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Enantioselective Total Synthesis of (−)-Napyradiomycin A1 via Asymmetric Chlorination of an Isolated Olefin

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Halogenated natural products are currently recognized to be a large class of agents dispersed throughout Nature, often possessing unique structures and potent biological activity.[1] One such group is the napyradiomycins (**1**−**3**, Figure 1), compounds isolated from terrestrial strains of *Streptomyces* bacteria and characterized by spectroscopic, degradative, and X-ray crystallographic means.[2] Indeed, apart from the synthetic challenges that their polycyclic frameworks are likely to provide, especially in light of their halogenation pattern, these agents have intriguing biological profiles, including activity as nonsteroidal estrogen antagonists.[3] More recently, Fenical et al. described the isolation and characterization of a group of compounds, such as **4**, from a marine source of *Streptomyces* bacteria that possess the napyradiomycin architecture plus an added aryl methyl group.[4] Many of these compounds demonstrated *in vitro* antibacterial activity against methicillin- and vancomycin-resistant strains as well as antitumor potency against colon carcinoma cells. In all cases, however, the specific structural bases for these activities remains unknown, and only Tatsuta et al. have reported a total synthesis of a complete family member (racemic **3**).[5] As such, additional synthetic solutions, particularly enantioselective ones, are needed.

Our retrosynthetic analysis of these targets is defined in Figure 1 and is based, in part, on Nature's putative biosynthesis.[6] As indicated, dissection of the pendant six-membered ring in napyradiomycin B4 (**2**) through a chloronium-induced cation-π-cyclization would lead directly to napyradiomycin A1 (**3**). We then anticipated that this natural product could potentially arise from **5** if that molecule's lone alkene could be enantioselectively halogenated, using the resultant chirality to direct the incorporation of the geranyl side chain and its adjacent chlorine in subsequent operations. This new goal structure (**5**) could, in turn, be accessed from the natural product flaviolin (**6**)[7] in a single step through an acid-mediated merger with 3-methylcrotonaldehyde.[8] While this plan appears simple, its execution requires the development of two methods, as no effective precedent exists for either the proposed asymmetric chlorination of the olefin within **5** or the chloronium-induced cation-π reaction converting **3** to **2**.[9] This communication details solutions that address the first of these issues, culminating in the first asymmetric synthesis of **3**.

Our efforts began by preparing flaviolin (**6**), a material synthesized previously in eight linear steps.[10] As indicated in Scheme 1, a shorter synthesis was achieved by applying an alkali fusion reaction to the inexpensive sulfonic acid salt **7** and then oxidizing the resultant tetraphenol in air. This two-step protocol proceeded in 64% overall yield on gram scale. Next, following exposure of flaviolin (**6**) to 3-methylcrotonaldehyde in the presence of EDDA[11] and selective protection of the non-H bonded phenol to produce **8**, we were able to achieve an asymmetric alkene chlorination that proceeded in 93% yield and 87% enantiomeric excess (ee; up to 95% ee after recrystallization) as determined by HPLC analysis. To the best of our knowledge, this step leading to **12**, inspired by one of the original attempts to achieve enantioselective Diels−Alder reactions,[12] represents the first highly asymmetric chlorination of an olefin.[13] In the event, 4 equiv of (*S*)-

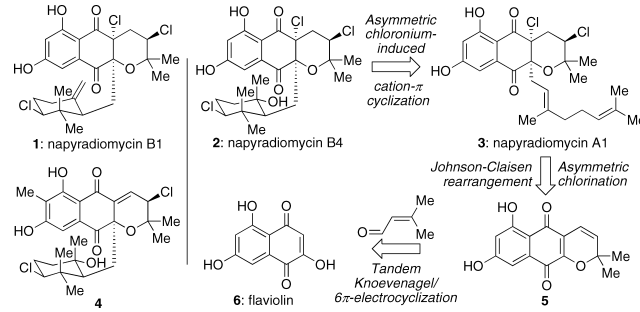

Figure 1. Napyradiomycin family of natural products and a generalized retrosynthetic analysis based on the development of new chiral halogenation reactions.

9[14] were treated with 4 equiv of BH_3·THF and AcOH in THF for 20 min. Upon removal of the solvent, a solution of **8** in THF was added and the resultant mixture was stirred for 1 h. When Cl_2 was then added at −78 °C, it reacted with the double bond of **10** selectively, with a terminating attack of chloride providing the 1,2-*trans*-stereochemistry of the product (**12**). Although X-ray crystallography verified the relative connectivities of the structure, a determination of the absolute configuration of **12** would have to await completion of the synthesis (vide infra). We note at this juncture, however, that while an ideal solution to this step would have employed less ligand, **9** could be recovered and recycled as long as the reaction was conducted in THF;[15] the complexed ligands also served an additional role in that they protected the aryl ring of **8** from chlorination.

We next took advantage of the stereochemical outcome of this halogenation step by replacing the activated chloride adjacent to the quinone system in **12** with retention. Phenol protection and acetate cleavage[16] then provided halohydrin **13** in 85% yield. This new intermediate proved suitable for the sterecontrolled incorporation of part of the remaining C atoms of the target via an acid-catalyzed Johnson−Claisen rearrangement[17] employing excess $CH_3C(OMe)_3$ in toluene in a sealed tube at 130 °C to generate ester **14** with the desired ring junction stereochemistry. This reaction proceeded in 27% yield with 68% recovered starting material and proved to be the only version of the Claisen rearrangement that succeeded when applied to **13**; its success also required that the highlighted functional group within **13** be a methyl ether. From **14**, three transformations adjusted the oxidation state to that of **15**.[18] This intermediate was then converted into **17** through a Wittig olefination using the ylide derived from **16**[19] (1.7:1 *E*/*Z* selectivity), followed by stereoselective enolate capture with electrophilic chlorine. All other olefination procedures (such as Julia−Kocienski reactions[20] and cross metathesis) failed to afford product in the first of these steps. Finally, controlled methyl ether hydrolysis (MgI_2 in Et_2O/THF at 50 °C),[21] followed by PPTS-induced MOM-ether cleavage, completed the target molecule (**3**). Though all spectral data were fully consistent, optical rotation measurements revealed that we had prepared the antipode of natural **3**.

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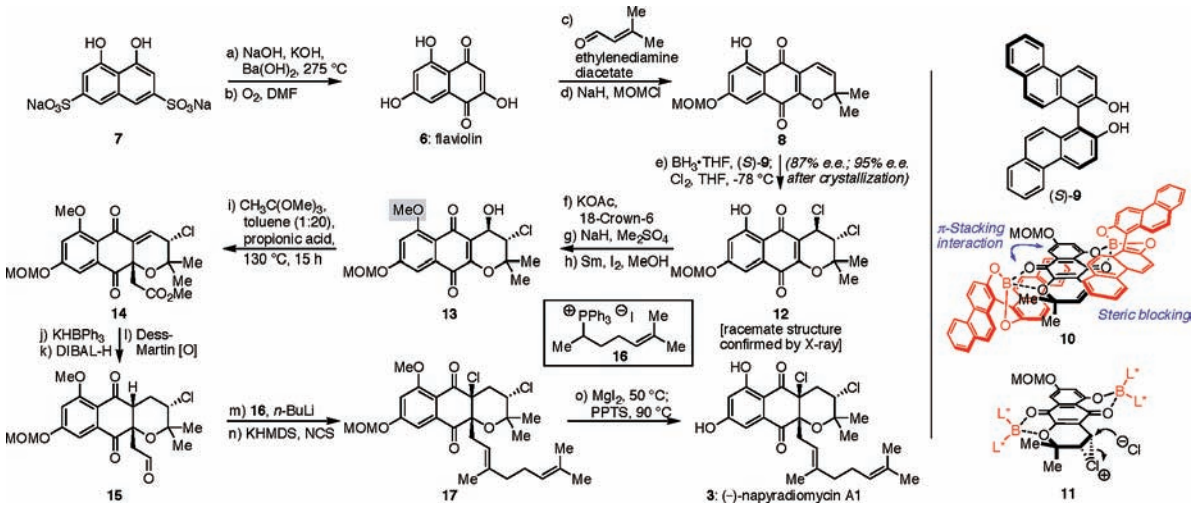
Scheme 1. Enantioselective Total Synthesis of (−)-Napyradiomycin A1 (**3**)[a]



[a] Reagents and conditions: (a) NaOH (37 equiv), KOH (40 equiv), $Ba(OH)_2$ (8.0 equiv), **7** (1.0 equiv), 275 °C, 7 h; (b) K_2CO_3 (excess), DMF, 25 °C, 10 h, 64% over two steps; (c) 3-methyl-2-butenal (1.5 equiv), EDDA (0.1 equiv), 25 °C, 2 h, 54%; (d) NaH (1.1 equiv), MOMCl (1.2 equiv), THF, 0 °C, 2 h, 65%, 21% r.s.m.; (e) **9** (4.0 equiv), BH_3·THF (4.0 equiv), glacial AcOH (4.0 equiv), THF, 25 °C, 20 min; concentrate; **8** (1.0 equiv), THF, 25 °C, 1 h; Cl_2 in CH_2Cl_2, 20 min, −78 °C, 93%; (f) KOAc (10 equiv), 18-crown-6 (0.3 equiv), THF, 25 °C, 1 h, 85%; (g) NaH (1.1 equiv), THF, 0 °C; Me_2SO_4 (2.0 equiv), 0→25 °C, 10 h, 79%, 16% r.s.m.; (h) Sm (0.6 equiv), I_2 (0.6 equiv), MeOH, 25 °C, 30 min, 95%; (i) propionic acid (0.12 equiv), $CH_3C(OMe)_3$ (7.0 equiv), toluene, 130 °C (sealed tube), 15 h, 27%, 68% r.s.m.; (j) $KHBPh_3$ (1.2 equiv), THF, −78 °C, 2 h, 54%; (k) DIBAL-H (2.2 equiv), toluene, −78 °C, 2 h; (l) Dess-Martin periodinane (2.0 equiv), $NaHCO_3$ (10 equiv), CH_2Cl_2, 25 °C, 1 h, 63% over two steps; (m) **16** (1.5 equiv), *n*-BuLi (1.45 equiv), THF, −78 °C, 30 min; **15** (1.0 equiv), −78 °C, 5 min, 34%, 50% r.s.m., 1.7:1 *E*/*Z*; (n) KHMDS (5.0 equiv), THF, −78 °C, 1 h; NCS (2.0 equiv), −78 °C, 30 min, 84%; (o) MgI_2 (11 equiv), Et_2O/THF (1:1), 50 °C, 8 h; concentrate; PPTS (10 equiv), *t*-BuOH, 90 °C, 4 h, 90%.

Given this outcome, it is possible to provide a rationale for the stereoselectivity of the halogenation reaction that led to **12**. As indicated in Scheme 1, we believe that, prior to the addition of Cl_2, mixing of the substrate with the ligands leads to complex **10**. This intermediate potentially possesses a cooperative effect between the two ligands wherein one achieves an organizational π-stacking interaction with the substrate that then helps orient the other to block the top face of the alkene. Consequently, chloronium formation occurs predominantly from the bottom face to deliver the product-determining intermediate **11**.[22] Although verifying this tentative picture is the subject of current study, it is circumstantially supported by the fact that enantioselection is poor when less than 2 equiv of chiral controller are used; active coordination through the MOM ether is unlikely given that the enantioselection is equivalent when that group is methyl.

In conclusion, the first asymmetric total synthesis of (−)-napyradiomycin A1 (**3**) has been achieved in 15 linear steps. Key elements include a two-step synthesis of flaviolin (**6**), the first highly asymmetric chlorination of an isolated alkene, and the use of a Johnson−Claisen rearrangement to forge a quaternary C next to a glucal-like O. The concise and flexible nature of the pathway should enable the facile synthesis of other members of this unique class of molecules, particularly if the yield and selectivity for the Claisen and olefination portions of the sequence can be enhanced; efforts are already underway to discover diastereoselective conversions of **3** into **2** as well as catalytic, enantioselective solutions for the synthesis of **12** from **8**.

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Supporting Information Available: Detailed experimental procedures, spectra, and full characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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