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The Sequential Annulation of an Arene with a Tetrahydrofuran Provides a New Route to the Pseudopterosins

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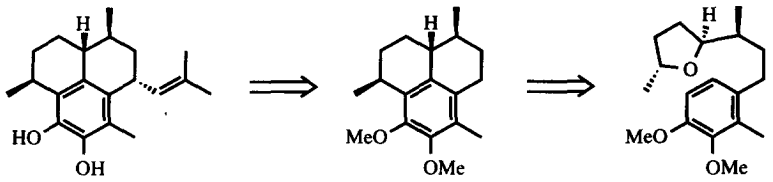
Abstract: The paper describes a new approach to the pseudopterosins in which a sequential arene alkylation with a tetrahydrofuran is used as a key step (*viz.* **2** → **1**).

Keywords: Annulation; Cyclisation; Lactones; Natural products; Terpenes and Terpenoids.

The pseudopterosins are a much studied family of marine natural products isolated from the sea whip *Pseudopterogorgia elisabethae*.[1] Pharmacological interest stems from their ability to function as anti-inflammatory and analgesic agents with a novel biological mode of action and potencies substantially greater than indomethacin.[1,2] Their limited availability from natural sources and recent commercialisation as the active ingredient in the topical skin cream *Resilience*® has likewise attracted the attention of synthetic chemists.[3] Indeed, the tricyclic phenalene core with its four stereogenic centres and fully substituted aromatic ring has inspired a number of interesting approaches and total syntheses.[4,5] In this *Letter* we describe a new approach to the main pseudopterosin aglycone in which a sequential annulation of an arene with a tetrahydrofuran features as the key step (Scheme 1).[6]



Pseudopterosin A-F aglycone **1** **2**

Scheme 1

Our synthesis of the tetrahydrofuran precursor **2** began with the known carboxylic acid **4**.[7] Iodolactonisation of this material under *kinetic* control gave **5** as a separable 6:1 mixture of *cis*- and *trans*-diastereoisomers.[8] Stepwise allylation to **6**, reduction to **7** and iodoetherification under *thermodynamic* control then gave tetrahydrofuran **8**.[9] Reduction of the halide to **9** and Swern oxidation of the alcohol produced aldehyde **10** which was efficiently coupled with aryllithium **11** to give alcohol **12** as a 1:1 mixture of diastereoisomers. Removal of the alcohol moiety by hydrogenolysis then produced the tetrahydrofuran precursor **2**.

Sequential cyclisation of **2** to hexahydrophenalenone **1** was then induced by exposure to a refluxing dichloromethane solution containing 5 equivalents of boron trifluoride. The product **1** was given in 81% yield as an 8:1 mixture of diastereoisomers that could be separated by column chromatography. Literature precedence and a good correlation between the NMR data obtained for **1** with those data reported for the main pseudopterosin aglycone lead us to conclude that the major diastereoisomer formed was as depicted.[1,4,5]

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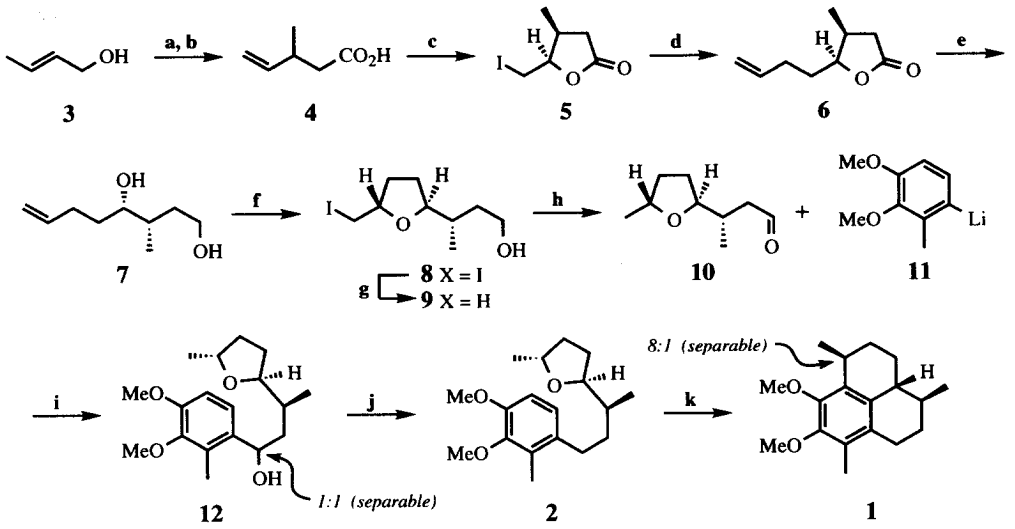

Reagents and Conditions: **a.** $CH_3C(OEt)_3$, *o*-nitrophenol, 98%;[7] **b.** 15M NaOH, THF, RT, 5h, 73%;[7] **c.** I_2, CH_3CN, 0°C, 5h, 82%;[8] **d.** allyltributyltin, AIBN, THF, 60°C, 40h, 63%; **e.** 3 eq. DIBAL-H, THF, PhMe, RT, 24h, 87%; **f.** I_2, CH_3CN, 0°C, 5h, 74%; **g.** Bu_3SnH, AIBN, THF, 60°C, 40h, 83%; **h.** $COCl_2$, DMSO, CH_2Cl_2, -78°C, 30 min; **9**, CH_2Cl_2, -78°C, 1h; Et_3N, to RT, 2h, 91%; **i.** THF, -78°C, 1h; to RT, 1h, 86%; **j.** H_2, Pd/C, EtOH, 18h, 95%; **k.** 5 eq. $BF_3.OEt_2$, CH_2Cl_2, 40°C, 72h, 81%.

Scheme 2

In conclusion, we have developed a stereospecific entry to the pseudopterosins that employs an unusual sequential arene alkylation reaction with a tetrahydrofuran serving as a bis-electrophile. We are currently seeking to install the four carbon fragment required to complete a formal total synthesis of pseudopterosin.

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