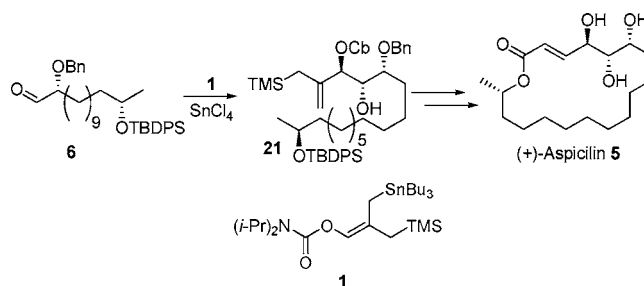# A Concise Total Synthesis of the Lichen Macrolide (+)-Aspicilin

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Received August 17, 2006

ABSTRACT
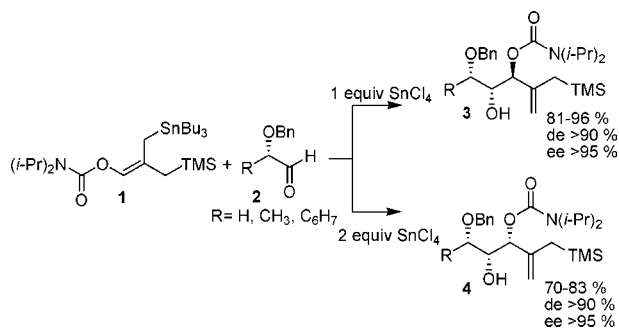

The total synthesis of the polyhydroxylated macrolide (+)-aspicilin 5 is described using as a key step a highly diastereoselective allylation of aldehyde 6 with the uniquely functionalized allylstannane 1. (+)-Aspicilin is obtained in 18 steps and 10% overall yield.

We have previously shown[1] that enantiomerically pure *syn−anti* and *syn−syn* configured triol units such as 3 and 4 could be synthesized efficiently by the SnCl₄-mediated allylation of chiral α-benzyloxyaldehydes 2 with the uniquely functionalized allylstannane 1. Remarkably, the relative stereochemistry of these adducts was governed solely by the

Scheme 1

amount of Lewis acid employed (Scheme 1). The resulting structures possess a stereodefined polyoxygenated triad present in a large number of natural products. (+)-Aspicilin, an 18-membered macrolide first isolated from *Lecanoraceae* lichen in 1900 by Hesse,[2] embodies a contiguous *syn−anti*

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triol motif[3] which represents an ideal synthetic target to benchmark our methodology.

Though devoid of biological activity, this natural product has attracted many synthetic chemists interested in its challenging architecture.[4] In this communication, we report our successful total synthesis of compound **5** using a highly diastereoselective allylation of the suitably functionalized α-benzyloxyaldehyde **6** as a key step. This aldehyde is readily available by condensation of a synthon equivalent to dianion **8** with (S)-propylene oxide **7**, to give the remote alcohol required for macrocyclization, and with the TBS-protected (S)-glycidol **9**, the precursor of the α-benzyloxy-aldehyde function of **6** (Scheme 2).
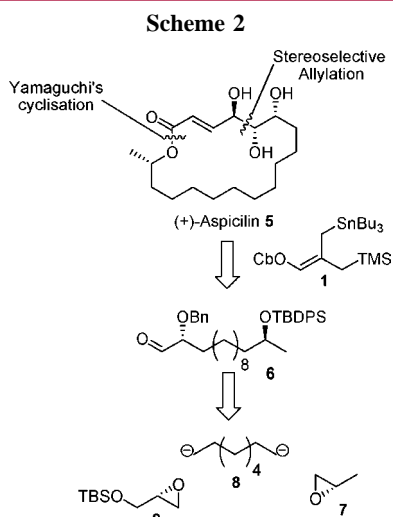
Scheme 2

Our synthesis (Scheme 3) begins with the preparation of the Grignard reagent derived from commercially available 1-bromooctene **10**, which was added to a solution of (S)-propylene oxide **7** and 5% CuCN in THF to afford the desired alcohol **11** in 85% yield and as a single stereoisomer. This compound was protected quantitatively as the TBDPS ether **12**, using standard procedure. Hydroboration of **12** with 9-BBN-H, followed by treatment with sodium hydroxide and H_2O_2, gave rise to alcohol **13**, in 90% yield, which was converted to the corresponding bromide **14** upon treatment

with CBr_4 and PPh_3 (82%). The preparation of the corresponding Grignard reagent was then accomplished in THF, and the resulting organometallic was added to a solution of the commercially available TBS-protected glycidol **9** and 5% $CuBr\cdot Me_2S$ at −25 °C. After purification over silica gel, the desired alcohol **15** was obtained in 88% yield as a single diastereoisomer. Subsequent protection of the free hydroxyl with benzyl-2,2,2-trichloroacetimidate, in the presence of triflic acid (10%), afforded the benzyl ether **16** in 89% yield after 3 days at room temperature. Quantitative deprotection of the TBS ether with TBAF in THF was achieved selectively in the presence of the TBDPS ether. Finally, subjecting the resulting primary alcohol **17** to oxidation with Dess−Martin reagent afforded the key aldehyde **6** in 89% yield. This aldehyde, embodying the correct functionalities and absolute stereochemistry required for our allylation process, was efficiently obtained in only eight steps (Scheme 3) with an overall yield of 50%.

On the basis of our previous studies with less elaborated α-benzyloxyaldehydes,[1b] we surmised that treating **6** with allylstannane **1**,[5] in the presence of 1 equiv of $SnCl_4$, would produce selectively the desired *syn−anti* triol possessing a pendant allylsilane moiety that could be conveniently employed for further transformations. This stereochemistry would arise from the bicyclic transition state **19** involving the transmetalated trichlorostannane **18** (Figure 1).
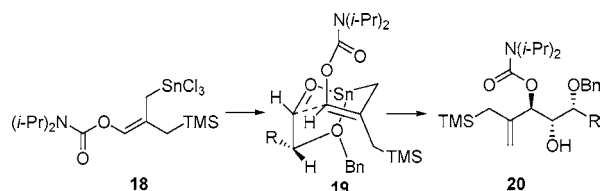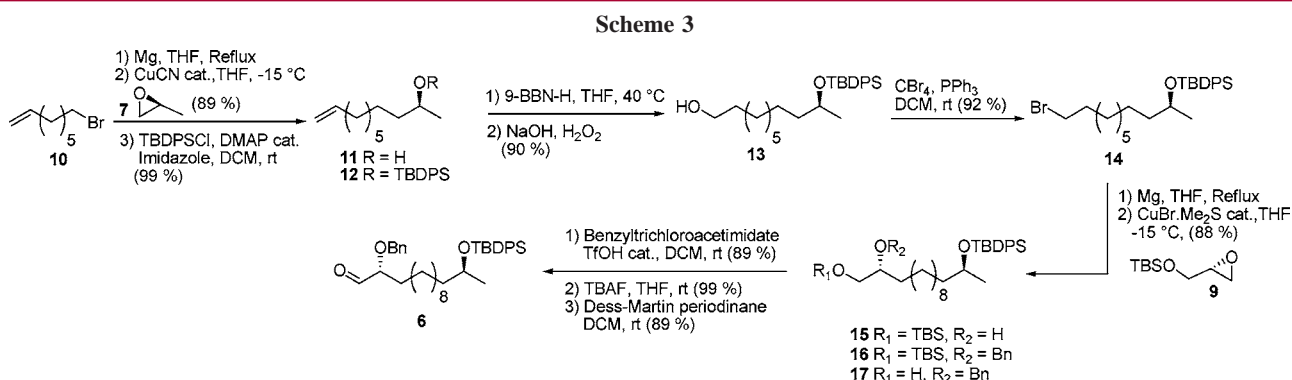

Figure 1. Proposed transition state for allylation.

In the event, treatment of allylstannane **1** with 1 equiv of $SnCl_4$, at −78 °C, followed by the addition of a cold (−78 °C) solution of aldehyde **6** afforded, after purification of the crude mixture, the desired *syn−anti* triol **21** as a single diastereoisomer and in 69% yield on a multigram scale.[6]

Scheme 3

Though we were quite pleased to obtain **21** with a good yield, we tried to further improve the reaction and discovered that using a higher dilution was beneficial. A careful control of the temperature also had to be exercised. For example, diluting the reaction 10 times and using a diethylether/N$_2$ cooling bath led to **21** in a gratifying 85% yield[7] (Scheme 4).
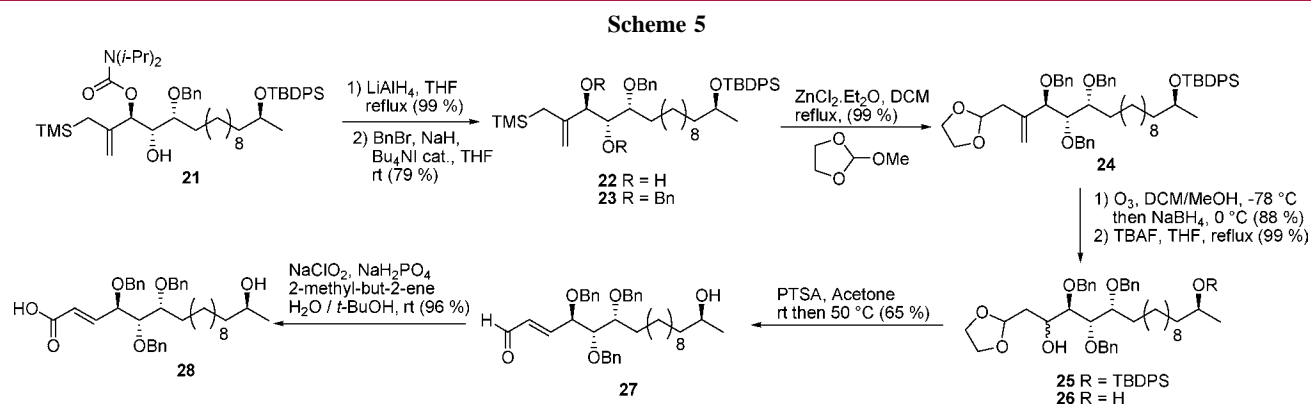
Scheme 4
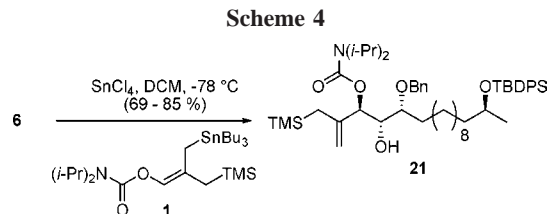
With product **21** in hand, we next focused on the conversion of the allylsilane moiety into the required unsaturated carbonyl system. Preliminary model studies indicated that the carbamate protecting group had to be removed as soon as possible because the harsh reducing conditions required for its deprotection (LiAlH$_4$ in refluxing THF) would be troublesome with the unsaturated carbonyl we aimed to introduce. Interestingly, treatment of **21** with LiAlH$_4$ in refluxing THF afforded smoothly the unprotected diol **22** in 99% yield (Scheme 5). Foreseeing a final global deprotection in one step, diol **22** was protected as the corresponding benzyl ether. The first attempts, using a sequential deprotonation with NaH followed by addition of benzyl bromide in the presence of Bu$_4$NI, were disappointing since only the desilylated starting material was observed. We assumed that a possible 5- or 6-membered "ate" complex could be formed by attack of an alkoxide on the TMS group of **22**. This activated allylsilane would then react with a proton during acidic aqueous workup. This problem was solved by mixing **22**, a large excess of benzyl bromide and Bu$_4$NI in THF, and adding NaH portionwise so that the formed alkoxide was immediately trapped by the alkylating agent. This procedure afforded the desired tri-benzylated product **23** in 79% yield along with some desilylated starting material.

A Sakurai reaction between **23** and 2-methoxy-1,3-dioxolane, mediated by ZnCl$_2$·Et$_2$O, was then successfully used to introduce an acetal moiety. Even though the reaction proceeded sluggishly, we were able to obtain the desired product **24** in 99% yield and 69% conversion after 72 h. The starting material could easily be recycled, and after three runs, the overall yield in **24** was almost quantitative.

Ozonolysis of **24** in a mixture of DCM and MeOH, at −78 °C, followed by addition of NaBH$_4$ to quench the ozonide, produced smoothly a mixture of two diastereoisomeric alcohols **25** in 88% yield. At this stage the removal of the TBDPS protecting group was successfully accomplished using TBAF in refluxing THF (99% yield) to give **26** ready for a one-pot deprotection of the acetal/dehydration sequence to produce the *trans*-unsaturated aldehyde **27**. In the event, treating **26** with PTSA in acetone, initially at room temperature and then at 40 °C for 2 h, gave **27** in a decent 65% yield as the sole (*E*)-double bond isomer.

With the recent improvements made in the field of tandem oxidation processes using MnO$_2$, we envisaged completing our approach with an ambitious tandem oxidation/macrocyclization[8] combination. Thus, **27** was submitted to Corey's procedure for the one-pot oxidation of allylic aldehydes to unsaturated esters[9] using 20 equiv of MnO$_2$ in the presence of 5 equiv of KCN in THF. Although the starting material was totally consumed within 24 h, our first attempts showed only small traces of the desired macrocycle **29**, even at reflux. We assumed that the acyl-cyanide, generated in situ, was not reactive enough to promote the macrocyclization. Therefore, the reaction was performed in toluene, at room temperature, and the excess of MnO$_2$ was filtered once all the starting material had disappeared by TLC. This solution was added to a refluxing solution of DMAP in toluene, using a syringe pump, over 2 h. With this improved protocol, we were pleased to obtain a modest 18% yield of macrocycle **29** after purification (Scheme 6). In parallel, we also oxidized **27** to acid **28**, using Pinnick's[10] protocol, in quantitative yield and submitted this compound to Yamaguchi's macrocyclization.[11] This reaction had already been reported in previous total syntheses but with less robust protecting groups than benzyl ethers. In our case, we were delighted to obtain the macrocyclized adduct **29** in 92% yield using 2,4,6-trichlo-

Scheme 5

Scheme 6
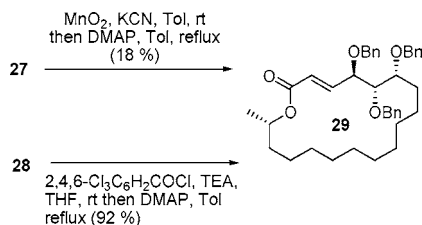
robenzoyl chloride to prepare the mixed anhydride and DMAP in refluxing toluene as the promoter.

The final step required the deprotection of three benzyl ethers at once. Our initial attempts implied hydrogenations with Pd/C at room temperature. These conditions produced a mixture of monobenzylated products and saturated macrocycles, formed by hydrogenation of the C=C double bond. We then focused on the use of Lewis acid-mediated deprotections. While $FeCl_3$ in DCM proved to be unreactive, treating **29** with a solution of BCl_3 in DCM[12] at -78 °C for 11 h, followed by quenching with MeOH, afforded (+)-aspicilin **5** (65%) as a white solid, after purification and

recrystallization from ether. The synthetic sample displayed spectral data in perfect agreement with those reported in the literature (Scheme 7).

Scheme 7
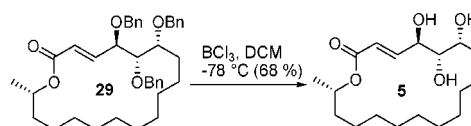
In summary, we have achieved the total synthesis of (+)-aspicilin in 18 steps and 10% overall yield. This synthesis compares favorably with other approaches already reported. We have also demonstrated that the allylation protocol developed in our laboratory is efficient and reliable in a multistep sequence and in large scale. Moreover, the preliminary results of a tandem oxidation/macrolactonization sequence are described for the first time. Although a modest yield is obtained at present, subsequent optimization might lead to an improved and shorter synthesis of (+)-aspicilin.

Supporting Information Available: Characterization, procedures, and full spectral data (including NMR spectra) for all intermediates and (+)-aspicilin. This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) See reference 1b for preparation of this product in a three-step procedure.

(6) Enantiomeric purity of **21** was determined to be 97.2 % by chiral HPLC (Chirex AD-H; hexane/*i*-PrOH, 99.55:0.45, 1 mL/min).

(7) The increase in yield is partly explained by the partial suppression of a possible migration of the trichlorotin residue at the α position of the carbamate.

(8) For comprehensive review on TOP with MnO_2, see: Taylor, R. J. K.; Reid, M.; Foot, J.; Raw, S. A. *Acc. Chem. Res.* **2005**, *38*, 851.

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