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The Total Synthesis of Favelanone

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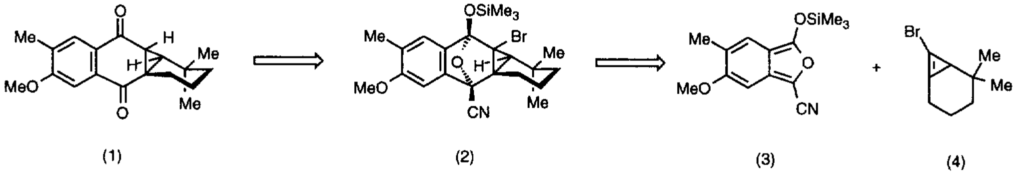
Abstract: (±)-Favelanone (1) has been synthesised by a sequence involving as the key step the cycloaddition of 6-methoxy-5-methyl-3-trimethylsilyloxyisobenzofuran-1-carbonitrile (3) to 7-bromo-5,5-dimethylbicyclo[4.1.0]hept-1(7)-ene (4). Copyright © 1996 Elsevier Science Ltd

(+)-Favelanone (1) is a novel tetracyclic dione isolated from the Brazilian plant Favela, *Cnidoscolus phyllacanthus* (Mart.) Pax et K. Hoffm. (Euphorbiaceae).[1,2] Favelanone is active against P-388 murine leukemia cells *in vitro* and although syntheses of the racemic modifications of its congeners[3] faveline, faveline dimethyl ether and deoxofaveline have appeared,[4] approaches to (1) and its novel skeleton have not been reported. We present here a convergent and highly regioselective synthesis of (±)-favelanone which is based on the retrosynthetic premise that Diels-Alder addition between the electron-rich push-pull isobenzofuran (3) and the polarised cyclopropene (4) should occur in the sense shown in Scheme 1. Liberation of the dione functionality followed by debromination should then deliver (1).

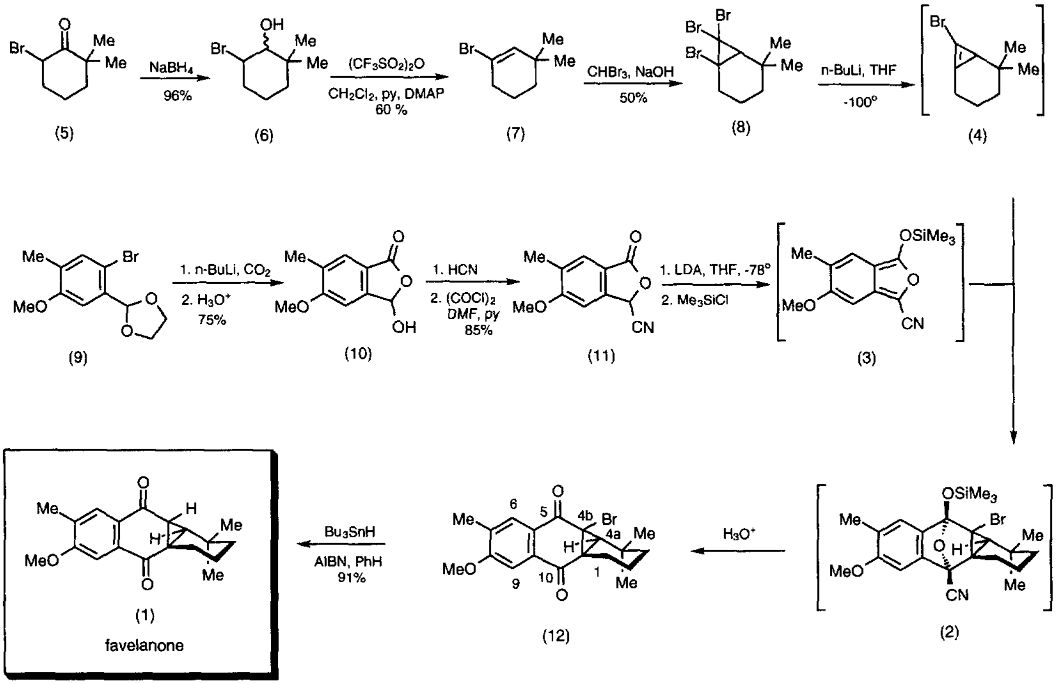


Scheme 1

1,7,7-Tribromo-5,5-dimethylbicyclo[4.1.0]heptane (8), the precursor to the cyclopropene (4) was prepared in a straight-forward manner as shown in Scheme 2. Reduction of the bromo ketone (5)[5] gave the *cis* and *trans* alcohols (6) in a ratio of 85:15. Treatment of this mixture with triflic anhydride afforded the bromo alkene (7) which was converted into the cyclopropane (8) by addition of dibromocarbene.

The specifically substituted cyano phthalide (11) was prepared from acetal (9), derived from 2-bromo-5-methoxy-4-methylbenzaldehyde,[7] by standard manipulations (Scheme 2). Deprotonation followed by quenching with Me_3SiCl gave an orange solution of the isobenzofuran (3). The cyclopropene (4), an example of a reactive 1,3-bridged cyclopropene,[6] was generated from (8) in solution by the action of n-butyllithium at -100°; addition of the solution of (3), warm-up to room temperature, followed by hydrolytic work-up afforded the bromo dione (12) (35%).[8,9] The regiochemistry of (12) was established by n.m.r. spectroscopy: nOe experiments permitted the assignment of the aryl protons H6 (δ 7.85) and H9 (δ 7.39), while three bond correlations were established between H6 and C5 (δ 187.9) and H9 and C10 (δ 192.9) respectively using

HMBC. H4a shows a three bond correlation with both carbonyl C5 and C10, but the regiochemistry shown follows from the observation that H1equatorial (δ 3.29) correlates with C10.



Scheme 2

(±)-Favelanone (1), m.p. 180-1°, spectroscopically identical with the natural material,[10] was obtained by debromination of (12) using tributylstannane. The above synthesis clearly illustrates the utility of 3-silyloxyisobenzofuran-1-carbonitriles as precursors for the rapid construction of moderately complex substituted naphthalene-1,4-diones.[11]

References and Notes

1. Endo, Y., Ohta, T., and Nozoe, S., *Tetrahedron Lett.*, 1991, **32**, 5555.
2. The absolute stereochemistry of (+)-favelanone is not known; enantiomer (1) is depicted arbitrarily.
3. Endo, Y., Ohta, T., and Nozoe, S., *Tetrahedron Lett.*, 1991, **32**, 3083.
4. Ghosh, A. K., Ray, C., and Ghatak, U. R., *Tetrahedron Lett.*, 1992, **33**, 655; Ghosh, A. K., Mukhopadhyay (née Ray) , C., and Ghatak, U. R., *J. Chem. Soc. Perkin Trans 1*, 1994, 327. For a different approach see Ho, T.-L., and Chen, C.-K., *Tetrahedron,* 1995, **51**, 5819.
5. Ramirez, F., and Kirby, A. F., *J. Am. Chem. Soc.*, 1952, **74**, 4331.
6 Billups, W. E., Haley, M. M., and Lee, G.-A., *Chem. Rev.*, 1989, **89**, 1147.
7. Kametani, T., Takahashi, K., Ihara, M., and Fukomoto, K., *J. Chem. Soc. Perkin Trans.1*, 1976, 389.
8. The addition is highly regioselective; signals ascribable to the isomeric product were not observed in the spectrum of the crude reaction product.
9. Bromo dione (12) was accompanied by favelanone (1) (*ca.* 15%) suggesting that metal-halogen exchange occurs in (4) and/or (2) during the reaction.
10. We thank Professor Tomihisa Ohta for providing spectral data of natural favelanone.
11. For a previous example see Evans, J. C., Klix, R. C., and Bach, R. D., *J. Org. Chem.*, 1988, **53**, 5519.

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