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Absolute Configuration of Falcarinol, a Potent Antitumor Agent Commonly Occurring in Plants

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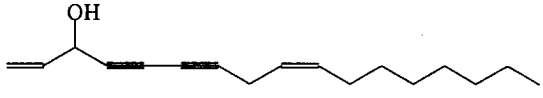
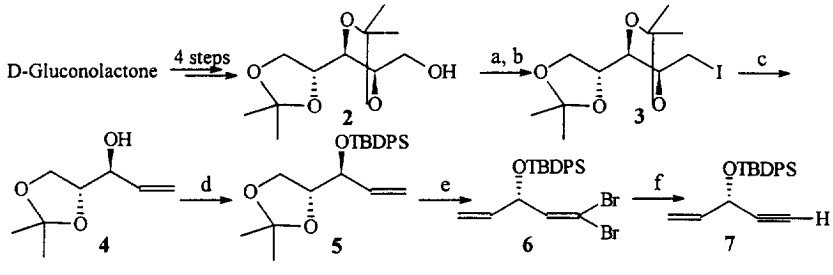
Abstract: The absolute configuration of falcarinol (1) was established by stereoselective total synthesis of the two enantiomers.

Falcarinol (**1**), also named panaxynol, is a common constituent of many plants[1] especially well known from *Panax ginseng* C. A. Meyer. Bioassays have shown that falcarinol has selective *in vitro* cytotoxicity against L-1210,[2] MK-1, B-16, and L-929 cancer cell lines compared to normal cell cultures.[3]



Falcarinol (**1**)

Interestingly, both (+) and (−) falcarinol (**1**) have been isolated from different plants, but the absolute configuration was not determined. Lemmich et al. proposed the 3*R* configuration for (−)-falcarinol.[4] Since then, two conflicting reports[5,6] have appeared discussing the configuration of this compound. Shim *et al.* applied the CD exciton chirality method to the *p*-bromobenzoate and concluded that (−)-falcarinol (**1**) possesses the 3*S* configuration.[5] On the other hand, by means of the modified Mosher method, Bernart *et al.*[6] defined the 3*S* configuration for (+)-falcarinol and claimed that Shim *et al.*'s falcarinol must possess a 3*R* configuration and that the CD exciton chirality method applied to secondary allylic alcohols was not applicable to secondary alcohols flanked by two unsaturated chromophores. To our knowledge, no total synthetic work on falcarinol (**1**) has yet been reported. In order to confirm the absolute configuration, we explored the enantioselective total synthesis of compound **1**.



Scheme 1: a) *p*-TsCl, Et_3N, DMAP, CH_2Cl_2, rt. b) NaI, acetone, reflux 24hr. c) Zn, ethanol, reflux 2hr. d) TBDPSCl, imidazole, CH_2Cl_2, rt., 81% in four steps. e) H_5IO_6, EtOAc, rt.; CBr_4, PPh_3, Zn, CH_2Cl_2, 0°C, 83% in two steps. f) i 1.5eq LDA, THF, -78°C, 30min, then 0°C, 30min, ii 2.2eq *n*-BuLi, -78°C, 2hr, 89%.

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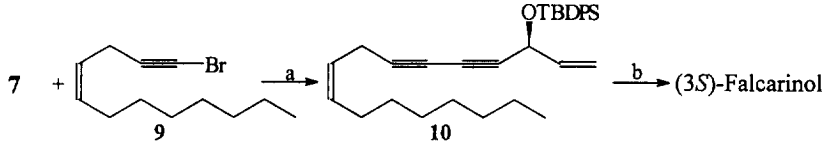
The 3*S* configuration of C-3 in (+)-falcarinol (**1**) was established using *D*-gluconolactone as a chiral template (Scheme **1**). 2,3; 4,5-Diisopropylidene *D*-arabinol **2** was prepared from *D*-gluconolactone by the published method.[7] **2** was converted to compound **4** via the iodide **3** using routine methods. Compound **4** was protected using a *tert*-butyldiphenylsilyl group, then oxidatively cleaved with periodic acid in ethyl acetate.[8] The resulting aldehyde was treated with a mixture of triphenylphosphine and carbon tetrabromide[9] in the presence of zinc dust to give dibromoalkene **6**. By treatment with lithium diisopropylamide and *n*-butyllithium, **6** was converted to 3(*S*)-(*t*-butyldiphenylsilyoxy)-1-penten-4-yne **7** in high yield.

By similar method, the 3*R* isomer[10] of **7** was obtained from *D*-xylose.

Using the classic Cadiot-Chodkiczwicz reaction,[11] fragment **7** was then coupled with C_6-C_{17} fragment **9**.[12] After deprotection of the TBDPS group, (3*S*)-falcarinol was obtained (Scheme **2**). (3*R*)-Falcarinol was also prepared in the same way.[12]



Scheme 2: a) CuCl, NH_2OHHCl, $EtNH_2$, methanol, 0°C, 74%. b) Bu_4NF, THF, rt, 85%.

The spectral data of the synthetic compounds **1**[13] were in agreement with the reported data[14] of the natural products. (3*S*)-Falcarinol showed a positive optical rotation ($[\alpha]_D$ +33.8°, c 0.53, $CHCl_3$), which was nearly identical to the value reported[6] ($[\alpha]_D$ +29°, c 0.57, $CHCl_3$). At the same time, (3*R*)-falcarinol was levorotatory ($[\alpha]_D$ −36.6°, c 0.92, $CHCl_3$), which is in consistent with the literature[14(a)] ($[\alpha]_D$ −36.93°, c 0.77, $CHCl_3$). Thus, we can confirm that (+)-falcarinol possesses the 3*S* configuration and (−)-falcarinol possesses the 3*R* configuration. We can also confirm Bernart *et al*'s conclusion[6] that the CD exciton chirality method is not suitable to these compounds.

References and notes:

1. (a) Bohlmann, F.; Burkhart, F. T.; Zero, C. *Naturally Occurring Acetylenes*, Academic Press, London and New York, **1973**. (b) Hansen, L.; Boll, P. M. *Phytochemistry*, **1986**, *25*, 285.
2. Y. S. Kim, Y. S.; Jin, S. H.; Kim, S. I.; Hahn, D. R. *Arch. Pharm. Res.*, **1989**, *12*, 207.
3. Matsunaga, H.; Katano, M.; Yamamoto, H.; Fujito, H.; Mori, M. Tukata, K. *Chem. Pharm. Bull.*, **1990**, *38*, 3480.
4. Larsen, P. K.; Nielsen, B. E.; Lemmich, J. *Acta Chem. Scand.*, **1969**, *23*, 2252.
5. Shim, S. C.; Koh, H. Y.; Chang, S. *Tetrahedron Lett.*, **1985**, *26*, 5775.
6. Bernart, M. W.; Hallock, Y. F.; Cardellina II, J. H.; Boyd, M. R. Tetrahedron Lett., **1994**, *35*, 993.
7. Regegling, H.; Ronville, E. De.; Chittenden, G. J. F. Rec. *Trav. Chim., Pays-Bas.*, **1987**, *106*, 461.
8. Xie, M.; Berges, D. A.; Robins, M. J. *J. Org. Chem.*, **1996**, *61*, 5178.
9. Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.*, **1972**, 3769.
10. Lu, W.; Zheng, G. R.; Cai, J. C. *Chinese Chem. Lett.*, **1998** (in press).
11. Grandjean, D.; Pall, P.; Chuche, J. *Tetrahedron Lett.*, **1992**, *33*, 5355.
12. Zheng, G. R.; Lu, W.; Aisa, H. A.; Cai, J. C. *Chinese Chem. Lett.*, **1998** (in press).
13. Data for **1**: IR(neat) 3346, 3090, 2990, 2256, 1645, 1114, 984, 932, 704cm^{-1}; ^{1}HNMR(300MHz, $CDCl_3$) δ_H 5.93(1H, ddd, J=17.0, 10.1, 5.5Hz), 5.45(2H, m), 5.43(1H, dd, J=17.0, 1.0Hz), 5.23(1H, dd, J=10.1, 1.0Hz), 4.90(1H, d, J=5.0Hz), 3.02(2H, d, J=6.8Hz), 2.01(2H, m), 1.29(10H, m), 0.87(3H, t, J=6.7Hz)ppm; ^{13}CNMR(300MHz, $CDCl_3$) δ_c 136.4, 133.3, 122.1, 117.2, 80.5, 74.5, 71.5, 64.2, 63.7, 32.0, 29.7, 29.4, 29.1, 27.4, 22.8, 17.9, 14.3; HREIMS (m/s) M^+ calcd for $C_{17}H_{24}O$: 244.1828, found: 244.1835.
14. (a) Terada, A.; Tanoue, Y.; Kishimoto, D. *Bull. Chem. Soc. Jpn.*, **1989**, *62*, 2977. (b) Hirakura, K.; Morita, M.; Nakajima, K.; Ikeya, Y.; Mitsuhashi, H. *Phytochemistry*, **1992**, *31*, 899.