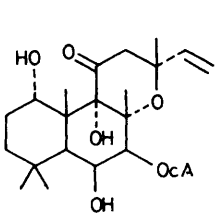
An Efficient Approach to the AB Ring System of Forskolin

Zhi-Yu Liu,* Xiao-Rui Zhou, and Ze-Min Wu

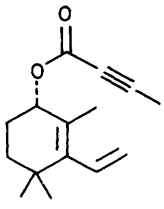
Shanghai Institute of Organic Chemistry, Academia Sinica, Shanghai 200032, China

An efficient intramolecular Diels–Alder reaction for the synthesis of the AB ring system of forskolin is described.

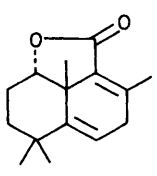
In recent years, forskolin (**1**) has attracted much attention prompted by its challenging chemical structure[1] and biological activity.[2,3] Several groups have reported their synthetic approaches to forskolin,[4] three groups[4b–d] using an intramolecular Diels–Alder reaction. However, effective reaction conditions for conversion of (**2**) into (**3**), a possible intermediate in the formation of forskolin, have not been found. Since compound (**2**) has an allylic alcohol ester moiety, which is a good leaving group but is unstable under the Diels–Alder reaction conditions, we decided to use the more stable ether compound (**6**) as substrate and have obtained satisfactory results.



(**1**)



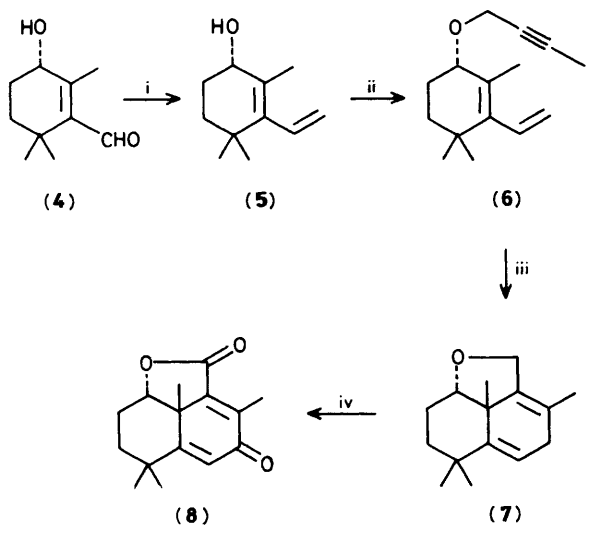
(**2**)



(**3**)

Methylenation of (±)-(**4**) by a Wittig reaction afforded (**5**) (m.p. 43—44 °C, 85% yield) (Scheme 1). Etherification of (**5**) produced (**6**) (97% yield), which then underwent a intramolecular Diels–Alder reaction to give the desired adduct (**7**) in 74% yield. Conversion of (**7**) into (**8**)† (m.p. 101—103 °C, 95% yield) was achieved by allylic oxidation with chromic anhydride–3,5-dimethylpyrazole complex.[5,6] Thus an effective synthesis of a highly functionalized AB ring compound (**8**) has been achieved and its elaboration to the target compound, forskolin, is in progress.

† All new compounds gave satisfactory spectral and analytical data. *Selected spectral data* for (**8**): i.r. (KCl): 1760, 1645, 1600, 1140, 880, 780 cm^{-1}; u.v.; λ_{max}(MeOH) 258 nm, ε_{max} 5600; ^1H n.m.r. ($CDCl_3$): δ 6.15 (s, 1H), 4.46 (dd, 1H, *J* 4 and 11 Hz), 2.25 (s, 1H), 2.2—2.05 (m, 1H), 1.9—1.65 (m, 2H), 1.57 (s, 3H), 1.33 (s, 3H), 1.25 (s, 3H), 1.2—1.0 (m, 1H); *m/z* 247 (M^+ + 1), 231 (M^+−Me), 203 (M^+− CO_2 + 1), 187 (M^+− CO_2−Me).



Scheme 1. *Reagents and conditions*: i, $Me\overset{+}{P}Ph_3Br^-$ (2.5 equiv.), Bu^nLi (2.5 equiv.), tetrahydrofuran, room temperature; ii, 60% NaOH–H_2O, Bu^n_4NI catalyst, $BrCH_2C{\equiv}CMe$; iii, 160 °C, 3 days, no solvent, in sealed tube; iv, CrO_3–3,5-dimethylpyrazole (30 equiv.), CH_2Cl_2, room temperature.

We are grateful to Miss Hai-Lan Chu for technical assistance.

Received, 8th June, 1987; Com. 772

References

1 S. V. Bhat, B. S. Bajwa, H. Dornauer, N. J. de Souza, and H.-W. Fehlhaber, *Tetrahedron Lett.*, 1977, 1669.
2 S. V. Bhat, A. N. Dohadwalla, B. S. Bajwa, N. K. Dadkar, H. Dornauer, and N. J. de Souza, *J. Med. Chem.*, 1983, **26**, 486.
3 H. P. T. Ammon, and A. B. Muller, *Planta Med.*, 1985, 473.
4 (a) T.-T. Li, Y.-L. Wu, and Z.-Y. Liu, presentation at the International Symposium on Chemistry of Medicinal Natural Products (IUPAC), November, 1985, Shanghai, China; (b) P. R. Jenkins, K. A. Menear, P. Barraclough, and M. S. Nobbs, *J. Chem. Soc., Chem. Commun.*, 1984, 1423; (c) K. C. Nicolaou, and W. S. Li, *ibid.*, 1985, 421; (d) F. E. Ziegler, B. H. Jaynes, and M. T. Saindane, *Tetrahedron Lett.*, 1985, 3307; (e) P. G. Baraldi, A. Barco, S. Benetti, G. P. Pollini, E. Polo, and D. Simoni, *J. Chem. Soc., Chem. Commun.*, 1986, 757; (f) S.-I. Hashimoto, M. Sonegawa, S. Sakata, and S. Ikegami, *ibid.*, 1987, 24; (g) J. H. Hutchinson, G. Pattenden, and P. L. Myers, *Tetrahedron Lett.*, 1987, **28**, 1313.
5 Z.-Y. Liu, and J.-J. Yang, *Synth. Commun.*, accepted for publication.
6 W. G. Salmond, M. A. Barta, and J. L. Havens, *J. Org. Chem.*, 1978, **43**, 2057.