An Intramolecular Diels–Alder Strategy to Forskolin

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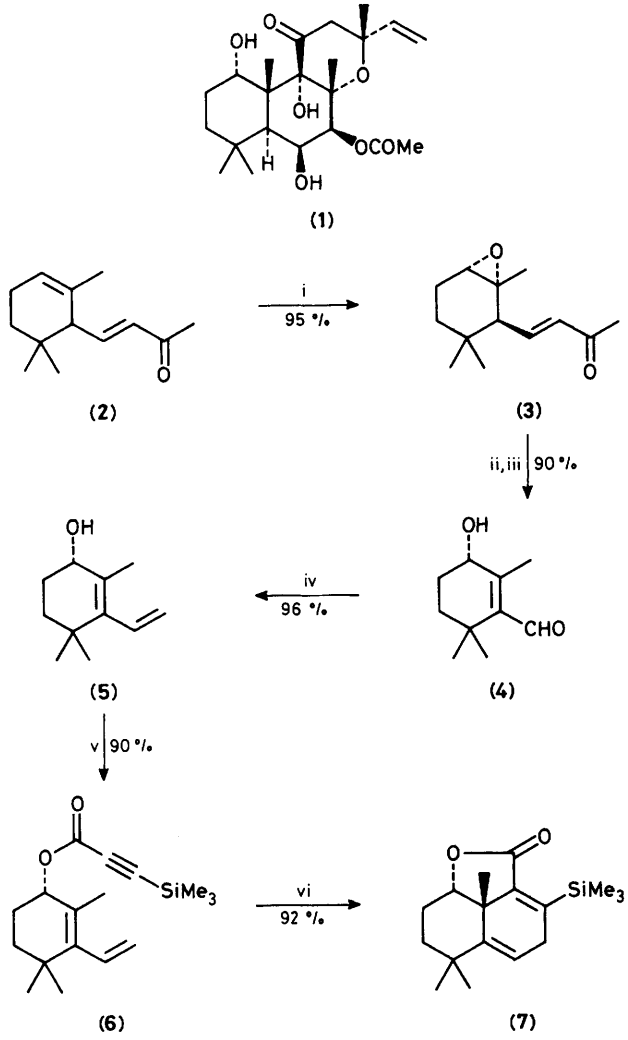
A strategy for the construction of the AB ring system of forskolin based on a novel intramolecular Diels–Alder reaction is reported.

Forskolin (**1**)[1] is a naturally occurring substance with a molecular structure of considerable interest and biological importance.[2,3] A recent report[4] on an intramolecular Diels–Alder approach to forskolin has prompted us to report our results using a similar strategy. The key deviation of our approach from that of the British workers[4] is the utilization of a doubly activated acetylene rather than a double bond as the dienophile in the intramolecular Diels–Alder precursor. Silicon activation of the acetylene group resulted in an excellent yield in the Diels–Alder reaction of a highly functionalized intermediate.



Scheme 1. *Reagents and conditions:* i, 1.3 equiv. *m*-chloroperbenzoic acid, CH_2Cl_2, −78 to 0 °C, 12 h; ii, O_3, CH_2Cl_2, 1.5 equiv. MeOH, −78 °C then 10 equiv. Me_2S, −78 to 25 °C; iii, 1.5 equiv. 1,8-diazabicyclo[5.4.0]undec-7-ene, 0—25 °C; iv, 3 equiv. $MePPh_3^+Cl^-$, 2.9 equiv. Bu^nLi, tetrahydrofuran, 0 °C; v, 1.5 equiv. $Me_3SiC{\equiv}CCOOH$, 1.5 equiv. dicyclohexylcarbodi-imide, 0.1 equiv. 4-*N*,*N*-dimethylaminopyridine, CH_2Cl_2, 0—25 °C; vi, benzene, sealed tube, 140 °C, 24 h.

Scheme 1† shows the synthetic route to the Diels–Alder precursor (**6**) and its conversion into compound (**7**). Thus, α-ionone (**2**) was selectively converted[5] into epoxide (**3**) which was sequentially subjected to ozonolysis and base-induced fragmentation to afford the hydroxyaldehyde (**4**). Methylenation of (**4**) by a Wittig reaction followed by esterification with 1-carboxy-2-trimethylsilylacetylene‡ resulted in the formation of precursor (**6**), [^{1}H n.m.r. (250 MHz, $CDCl_3$) δ: 6.20 (dd, *J* 15.5, 10.0 Hz, 1H, olefinic), 5.34 (m, 2H, olefinic and CHO), 5.05 (dd, *J* 15.5, 2.5 Hz, 1H, olefinic), 1.95—1.75 (m, 2H, CH_2), 1.70 (s, 3H, Me), 1.69—1.35 (m, 2H, CH_2), 1.05 (s, 3H, Me), 1.00 (s, 3H, Me), and 0.25 (s, 9H, $SiMe_3$)]. Thermolysis of (**6**) in benzene at 140 °C led exclusively to the tricyclic system (**7**) {^{1}H n.m.r. (250 MHz, $CDCl_3$) δ: 5.72 (dd, *J* 5.0, 2.0 Hz, 1H, olefinic), 4.34 (dd, *J* 10.0, 4.0 Hz, 1H, CHO), 3.20 [dd, *J* 20.0, 5.0 Hz, 1H, bis(allylic)], 2.82 [dd, *J* 20.0, 2.0 Hz, 1H, bis(allylic)], 1.95 (m, 1H, CH_2), 1.52—1.15 (m, 3H, CH_2), 1.22 (s, 3H, Me), 1.70 (s, 3H, Me), 1.60 (s, 3H, Me), and 1.25 (s, 9H, $SiMe_3$)} in 92% yield. The expected relative stereochemistry in (**7**) was supported by a positive nuclear Overhauser experiment (n.O.e.) pointing to a *cis* relationship between the methyl group at δ 1.22 and the proton at δ 4.34. Although these experiments were performed with racemic compounds, the ready resolution[6] of α-ionone (**2**) into its antipodes makes this strategy potentially enantioselective.

Substitution of the trimethylsilyl group in (**6**) by a hydrogen, methyl, or methoxycarbonyl group resulted in similar Diels–Alder products under the same conditions, but in lower yields, thus demonstrating the unique effect of the silicon group on the 4 + 2 cycloaddition reaction, presumably due to interactions of the silicon d orbitals.

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† All new compounds gave satisfactory spectroscopic and analytical data.

‡ Prepared from the corresponding alcohol by Jones oxidation (acetone, 0 °C, 90% yield).