Synthesis of 3-Methyl-6-(2′-hydroxyethyl)-7-formyl-1,8-diethoxyisoquinoline: a Key Synthon for Fredericamycin A

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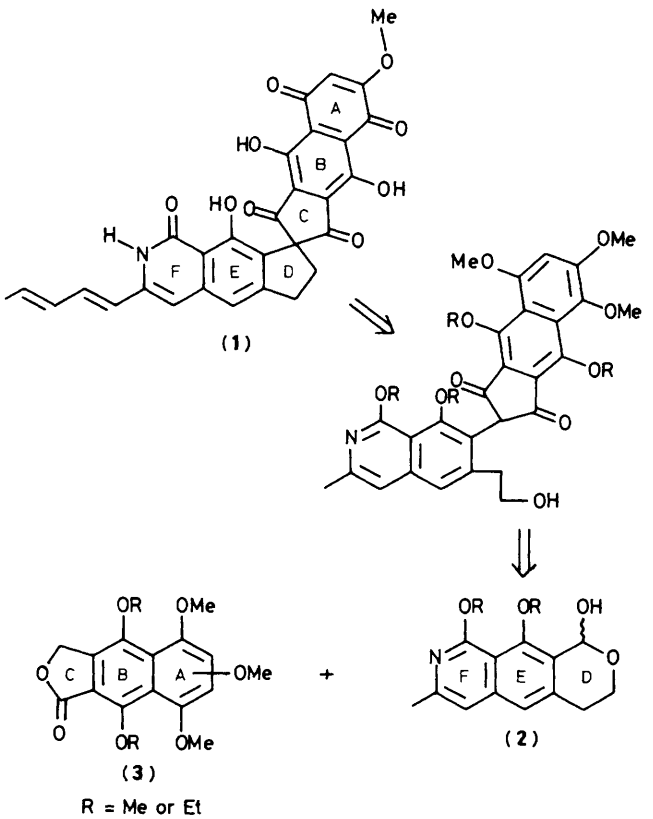
Synthesis of an isoquinoline moiety comprising the DEF rings in fredericamycin A has been accomplished in seven steps starting from 4-methyl-5-ethoxyoxazole.

Since its discovery, fredericamycin A (**1**)[1] has been of special interest to many workers owing to its novel structure and biological activity. For example, the spiro (4,4) nonane system present in (**1**), for which several synthetic methodologies have since been developed,[2] was previously unknown in natural products. We have planned a strategy towards the total synthesis of (**1**) which reveals the benzophthalide (**3**) (ABC rings) and the isoquinoline (**2**) (DEF rings) as the key intermediates (Scheme 1). Herein we report the synthesis of the isoquinoline derivative (**2**) *via* successive cycloaddition reactions.

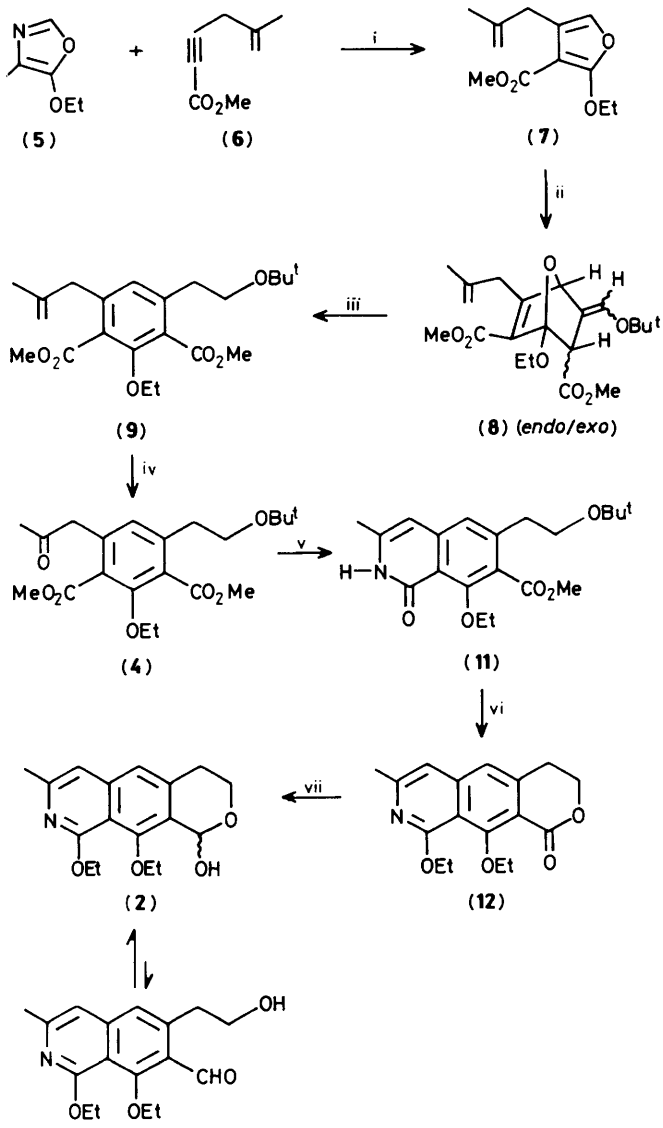
Compound (**2**) was formed from a penta-substituted aromatic compound (**4**) in which all the substituents were arranged so as to provide easy access to the hemiacetal (D ring) and pyridone (F ring). The cycloaddition reaction of 4-methyl-5-ethoxyoxazole (**5**)[3] with methyl 5-methylhex-5-en-2-ynoate (**6**)[4] in refluxing toluene furnished the trisubstituted furan (**7**)† (65%) after 24 h.[5] Further cycloaddition of (**7**) with methyl 5-t-butoxypenta-2,3-dienoate (**10**)[6] in acetonitrile at 75 °C[7] afforded the *endo*/*exo* bicyclic derivatives (**8**) (80%). No attempts were made to separate the *endo*/*exo* mixture, as both the isomers led to the desired compound after reductive aromatization. For example, treatment of (**8**) with titanium trichloride–lithium aluminium hydride complex in tetrahydrofuran (THF) containing triethylamine[8] furnished (**9**) (60%), which on ozonolysis gave the penta-substituted aromatic compound (**4**) (80%) (Scheme 2).

Compound (**4**) was treated with saturated methanolic ammonia[9] for 10 h at room temperature and the resulting



Scheme 1

† All new compounds gave satisfactory elemental and spectroscopic analyses.



Scheme 2. *Reagents and conditions:* i, toluene, 120 °C; ii, $Bu^tOCH_2CH{=}C{=}CHCO_2Me$ (**10**), MeCN, 75 °C; iii, $TiCl_3$–$LiAlH_4$, THF–Et_3N; iv, O_3, Me_2S, CH_2Cl_2, −20 °C; v, MeOH–NH_3; vi, $Et_3O^+ \cdot BF_4^-$, CH_2Cl_2, room temp.; vii, DIBAL, CH_2Cl_2, −78 °C.

cyclic amide (**11**) (90%) was then treated with an excess of triethyloxonium tetrafluoroborate[10] to give lactone (**12**) (45%). In the latter reaction the following occurred simultaneously: (a) formation of the ethoxyisoquinoline ring;[11] (b) hydrolysis of the t-butyl group; and (c) cyclization of the lactone ring. Finally conversion of (**12**) into the lactal derivative (**2**) (80%)‡ was achieved by reaction with diisobutylaluminium hydride (DIBAL)[12] at −78 °C.§

Received, 10th November 1986; Com. 1599

References

1 R. Misra, R. C. Pandey, and J. V. Silverton, *J. Am. Chem. Soc.*, 1982, 104, 4478 and references cited therein.
2 A. V. Rama Rao, D. Reddeppa Reddy, and V. H. Deshpande, *J. Chem. Soc., Chem. Commun.*, 1984, 1119; K. A. Parker, K. A. Koziski, and G. Breault, *Tetrahedron Lett.*, 1985, **26**, 2181; A. S. Kende, F. H. Ebetino, and T. Ohta, *ibid.*, 1985, **26**, 3063; G. Eck, M. Julia, B. Pfeiffer, and C. Rolando, *ibid.*, 1985, **26**, 4723 and 4725; M. Braun and R. Veith, *ibid.*, 1986, **27**, 179; R. D. Bach and R. C. Klix, *J. Org. Chem.*, 1986, **51**, 549; *Tetrahedron Lett.*, 1986, **27**, 1983; S. M. Bennet and D. L. J. Clive, *J. Chem. Soc., Chem. Commun.*, 1986, 878.
3 E. E. Harris, R. A. Firestone, K. Pfister, III, R. R. Boettcher, F. J. Cross, R. B. Carrie, M. Monaco, E. R. Pelerson, and W. Reuter, *J. Org. Chem.*, 1962, **27**, 2705; R. A. Firestone, E. E. Harris, and W. Reuter, *Tetrahedron*, 1967, **23**, 943.
4 A. V. Rama Rao and D. Reddeppa Reddy, unpublished results.
5 D. Liotta, M. Saindane, and Walter Ott, *Tetrahedron Lett.*, 1983, **24**, 2473.
6 M. E. Jung, J. A. Lowe, III, M. A. Lyster, M. Node, R. W. Pflunger, and R. B. Brown, *Tetrahedron*, 1984, **40**, 4751.
7 A. P. Kozikowski, W. F. Floyd, and M. P. Kuniak, *J. Chem. Soc., Chem. Commun.*, 1977, 582.
8 Y. D. Xing and N. Z. Haung, *J. Org. Chem.*, 1982, **47**, 140.
9 R. B. Titodkar and R. N. Usgaonkar, *Ind. J. Chem.*, 1972, **10**, 1060.
10 M. Meerwein, *Org. Synth.*, 1966, **46**, 113.
11 D. G. McMinn, *Synthesis*, 1976, 824.
12 E. Winterfeidt, *Synthesis*, 1975, 617.

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§ During preparation of this manuscript, K. A. Parker and G. A. Breault reported the synthesis of an isoquinoline synthon suitable for their methodology, K. A. Parker and G. A. Breault, *Tetrahedron Lett.*, 1986, **27**, 3835.