Pergamon

Tetrahedron Letters 42 (2001) 1193–1195

TETRAHEDRON LETTERS

A new approach to the pseudopterosins using an arene alkylation with a γ-methylene-γ-butyrolactone

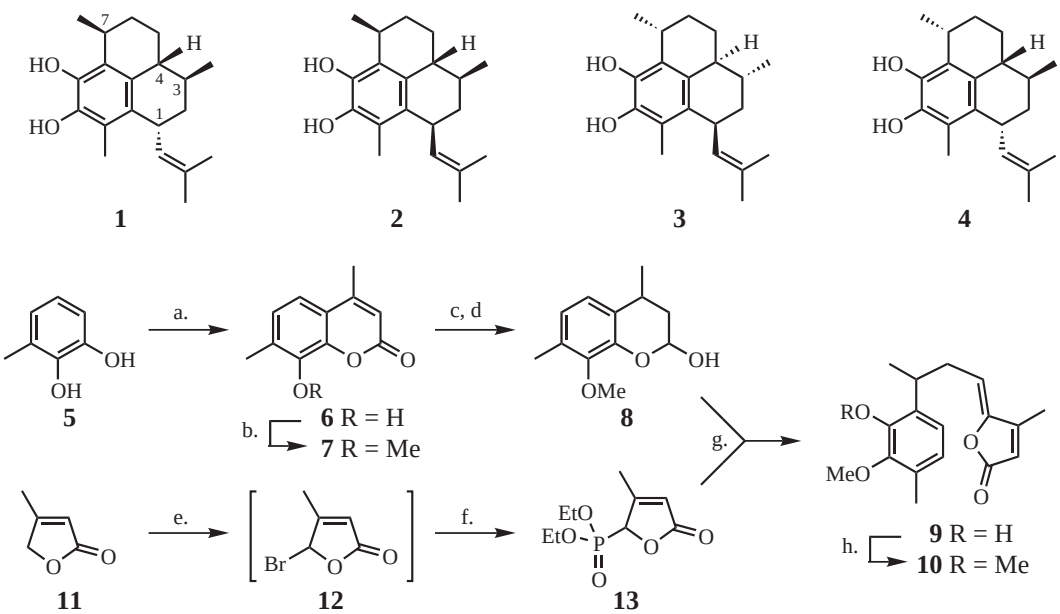
David C. Harrowven,* Jonathan D. Wilden, Melloney J. Tyte, Michael B. Hursthouse and Simon J. Coles

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

Received 9 November 2000; accepted 29 November 2000

Abstract—A short and practical route to the tricyclic core of an unnatural pseudopterosin diastereoisomer is presented. Key features are an arene alkylation with a γ-methylene-γ-butyrolactone, viz. **10→14**, and an elaborate reduction sequence **14→17** which both proceed diastereoselectively.

The pseudopterosins are a small family of glycosidal diterpenes found in the Caribbean sea whip *Pseudopterogorgia elisabethae*.[1,2] They have attracted considerable attention from synthetic and medicinal chemists alike because they function as anti-inflammatory and analgesic agents with potencies substantially greater than indomethacin.[1–3] Their limited availability from natural sources and the recent commercialisation of pseudopterosin C as the active principle of the topical skin cream *Resilience*® has done much to popularise these molecules as synthetic targets.[4–8]



Scheme 1. *Reagents and conditions*: (a) Ethyl acetoacetate, H_2SO_4, 0°C, 1 h;[10] (b) MeI, K_2CO_3, acetone, reflux, 18 h, 94%; (c) H_2, Pd–C, EtOAc, rt, 10 h, 98%; (d) DIBAL-H, THF, −78°C, 90 min, 82%; (e) NBS, AIBN, CCl_4, reflux, 2 h; (f) $P(OEt)_3$, 100°C, 1 h, 63%; (g) 3 equiv. **13**, KO′Bu, THF, rt, 1 h, 88%; (h) MeI, K_2CO_3, acetone, reflux, 18 h, 88%.

Keywords: annulation; cyclisation; lactones; natural products; terpenes and terpenoids.

* Corresponding author.

0040-4039/01/$ - see front matter
PII: S0040-4039(00)02207-3

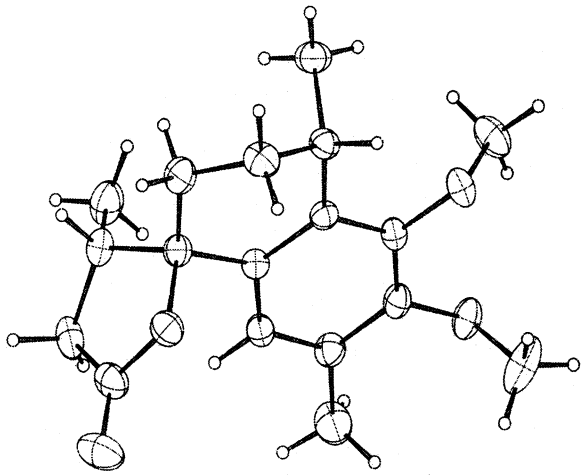


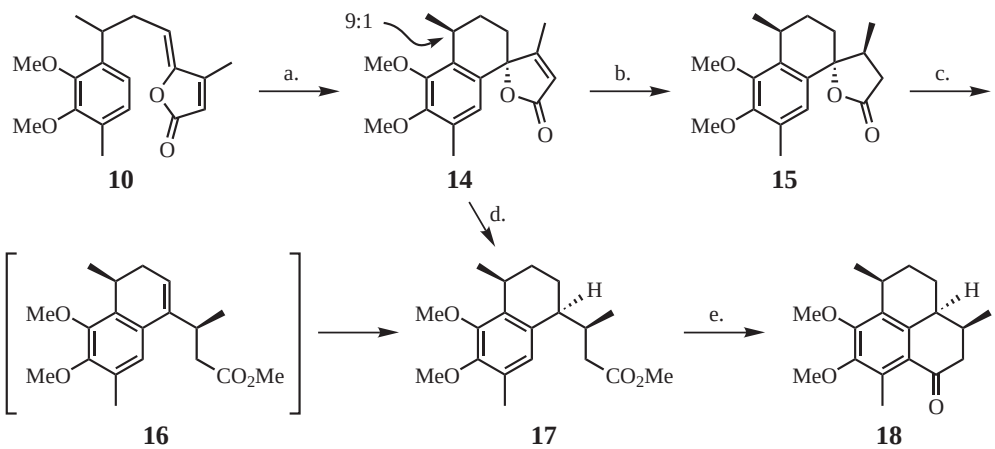
Figure 1. ORTEP diagram of **15**.

Twelve pseudopterosins (A–L) have been identified to date. These are differentiated by a sugar moiety attached to the catechol, the point of attachment of that sugar to the catechol and by stereochemical differences in the aglycone. Four aglycones have been reported: pseudopterosin A to F aglycone **1**,[1] pseudopterosin G to J aglycone **2**,[2,7] pseudopterosin K and L aglycone **3**,[2] and the unnatural diastereoisomer **4** (which until recently was thought to be pseudopterosin G to J aglycone).[2,7,8] In this *Letter* we report an approach to a further stereoisomer of pseudopterosin in which the hydrogen at C-4 and the methyl groups at C-3 and C-7 are axially disposed.[9] The key-step involves is an arene alkylation with a γ-methylene-γ-butyrolactone which proceeds with remarkable diastereoselectivity.

Our approach began with a Pechmann reaction between 3-methylcatechol **5** and ethyl acetoacetate to give coumarin **6**.[10] The phenol was then protected as its methyl ether **7** and the alkene and carbonyl moieties were reduced to give lactol **8**. Union with phosphonate **13** next provided γ-methylene-γ-butyrolactone **9** as a single geometric isomer, the phenol of which was protected as its methyl ether to provide our cyclisation precursor **10** (Scheme 1).

Pleasingly, when **10** was warmed with triflic acid to 79°C for 15 minutes, spirolactone **14** was furnished in 91% yield as a 9:1 mixture of diastereoisomers. Catalytic hydrogenation of the alkene next gave **15** with complete control at the newly created stereogenic centre (Fig. 1). With the stereocentres at C-3 and C-7 established correctly for the pseudopterosin A–F aglycone **1** we expected to complete that synthesis via hydrogenolysis of the benzyl ether: a reaction known to proceed with inversion of configuration under neutral conditions.[11] However, lactone **15** remained stubbornly intact even when exposed to a stoichiometric equivalent of palladium on carbon at 200 atmospheres hydrogen pressure! By contrast, reduction was readily accomplished when conducted in acidified methanol but furnished ester **17** as single diastereoisomer, rather than the anticipated C-4 epimer. Likewise, treatment of **14** under the aforementioned conditions also provided **17** in a near quantitative yield, again as a single diastereoisomer (Scheme 2). The relative stereochemistry was confirmed by cyclisation to hexahydrophenalene **18**, an X-ray crystal structure of which revealed that the C-4 hydrogen and the C-3 and C-7 methyl groups each adopt an axial orientation (Fig. 2).

The reduction of **14** and **15** was then examined in more detail in order to determine the sequence of events leading to **17**. Interestingly, when **15** was stirred in methanol containing a trace of dilute hydrochloric acid it was smoothly transformed into alkene **16** in near quantitative yield. Hydrogenation of **16** could then be effected at ambient temperature and pressure under neutral conditions giving **17** in 99% yield as a single diastereoisomer. These results suggest that steric encumbrance prevents direct hydrogenolysis of **15** and that the stereochemical course of the reaction is dictated by the axial C-7 methyl group.



Scheme 2. *Reagents and conditions*: (a) CF_3SO_3H, 79°C, 15 min, 91%; (b) H_2, Pd–C, EtOAc, rt, 3 h, 99%; (c) H_2, Pd–C, MeOH, cat. 2 M $HCl_{aq.}$, 16 h, rt, 94%; (d) H_2, Pd–C, MeOH, cat. 2 M $HCl_{aq.}$, 16 h, rt, 89%; (e) CF_3SO_3H, 85°C, 10 min, 90%.

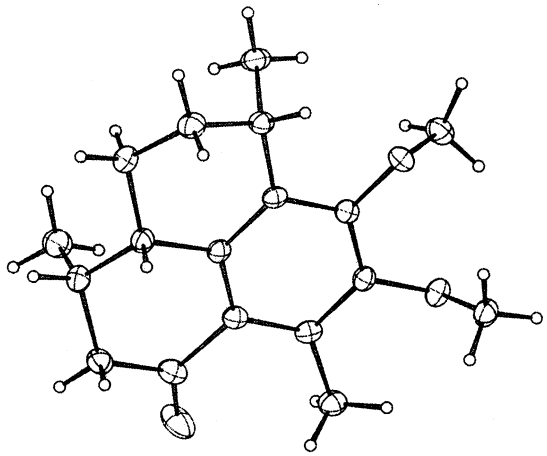


Figure 2. ORTEP diagram of **18**.

In conclusion, we have developed a short and practical route to the tricyclic core of an unnatural pseudopterosin diastereoisomer. Key features of our approach are an arene alkylation with a γ-methylene-γ-butyrolactone, viz. **10**→**14**, and an elaborate reduction sequence **14**→**17**; both processes proceeding with remarkable diastereoselectivity. We are presently seeking a method to effect the hydrogenolysis of **14** with inversion at the C-4 stereogenic centre as this would provide a route to the pseudopterosin A–F aglycone **1**.

Acknowledgements

The authors thank EPSRC for a Project Studentship and a Quota Studentship (to J.D.W. and M.J.T., respectively).

References

1. Look, S. A.; Fenical, W.; Matsumoto, G. K.; Clardy, J. *J. Org. Chem.* **1986**, *51*, 5140.
2. Roussis, V.; Wu, Z. D.; Fenical, W.; Strobel, S. A.; Van Duyne, G. D.; Clardy, J. *J. Org. Chem.* **1990**, *55*, 4916.
3. (a) Ettouati, W. S.; Jacobs, R. S. *Mol. Pharmacol.* **1987**, *31*, 500; (b) Fenical, W. *J. Nat. Prod.* **1987**, *50*, 1001; (c) Potts, B. C. M.; Faulkner, D. J.; Jacobs, R. S. *J. Nat. Prod.* **1992**, *55*, 1701; (d) Rodríguez, A. D. *Tetrahedron* **1995**, *51*, 4571; (e) Mayer, A. M. S.; Jacobson, P. B.; Fenical, W.; Jacobs, R. S.; Glaser, K. B. *Life Sci.* **1998**, *62*, 401.
4. Rouhi, A. M. *Chem. Eng. News* **1995**, *November 20*, 42.
5. (a) Kozikowski, A. P.; Wu, J. P. *Synlett* **1991**, 465; (b) Jung, M. S.; Siedem, C. S. *J. Am. Chem. Soc.* **1993**, *115*, 3822; (c) Harrowven, D. C.; Dennison, S. T.; Howes, P. *Tetrahedron Lett.* **1994**, *35*, 4243; (d) Schmalz, H. G.; Schwarz, A.; Dürner, G. *Tetrahedron Lett.* **1994**, *37*, 6861; (e) Schmalz, H. G.; Majdalani, A.; Geller, T.; Hollander, J.; Bats, J. W. *Tetrahedron Lett.* **1995**, *36*, 4777; (f) Eklund, L.; Sarvary, I.; Frejd, T. *J. Chem. Soc., Perkin Trans. 1* **1996**, 303; (g) Harrowven, D. C.; Sibley, G. E. M. *Tetrahedron Lett.* **1999**, *40*, 8299; (h) Benoit-Marquie, F.; Csaky, A. G.; Esteban, G.; Martinez, M. E.; Plumet, J. *Tetrahedron Lett.* **2000**, *41*, 3355.
6. (a) Broka, C. A.; Chan, S.; Peterson, B. *J. Org. Chem.* **1988**, *53*, 1584; (b) Corey, E. J.; Carpino, P. *J. Am. Chem. Soc.* **1989**, *111*, 5472; (c) Corey, E. J.; Carpino, P. *Tetrahedron Lett.* **1990**, *31*, 3857; (d) McCombie, S. W.; Cox, B.; Ganguly, A. K. *Tetrahedron Lett.* **1991**, *32*, 2087; (e) McCombie, S. W.; Ortiz, C.; Cox, B.; Ganguly, A. K. *Synlett* **1993**, 541; (f) Buszek, K. R.; Bixby, D. L. *Tetrahedron Lett.* **1995**, *36*, 9129; (g) Gill, S.; Kocienski, P.; Kohler, A.; Pontiroli, A.; Qun, L. *Chem. Commun.* **1996**, 1743; (h) Majdalani, A.; Schmalz, H. G. *Synlett* **1997**, 1303; (i) Corey, E. J.; Lazerwith, S. E. *J. Am. Chem. Soc.* **1998**, *120*, 12777.
7. Lazerwith, S. E.; Johnson, T. W.; Corey, E. J. *Org. Lett.* **2000**, *2*, 2389.
8. LeBrazidec, J. Y.; Kocienski, P. J.; Connolly, J. D.; Muir, K. W. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2475.
9. We have used pseudopterosin numbering to describe stereogenic centres.
10. Mills, F. D. *J. Heterocyclic Chem.* **1980**, *17*, 1597.
11. That hydrogenolysis of benzylic esters proceeds with inversion of configuration under neutral conditions is well established. See: (a) Nagaoka, H.; Shimano, M.; Yamada, Y. *Tetrahedron Lett.* **1989**, *30*, 971; (b) Khalaf, A. A.; Roberts, R. M. *J. Org. Chem.* **1973**, *38*, 1388; (c) Chakraborti, A. K.; Ray, J. K.; Kundu, K. K.; Chakrabarty, S.; Mukherjee, D.; Ghatak, U. R. *J. Chem. Soc., Perkin Trans. 1* **1984**, 261; (d) Baldwin, J. E.; Bamford, S. J.; Fryer, A. M.; Rudolph, M. P. W.; Wood, M. E. *Tetrahedron* **1997**, *53*, 5255.