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Concise, protecting group free total syntheses of (+)-sattabacin and (+)-4-hydroxysattabacin

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ABSTRACT

The first asymmetric total syntheses of the antiviral natural products (+)-sattabacin and (+)-4-hydroxysattabacin are reported. Both total syntheses are remarkably concise and were completed without the use of protecting groups. These syntheses allowed the unambiguous assignment of the absolute configuration of both natural products. The syntheses of these natural products, which exhibit marked antiviral activity, are readily amenable to the preparation of structural analogs and progress in this regard is also reported.

The natural products sattabacin (**1**) and 4-hydroxysattabacin (**2**) were isolated from the soil bacteria, *Bacillus* sp., by Satta and coworkers (Fig. 1), and these compounds were shown to exhibit antiviral activity, most notably against herpes simplex virus type 1 (HSV1) and 2 (HSV2).[1] Both natural products are potent antiviral agents, with ID_{50} values in the μg-ng/mL range. The ID_{50} of sattabacin was 3 μg/mL against both HSV1 and HSV2, and 4-hydroxysattabacin was an order of magnitude or more potent with ID_{50} values of 0.32 and 0.08 μg/mL against HSV1 and HSV2, respectively. A large majority of the world population is infected with some member of the human herpesvirus family,[2] and HSV infections can be life threatening particularly in immunocompromised patients, pregnant women, and newborns.[2] Nucleoside analogs such as acyclovir and related compounds remain the standard of care to treat HSV infections,[3] but nucleoside-resistant HSV infections have become more common especially among immunocompromised individuals.[4] These drawbacks have led to the exploration of new classes of treatments for HSV infection,[5] and these considerations sparked our interest in studying the sattabacins whose mechanism of action remains unknown.

To date, no total syntheses of these natural products have been reported,[6] and while specific rotations were originally disclosed, the isolation chemists did not determine the absolute configuration of either sattabacin or 4-hydroxysattabacin. Due to the interesting biological activity of these natural products, in order to confirm the absolute configuration of the sattabacins, and to provide access to the natural products and analogs for further study, the total syntheses of both sattabacins were undertaken.

The retrosynthesis of these natural products was guided by a number of factors (Scheme 1). We sought an asymmetric total synthesis, so access to each natural product in an enantioenriched form was a priority. Also, in order to prepare structural analogs, we sought a divergent synthesis in which a key intermediate could be elaborated to a family of structurally different potential antiviral compounds at a late stage. Last, to maximize the greenness and brevity of each synthesis, protecting groups would be avoided.[7] With these goals in mind, we envisioned preparing **1** and **2** from the addition of an isobutyl organometallic reagent to the appropriate Weinreb amide **3** and **4**, respectively. Addition of various other alkyl and aryl organometallic reagents to these amides would lead to analogs with varying side chains. The amides **3** and **4** would arise from the aryl lactic acids **5** and **6**, both of which could be obtained in an enantiomerically enriched form.[8,9]

The synthesis of sattabacin commenced with L-phenylalanine (**7**) (Scheme 2). Diazotization with retention of configuration afforded phenyllactic acid **5**,[8b] which underwent smooth conversion into the corresponding Weinreb amide **3** in the presence of *N,O*-dimethylhydroxylamine, *N*-methylmorpholine (NMM), and dicyclohexylurea (DCC). Initial attempts to form **1** by the addition of isobutyl magnesium bromide to **3** in either THF or Et_2O were low yielding and purification proved difficult. However, to our delight treatment of **3** with 2.5 equiv of isobutyl lithium at low temperature afforded (+)-sattabacin (**1**) cleanly in excellent yield. The spectral data for synthetic **1** (^1H and ^{13}C NMR) were identical with those previously reported,[1] and the optical rotation ($[\alpha]_D^{25}$ +41 (*c* 0.1, CH_2Cl_2)) was comparable to that reported in the literature

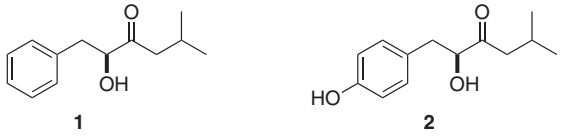

Figure 1.

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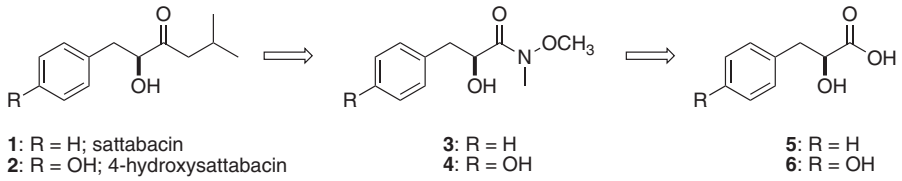
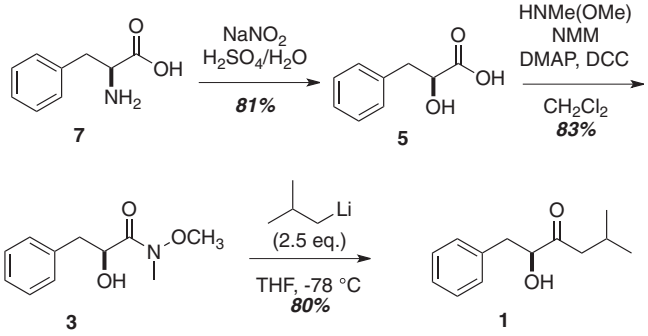


Scheme 1.

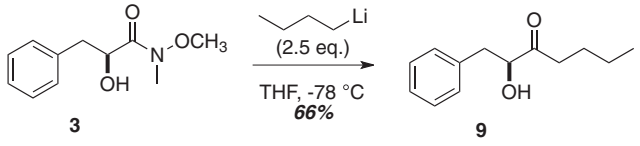


Scheme 2.

([α]$_D^{25}$ +35 (*c* 0.7, $CHCl_3$)).[1] Upon confirming identical optical rotations, both magnitude and sign, we could assign the stereochemistry of the hydroxyl group of (+)-sattabacin as (*S*).

Attempts to prepare **6** by a similar diazotization of L-tyrosine led to a complicated reaction mixture presumably from oxidation of the phenol. While one could envision protection of the phenolic oxygen to avoid these side reactions, we sought a more streamlined, protecting group free approach. Thus, asymmetric reduction of commercially available 4-hydroxyphenylpyruvic acid with (+)-DIP-Cl gave the alcohol **6** in excellent yield and enantiomeric excess (Scheme 3).[9] Chemoselective coupling of the carboxylic acid moiety under standard conditions gave the amide **4**, and treatment of this amide with excess *iso*-butyllithium at low temperature gave the natural product (+)-4-hydroxysattabacin (**2**) in modest yield. Again NMR spectral data were identical to those previously reported and the optical rotation was comparable to that previously described, both in magnitude and sign. Thus, the absolute configuration of the chiral hydroxyl group in (+)-4-hydroxysattabacin could also be assigned as (*S*).

The syntheses of these natural products are readily amenable to the preparation of various structural analogs. Addition of organometallic reagents to the amide **3** is expected to give several analogs differing in the nature and substitution of the ketone side chain.



Scheme 4.

For example, treatment of **3** with *n*-butyllithium under our previously optimized conditions gave the *n*-butyl analog **9** in comparable yield (Scheme 4). Efforts are currently underway to prepare other side chain analogs and screen these compounds for antiviral activity.

In conclusion, the first asymmetric total syntheses of the antiviral natural products (+)-sattabacin and (+)-4-hydroxysattabacin were each completed in three overall steps from commercially available starting materials. These syntheses were concise, high yielding, and protecting group free. The total syntheses of both **1** and **2** allowed for the unequivocal establishment of their absolute configuration, which was previously unknown. Further, the synthetic strategy employed allows for the simple preparation of side chain analogs. Preparation of these structural analogs and evaluation of antiviral activity are in progress and will be reported in due course.

Acknowledgments

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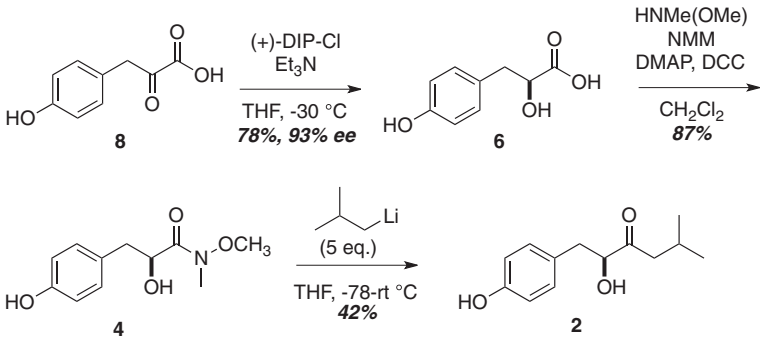
Supplementary data

Supplementary data (full characterization of all new compounds (**1**–**4, 9**) and copies of NMR spectra) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.09.147.



Scheme 3.

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