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Total Synthesis of UCS1025A

Tristan H. Lambert and Samuel J. Danishefsky*

Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, 1275 York Avenue, New York, New York 10021, and Department of Chemistry, Columbia University, Havemeyer Hall, 3000 Broadway, New York, New York 10027

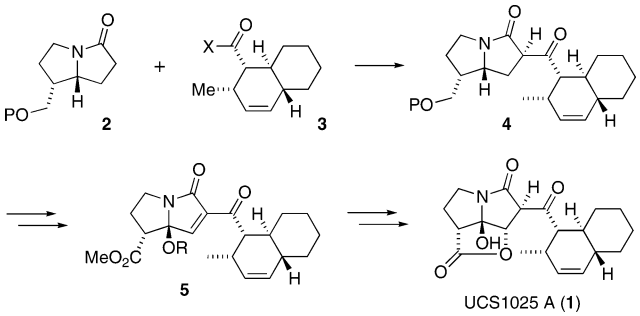
Received November 1, 2005; E-mail: s-danishefsky@ski.mskcc.org

Cellular immortality is a basic defining trait of cancer. Indeed, the unlimited proliferative potential of transformed cells enables many of the most insidious characteristics of cancerous diseases. It stands to reason that disrupting the mechanism by which aberrant cells escape mortality offers a significant opportunity for chemotherapy. The primary mutation that facilitates the achievement of immortality in tumorigenic cells is upregulation of the enzyme telomerase, the ribonucleoprotein that catalyzes lengthening of telomeres.[1] In the absence of telomerase, telomere shortening eventually leads to chromosomal instability and, hence, to the onset of senescence or apoptosis. In this way, telomeres serve as a sort of molecular clock, effectively limiting the number of times a cell may divide. It is of great interest then that telomerase, while absent in the majority of somatic tissues, is upregulated in more than 85% of cancer cell lines. Accordingly, the identification of small molecule telomerase inhibitors constitutes an appealing new chemotherapeutic strategy.

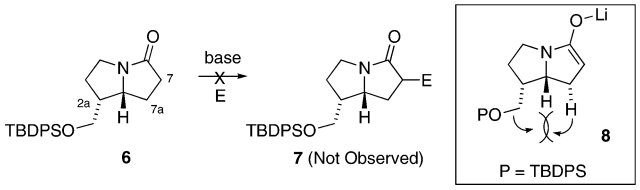
UCS1025A (**1**), isolated from the fermentation broth of the *Acremonium* sp. KY4917 fungus, has been shown to possess antiproliferative activity against human cancer cell lines by inhibition of the telomerase enzyme.[2] UCS1025A exists as three tautomeric isomers and consists of a compact pyrrolizidine core connected by an acyl bond to a octahydronaphthalene fragment. The telomerase inhibitory activity as well as the compact structure of UCS1025A compelled us to undertake its total synthesis.

Before describing a plan that solves the UCS1025A total synthesis problem in a novel and remarkably straightforward way, we relate an earlier approach that provides a context for the discoveries set forth here. Under our original synthetic plan, pyrrolizidine **2** would be coupled to fragment **3** via an aldol or Claisen condensation to afford an intermediate of the type **4**. This late stage intermediate would be converted to UCS1025A through a series of oxidations. Thus, the core pyrrolizidine fragment (cf. **6**) was prepared.[3] Unfortunately, all attempts to introduce functionality at C_7 (UCS1025A numbering) of compound **6** were unsuccessful. This resistance was particularly confounding given the known success of functionalization of similar substrates.[4] To rationalize this result, we postulate that there exists a severe steric interaction between the silyloxymethyl substituent and the *endo* C_{7a} proton. Trigonalization of C_7, required for enolization, would result in an increase in the bicyclic cup angle and thus an amplification of this highly unfavorable interaction (cf. **8**).[5] In support of this argument, we have found that the opposite pyrrolizidine diastereomer (cf. **9**), which does not suffer from this type of steric interaction, is amenable to LiHMDS-induced enolization (eq 1). Thus, to go forward with our original coupling plan, we would have to operate via a structure of the type **9**, which is epimeric at C_{2a} with that needed to reach **1**, thereby necessitating a late stage epimerization at this center. We were accordingly reluctant to follow such a course. Disappointing as the finding concerning the remarkable resistance of **6** to enolization at

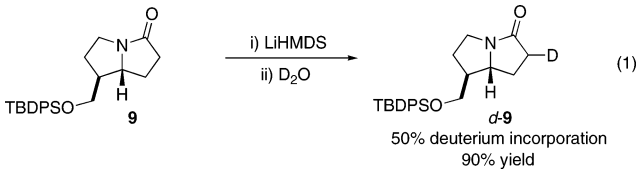
Scheme 1. Original Synthetic Strategy toward UCS1025A



Scheme 2. Attempted Functionalization of Core Fragment **2**



C_7 was at the time, it did serve to lead us to some novel chemistry resulting in a highly concise route to **1**.



(1)

We came to consider the possibility of coupling the fully functionalized UCS1025A core, wherein the γ-lactone would already be in place at the coupling stage. Importantly, we were not unmindful of the potential complications associated with enolate formation in the context of a labile β-acyloxy bond.

An obvious disconnection would entail a cyclization of a compound of the type **10**.[6] Thus, maleimido ester **10**, which is readily available from maleic anhydride and γ-aminobutyric acid, was subjected to "soft enolization" conditions, affording the bicyclic pyrrolizidine ester **11** in high yield as a single diastereomer. Saponification to acid **12** followed by iodolactonization then provided the target intermediate **13**. Though racemic **13** is readily separable in useful quantities using HPLC on a chiral support, we preferred to focus on a diastereoselective "aldolization" to gain access to optically pure material. Thus, in the interest of achieving asymmetric access to compound **13**, we investigated the employment of a chiral imide. In this context, condensation of diacetyltartaric anhydride with commercially available methyl-4-aminobutyrate hydrochloride yielded an ester imide which, upon acetate removal followed by TMS protection, afforded **14**. Cyclization of **14**, in this case using $^{i}Pr_2$-NEt, provided adduct **15** as a 10:1 mixture of diastereomers. The

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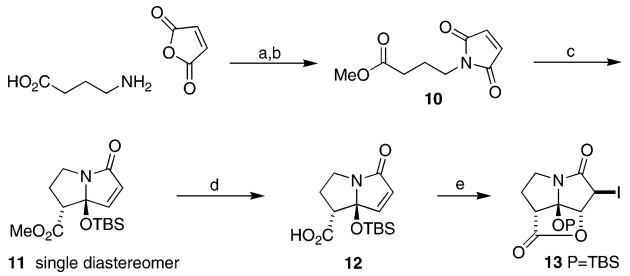
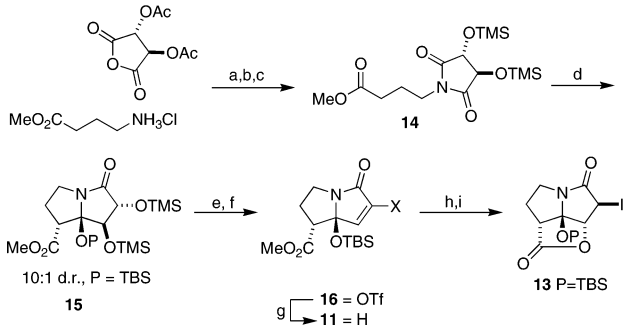
Scheme 3. Synthesis of Iodolactone **13**[a]



[a] Key: (a) AcOH, then toluene, Et_3N, reflux, Dean−Stark trap (75%); (b) $SOCl_2$, MeOH (77%); (c) TBSOTf, Et_3N, CH_2Cl_2, r.t. (80%); (d) $LiOH{\cdot}H_2O$, 3:1 THF:H_2O (99%); (e) I_2, sat. $NaHCO_3$, Et_2O, THF (84%).

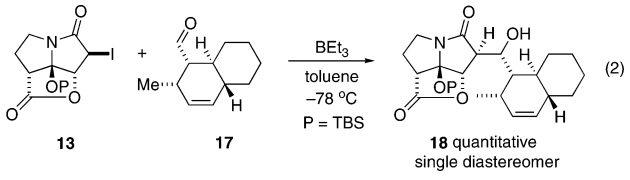
Scheme 4. Asymmetric Synthesis of **13**[a]



[a] Key: (a) (i) Et_2NH, THF; (ii) AcCl, reflux (51%); (b) AcCl, MeOH (79%); (c) TMSCl, Et_3N, CH_2Cl_2 (85%); (d) TBSOTf, $^iPr_2NEt$, CH_2Cl_2, −78 °C to r.t. (79%); (e) AcOH, 1 N HCl, THF; (f) Tf_2O, pyridine, CH_2Cl_2, −78 °C to r.t., then pyridine (76%, two steps); (g) Bu_3SnH, $Pd(PPh_3)_4$, LiCl, THF (52%); (g) LiOH, 3:1 THF:H_2O (99%); (h) I_2, sat. $NaHCO_3$, Et_2O, THF (84%).

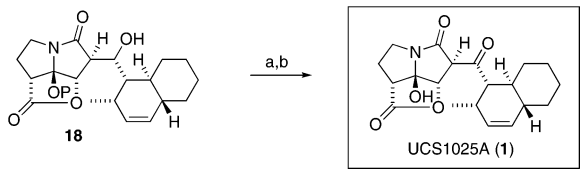
TMS protecting groups were then removed, and the resulting diol was treated with triflic anhydride in pyridine to produce vinyl triflate **16**. Subsequent cross-coupling of **16** with tributyltin hydride then provided enantiopure **11**.[7] This material was converted as before to tricyclic iodolactone **13**. For the synthesis of the octahydronaphthalene fragment of UCS1025A, we took advantage of the recently disclosed organocatalytic synthesis of decalin aldehyde **17**, which corresponds precisely to our required coupling fragment.[8]

Despite our concerns regarding the feasibility of accessing an enolate intermediate from **13**, the strategic conciseness that would be achieved through direct coupling of **13** and aldehyde **17** prompted us to attempt a Reformatsky-type merger of these two fragments.[9] In this vein, *we have found that treatment of* ***13*** *and 2 equiv of* ***17*** *with triethylborane in toluene at −78 °C effects a rapid, quantitative, and completely stereoselective aldol coupling to provide the full UCS1025A skeleton* (eq 2).[10] This remarkable process, which presumably passes through the intermediacy of a boron enolate, produces no β-elimination product (cf. **12**), and excess aldehyde may be recovered intact.



The exceptional simplification in strategy enabled by the success of this fragment coupling reaction allows access to **1** in only two simple steps from adduct **18** (Scheme 5). Thus, deprotection with TBAF followed by Dess−Martin periodinane oxidation provided UCS1025A as a tautomeric mixture. As reported, this mixture coalesced to **1** upon standing in $CDCl_3$.[2]

Scheme 5. Synthesis of UCS1025A[a]



[a] Key: (a) TBAF, THF (85%); (b) Dess−Martin periodinane, CH_2Cl_2 (84%).

In summary, we have developed a highly concise synthesis of UCS1025A. The key transformation in our sequence was a remarkable boron Reformatsky fragment coupling that allowed direct use of a tricyclic iodolactone. This protocol was discovered following the failure of a more traditional aldol reaction due to a structural peculiarity of the pyrrolizidine nucleus.

Preliminary investigations of the biological profile of UCS1025A have been very encouraging, particularly in regards to its telomerase inhibiting activity. Furthermore, we are applying our synthetic sequence to the synthesis of analogue structures with the aim of identifying a superior therapeutic target. Results of these studies will be forthcoming.

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Supporting Information Available: Experimental procedures and characterization, including polarimetric data, for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) The stereochemistry of the hydroxy group of **18** has not yet been determined.

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