An Efficient Synthesis of a Key Intermediate of Forskolin

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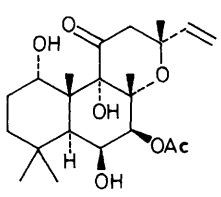
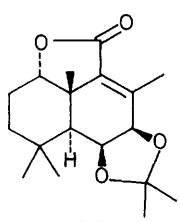
A strategy for the construction of a key intermediate of forskolin based on an intramolecular Diels–Alder reaction of an allenyl ether is described.

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**).

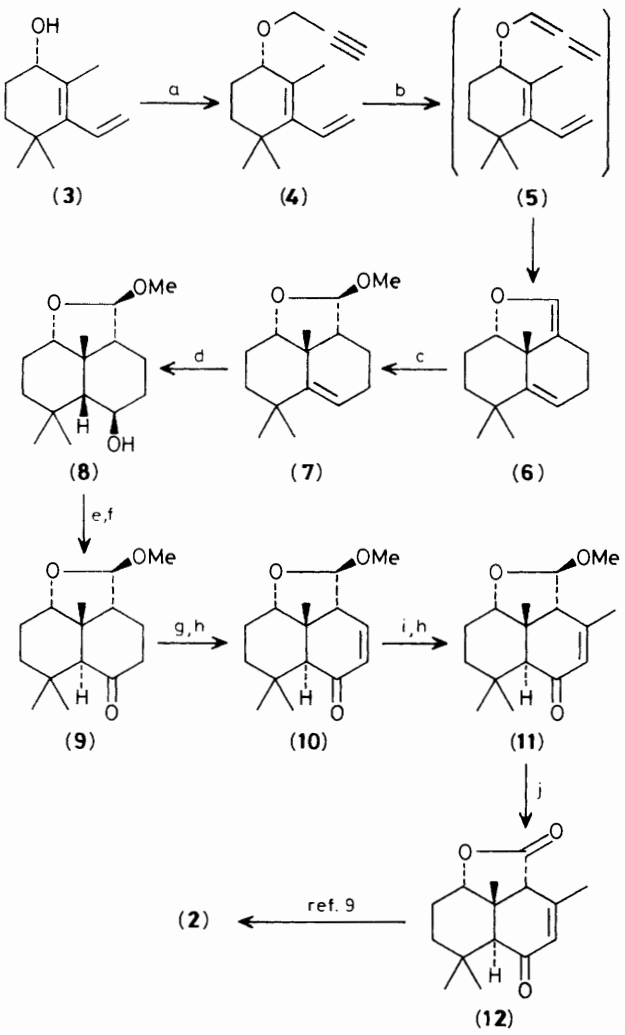
The synthetic sequence is detailed in Scheme 1. Propynylation of (±)-(**3**)[7] afforded (**4**) (83%; 100% based on recovery of starting material). The propynyl ether (**4**) was heated in Bu^{t}OH in the presence of Bu^{t}OK (excess) for 1 h; adduct (**6**)



(**1**)



(**2**)



Scheme 1. Synthesis of a forskolin intermediate. *Reagents and conditions*: a, (i) Bu^nLi, hexamethylphosphoramide (HMPA), tetrahydrofuran (THF), (ii) $CH{\equiv}CCH_2Br$, 0 °C; b, Bu^tOK, Bu^tOH, 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, $BF_3{\cdot}Et_2O$, *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.†

We are grateful to Dr. Kenji Hayakawa for valuable suggestions and discussions.

Received, 21st March 1989; Com. 9/01214A

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