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Total synthesis of (−)-centrolobine: β-*C*-glycoside formation via a tandem Grignard addition and stereoselective hemi-ketal reduction

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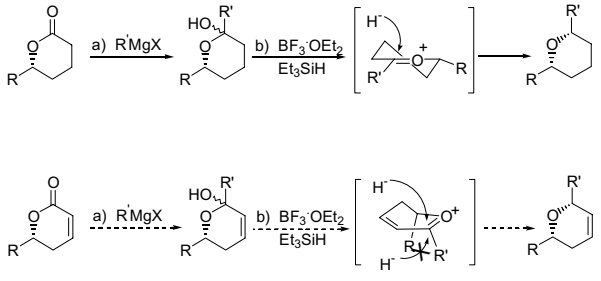
Abstract—It has been demonstrated that an aryl-β-*C*-glycoside can be efficiently constructed via a sequence consisting of Brown asymmetric allylation, ring-closing metathesis, hydrogenation, nucleophilic addition, and stereoselective Et_3SiH reduction. The antibiotic natural product (−)-centrolobine was synthesized in this manner utilizing only five steps with an overall 53% yield.

Over the past two decades, the construction of α- and β-*C*-glycosides has become increasingly important in the synthesis of biologically active natural products. Along this line, there has been substantial growth in new synthetic methodology within this area. Such building blocks have been synthesized by using several methodologies including the hetero-atom Diels–Alder reaction,[1] Petasis–Ferrier rearrangement,[2] intermolecular silyl-modified Sakurai and Prins cyclizations,[3] *exo*-Pd-mediated allylic etherification,[4] radical cyclization,[5] and intramolecular Michael addition with oxygen nucleophiles.[6]

With this in mind, we were interested in expanding Kishi's strategy for the synthesis of β-*C*-glycosides.[7] To the best of our knowledge, there are no reports of a nucleophilic addition/reduction sequence to an α,β-unsaturated lactone as shown in Scheme 1. We envisioned utilizing such a methodology for the synthesis of dehydro-β-*C*-glycosides. In turn, these compounds could readily serve as advanced intermediates for the synthesis of a variety of natural products. As reported for the synthesis of dehydro-α-*C*-glycosides[8] and shown in Scheme 1, it was reasoned that the reduction of the in situ generated α,β-unsaturated oxonium cation with



Scheme 1.

Et_3SiH should proceed in a very stereoselective manner to provide the dehydro-β-*C*-glycoside.

(−)-Centrolobine (**1**) is a naturally occurring antibiotic, isolated from the heartwood of *Centrolobium robustum* and from the stem of *Brosimum potabile*, both indigenous to tropical South America.[9] Solladie and co-workers were the first to disclose the asymmetric total synthesis and thus determined the absolute configuration of (−)-centrolobine.[10] Three other total syntheses of **1** have independently since been reported.[11] The relatively simple structure of (−)-centrolobine makes it an ideal target for testing synthetic methodologies of β-*C*-glycosides.

As shown in Scheme 2, our initial approach to the synthesis of **1** was based on a stereoselective reduction of a cyclic α,β-unsaturated oxonium cation mediated by the treatment of an appropriate hemi-ketal with Lewis acid.

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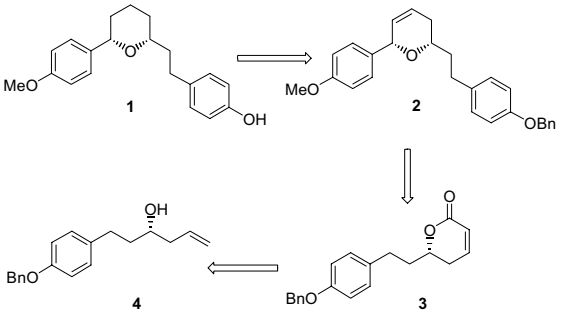
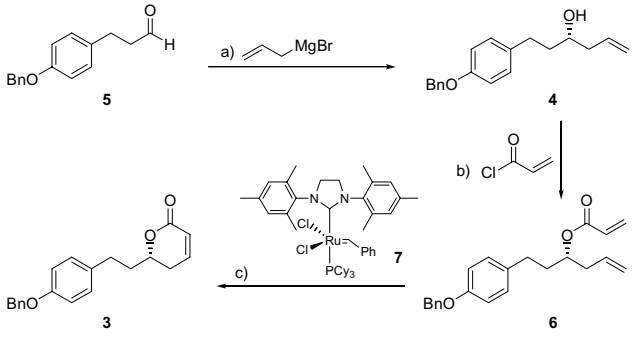


Scheme 2. Retrosynthetic analysis of **1**.

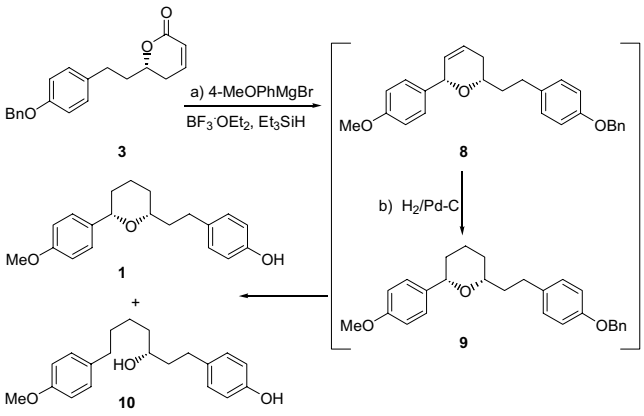
In turn, the hemi-ketal was envisaged to be derived from a nucleophilic addition of the 4-methoxyphenyl Grignard reagent to the corresponding lactone **3**. With the dehydro-β-*C*-glycoside in hand, a global hydrogenation was reserved for the concomitant removal of both the unsaturation and the benzyl protecting group resident in **2** to provide the natural product **1**.

The synthesis of **1** was initiated with the previously reported benzyl protected aldehyde **5** as shown in Scheme 3. Thus, allylation of **5**[11a] with allyl magnesium bromide furnished the homoallylic alcohol **4** in 84% yield. Esterification of **4** with acryloyl chloride and subsequent ring-closing olefin metathesis (0.017 M) with 5 mol% of Grubbs' second-generation catalyst (**7**) proceeded smoothly and provided lactenone **3** in a 75% yield over two steps.[12]

The attempted transformation of lactenone **3** into centrolobine over two steps is highlighted in Scheme 4. With this in mind, nucleophilic addition of 4-methoxyphenylmagnesium bromide to lactenone **3** followed by Lewis acid promoted α,β-unsaturated oxonium formation and subsequent stereoselective Et_3SiH reduction furnished the *cis*-2,6-disubstituted dehydro-pyran intermediate **8** in 24% yield. Initially, we were pleased by the stereoselective nature of the addition/reduction sequence. It was deemed that the unsaturation resident in **3** hindered the nucleophilic addition to the carbonyl moiety and thus lowered the overall yield for the two-step process. Unfortunately, several attempts were made



Scheme 3. Synthesis of the α,β-unsaturated lactone **3**: Reagents and conditions: (a) allylMgBr (2.0 equiv), Et_2O, −78 °C, 1 h, 84%; (b) acryloyl chloride (5.0 equiv), Et_3N (10 equiv), DMAP (5% mol), CH_2Cl_2, 0 °C, 6 h, 86%; (c) catalyst **7** (5% mol), CH_2Cl_2, reflux, 5 h, 87%.

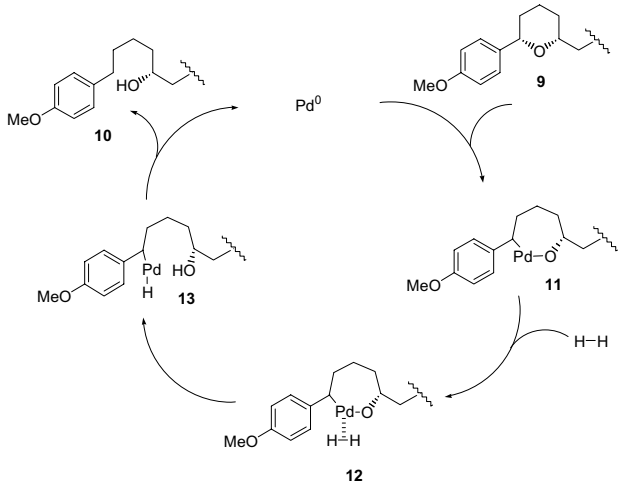


Scheme 4. Attempted synthesis of **1**: Reagents and conditions: 4-MeOPhMgBr (1.0 equiv), THF, −78 °C, 1.5 h, then Et_3SiH (10.0 equiv), $BF_3{\cdot}OEt_2$ (5.0 equiv), CH_3CN, −30 °C, 45 min, then 0 °C to rt, 1 h, 24%; (b) Pd/C (1.0% mol), EtOH, rt, 10 h, 10%.

to optimize the nucleophilic addition to **3** with the 4-methoxyphenyl Grignard reagent, but these efforts were unsuccessful beyond a 30% yield. We are currently investigating this addition/reduction sequence with a variety of other nucleophilic coupling partners.

In the short term, we were interested in completing the targeted natural product and treatment of **8** with the standard catalytic hydrogenation protocol (Pd/C, 1 atm of H_2, EtOH, 2 h) readily removed the olefin double bond, but did not cleave the benzyl-protecting group. Further hydrogenation of the Bn protected intermediate **9**, for additional 10 h surprisingly afforded only 10% of the desired final natural product **1**, coupled with the ring cleaved compound **10** in 82% yield.[13] The proposed mechanism leading to the formation of **10** is delineated in Scheme 5.

It seems likely that the catalytic hydrogenation of a benzyl (or derivative thereof) protecting group with Pd/C occurs via an oxidative insertion of the Pd^0 into the benzylic carbon–oxygen bond. Specifically in our case, this required a peculiar ring expansion from the pyran ring



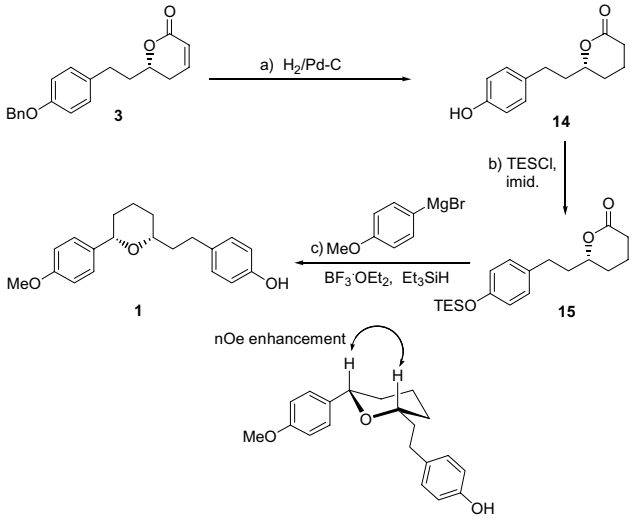
Scheme 5. Proposed Pd catalyzed ring-expansion/cleavage of **9**.

to a seven-membered Pd^{II} palladacycle **11**. An ensuing coordination-insertion of H_2 with the Pd^{II} complex **11** allows for the creation of **12** and resulting protonation of the Pd–O bond set the stage for reductive elimination of **13** to provide the observed ring-cleaved product. It is worth noting that an alternative mechanism can be envisioned via a sigma bond metathesis between H_2 and the corresponding palladacycle to afford the alcohol product **13** directly from intermediate **11**. In either case, reductive elimination of the Pd^{II}–hydride complex **13** would allow for the regeneration of the Pd^0 catalyst and the observed product **9**.

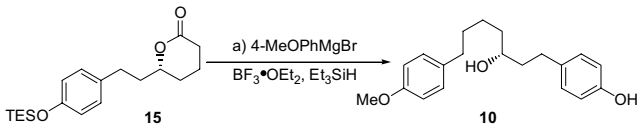
In an attempt to obtain more desirable results we abandoned the initial strategy and devised a new route incorporating the removal of the olefin to give the corresponding saturated lactone (Scheme 6). Thus, simultaneous reduction of the double bond and debenzylation by means of Pd/C catalyzed hydrogenation furnished lactone **14** with an 84% yield over two steps from **3**.

Subsequent protection of the corresponding free hydroxyl moiety as a TES ether provided lactone **15** and set the stage for the ensuing addition/reduction sequence in anticipation of stereoselectively obtaining **1**. With this in mind, addition of 4-methoxyphenylmagnesium bromide to **15** furnished the lactol, which was immediately reduced via the oxonium cation with Et_3SiH in the presence of $BF_3{\cdot}OEt_2$ to furnish (+/−)-centrolobine with combined 96% yield for the one-pot, four step sequence consisting of nucleophilic addition, oxonium cation formation, stereoselective reduction, and final desilylation of the phenolic TES group.[14] The relative configuration of (+/−)-centrolobine was confirmed by NOE enhancements as shown in Scheme 6.

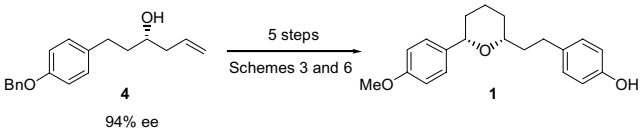
Similar to that of the overreduction of intermediate **9** with H_2 and Pd/C, it was observed that warming the



Scheme 6. Synthesis of (+/−)-centrolobine: Reagents and conditions: (a) Pd/C (3% mol), EtOH, rt, 40 h, 84%; (b) TESCl (12 equiv), imidazole (5 equiv), DMF, rt, 87%; (c) 4MeOPhMgBr (1.0 equiv) THF, −78 °C, 2.5 h; then Et_3SiH (10.0 equiv), CH_3CN, −40 °C, 96%.



Scheme 7. Lewis acid promoted pyran ring cleavage: Reagents and conditions: 4MeOPhMgBr (1.0 equiv) THF, −78 °C, 2.5 h; then Et_3SiH (10.0 equiv), $BF_3{\cdot}OEt_2$ (5.0 equiv), CH_3CN, −40 °C warm to 0 °C, 4 h, 90%.



Scheme 8. Asymmetric total synthesis of **1**.

oxonium reduction step to 0 °C after the addition of the corresponding Grignard reagent to **15** provided the ring cleaved product **10** in very good yields. As shown in Scheme 7, this one-pot, six step sequence consisting of nucleophilic addition, oxonium cation formation, stereoselective reduction, desilylation of the phenolic TES group, Lewis acid promoted cleavage of the pyran ring, and final hydride reduction of the presumed carbocation intermediate proceeded in an overall 90% yield.[15]

With all of this information in hand, the asymmetric synthesis of (−)-centrolobine was conducted with the chiral benzyl protected homoallylic alcohol **4**. Thus, intermediate **4** was prepared via an asymmetric allylation with Brown's Ipc_2B allyl reagent[16] of the corresponding protected aldehyde **6** in 75% yield with an ee of 94% as shown in Scheme 8. The completion of the enantioselective synthesis of (−)-centrolobine from **4** utilized the identical strategy as delineated in both Schemes 3 and 6. Thus, **1** was obtained in a 53% overall yield from the chiral homoallylic alcohol **4**.

In conclusion, we have demonstrated that an aryl-β-*C*-glycoside can be efficiently constructed via a sequence consisting of Brown asymmetric allylation, ring-closing metathesis, hydrogenation, nucleophilic addition, and stereoselective Et_3SiH reduction. The antibiotic natural product (−)-centrolobine was synthesized in this manner utilizing only five steps with an overall 53% yield. Further investigation into a nucleophilic addition/stereoselective reduction protocol of an α,β-unsaturated lactone for the synthesis of dehydro-β-*C*-glycosides will be reported in due course.

Acknowledgements

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