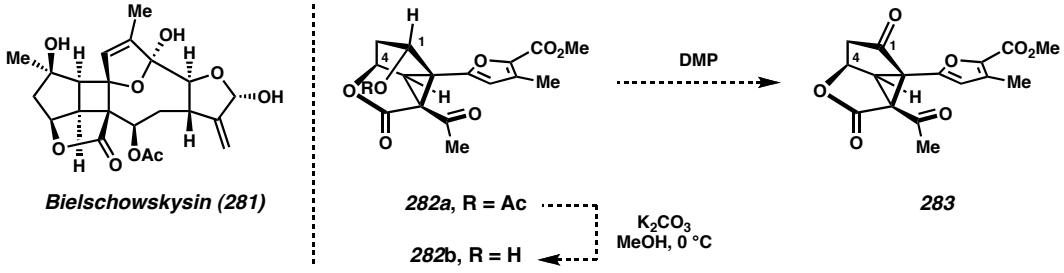
APPENDIX FIVE

Similar Translactonization in Bielshowskysin, a Related System

We recently observed a similar intramolecular translactonization of secondary γ-lactones.[i] This translactonization was observed to occur in intermediates prepared en route to the synthesis of bielschowskysin (**281**). One of the intermediates prepared for this synthesis was [5–5–3]-fused **282a**. We expected to easily cleave the acetate in intermediate **282a** and form alcohol **282b** (Scheme A0.0.2). Indeed, treatment of [5–5–3]-fused **282a** furnished 95% yield of a single product that we assigned as alcohol **282b**. Dess-Martin periodinane alcohol oxidation of what we thought to be alcohol **282b** provided a ketone that was initially assigned as ketone **283**. Both of these assignments were made on the basis of ^{1}H, ^{13}C, infrared and high resolution mass spectroscopy.

Scheme A0.0.1 Anticipated synthetic sequence en route to bielschowskysin



These assigments did not withstand further chemical transformations. Lewis acid-mediated methanolysis of what was thought to be ketone **283** formed a product

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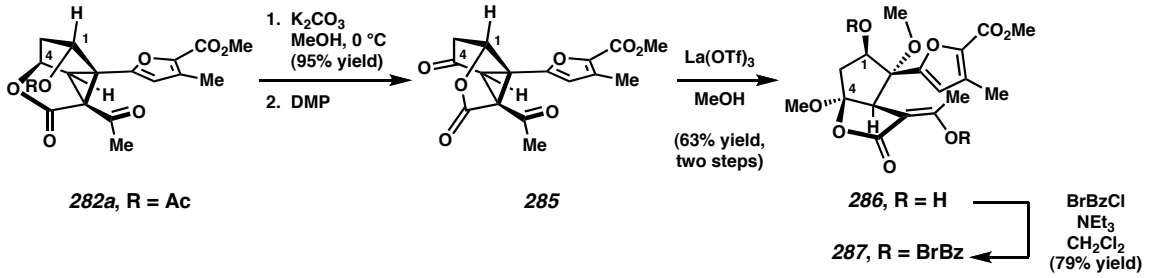
[i] This work was carried out by Michael Meyer, a graduate student, and Dr. John Phillips, a postdoctoral scholar, in the laboratories of Brian Stoltz.

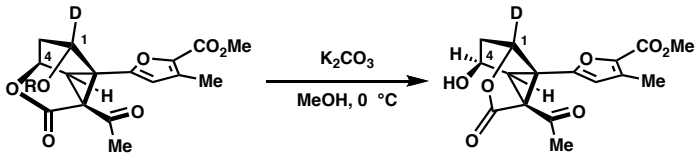
incorporating a methyl ether (e.g., **286**). We were only able to identify this product upon derivatization with *p*-bromobenzoyl chloride, which provided bromobenzoylated **287**. Crystallographic analysis of bromobenzoylated **287** demonstrated that alcohol oxidation with Dess-Martin periodinane had occurred at the C(4), rather than the C(1) position to provide **285**, indicating that two undesired translactonizations had taken place (e.g., intermediate **282a** → ketone **285** and ketone **285** → methyl ether **286**).

Scheme A0.0.2 Crystallographic evidence for translactonization

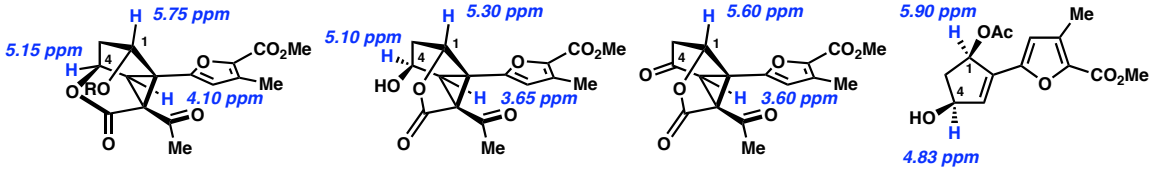


At this point, the initial translactonization could have occurred during acetate cleavage or alcohol oxidation. To distinguish between proton resonances associated with C(1) and C(4), we constructed deuterated **282c** (Scheme A0.0.3). With this new spectroscopic handle, it was possible to differentiate between proton resonances associated with C(1) and C(4), revealing that the product of acetate cleavage on [5-5-3]-fused **282a** was, in reality, translactonized **284a**.

Scheme A0.0.3 Deuterium labeling experiments provide evidence of translactonization



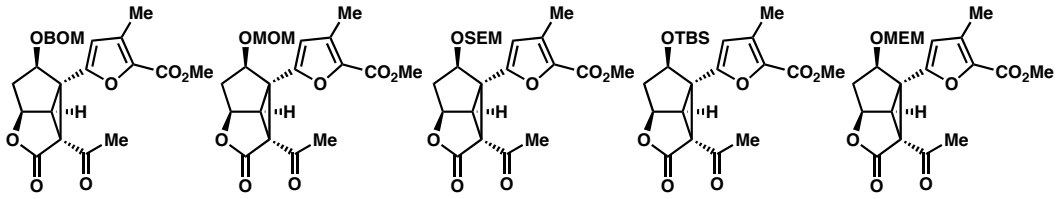
282c*, R = Ac** ***283b



282a*, R = Ac** ***283a ***287*** ***288***

In an effort to circumvent translactonization, we constructed a series of tricycles (**282d–h**, Figure A0.0.1). It was thought that alternative secondary ethers would be labile to more mild cleavage conditions. To our dismay, all efforts to unmask the alcohol resulted either in undesired cyclopropyl ring opening or translactonization. Furthermore, efforts to concurrently remove the protecting group and oxidize the alcohol before translactonication were also unsuccessful.

Figure A0.0.1 Tricycles that undergo translactonization on ether cleavage



282d ***282e*** ***282f*** ***282g*** ***282h***

Even the mildest of conditions could not avoid this translactionization. Evidently, the C(1) oxygenation was in too close a proximity to the *cis*-fused lactone to avoid any favorable translactonization. As a consequence of these investigations, we were careful to seek out evidence for or against translactonization in our related system. When we did

discover a similar translactonization, we approached it with the knowledge that this was not a problem we would circumvent, but instead to incorporate strategically into our synthesis.