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An Efficient Synthesis of a Key Intermediate of Forskolin

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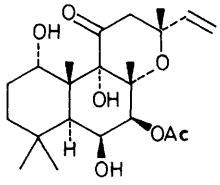
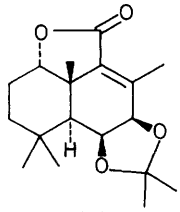
A strategy for the construction of a key intermediate of forskolin based on an intramolecular Diels–Alder reaction of an allenyl ether is described.

Forskolin (**1**) is the labdane diterpene isolated from the Indian plant *Coleus forskohlii*.[1] This natural product is known to be an activator of adenylate cyclase in various tissues, which has a number of physiological effects.[2] Therefore, many laboratories have embarked on the synthesis of (**1**), and three groups have recently reported the total synthesis of (±)-(**1**).[3—5] It is noteworthy that they used the tricyclic lactone (**2**) as an important key intermediate. As part of our programme of research on the allene intramolecular cycloaddition reaction,[6] we report here a significantly different synthetic approach to the key intermediate (**2**).

The synthetic sequence is detailed in Scheme 1. Propynylation of (±)-(**3**)[7] afforded (**4**) (83%; 100% based on recovery of starting material). The propynyl ether (**4**) was heated in Bu^{t}OH in the presence of Bu^{t}OK (excess) for 1 h; adduct (**6**)



(**1**)



(**2**)

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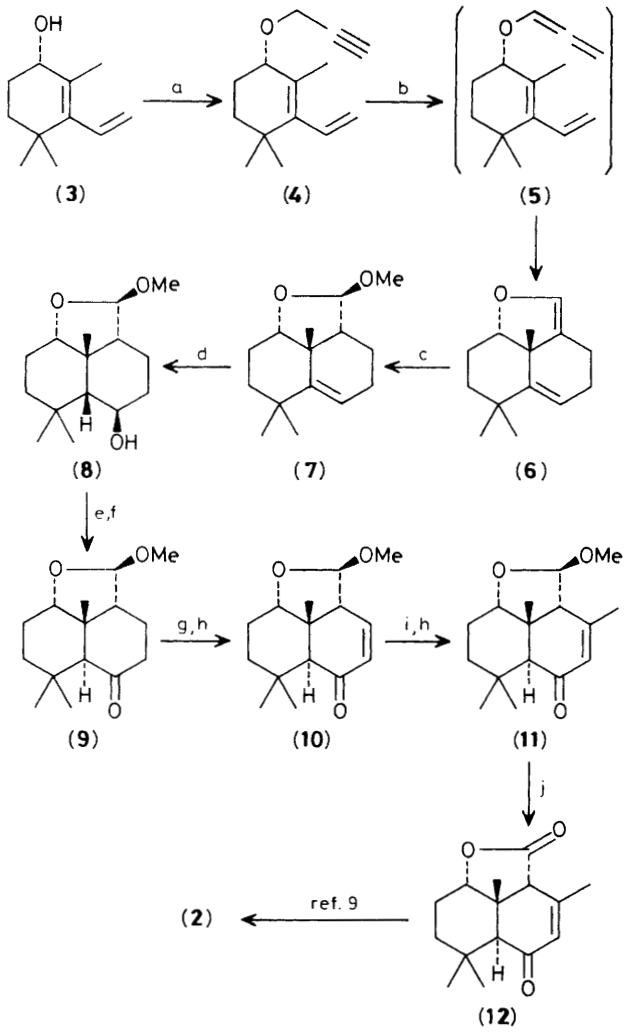

Scheme 1. Synthesis of a forskolin intermediate. *Reagents and conditions*: a, (i) Bu^{n}Li, hexamethylphosphoramide (HMPA), tetrahydrofuran (THF), (ii) CH≡CCH$_2$Br, 0 °C; b, Bu^{t}OK, Bu^{t}OH, reflux, 1 h; c, 5% CSA in MeOH, 0 °C, 2 h; d, (i) BH_3–THF complex, THF, 0 °C, 20 h, (ii) 10% NaOH, 30% H_2O_2; e, PCC, Celite, CH_2Cl_2, 0 °C, 2 h; f, MeONa, MeOH, reflux, 2 h; g, (i) lithium diisopropylamide (LDA), THF, −78 °C, (ii) PhSeCl, −78 °C to room temp.; h, 30% H_2O_2, pyridine, CH_2Cl_2, 0 °C, 3 h; i, (i) Me_2CuLi, Et_2O, −20 °C, (ii) PhSeCl, −20 °C to room temp.; j, BF_3·Et_2O, *m*-chloroperbenzoic acid, CH_2Cl_2, 0 °C, 3 h.

was obtained as the sole product in quantitative yield, *via* the allenyl ether intermediate (**5**). Treatment of (**6**) with methanol in the presence of 10-camphorsulphonic acid (CSA) gave a quantitative yield of (**7**).

Hydroboration of (**7**) gave rise to (**8**) in 74% yield (90% based on recovery of starting material), which was readily oxidized by pyridinium chlorochromate (PCC), and epimerized (MeONa, MeOH, reflux) to afford (**9**) (98% overall). The ketone (**9**) was converted to the enone (**10**) (80%), and conjugate methylation and *in situ* selenenylation, followed by selenoxide elimination, led to (**11**) (71%). The enone (**11**) was converted into the lactone (**12**) in moderate yield.[8] According to Ziegler's method, (**12**) could be converted to the key intermediate (**2**) in four steps.[9]

Although these experiments were performed with racemic compounds, the ready resolution of the alcohol (**3**) into its antipodes makes this strategy potentially enantioselective. Thus an efficient synthesis of the key intermediate (**2**) has been achieved and its elaboration to the target compound, forskolin, is in active progress.†

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† All new compounds gave satisfactory analytical and/or spectral data.