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# An efficient approach toward the synthesis of the A/B rings of ouabain

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**Abstract**—The synthesis of the highly functionalized A/B ring related to ouabain has been accomplished efficiently from commercially available α-tetralone. A key Birch reductive alkylation allows the building of an angularly substituted decalone that was adequately functionalized to produce the intermediate **2c**.


The cardiotonic steroid ouabain **1** isolated in 1888 from the bark and roots of the *ouabaio* tree by Arnaud,[1] has been utilized for centuries in the treatment of congestive heart failure. Structurally, this cardenolide possesses A/B and C/D cis fused rings that together with substituents on C-14, C-17 and C-19, make it different to most common steroids. Also, its high degree of oxidation has made its synthesis extremely difficult, without any reported total synthesis up to date. Different efforts have been reported on the construction of Ouabain intermediates and related compounds.[2] Between them, Jung and Piizzi[3] recently reported the first synthesis of a fully functionalized all *cis*-decalin tetralol **3a** corresponding to the A/B ring system of that cardenolide. On that approach, the synthesis was achieved using a Robinson annelation to construct the decalin mainframe (Fig. 1).

As part of our studies on highly functionalized decalin systems, we became familiar with the very useful intermediaries obtained from the Birch-alkylation reaction (BAR) performed on benzylic ketones.[4] When this reaction is performed over α-tetralones it produces very versatile, angularly substituted, bicyclic 1,4-dienes that are perfect precursors of substituted decalins. Based on Jung's approach we envisioned that epoxy-alcohol **2a**, prepared on that work, could be synthesized starting from α-tetralone through a BAR to introduce the angularly functionalized substituent. After that, by a series of stereoselective reactions, the final product would be prepared. The advantage of our approach relays on the additional functionalization over C-5 of the intermediate **2c** which would allow future C/D rings construction.

Our initial approach was an exploratory study using a methyl group as alkylating agent, to optimize the sequence after the BAR. First, to prepare the epoxy-alcohol intermediate, the proposed synthesis involves the dienone epoxidation and ketone reduction in that order. Following our reported procedure,[4a] the enone was epoxidized obtaining a mixture of inseparable α/β epoxides (2.7:1) completely selective toward the C4a–C5 double bond, as we have shown before. Then, the epoxide mixture **8** was reduced with sodium borohydride, producing a mixture of 3 epoxy-alcohols **9**, α-epoxy-α-ol, and a mixture of β-epoxy-β-ol, α-epoxy-β-ol, on 1:1.6 ratio (β-epoxy ketone gave only β-ol but from α-epoxy ketone, a mixture 1:1 of both alcohols were obtained). Alternatively, the enone was generated by protection of the β-alcohol as benzoate using standard procedure followed by oxidation with PDC/*t*-BuOOH as have been reported before, obtaining the dienone **10** in good yield. When this dienone was submitted to classical enone epoxidation conditions with $H_2O_2$/NaOH, instead of getting the expected epoxide, the aldehyde **11** was found. The formation of that product can be explained by the hydrolysis of the benzoate and the subsequent rearomatization to produce the phenylbutyraldehyde **11**. Finally, the alcohol **6** was epoxidized

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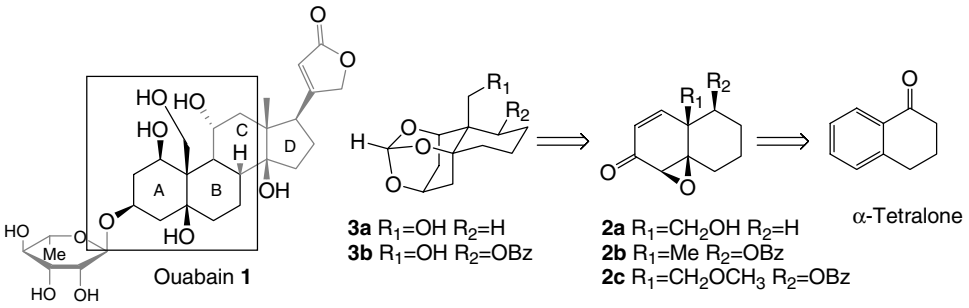
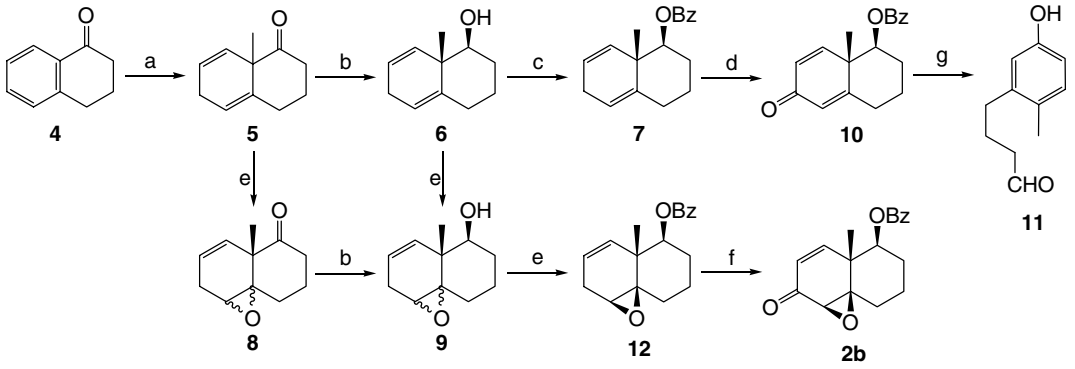


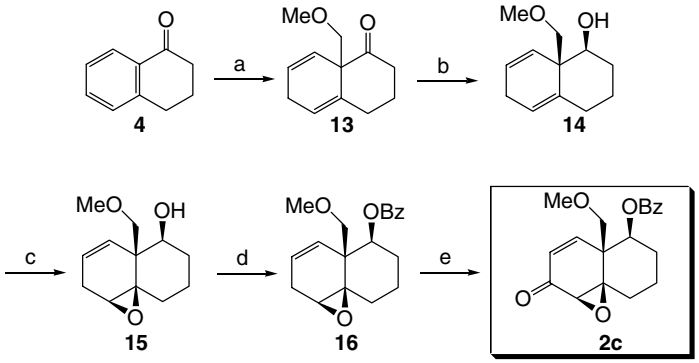

**Figure 1.**

under the conditions mentioned before,[4a] to induce the attack of the peracid over the beta face. This reaction produces the epoxy alcohol **9** as a α/β mixture 1.5:1, being the best selectivity obtained over all. Both diastereomers were easily separated by flash chromatography and relative stereochemistry of the products was established straightforward by NMR.[5] Then, the alcohol **9** was esterified with PhCOCl, DMAP in pyridine at room temperature[6] producing the benzoyl ester **12** in 92% yield. Allylic oxidation of **12** was first attempted using 3,5-dimethylpyrazole–$CrO_3$ complex[7] producing the desired α,β-unsaturated ketones **2b** in 80–85% yields. To our satisfaction, by using pyridinium dichromate/*tert*-butyl hydroperoxide/Celite in benzene,[8] a cleaner transformation was observed obtaining the epoxy-enone[9] in 91% yield (Scheme 1).

With all that in mind, we decided to move to the oxidized angular substituent. From the possible different alkylating reagents (MOMCl, BOMCl, $CH_2{=}CHCH_2Br$), MOMCl was chosen based on our previous experience.[4a] Starting from α-tetralone as before, under BAR conditions, dienone **13** was produced in high yield. Then, the ketone was reduced with sodium borohydride, obtaining exclusively the beta alcohol **14** as for the methyl derivative. The alcohol was then epoxidized




**Scheme 1.** Reagents and conditions: (a) 1. $NH_3$, K, $Et_2O$, *t*-BuOH, −78 °C; 2. LiBr, 3. MeI, −78 °C to rt; (b) $NaBH_4$, MeOH, −78 °C, 30 min, 90%; (c) PhCOCl, Py, DMAP, 0 °C, 2 h, 92%; (d) PDC, *t*-BuOOH, DCM; (e) *m*-CPBA, $CH_2Cl_2$, 0.5 M $NaHCO_3$, 4 °C, overnight, 71%; (f) PDC, *t*-BuOOH, Celite, benzene, room temperature, overnight, 91%; (g) $H_2O_2$, 1 M NaOH, THF, 94%.




**Scheme 2.** Reagents and conditions: (a) 1. $NH_3$, K, $Et_2O$, *t*-BuOH, −78 °C; 2. LiBr; 3. MOMCl, benzene, −78 °C to rt, 91%; (b) $NaBH_4$, MeOH, −78 °C, 30 min, 98%; (c) *m*-CPBA, $CH_2Cl_2$, 0.5 M $NaHCO_3$, 4 °C, overnight, 71%; (d) PhCOCl, Py, DMAP, 0 °C, 2 h, 95%; (e) PDC, *t*-BuOOH, Celite, benzene, room temperature, 48 h, 66%.

under conditions mentioned above obtaining the epoxy-alcohols **15** in 1:9.2 α/β ratio. As can be seen, the presence of methoxy-methyl group produces an enhancement on the selectivity to the β-face increasing almost 14 times over the reaction on the methyl derivative **6**. This can also be seen when the methyl and the methoxy-methyl series were compared. In fact, the epoxidation α/β ratio goes from 2.3:1 to 1.5:1 from the ketone compared to the β-ol. On the mom-series, α/β ratio goes from 2.3:1 for the ketone to 1:9.2 for the epoxidation of the beta-alcohol. The synthesis is completed by the epoxide separation, and alcohol protection as benzoate producing the benzoate protected alcohol **16**. Finally, by allylic oxidation with PDC, *t*-BuOOH, Celite in benzene, the final product **2c** was obtained in 66% yield (Scheme 2).[10]

In conclusion we have developed a simple procedure for preparing the decalin **2c** in five steps starting from α-tetralone with BAR as a key step. This intermediate, has provided a compound with adequate functionalities that can be transformed on Jung's intermediate having additional functionalities and protections that would allow future work on a most advanced intermediate.

## Acknowledgements

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9. *(1aR,4aS,5S,8aR)-4aβ-(Methyl)-2-oxo-2,4a,5,6,7,8-hexahydro-1aH-naphtho[1,8a-b]oxiren-5β-yl benzoate* (**2b**): Colorless oil (hexane–EtOAc 85:15, 20.5 mg, 92%). IR (film) 2953, 1715, 1688, 1620, 1448, 1372, 1189, 1097, 980, 941, 861, 820, 750, 689 $cm^{-1}$. $^1H$ NMR: $\delta$ 7.94 (m, 2H, H-2′), 7.63 (m, 3H, H-3′ and H-4′), 6.40 (d, 1H, $J = 12$ Hz, H-4), 5.73 (dd, 1H, $J = 2$ and 14.0 Hz, H-3), 4.70 (dd, 1H, $J = 6.0$ and 10.5 Hz, H-5), 3.31 (s, 1H, H-1), 2.32–2.15 (dt, 2H, $J = 14$ and 4 Hz, H-7), 1.97–1.78 (m, 2H, H-6), 1.79–1.65 (m, 2H, H-8), 1.21 (s, 3H, $CH_3$). $^{13}C$ NMR 194.7 (C=O), 151.3 (OC(O)Ph), 148.7 (C-4), 136.6 (C-1′), 134.0 (C-4′), 129.3 (C-2′), 127.6 (C-3′), 123.4 (C-3), 81.6 (C-5), 66.3 (C-8a), 60.8 (C-1), 43.3 (C-4a), 27.7 (C-8), 27.4 (C-6), 20.8 (C-7), 19.1 ($CH_3$). MS: *m/z* (%) = 227 (30), 177 ($M^+$−benzoate, 100), 147 (20), 91 (38), 77 (25).
10. *(1aR,4aS,5S,8aR)-4aβ-(Methoxymethyl)-2-oxo-2,4a,5,6,7,8-hexahydro-1aH-naphtho[1,8a-b]oxiren-5β-yl benzoate* (**2c**): Oily solid (hexane–EtOAc 75:25, 167.8 mg, 85%). IR (film) 2942, 1732, 1659, 1450, 1070, 986, 758 $cm^{-1}$. $^1H$ NMR: $\delta$ 8.00 (m, 2H, H-2′), 7.59 (m, 3H, H-3′, H-4′), 6.41 (d, 1H, $J = 10.7$ Hz, H-4), 5.77 (dd, 1H, $J = 1.3$ and 9.8 Hz, H-3), 4.73 (dd, 1H, $J = 5.2$ and 10.4 Hz, H-5), 3.76 (d, $J = 9.3$ Hz, 1H, $CH_2OCH_3$), 3.50 (d, $J = 9.4$ Hz, 1H, $CH_2OCH_3$), 3.34 (s, 3H, $OCH_3$), 3.20 (br s, 1H, H-1), 2.22–1.78 (m, 6H, H-6, H-7 and H-8). $^{13}C$ NMR 194.3 (C=O), 150.7 (OC(O)Ph), 148.3 (C-4), 133.6 (C-1′), 133.7 (C-4′), 128.9 (C-2′), 127.3 (C-3′), 123.5 (C-3), 81.2 (C-5), 65.8 ($CH_2OCH_3$), 64.6 (C-8a), 60.5 (C-1), 58.8 ($OCH_3$), 42.9 (C-4a), 27.3 (C-6), 27.2 (C-8), 20.4 (C-7). ESI-HRMS Calcd for ($M^+$+Na) $C_{19}H_{20}O_5Na$ 351.1208; found 351.1208.