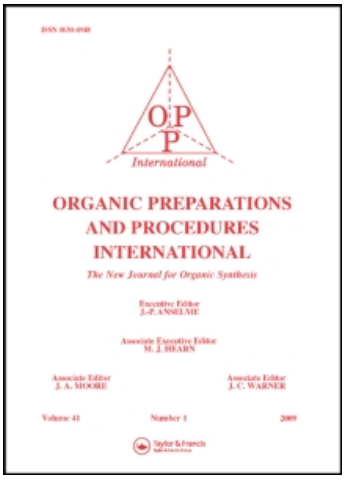

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

A SYNTHETIC APPROACH TO THE AB-RING SYSTEM OF FORSKOLIN

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To cite this Article Kulkarni, Yashwant S. and Snider, Barry B.(1986) 'A SYNTHETIC APPROACH TO THE AB-RING SYSTEM OF FORSKOLIN', Organic Preparations and Procedures International, 18: 1, 7 — 10
To link to this Article: DOI: 10.1080/00304948609356820
URL: http://dx.doi.org/10.1080/00304948609356820

ORGANIC PREPARATIONS AND PROCEDURES INT. 18(1), 7-15 (1986)

OPPI BRIEFS

A SYNTHETIC APPROACH TO THE AB-RING SYSTEM OF FORSKOLIN

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(06/26/85)

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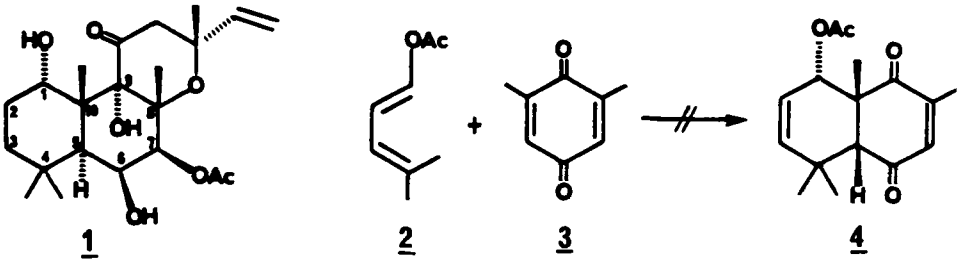
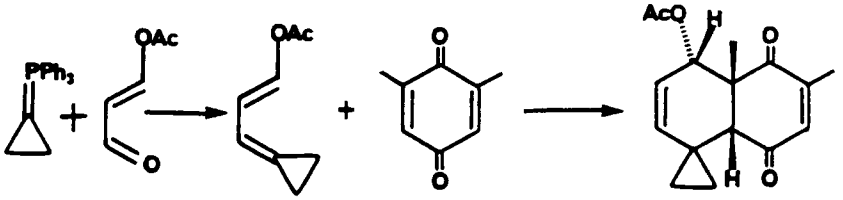
Forskolin (1), a diterpene isolated from the Indian Plant Coleus forskohlii,[1] activates adenylate cyclase, lowers blood pressure and has positive inotropic activity.[2,3] Although the carbon skeleton is quite simple, the plethora of functionality and substituents makes the synthesis of forskolin a challenging problem. An obvious approach to the carbocyclic framework of forskolin is the Diels-Alder reaction of E-4-methyl-1,3-pentadienyl acetate (2) with 2,6-dimethylbenzoquinone (3) to give 4. Unfortunately, geminally disubstituted butadienes are unreactive in the Diels-Alder reaction;[4] even if the Diels-Alder reaction could be made to occur, a mixture of regioisomers would be expected due to competing substituent effects since Schmidt[5] has shown that E,E-1,3-pentadienyl acetate reacts with 3 at 150° to give an 85% yield of a 4:1 mixture of regioisomers.



1 2 3 4

Zutterman and Krief have reported that allylidenecyclopropane (8) exhibits a much higher reactivity as a Diels-Alder diene than 4-methyl-1,3-pentadiene (9) and that the cyclopropane ring of the adduct can be reduced to a gem-dimethyl group.[4] Furthermore, the regioselectivity observed in the Diels-Alder reactions of 8 was "meta" rather than "ortho" as with 9 and other normal 1-substituted dienes. The Diels-Alder reaction of 6 with 3 to give 7 should solve both the reactivity and regioselectivity problems of 2 as a Diels-Alder diene.



5 6 3 7

The presence of the acetoxy group makes the synthesis of 6 much more challenging than that of 8. Furthermore 6 will be very unstable since protonation on the cyclopropane end of the diene will give an allylic cation that is also cyclopropylcarbinylic and α to an oxygen. The Wittig reaction of cyclopropylidenetriphenylphosphorane with β-acetoxyacrolein (5)[6] followed by non-aqueous workup and evaporative distillation gave a 20% yield of a 70% pure mixture of 6 and its Z-isomer; all attempts at further purification were unsuccessful because of its instability.

Diels-Alder reaction of 6 with 3 occurred smoothly on heating in benzene containing a trace of hydroquinone at 150° for 24 hrs to give a 38% yield of 7 as the sole Diels-Alder adduct. The expected regiochemistry of 7, with acetoxy and methyl groups ortho and cyclopropyl and methyl groups meta, was established by examination of the NMR spectrum which shows a singlet at δ 2.38 for the ring fusion proton and a doublet at δ 4.98 for the proton on the carbon bearing the acetoxy group. The expected endo

stereochemistry is assigned based on an NOE experiment carried out by irradiation of the absorption due to the ring fusion methyl group at δ 1.48 which gave 16% and 15% enhancements of the peaks at δ 2.38 and 4.98, respectively, indicating that the C-10 methyl and C-1 and C-5 hydrogens are on the same side of the ring system.

Diels-Alder adduct 7 has the relative stereochemistry at C-1 and C-10 of forskolin with C-5 readily epimerizable; the desired methyl group at C-8, C-10 and latent methyl groups at C-4 as well as oxygen functionality required at C-1, C-6 and C-9 are present. Unfortunately, the low yields of the Wittig and Diels-Alder reactions, coupled with further decreases in yield on attempted scale up of the Wittig reaction, prevent the further elaboration of this route to forskolin.

EXPERIMENTAL SECTION

Preparation of 3-Acetoxyprop-2-enylidenecyclopropane (6).- n-BuLi (2.4 ml of 2.5 M in hexane, 6 mmol) was added to a suspension of cyclopropyltriphenylphosphonium bromide (2.3 g, 6 mmol) in 12 ml of anh. THF at 0° under N_2. The resulting mixture was stirred for 1 h at 25° and cooled to 0°. A solution of 0.57 g (5 mmol) of 5 in 10 ml of anh. THF was added with vigorous stirring and the resulting mixture was stirred for 1 hr at 0° and diluted with 50 ml of hexane at 0°. The solid was removed by filtration and washed with hexane. The combined filtrate was treated with 5 mg of hydroquinone and evaporated in vacuo. Evaporation distillation (25°, 0.08 Torr) gave 0.13 g (20%) of ~70% pure 6 and its Z-isomer: NMR ($CDCl_3$): δ 0.80-1.60 (m, 4), 2.13 (s, 3), 5.80-6.50 (m, 2), 7.20-7.50 (m, 1); IR (neat): 3045, 3030, 2830, 1762, 1650, 1370, 1210, 1105 cm^{-1}. The diene was exceedingly unstable and was stored as a 1% solution in hexane at -10° under N_2.

Diels-Alder Reaction of 6 and 3.- A solution containing diene 6 (42 mg, 70%

pure, 0.2 mmol), 3 (27 mg, 0.2 mmol) hydroquinone (1.3 mg, 5-10 mol %) in 1 ml of anh. benzene was degassed four times by a freeze-pump-thaw cycle and sealed in vacuo. The mixture was heated for 24 hrs at 150°, cooled and evaporated in vacuo. Purification by MPLC (silica gel, 4:1 hexane-EtOAc) gave 21 mg (38%) of pure adduct 7: NMR ($CDCl_3$, 300 MHz): δ 0.60-0.80 (m, 2), 0.95-1.05 (m, 1), 1.12-1.25 (m, 1), 1.48 (s, 3), 1.81 (s, 3), 1.97 (d, 3, J = 1.5 Hz), 2.38 (s, 1), 4.98 (d, 1, J = 5.4 Hz), 5.36 (d, 1, J = 10.3 Hz), 5.78 (dd, 1, J = 10.3, 5.4 Hz), 6.73 (q, 1, J = 1.5 Hz); ^{13}C NMR ($CDCl_3$): δ 13.2, 15.0, 15.7, 16.2, 20.5, 20.6, 51.8, 57.7, 71.9, 120.0, 138.4, 139.2, 148.9, 169.1, 169.8, 200.4; IR ($CHCl_3$): 2965, 1740, 1695, 1672, 1370 cm^{-1}; UV (95%, EtOH), λ_{max} (ε): 244 nm (6250). The adduct turned red on standing at room temperature.

Acknowledgment.- We are grateful to the National Institutes of Health for financial support.

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