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Enantiospecific Formal Total Syntheses of (−)-Salicylihalamides A and B from D-Glucose and L-Rhamnose

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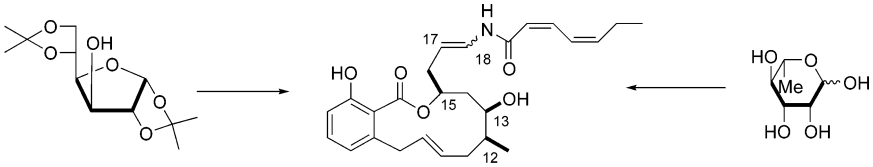
ABSTRACT



1 17-E
2 17-Z

Two formal chiral pool syntheses of the (−)-salicylihalamides A and B were achieved from commercially available 1,2,5,6-diacetone-D-glucose and L-rhamnose.

The salicylihalamides A and B[1] belong to a family of recently discovered natural products that contain a salicylic acid moiety, a macrolactone, and an unusual enamide side chain. This class of molecules, which includes the oximidines I and II,[2] the lobatamides A−F,[3] and apicularens A and B,[4] shows considerable potency and differential cytotoxicity in the 60-cancer cell line assay of the NCI.[5] The salicylihalamides **1** and **2**, isolated from *Haliclona* sp. in 1997,[1] have received substantial attention, resulting in several partial and total syntheses.[6] In our initial approach toward the synthesis of the macrocyclic core of the salicylihalamides, we chose a chiral pool strategy using commercially available 1,2,5,6-diacetone-D-glucose as the starting material.[6e] However, since the absolute stereochemistry of the salicylihalamides was revised by total synthesis,[6a] we needed to modify our strategy in order to prepare the naturally occurring salicylihalamides.

Herein, we report two chiral pool approaches toward the synthesis of the (−)-salicylihalamides A and B. One of them is also based on using 1,2,5,6-diacetone-D-glucose[6e] as the starting material, while the other one employs L-rhamnose, both leading to the formal total synthesis of the salicylihalamides.

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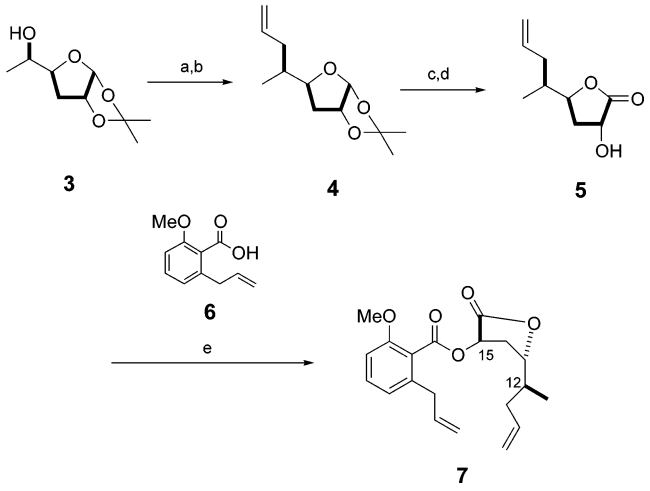
In our first approach, 1,2,5,6-diacetone-D-glucose was transformed into alcohol **3** in five steps as described previously.[7] To obtain the correct stereochemistry at C12, we first converted the alcohol into the corresponding bromide and then introduced the allyl group, giving rise to intermediate **4** (Scheme 1).

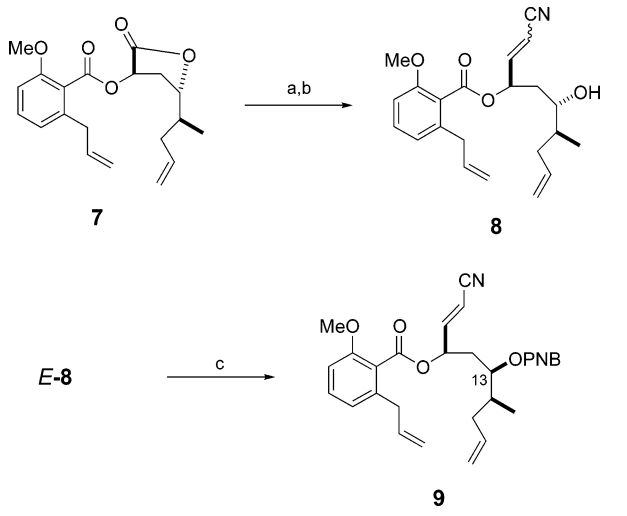
Scheme 1[a]



[a] Reagents and conditions: (a) CBr_4, PPh_3, THF, 0 °C to rt, 6 h, 90%. (b) $(allyl)_2Cu(CN)Li_2$, THF, Et_2O, −78 °C, 30 min, 83%. (c) AcOH, H_2O, 70 °C, 3 h, 85%. (d) $AgCO_3$/Celite, PhH, reflux, 1 h, 81%. (e) **6**, DCC, CH_2Cl_2, rt, 24 h, 95%.

Deprotection of the ketal and subsequent oxidation led to building block **5**. Esterification of **5** with the aromatic fragment **6**[8] using DCC provided compound **7** with the correct stereochemistry at C15. Reduction of lactone **7** to the corresponding lactol and subsequent Wittig olefination with (triphenylphosphoranylidene)acetonitrile resulted in acryl nitrile **8** as a separable 3.6:1 mixture of *E*:*Z* isomers (Scheme 2). The conversion of (*E*)-**8** into **9** under Mitsunobu conditions using *p*-nitrobenzoic acid (PNBA) proceeded in good yield (74%). Interestingly, (*Z*)-**8** did not react in satisfactory yields under the same conditions, presumably due to steric hindrance. Reduction of acryl nitrile **9**, leading to the saturated nitrile **11**, was carried out with hydrido-(triphenylphosphine)copper(I) hexamer[9] (Scheme 3). The moderate yield of this reaction (45%) can be attributed to the presence of the nitro functionality of the PNB group, interfering with the reducing agent. This problem could be avoided by replacing the PNB group with an acetate (**10**). Although this procedure adds two steps to the synthesis, it saves material because the double-bond reduction of acetate

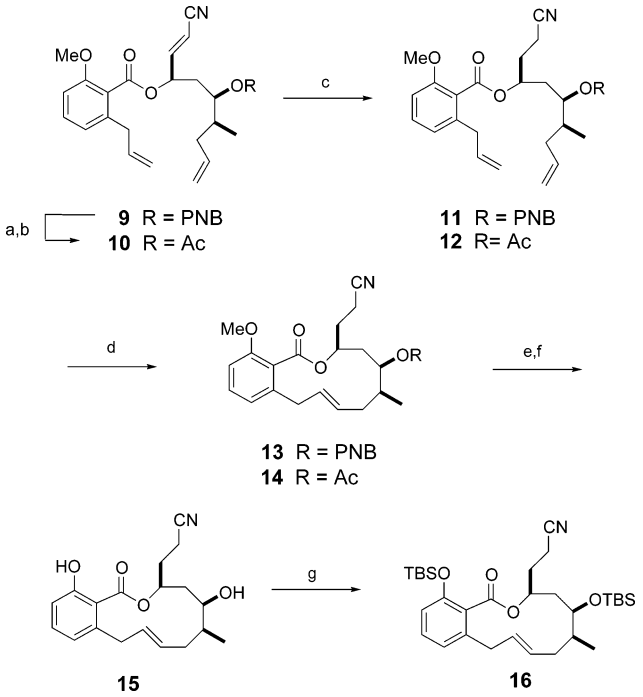
Scheme 2[a]



[a] Reagents and conditions: (a) DIBAL-H, Et_2O, −78 °C, 30 min, 93%. (b) PPh_3=CHCN, PhMe, 80 °C, 2 h, 97%. (c) PNBA, DEAD, PPh_3, PhMe, −30 °C to rt, 24 h, 74%.

10, which affords **12**, proceeded in very good yield (89%). The same reaction failed with the unprotected alcohol because the hydroxy group tends to add into the acryl nitrile in a Michael fashion under the given reaction conditions.

Scheme 3[a]



[a] Reagents and conditions: (a) K_2CO_3, MeOH, rt, 3 h, 95%. (b) Ac_2O, TEA, CH_2Cl_2, 2 h, rt, 97%. (c) $[CuHPPh_3]_6$, PhH, H_2O, reflux, 30 min, 45% for **11**, 89% for **12**. (d) $(PCy_3)_2Cl_2Ru$=CHPh, CH_2Cl_2, reflux, 3 h, 89% (*E*/*Z* = 18:1) for **13**, 87% (*E*/*Z* = 26:1) for **14**. (e) BBr_3, CH_2Cl_2, −78 °C, 30 min, 85% from **13**, 89% from **14**. (f) K_2CO_3, MeOH, RT, 5 h, 95% (both). (g) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt, 1 day, 82%.

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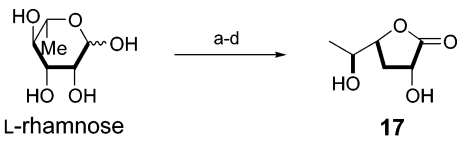
The ring-closing metathesis of **11** and **12** using the first-generation Grubbs catalyst afforded the cyclized products **13** and **14** in good yields (87−89%) and excellent *E*:*Z* ratios (18:1 and 26:1, respectively). Deprotection of each compound, **13** and **14**, provided compound **15**, which in comparison with previously synthesized enantiomer *ent*-**15**,[8] exhibited identical physical properties except opposite optical rotation. TBS protection generates the fully protected compound **16** that can be used for the enamide side chain introduction. In our previous report, we converted the nitrile functionality of TIPS- and TBDPS-protected *ent*-**15** to the corresponding aldehyde, which matches the intermediate synthesized by Labrecque et al.,[6d] and thus constitutes a formal synthesis of the (−)-salicylihalamides.

Our second approach toward the synthesis of the salicylihalamides employs L-rhamnose as the chiral source, which was first converted to known intermediate **17** in four steps using a modified literature procedure (Scheme 4).[10] The

Scheme 4[a]



L-rhamnose **17**

[a] Reagents and conditions: (a) $BaCO_3$, Br_2, H_2O, rt, 1 day, 99%. (b) BzCl, pyridine, 0 °C to rt, 99%. (c) H_2 (50 psi), 10% Pd/C, TEA, EtOAc, rt, 1 day, 99%. (d) (i) NaOMe, MeOH, rt, 3 h; (ii) 1,4-dioxane, H_2SO_4, rt, 1 h, 87%.

coupling reaction between **17** and the aromatic building block **6** (Scheme 5) revealed that the secondary hydroxy function attached to the ring showed significantly higher reactivity than the secondary hydroxy group of the side chain. Therefore, the reaction gave rise to the desired intermediate **18** in 90% yield (Scheme 5). Reduction of lactone **18** and methyl acetal formation in a one-pot procedure resulted in **19**, which was obtained as a mixture of anomers. Triflate activation of the secondary alcohol in **19** and its reaction with a higher order allylcuprate formed the corresponding allylated compound in moderate yield (30% over two steps). Restricted reactivity, which might be due to the presence of the anomeric methoxy group, and competing ester cleavage seem to be the limiting factors in this reaction. Deprotection of the allylated product gave compound **20**, which was then subjected to a Wittig two-carbon elongation using (triphenylphosphoranylidene) acetonitrile leading to the unsaturated nitrile. Subsequent reduction and double TBS protection gave compound **21**, which on treatment with the first generation Grubbs catalyst resulted in the formation of compound **16**, as well as the undesired (*Z*)-isomer in a 4.7:1 ratio of (*E*)- and (*Z*)-isomers.

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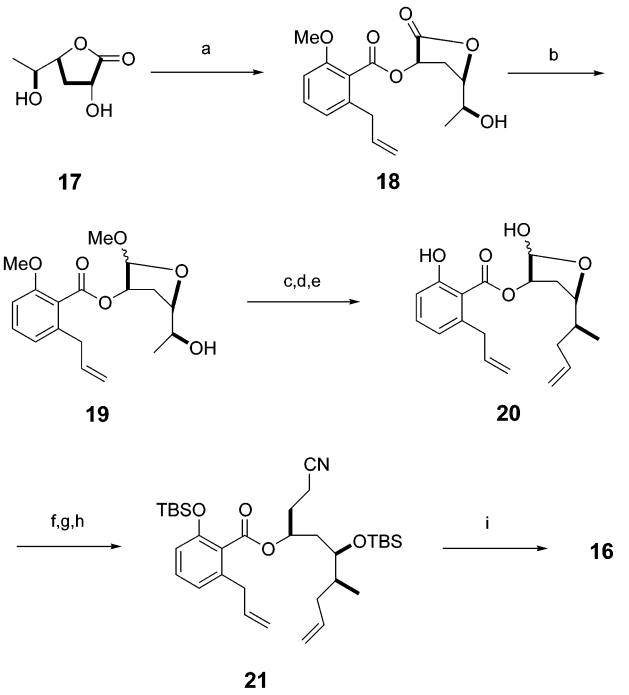
Scheme 5[a]



[a] Reagents and conditions: (a) **6**, EDCI, DMAP, CH_2Cl_2, rt, 1 day, 90%. (b) (i) DIBAL-H, toluene, −78 °C, 15 min; (ii) HCl, dioxane, MeOH, rt, 4 h, 70%. (c) Tf_2O, pyridine, 0 °C, 15 min. (d) $(allyl)_2Cu(CN)Li_2$, −78 °C, 30% (two steps). (e) BCl_3, CH_2Cl_2, −78 °C, 30 min, 72%. (f) PPh_3=CHCN, PhMe, 75 °C, 1 h, 98%. (g) $[CuHPPh_3]_6$, PhH, 0 °C to rt, 15 min, 80%. (h) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to rt, 4 h, 91%. (i) $(PCy_3)_2Cl_2Ru$=CHPh, CH_2Cl_2, reflux, 3 h, 81%.

In summary, we have achieved two efficient formal chiral-pool syntheses of the salicylihalamides A and B. In the first approach, the synthesis of macrocycle **16** from known alcohol **3** was completed in 13 steps and 7% overall yield or in 15 steps in 12% overall yield. The second approach allows the synthesis of **16** from known diol **17** in 10 steps and 8% overall yield.

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Supporting Information Available: Physical data, ^1H NMR spectra, and ^{13}C NMR spectra of compounds **15** and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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