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Novel Annulation Products Derived by Selective Attack on the C(18) Angular Methyl Group of the Cardenolide Ouabain

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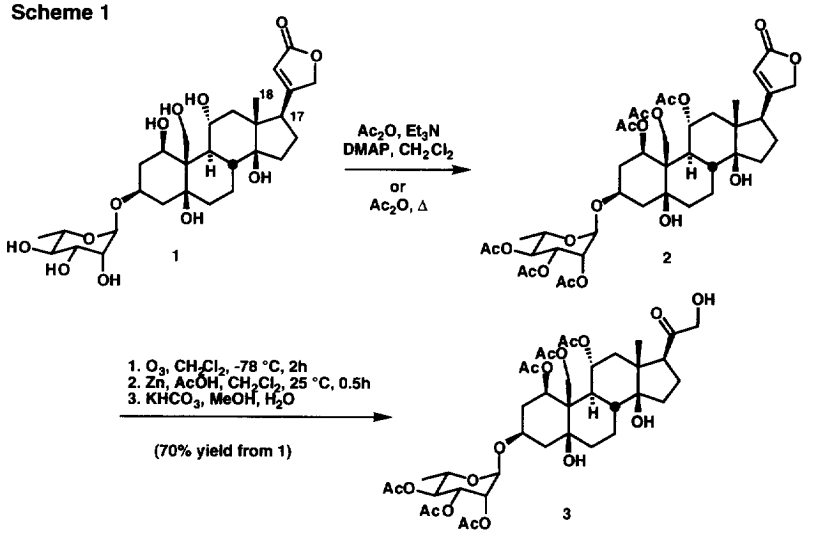
Abstract: *Selective reactions at the C(18) angular methyl group of ouabain derivatives employing rhodium- and photochemically-mediated C–C bond formation allow the synthesis of annulation products* ***4*** *and* ***13****.*

Cardenolides such as digoxin and ouabain (**1**) are positive inotropic agents which are medically useful in the treatment of heart failure and other cardiac conditions.[1] In connection with a program to develop more effective cardenolides for medical use, we have investigated the synthesis of new ouabain derivatives which contain an additional ring formed by the connection of C(17) with the C(18) angular methyl group. Described herein are two complementary strategies for the intramolecular functionalization of ouabain at C(18), one relying on photochemical $n \rightarrow \pi^*$-induced C–C bond formation, and the other on rhodium-carbenoid C–H insertion chemistry. In a broader sense these studies address a major challenge to synthesis, i.e. effective methodology for selective attack on unfunctionalized and unactivated carbons in organic molecules.[2]

Scheme 1



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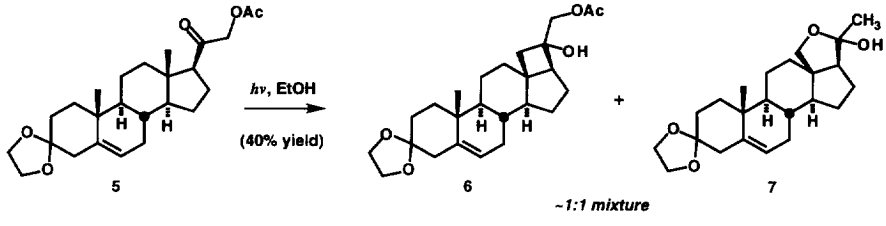
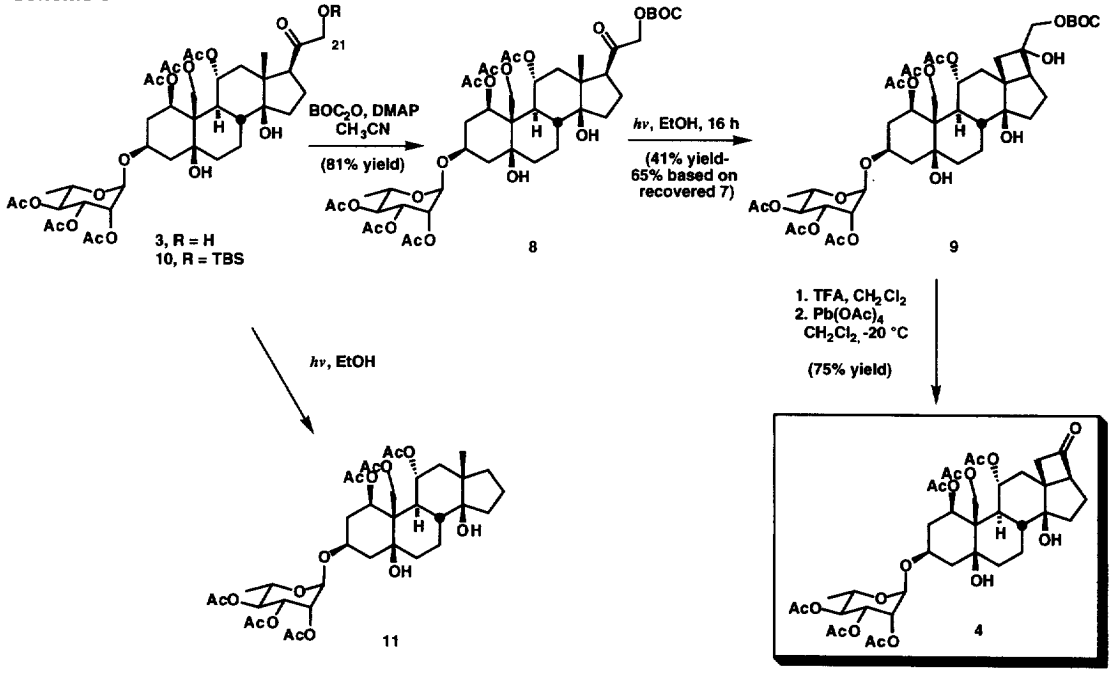
Ouabain (**1**) was converted to hydroxy ketone **3** by a route similar to that described by Templeton.[3] Protection of **1** as its hexaacetate (**2**), followed by reductive ozonolysis furnished hydroxy ketone **3** in good yield (see Scheme 1).

With hydroxy ketone **3** readily available, we turned our attention to the preparation of cyclobutanone **4**, using a reaction described by Jeger et al. for the photocyclization of ketone **5** to a mixture of alcohol **6** and tetrahydrofuran **7** (Scheme 2).[4] Carbonate **8** was prepared and photolyzed under the Jeger conditions, and after 16 h cyclobutanol **9** had formed, but none of the hemiketal byproduct could be detected.[5] In fact, under no conditions attempted in the ouabain series were products analogous to **7** identified. Interestingly, by altering the group at C(21) to hydroxy (i.e., **3**) or silyloxy (i.e., **10**), a striking reactivity difference was noted in the photochemical reaction, with the clean conversion of both of these substrates to hexaacetate **11**, the product of

Scheme 2



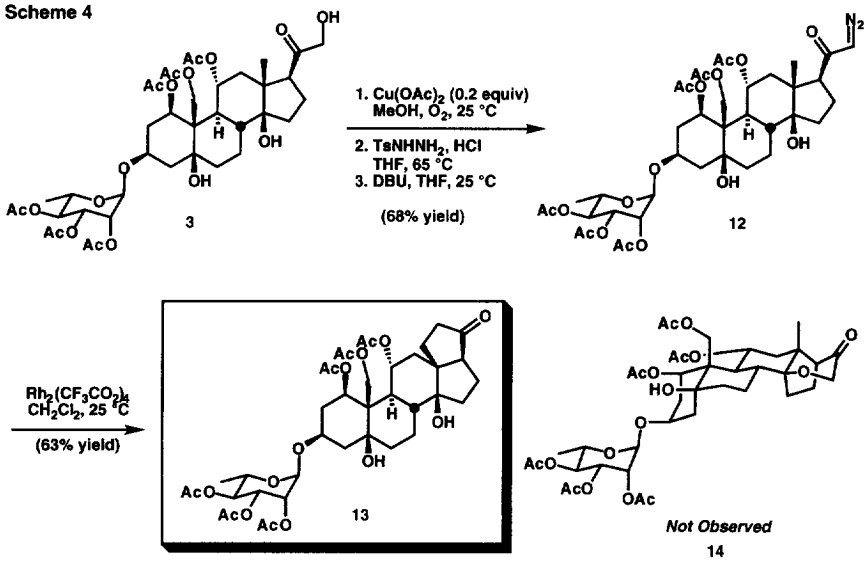
Scheme 3



Norrish type I cleavage. In order to complete the preparation of cyclobutanone **4**, carbonate **9** was treated with trifluoroacetic acid followed by $Pb(OAc)_4$ to furnish ketone **4** (75% yield, 2 steps).

With the preparation of cyclobutanone **9** complete, efforts turned to the synthesis of cyclopentanone **13** and focused on diazo ketone **12**, a compound suitable for carbenoid C–H insertion at C(18). Air oxidation of hydroxy ketone **3** in the presence of catalytic $Cu(OAc)_2$,[6] followed by reaction of the resulting α-ketoaldehyde with tosyl hydrazine and DBU produced the desired diazo ketone **12**. Exposure of **12** to $Rh_2(CF_3CO_2)_4$ in CH_2Cl_2 at ambient temperature cleanly furnished a single product, characterized as the desired cyclic ketone **13** (see Scheme 4).[7] Ether **14**, a potential byproduct resulting from O–H insertion, was not observed.

Scheme 4



In summary, efficient preparations of novel annulation products **4** and **13** derived from the cardenolide ouabain have been developed. The selective activation of C(18) in the ouabain series was achieved by photochemical C–C bond formation in the cyclobutanone case, and rhodium–carbenoid C–H insertion in the cyclopentanone case. An interesting substituent effect at C(21) was noted in the photochemical reaction, effectively allowing a switch between Norrish I and C–H insertion pathways.

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Notes and References:

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3. (a) Templeton, J. F.; Ling, Y.; Zeglam, T. H.; LaBella, F. S. *J. Med. Chem.* **1993**, *36*, 42. (b) Templeton, J. F.; Ling, Y.; Zeglam, T. H.; Marat, K.; LaBella, F. S. *Eur. J. Med. Chem.* **1994**, *29*, 799.
4. (a) Wehrli, H.; Cereghetti, M.; Schaffner, K.; Jeger, O. *Helv. Chim. Acta* **1960**, *47*, 367. (b) Schaffner, K.; Arigoni, D.; Jeger, O. *Experientia* **1960**, *16*, 169.
5. **Preparation of cyclobutanol 9.** A solution of ketone **8** (170 mg, 0.19 mmol, 1.0 equiv) in abs. EtOH (56 mL) was photolyzed using a Hanovia 450 W bulb through a quartz jacket for 16 h at 25 °C. TLC analysis indicated incomplete conversion from starting material to a new, more polar product. Prolonged photolysis did not significantly change this ratio. Solvent was removed *in vacuo* to a crude residue which was purified by flash chromatography (1:1→3:1 ethyl acetate:hexane) to provide unreacted ketone **8** (60 mg, 35% recovery) and cyclobutanol **9** (70 mg, 41% yield, 65% yield based on recovered **8**) as white solids: R_f 0.2 (3:1 ethyl acetate:hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.15 (app.t, *J* = 2.8 Hz, 1H), 5.20-5.04 (comp.m, 3H), 5.00 (d, *J* = 12.0 Hz, 1H), 4.95 (m, *J* = 1.4 Hz, 1H), 4.82 (app.td, *J* = 3.4, 9.8 Hz, 1H), 4.27 (d, *J* = 11.9 Hz, 1H), 4.26 (s, 1H), 4.04 (s, 2H), 3.98 (s, 1H), 3.75 (m, 1H), 2.15 (s, 3H), 2.15 (s, 3H), 2.15 (s, 3H), 2.05 (s, 3H), 1.96 (s, 3H), 1.93 (s, 3H), 1.48 (s, 9H), 1.21 (d, *J* = 6.3 Hz, 3H), 2.36-1.28 (comp.m, 20H); IR (thin film) 1224, 1247, 1370, 1741, 2938 cm^{-1}; MS *m/e* calc'd for $C_{44}H_{64}O_{20}$ $(M+Na)^+$: 935.3889, found 935.3877.
6. Lewbart, M. V.; Mattox, V. R. *J. Org. Chem.* **1963**, *28*, 2001.
7. **Preparation of ketone 13.** To a solution of diazo ketone **12** (620 mg, 0.75 mmol, 1.0 equiv) in CH_2Cl_2 (75 mL) was added a solution of $Rh_2(CF_3CO_2)_4$ (6 mg, 0.009 mmol, 0.012 equiv) in CH_2Cl_2 (0.5 mL). The solution slowly evolved gas over the course of 10 min, whereupon TLC analysis of the crude reaction mixture indicated complete consumption of staring material. Solvent was removed *in vacuo* and the residue purified by flash chromatography (3:1 ethyl acetate:hexane→ethyl acetate eluent) to provide ketone **13** (438 mg, 73% yield) as a pale yellow solid: R_f 0.2 (3:1 ethyl acetate:hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.20 (s, 1H), 5.19-4.95 (comp.m, 5H), 4.98 (d, *J* = 12.2 Hz, 1H), 4.42 (d, *J* = 12.1 Hz, 1H), 4.28 (s, 1H), 4.03 (s, 1H), 3.76 (m, 1H), 2.41 (app.t, *J* = 8.3 Hz, 2H), 2.19 (s, 3H), 2.16 (s, 3H), 2.16 (s, 3H), 2.06 (s, 3H), 1.97 (s, 3H), 1.95 (s, 3H), 1.21 (d, *J* = 6.2 Hz, 3H), 2.30-1.25 (comp.m, 19H); MS *m/e* calc'd for $C_{39}H_{54}O_{17}$ $(M+Na)^+$: 817.3259, found 817.3268.