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Concise enantioselective synthesis of diospongins A and B

Eric Stefan, Ansel P. Nalin, Richard E. Taylor *

Department of Chemistry and Biochemistry and the Mike and Josie Harper Cancer Research Institute, University of Notre Dame, 251 Niewland Science Hall, Notre Dame, IN 46556, United States

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Dedicated to Paul A. Wender, an inspirational teacher and scholar and a generous mentor, on receipt of the 2013 Tetrahedron Prize

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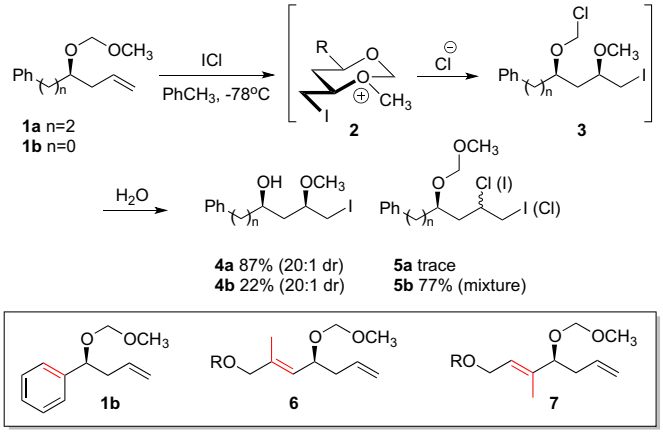
ABSTRACT

Ether transfer methodology is capable of stereoselectively generating 1,3-diol mono- and diethers in good yield. Surprisingly, allylic and benzylic substrates provide none of the desired products when exposed to previously optimized conditions of iodine monochloride. Herein, second-generation activation conditions for ether transfer have been developed that circumvents undesired side reactions for these substrates. The application of this chemistry to the enantioselective synthesis of diospongins A and B has now been accomplished.

1. Introduction

Polyketide natural products have attracted the attention of numerous academic laboratories for their potential use as chemotherapeutic agents. Often limited by natural supplies, the community has harnessed powerful synthetic methods for practical syntheses of complex molecules to enable exploration of their therapeutic potential. The repeating pattern of 1,3-oxygenation is very common to polyketides. We have recently developed an ether transfer methodology that enables the formation of *syn*-1,3-diol mono- or diethers through electrophilic activation of a homoallylic alkoxyether.[1] As highlighted in Scheme 1, activation of **1a** with iodine monochloride in toluene at low temperature led to the formation of ether transfer product **4a** in excellent yield and diastereoselectivity. The use of iodine monochloride proved critical by generating the chloromethyl ether intermediate **3** in situ, as observed by NMR analysis.

However, during the course of these studies we observed that certain substrates failed to provide the expected reactivity. A comparison of substrates **1a** and **1b** demonstrated a remarkable effect of the proximity of phenyl substitution on the ether transfer. In fact, subjecting **1b** to the identical conditions led predominantly to the isolation of a complex mixture of ICl addition products, **5b** (Scheme 1). Similarly, in planned application of this methodology to the syntheses of synthetic fragments related to zampanolide and peluroside A, undesired ICl addition products were also observed with diene substrates **6** and **7**. Thus, the proximity of sp^2-hybridized substituents adjacent to the reacting alkoxymethyl ether had



Scheme 1. Electrophile-induced ether transfer.

* Corresponding author. Tel.: +1 574 631 5674; e-mail address: taylor.61@nd.edu (R.E. Taylor).

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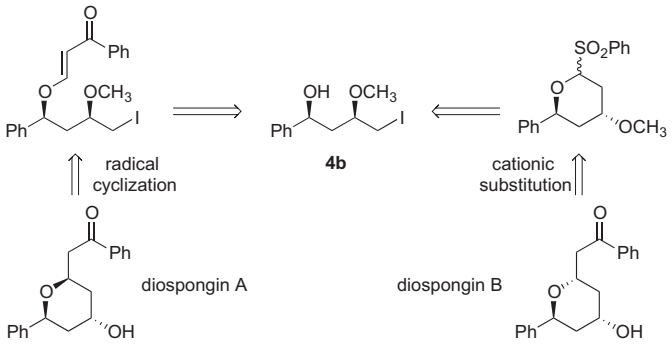
a significant effect on the rate of cyclization. Application of ether transfer to the syntheses of the diastereomeric pyran natural products, diospongins A and B, would require a solution to this issue.

Diospongins A and B were isolated in 2004 from rhizomes of *Dioscorea spongiosa*,[2] a Chinese plant used for the treatment of rheumatism as well as urethra and renal infections in traditional medicine.[3] Diospongin B has shown significant antiosteoporotic activity and potent inhibitory activities on bone resorption by inhibiting calcium release. Due to their relatively simple structure and their potential application to the treatment of osteoporosis, diospongins A and B have attracted the attention of the synthetic community leading to several syntheses.[4] We envisioned a divergent synthetic strategy that would allow access to both diospongins from a common intermediate, such as 1,3-*syn*-diol monoether **4b**. As proposed in Scheme 2, complementary methods for pyran generation would provide stereoselective access to each of the diastereomeric natural products.

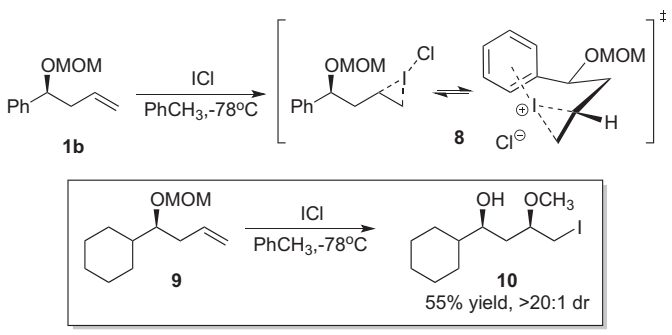


Scheme 2. Divergent strategy for the syntheses of diospongins.

2. Results and discussion

2.1. Access to *syn*-1,3-diol monoether

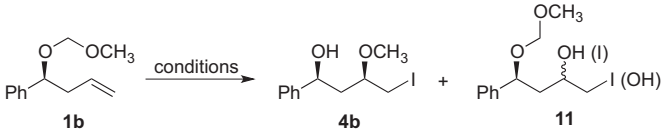
Iodine monochloride has shown unique ability to affect stereoselective ether transfer in good yield. However, it has also shown limitations with some substrates, vide supra. For example, significant amount of ICl addition was observed with **1b** leading to lower yield of the desired ether transfer product **4b**. The inductively electron-withdrawing aryl or vinyl group is likely to slow the rate of cyclization and formation of the intermediate oxonium ion **2**. However, an alternative rationale includes the potentially stabilizing cationic-pi interaction, such as intermediate **8**, which would populate an unproductive conformation and allow intermolecular chloride addition to compete with the ether transfer (Scheme 3). Sterics were eliminated as a factor by substituting the aromatic ring in **1b** with a cyclohexyl group. Here, only trace amounts of dihalogenation products were detected and the *syn*-1,3-diol monoether **10** was isolated in good yield and excellent diastereoselectivity.[5]



Scheme 3. Through-space stabilization of the iodonium ion.

We envisioned that modulating the nucleophilicity and availability of counterions in solution, such as chloride, could eliminate undesired olefin addition products. We thus focused our efforts on finding alternative electrophilic activating conditions, to induce ether transfer in substrate **1b** and the results are listed in Table 1. Substitution of ICl by other sources of I^+, such as Ipy_2BF_4, I(collidine)$_2PF_6$, bromodiethylsulfonium bromopentachloroantimonate (BDSB), and the iodine analogue (IDSI) led to either poor reactivity or decomposition (Entries 3–7). However, much to our delight, we found that conditional adjustments to *N*-iodosuccinimide enabled the formation of *syn*-1,3-diol monoether **4b** in higher yield and satisfactory diastereoselectivity (Entry 8). Unfortunately, an appreciable amount of the water addition product **11** was also observed. However, changing the solvent to nitromethane not only diminished the formation of this undesired product but also increased the yield and diastereoselectivity of the transformation (Entry 12).

Table 1
Ether transfer activated with *N*-iodosuccinimide

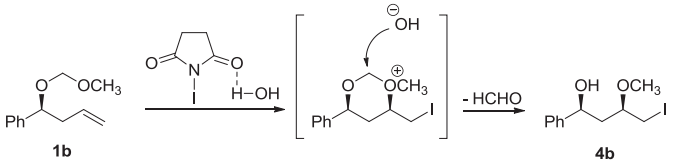


Entry	Conditions	**4b** Yield[a] (dr)[b]	**4b**:**11**[c]
1	ICl, $PhCH_3$, −78 °C, 10 min	22% (20:1)	—
2	IBr, $PhCH_3$, −78 °C, 10 min	20% (20:1)	—
3	I_2, $PhCH_3$, −78 °C	NR	—
4	Ipy_2BF_4, DCM, rt	NR	—
5	I(collidine)$_2PF_6$, DCM, rt	NR	—
6	IDSI, CH_3NO_2, rt	Decomp.	—
7	BDSB, CH_3NO_2, rt	Decomp.	—
8	NIS, 10% H_2O in CH_3CN, rt, 1 h	40%	3:2
9	NIS, 10% H_2O in $PhCH_3$, rt, 1 h	0%	0:1
10	NIS, 10% H_2O in DCM, rt, 1 h	75% (11:1)	1:1
11	NIS, 10% H_2O in CH_3NO_2, rt, 1 h	72% (6:1)	3.5:1
12	NIS, H_2O (2 equiv), CH_3NO_2, rt, 6 h	64% (6:1)	5:1
13	NIS, H_2O (5 equiv), CH_3NO_2, rt, 5 h	64% (6:1)	5:1
14	NIS, CH_3NO_2, 4 ÅMS	NR	—

[a] Isolated yield.
[b] Diastereomeric ratio determined by NMR analysis.
[c] Regioisomeric ratio of **11** was 1:1 by ^{13}C NMR analysis.

2.2. Access to *syn*-1,3-diol diether

The results of this study make clear that the presence of water was crucial in the transfer as it likely both activates *N*-iodosuccinimide and also serves as a nucleophilic trap for the intermediate oxonium ion (Scheme 4). Intrigued by this transformation, we thought to access *syn*-1,3-diol diethers by replacing water with other weak Brønsted acids.



Scheme 4. Activation of *N*-iodosuccinimide with water.

Successful demonstration of this concept is highlighted in Table 2. In the presence of *N*-iodosuccinimide, a variety of activating agents, such as acetic acid, 1-phenyl-1*H*-tetrazole-5-thiol, benzyl imidate, or propionaldehyde oxime were able to initiate the ether transfer providing access to *syn*-1,3-diol diethers in good yield and diastereomeric ratio. In some cases a significant amount of byproduct **13** was observed, although sensitivity of the reaction to the