ChemComm

Short and efficient chiral pool and RCM approach towards the synthesis of the macrocyclic core of the salicylihalamides

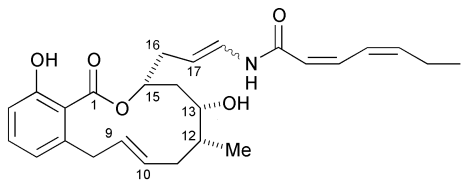
Gunda I. Georg,* Yu Mi Ahn, Burchelle Blackman, Faryar Farokhi, Patrick T. Flaherty, Craig J. Mossman, Subho Roy and KyoungLang Yang

Department of Medicinal Chemistry, Center for Cancer Experimental Therapeutics, and Drug Discovery Program, Higuchi Biosciences Center, University of Kansas, Lawrence, KS 66045, USA. E-mail: georg@ku.edu

Received (in Corvallis, OR, USA) 1st November 2000, Accepted 20th December 2000
First published as an Advance Article on the web 23rd January 2001

The macrolactone core structure of the salicylihalamides was prepared from diacetone-D-glucose and *via* a ring-closing metathesis reaction.

Salicylihalamides A and B (**1** and **2**) are naturally occurring



1 Salicylihalamide A (*E*)-enamide
2 Salicylihalamide B (*Z*)-enamide

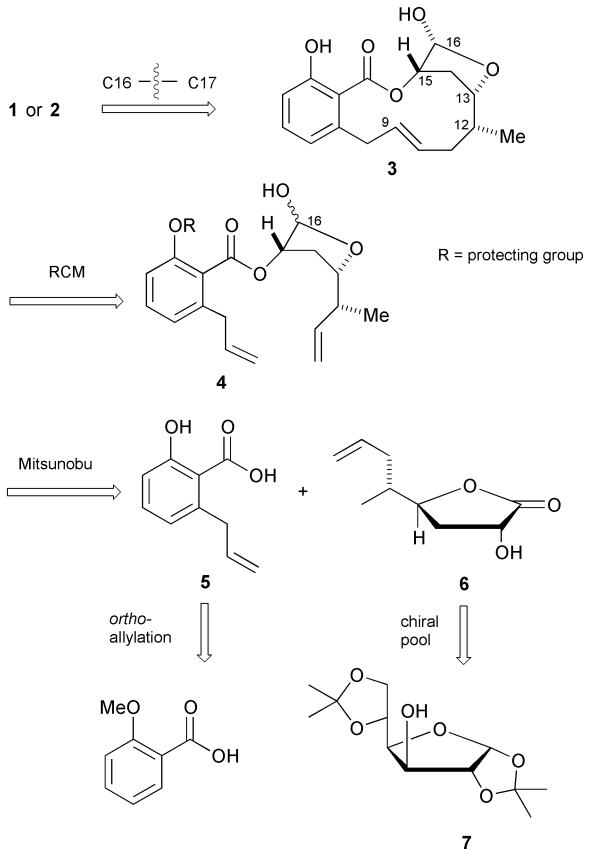
cytotoxic macrolides isolated from an Australian sponge *Haliclona* sp. in 1997.[1] They were the first examples of a novel class of macrolides that have in common the salicylic acid moiety and an unsaturated enamide side chain.[2–6]

This class of compounds possesses diverse biological activities, including inhibition of tumor cell proliferation.[1–6] Salicylihalamide A displayed a striking pattern of differential cytotoxicity in the NCI's 60-cancer cell line human tumor screen.[1] COMPARE pattern-recognition analyses[7] of the mean-graph profiles of salicylihalamide A suggest that the salicylihalamides may act by a novel mechanism of action. Despite their promise as potential anticancer agents, further studies of this new class of compounds are hampered by limited availability from natural sources. The unique structural features of the salicylihalamides coupled with promising biological activity prompted us to develop a flexible approach toward the synthesis of these molecules and related analogues.

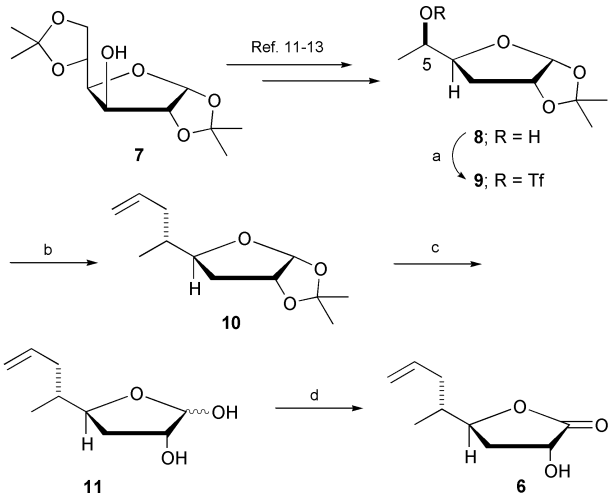
We initially focused on the synthesis of intermediate **3** (Scheme 1), the macrocyclic core structure of the salicylihalamides containing the three chiral centers and the $\Delta^{9,10}$ *E*-alkene. The masked aldehyde functionality in **3** provides an opportunity for side chain attachment at C16 and subsequent completion of the total synthesis.

Our synthetic strategy for the preparation of building block **3** features the use of readily available diacetone-D-glucose as the source for the three chiral centers of the molecule (chiral pool approach). The regioselective formation of the *E*-double bond at C9 was accomplished through a ring-closing metathesis (RCM) reaction employing intermediate **4**. Although the RCM strategy has been used before to form the 12-membered macrolactone ring of unsubstituted or side chain truncated salicylihalamides,[8,9] we herein report the use of the same protocol with a fully-substituted salicylihalamide macrocyclic core. Intermediate **4** can be obtained from lactone **6** *via* Mitsunobu esterification with 6-allylsalicylic acid (**5**). 6-Allylsalicylic acid (**5**) can be prepared from *O*-methylsalicylic acid[10] and diacetone-D-glucose **7** is the precursor for lactone **6**.[11,12]

The macrolide synthesis started with known alcohol **8**, which was prepared in five straightforward steps from diacetone-D-glucose (Scheme 2).[11–13] The secondary hydroxy group in **8**

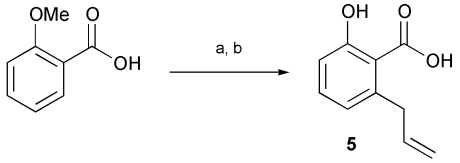


Scheme 1 Retrosynthesis for the salicylihalamide macrolide.



Scheme 2 *Reagents and conditions*: (a) Tf_2O, 2,6-dimethylpyridine, 0 °C, 1.5 h; (b) $(CH_2{=}CHCH_2)_2Cu)CN)Li_2$, THF, −78 °C, 2 h, 78%; (c) 70% aq. acetic acid, 70 °C, 6 h, 98%; (d) Ag_2CO_3–Celite, 80 °C, 1 h, 85%.

DOI: 10.1039/b008842k

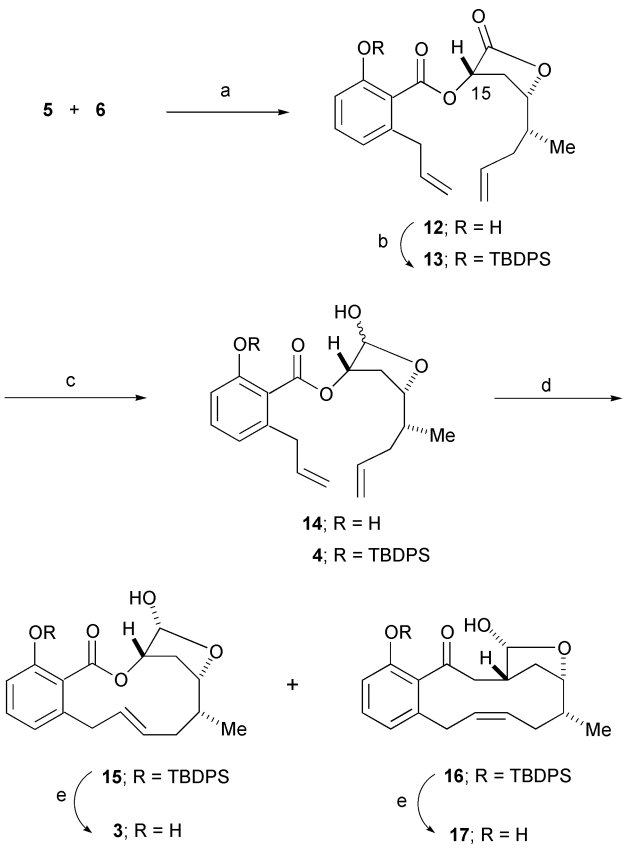


Scheme 3 *Reagents and conditions*: (a) *sec*-BuLi, TMEDA, THF, allyl bromide, −90 °C to rt, 0.5 h, 46% (based on recovered starting material); (b) BCl_3, $(n\text{-Bu})_4NI$, DCM, −78 °C, 2 h, 80%.

was converted to its corresponding triflate **9**, which was reacted immediately and without purification with a higher order allylcyanocuprate to provide **10** with inversion of configuration in 78% yield† (Scheme 2). Deprotection of the acetonide group was carried out with 70% acetic acid to yield alcohol **11**. Selective oxidation of the anomeric hydroxy group with Ag_2CO_3–Celite afforded lactone **6** in excellent yield. The synthesis of **5** was carried out in a two-step sequence as outlined in Scheme 3. Ortho-lithiation of *O*-methylsalicylic acid with *sec*-BuLi–TMEDA and quenching the carbanion with allyl bromide,[10] followed by deprotection of the methyl ether using BCl_3–$(n\text{-Bu})_4NI$,[14] afforded **5** in moderate overall yield.

Esterification of carbohydrate building block **6** with **5** under Mitsunobu conditions (Scheme 4) afforded intermediate **12** in good yield.

After the three stereogenic centers had been installed, the next step was the RCM reaction to form the $\Delta^{9,10}$ alkene. Surprisingly, RCM employing lactone **12** failed to give any of the desired product. Therefore the lactone functionality of **12** was reduced to lactol **14** (88:12, α:β; 80% yield) using DIBAL-H at −78 °C. RCM reaction with this substrate provided the desired reaction product. However, the *Z* isomer



Scheme 4 *Reagents and conditions*: (a) Ph_3P, DEAD, THF, −20 °C to 0 °C, 1 h, 85%; (b) TBDPSCl, imidazole, DMF, rt, 1 h, 85%; (c) DIBAL-H, ether, −78 °C, 2 h, 80%; (d) $RuCl_2$=CHPh)$(PCy_3)_2$, DCM, reflux, 3 h, 60%; (e) TBAF, THF, rt, 1 h, 85%.

was found to be the major reaction product (*E*:*Z* ratio 15:85; 60% yield). When the phenolic hydroxy of **12** was protected as its TBDPS ether **13** (85% yield) and lactone **13** was reduced to lactol **4** (80% yield), RCM of intermediate **4** furnished the two stereoisomeric lactols **15** and **16** in a 70:30 *E*:*Z* ratio and in 60% yield. The introduction of the sterically demanding TBDPS protecting group apparently promotes a conformational change in the transition state of the RCM reaction that favors the formation of the *E*-alkene. After deprotection of the silyl ethers **15** and **16**, the stereoisomers **3** and **17** (85% yield) were separated by column chromatography furnishing the desired *E*-isomer **3** in 60% yield.

Having completed the synthesis of the macrolactone with correct stereo- and regiochemistry,[15] studies directed at introducing the enamide side chain are in progress.

This work was financially supported by the National Cancer Institute (N01-CM-67259 and RO1 CA84173), and the Drug Discovery Program of the Higuchi Biosciences Center at the University of Kansas. B. B. gratefully acknowledges financial support from predoctoral NIH training grant GM-07775 and the American Foundation for Pharmaceutical Education (AFPE) for a predoctoral fellowship. F. F. is grateful for an AAPS-AFPE 'Gateway' Research Scholarship for undergraduate students.

Note added in proof. For a revision of the absolute configuration of salicylihalamide A through total synthesis, see: Y. Wu, L. Esser and J. K. Brabander, *Angew. Chem., Int. Ed.*, 2000, **39**, 4308.

Notes and references

† All new compounds exhibited satisfactory spectral data in accordance with their structures. Yields refer to chromatographically pure compounds.

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