A Strategy for Total Synthesis of Complex Cardenolides

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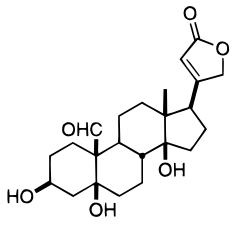
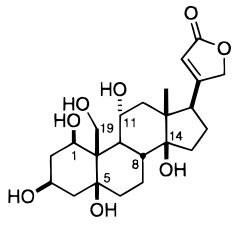
The cardiac glycosides (*digitalis*), which are found in a variety of plant species, are a large group of steroids having a sugar residue at the 3β position.[2] Cardiac glycosides display a range of pharmacological activities, and extracts from leaves of *Digitalis lonata* are extensively used in the clinical treatment of congestive heart failure.[3] Cardenolides, the genins of cardiac glycosides, differ from other steroids in having a β-oriented butenolide ring at C17, a *cis* C/D ring fusion, and a hydroxy substituent at C14. In addition, most cardenolides also have a *cis* A/B ring fusion. The most complex cardenolides, exemplified by strophanthidin (**1**) and ouabagenin (**2**), contain two to four additional sites of oxidation at

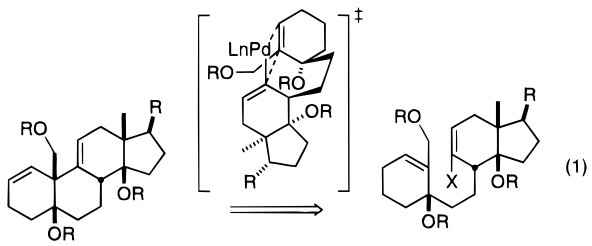


strophanthidin (**1**)



ouabagenin (**2**)

carbons 1, 5, 11, and 19.[2] The high degree of oxidation of the steroid skeleton and the *cis* A/B and C/D ring fusions render complex cardenolides challenging targets for total synthesis. To date, nearly all synthetic accomplishments in this area have been partial syntheses from steroid starting materials.[4,5] One of the most attractive features of palladium-catalyzed methods for carbon−carbon bond formation are their broad functional group compatibility.[6] Attracted by this feature, and the propensity of intramolecular Heck insertions to form *cis*-fused polycyclic products, we have been developing a total synthesis approach to complex cardenolides that features an intramolecular Heck reaction to fashion the B ring and establish the *cis* A/B ring fusion (eq 1).[7] We report here verification of this general strategy through synthesis of a cardenolide congener having 8,14 unsaturation.



A suitably protected A-ring fragment containing oxidation at carbons 5 and 19 was prepared in high enantiopurity as summarized in Scheme 1. Cyclohexenone **3**, which is available on a large scale in one step from 1,3-cyclohexanedione,[8] was reduced under carefully optimized conditions with BH_3·SMe_2 in the presence of oxazaborolidine catalyst **4**[9] to provide the (*S*)-allylic alcohol **5** in 98% yield and 92−94% enantiomeric excess (ee).[10,11] It was critical in this reduction to slowly add BH_3·SMe_2 to a cold (−25 °C) solution of **3** and **4** (0.1 equiv) or else significant amounts of the deoxygenated alkene **6** were produced.[12] Acetylation of **5** provided sensitive acetate **7**, which upon conversion to the ketene silyl acetal derivative underwent smooth Ireland−Claisen rearrangement at room temperature.[13] The silyl ester product was converted, without purification, to methyl ester **8** by treatment with KF, K_2CO_3, and MeI as a prelude to reduction to the primary alcohol.[14] This sequence for converting **5** to **8** could be accomplished on a large scale in 77% overall yield. Reduction of **8** then delivered alcohol **9**, whose high ee (91%)[15] confirmed that the key Claisen rearrangement occurred with high stereochemical fidelity. Finally, alcohol **9** was activated for coupling by conversion to iodide **10**.

The starting material for construction of the C/D fragment was enone **12**, which can be prepared in three steps and good yield from the (*S*)-Hajos-Parrish ketone **11** (Scheme 2).[16] Protection of the carbonyl group of **12**[17] followed by reduction of the nitrile with DIBALH gave aldehyde **13**, which was converted to enone **14** in three routine steps and 68% overall yield from **12**. All attempts

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(10) New compounds were fully characterized by ^{1}H and ^{13}C NMR, IR, and MS analysis, while elemental composition was confirmed by combustion analysis or high-resolution mass spectrometry.

(11) Determined by GLC analysis on a Cyclodex B capillary column.

(12) The ee of **5** was 96−98% when 0.5 equiv of oxazaborolidine **4** was employed.

(13) (a) Ireland, R. E.; Thaisrivongs, S.; Vanier, N.; Wilcox, C. S. *J. Org. Chem.* **1980**, *45*, 48. (b) For a recent review of the Ireland−Claisen rearrangement, see: Pereira, S.; Srebnik, M. *Aldrichim. Acta* **1993**, *26*, 17.

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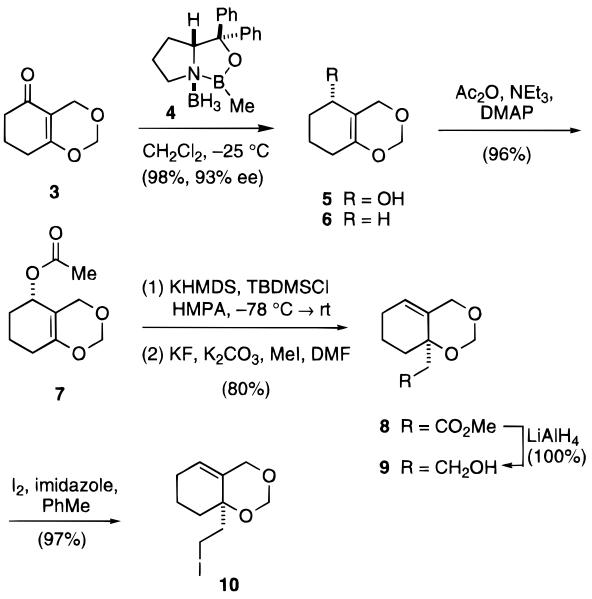
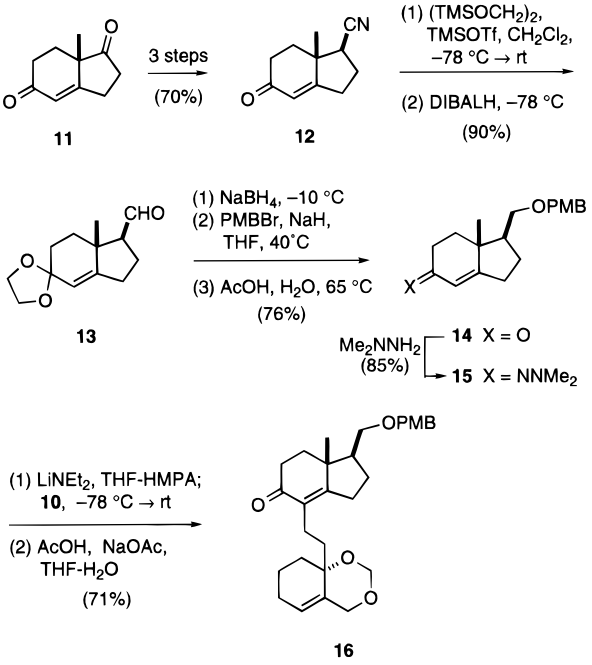
Scheme 1



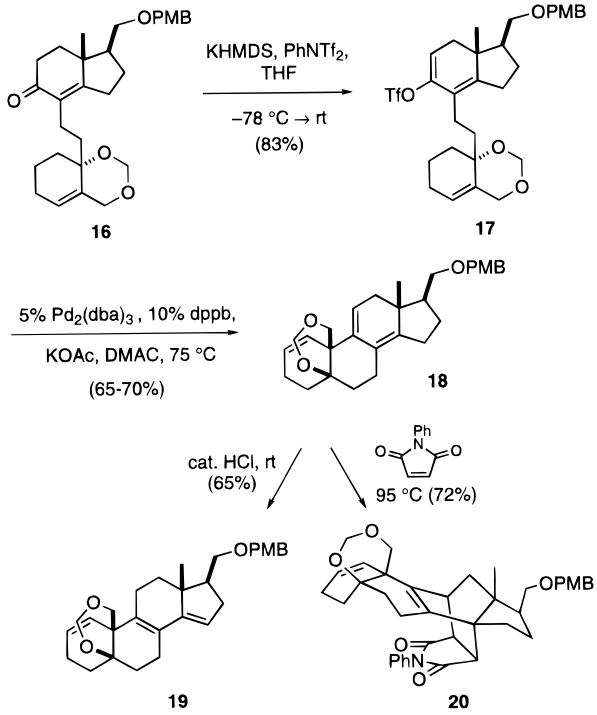
Scheme 2



to directly couple an enolate derivative of **14** with iodide **10** gave the desired dienone **16** in low yield. However, the lithium salt of 1,1-dimethylhydrazone derivative **15** reacted smoothly with iodide **10** to provide **16** in 71% yield after cleavage of the hydrazone group.[18]

Dienone **16** then was converted into trienyl triflate **17** in 83% yield by treatment with KHMDS and *N*-phenyltriflamide (Scheme 3). Triflate **17** initially was exposed to Heck cyclization conditions that we had employed in an earlier model study (10 mol % Pd(dppb) and excess KOAc in *N*,*N*-dimethylacetamide at 120 °C).[19] These conditions provided none of the desired Heck product; however, when the reaction was performed at 75 °C, a single pentacyclic product **18** was isolated in 65−70%

Scheme 3



yield. The conjugated diene **18** (λ_{max} 274 nm) was quite sensitive to acid and, for example, was converted to s-*trans* isomer **19** (λ_{max} 251 nm) when left overnight in unpurified $CHCl_3$. The structure of pentacycle **18** was secured by reaction with *N*-phenylmaleimide at 100 °C to provide *endo* Diels−Alder adduct **20**. This material yielded crystals (mp 95−97 °C) suitable for X-ray analysis, thus allowing unambiguous confirmation of the expected *cis* stereochemistry of the A/B ring fusion.[20]

In summary, we have shown that an intramolecular Heck reaction can be employed to form the basic skeleton of complex cardenolides. Pentacycle **18** displays a *cis* A/B ring fusion and oxidation at C5 and C19 along with unsaturation at carbons 1, 11, and 14 that could conceivably be employed to incorporate additional oxidation characteristic of complex cardenolides. The lability of the diene moiety of **18**, however, suggests that it would be preferable to incorporate C14 oxygenation prior to the central Heck reaction. The results of our investigations of this latter strategy will be reported in due course.

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Supporting Information Available: Experimental procedures and spectroscopic and analytical data for new compounds reported in Schemes 1−3 (11 pages).

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(20) Crystallographic data for this intermediate have been deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.