams, D.R.; Coleman, P.J.; Nevill, C.R.; Robinson, L.A. *Tetrahedron Lett.* **1993**, *34*, 7895.

(*Received in USA* 6 *June* 1994; *accepted* 28 *July* 1994)