Pergamon

Bioorganic & Medicinal Chemistry Letters 8 (1998) 1635–1638

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Synthesis and Biological Activity of Lactones *en route* to Altohyrtin A

Stephen A. Hermitage*, Alison Murphy and Stanley M. Roberts[†]

Department of Chemistry, Robert Robinson Laboratories, University of Liverpool, Liverpool, England, L69 7ZD.

Received 19 March 1998; accepted 20 May 1998

Abstract: Lactones **2** and **7** were synthesised and tested against six human tumour cell lines (*Pancreas-a*, BXPC-3), (*Thyroid ca*, KAT-4), (*Thyroid ca*, SW1736), (*Lung*-NSC, NCI-H460), (*Pharynx*-sq, FADU) and (*Prostate*, DU-145). Lactone **7** proved inactive, but lactone **2** displayed some activity against four of the six cell lines examined. Both lactones were converted into an intermediate **5** *en route* to Altohyrtin A. © 1998 Elsevier Science Ltd. All rights reserved.

We have previously reported[1] some of our synthetic approaches to the cytotoxic marine macrolide Altohyrtin A[2,3] (Figure 1). Herein we report the elaboration of ene-ester **1**[1] and diol **6**[1] to the lactone aldehyde **5**, confirming the stereochemical integrity of our synthetic route and providing key building blocks for the C-37 to C-43 perimeter in our synthesis. The lactones **2** and **7** were evaluated for their biological activity against six human tumour cell lines.[4]

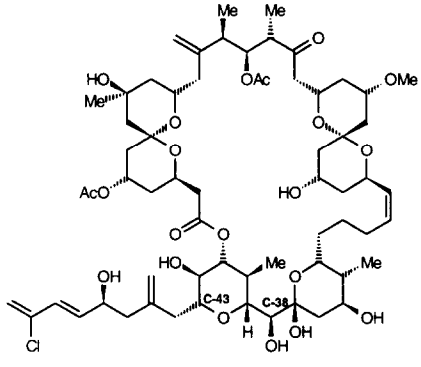
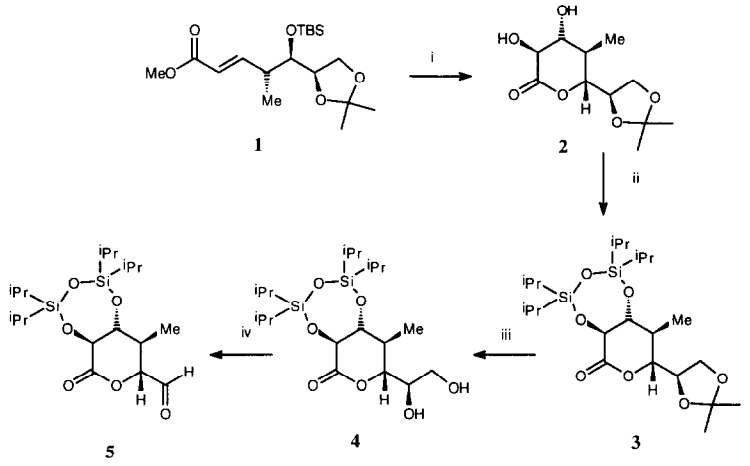


Figure 1

[†] *e-mail:* sj11@liv.ac.uk, *fax:* 0151 7943587

PII: S0960-894X(98)00268-6

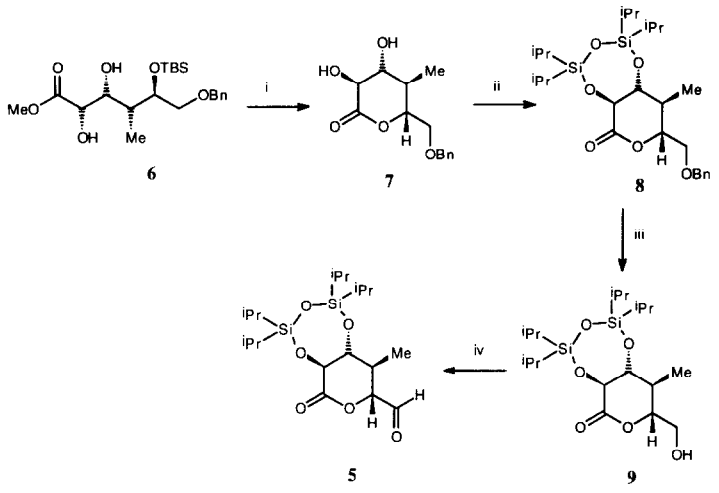
Ene ester **1** was subjected to a Sharpless type *bis*-hydroxylation using a 'Super AD-mix β' formulation[1] and the intermediate diol was purified by flash column chromatography prior to desilylation. Under the TBAF deprotection conditions spontaneous cyclisation furnished the lactone diol **2** in a 50% overall yield from the ene-ester **1**. It was necessary to leave the diol unprotected for successful cyclisation, since treatment of the *bis*-acetonide or *bis*-MOM derivative of **2** with TBAF in THF led to decomposition.



Reagents and Conditions : i)a) Super AD-mix β formulation, $MeSO_2NH_2$, $^tBuOH/H_2O$ (1:1), b)TBAF, THF, (50% over 2 steps); ii) $(^iPr_2SiCl)_2O$, DMF, imidazole, (100%); iii)TFA/$CHCl_3$ (1:8); iv) $NaIO_4$, H_2O/THF (1:20), (73% over 2 steps).

Scheme 1

Elaboration of the lactone diol **2** to the bridged silyloxy compound **3** was achieved in quantitative yield by treatment with $(^iPr_2SiCl)_2O$ and imidazole in DMF. Chemoselective removal of the isopropylidene group of **3** was achieved by brief treatment with TFA in $CHCl_3$.[5] Oxidative cleavage of the diol **4** using $NaIO_4$ in aqueous THF gave the lactone aldehyde **5** in a respectable yield of 73% over the two steps. An alternative strategy for the synthesis of the lactone aldehyde **5** is described in Scheme 2.



Reagents and Conditions : i)TBAF, THF, (65%); ii) $(^{i}Pr_2SiCl)_2O$, DMF, Im, (76%); iii)H_2, Pd/C, EtOAc, (19%); iv) Swern Oxidation (70%).

Scheme 2

The known diol **6**[1] was treated with TBAF in THF to generate the triol which spontaneously lactonised under the reaction conditions to give the lactone diol **7**. This diol **7** was protected as the bridged siloxy adduct **8**. Debenzylation furnished the primary alcohol **9** in a disappointing yield. The alcohol **9** was oxidised using the Swern protocol[6] to give the lactone aldehyde **5**.[7] The two lactone diol intermediates **2** and **7** were tested for biological activity against six human tumour cell lines.[4] In each case, the GI_{50}, TGI and LC_{50} were measured. A value of <10 μg / ml is considered to be active.

Cell Type	Cell Line	GI_{50}/(μg/ml)	TGI/(μg/ml)	LC_{50}/(μg/ml)
Pancreas-a	BXPC-3	>10	>10	>10
Thyroid ca	KAT-4	>10	>10	>10
Thyroid ca	SW1736	8.5	>10	>10
Lung-NSC	NCI-H460	2.9	>10	>10
Pharynx-sq	FADU	3.7	>10	>10
Prostate	DU-145	2.7	>10	>10

Table - Biological data for lactone **2**

Compound **7** showed no biological activity, whereas compound **2** displayed a marginal activity against thyroid, lung, pharynx and prostate cancer cell lines (Table). Although the Altohyrtin family of compounds typically show values in the 10^{-5} μg / ml range the noteworthy activity of compound **7** may provide a lead into the development of simpler, more accessible, analogues of Altohyrtin that are amenable to commercial development.

Acknowledgements

We thank Chiroscience and the BBSRC for funding (SAH and AM) and Professor G.R. Pettit for the biological results.

References

1. Hermitage, S.A., Nielson, P., Murphy, A., Roberts, S.M., *Tetrahedron*, in press.
2. Kobayashi, M., Aoki, S., Kitagawa, I., *Tetrahedron Lett.*, 1994, 35, 1243.
3. Pettit, G.R., Cichacz, Z.A., Herald, C.L., Gao, F., Boyd, M.R., Schmidt, J.N., Hamel, E., Bai, R., *J. Chem. Soc., Chem. Comm.*, 1994, 1605.
4. We thank Professor G.R. Pettit for communication of these results from his laboratory at the Arizona State University.
5. Bruzik, K.S., Tsai, M-D., *J. Am. Chem. Soc.*, 1992, 114, 6361.
6. Swern, D., Omura, K., *Tetrahedron*, 1978, 34, 1651.
7. Physical characteristics of compound **5** - R_f (EtOAc) 0.67; (Found: M^++H, 417.21353. $C_{19}H_{37}O_6Si_2$ requires *M+H*, 417.21287); $[\alpha]_D^{22}$ +4.7 (*c* 2.33, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3020, 2948 and 2869 (sp^3 CH_3), 1746s (C=O); δ_H (300 MHz; $CDCl_3$) 0.96-1.13 (28H, m, 4 x ^{i}Pr), 1.20 (3H, d, *J*=6.6Hz, MeCH), 2.07-2.18 (1H, m, MeCH), 3.80 (1H, dd, *J*=9.0Hz and 9.6Hz, O=CCH(O)CH(O)), 4.19 (1H, d, *J*=8.7Hz, O=CCH(O)), 4.23 (1H, dd, *J*=2.1Hz and 10.5Hz, MeCH(O)CHCHO), 9.60 (1H, d, *J*=2.1Hz, CHO); δ_C (75 MHz; $CDCl_3$) 11.22, 11.56, 11.91, 12.09 and 13.19 (CH of 4 x ^{i}Pr and MeCH), 16.08, 16.17, 16.23 and 16.33 (CH_3 of ^{i}Pr), 35.43 (MeCH), 75.50 and 76.36 (2 x CH(OSi)), 82.65 (CH(O)CHO), 167.19 (lactone C=O), 194.89 (aldehyde C=O); *m/z* (CI) 434 (M^++NH_4, 100%), 417 (M^++H, 15%).