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A Synthetic Approach to the Pseudopterosins Using Cascade Technology.

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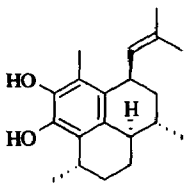
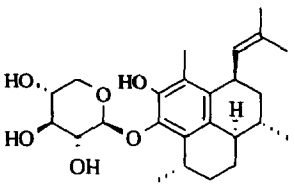
Abstract : A rapid synthetic entry towards the pseudopterosins, a class of diterpenes which display potent anti-inflammatory and analgesic properties, is described. The key feature of this approach is the use of a sequential intramolecular, Lewis acid mediated Friedel-Crafts alkylation - Friedel-Crafts acylation sequence, viz 14 to 15, to establish the tricyclic carbon framework.

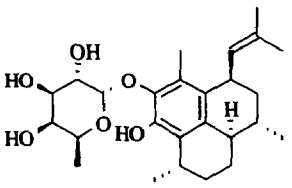
Few ailments are as painful as those involving inflammation. Common conditions such as arthritis, gout, psoriasis and many chemically induced oedemas, though not life threatening, are both debilitating and a cause of great discomfort. The search for therapeutic agents that provide an effective treatment for such disorders has been the focus of considerable attention; the commercial potential for such a remedy undoubtedly inspiring much of the current effort. One surprising, yet valuable source of new anti-inflammatory agents would appear to be marine organisms.[1] These have revealed a diverse array of structures including the manoalides, the scalaranes, the furodysins and the pseudopterosins, which have been shown to be potent inhibitors of PLA_2 activity. The pseudopterosins are of particular significance since they do not act as prostoglandin H_2 synthase inhibitors.[2]



1 pseudopterosin

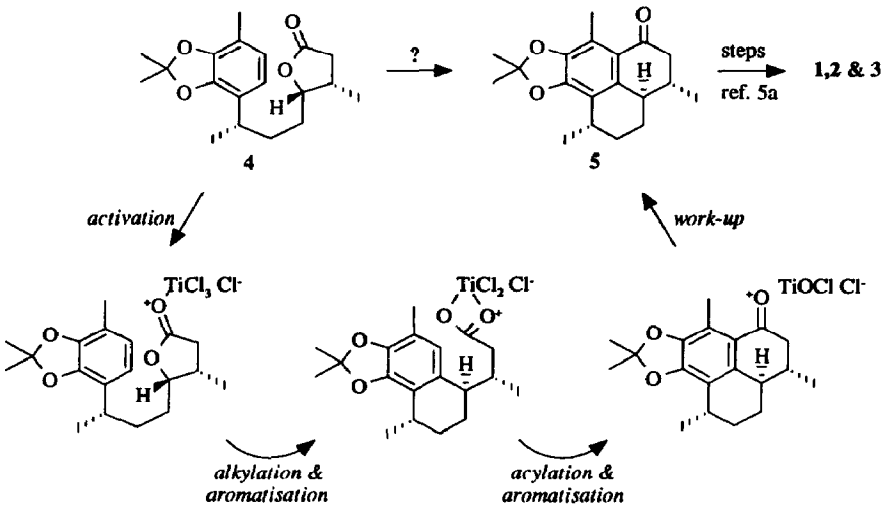


2 pseudopterosin A



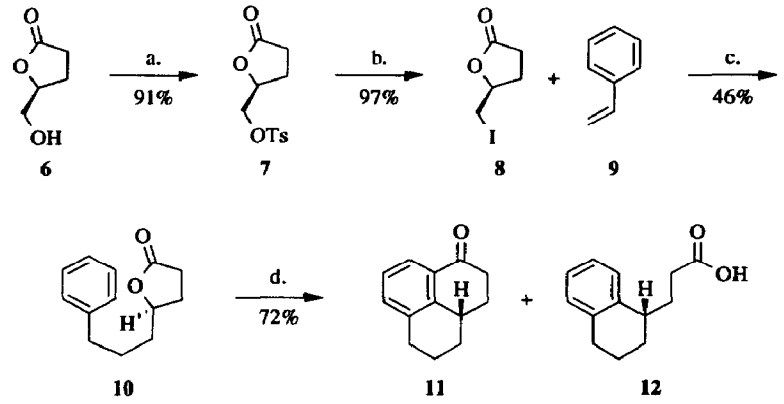
3 pseudopterosin E

Our interest in the development of useful cascade reaction sequences to accomplish the rapid elaboration of complex molecular architectures from simple substrates,[3] prompted us to explore a novel entry towards the pseudopterosins[4,5] based on a sequential Friedel-Crafts alkylation - Friedel-Crafts acylation protocol as shown in Scheme 1.[6] In this *letter* we wish to report some encouraging preliminary studies that appear to demonstrate both the validity and rapidity with which this tactic may be used to accomplish that aim.



Scheme 1

To that end, we first prepared the simple analogue **10** through union of the iodolactone **8** with styrene **9** under standard, tin mediated radical coupling conditions.[7,8] To our delight, exposure of the lactone **10** to aluminium trichloride produced an easily separable mixture of the desired tricyclic ketone **11** (8%) and the bicyclic acid **12** (64%) (Scheme 2).[9]

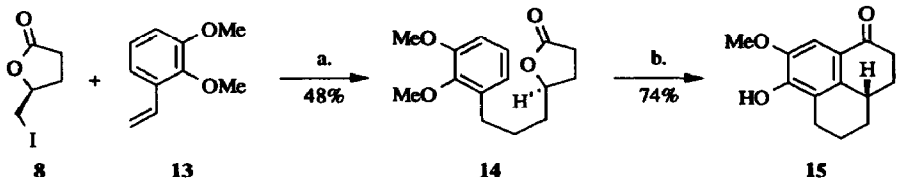


Reagents and Conditions:
a. TsCl, py, CH_2Cl_2, 16h, ref. 10. b. NaI, acetone, reflux, 6h, ref. 11.
c. Bu_3SnH, AIBN, 2.5eq. **9**, PhH, reflux, 6h.; aq. KF. d. 3eq. $AlCl_3$, CH_2Cl_2, C_6H_{14}, reflux, 16h.

Scheme 2

Rather than expend considerable effort towards the optimisation of this 'less than ideal' model system, we chose to examine the closer analogue **14**. Once again a tin mediated radical coupling was used to establish this material, through union of the iodide **8** with 2,3-dimethoxystyrene **13**.[8] On this occasion exposure of the

lactone **14** to titanium tetrachloride smoothly effected the sequential Friedel-Crafts alkylation - Friedel-Crafts acylation procedure and in addition unmasked the para-phenolic moiety (Scheme 3).



8 **13** **14** **15**

Reagents and Conditions:
a. Bu_3SnH, AIBN, 2.5eq. **13**, PhH, reflux, 3h.; aq. KF. b. 3.5eq. $TiCl_4$, CH_2Cl_2, reflux, 36h.

Scheme 3

The latter observation is of particular importance given the necessity to differentiate between the two phenolic groups when attaching the respective glycosidal residues. Moreover, when we examined the ketone **15** for optical activity we observed $[\alpha]_D^{16} = +1.0^O$ ($CHCl_3$, c = 1.02). This clearly indicates that the initial Friedel-Crafts alkylation proceeds, at least in part, with inversion of configuration about the lactone centre. Unfortunately, our efforts to determine the level of enantiomeric excess have thus far proved intractable. However, a failure to detect intermediates arising from the homolysis of the lactone prior to cyclisation and the report by Brauman *et al.* that the intermolecular variant of this process occurs with nearly 50% net inversion of configuration[12] are clearly encouraging.

We are presently investigating the extension of this tactic towards the pseudopterosins *via* the Corey intermediate **5**. It is hoped that this will not only provide the most rapid and concise entry to this valuable class of natural products, but in addition demonstrate further the synthetic potential of lactones to act as the electrophilic component in asymmetric and intramolecular Friedel-Crafts alkylation processes.

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References and Notes:

1. Potts, B.C.M.; Faulkner, D.J.; *J. Nat. Prod.*, **1992**, *55*, 1701.
2. **a.** Look, S.A.; Fenical, W.; Jacobs, R.S.; Clardy, J.; *Proc. Natl. Acad. Sci. USA.*, **1986**, *83*, 6238; **b.** Roussis, V.; Wu, Z.; Fenical, W.; Strobel, S.A.; van Duyne, G.D.; Clardy, J.; *J. Org. Chem.*, **1990**, *55*, 4916.
3. **a.** Harrowven, D.C.; *Tetrahedron*, **1993**, *49*, 9039; **b.** Harrowven, D.C.; *Tetrahedron Lett.*, **1993**, *34*, 5653; **c.** Harrowven, D.C.; *Tetrahedron Lett.*, **1992**, *33*, 2879; **d.** Harrowven, D.C.; Dennison, S.T.; *Tetrahedron Lett.*, **1993**, *34*, 3323; **e.** Harrowven, D.C.; *Tetrahedron Lett.*, **1991**, *32*, 3735.
4. The pseudopterosins were isolated from the sea coral *Pseudopterogorgia elisabethae* by **a.** Look, S.A.; Fenical, W.; Matsumoto, G.K.; *J. Org. Chem.*, **1986**, *51*, 5140; **b.** Harvis, C.A.; Burch, M.T.; Fenical, W.; *Tetrahedron Lett.*, **1988**, *29*, 4361; **c.** Look, S.A.; Fenical, W.; *Tetrahedron*, **1987**, *43*, 3363; and ref 2.
5. For previous syntheses see **a.** Broka, C.A.; Chan, S.; Peterson, B.; *J. Org. Chem.*, **1988**, *53*, 1586; **b.** Corey, E.J.; Carpino, P.; *J. Am. Chem. Soc.*, **1989**, *111*, 5472; **c.** Kozikowski, A.P.; Wu, J.-P.; *Synlett*,

1991, 465; **d.** S.W. McCombie, C. Ortiz, B. Cox and A.K. Ganguly; *Synlett*, **1993**, 541. Details of one further synthesis are due to be published shortly, Kocienski, P.J.; private communication.

6. The intermolecular variant of this reaction *e.g.* for the preparation of α-tetralone from benzene and γ-butyrolactone has been well studied: **a.** Truce, W.E.; Olson, C.E.; *J. Am. Chem. Soc.*, **1952**, *74*, 4721; **b.** Olson, C.E.; Bader, A.R.; *Org. Synth. Coll. Vol. IV*, **1963**, 898. However, extensions of this protocol to substituted aromatic systems often leads to indanones and other rearranged materials: **c.** Kerr, C.A.; Rae, I.D.; *Aust. J. Chem.*, **1978**, *31*, 341.
7. For an excellent overview of radical addition reactions see: Curran, D.P. Radical Addition Reactions. In *Comprehensive Organic Synthesis*, Trost, B.M. Ed.; Pergamon: Oxford, Vol. 4, 1991, pp 715.
8. We have found that using higher concentrations of styrenes **9** or **13** in these radical coupling reactions is deleterious due to the production of substantial quantities of polymeric material. When these styrenes **9** and **13** are used more sparingly however, production of (R)-γ-valerolactone predominates.
9. All new compounds gave satisfactory analytical and spectroscopic characteristics *e.g.* For **12**: FT-IR υ_{max} 3020m, 2930m, 2855m, 1710m, 1450w and 1215m cm^{-1}; UV λ_{max} (ε) ($CHCl_3$) 274 (330) and 247 (700) nm; ^1H NMR (250MHz, $CDCl_3$) δ_H 7.19 (4H, m, Ar*H*), 2.88 (1H, m, C*H*), 2.81 (2H, app. *br.* td, *J* = 6.2 & 5.5Hz, CH_2CO_2H), 2.50 (2H, m, $=CCH_2$), 2.13 (1H, m, $=CCH_2CHH$), 1.91 (3H, m, $=CCH_2CHH$, $=CCH_2CH_2CH_2CH$) and 1.69 (2H, m, $CH_2CH_2CO_2H$)) p.p.m.; ^{13}C NMR (61.3MHz, $CDCl_3$) δ_C 180.4 (s), 140.0 (s), 137.2 (s), 129.2 (d), 128.6 (d), 125.8 (d), 125.7 (d), 37.1 (d), 31.9 (t), 31.3 (t), 29.6 (t), 28.9 (t), 27.3 (t) and 19.7 (t) p.p.m.; m/z (EI) 204 ($[M]^+$, 2%), 186 ($[M-H_2O]^+$, 52), 144 (5), 131 (8), 117 ($[PhC_3H_5]^+$, 9), 105 ($[PhC_2H_5]^+$, 100), 91 ($[PhCH_3]^+$, 48), 85 ($[C_4H_5O_2]^+$, 12), 77 ($[C_6H_5]^+$, 7) and 65 (13) amu. For **14**: $[\alpha]_D^{16}$ = +18.9° ($CHCl_3$, c = 0.77); FT-IR υ_{max} 3020m, 2935w, 2845w, 1770m, 1585w, 1480m, 1450w, 1430w, 1275w, 1215s, 1179w, 1085w and 670m cm^{-1}; UV λ_{max} (ε) ($CHCl_3$) 275 (520) 271 (540) and 240 (510) nm; ^1H NMR (250MHz, $CDCl_3$) δ_H 7.00 (1H, dd, *J* = 8.1 & 7.7Hz, Ar*H*), 6.79 (1H, dd, *J* = 8.1 & 7.7Hz, Ar*H*), 6.76 (1H, dd, *J* = 7.7 & 1.5Hz, Ar*H*), 4.51 (1H, m, OC*H*), 3.87 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 2.69 (2H, app. t, *J* = 6.9Hz, $COCH_2$), 2.52 (2H, 4bands, $COCH_2$), 2.30 (1H, app. dq, *J* = 13.3 & 6.7Hz, $COCH_2CHH$) and 1.77 (5H, m) p.p.m.; ^{13}C NMR (61.3MHz, $CDCl_3$) δ_C 177.1 (s), 152.6 (s), 147.0 (s), 135.4 (s), 123.7 (d), 121.7 (d), 110.2 (d), 80.8 (d), 60.5 (q), 55.5 (q), 35.0 (t), 29.2 (t), 28.7 (t), 27.8 (t) and 26.2 (t) p.p.m.; m/z (EI) 264 ($[M]^+$, 73%), 236 (2), 191 (14), 164 ($[(MeO)_2ArCHCH_2]^+$, 97), 151 ($[(MeO)_2ArCH_2]^+$, 44), 149 (41), 136 ($[C_8H_8O_2]^+$, 7), 121 ($[C_7H_5O_2]^+$, 7), 105 (12), 91 (49), 85 (14), 77 ($[C_6H_5]^+$, 21) and 65 (19) amu. For **15**: $[\alpha]_D^{16}$ = +1.0° ($CHCl_3$, c = 1.02); FT-IR υ_{max} 3385*br.*m, 2925s, 2855m, 1655s, 1600m, 1580s, 1480s, 1460s, 1375m, 1340m, 1305s, 1180m, 1110m, 1075m, 860m and 810m cm^{-1}; UV λ_{max} (ε) ($CHCl_3$) 312 (14,200), 281 (27,000) and 240 (15,700) nm; ^1H NMR (250MHz, $CDCl_3$) δ_H 7.47 (1H, s, Ar*H*), 6.19 (1H, s, O*H*), 3.93 (3H, s, OCH_3), 2.93 (1H, *br*dd, *J* = 17.5 & 6.0Hz, $CHHCH_2CH_2CH$), 2.77 (1H, obscured, CH_2CHCH_2), 2.75 (1H, ddd, *J* = 17.6, 4.4 & 2.5Hz, $OCCHH$), 2.57 (1H, obscured, $CHHCH_2CH_2CH$), 2.18-1.95 (3H, m, CH_2CHHCH_2, $CHCHHCH_2CH_2$ & $CHHCH_2CO$) and 1.34 (1H, m, $CHCHHCH_2CH_2$) p.p.m.; ^{13}C NMR (61.3MHz, $CDCl_3$) δ_C 197.8 (s), 148.2 (s), 144.7 (s), 139.6 (s), 124.3 (s), 122.1 (s), 106.4 (d), 56.1 (q), 36.0 (t), 36.5 (d), 31.3 (t), 30.2 (t), 22.9 (t) and 22.0 (t) p.p.m.; m/z (EI) 232 ($[M]^+$, 100%), 217 ($[M-Me]^+$, 2), 215 ($[M-OH]^+$, 18), 204 ($[M-C_2H_4]^+$, 47), 190 ($[M-C_3H_6]^+$, 37), 173 ($[M-C_3H_4O]^+$, 42), 161 ($[M-C_3H_4O-Me]^+$, 25), 115 (28), 91 (15) and 77 (23) amu.
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