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Synthetic studies on the salicylihalamides: macrolactone formation via ring closing metathesis versus macrolactonization

John T. Feutrill,[a] Georgina A. Holloway,[a] Ferdows Hilli,[a] Helmut M. Hügel[b] and Mark A. Rizzacasa[a,*]

[a]*School of Chemistry, The University of Melbourne, Parkville, Victoria 3010, Australia*
[b]*Department of Applied Chemistry, RMIT University, Plenty Road, Bundoora, Victoria 3083, Australia*

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Abstract

Two routes to the unusual 12-membered unsaturated benzolactone of the highly cytotoxic marine metabolites the salicylihalamides are presented. The first involves an RCM step to construct the C9–C10 alkene bond and this provided the model macrolactones **9** and **10** in a ratio of 77:23, respectively. An alternative route involved a Stille coupling to construct the C8–C9 bond followed by a macrolactonization to give the lactones **9** and **10** in a ratio of 96:4. © 2000 Elsevier Science Ltd. All rights reserved.

Marine organisms are a source of a large number of secondary metabolites that have a range of biological activities.[1] Marine sponges in particular, supply compounds with highly varied molecular architecture and pharmacological properties.[2] Recently, a pair of compounds named salicylihalamides A (**1**) and B (**2**) (Fig. 1) were isolated from a sponge of the genus *Haliclona* collected from waters around Rottnest island off the coast of Western Australia.[3] These compounds were identified as novel highly cytotoxic macrolides which possess a new 12-mem-

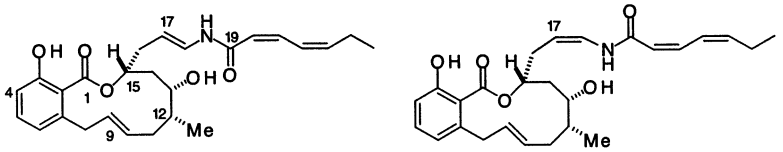

Figure 1.

* Corresponding author.

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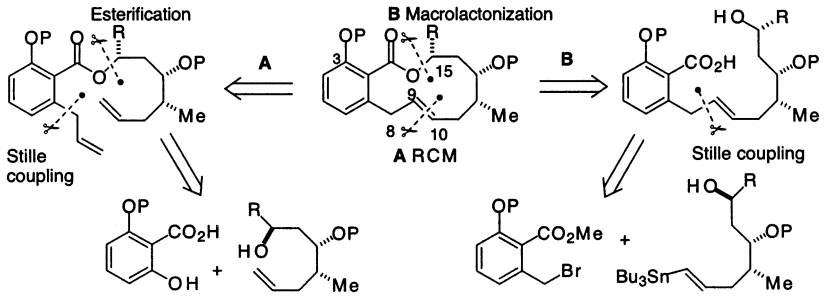
bered unsaturated benzolactone ring system as well as an unusual enamide sidechain[4] and differ only in the geometry about the C17–C18 enamide double bond. Testing of salicylihalamide A (**1**) in the USA National Cancer Institute (NCI) 60-cell line human tumor screen gave a pattern of differential toxicity which did not correlate with the profiles of any known antitumor compounds in the NCI standard database.[3] These results suggest that compound **1** has a novel mechanism of action and would make an interesting synthetic target for the potential development of a new class of antitumor compound.

As part of a program directed towards the synthesis of Australian marine sponge metabolites[5] we have targeted the salicylihalamides and decided to compare two different approaches to the novel 12-membered unsaturated lactone system (Scheme 1). The first (path **A**) involves the construction of the macrolactone by formation of the C9–C10 alkene bond via ring-closing-metathesis (RCM).[6,7] The RCM approach to macrolactones has been extensively developed by Fürstner who has reported that a properly positioned coordinating group such as an ester is needed for effective ring closure to occur.[8] This protocol was recently applied in the total synthesis of the macrolide (+)-lasiodiplodin in which the key step involved RCM to form an intermediate which represented a truncated salicylihalamide.[9]

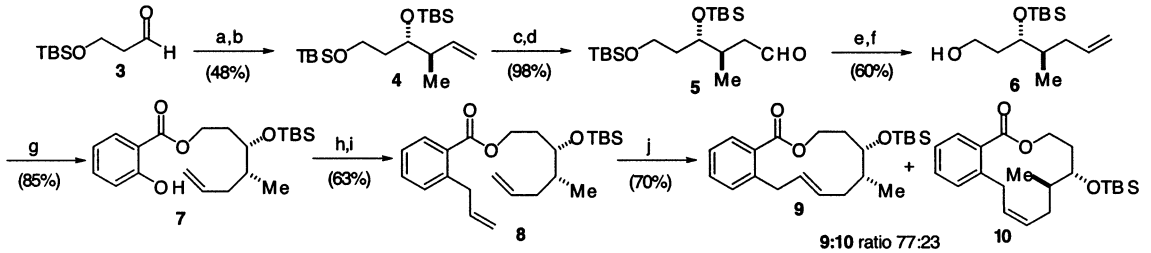


Scheme 1.

One possible problem with the RCM methodology is that the stereoselectivity is often low and difficult to predict.[6] We therefore elected to also examine an alternative route (path **B**) which involves an intermolecular palladium-catalyzed Stille coupling[10] between a vinyl stannane and benzylic bromide[11] to form the C8–C9 sigma bond followed by macrolactonization to provide the salicylihalamide ring system (Scheme 1). This route may provide the lactone with greater stereocontrol in a more convergent fashion.

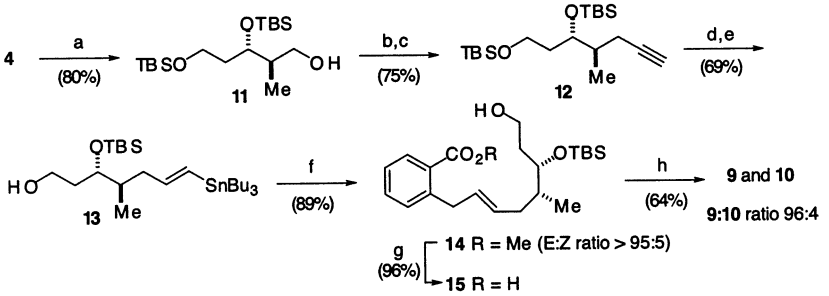
Our comparison study of the two approaches began with the synthesis of a model system which does not possess the substituents at C3 and C15 (Scheme 2). Asymmetric crotylmetallation[12] of aldehyde **3** and subsequent silylation of the adduct[13] provided the known alkene **4**[14] in good yield. Hydroboration with 9-BBN followed by oxidation gave aldehyde **5**, which upon one carbon Wittig extension and monodesilylation with HF·pyridine in THF buffered with pyridine[15] gave the alcohol **6**.[16] The methodology developed by Füstner[8,9] was then utilized to provide the RCM precursor **8**. Thus, esterification of salicylic acid with alcohol **6** under Mitsunobu conditions[17] gave ester **7** which was transformed into the corresponding triflate. Stille coupling of the triflate with allyltributylstannane mediated by $Pd_2(dba)_3$ in the presence of TFP[18] gave the RCM substrate **8** in fair yield. Treatment of diene with Grubbs catalyst in boiling CH_2Cl_2 then gave the two macrocycles **9**[19] and **10** in a ratio of 77:23, respectively, which were separated by preparative HPLC (normal phase, 2.5% EtOAc/petrol

eluent). The stereochemistry of the major unsaturated macrolactone **9** was determined to be *E* by homonuclear decoupling experiments ($J_{H9-H10} = 15.0$ Hz).



Scheme 2. Reagents and conditions: (a) (+)-Ipc_2B-(*E*)-crotyl then $H_2O_2/NaHCO_3$, 2 h; (b) TBSCl, imidazole, DMF, 16 h; (c) 9-BBN then $H_2O_2/NaHCO_3$, rt, 1 h; (d) Dess–Martin reagent, CH_2Cl_2, rt, 1 h; (e) $Ph_3P{=}CH_2$, THF, 16 h (71%); (f) HF·pyridine/pyridine, THF, rt, 3 h; (g) salicylic acid, DEAD, Ph_3P, Et_2O, rt, 16 h; (h) Tf_2O, pyridine, CH_2Cl_2, 1.5 h; (i) allyltributylstannane, $Pd_2(dba)_3$, TFP, LiCl, NMP, 36 h; (j) $RuCl_2(=CHPh)(PCy_3)_2$, CH_2Cl_2, reflux, 16 h

The Stille coupling macrolactonization approach to the macrolactone **9** is shown in Scheme 3. Alkene **4**, utilized in the RCM study, was treated with ozone and $NaBH_4$ to yield the alcohol **11**,[20] which on tosylation and acetylide anion displacement afforded alkyne **12**. Selective deprotection of the primary TBS group and subsequent radical hydrostannylation proceeded smoothly to give the stannane **13** in good yield. The Stille coupling[11] between stannane **13** and methyl 2-bromomethylbenzoate was best effected under conditions reported by Farina[18] to give the *E* alkene **14** (*E*:*Z* selectivity>95:5) in excellent yield. The use of other catalysts such as $Pd(MeCN)_2Cl_2$ or $Pd(Ph_3P)_4$ resulted in poorer *E*:*Z* ratios and yields. Hydrolysis of the methyl ester **14** then gave the *seco* acid **15** which underwent lactonization using the Mitsunobu protocol[17] to provide macrolactones **9** and **10** in 64% yield in a 96:4 ratio. Some dimer[21] was formed in competition with the desired macrolactone and dilution experiments did not improve the yield. An attempt at macrolactonization using the Yamaguchi protocol failed.[22]



Scheme 3. Reagents and conditions: (a) O_3, CH_2Cl_2MeOH, −78°C, $NaBH_4$, 20 min; (b) TsCl, pyridine, DMAP, CH_2Cl_2, rt, 16 h; (b) HC≡CLi·EDA, DMSO, rt, 18 h; (d) HF·pyridine, pyridine, THF, rt, 3 h; (e) Bu_3SnH, AIBN, benzene reflux, 2 h; (f) methyl 2-bromomethylbenzoate, $Pd_2(dba)_3$, TFP, NMP, rt, 24 h; (g) LiOH, $THF/H_2O/MeOH$, rt, 16 h; (h) Ph_3P, DEAD, benzene 0.04 M, rt, 16 h

In conclusion, the unusual 12-membered benzolactone ring system of the salicylihalamides has been synthesized by two different routes. The stereoselectivity for Stille macrolactonization

approach was far higher than that for the RCM route. In addition, a higher overall yield of pure **9** from the common intermediate **4** was obtained for the macrolactonization route versus the metathesis sequence (both eight steps, 21% versus 17%). Work towards the introduction of the interesting C15 alkenamide sidechain is underway and will be reported in due course.

Acknowledgements

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References

1. Faulkner, D. J. *Nat. Prod. Rep.* **2000**, *17*, 1–6.
2. Faulkner, D. J. *Nat. Prod. Rep.* **2000**, *17*, 7–55. Faulkner, D. J. *Nat. Prod. Rep.* **1999**, *16*, 155–198.
3. Erickson, K. L.; Beutler, J. A.; Cardellina, I. J. H.; Boyd, M. R. *J. Org. Chem.* **1997**, *62*, 8188–8192.
4. For an elegant synthesis of the alkenamide sidechain of salicylihalamide A see: Snider, B. B.; Song, F. *Org. Lett.* **2000**, *2*, 407–408.
5. Czuba, I. R.; Rizzacasa, M. A. *J. Chem. Soc., Chem. Commun.* **1999**, 1419–1420.
6. Grubbs, R. H.; Miller, S.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446–452.
7. Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2037–2056.
8. Fürstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 3942–3943.
9. Fürstner, A.; Kindler, N. *Tetrahedron Lett.* **1996**, *37*, 7005–7008. Fürstner, A.; Seidel, G.; Kindler, N. *Tetrahedron* **1999**, *55*, 8125–8230.
10. (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508–524. (b) Farina, V.; Krishnamurthy, V.; Scott, W. J. In *Organic Reactions*; Paquette, L. A., Ed.; J. Wiley and Sons: New York, 1997; Vol. 50, pp. 1.
11. Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4992–4998.
12. Brown, H. C.; Blat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 293–294.
13. Nicolaou, K. C.; Piscopio, A. D.; Bertinato, P.; Chakraborty, T. K.; Minowa, N.; Koide, K. *Chem. Eur. J.* **1995**, *1*, 318–333.
14. White, J. D.; Hong, J.; Robarge, L. A. *J. Org. Chem.* **1999**, *64*, 6206–6216.
15. Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 9434–9453.
16. New compounds were characterized by ^{1}H and ^{13}C NMR, IR and $[\alpha]_D$.
17. Mitsunobu, O. *Synthesis* **1981**, 1–28.
18. Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585–9595.
19. Data for macrolactone **9**: $[\alpha]$ −17.6 (*c* 0.6, $CHCl_3$): R_f 0.63 (5% EtOAc/petrol); IR (film) ν_{max} 1729, 1463, 1380, 1268, 1129, 1102, 1077, 1053 cm^{-1}; ^{1}H NMR δ −0.01 (s, 3H), 0.06 (s, 3H), 0.88 (s, 9H), 0.89 (d, J=6.6 Hz, 3H), 1.24–1.43 (m, 1H), 1.75–1.96 (m, 2H), 2.04–2.26 (m, 2H), 3.35 (dd, J=3.3, 16.0 Hz, 1H), 3.78 (dd, J=6.6, 16.0 Hz), 3.86 (ddd, J=2.1, 2.2, 9.3 Hz, 1H), 4.21 (ddd, J=1.5, 11.1, 11.1 Hz, 1H), 4.57 (ddd, J=3.3, 3.3, 11.1 Hz, 1H), 5.31 (m, 1H), 5.43 (ddd, J=3.3, 6.6, 15.0 Hz, 1H), 7.18–7.24 (m, 2H), 7.34 (ddd, J=1.5, 7.5, 7.8 Hz), 7.43 (dd, J=1.5, 7.8 Hz); ^{13}C NMR δ −4.64, −4.60, 14.1, 18.0, 25.8, 30.8, 36.6, 37.4, 37.9, 62.9, 71.1, 126.1, 127.8, 129.5, 130.27, 130.32, 131.5, 133.7, 139.8, 169.8. HRMS (ESI) calcd for $C_{22}H_{34}NaO_3Si$ [M+Na^+]: 397.2175. Found: 397.2188.
20. Ali, S. M.; Georg, G. I. *Tetrahedron Lett.* **1997**, *38*, 1703–1706.
21. Seebach, D.; Searing, B.; Kalinowski, H.; Lubosch, W.; Renger, B. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 264–265. Gerlach, H.; Oertle, K.; Thalmann, A. *Helv. Chim. Acta* **1977**, *60*, 860–865.
22. Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.