Synthesis of ($\pm$)-tetramethoxy-sinensigenin A via an intramolecular Marson-type cyclization.

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Abstract—The concise synthesis of ($\pm$)-tetramethoxy-sinensigenin A (**2**) is reported. The key C-C bond formation, which forged the [3.2.1]-bicyclic ether moiety, was the result of a regio- and diastereoselective intramolecular Marson-type cyclization *via* a pendent oxocarbenium cation intermediate. © 2014 Elsevier Science. All rights reserved.

Keywords: Oxocarbenium Cation; Epoxidation; Natural products; Cross-metathesis; Sinensigenin

A multitude of both marine and terrestrial sources repeatedly afford the synthetic organic community an assortment of structurally inspiring natural products.¹ Biologically active natural products continue to attract the attention of both synthetic as well as medicinal chemists alike.² As disclosed by Li and co-workers in 2010, the norlignan natural products, sinensigenins A (**1**) and C, were isolated from the rhizomes of *Curculigo sinensis* and *Curculigo capitulate*, respectively.^{3,4} As shown in Figure 1, sinensigenins A and C share a [3.2.1]-bicyclic ether core fused at the C1-C5 location to a catechol ring at the C1'-C6' position. An additional substituted catechol moiety is affixed to the bicyclic ether core at the C1 or C5 positions for sinensigenin A and C, respectively.

Figure 1: Natural products with a fused catechol ring to the [3.2.1]-bicyclic ether moiety

The catechol fused [3.2.1]-bicyclic ether core of **1** is also shared among other natural products (i.e. brussanol and bruguierol B) as highlighted in Figure 1.^{5,6} Surprisingly, to date, there have been no reported synthetic attempts for either sinensigenin A or C.

Scheme 1: Retrosynthetic analysis of sinensigenin A (**1**)

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Based on our previous synthetic work on brugueriol C and brissonol, we envisaged that the key C-C bond formation to forge the bicyclic ether moiety would be the result of an intramolecular Marson-type cyclization *via* a pendent oxocarbenium cation intermediate.⁷⁻⁹ With this idea in mind, the retrosynthetic analysis of **1** is delineated in Scheme 1. Thus, a global deprotection of the methoxy ethers resident in **2** would be carried out under basic conditions due to the potential instability of the unprotected tertiary hydroxyl moiety at C1 to ultimately afford **1**. Working backward, the protected natural product **2** was envisioned to arise from a diastereoselective Grignard addition to the ketone carbonyl of bicyclic intermediate **3**. The synthesis of the [3.2.1]-bicyclic ether of **3** would take place by means of a regio- and diastereoselective Marson-type cyclization of the corresponding lactol coupled with an appropriate Lewis acid after a DIBAL reduction of lactone **4**. We envisioned that a tandem epoxidation-lactonization process of the styrene-acid **5** under basic reaction conditions should allow for the completion of **4**. Lastly, the strategic convergence of the aromatic and aliphatic portions to provide **5** should be accomplished *via* a Ru-catalyzed cross-metathesis between substituted the dimethoxy styrene **6** and olefinic acid **7**.

Scheme 2. Synthesis of intermediate **11**: Reagents and conditions: a) **6** (1.0 equiv.), **7** (10.0 equiv.), Grubbs' catalyst **8** (0.1 equiv.), CH₂Cl₂, 40 °C, 15 h, 41%, b) KHSO₅ (1.41 equiv.), NaHCO₃ (2.5 equiv., 1M aq.), NaOH (1 equiv., 1 M aq.) MeCN (15% aq.), rt, 3h, 76%, c) TBDPSCl (2.0 equiv.), DMAP (0.20 equiv.), imidazole (4.0 equiv.), CH₂Cl₂, rt, 16 h, 84%. d) DIBAL (1.25 equiv.), CH₂Cl₂, -78 °C, 1h, 87%.

With the synthetic blueprint in mind, our initial attention was focused on investigating the Ru-catalyzed cross-metathesis between **6** and **7** as a convergent focal point. As described in Scheme 2, a solution containing a 10:1 ratio of **7** to **6** added dropwise over a 6h period to a refluxing solution of Grubbs' second-generation catalyst (**8**) in CH₂Cl₂ afforded the desired styrene derivative **5** with an *E/Z* ratio of ~20:1 as determined by ¹H NMR in a modest 41% yield.¹⁰ It is worth noting the major byproducts of the reaction were the homo-dimerized starting materials **6** and **7** due to their classification as type I olefins.¹¹ Initially we attempted the tandem epoxidation/lactonization sequence *en route* to **10** by means of intermediate **9** using Yang's methyl(trifluoromethyl)dioxirane (TFDO) protocol.¹² Unfortunately, only the δ -lactone was formed *via* a 6-*endo* cyclization as determined by extensive correlation spectroscopic analysis (HMBC).¹³ Upon altering the reaction to maintain a pH of 10, we prepared predominately the γ -lactone **10** by way of a 5-*exo* cyclization, nevertheless the yield was rather low (<20%).¹³ Our attention was subsequently turned to the Burrows' report in which they observed a tandem epoxidation/lactonization of a similar substrate to **5** utilizing Oxone under basic conditions.¹⁴ Thus, treatment of **5** with Oxone, NaHCO₃, and NaOH in aq. MeCN presumably afforded the epoxide intermediate **9** followed by an ensuing intramolecular cyclization of the carboxylate anion to afford lactone **10** in 76% yield. Silyl ether formation of the free hydroxyl group resident in **10** was readily accomplished with TBDPSCl, imidazole, and DMAP and furnished the fully protected lactone **4** in 84% yield.¹⁵ Partial reduction of lactone **10** with DIBAL furnished lactol **11** as a mixture of diastereomers and set the stage for the Marson-type cyclization by means of an oxocarbenium cation intermediate.

Scheme 3. Synthesis of intermediate **14**: Reagents and conditions: a) SnCl₄ (3.0 equiv.), CH₂Cl₂, -78 °C, 12 h, 71%.

With lactol **11** readily in hand, attention was turned to completing the [3.2.1]-bicyclic ether core of **1** by utilizing an intramolecular Marson-type cyclization as delineated in Scheme 3. Thus, treatment of **11** with 2 equiv. of SnCl₄ at

-78 °C in CH₂Cl₂ provided solely the desired cyclized product **14** in a 71 % overall yield.^{9a} A few observations are worth noting. Based on the observed product formation, the cyclization was very regioselective. There were two possible reactive sites on the aromatic ring, C2' and C6'. While both positions would have provided a six-membered ring product, it appeared that C2' was too sterically hindered to allow for the acylation reaction. Thus, the reaction was highly regioselective for the C6' position and led to the desired product **14**. With respect to diastereoselectivity, when lactol **11** is treated with SnCl₄ it was presumed that the oxocarbenium cation was formed in which two reactive conformations exist. Most likely the lowest energy conformation would be intermediate **12** where the substituted benzyl group would occupy a pseudo-equatorial position. Unfortunately, cyclization *via* an intramolecular acylation reaction cannot occur due to geometric constraints. The other reactive conformer would have been **13** and was the product of a ring-flip of compound **12**. Conformer **13** would have placed the pendent benzyl moiety in the pseudo-axial position and readily allowed for the Marson-type cyclization. Based on the isolated product, it was expected that conformer **13** was indeed the reactive one leading exclusively to the cyclized product **14**. Finally, a concomitant deprotection of the TBDPS ether resident in **11** was also observed due most likely to the byproduct HCl produced during the reaction.

Scheme 4. Attempted synthesis of sinensigenin A (**1**): Reagents and conditions: a) TPAP (0.15 equiv.), NMO (3.0 equiv.), CH₂Cl₂, rt, 2 h, 51%, b) **15** (1.3 equiv.), THF, 0 °C to rt, 12 h, 55%, c) NaH (10 equiv.), EtSH (20 equiv.), DMF, 120 °C, 12 h.

With the completion of **14** readily in hand, we were only a few steps away from the targeted natural product **1**. With this in mind, an oxidation of the free secondary hydroxyl moiety resident in compound **14** with TPAP (15 mol%) and NMO (3 equiv.) furnished ketone **3** in 51% yield.^{16,17} An ensuing addition of the corresponding 3,4-dimethoxyphenyl Grignard reagent (**15**) to the ketone functionality of **3** afforded the tertiary alcohol product **2** in 55% as a single diastereomer as determined by ¹H NMR.¹⁸ With the synthesis of **2**, we were poised for the completion of **1** upon

a global deprotection of all four methoxy ether protecting groups. Initially we envisioned that the deprotection of **2** would be carried out under basic conditions due to the potential instability of the unprotected tertiary hydroxyl moiety at C1. Using the prior reports of Sarpong and Majetich as a guide,¹⁹ we treated **2** with a large excess (10 equiv.) of NaSEt (NaH and EtSH) in DMF at 120 °C for 12h but did not observe the desired product **1**. Unfortunately, we isolated only decomposed material. Subsequent attempts at lower temperatures in DMF, shortened reaction time, and lesser equivalents of NaSEt did not provide **1**, and afforded only decomposed material. A final attempt at deprotection of **2** under acidic conditions with BBr₃ (CH₂Cl₂, -78 °C) was also unsuccessful and furnished decomposed material as well.

In conclusion, we have completed the synthesis of (±)-tetramethoxy-sinensigenin A (**2**). The key C-C bond formation, which forged the [3.2.1]-bicyclic ether moiety, was the result of a highly regio- and diastereoselective intramolecular Marson-type cyclization *via* a pendent oxocarbenium cation intermediate. Studies toward the total syntheses of both sinensigenins A and C utilizing an intramolecular Marson-type cyclization from a common intermediate are ongoing and will be reported in due course.

Acknowledgments

Support for this project was provided by the University of Alabama and the National Science Foundation CAREER program under CHE-0845011.

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15. Data for **4**: TLC R_f = 0.35 in 30% EtOAc/hexanes; ^1H NMR (500 MHz, CDCl_3) δ 7.61 (m, 2H), 7.47 (m, 2H), 7.39 (m, 1H), 7.31 (m, 3H), 7.21 (m, 2H), 6.72 (d, J = 1.6 Hz, 1H), 6.67 (d, J = 8.2 Hz, 1H), 6.62 (dd, J = 8.2, 1.6 Hz, 1H), 4.86 (d, J = 3.2 Hz, 1H), 4.53 (m, 1H), 3.83 (s, 3H), 3.72 (s, 3H), 2.32 (m, 2H), 2.24 (m, 1H), 1.96 (m, 1H), 1.07 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 177.0, 148.7, 148.6, 135.9, 135.8, 133.2, 132.9, 131.4, 129.8, 129.6, 127.5, 127.3, 119.3, 110.7, 110.3, 83.7, 75.9, 55.8, 55.7, 28.3, 26.9, 21.5, 19.4; IR (neat) cm^{-1} 3443, 2957, 2857, 1777, 1644, 1514, 1111, 732; HRMS (EI) calcd for $\text{C}_{29}\text{H}_{34}\text{O}_5\text{Si}$ $[\text{M}]^+$ 490.2176, found 490.2193.
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17. Data for **3**: TLC R_f = 0.20 in 30% EtOAc/hexanes; ^1H NMR (500 MHz, CDCl_3) δ 7.46 (s, 1H), 6.69 (s, 1H), 5.22 (d, J = 6.3 Hz, 1H), 4.71 (d, J = 6.9 Hz, 1H), 3.96 (s, 3H), 3.91 (s, 3H), 2.30 (m, 2H), 1.75 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 195.1, 154.0, 148.8, 142.3, 121.3, 108.4, 105.8, 81.0, 77.3, 56.2, 56.1, 30.5, 25.0; IR (neat) cm^{-1} 2957, 2872, 1735, 1597, 1463, 1315, 782; HRMS (EI) calcd for $\text{C}_{13}\text{H}_{14}\text{O}_4$ $[\text{M}]^+$ 234.0892, found 234.0891.
18. Data for **2**: TLC R_f = 0.20 in 45% EtOAc/hexanes; ^1H NMR (500 MHz, CDCl_3) δ 7.01 (d, J = 2.0 Hz, 1H), 6.72 (d, J = 9.3 Hz, 2H), 6.63 (dd, J = 8.4, 2.0 Hz, 1H), 6.55 (s, 1H), 5.02 (d, J = 5.2 Hz, 1H), 4.44 (d, J = 7.5 Hz, 1H), 3.91 (s, 3H), 3.84 (s, 3H), 3.83 (s, 3H), 3.78 (s, 3H), 2.22 (m, 1H), 2.14 (m, 2H), 1.84 (m, 1H). ; ^{13}C NMR (125 MHz, CDCl_3) 148.8, 148.6, 148.5, 148.1, 140.5, 133.2, 129.8, 119.9, 110.4, 110.3, 110.0, 106.0, 83.1, 77.1, 76.4, 56.0 (3), 55.9, 34.0, 23.4; HRMS (EI) calcd for $\text{C}_{21}\text{H}_{24}\text{O}_6$ $[\text{M}]^+$ 372.1573, found 372.1579.
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