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Intramolecular 1,3-Dipolar Cycloaddition as a Tool for the Preparation of Azaspirocyclic Keto Aziridines. Synthesis of Intermediates for the Total Synthesis of (±)-Cephalotaxine

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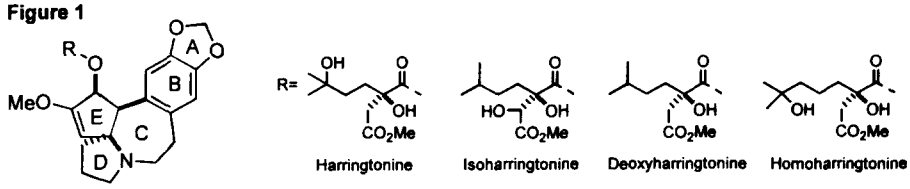
Abstract: The thermal intramolecular azide-enone 1,3-dipolar cycloaddition to azaspirocyclic keto aziridines **17** and **18** is reported. α-Hydroxylation and oxidation to the corresponding diketo aziridine **2** provided an intermediate in a synthetic approach toward cephalotaxine **1**. © 1997 Elsevier Science Ltd.

Cephalotaxine **1** is the major alkaloid of *Cephalotaxus fortunei* (Chinese plum-chew), *C. harringtonia* and *C. harringtonia var. drupacea* (Japanese plum-yew).[1] It is a minor constituent of *C. Wilsonia*.[2] The structure of cephalotaxine was determined by NMR and X-ray diffraction analysis.[3] The interest in this structurally unique class of alkaloids was stimulated by the finding that an extract of *C. harringtonia* seed shows antitumor activity against experimental lymphoid leukemia systems L-1210 and P-338 in mice. It was found that complex esters of cephalotaxine **1**, e.g., the harringtonines, are the active antitumor alkaloids from *Cephalotaxus sp.* (Figure 1).[4,5]

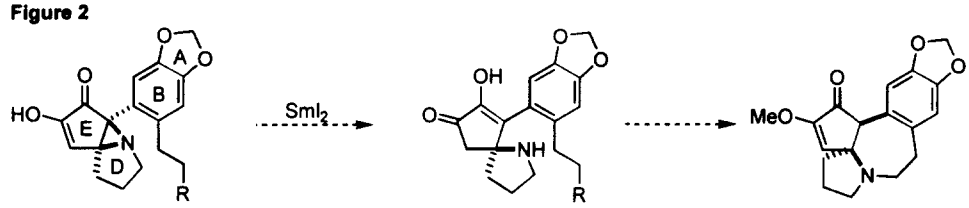
Figure 1



1: R=H (-)-Cephalotaxine

Our synthetic approach toward cephalotaxine is part of a general approach to the total synthesis of azaspirocyclic natural products based upon the reductive ring opening of keto aziridines with samarium(II) iodide (SmI_2).[6,7] We envisioned diketo aziridine **2** as a possible precursor for the SmI_2-mediated ring opening to spirocyclic diketo amine **4** (Figure 2). Cleavage of the silyl ether followed by intramolecular cyclization and methyl enol ether generation (or *vice versa*) would lead to cephalotaxinone **6** which can be reduced with $NaBH_4$ to afford cephalotaxine **1**.[7e] It is hoped that the presence of a chloride substituent in the aryl side chain of **3** will open the possibility of a sequenced SmI_2-mediated ring opening/ring closing reaction. This would provide ketone **6** without isolation of azaspirocyclic diketo amine **5**.

Figure 2



2, R= OTBS
3, R= Cl

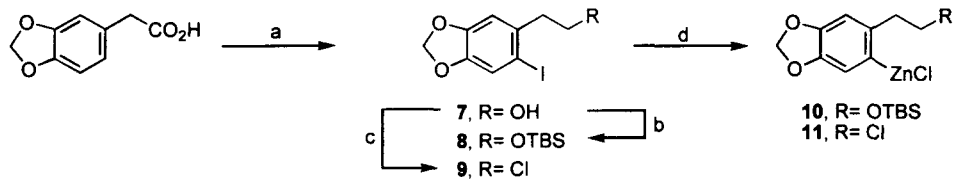
4, R= OTBS
5, R= Cl

6

We report here the intramolecular azide-enone 1,3-dipolar cycloaddition reaction as a tool for the synthesis of aziridines **2** and **18** (Scheme 4), intermediates under investigation for use in a synthetic approach toward cephalotaxine **1**.[8]

Reduction of commercial 3,4-(methylenedioxy)phenylacetic acid followed by iodination and protection of the hydroxy function gave the aryl iodide **8** (Scheme 1).[7d,7l] The alkyl chloride **9** was prepared from alcohol **7** under *Appel* conditions.[9] Lithium-halogen exchange followed by transmetallation with $ZnCl_2$ provided aryl zinc compounds **10** and **11**.

Scheme 1



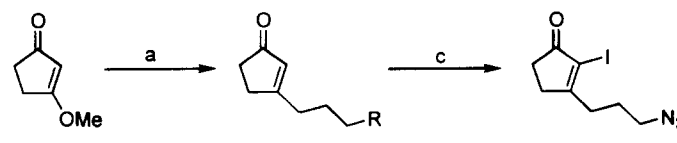
7, R= OH
8, R= OTBS
9, R= Cl

10, R= OTBS
11, R= Cl

(a) 1. LAH, ether; 95 %; 2. I_2, AgO_2CCF_3, $CHCl_3$; 85 %. (b) TBSCl, imidazole, DMF; 91 %. (c) PPh_3, CCl_4, Et_3N, DMF; 87 %. (d) *n*-BuLi, THF, -100 °C, 10 min then $ZnCl_2$, -100 °C, 10 min then 15 min at 25 °C.

Vinyl iodide **14** was prepared from commercial 3-methoxy-2-cyclopentenone by treatment with the *Grignard* reagent[10] from 3-chloro-1-propanol (Scheme 2). Careful acidic workup afforded alcohol **12**, which was tosylated and subsequently treated with sodium azide to afford the azido enone **13**. The iodination to vinyl iodide **14** was accomplished in 50 % yield (40 % of recovered starting material) under conditions recently reported by *Sha*.[11]

Scheme 2



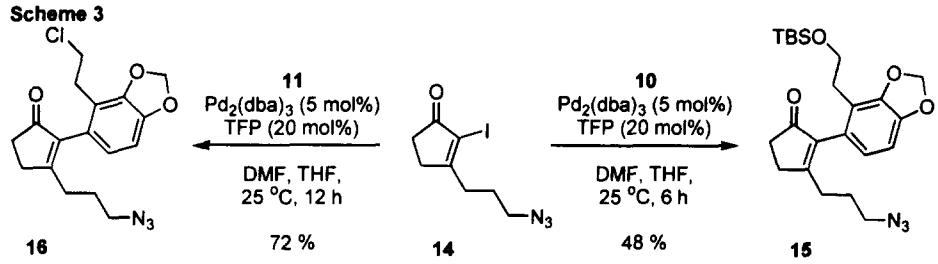
12, R= OH
13, R= N_3

14

(a) $ClMgCH_2CH_2CH_2OMgCl$, THF, 0 °C then 1 M aq. H_2SO_4, 30 min then solid Na_2HPO_4/NaH_2PO_4; 81 %. (b) 1. *p*-TsCl, CH_2Cl_2, DMAP, Et_3N; 76 %. 2. NaN_3, DMF, 25 °C; 96 %. (c) $TMSN_3$, CH_2Cl_2, 25 °C, 2 h then I_2, pyridine, 0 °C to 25 °C 12 h; 50 %.

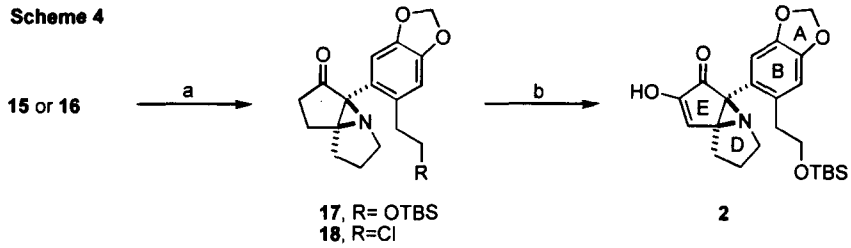
The crucial coupling reaction between vinyl iodide **14** and aryl zinc compounds **10** (or **11**) was accomplished under Pd(0)-catalysis in the presence of tri-2-furylphosphine (TFP) (Scheme 3).[12,13]

Scheme 3



The thermal intramolecular 1,3-dipolar cycloaddition of azido enone **15** in boiling xylene (131 °C) gave the desired keto aziridine **17**[14] in high yield (76 %) after 48 h along with starting material (18 %) (Scheme 4). Heating azido enone **15** in DMF (152 °C) for 12 h afforded only 20 % of aziridine **17**. Extensive decomposition occurred possibly because of the competing formation of a nitrene at elevated temperature. The thermolysis of azido enone **16** in boiling xylene had to be stopped after 18 h because of extensive decomposition. The keto aziridine **18** was isolated in 26 % yield along with 30 % of starting material. An attempt to perform the cycloaddition at lower temperature (105 °C, toluene) led only to decomposition of the starting azide **16**.

Scheme 4



(a) For **15**: xylene, 131 °C, 48 h; 76 %. For **16**: xylene, 131 °C, 18 h; 26 %. (b) 1. KHMDS, THF, -100 °C, 10 min; 2-(phenylsulfonyl)-3-phenyloxaziridine, -100 °C→-78 °C; 83 %. 2. *Dess-Martin* periodinane, CH_2Cl_2, -10 °C, 10 min; 90 %.

The introduction of the diketone oxidation state into the E-ring of keto aziridine **17** was conveniently accomplished *via Davis* hydroxylation[15] and *Dess-Martin* oxidation[16] in high yield to afford diketone **2** (75 % over 2 steps).

In conclusion, keto aziridines **2** and **18** have been synthesized as intermediates for an approach toward the synthesis of cephalotaxine **1**. The thermal intramolecular azide-enone 1,3-dipolar cycloaddition has been demonstrated to be effective for the construction of azaspirocyclic keto aziridines **17** and **18**. The presence of a chloride substituent dramatically influences the thermal intramolecular cycloaddition of azido enone **16**, resulting in a decrease of yield compared to the cycloaddition of azido enone **15**. We are currently establishing the reaction conditions for the SmI_2-mediated ring opening of keto aziridine **2**.

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14. NMR data for **17** indicating a mixture of two diastereomeric (axial chiral) compounds, 3:1 ratio. ^{1}H NMR (400 MHz, $CDCl_3$, mixture of isomers) δ -0.03 (s, 6H^{minor}); -0.02 (s, 6H^{major}), 0.80 (m, 1+1H); 0.83 (s, 9H^{minor}); 0.84 (s, 9H^{major}); 1.48 (m, 1+1H); 2.06-2.30 (m,4+4H); 2.34 (m, 2H^{minor}); 2.48 (m, 2H^{major}); 2.60 (m, 2H^{minor}); 2.70-2.90 (m, 2+2H); 3.10 (m, 2H^{major}); 3.58 (m, 2H^{minor}); 3.85 (m, 1H^{major}); 3.90 (m, 1H^{major}); 5.88 (s, 1H^{major}); 5.90 (s, 1H^{minor}); 5.91 (s, 1H^{major}); 5.92 (s, 1H^{minor}); 6.49 (s, 1H^{major}); 6.72 (s, 1H^{minor}); 6.74 (s, 1H^{minor}); 6.94 (s, 1H^{major}). ^{13}C NMR (100 MHz, $CDCl_3$, mixture of isomers) δ -5.6; -5.5; 18.1; 24.0; 24.5; 25.7; 25.8; 26.1; 26.5; 28.3; 28.5; 29.6; 33.8; 35.4; 36.0; 50.5; 50.8; 55.3; 57.0; 63.6; 63.8; 64.9; 66.3; 101.0; 101.1; 109.1; 109.75; 109.77; 110.1; 121.2; 122.4; 131.6; 134.9; 145.9; 146.0; 147.6; 147.9; 211.5; 212.2. HRMS calcd for $[C_{23}H_{33}NO_4Si]^+$ 415.2179, found 415.2170. LRMS (EI+) *m/z* 415 (16); 387 (37); 358 (55); 290 (65); 214 (70); 124 (100); 96 (86); 73 (66), 41 (22). IR ν 1737 cm^{-1}.
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