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Enantioselective Synthesis of Cardenolide Precursors Using an Intramolecular Heck Reaction

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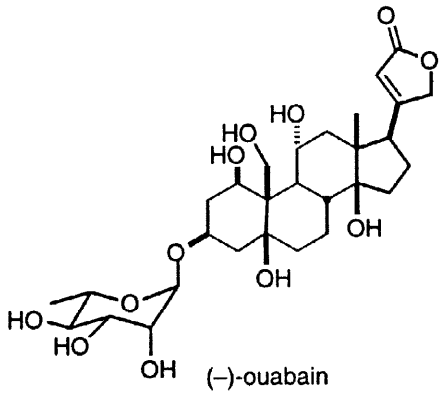
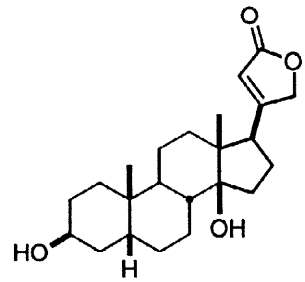
Abstract. Synthesis of a complex steroid having *cis* A/B and C/D ring fusions and hydroxyl functionality at C-5, C-14 and C-19 is described.

Keywords: Heck reactions; cardiac glycosides; sterols; enantiospecificity

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.[1] They have been used by indigenous populations in Africa as dart poisons and have found extensive use in modern medicine in the treatment of congestive heart failure.[2] The high degree of oxidation of the steroid skeleton and the *cis* A/B and C/D ring fusions make complex cardenolides such as ouabain challenging targets for total synthesis. With the exception of the recent synthesis of digitoxigenin by Stork and co-workers,[3] all synthetic endeavors in the cardenolide area have been partial syntheses from steroid starting materials.[4] Attracted by the functional group tolerance of the Heck reaction, and the propensity of intramolecular Heck insertions to form *cis*-fused polycyclic products,[5,6] we have developed a synthetic approach to complex cardenolides that features an intramolecular Heck reaction to fashion the B ring and establish the *cis* A/B ring fusion.[7] In this report we describe use of this strategy to construct a steroid containing much of the functionality of complex cardenolides.



(–)-ouabain



(+)-digitoxigenin

The synthesis began with (*S*)-Hajos-Parrish ketone (**1**) which was converted in three standard steps to hydrazone **2** (Scheme 1). The lithium salt of **2** was coupled with enantioenriched A ring iodide **3** to afford hydrindenone **4** in 90% yield.[7,8] We next installed a β-nitrile at C-17 which should eventually serve as a precursor of the butenolide. Conversion of **4** to the mesylate derivative followed by reaction with KCN in the presence of 18-crown-6 provided **5** in 80% yield. This transformation occurred with net retention of configuration as is precedented in related systems.[9,10]

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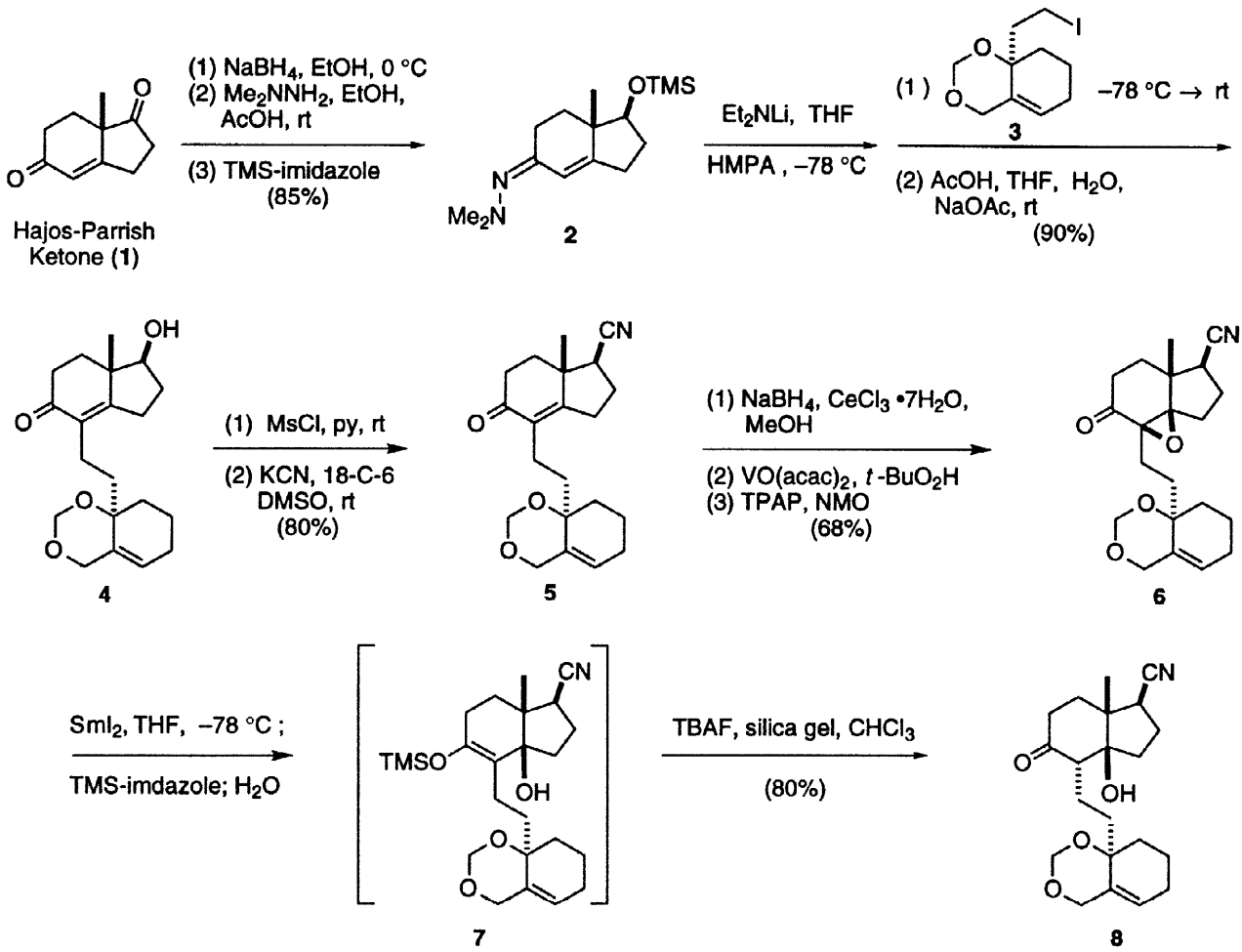
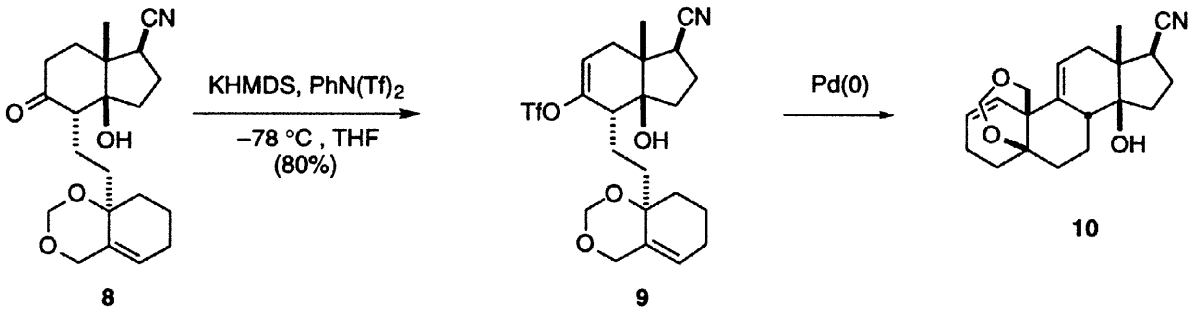


Scheme 1

Introduction of the C-14 hydroxyl was accomplished through a conventional sequence in which ketone **5** was reduced to the β allylic alcohol, this intermediate was epoxidized, and the resulting epoxy alcohol was oxidized to provide β-epoxy ketone **6** in 68% overall yield.[11] Reductive opening of **6** with excess SmI_2 and *in situ* silylation yielded enoxysilane **7**, which was selectively protonated from the β face to provide **8** upon exposure to TBAF and silica gel. In the absence of silica gel, protonation afforded a 3:1 mixture of epimers.[12,13] Enol triflation of **8** to provide triflate **9** was accomplished in good yield by addition of **8** to excess KHMDS at −78 °C to generate the dianion, followed by quenching with excess *N*-phenyltriflimide (Scheme 2). Addition of KHMDS to a solution of **8** at −78 °C resulted mainly in retroaldol cleavage.

A variety of palladium catalysts (10 mol%) were screened in *N,N*-dimethylacetamide (DMA) for the critical Heck cyclization to generate **10** (Table 1). Use of $Pd(OAc)_2$/ 2 Ph_3P at 75 °C, or Herrmann's catalyst[17] at 50 °C, failed to mediate Heck closure. In contrast, the precursor of Herrmann's catalyst, Pd-bis(tri-*o*-tolylphosphine)[18] afforded steroid **10** in good yield at 45 or 75 °C.[19] Steroid **10** was produced in an optimum yield of 90% using Pd(dppb) as catalyst at 75 °C. At temperatures above 90 °C, the yield of **10** was reduced by partial isomerization of the $\Delta^{1,2}$ double bond. The structure of **10** was established by extensive 2D NMR studies and by chemical correlation with the Heck products described in the following paper.[21,22]



Scheme 2

Table 1. Intramolecular Heck Reaction to Yield **10**.

Conditions[a]	Yield of **10**
$Pd(OAc)_2$, 2 Ph_3P, DMA, 75 °C	trace
Herrmann's catalyst, KOAc, DMA, 50 °C	trace
Pd bis(tri-*o*-tolylphosphine), KOAc, DMA, 75 °C	75 %
Pd bis(tri-*o*-tolylphosphine), KOAc, DMA, 45 °C	72 %
Pd bis(tri-*o*-tolylphosphine), KOAc, DMA, 35 °C	0 %
Pd(dppb), KOAc, DMA, 90 °C	50 %
Pd(dppb), KOAc, DMA, 75 °C	90 %
Pd(dppb), KOAc, DMA, 50 °C	0 %

[a] 10 mol % of palladium was employed.

In summary, the highly functionalized steroid **10** was prepared in 24% overall yield from (*S*)-Hajos-Parrish ketone. A more concise synthesis of a related intermediate containing thiophenyl functionality at C-11 is described in the accompanying communication.[22] We anticipate that **10** or related intermediates will prove useful for total synthesis of complex cardenolides such as ouabain.

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21. The TMS ether derivative of compound **15a** described in the following communication[22] was treated with Raney-Ni in EtOH at rt to provide the TMS derivative of **10**, which was prepared by heating **10** and neat TMS-imidazole at reflux for 1 d: $[\alpha]_D^{25}$ +155° (*c* 1.0, CH_2Cl_2); FTIR (film) 2953, 2865, 2234 and 1464, 1447 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.03–5.90 (m, 1H), 5.60 (br d, *J* = 9.6 Hz, 1H), 5.46–5.40 (m, 1H), 5.15 (d, *J* = 6.5 Hz, 1H), 4.85 (d, *J* = 6.5 Hz, 1H), 4.03 (d, *J* = 11.2 Hz, 1H), 3.39 (d, *J* = 11.2 Hz, 1H), 2.67 (dt, *J* = 13.5, 3.5 Hz, 1H), 2.59 (dd, *J* = 9.3, 4.4 Hz, 1H), 2.41–2.30 (m, 1H), 2.30–2.08 (m, 3H), 2.05–1.93 (m, 1H), 1.93–1.70 (m, 3H), 1.69–1.20 (s, 6H), 1.13 (s, 3H), 0.27 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.7, 130.9, 128.3, 121.5, 87.7, 86.6, 73.6, 72.1, 47.4, 44.6, 40.9, 38.4, 33.2, 30.2, 29.2, 25.3, 25.1, 22.0, 20.9, 16.7, 2.5; HRMS (FAB, mNBA) *m/z* 414.2481 (414.2464 calcd for $C_{21}H_{36}O_3NSi$, MH).
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