COMMUNICATION

Enantioselective total synthesis of heliannuols D and A †

Kenya Takabatake, Izumi Nishi, Mitsuru Shindo and Kozo Shishido *

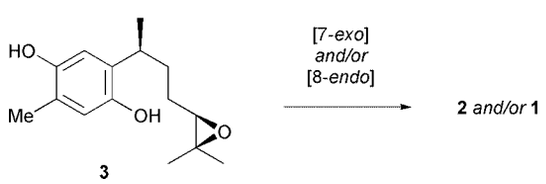
Institute for Medicinal Resources, University of Tokushima, Sho-machi 1, Tokushima 770-8505, Japan

Received (in Cambridge, UK) 21st March 2000, Accepted 10th May 2000
Published on the Web 23rd May 2000

Heliannuols D and A, which exhibit allelopathic activity, were synthesized enantioselectively *via* a base-mediated intramolecular cyclisation of a phenolic epoxide for the first time, and the absolute structures were established by total synthesis.

Heliannane type sesquiterpenoids heliannuol D **1**[1] and A **2**[2] (Fig. 1) were isolated by Macías from the extracts of cultivated sunflowers (*Helianthus annuus* L. SH-222) and are believed to be involved in the allelopathic action of sunflowers.[3] The characteristic phytotoxic activity, coupled with their unique structural features, has made these terpenoids desirable targets for synthetic chemists. Although total syntheses of the racemates of these compounds have been reported,[4,5] no enantioselective total synthesis has thus far been accomplished.

We now report the first enantiocontrolled total synthesis of **1** and **2**, thereby establishing their absolute stereochemistries, *via* a base-mediated intramolecular cyclisation of a phenolic epoxide as the key step. The synthetic strategy required the preparation of the key configurationally defined enantiopure epoxide **3**, whose intramolecular aryl ether-forming reaction would provide heliannuol D **1** and/or heliannuol A **2** *via* a [7-*exo*] and/or an [8-*endo*] mode of cyclisation, respectively (Scheme 1).



Scheme 1

Treatment of 2-*tert*-butyl-5-(2,5-dimethoxy-4-methylphenyl)-4,5-dihydro-1,3-dioxepine **4**, prepared by the Heck reaction[6] between 2,5-dimethoxy-4-methyliodobenzene[7] and 2-*tert*-butyl-4,7-dihydro-1,3-dioxepine,[8] under ozonolytic cleavage conditions followed by reductive workup with $NaBH_4$ provided the prochiral 1,3-diol **5** in 93% yield (Scheme 2). *Candida antarctica* lipase (CAL)-catalyzed[9] transesterification in diethyl ether using vinyl acetate as an acetyl donor at room temperature produced the optically active monoacetate **6**‡ in 87% yield. The enantiomeric excess was >99% as determined by HPLC on a Chiralcel OD column. Although the absolute configuration of the stereogenic centre could not be determined at this stage, it was established by the following conversion of **6** into 2-(1,5-dimethylhex-4-enyl)-5-methylbenzene-1,4-diol (curcuhydroquinone) **13**.[10] The hydroxy moiety in **6** was removed by tosylation and subsequent reduction with $NaBH_4$ in DMSO[11] to furnish the deoxygenated acetate, which was reduced with LAH to give the alcohol **7**. Sequential Hata reaction[12] and oxidation of the resulting sulfide **8** gave the sulfone **9** in 90% overall yield for the 5 steps. Treatment of **9** with ^{n}BuLi–HMPA

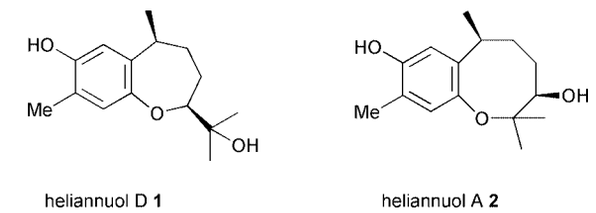
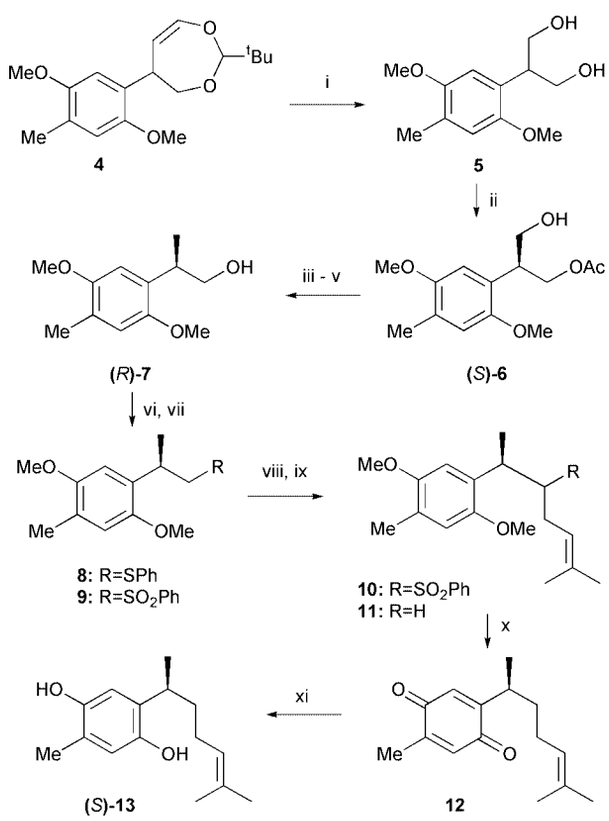


Fig. 1

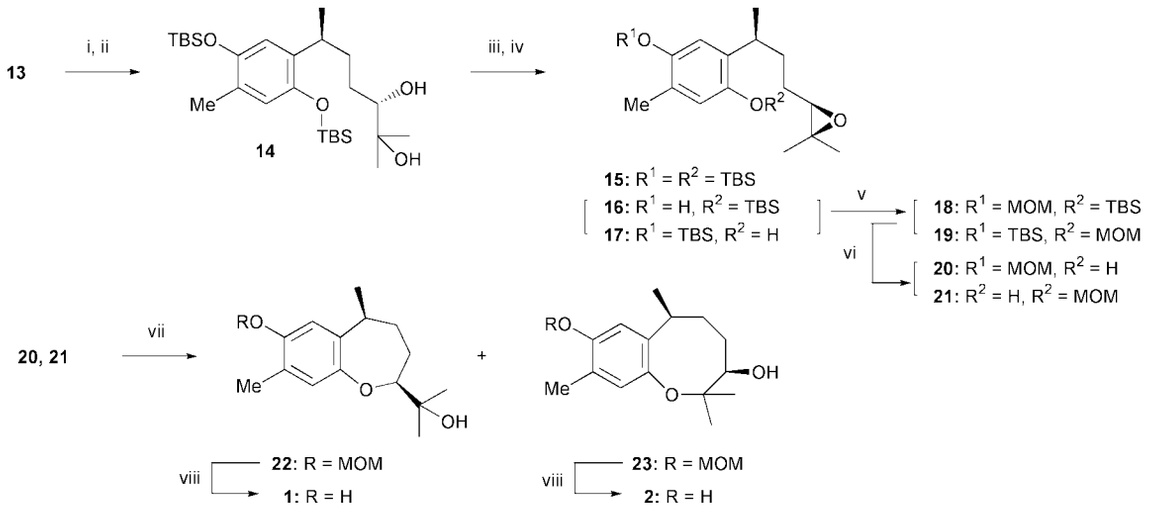


Scheme 2 *Reagents and conditions*: i, O_3, MeOH then $NaBH_4$ (93%); ii, CAL, Et_2O, rt (87%, >99% ee); iii, TsCl, Et_3N, 4-DMAP, CH_2Cl_2, rt (95%); iv, $NaBH_4$, DMSO, 60 °C; v, $LiAlH_4$, THF, rt (99%, 2 steps); vi, PhSSPh, ^{n}Bu$_3$P, pyridine, rt (99%); vii, MCPBA, $KHCO_3$, CH_2Cl_2, rt (97%); viii, ^{n}BuLi, HMPA, THF, $Me_2C{=}CHCH_2Br$, −78 °C (98%); ix, 5% Na–Hg, $NaHPO_4$, MeOH, sonication, rt, 84%; x, $(NH_4)_2Ce(NO_3)_6$, MeCN, MeOH, H_2O, rt (96%); xi, $Na_2S_2O_4$, THF, H_2O, rt (96%).

and prenyl bromide (1-bromo-3-methylbut-2-ene) yielded the carbon-elongated sulfone **10**, which was reduced with 5% Na–Hg under sonication[13] to give **11**. Sequential oxidation of **11** with CAN and reduction of the resulting quinone **12** with sodium dithionite gave curcuhydroquinone **13**, $[\alpha]_D$ +39.4 (*c* 0.64, $CHCl_3$) {lit. for the natural (*R*)-isomer $[\alpha]_D$ −21 (*c* 0.9, $CHCl_3$)}, in 76% overall yield from compound **7**. From this result, the absolute configuration at the benzylic tertiary stereogenic centre in **6** was established to be *S*.

† Presented at the 40th Symposium on the Chemistry of Natural Products, Oct. 7–9, 1998, Fukuoka, Japan, Abstract 93, pp. 547–552.

DOI: 10.1039/b003553j



Scheme 3 *Reagents and conditions*: i, ^{t}Bu(Me)$_2$SiCl, imidazole, 4-DMAP, CH_2Cl_2, rt (quant.); ii, AD-mix-α, $MeSO_2NH_2$, ^{t}BuOH, H_2O, 0 °C (99%, 94% de); iii, MsCl, pyridine, CH_2Cl_2, rt (86%); iv, K_2CO_3, MeOH, rt (quant.); v, MOMCl, $^{i}Pr_2NEt$, 4-DMAP, CH_2Cl_2, rt (81%); vi, CsF, DMF, rt (93%); vii, 5% NaOH (aq.), rt (54% for **22**, 4% for **23**); viii, 6 M HCl, THF, rt (quant. for **1**, 75% for **2**).

For the preparation of the key epoxide **3**, the di-*tert*-butyldimethylsilyl (TBS) ether of (*S*)-**13** was subjected to asymmetric dihydroxylation employing AD-mix-α[14] to give the diol **14** in 99% yield (Scheme 3). The diastereomeric excess was 94% as determined by ^{1}H NMR analysis of its (*R*)-MTPA [α-methoxy-α-(trifluoromethyl)phenylacetic acid] ester derivative. The absolute configuration of the newly formed stereogenic centre was confirmed to be *S* by means of the modified Mosher method.[15] Mesylation followed by basic treatment provided an inseparable 4 : 1 mixture of the monophenolic epoxides, **16** and **17**, along with the di-TBS epoxide **15** in 71% and 4% yield, respectively. It was postulated that the major isomer would be **16**, which should be generated from the hydrolysis of the sterically less hindered TBS ether. The confirmation was made by NOE experiments of the corresponding MOM ethers, **18** and **19**. Desilylation of a mixture of **16** and **17** with tetra-*n*-butylammonium fluoride did not give the expected epoxide **3** but instead the corresponding quinone. Therefore, the phenolic hydroxy moiety was protected as the methoxymethyl (MOM) ether and the resulting mixture of **18** and **19** was reacted with caesium fluoride to give the MOM protected phenolic epoxides, **20** and **21**, in 75% yield for the two steps. The crucial cyclisation was realized by treatment of a mixture of **20** and **21**§ with 5% aqueous NaOH solution at room temperature to give an easily separable mixture of the 7- and 8-membered cyclic ethers, **22** and **23**, in 54% and 4% yield, respectively. Finally, acidic hydrolysis of each produced heliannuol D **1**, $[a]_D$ −20.1 (*c* 2.27, $CHCl_3$), and heliannuol A **2**, $[a]_D$ +61.0 (*c* 0.38, MeOH), whose spectral properties were identical with those of the natural products except for the sign of the optical rotations: for natural **1**,[1] $[a]_D$ +16 (*c* 0.16, $CHCl_3$); for natural **2**,[2] $[a]_D$ −55.4 (*c* 0.3, MeOH).

In summary, the first enantiocontrolled total syntheses of two allelopathic sesquiterpenoids, heliannuol D and heliannuol A, have been accomplished and the absolute configurations were found to be the enantiomers of those shown in Fig. 1.

Acknowledgements

We are grateful to Professor Francisco Macías, University of Cádiz, for providing spectral data of the natural heliannuols D and A and for valuable discussions. We also thank Mr Hidetoshi Shimizu, Novo Nordisk Bioindustry Ltd., for providing CAL.

Notes and references

‡ In order to prepare the enantiomeric series, (*S*)-**6** was converted into (*S*)-**7** by the following 5-step sequence: i) MOMCl, $^{i}Pr_2NEt$, 4-DMAP, CH_2Cl_2 (95%); ii) K_2CO_3, MeOH (98%); iii) TsCl, Et_3N, 4-DMAP, CH_2Cl_2 (94%); iv) $NaBH_4$, DMSO (87%); v) c·HCl, MeOH (98%). The enantiomeric alcohol (*S*)-**7** was also successfully converted into the natural (+)-heliannuol D and (−)-heliannuol A by the same sequence of reactions. Details will be reported in due course.
§ Unreacted **21** was not recovered from the reaction mixture.

1 F. A. Macías, J. M. G. Molinillo, R. M. Varela, A. Torres and F. R. Fronczek, *J. Org. Chem.*, 1994, **59**, 8261.
2 F. A. Macías, R. M. Varela, A. Torres, J. M. G. Molinillo and F. R. Fronczek, *Tetrahedron Lett.*, 1993, **34**, 1999.
3 *Recent Advances in Allelopathy. Vol. I. A Science for the Future*, ed. F. A. Macías, J. C. G. Galindo, J. M. G. Molinillo and H. G. Cutler, Servico de Publicaciones-Universidad de Cádiz, Spain, 1999.
4 For (±)-heliannuol D: J. R. Vyvyan and R. E. Looper, *Tetrahedron Lett.*, 2000, **41**, 1151.
5 For (±)-heliannuol A: E. L. Grimm, S. Levac and L. A. Trimble, *Tetrahedron Lett.*, 1994, **35**, 6847.
6 (*a*) S. Takano, K. Samizu and K. Ogasawara, *Synlett*, 1993, 393; (*b*) T. Sakamoto, Y. Kondo and H. Yamanaka, *Heterocycles*, 1993, **36**, 2437; (*c*) Y. Koga, M. Sodeoka and M. Shibasaki, *Tetrahedron Lett.*, 1994, **35**, 1227.
7 S. M. Hubig, W. Jung and J. K. Kochi, *J. Org. Chem.*, 1994, **59**, 6233.
8 H. Frauenrath, *Synthesis*, 1989, 721.
9 For an example of the use of this lipase: I. Yamamura, Y. Fujiwara, Y. Yamato, O. Irie and K. Shishido, *Tetrahedron Lett.*, 1997, **38**, 4121.
10 F. McEnroe and W. Fenical, *Tetrahedron*, 1978, **34**, 1661.
11 G. Guanti, E. Narisano, T. Podgorski, S. Thea and A. Williams, *Tetrahedron*, 1990, **46**, 7081.
12 I. Nakagawa, K. Aki and T. Hata, *J. Chem. Soc., Perkin Trans. 1*, 1983, 1315.
13 E. Schrötter, E. Landmann, H. Schick, B. Schönecker, U. Hasuchild and P. Droescher, *J. Prakt. Chem.*, 1988, **330**, 501.
14 K. B. Sharpless, W. Amberg, Y. L. Bennani, G. A. Crispino, J. Hartung, K. S. Jeong, H. L. Kwong, K. Morikawa, Z. M. Wang, D. Xu and X. Zhang, *J. Org. Chem.*, 1992, **57**, 2768.
15 I. Ohtani, T. Kusumi, Y. Kashman and H. Kakisawa, *J. Am. Chem. Soc.*, 1991, **113**, 4092.