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Enantioselective total synthesis of salicylihalamides A and B

Denis Labrecque,* Sylvie Charron, Rabindra Rej, Charles Blais and Serge Lamothe

Department of Medicinal Chemistry, Biochem Pharma Inc., 275 Armand-Frappier Blvd, Laval, Québec, Canada H7V 4A7

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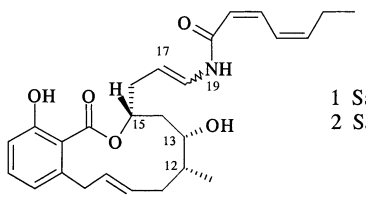
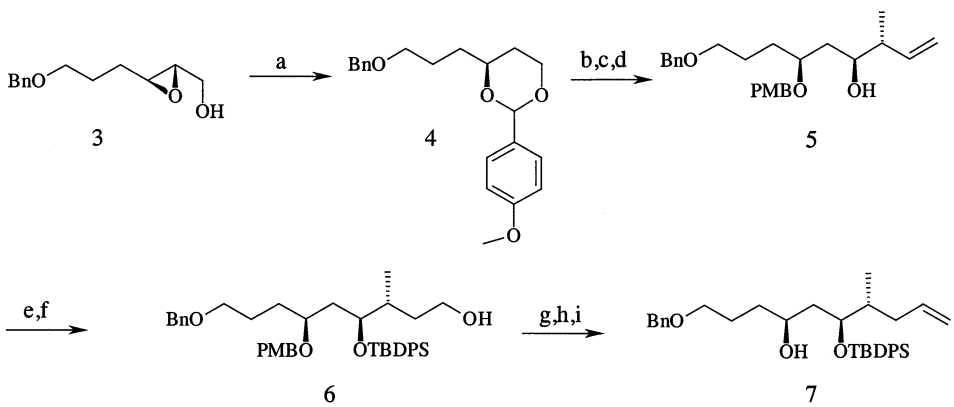
Abstract—We have devised a total synthesis of (12*R*,13*S*,15*R*) salicylihalamides A and B, which allowed revision of the absolute stereochemistry of the natural compounds. The same strategy was then applied to the preparation of naturally occurring salicylihalamides.

Salicylihalamides A (**1**) and B (**2**) were recently reported by Boyd and co-workers as novel cytotoxic macrolides possessing an unusual conjugated enamide side-chain.[1] The lack of correlation of cytotoxicity profile of these compounds in the NCI 60-cell line human tumor assay with known antitumor agents suggested a potential novel mechanism of action. The emergence of several novel biologically active macrolides bearing similar structural features[2] prompted us and others[3] to devise synthetic routes to these compounds. The absolute configuration of salicylihalamide A (**1**) was recently revised through total synthesis by De Brabander and co-workers.[3a,b] We have independently reached the same conclusion and we present herein our total synthesis of both enantiomers of salicylihalamides A (**1**) and B (**2**).



The two main synthetic challenges associated with these target molecules are the efficient preparation of the macrocyclic core structure in an enantioselective fashion and the stereoselective construction of the enamide



Scheme 1. (a) $NaAl(OMe)_3H$, THF, 0°C, then warm to rt and add methanol, TMSCl and *p*-anisaldehyde, 16 h (80%); (b) DIBAL-H, CH_2Cl_2, 0°C, 1 h; (c) Dess–Martin reagent, CH_2Cl_2, rt, 1 h; (d) (*S*,*S*)-diisopropyl tartrate-(*E*)-crotylboronate, toluene, −78°C, 8 h (75% from **4**); (e) TBDPSCl, imidazole, DMF, 100°C, 16 h; (f) 9-BBN, THF, rt, 30 min, then $NaBO_3$, 16 h (67% from **5**); (g) Dess–Martin reagent, CH_2Cl_2, rt, 30 min; (h) $Ph_3P{=}CH_2$, THF, −78°C to rt, 1 h; (i) DDQ, CH_2Cl_2, rt, then H_2O, 30 min (24% from **6**).

* Corresponding author.

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side-chain. Recent work by Fürstner and co-workers describing the use of olefin metathesis strategy for the preparation of macrocyclic lactones provided an attractive solution to the formation of the core structure of the salicylihalamides.[4]

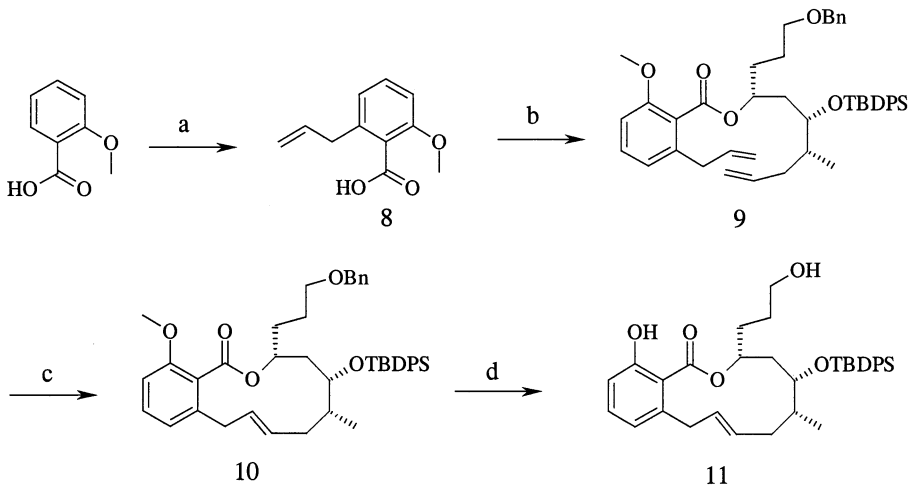
The known epoxide **3**[5] served as the chiral template for our synthesis (Scheme 1). This epoxide was transformed using a one-pot procedure to the protected 1,3-diol **4** in 80% yield via sequential reduction and in situ protection. Cleavage using DIBAL-H followed by Dess–Martin oxidation and reaction with (*S*,*S*)-diisopropyl tartrate-(*E*)-crotylboronate following the procedure developed by Roush[6] afforded **5** (contaminated with 25% of a diastereomer) in 75% yield. Since separation of the minor isomer was not possible at this stage, the one carbon homologation sequence was accomplished on the mixture. Silylation of the secondary alcohol and hydroboration of the terminal olefin afforded **6** in 67% yield. Dess–Martin oxidation and coupling of the resulting aldehyde with methylene triphenylphosphorane gave the homologated product. Subsequent release of the PMB protected alcohol with DDQ in wet dichloromethane afforded compound **7**,[7] which was separated from its diastereomeric contaminant via flash chromatography in 24% overall yield from **6**.

Compound **7** was coupled to the allyl-anisic acid **8**[8] (Scheme 2) via the Mitsunobu esterification procedure with inversion at C-15 providing the cyclization precursor **9** having all the required stereogenic centers in place.

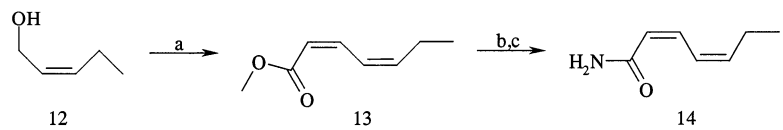
Diene **9** was cyclized via a metathesis reaction using Grubb's catalyst giving the macrocycle **10** in high yield with a 9:1 selectivity favoring the *E*-olefin. The minor *Z* isomer was separated by flash chromatography on silica gel. Concomitant cleavage of the benzyl and the methyl ethers with BBr_3[9] provided phenol **11**[7] in high yield.

In our efforts to devise a synthetic route to the enamide side-chain, we reasoned that elimination of an amide group from a symmetrical *N*,*N*′-bis-acylated aminal under the conditions reported by Katritzky and co-workers[10] could provide the desired product. The appropriate precursor amide with correct stereochemistry was prepared in four steps from alcohol **12** as described in Scheme 3. TPAP oxidation[11] followed by Horner–Emmons coupling[12] in a one-pot operation afforded *Z*,*Z*-diene ester **13** in good yield. Subsequent hydrolysis[13] using barium hydroxide and amidation via mixed anhydride afforded amide **14**.[7]

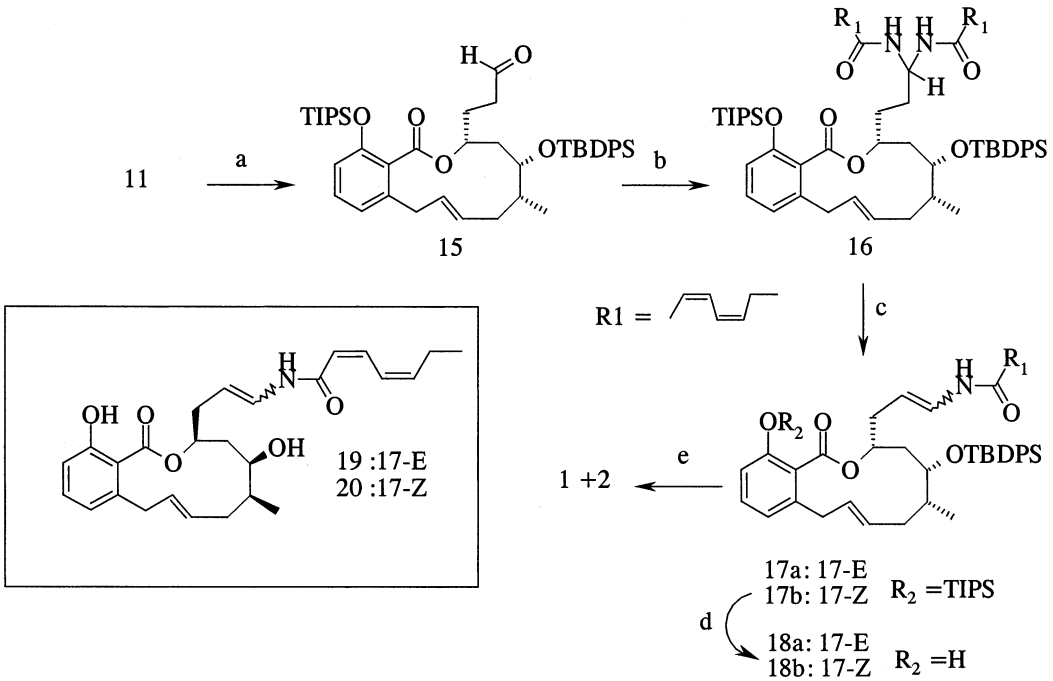
Oxidation[11] of alcohol **11** (Scheme 4) followed by protection of the phenolic hydroxyl with a triisopropylsilyl group gave aldehyde **15** as the template for introduction of the enamide moiety. Condensation of amide **14** with this aldehyde provided the key *N*,*N*′-bis-acylated aminal **16** in 38% overall yield from **11**. This compound underwent elimination when treated with sodium hydride in trifluorotoluene at 60°C for 4.5 hours to yield a mixture of enamides **17a** and **17b** which were separated by column chromatography. The TBDPS group on the secondary alcohol was found to be particularly resistant to standard deprotection conditions.



Scheme 2. (a) 1. *s*-BuLi, TMEDA, THF, –95°C; 2. $MgBr_2$, allyl bromide, –78°C to rt, 16 h (18%); (b) **7**, DEAD, PPh_3, Et_2O, 0°C to rt, 1 h (73%); (c) bis(tricyclohexylphosphine)benzylidine ruthenium(VI) dichloride, CH_2Cl_2, reflux, 3 h (75%); (d) BBr_3, CH_2Cl_2, –78°C, 30 min (80%).



Scheme 3. (a) TPAP, NMO, CH_2Cl_2, 4 Å mol. sieves, 0°C, 1 h, then $(CF_3CH_2O)_2POCH_2COOCH_3$, KH 60%, 18-crown-6, THF, –78°C, 15 min (73%); (b) $Ba(OH)_2{\cdot}H_2O$, MeOH, 16 h (93%); (c) ClCOOEt, Et_3N, THF, 0°C, 20 min, then NH_3(g), 15 min, rt (63%).



Scheme 4. (a) 1. TPAP, NMO, CH_2Cl_2, 4 Å mol. sieves, rt, 30 min; 2. TIPSCl, DIPEA, DMAP, DMF, 70°C, 1 h; (b) **14**, TMSOTf (0.5 equiv.), $ClCH_2CH_2Cl$, rt, 2 h then $NaHCO_3$ work-up (38% from **11**); (c) NaH 60%, $PhCF_3$, 60°C, 4.5 h (48%); (d) TBAF, THF, rt, 1 h (70% for **17a→18a** and 76% for **17b→18b**); (e) TBAF, HMPA, THF, 40°C, 48 h (52% of a 1:1 mixture of **1** and **2** for **18a** and 35% of a 1:2 mixture of **1** and **2** for **18b**).

Treatment of **17a** or **17b** under such conditions (TBAF in THF) afforded **18a** or **18b**, respectively. Removal of the remaining silyl group required more drastic conditions (TBAF in THF–HMPA at 40°C for 48 hours) which caused isomerization of the enamide double bond. Therefore, reaction of pure isomers **18a** or **18b** both provided mixtures of **1** and **2**. Direct formation of the mixture of **1** and **2** from unseparated **17a** and **17b** using these conditions gave lower yields. The two isomers were separated by HPLC and their spectroscopic characteristics were in agreement with those reported for the natural products[1] except for optical rotation which was of the same magnitude but of opposite sign.[14] These results suggested that the absolute configuration of the products as described previously was incorrect and that the structures of natural (−)-salicylihalamides A and B should be represented by **19** and **20**[1,3] respectively. Therefore, using the same synthetic sequence and starting from the enantiomer of **3**, we have prepared the natural compounds **19** and **20**.[14] Biological profiles of the presented compounds as well as closely related analogues will be reported in due course.

Acknowledgements

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7. ^{1}H NMR data for key intermediates. For **7**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (d, $J=6.8$ Hz, 3H), 1.04 (s, 9H), 1.22–1.80 (m, 10H), 3.37 (t, $J=6.3$ Hz, 2H), 3.66 (app. sept., $J=3.8$ Hz, 1H), 3.84 (dt, $J=3.5$, 9.0 Hz, 1H), 4.42 (s, 2H), 4.77 (m, 2H), 5.31 (m, 1H), 7.24–7.45 (m, 11H), 7.66 (m, 4H). For **11**: ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 0.88 (d, $J=6.4$ Hz, 3H), 1.08 (s, 9H), 1.53–1.82 (m, 9H), 3.24 (dd, $J=2.6$, 16.1 Hz, 1H), 3.29 (dd, $J=7.5$, 16.2 Hz, 1H), 3.48 (m, 1H), 3.56 (m, 2H), 4.09 (dd, $J=2.3$, 8.5 Hz, 1H), 4.50 (m, 1H), 4.97 (dm, $J=13.2$ Hz, 1H), 5.39 (dt, $J=6.3$, 8.6 Hz, 1H), 6.62 (d, $J=7.3$ Hz, 1H), 6.79 (d, $J=7.6$ Hz, 1H), 7.14 (dd, $J=7.6$, 8.0 Hz, 1H), 7.41 (m, 6H), 7.73 (m, 2H), 7.85 (m, 2H), 9.39 (s, 1H). For **14**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (t, $J=7.5$ Hz, 3H), 2.21–2.29 (m, 2H), 5.63 (m, 1H), 5.65 (dd, $J=1.2$, 11.5 Hz, 1H), 5.82 (m, 1H), 5.99 (m, 1H), 6.79 (dt, $J=1.2$, 11.6 Hz, 1H), 7.19 (m, 1H).
8. Reagent **8** was prepared by reacting the dilithium salt of *o*-anisic acid with allyl bromide in the presence of magnesium bromide in THF, see: Hodge, P.; Perry, G. M.; Yates, P. *J. Chem. Soc., Perkin Trans. 1* **1977**, 680 for the formation of the dilithium salt of *o*-anisic acid.
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14. For compound **1**, $[\alpha]_D$ +25° (*c* 0.19, MeOH); lit. (Ref. 1) for salicylihalamide A: $[\alpha]_D$ −35° (*c* 0.7, MeOH); for compound **2**, $[\alpha]_D$ +86° (*c* 0.18, MeOH); lit. (Ref. 1) for salicylihalamide B: $[\alpha]_D$ −73° (*c* 0.3, MeOH); for compound **19**, $[\alpha]_D$ −27° (*c* 0.2, MeOH); for compound **20**, $[\alpha]_D$ −85° (*c* 0.32, MeOH).