Pergamon

Tetrahedron Letters 40 (1999) 8271–8272

TETRAHEDRON LETTERS

A Diastereoselective Radical to Polar Crossover Sequence For The Synthesis of The Isolaurinterols and Aplysins

David C. Harrowven,* Matthew C. Lucas and Peter D. Howes†

Department of Chemistry, The University, Southampton, S017 1BJ.

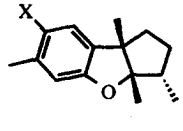
†Enzyme Medicinal Chemistry 2, GlaxoWellcome Medicines Research Centre, Gunnels Wood Road, Stevenage, Herts, SG1 2NY.

Received 5 August 1999; accepted 10 September 1999

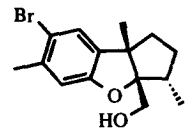
Abstract: Total syntheses of aplysin **1**, debromoaplysin **2**, aplysinol **3**, debromoaplysinol **4**, isoaplysin **5**, isolaurinterol **6** and debromoisolaurinterol **7** are described. Key features are a diastereoselective radical to polar crossover sequence to transform diene **8** into debromoisolaurinterol **7** and a series of biomimetic cyclisation and oxidation reactions.

Keywords: Terpenes and terpenoids; Natural products; Radicals and radical reactions; Cyclisations; Oxygen Heterocycles.

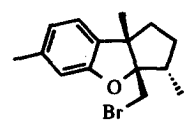
The aplysins (**1** to **5**) and isolaurinterols (**6** and **7**) are naturally occurring sesquiterpenes found widely in *Aplysia* sea hares and *Laurencia* sea alga.[1,2] First discovered during a programme to identify natural anti-tumour agents from marine organisms, their unusual architecture soon attracted the attention of synthetic chemists. Thus, while marine scientists were able to show that the aplysins act as both antifeedants and antioxidants in Nature,[2,3] synthetic chemists devised several interesting routes to these compounds.[4]



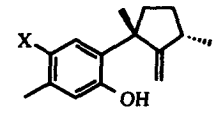
1 X = Br, aplysin
2 X = H, debromoaplysin



3 X = Br, aplysinol
4 X = H, debromoaplysinol

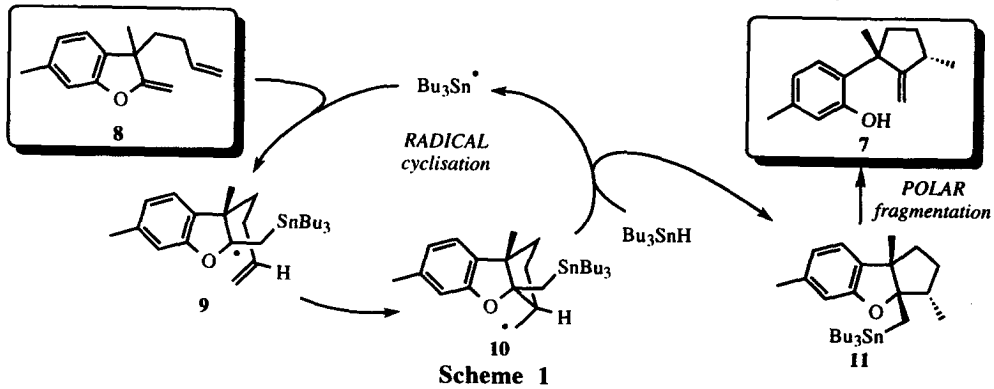


5 isoaplysin



6 X = Br, isolaurinterol
7 X = H, debromoisolaurinterol

The co-occurrence of these families in all natural sources led us to surmise that **7** was the biological precursor of all the aplysins. Mindful of this, we decided to target debromoisolaurinterol **7** using the radical to polar crossover sequence outlined in Scheme 1 and then explore its conversion into **1** - **6** using biomimetic cyclisation and oxidation reactions.[1-3] In this *Letter* we describe our realisation of those objectives.

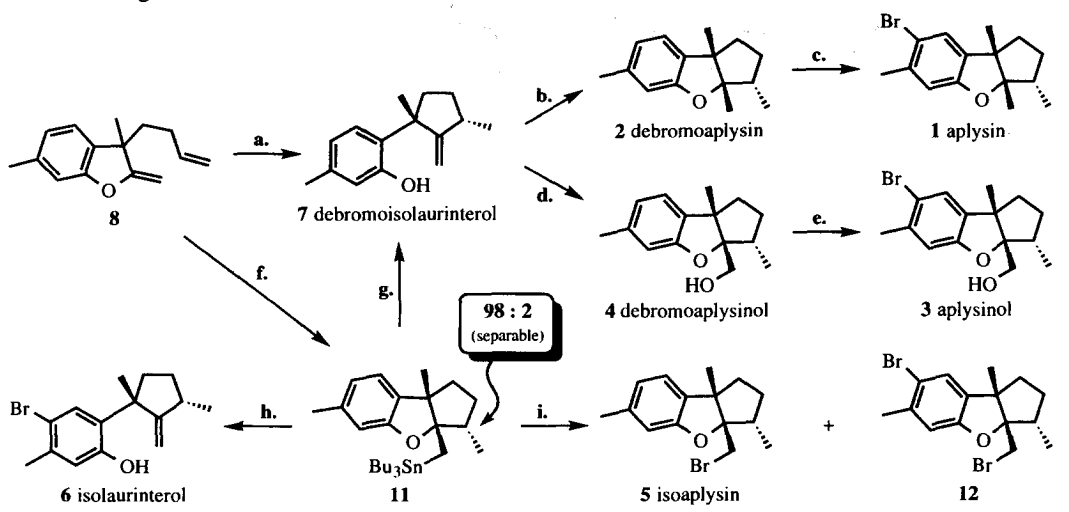


Scheme 1

A synthesis of debromoisolaurinterol **7** was first accomplished through exposure of diene **8**[4] to tributylstannyl radicals formed under standard conditions using thermolysis to initiate the breakdown of AIBN. This provided **7** as a 5 : 1 mixture of diastereoisomers in 79% yield. Though reasonable, diastereoselectivity

0040-4039/99/$ - see front matter
PII: S0040-4039(99)01739-6

was improved dramatically by conducting reactions at 15°C using light to induce cleavage of the initiator. Under these conditions the tricyclic stannane **11** was provided as a 98 : 2 mixture of diastereoisomers in 69% yield. Refluxing a toluene solution of **11** for 24 hours then gave debromoisolaurinterol **7** (Scheme 2).



Reagents and Conditions: **a.** Bu_3SnH, AIBN, PhMe, reflux, 18h, 79%; **b.** H^+, $CDCl_3$, RT, 16h, 100%; **c.** Br_2, $KHCO_3$, CH_2Cl_2, 0°C, 30 min, 82%; **d.** MCPBA, CH_2Cl_2, 0°C, 24 h, 52% (+ **7**, 10%); **e.** Br_2, $NaHCO_3$, $CHCl_3$, 0°C, 1h, 51% (+ **4**, 24%); **f.** Bu_3SnH, AIBN, C_6H_{14}, hv, 15°C, 20h, 69%; **g.** PhMe, reflux, 24h, 80% (+ **11**, 10%); **h.** NBS, $CHCl_3$, reflux, 72h, 50%; **i.** Br_2, $NaHCO_3$, $CHCl_3$, 0°C, 1h giving **5**, 51% & **12**, 39%.

Scheme 2

Acid catalysed cyclisation of **7** to debromoaplysin **2** was extremely facile. Indeed, when a $CDCl_3$ solution of this compound was allowed to stand for 16 hours prior to NMR analysis a quantitative conversion to debromoaplysin **2** was observed ($CDCl_3$ stored over anhydrous potassium carbonate failed to induce cyclisation). Bromination of **2** then provided aplysin **1** in 82% yield. Epoxidation of **7** with MCPBA likewise induced spontaneous cyclisation to give debromoaplysinol **4** in 52% yield together with traces of recovered starting material (10%) and an oxirane intermediate (12%). Bromination of **4** then gave aplysinol **3**. Attempts to effect conversion of debromoisolaurinterol **7** into isoaplysin **5** and isolaurinterol **6** through halogenation were less rewarding, affording complex mixtures containing these materials, recovered **7** and dibromide **12**. However, exposing a cooled solution of stannane **11** to bromine gave isoaplysin **5** in an acceptable 51% yield while simply refluxing a chloroform solution of **11** with NBS gave isolaurinterol **6** (Scheme 2).

Thus, we have completed total syntheses of all the known aplysin and isolaurinterol natural products and provided evidence that each is derived in Nature from **7**. Additionally, we have developed a new method for effecting a vinyl group transfer from oxygen to carbon that is highly diastereoselective and a halide free radical cyclisation mediated by tributyltin hydride.

References and Notes

1 **a.** Yamamura, S.; Hirata, Y. *Tetrahedron*, **1963**, *19*, 1485; **b.** Irie, T.; Suzuki, M.; Kurosawa, E.; Masamune, T. *Tetrahedron*, **1970**, *26*, 3271; **c.** Ohta, K.; Takagi, M. *Phytochemistry*, **1977**, *16*, 1062; **d.** Suzuki, M.; Kurosawa, E. *Tetrahedron Lett.*, **1978**, 2503; **e.** Selover, S.J.; Crews, P. *J. Org. Chem.*, **1980**, *45*, 69; **f.** Ojika, M.; Shizuri, Y.; Yamada, K. *Phytochemistry*, **1982**, *21*, 2410; **g.** Shizuri, Y.; Yamada, A.; Yamada, K. *Phytochemistry*, **1984**, *23*, 2672; **h.** Blunt, J.W.; Lake, R.J.; Munro, M.H.G. *Phytochemistry*, **1984**, *23*, 1951; **i.** Suzuki, M.; Kurosawa, E. *Phytochemistry*, **1985**, *24*, 1999; **j.** Crews, P.; Selover, S.J. *Phytochemistry*, **1986**, *25*, 1847.

2 **a.** Stallard, M.O.; Faulkner, D.J. *Comp. Biochem. Physiol.*, **1974**, *49B*, 37; **b.** Fenical, W.; Sleeper, H.L.; Paul, V.J.; Stallard, M.O.; Sun, H.H. *Pure Appl. Chem.*, **1979**, *51*, 1865.

3 Biswas, S.; Ghosh, A.; Venkateswaran, R.V. *J. Org. Chem.*, **1990**, *55*, 3498.

4 Harrowven, D.C.; Lucas, M.C.; Howes, P.D. *Tetrahedron Lett.*, **1999**, *40*, 4443 and references cited therein.