An Intramolecular Diels–Alder Approach to Forskolin

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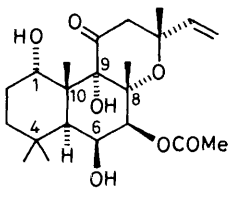
A Diels–Alder route to two tricyclic lactones with the same relative stereochemistry as C-1 and C-10 in forskolin is described.

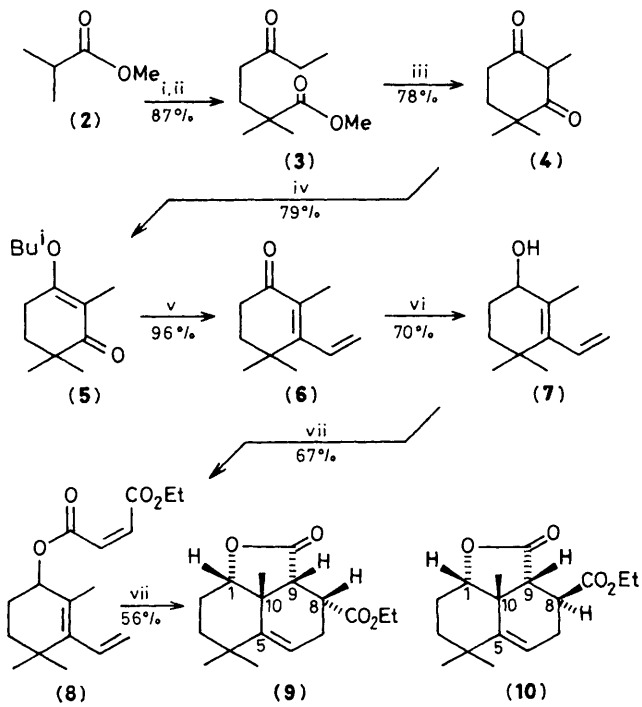
Forskolin (**1**) is a natural product isolated from the Indian plant *Coleus forskohlii*.[1] The compound has attracted attention because of its positive inotropic activity and its ability to indirectly activate adenylate cyclase.[2] Structures related to forskolin have to date been derived by chemical conversion on the natural product itself,[3] and no synthetic approaches to forskolin are known. Our previous use of the intramolecular Diels–Alder reaction in a synthesis of the taxane ring system[4] led us to consider a related strategy for forskolin. We now report the synthesis of two key intermediates which have the same relative stereochemistry as C-1 and C-10 in forskolin.

The lithium enolate of (**2**) underwent Michael addition to give the keto-ester† (**3**) after protonation (Scheme 1). Cyclisation leads to 1,3-diketone (**4**) and treatment with butan-2-ol under acidic conditions gave (**5**).[5] No evidence for the alternative isomer was obtained, probably because the carbonyl group at the 3-position is hindered by the three adjacent methyl groups. Dienone (**6**) was obtained by treatment of (**5**) with vinylmagnesium bromide followed by acidic work up. Lithium aluminium hydride reaction of (**6**)

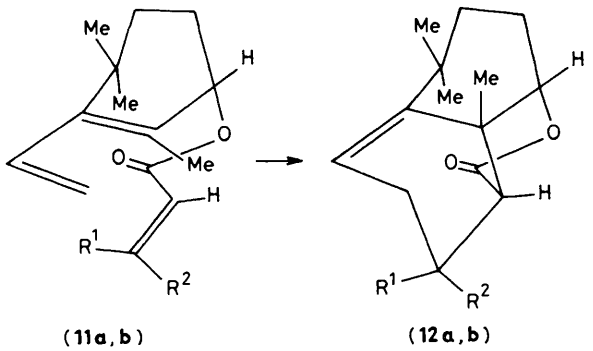


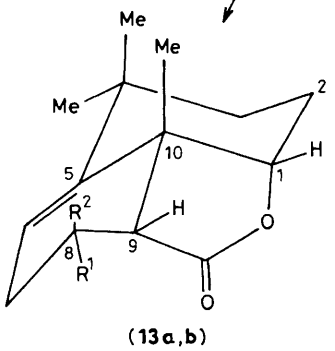
(**1**)

† All new compounds gave satisfactory ^1H, ^{13}C n.m.r., i.r., and mass spectral data; compounds (**3**), (**4**), (**8**), and (**9**) gave correct microanalysis results while (**5**), (**6**), (**7**), and (**10**) gave satisfactory accurate mass measurements.



Scheme 1. *Reagents and conditions:* i, lithium di-isopropylamide, tetrahydrofuran (THF), −78 °C; ii, ethyl vinyl ketone; iii, NaH (1.25 equiv.), reflux 4 h, THF; iv, butan-2-ol (6 equiv.), *p*-$MeC_6H_4SO_3OH$, (0.028 equiv.), benzene, reflux 24 h; v, CH_2=CHMgBr (3.5 equiv.), diethyl ether, reflux 4 h, then H_2SO_4, H_2O; vi, $LiAlH_4$ (1 equiv.), diethyl ether reflux 2 h; vii, maleic acid mono ethyl ester (3 equiv.), dicyclohexylcarbodiimide (3 equiv.), 4(*N*,*N*-dimethylamino)pyridine (0.1 equiv.), CH_2Cl_2, room temperature, 4 h; viii, 150 °C, benzene, sealed tube, 6 days.





a; $R^1 = CO_2Et$, $R^2 = H$
b; $R^1 = H$, $R^2 = CO_2Et$

Scheme 2

gave the alcohol (**7**) which was readily converted into the maleate ester (**8**). Only after considerable experimentation were conditions found for intramolecular Diels–Alder reaction of ester (**8**). No effective conditions were obtained with the but-2-ynoate ester of alcohol (**7**). However, the maleate ester (**8**) cyclised in 56% total yield on heating in benzene for six days; the reaction was followed to a maximum by capillary g.c. A 1 : 3 mixture of (**9**) and (**10**) was readily separated from starting material and some elimination product. Chromatography separated (**9**) as a white crystalline solid, m.p. 99—101 °C and (**10**) as an oil; the structures of these compounds are based on spectroscopic evidence.‡ In particular the assignment of the lactone ring in (**9**) and (**10**) as being on the lower α-face rests on the observation that the coupling constant between 8-H and 9-H is similar in both isomers, and on nuclear Overhauser enhancement (n.O.e.) between the Me at C-10 and 1-H (4%), 8-H (5%), and 9-H (7%) in lactone (**9**) ($CDCl_3$), and between the Me at C-10 and 1-H (5%) and 9-H (7%) in lactone (**10**) (C_6D_6). A probable explanation of the formation of (**9**) and (**10**) is shown in Scheme 2. From Dreiding models it appears that the most favourable mode of cyclisation occurs when rings A and B define approximate boat conformations in the conversion of (**11a,b**) into (**12a,b**). However, conformation (**12a,b**) is apparently not the most stable for this ring system and a ring flip occurs to accommodate a chair conformation for ring A with C-8 pointing in the upper β-direction as shown in (**13a, b**). Conformation (**13a, b**) explains why the coupling constant between 8-H and 9-H is very similar in both epimers; the dihedral angle 8-H to 9-H in (**13a**) and (**13b**) is *ca.* 60°; the n.O.e. data provides further evidence for structure (**13a, b**). It appears that *endo* cyclisation has occurred in the conversion of (**11a,b**) into (**12a,b**). The alternative *exo* cyclisation leads to a product in which the 8-H, 9-H coupling constant would be expected to be substantially different in each epimer at C-8, where the dihedral angle 8-H to 9-H is *ca.* 180° and 60°.

The mixture of epimers at C-8 might be expected to arise from thermal *cis–trans* isomerisation of the double bond. However, Diels–Alder cyclisation of the fumarate ester of (**8**) leads mainly to a different product isomer which we believe to be the result of *exo* cyclisation. One possibility is that a non-synchronous cyclisation of a diradical intermediate in the double bond isomerisation reaction is occurring.

Cyclisation occurred *via* an *endo*-transition state in the presence of a methyl substituent on the diene and a dienophile attached *via* an ester linkage; there appears to be no literature precedent for this. Although *trans*-fused decalins and related systems have been obtained by intramolecular Diels–Alder reactions,[6] previous reports indicated either elimination products[7] or *exo* cyclisation[8] with ester functionality, and mixed cyclisation modes[7] with ethers when specifically attempting to prevent elimination. This key step introduces three contiguous chiral centres in a stereocontrolled manner, the C-8 epimers posing no problem since further elaboration will involve the formation of a double bond between this centre and C-9.

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‡ ^{1}H N.m.r. (400 MHz, $CDCl_3$): (**13a**) δ 1.09 (3H, s, 4α-Me), 1.13 (3H, s, 4β-Me), 1.29 (3H, t, *J* 7.1 Hz, $MeCH_2$–), 1.43 (3H, s, 10-Me), 1.50—1.60 (2H, m, 3-Hα, Hβ), 1.92—2.08 (2H, m, 2-Hα, Hβ), 2.37 [1H, ddd, *J*(7β,6) 4.4, (7β,8) 7.2, and (7β, 7α) 18.8 Hz, 7β-H], 2.54 [1H, ddd, *J*(7α, 6) 3.1, (7α, 8) 11.3, and (7α, 7β) 18.9 Hz, 7α-H], 2.74 [1H, ddd, *J*(8,9) 4.0, (8, 7β) 7.3, and (8, 7α) 11.3 Hz, 8-H], 3.00 [1H, d, *J* (9,8) 4.0 Hz, 9-H], 4.19 [2H, q, *J* 7.2 Hz, $-OCH_2Me$), 4.31 (1H, dd, *J* 3.17 and 3.18 Hz, 1-H), and 5.64 (1H, dd, *J* 3.9 and 3.6 Hz, 6-H). (**13b**) δ 1.09 (3H, s, 4β-Me), 1.10 (3H, s, 4α-Me), 1.29 (3H, t, *J* 7.1 Hz, $MeCH_2$–), 1.32 (3H, s, 10-Me), 1.43—1.63 (2H, m, 3-Hα,Hβ), 1.94—2.02 (2H, m, 2-Hα, Hβ), 2.37—3.08 (2H, m, 7-Hα, Hβ), 3.09 [1H, d, *J* (9,8) 3.0 Hz, 9-H], 3.13 [1H, ddd, *J* (8,9) 3.0, (8,7) 5.6, and (8,7) 8.0 Hz, 8-H], 4.19 (2H, q, *J* 7.1 Hz, $-OCH_2Me$), 4.23 (1H, dd, *J* 2.7 and 3.1 Hz, 1-H), and 5.70 (1H, dd, *J* 4.2 and 4.1 Hz, 6-H).

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