First Synthesis of the A/B Ring of Ouabain

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ABSTRACT

The synthesis of the fully functionalized A/B ring of ouabain has been accomplished efficiently from commercially available starting materials. A key Robinson annulation allows for the building of the desired carbon framework in one high-yielding step. Directed epoxidation followed by selective epoxide opening furnished the final tetraol with the desired all-cis stereochemistry.

Ouabain (1) was discovered and so named in 1888 by Arnaud1 who isolated the crystalline glucoside from the bark and roots of the ouabaio tree, used by the Somalis of East Africa as an arrow poison. This cardenolide is part of a family of cardiotonic steroids (digitalis glucosides) that have been used for more than two centuries to treat congestive heart failure (CHF).

The novel stereochemistry along with the high degree of oxygenation render ouabain a challenging synthetic target. To date, no total syntheses but only few synthetic studies have been reported in the literature.2 As part of our investigations directed toward the synthesis of ouabain, we explored the use of a Robinson annulation strategy to build the A/B ring of this oxygenated steroid.

The first annulation approach involved \( \alpha \)-silyl enone 2 and commercially available \( \alpha \)-keto ester 3 as described in Scheme 1. This synthetic strategy relied on the use of phenyldimethylsilyl as a masked hydroxyl group.4 Unfortunately, despite the encouraging selectivity for the desired cis diastereomer, the Robinson annulation gave only a modest yield.2d The process was plagued by an unexpected silicon-to-carbon migration of the phenyl group that quenched intramolecularly Michael acceptor 2.3

Every attempt to limit this rearrangement failed, thus preventing an improvement of the yield of 4.

Next, we moved to the oxidation of the silyl group to install the C1 hydroxyl. To our great disappointment, the

(1) Jacobs, W. A.; Bigelow, N. M. J. Biol. Chem. 1932, 96, 647.
standard Fleming oxidation protocols (BF3·2AcOH followed by mCPBA and TBAF or H2O2, KF, and NaHCO3 or, alternatively, KBr, NaOAc, and AcOOH in TFA and AcOH) gave only a poor yield of the desired alcohol 5 due to competing Bayer–Villiger, elimination, and retro-aldol pathways. Fortunately, the modification of the Fleming protocol described by Ley and co-workers6 smoothly yielded oxidized product 5 (Scheme 2).

Protection of the β-hydroxy alcohol 5 without elimination could be achieved using a large excess of TBSCl and imidazole. Luche reduction7 of silyl ether 6 afforded β-allylic alcohol 7, exclusively. The last required oxygenation of the substrate was accomplished via directed epoxidation using mCPBA to afford the epoxy alcohol 8 in high yield. This advanced intermediate clearly possesses all the oxygenated centers resulting in a mixture of products. The same epoxide could be achieved using a large excess of TBSCl and imidazole. Luche reduction of silyl ether 6 afforded β-allylic alcohol 7, exclusively. The last required oxygenation of the substrate was accomplished via directed epoxidation using mCPBA to afford the epoxy alcohol 8 in high yield. This advanced intermediate clearly possesses all the oxygenated centers resulting in a mixture of products. The same epoxide occurred both at the secondary and tertiary hydroxyl as the acetonide. Unexpectedly, the opening of the epoxide occurred at the secondary hydroxyl due to the more stable, equatorial alcohol. In agreement with literature precedents, treatment of ketone 10 with (iBu)3Al gave only the expected alcohol 11 in excellent yield. Ester reduction followed by protection of the primary and tertiary hydroxyl groups as the acetone would finally give the target A/B ring with the C3 hydroxyl available to bind the sugar moiety. Unfortunately, upon treatment with excess LiBH4 or LiAlH4, the sterically hindered ester was found to be unreactive or yielded a complex mixture of products.

These results prompted us to consider a new synthetic strategy in which the reduction of the neopentyl ester is accomplished at an early stage while avoiding expeditious protection/deprotection sequences. Thus, we desisted from using phenyldimethylsilyl as a C1 hydroxyl surrogate. The Robinson annulation with the commercially available and inexpensive methyl vinyl ketone (12) and β-keto ester 13 would not be plagued by the silyl rearrangement. Moreover, delaying the introduction of a protected C1 hydroxyl would make the ester more sterically accessible. Therefore, the well-known annulation product 14 was prepared according to the procedure described by Ley and co-workers12 (Scheme 4).

Selective reduction of the ester could be obtained with LiAlH4 after protecting the enone as the 1,3-dioxolane (this procedure is particularly suitable for large-scale synthesis.

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of 16 because the intermediates can be easily purified by distillation.\(^\text{13}\) Alternatively, the enone present in annulation product 14 can be temporarily protected as the silyl enol ether allowing for selective reduction of the ester group.

With carbinol 16 in our hands, we moved to installing the remaining hydroxyl groups with the required stereochemistry. First, epoxidation of the enone double bond with H\(_2\)O\(_2\) in methanol was directed by the primary hydroxyl as described by Morand and co-worker\(^\text{14}\) (Scheme 5).

\[\text{Scheme 5}^a\]

\[
\begin{align*}
\text{16} & \rightarrow \text{17} \\
\text{17} & \rightarrow \text{18} \\
\text{19} & \rightarrow \text{20}
\end{align*}
\]

\(^a\) Reagents and conditions: (a) H\(_2\)O\(_2\), 10% NaOH, MeOH, 0 °C, 1 h; (b) SeO\(_2\), BuOH, AcOH, reflux, 22 h; (c) H\(_2\)O\(_2\), NaHCO\(_3\), EtOH, H\(_2\)O, rt, 11 h, 33% (from 16); (d) Ac\(_2\)O, py, rt, 1.5 h, 75% (from 18).

Dehydrogenation of epoxy ketone 17 with SeO\(_2\) afforded enone 18, which underwent a new directed epoxidation to give bis-epoxy ketone 19, exclusively. Attempted dehydrogenation of enone 16 failed due to the facile aromatization of the resulting dienone derivative, well known in the literature.\(^\text{15}\) Finally, the primary hydroxyl could be smoothly protected as its acetate 20 under standard conditions.

With all the oxygenated carbons required by the A/B ring of ouabain already present in intermediate 20, we moved to the conclusive part of our synthesis (Scheme 6).

\[\text{Scheme 6}^a\]

\[
\begin{align*}
\text{19}, R = H & \rightarrow \text{21a}, R = H \\
\text{20}, R = Ac & \rightarrow \text{21b}, R = Ac \\
\text{21a} & \rightarrow \text{22} \\
\text{21b} & \rightarrow \text{23}
\end{align*}
\]

\(^a\) Reagents and conditions: (a) Al foil, HgCl\(_2\), THF, H\(_2\)O, EtOH, NaHCO\(_3\), 0 °C, 50 min; (b) LiEt\(_3\)BH, THF, 0 °C, 1 h; (c) xs HC(OEt)\(_3\), 0.5% HCl, MeOH, rt, 6 h, 42% (from 19) or 46% (from 20); (d) Ac\(_2\)O, py, 0 °C, 1 h, 92%.

Opening of bis-epoxy ketones 19 and 20 smoothly took place under the aluminum amalgam conditions described above. Attempted protection of the two resulting hydroxyl groups of ketone 21a as the dimethyl acetonide (dimethoxy propane, PPTS, DMF, rt) gave only elimination products. The same result was obtained while attempting to protect the secondary ketone with BzCl and DMAP at 0 °C.\(^\text{16}\) However, reduction of either ketone 21a or 21b with Super Hydride afforded the desired all-cis tetraol. The isolation of this very polar intermediate was less challenging than expected. Probably, a less hydrophilic boron chelate, also suggested by Nakanishi and co-workers\(^\text{17}\) for endogenous ouabain, was formed during the reduction and isolated after aqueous workup.

Subsequently, the tetraol–boron chelate was treated with triethyl orthoformate and 0.5% HCl in methanol, hoping to leave only the C3 hydroxyl unprotected. However, only orthoformate 22 was isolated in which the primary hydroxyl had not reacted. The assignment of the structure of the orthoformate was confirmed by the downfield shift of the two hydroxymethyl hydrogens of 22 after conversion to acetate 23.

To rationalize these unexpected results, we calculated (MM2, molecular mechanics) the conformational energies of the two possible orthoformates for the A/B ring system (Figure 1). Interestingly, the observed orthoformate 22 was more stable than the desired C3-protected orthoformate 24 by 3.77 kcal/mol. Thus, these findings explain the exclusive formation of thermodynamic orthoformate 22 when all four hydroxyl groups are available for protection.

Intrigued and challenged by the behavior of our tetraol, we decided to change the sequence of steps to form the desired orthoformate before the reduction of the C3 keto group. For this purpose, bis-epoxy alcohol 19 was reductively opened with aluminum amalgam, as shown (Scheme 7).

The resulting triol was treated with triethyl orthoformate in the presence of catalytic PPTS. Under these conditions, we were pleased to find no elimination products. Instead, the triol was successfully converted into orthoformate 26.


Unfortunately, during the reduction with NaBH₄, the desired orthoformate (C3-protected) rearranged to the previously observed thermodynamic product 22. We were disappointed to find that even a fast quenching of the reduction step, without chromatographic purification, did not prevent the rearrangement from occurring. Even though chelation-assisted opening of orthoformate derivatives is known in the literature, this usually takes place in the presence of a strong Lewis acid such as AlMe₃.

Finally, with a modification in the sequence of addition during the formation of the orthoformate, a mixture of 22 and the desired orthoformate 24 was isolated (Scheme 8).

We postulated that the formation of the desired kinetic orthoformate 24 can be explained by evoking the intermediacy of boron chelate 27. During the reduction of bis-epoxy ketone 19, a boron chelate can be formed with the same thermodynamic preference as in orthoformate 22 (i.e., the primary hydroxyl group is not involved). When 27 and a large excess of triethyl orthoformate are treated with HCl, the primary hydroxyl can react even before the boron chelate is hydrolyzed. In this way, the formation of the orthoformate can begin, in a significant amount, on the primary hydroxyl to afford the desired C3-unprotected compound 24. The assignment of the structure of the latter could be confirmed by the downfield shift of the C3 hydrogen of acetate derivative 28.

Several attempts to improve the selectivity for the kinetic orthoformate were undertaken. Decreasing the strength and the amount of acid (PPTS or TsOH) resulted in unreacted starting chelate. The same result was obtained while attempting the formation of the desired orthoacetate using a protocol known to yield kinetic products, exclusively (ketene diethyl acetal, TsOH, DMF). Finally, when the same procedure as that in Scheme 8 was repeated at 0 °C, the same mixture of orthoformates 22 and 24 was obtained. This seems to confirm that the process is under thermodynamic control and that the formation of kinetic orthoformate 24 is the result of the temporary “protection” of the C3 hydroxyl as boron chelate 27.

In summary, we have described a fast and efficient way to access the all-cis decalin tetraol found in the cardenolide ouabain, which has no precedent in the literature. The complete carbon framework is built in one high-yielding step starting from inexpensive starting materials. Both orthoformate derivatives of the desired tetraol can be accessed despite the significant difference in stability.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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![](org.letts.2003.003_0140 Scheme7.png)  
*Reagents and conditions: (a) Al foil, HgCl₂, THF, H₂O, EtOH, NaHCO₃, 0 °C, 50 min; (b) xe HC(OEt)₃, PPTS, 0 °C to room temperature, 16 h; (c) NaBH₄, MeOH, 0 °C, 1 h; (d) Ac₂O, py, 0 °C, 1 h, 25% (from 19).

![](org.letts.2003.003_0141 Scheme8.png)  
*Reagents and conditions: (a) Al foil, HgCl₂, THF, H₂O, EtOH, NaHCO₃, 0 °C, 1 h; (b) LiEt₂BH, THF, 0 °C, 1 h; (c) xe HC(OEt)₃, MeOH, then 0.5% HCl, rt, 3 h, 34% (from 19); (d) Ac₂O, py, 0 °C, 1 h, 89%.
