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Total Synthesis of (−)-Salicylihalamide A

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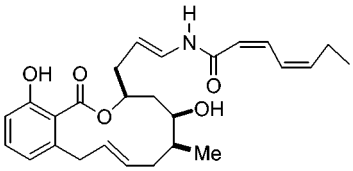
ABSTRACT



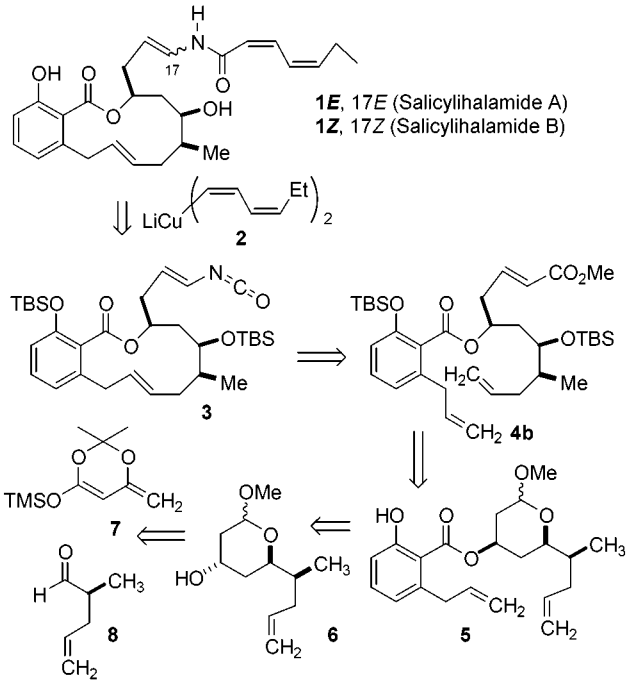
Salicylihalamide A

A 16-step synthesis of the novel cytotoxin salicylihalamide A (1*E*) has been achieved in 3.3% overall yield using ring closing metathesis to generate the macrolide and addition of (1*Z*,3*Z*)-hexadienylcuprate (2), which was generated in situ from ethylcuprate and acetylene, to alkenyl isocyanate 3 to form the side chain.

The novel cytotoxic macrolide salicylihalamide A (**1*E***) was isolated from the sponge *Haliclona* sp. in 1997 by Boyd, Erickson, and co-workers (see Scheme 1).[1] Salicylihalamide A was accompanied by a small amount of salicylihalamide B (**1*Z***) with a *Z*-enamide double bond. The structure was determined by NMR spectroscopic methods, and the absolute stereochemistry was assigned by the use of Mosher esters. The structure was originally assigned as the enantiomer as a result of the failure to take into account the priority order change on conversion of the acid chloride to the ester.[2] De Brabander corrected the absolute stereochemistry assignment in the first synthesis of **1*E***.[3,4]

Salicylihalamide A shows a striking pattern of differential cytotoxicity in the NCI 60-cell line screen. The mean GI_{50} concentration was approximately 15 nM with a range of differential sensitivity $\leq 10^3$.[1] The melanoma cell lines showed the highest average sensitivity (GI_{50} 7 nM, TGI 60 nM). More importantly, the mean-graph profiles of **1*E*** show no significant correlations to those of any other antitumor compounds contained in the NCI database, suggesting a new mechanism of action.

Scheme 1. Retrosynthetic Analysis



(1) Erickson, K. L.; Beutler, J. A.; Cardellina, J. H., II; Boyd, M. R. *J. Org. Chem.* **1997**, *62*, 8188−8192.

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(4) For other syntheses, see: (a) Labrecque, D.; Charron, S.; Rej, R.; Blais, C.; Lamothe, S. *Tetrahedron Lett.* **2001**, *42*, 2645−2648. (b) Smith, A. B., III; Zheng, J. *Synlett*, in press.

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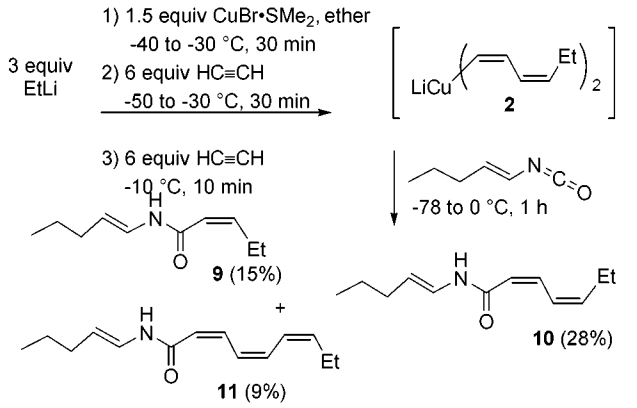
Since the discovery of the salicylihalamides, an emerging class of structurally related, novel, cytotoxic salicylate macrolides has been isolated. This family includes the apicularens with an identical enamide side chain[5] and the lobatamides A−F,[6] oximidines I and II,[7] CJ-12,950, and CJ-13,357[8] with an enamide side chain terminating in an *O*-methyl oxime.

The novel structure and potent biological activity of salicylihalamide A has prompted intense synthetic interest culminating in syntheses by De Brabander,[3,9] Labrecque,[4a] and Smith[4b] and several routes to the ring system.[10−12] All of these routes used ring closing metathesis (RCM) to form the macrolide.

We thought that the *N*-(1*E*-alkenyl)-(2*Z*,4*Z*)-heptadienamide side chain posed the major challenge in the synthesis of salicylihalamide A. We therefore started by developing a procedure for the introduction of the side chain. Taylor reported that organocuprates add to acetylene at −50 °C to give the (1*Z*)-alkenylcuprate.[13] At −10 to 0 °C, the (1*Z*)-alkenylcuprate adds to a second equivalent of acetylene to give a (1*Z*,3*Z*)-alkadienylcuprate (see Scheme 2). This

Scheme 2. Introduction of the Side Chain

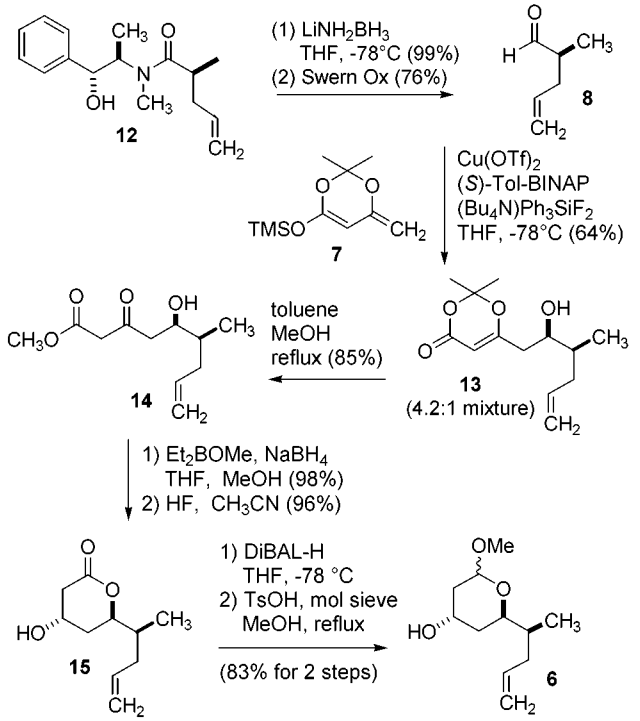


cuprate adds to a wide variety of electrophiles. We reported last year that (1*Z*,3*Z*)-hexadienylcuprate (**2**) adds to (1*E*)-hexenyl isocyanate to give 28% of the desired heptadienamide **10**, 15% of the pentenamide **9**, and 9% of the nonatrienamide **11**.[14] De Brabander used a similar strategy to introduce the side chain, using (1*Z*,3*Z*)-hexadienyllithium, which was prepared by halogen metal exchange from the difficultly accessible (1*Z*,3*Z*)-1-bromohexadiene.[3] Similar lithium based strategies have been reported for the *O*-methyl oxime terminated side chain of the lobatamides.[15]

Our approach to salicylihalamide A (**1*E***) was developed to minimize the use of protecting groups and functional group interchanges. The key alkenyl isocyanate **3** should be available from the α,*β*-unsaturated ester. The macrolide will be formed by RCM of **4b**. Hydrolysis of the acetal of **5**, Wittig reaction, and protection will provide **4b**. The ester linkage of **5** will be prepared by Mitsunobu esterification of **6** with 6-allylsalicylic acid. Finally, **6** will be prepared by an asymmetric aldol reaction of dienyl silyl ether **7** and aldehyde **8** by Carreira's procedure.[16]

Amide **12** was prepared by Myers' procedure from allyl bromide and (−)-pseudoephedrine propanamide (see Scheme 3).[17] Reduction of **12** with $LiNH_2BH_3$[17] gives 99% of the

Scheme 3. Preparation of Alcohol **6**



alcohol, which undergoes Swern oxidation to provide 76% of aldehyde **8**.[18] Asymmetric aldol reaction of **7**[19] with aldehyde **8** by the Carreira procedure using $Cu(OTf)_2$, (*S*)-

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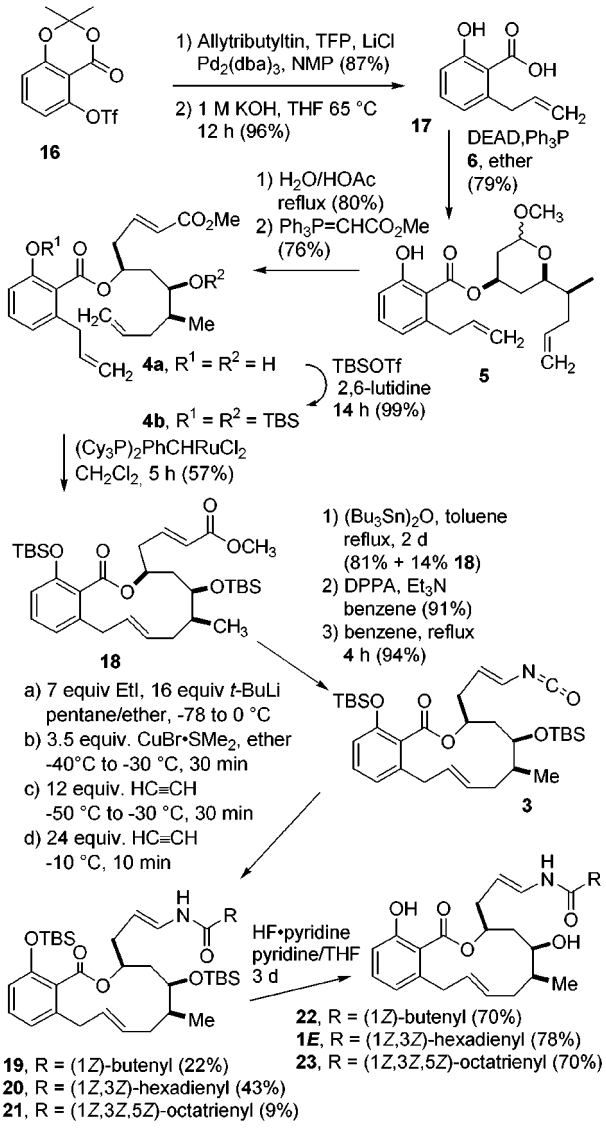
Tol-BINAP, and $(Bu_4N)Ph_3SiF_2$ gives 64% of an inseparable 4.2:1 mixture of **13** and the diastereomer that was carried on through the RCM that gives **18**. Carreira developed this procedure for conjugated aldehydes and reported that unbranched aliphatic aldehydes give low yields of aldol products in high ee.[16] We obtain an acceptable yield, but only modest de, with branched aldehyde **8**. Although the inherent Cram selectivity with aldehyde **8** is low, **13** is the anti-Cram product. The chiral catalyst must overcome a slight preference for the diastereomer of **13**. A 6:1 mixture favoring the diastereomer of **13** is obtained in the matched case with (*R*)-Tol-BINAP. We briefly investigated other routes to **13**. Condensation of **7** and **8** by the Sato procedure using $Ti(O\text{-}i\text{-}Pr)_4$ and binaphthol proceeds in lower yield with reduced selectivity.[20] Coupling of the lithium enolate prepared from the menthone−diketene adduct[21] with **8** affords selectivity comparable to that of the Carreira procedure.

Heating **13** with MeOH in toluene at reflux[22] provides 85% of β-keto ester **14**,[23,24] which is reduced to the syn alcohol with Et_2BOMe and $NaBH_4$ in 98% yield.[25,26] Lactonization of the dihydroxy ester with catalytic HF in CH_3CN[27] yields 96% of hydroxylactone **15**. Elimination to the unsaturated lactone is the only reaction on attempted Mitsunobu coupling of **15** with salicylate **17**. Therefore, the lactone carbonyl group was reduced prior to coupling. Reduction of **15** with DIBAL-H affords the lactol, which is protected as the methyl ether with TsOH and molecular sieves in MeOH to give 83% of **6** as 2.6:1 mixture of β- and α-methoxy anomers that were separated, and both were carried on to give the same mixture of lactols from hydrolysis of **5**.

6-Allylsalicylic acid (**17**) is prepared by Stille coupling of **16**[28] with allyltributyltin using $Pd_2(dba)_3$ and trifurylphosphine (TFP) (87%)[3,29,30] and hydrolysis of the acetonide in a 1:1 mixture of 1 M KOH and THF at reflux to give 96% of **17** (see Scheme 4). Mitsunobu coupling of **17** with **6** using DEAD and Ph_3P in ether affords 79% of **5**.

Scheme 4. Completion of the Synthesis



RCM of **5** did not proceed, presumably because the diequatorial substituents on the tetrahydropyran ring keep the alkenes too far apart. Hydrolysis of **5** in 1:1 $AcOH/H_2O$ at reflux yields 80% of the lactol, which is treated with $Ph_3P{=}CHCO_2Me$ to give 76% of **4a** and 10% of the easily separable *Z* isomer. RCM of **4a** with $(Cy_3P)_2PhCH{=}RhCl_2$ in CH_2Cl_2 requires reaction for 3−4 d and gives mainly the undesired *Z* isomer. Since the alcohol and phenol need to be protected before addition of cuprate **2** to the alkenyl isocyanate, we converted **4a** to bis TBS ether **4b** in 99%

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(29) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585−9595.

(30) This compound has also been prepared from **16** by a Suzuki coupling: Fürstner, A.; Seidel, G. *Synlett* **1998**, 161−162.

yield by reaction with TBSOTf and 2,6-lutidine for 14 h. RCM of **4b** proceeded completely in 5 h, giving a 4:1 mixture of *E*/*Z* isomers. The desired product **18** was isolated free of the *Z* isomer and diastereomer in 57% yield (71% based on **4b** in the 4.2:1 mixture of diastereomers) by chromatography on silver nitrate impregnated silica gel.

Protection of the phenol is crucial for the formation of the desired *E* isomer. RCM of the monosilyl ether with a free phenol, which was prepared by reaction of **4a** with TBSOTf and 2,6-lutidine for 1 h, is also sluggish and gives mainly the *Z* isomer. Fürstner has also noted that the *Z* isomer is obtained exclusively in related substrates with a free phenol,[10b] and De Brabander found that protecting groups have a marked effect on the stereoselectivity of the RCM.[3]

Basic hydrolysis of the methyl ester of **18** could not be achieved without hydrolysis of the TBS ethers; the phenolic TBS ether is especially sensitive. Selective hydrolysis of the methyl ester is accomplished in 81% yield (94% yield based on recovered **18**) by heating with $(Bu_3Sn)_2O$ in toluene for 2 d.[31] Reaction of the acid with DPPA as described by De Brabander gives the acyl azide (91%), which is heated in benzene at reflux for 4 h to give alkenyl isocyanate **3** (94%) that can be used without purification.

Addition of **3** to excess (1*Z*,3*Z*)-hexadienylcuprate (**2**), which is prepared in situ from EtLi, $CuBr{\cdot}Me_2S$, and acetylene,[13,14] affords 22% of enamide **19**, 43% of protected salicylihalamide A **20**, and 9% of trienamide **21**, which are easily separable by chromatography on silver nitrate impregnated silica gel. Deprotection of **19**−**21** as described by De Brabander[3] with HF·pyridine and pyridine in THF for 3 d provides enamide **22** (70%), salicylihalamide A (**1*E***, 78%), and trienamide **23** (70%), respectively. The spectral data of **1*E*** are identical to those previously reported;[1,3] the optical rotation, $[\alpha]^{25}_D = -41$ ($c = 0.067$, MeOH), is larger than that reported for the natural product,[1] $[\alpha]^{25}_D = -35$ ($c = 0.7$, MeOH), and its enantiomer,[3a] $[\alpha]^{25}_D = +20.8$ ($c = 0.12$, MeOH).

De Brabander has shown that the nature of the enamide side chain is not crucial for the cytotoxicity of salicylihalamide A derivatives but does play a role. The analogue with a saturated heptanamide side chain is 15−20% as potent as salicylihalamide A (**1*E***).[3b] Our synthetic **1*E*** and analogues **22** and **23** were evaluated at NCI to further define the role of the side chain in the biological activity. Synthetic **1*E*** has essentially the same potency as the natural product, while **22** and **23** are about 20% as potent.[32,33]

In conclusion, we have completed the synthesis of (−)-salicylihalamide A (**1*E***) in 16 steps from aldehyde **8** in 3.3% overall yield with minimal use of protecting groups. The key step is the efficient introduction of the unsaturated side chain by addition of (1*Z*,3*Z*)-hexadienylcuprate (**2**), which was generated in situ from ethylcuprate and acetylene, to alkenyl isocyanate **3**.

Acknowledgment. We are grateful to the NIH for generous financial support (GM-46470).

Supporting Information Available: Experimental details and NMR spectral data for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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