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Tetrahedron Letters 45 (2004) 2089–2091
Tetrahedron Letters

Total synthesis of (±)-pseudopterosin A–F and K–L aglycone

David C. Harrowven* and Melloney J. Tyte

Department of Chemistry, The University of Southampton, Southampton SO17 1BJ, UK

Received 26 November 2003; accepted 15 January 2004

Abstract—A total synthesis of (±)-pseudopterosin A–F and K–L aglycone is described in which three aromatic alkylation reactions are used to construct the hexahydrophenalene ring system.

The pseudopterosins are a small family of glycosidal diterpenes found in the Caribbean sea whip *Pseudopterogorgia elisabethae*.[1] They have attracted considerable attention because they function as anti-inflammatory and analgesic agents with potencies substantially greater than indomethacin.[1–3] Their limited availability from natural sources, coupled to the recent commercialisation of pseudopterosin C **1C** as the active principle of the topical skin cream *Resilience*®,[3] has done much to popularise these molecules as synthetic targets and a number of total syntheses[4–7] and synthetic approaches have been reported.[8]

Fifteen pseudopterosins have been identified to date (A–O) and these differ in respect of (i) the sugar moiety; (ii) the point of attachment of that sugar to the catechol and/or (iii) stereochemical differences in the aglycone.[1,7] Pseudopterosins A–F share a common aglycone **2**. The enantiomer of **2** is also a natural ring system, being the aglycone of pseudopterosins K and L.[1] Pseudopterosin G–J and M–O aglycone **3** has the opposite configuration at C1 and was recently the subject of a structural revision [the opposite configuration at C7 had been proposed in the isolation paper].[7] In this communication we report a new synthesis of (±)-pseudopterosin A–F and K–L aglycone **2** (Fig. 1).

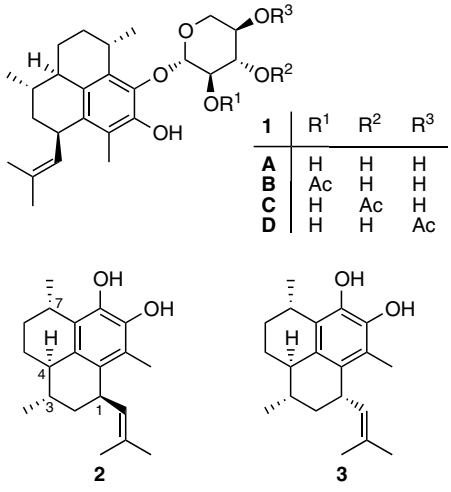


Figure 1. Pseudopterosins A–D (**1A**–**D**), pseudopterosins A–F aglycone **2** and pseudopterosins G–J and M–O aglycone **3**.

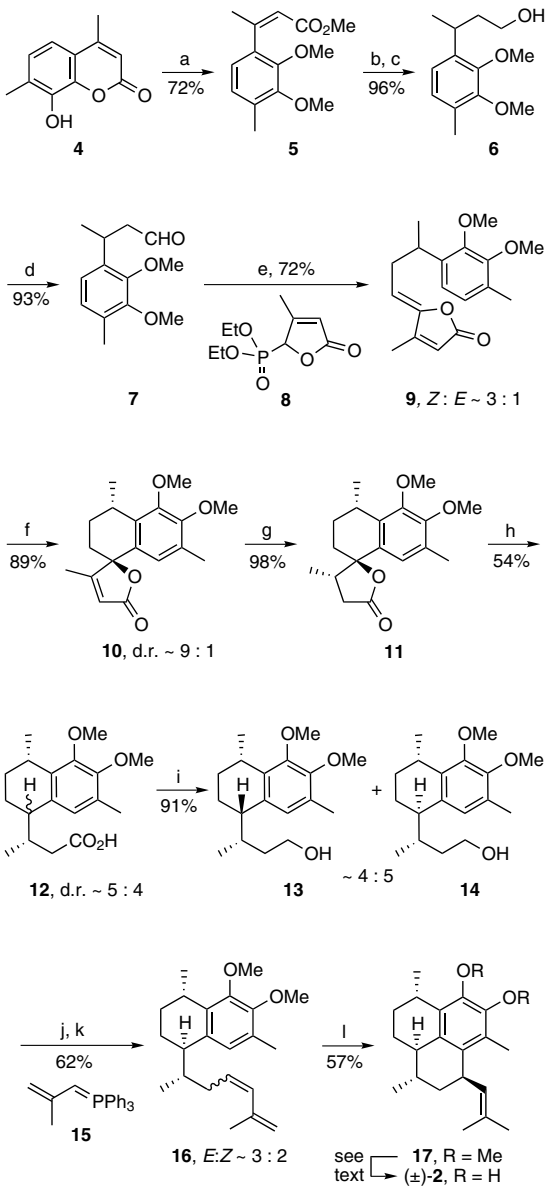
Our synthesis began with the known coumarin **4**, which was conveniently prepared in one step from 3-methylcatechol by means of a Pechmann condensation.[9] Exposure of **4** to dimethylsulfate and potassium hydroxide led to scission of the lactone and gave ester **5**. Sequential reductions of the alkene and ester functions, followed by oxidation of the resulting alcohol **6** with the Dess–Martin periodinane reagent, gave aldehyde **7**. A Horner–Wadsworth–Emmons coupling reaction with phosphonate **8** next provided a 3:1 mixture of (*Z*)- and (*E*)-γ-methylene-γ-butyrolactone **9**.[10] Although these isomers could be separated by column chromatography, this was unnecessary as each gave spirolactone **10** with the same diastereoisomeric ratio when warmed with triflic acid.

Hydrogenation of spirolactone **10** (H_2, Pd–C, PtO_2, EtOAc, rt, 3 h) provided **11** in 98% yield as a single diastereoisomer. Notably, even at elevated pressure we

Keywords: Total synthesis; Marine natural products; Aromatic chemistry.

* Corresponding author. Tel.: +44-02380593302; fax: +44-023805937-81; e-mail: dch2@soton.ac.uk

0040-4039/$ - see front matter © 2004 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2004.01.060



Scheme 1. Reagents and conditions: (a) Me_2SO_4, KOH, acetone, rt, 48 h; (b) H_2, PtO_2, EtOAc, rt, 2 h; (c) $LiAlH_4$, THF, −78–0 °C, 30 min; (d) Dess–Martin periodinane, CH_2Cl_2, 0 °C, 45 min; (e) **8**, KOBu^t, THF, 0 °C, 45 min then **7**, 0 °C, 40 min; (f) TfOH, 77 °C, 15 min; (g) H_2, Pd–C, PtO_2, EtOAc, rt, 3 h; (h) Na, NH_3, THF, 10 min; (i) BH_3·THF, 0 °C to rt, 16 h; (j) Dess–Martin periodinane, CH_2Cl_2, 0 °C, 45 min; (k) **15**, THF, rt, 2 h; (l) BF_3·OEt_2, CH_2Cl_2, −78–0 °C, 2 h.

were unable to effect the concomitant hydrogenolysis of **11** to acid **12**. To achieve that conversion it was necessary to employ a dissolving metal reduction, with **12** being given as an inseparable 5:4 mixture of diastereoisomers. Separation of the diastereoisomers could be achieved after reduction of these carboxylic acids to alcohols **13** and **14** with borane–THF complex.

To complete the total synthesis, **14** was oxidised to the corresponding aldehyde using the Dess–Martin periodinane reagent. A Wittig olefination with ylide **15** then installed the final four carbons, providing diene **16** as a 3:2 mixture of (*E*)- and (*Z*)-isomers in 63% yield. Exposure of that mixture to BF_3·OEt_2 induced cyclisation to hexahydrophenalene **17** in 57% yield. A minor component, displaying similar spectral characteristics and accounting for 9% of the mass balance, was also given and assigned as pseudopterosin G–J aglycone dimethyl ether (Scheme 1).

The final deprotection of **17** to (±)-pseudopterosin A–F and K–L aglycone **2** was accomplished with boron tribromide in the manner described by Buszek and Bixby.[5] In our hands this gave **2** in a pitiful yield of 9%. Notably, Majdalani and Schmalz have effected the same conversion in 95% yield by heating **16** with LiSEt in DMF.[6]

In conclusion, a total synthesis of (±)-pseudopterosin A–F and K–L aglycone **2** has been completed in 14 steps from 3-methylcatechol using three acid mediated cyclisation reactions to construct the hexahydrophenalene ring system. Work is in progress to adapt the approach described to address related natural products such as elisapterosin and colombiasin A.[10]

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