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Intramolecular Heck Cyclization of α-Sulfenyl Enol Triflates. Asymmetric Synthesis of a Pentacyclic Cardenolide Precursor Having Functionality at C-11.

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Abstract. A concise route to the core of complex cardenolides is described. The sequence features use of a sulfone to join enantioenriched A and D ring fragments and also control intramolecular aldolization to generate ring C and an intramolecular Heck cyclization of an α-sulfenyl enol triflate to form the steroid skeleton.

Keywords: aldol reactions; Heck reactions; enantiospecificity; sterols; sulfones

In the preceding communication, we described use of an intramolecular Heck reaction to construct an enantioenriched steroid having much of the functional signature of complex cardenolides: *cis* A/B and C/D ring fusions, oxygen functionality at carbons 5, 14 and 19, and a β-oriented substituent at C-17.[1] This intermediate also contained a 9,11 double bond, which potentially could be elaborated to install the 11-hydroxyl group of complex cardenolides such as ouabain (**1**). However, in light of the difficulty often encountered in elaborating the 9,11-alkene of *cis* A,B-fused steroids,[2] we wished to develop a companion strategy that directly delivered a cardenolide precursor having C-11 at the carbonyl oxidation state. Such a strategy is outlined in Figure 1. In this communication we report a streamlined method for assembling cyclization precursors and successful intramolecular Heck cyclization to form enantiopure cardenolide precursors containing vinylsulfide functionality at C-11.

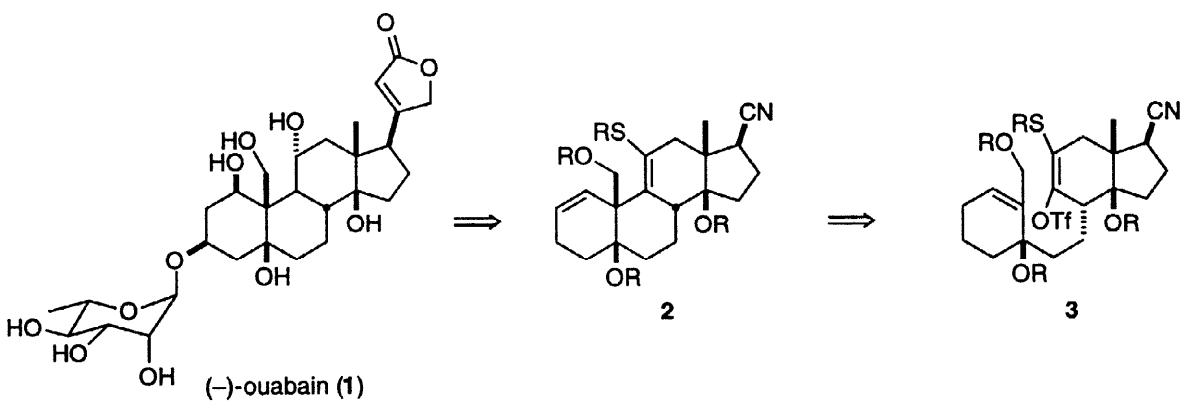

Figure 1

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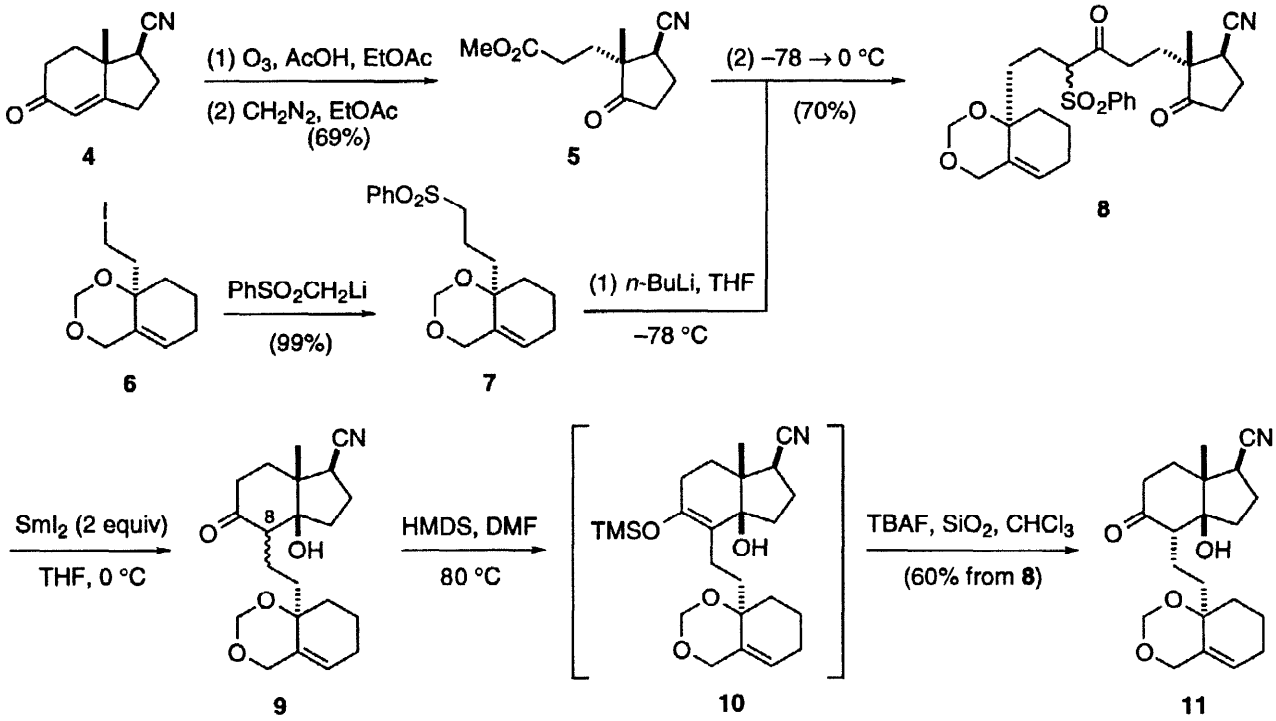
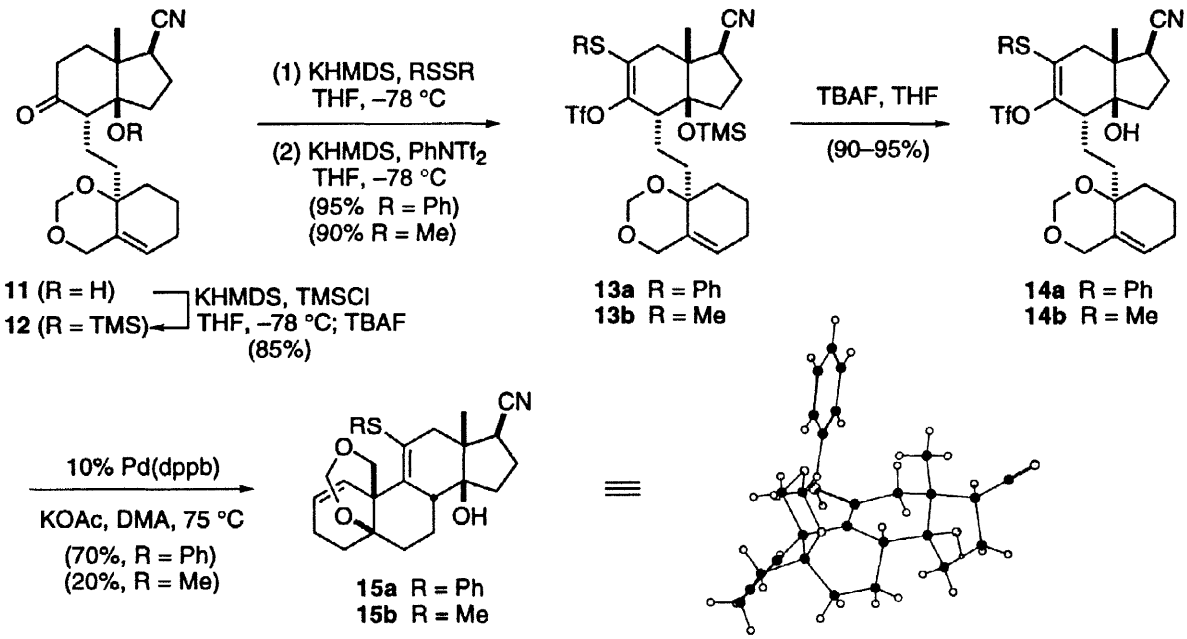
An improved preparation of tetracyclic ketone intermediate **11**, which exploits methyl phenyl sulfone to link enantiopure A and C ring units and an intramolecular aldol reaction to form ring C,[3] is outlined in Scheme 1. Hydrindenone nitrile **4**, which is available in three steps and high overall yield from (*S*)-Hajos-Parrish ketone,[4,5] was cleaved with ozone and esterified to give **5**.[6] Addition of 1 equiv of this ester to the lithium salt of sulfone **7** (2.5 equiv, available in quantitative yield from enantioenriched iodide **6**[7]), provided **8**, a mixture of sulfone epimers, in high yield. Treatment of **8** with 2 equiv of SmI_2[8] yielded a 1:1 mixture of hydrindanone epimers **9**.[9] Without separation, this mixture was converted to the desired stereoisomer **11** by initial treatment with HMDS at 80 °C in DMF to generate **10** and subsequent exposure of this intermediate to excess TBAF in $CHCl_3$ containing silica gel.[15] This intramolecular aldol approach provided **11** in 60% overall yield from **8** and is four steps shorter than the first route we developed.[1]



Scheme 1

Bis-silylation of **11** with excess KHMDS and TMSCl followed by selective desilylation yielded **12** (Scheme 2).[16] Sulfenylation of the potassium enolate of **12** at −78 °C,[17] followed by a second enolization with KHMDS and trapping with $PhNTf_2$ provided enol triflates **13** in high yield. Attempted Heck closure of **13a** was complicated by loss of the TMS group, so this group was removed. Heck cyclization of **14a** using conditions optimized in our previous study[1] produced pentacycle **15a**[18] in 70% yield. This crystalline product (mp 125–127 °C) provided single crystals which allowed the structure of this product to be confirmed by X-ray diffraction analysis.[19] In contrast, intramolecular Heck cyclization of **14b** (R = Me) proceeded in low yield due to competing reduction of the enol triflate.



Scheme 2

The sequence reported here represents a practical way to prepare highly functionalized steroids that contain much of the functionality found in complex cardenolides. The overall sequence from commercially available 1,3-cyclohexanedione and (*S*)-Hajos-Parrish ketone involves 17 total steps and 14 isolated and purified intermediates. The synthesis strategy disclosed here has several notable aspects of potential general utility in synthesis: (a) use of a sulfone group to join fragments and then control regiochemistry of a subsequent reductive enolization and aldol cyclization, (b) the first demonstration of intramolecular Heck reaction of an α-sulfenyl enol triflate,[20] and (c) an additional illustration that highly substituted alkenes, in this case tetra- and trisubstituted, can be joined by intramolecular Heck reactions. We anticipate that intermediates such as **14** will prove useful in the total synthesis of complex cardenolides such as ouabain (**1**).

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9. This mixture undoubtedly arises by indiscriminate formation of a mixture of *E*- and *Z*- samarium enolates. This scenario has been rigorously established in a related system. Unpublished studies of M. Jensen of this laboratory.

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15. We have independently demonstrated that the β epimer of **9** is converted to **11** under these conditions. It is notable that **10** can be prepared and cleaved without unraveling to an enone.

16. $[\alpha]_D^{25}$ +81.9° (*c* 1.0, $CHCl_3$); FTIR (thin film) 2237 and 1713 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.52 (br s, 1H), 4.98 (d, *J* = 6.5 Hz, 1H), 4.88 (d, *J* = 6.5 Hz, 1H), 4.38 (br d, *J* = 12.4 Hz, 1H), 4.05 (d, *J*= 12.4 Hz, 1H), 2.65 (app t, *J* = 6.6 Hz, 1H), 2.57-2.49 (m, 2H), 2.26-1.90 (m, 6H), 1.81-1.52 (m, 9H), 1.45-1.40 (m, 2H), 1.48 (s, 3H), 0.26 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.1, 134.9, 124.6, 121.7, 91.3, 88.1, 75.7, 68.5, 56.5, 49.9, 38.4, 38.0, 35.1, 33.9, 32.1, 30.0, 26.0, 24.6, 18.8, 18.1, 17.7, 2.7; HRMS (FAB, mNBA) *m/z* 432.2578 (432.2570 calcd for $C_{24}H_{38}O_4NSi$, MH).

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18. $[\alpha]_D^{25}$ +184.2° (*c* 0.45, $CHCl_3$); FTIR (thin film) 3474, 2237 and 1731 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35-7.32 (m, 2H), 7.24-7.21 (m, 3H), 5.95 (br d, *J* = 10.1 Hz, 1H), 5.63 (dt, *J* = 10.1, 3.2 Hz, 1H), 5.11 (br s, 1H), 5.10 (d, *J* = 6.2 Hz, 1H), 4.95 (d, *J* = 6.2 Hz, 1H), 3.73 (d, *J* = 11.7 Hz, 1H), 3.17 (br d, *J* = 11.1 Hz, 1H), 2.61 (br s, 1H), 2.51 (dd, *J* = 9.1, 4.5 Hz, 1H), 2.29-2.00 (m, 8H), 1.80-1.75 (m, 3H), 1.60 (br m, 1H), 1.46-1.30 (m, 2H), 1.28 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.6, 129.2, 128.8, 128.3, 127.5, 126.3, 122.3, 87.2, 83.8, 74.3, 72.1, 47.3, 45.8, 45.2, 43.4, 37.4, 32.6, 29.8, 29.7, 25.2, 23.7, 20.9, 15.7; HRMS (FAB, mNBA) *m/z* 449.2023 (449.2024 calcd for $C_{27}H_{31}O_3NS$, M).

19. The authors have deposited atomic coordinates for this compound 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.

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