

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

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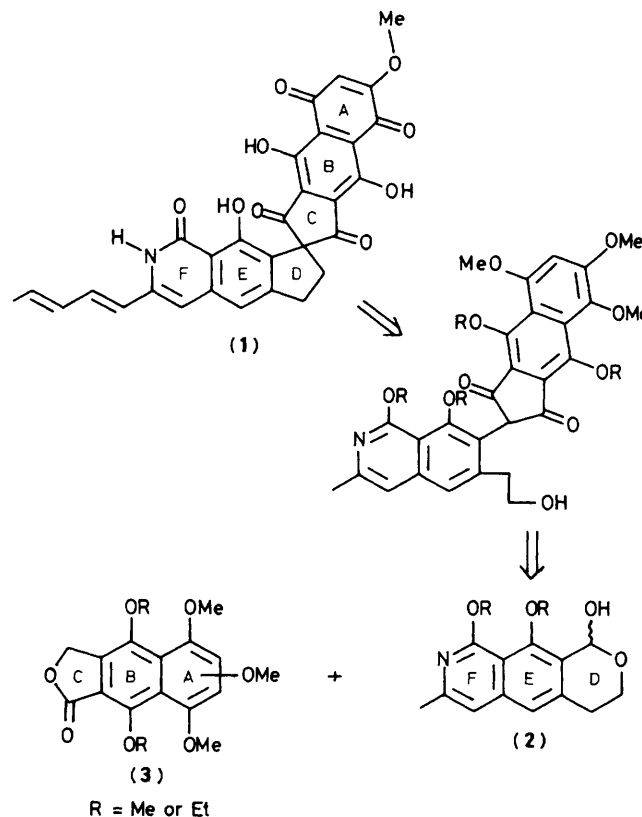
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Synthesis of an isoquinoline moiety comprising the DEF rings in fredericamycin A has been accomplished in seven steps starting from 4-methyl-5-ethoxyoxazole.

Since its discovery, fredericamycin A (1)<sup>1</sup> 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,<sup>2</sup> 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.

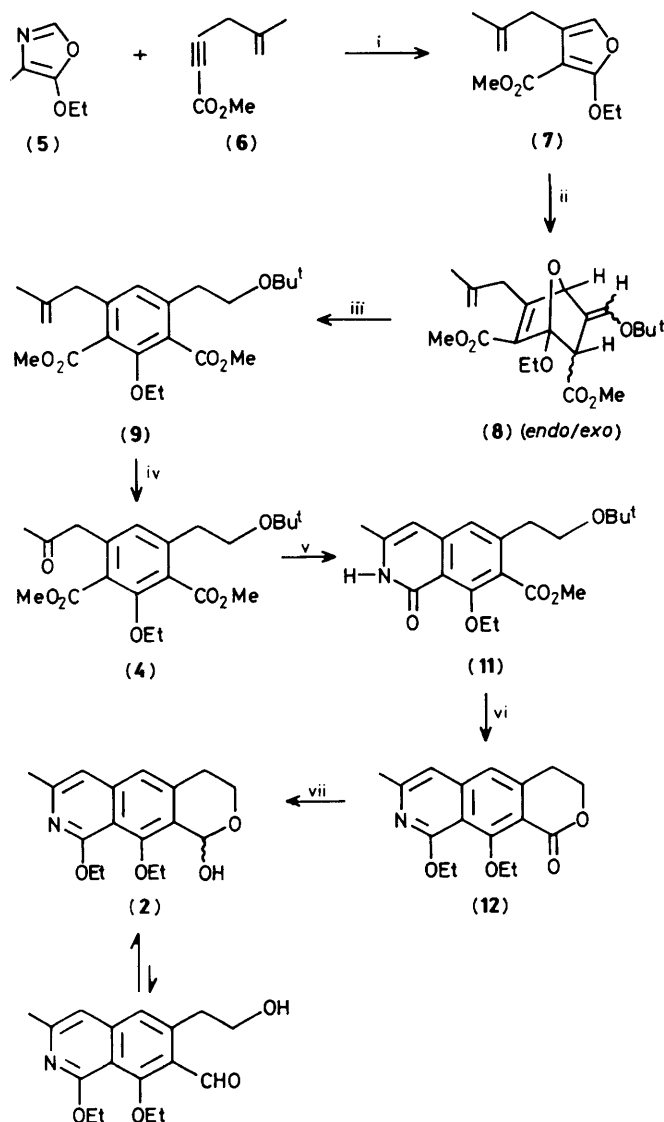
Compound (2) was formed from a penta-substituted aromatic compound (4) in which all the substituents were arranged so as to provide easy access to the hemiacetal (D ring) and pyridone (F ring). The cycloaddition reaction of 4-methyl-5-ethoxyoxazole (5)<sup>3</sup> with methyl 5-methylhex-5-en-2-ynoate (6)<sup>4</sup> in refluxing toluene furnished the trisubstituted furan (7)<sup>†</sup> (65%) after 24 h.<sup>5</sup> Further cycloaddition of (7) with methyl 5-t-butoxypenta-2,3-dienoate (10)<sup>6</sup> in acetonitrile at 75 °C<sup>7</sup> 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<sup>8</sup> furnished (9) (60%), which on ozonolysis gave the penta-substituted aromatic compound (4) (80%) (Scheme 2).

Compound (4) was treated with saturated methanolic ammonia<sup>9</sup> for 10 h at room temperature and the resulting



Scheme 1

<sup>†</sup> All new compounds gave satisfactory elemental and spectroscopic analyses.



**Scheme 2.** Reagents and conditions: i, toluene, 120°C; ii,  $\text{Bu}^t\text{OCH}_2\text{CH}=\text{CHCO}_2\text{Me}$  (10), MeCN, 75°C; iii,  $\text{TiCl}_3\text{-LiAlH}_4$ , THF- $\text{Et}_3\text{N}$ ; iv,  $\text{O}_3$ ,  $\text{Me}_2\text{S}$ ,  $\text{CH}_2\text{Cl}_2$ , -20°C; v,  $\text{MeOH-NH}_3$ ; vi,  $\text{Et}_3\text{O}^+\text{BF}_4^-$ ,  $\text{CH}_2\text{Cl}_2$ , room temp.; vii, DIBAL,  $\text{CH}_2\text{Cl}_2$ , -78°C.

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

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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.