Rapid stereocontrolled assembly of the fully substituted *C*-aryl glycoside of kendomycin with a Prins cyclization: a formal synthesis†

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Prins cyclization using an electron-rich benzaldehyde and a homoallylic alcohol efficiently delivered the fully substituted *C*-aryl tetrahydropyranoside of kendomycin.

Kendomycin (**1**, Fig. 1), a polyketide metabolite of the common soil bacteria *Streptomyces violaceoruber*, has shown remarkable potential for use as a medicinal agent since its initial isolation by Funahishi and coworkers in 1996[1] and Bode and Zeeck's subsequent reisolation and structure determination by Mosher's ester and X-ray crystallographic analysis in 2000.[2] Pharmacologically,[1–3] kendomycin has shown impressive cytotoxicity against human breast, stomach, and liver carcinoma cell lines ($GI_{50} < 100$ nM), as well as anti-bacterial activity against both methicillin- and vancomycin-resistant *Staphylococcus aureus*. Additionally, kendomycin exhibits anti-osteoporotic activity and potent antagonism against the endothelin receptor.

Kendomycin's potential as a medicinal agent and its demanding structural topography have generated considerable interest in the synthetic organic community. Synthetically challenging features of this macrocyclic natural product include a fully substituted *C*-aryl glycosidic core, bridged by a lipophilic *ansa*-polyketide chain containing an (*E*)-trisubstituted olefin. The Lee group[4] and the Smith[5] group have reported total syntheses of kendomycin. Seminal investigations by Mulzer *et al.* developed much of the chemistry of the natural product,[6a–e] and a number of other groups have reported diverse synthetic approaches to this fascinating compound.[6]

Our group[7] and others[8–10] have studied the Prins cyclization as a convergent and highly diastereoselective means of synthesizing tetrahydropyranols, such as that found in **1**. Fig. 1 illustrates our retrosynthetic strategy utilizing this approach. Tetrahydropyran (THP) **2** was envisaged to arise from a Prins cyclization between homoallylic alcohol and benzaldehyde components of roughly equal complexity. This Prins approach would efficiently generate three new stereocenters in a single synthetic transformation. While the potential of the Prins cyclization is well precedented,[7–10] its scope and generality with highly substituted aromatic aldehydes have not been fully developed. Our proposed strategy would provide a concise assembly of the *C*-aryl pyranoside scaffold found in **1**, and it would extend the scope of the Prins reaction. Here we present a successful application of the Prins cyclization as the key step in the convergent synthesis of the fully substituted 2-aryl tetrahydropyranol **2** found in kendomycin.

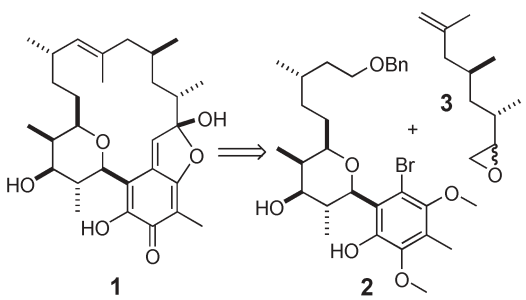

Fig. 1 Retrosynthetic analysis of kendomycin.

The homoallylic alcohol and benzaldehyde components for the key Prins cyclizations were prepared from known compounds **4**–**6** (Scheme 1). Allylation of aldehyde **4**[11] with Hoffmann's boronate **5**[12] forged (*E*)-homoallylic *syn*-alcohol **7** in excellent yield with >95% diastereoselectivity.[13,14] Acylation of known phenol **6**[15] provided acetyloxy benzaldehyde **8**.

These readily available components were then studied in the key Prins cyclization reaction. Treatment of homoallylic alcohol **7** and benzaldehyde **8** with $BF_3{\cdot}OEt_2$ and HOAc in hexane generated tetrahydropyran acetate **9a** and alcohol **9b** as single diastereomers in 65% combined yield. This Prins cyclization efficiently delivered a *C*-aryl glycoside containing 19 of the 29 carbons of **1** and six of its nine stereocenters. Reductive cleavage of the acetates and subsequent bromination of the arene then provided target THP **2** in 35% yield over four steps from aldehyde **4**. An analogous Prins cyclization with alcohol **7** and sulfonyloxy benzaldehyde **10** generated tetrahydropyrans **11** in excellent yield; however, the sulfonate group could not be hydrolyzed under basic methanolysis conditions without extensive decomposition, in accordance with a similar observation by the Willis group.[9b]

Our mechanistic rationale for the key Prins cyclization is shown in Fig. 2. Condensation of alcohol **7** and benzaldehyde **8** with $BF_3{\cdot}OEt_2$ and HOAc generates (*E*)-oxocarbenium ion **12a**. Nucleophilic capture from an equatorial trajectory in the expected chair-like transition state at the C(4)-position of cation **12a** delivers THP **9a**. With a poorly nucleophilic anion, trapping and cyclization to THP **9** become slow relative to oxonia-Cope equilibration to the higher energy, non-conjugated cation **12b**. Because each oxocarbenium ion **12** preserves the inherited stereochemistry, trapping either entity at the C(4) position leads to THPs **9**. Slower trapping, however, provides oxocarbenium ion **12b** increased opportunity to undergo an undesired fragmentation or hydrolysis to generate aldehyde **4**.[9b,e] Alcohol **7** reacts

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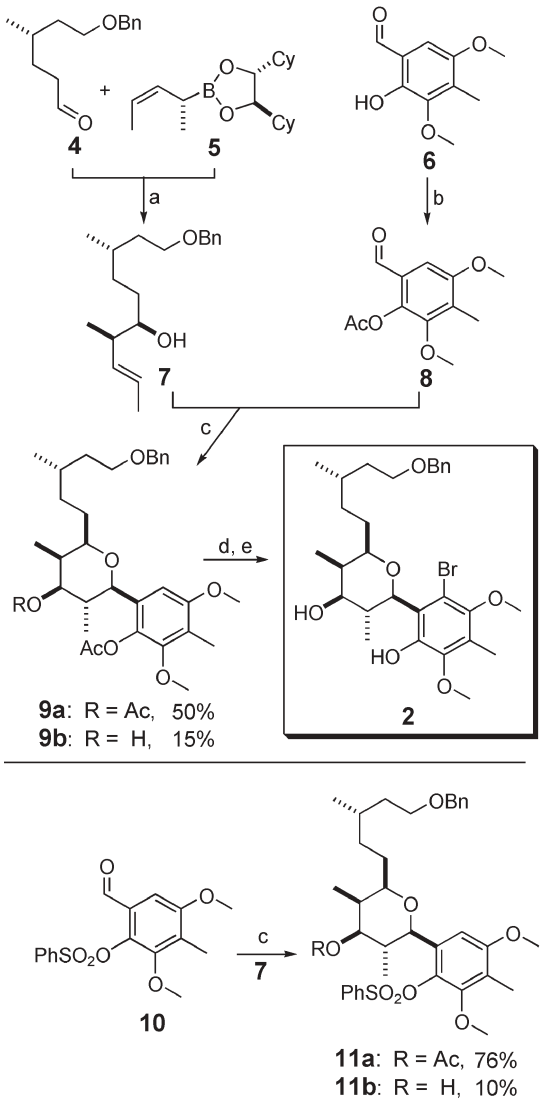
† Electronic supplementary information (ESI) available: Complete experimental procedures and characterization for all compounds, including improved laboratory-scale preparations of known intermediates **5** and **6**. See DOI: 10.1039/b602937j



Scheme 1 (a) i. n-hexane, 0 °C, 36 h; ii. NaOH, H_2O_2, 91%; (b) AcCl, pyr., 88%; (c) BF_3-OEt_2, AcOH, n-hexane, 0 °C to rt, 12 h; (d) DIBAL-H, −78 °C, DCM, 91%; (e) Br_2, $CHCl_3$ 65%.

preferentially with newly formed aldehyde **4** in a Prins cyclization, leading to side-chain exchange product **13**. Yields of THP **13** were used to estimate the amount of aldehyde **4** formed during the Prins cyclization reactions.

The successful Prins cyclizations depicted in Scheme 1 required the optimization of several parameters to control the problematic fragmentation. First, we found that attenuation of the phenolic electrons with an electron-withdrawing group was necessary to suppress the fragmentation of oxocarbenium ion **12b**.[9b] Acetylation (**8**) and sulfonylation (**10**) of the phenol successfully accomplished this requirement.[16] A second consideration was the competency of the trapping agent. Initial cyclization studies using TFA in DCM as solvent[9] generated the trifluoroacetate analogs of **9a** and **11a** in only 25–35% yields, while side-chain exchange products such as **13** (35–55%) and decomposition dominated the product mixtures. We hypothesize that the poor nucleophilicity of the trifluoroacetate anion prevents efficient trapping of cations **12** and thus increases the population of the kinetically competitive

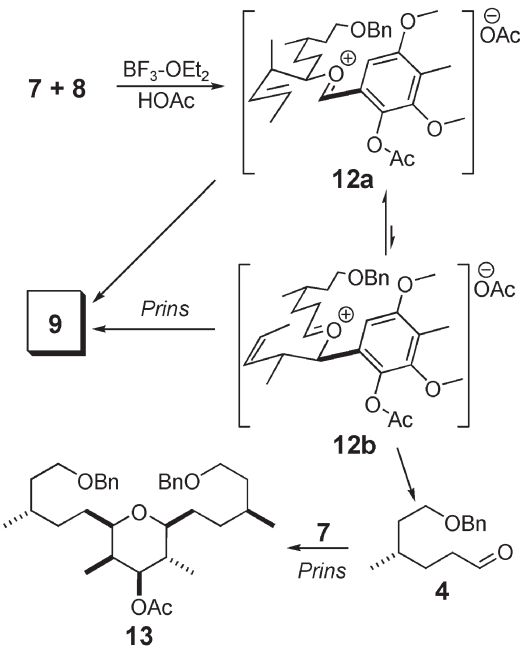
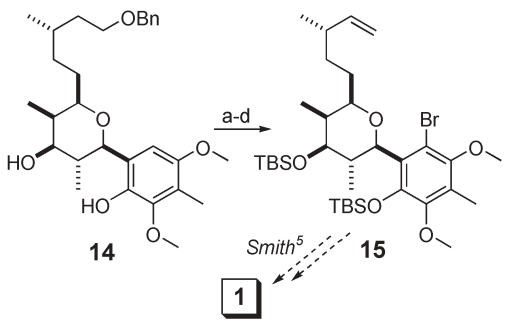


Fig. 2 Mechanistic rationale for cyclizations to THPs **9** and **13**.

and counterproductive side processes, such as fragmentation. Replacing TFA with AcOH as a trapping agent and using $BF_3{\cdot}OEt_2$ as a promoter strongly suppressed the production of THP **13** to <10%. Finally, we reasoned that a less polar solvent should further disfavor fragmentation. Changing the solvent from DCM to non-polar n-hexane increased the yields of THPs **9** and **11** to 65% and 86%, respectively. The optimized reaction conditions are heterogeneous, as the benzaldehyde and THP product are essentially insoluble in the hexane solvent. The low solubilities of the aldehydes **8** and **10** result in their low reaction concentrations, which presumably play a role in reducing the formation of side product **13**.

The tetrahydropyran **15** was an intermediate in Smith and coworkers' synthesis of kendomycin.[5] We set out to prepare THP **15** using our Prins cyclization approach, both to secure the structure of **2** and to complete a formal synthesis of kendomycin (Scheme 2). Introduction of the terminal olefin of **15** was first pursued using a Prins cyclization with an unsaturated analog of alcohol **7**.[17] The Prins reaction between benzaldehyde **10** and the diene alcohol,[17] however, generated a complex product mixture.



Scheme 2 (a) TBSOTf, 2,6-lutidine, 80%; (b) H_2, Pd/C, 89%; (c) Br_2, propylene oxide, CH_2Cl_2, 75%; (d) i. 2-(NO_2)-C_6H_4-SeCN, PBu_3; ii. H_2O_2, THF, 73%.

Apparently the remote alkene reacts with the oxocarbenium ion intermediates (*e.g.* Fig. 2). Undaunted by this result, we employed a five step procedure to convert THPs **9** to Smith and coworkers' intermediate **15**. Silylation of diol **14**, available by reductive cleavage of acetates **9**, and subsequent hydrogenolysis of the benzyl group provided a primary alcohol. After arene bromination,[18] the alcohol was eliminated using Grieco and coworkers' procedure[19] to deliver alkene **15** in 35% yield from THPs **9**. The spectral data for **15** matched that reported by the Smith group, and this correlation completes a formal synthesis of kendomycin.

In conclusion, we have successfully synthesized the *C*-aryl glycoside found in kendomycin with a highly diastereoselective Prins cyclization. Attenuation of the electron rich benzaldehyde and the use of acetic acid as a trapping agent were necessary to suppress problematic side reactions. The selective generation of three new stereocenters in the Prins cyclization facilitated the short and highly convergent assembly of the kendomycin fragment.

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Dedicated to the life and memory of Norman Bahnck.

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