

A Facile and Efficient Synthesis of 4-Hydroxy-2,6-*cis*-tetrahydropyrans via Tandem Cross-Metathesis/Thermal S_N2' Reaction: Protecting-Group-Free Synthesis of (±)-Diospongin A

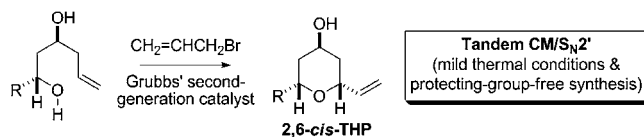
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ABSTRACT



The tandem cross-metathesis/thermal S_N2' reaction was explored for the facile and efficient synthesis of 4-hydroxy-2,6-*cis*-tetrahydropyrans. The mildness of the thermal conditions allowed for the synthesis of 4-hydroxy-2,6-*cis*-tetrahydropyrans from base-sensitive substrates without the use of protecting groups. The tandem reaction enabled a protecting-group-free synthesis of (±)-diospongin A.

The development of tandem reactions is a rapidly growing area of synthetic organic chemistry.¹ Tandem reactions complete several chemical transformations in a single step and offer a powerful approach for rapidly increasing molecular complexity from simple starting materials. The main advantages of tandem reactions are reduction in overall steps by avoiding isolation of often highly reactive intermediates, minimal use of protecting groups, and the benefits of green chemistry by saving time and reducing waste.

Recently, we reported the feasibility of the S_N2' reaction for the stereoselective synthesis of substituted O-heterocycles.² We applied the intramolecular S_N2' reaction in conjunction with olefin cross-metathesis (CM) reaction (tandem CM/S_N2' reaction) to the stereoselective synthesis of the 2,3-*trans*-2,5-*trans*-tetrahydrofuran of subglutinol B.

Intrigued by the potential of the tandem CM/S_N2' reaction

for rapid construction of substituted O-heterocycles, we decided to extend this methodology to the synthesis of tetrahydropyrans (THPs). Structurally complex tetrahydropyrans are found in a wide range of biologically interesting natural products including macrolides and polyether ionophores.³ Although considerable efforts have been devoted toward the development of synthetic routes for natural and unnatural tetrahydropyrans,^{4,5} there still exists a great need for a synthetic approach toward these classes of molecules

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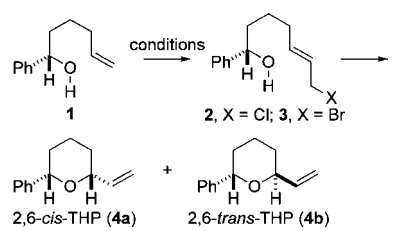
(4) For reviews on tetrahydropyran synthesis, see: (a) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309–3362. (b) Clarke, P. A.; Santos, S. *Eur. J. Org. Chem.* **2006**, 2045–2053. (c) Larrosa, I.; Romea, P.; Urpí, F. *Tetrahedron* **2008**, *64*, 2683–2723.

that allows for rapid access to substrates and requires mild reaction conditions compatible with various functional groups.

Herein, we report the facile and efficient synthesis of 4-hydroxy-2,6-*cis*-tetrahydropyrans via a tandem CM/thermal S_N2' reaction under mild reaction conditions and its application to a protecting-group-free synthesis of (\pm)-diospongins A.

To test the feasibility of the tandem reaction, we prepared hydroxy alkene **1**⁶ by the addition of $\text{CH}_2=\text{CH}(\text{CH}_2)_3\text{MgBr}$ to PhCHO (84%). Treatment of **1** with $\text{CH}_2=\text{CHCH}_2\text{Cl}$ in the presence of Grubbs' second-generation catalyst (Grubbs II, $(\text{IMesH}_2)(\text{PCy}_3)(\text{Cl})_2\text{Ru}=\text{CHPh}$)⁷ and subsequent intramolecular S_N2' reaction^{8,9} of the corresponding allylic chloride **2** under thermal conditions (*tandem CM/thermal S_N2' reaction*, Table 1)^{10,11} provided a mixture of **4a** and **4b**

Table 1. Initial Attempts for the Tandem CM/Thermal S_N2' Reaction

			
entry	conditions	yield (%) ^a	dr ^b
1	$\text{CH}_2=\text{CHCH}_2\text{Cl}$, Grubbs II (10 mol %), CH_2Cl_2 (0.1–0.02 M), reflux, 16 h	66	2:1
2	$\text{CH}_2=\text{CHCH}_2\text{Cl}$, Grubbs II (10 mol %), CH_2Cl_2 (0.1 M), reflux, 3 h, then toluene (0.02 M)	79	2:1
3	$\text{CH}_2=\text{CHCH}_2\text{Br}$, Grubbs II (10 mol %), CH_2Cl_2 (0.1 M), reflux, 2 h, then toluene (0.02 M), reflux, 10 h	78	2:1

^a Combined yield of **4a** and **4b**. ^b Diastereomeric ratio (**4a**:**4b**) determined by integration of the ^1H NMR of the crude product.

in 66% yield but in poor stereoselectivity (**4a**:**4b** = 2:1, entry 1).¹² On the basis of the fact that we isolated the intermediate **2** in addition to **4a** and **4b**, we anticipated that a higher reaction temperature would promote the S_N2' cyclization step. After the completion of the CM reaction of **1** and $\text{CH}_2=\text{CHCH}_2\text{Cl}$ in CH_2Cl_2 as monitored by TLC, addition of toluene to the reaction mixture increased the yield of the reaction from 66% to 79% (entry 2). Use of $\text{CH}_2=\text{CHCH}_2\text{Br}$ instead of $\text{CH}_2=\text{CHCH}_2\text{Cl}$ had no effect on yield, but slightly shortened the reaction time (entry 3). We attributed the low stereoselectivity to a less well-defined transition state of the intramolecular S_N2' reaction.⁸

To improve the low stereoselectivity of the tandem reaction, we envisioned the introduction of an axially oriented

functional group at the C4 position that would increase the 1,3-diaxial interaction with the C6 allyl substituent (Figure 1). The unfavorable 1,3-diaxial interaction of the axially

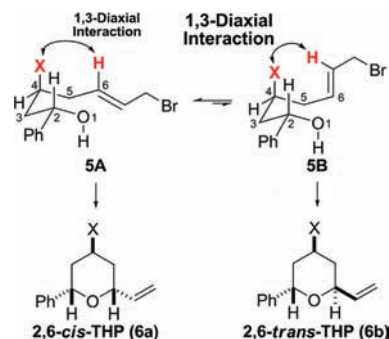


Figure 1. Introduction of 1,3-diaxial interactions to the tandem CM/thermal S_N2' reaction.

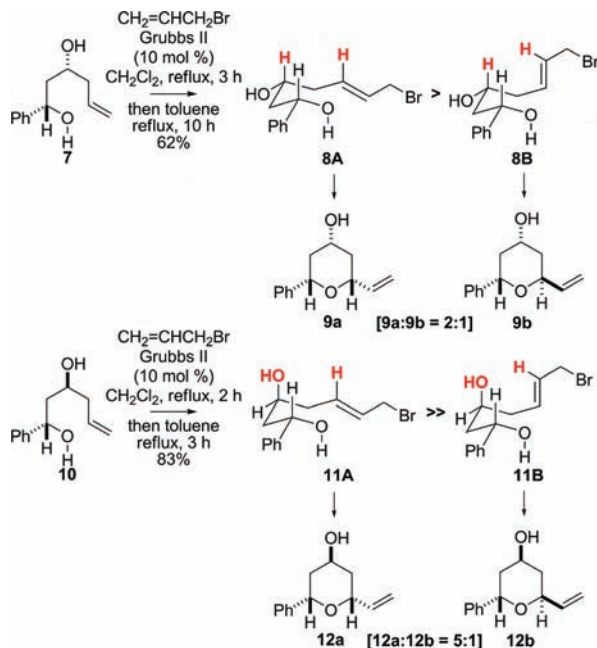
oriented C4 substituent and the C6 allyl substituent in conformation **5B** is larger than that of the hydrogen and the C4 substituent in conformation **5A**, thus preferentially affording 2,6-*cis*-tetrahydropyran **6a**. In addition, the C4 substituent could be transformed to other useful functional groups. Since 4-hydroxy-2,6-*cis*-tetrahydropyrans and 2,6-*cis*-tetrahydropyran-4-ones are abundant structural motifs in biologically important natural products,³ we hypothesized that a hydroxy group at the C4 position could satisfy these requirements.

To test the hypothesis, we prepared hydroxy alkenes (**7** and **10**)¹³ and subjected them to the tandem reaction

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conditions (Scheme 1). Treatment of α -hydroxy alkene **7** with $\text{CH}_2=\text{CHCH}_2\text{Br}$ under the tandem reaction conditions

Scheme 1. Synthesis of 4-Hydroxy-2,6-*cis*-tetrahydropyrans



provided the desired 4-hydroxy-2,6-*cis*-tetrahydropyran **9a**, but in low stereoselectivity (2:1 dr). However, under the same reaction conditions, the β -hydroxy alkene **10** provided **12a** with higher stereoselectivity (5:1 dr). These results demonstrated that the increased 1,3-diaxial interaction by the axially oriented C4 hydroxy group in **10** enhanced the stereoselectivity.¹⁴

To assess the effect of thermal conditions on the intramolecular $\text{S}_{\text{N}}2'$ reaction, **13** and **14** were treated with a base such as NaH or KO^tBu. The $\text{S}_{\text{N}}2'$ reaction of **13** under basic

conditions (NaH or KO^tBu) completely failed to provide the corresponding tetrahydropyran, but significant decomposition was observed (Table 2). When Bn-protected allylic bromide

Table 2. Intramolecular $\text{S}_{\text{N}}2'$ Reactions under Basic Conditions

entry	conditions	yield (15/16 , %)	dr ^a
1	NaH, THF, 0–25 °C, 9 h	30/26	2.6:1
2	NaH, THF/DMF (2/1), 0–25 °C, 3 h	26/73	1.8:1
3	KO ^t Bu, THF, –78 °C, 20 min	0/62	NA ^b
4	KO ^t Bu, THF, 0 °C, 30 min	29/45	1.5:1
5	KO ^t Bu, THF, 25 °C, 20 min	22/49	1.6:1

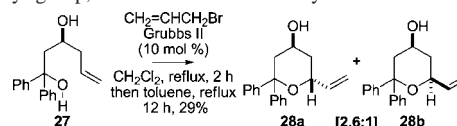
^a Diastereomeric ratio (2,6-*cis*-THP:2,6-*trans*-THP) of **15** determined by integration of ¹H NMR of crude product. ^b Not applicable.

14 was subjected to the basic conditions (NaH or KO^tBu), the $\text{S}_{\text{N}}2'$ reaction provided the elimination products **16** as well as tetrahydropyrans **15**. On the basis of these results, we concluded that the mildness of the thermal conditions was critical to the synthesis of 4-hydroxy-2,6-*cis*-tetrahydropyran **12a** from base-sensitive substrate **13** without the use of protecting groups.¹⁵

To investigate the scope and stereochemical outcome of the tandem reaction with respect to substituents at the C2 position, we prepared 1,3-*syn*-diols (**17–19**)¹⁶ and subjected them to the tandem reaction conditions (Table 3). We were pleased to find that the tandem reaction of **17–19** in the presence of $\text{CH}_2=\text{CHCH}_2\text{Br}$ and Grubbs II proceeded smoothly to provide the corresponding 4-hydroxy-2,6-*cis*-tetrahydropyrans (**20a**, **21a**, and **22a**) with decent stereoselectivities (entries 1–4).¹⁷

To the best of our knowledge, the tandem CM/ $\text{S}_{\text{N}}2'$ reaction has never been reported for the stereoselective synthesis of tetrahydropyrans. Indeed, few approaches for the stereoselective synthesis of tetrahydropyrans involve intramolecular $\text{S}_{\text{N}}2'$ reactions,^{51–n} perhaps due to the low nucleophilicity of oxygen and a less well-defined transition state.

(17) The tandem reaction of the sterically hindered tertiary alcohol **27** afforded tetrahydropyrans (**28a** and **28b**) but in low yield (29%). Due to the diphenyl group, elimination of the tertiary alcohol was observed.



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(11) It has been reported that ruthenium species can play a role as a Lewis acid: see ref 10a. But, in our case, isolation of allylic chloride **2** from the reaction mixture and subsequent refluxing in toluene also afforded tetrahydropyran **4a**, demonstrating that the intramolecular $\text{S}_{\text{N}}2'$ reaction was a thermal process.

(12) The relative stereochemistries of the 2,6-disubstituted tetrahydropyrans were determined by ¹H NMR coupling constants and 2D-NMR (see Supporting Information for details).

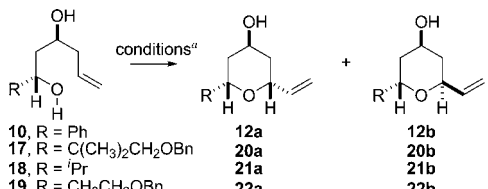
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(14) Protection of **10** with Bn, Bz, or Piv groups and subsequent reaction to the tandem reaction conditions ($\text{CH}_2=\text{CHCH}_2\text{Br}$, 10 mol % of Grubbs II, CH_2Cl_2 , reflux, 3 h, then toluene, reflux, 10 h) did not further improve the stereoselectivity of the tandem reaction (5:1 dr, see Supporting Information for details).

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(16) The relative stereochemistries of 1,3-*syn*-diols (**10** and **17–19**) were determined by ¹³C NMR chemical shifts of the corresponding acetonides (see Supporting Information for details).

Table 3. Substrate Scope of the Tandem CM/Thermal S_N2' Reaction



entry	substrate	yield ^b	dr ^c
1	10	83%	5:1
2	17	85%	4:1
3	18	80%	3:1
4	19	95%	4:1

^a $\text{CH}_2=\text{CHCH}_2\text{Br}$, Grubbs II (10 mol %), CH_2Cl_2 (0.1 M), reflux, 2 h, then toluene (0.02 M), reflux, 3–10 h. ^b Combined yield of 2,6-*cis*- and 2,6-*trans*-THPs. ^c Diastereomeric ratio (2,6-*cis*-THP:2,6-*trans*-THP) determined by integration of ^1H NMR of crude product.

To demonstrate the utility of the tandem CM/thermal S_N2' reaction, we embarked on a synthesis of (±)-diospongins A (23). The diarylheptanoids diospongins A and B (23 and 24, Figure 2) were isolated from the rhizomes of *Dioscorea*

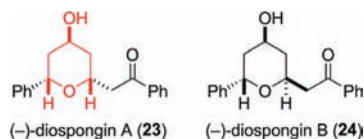
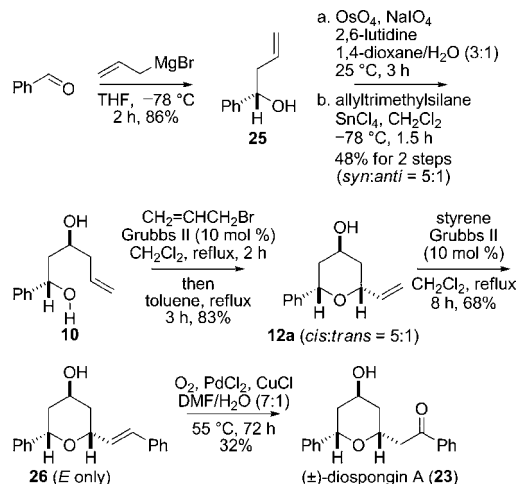


Figure 2. Structure of (–)-diospongins A (23) and B (24).

*spongiosa*¹⁸ and have attracted considerable synthetic interest due to their antiosteoporotic activity (diospongin B).¹⁹ We envisioned that the embedded 4-hydroxy-2,6-*cis*-tetrahydropyran of 23 could be constructed using the tandem CM/thermal S_N2' reaction as the key bond-forming event.

The addition of $\text{CH}_2=\text{CHCH}_2\text{MgBr}$ to PhCHO , followed by an oxidative cleavage of alkene 25, and treatment of the corresponding aldehyde with allyltrimethylsilane and SnCl_4 ²⁰ afforded a mixture of 1,3-diols (*syn:anti* = 5:1) which were readily separated by SiO_2 chromatography (Scheme 2). The

Scheme 2. Synthesis of (±)-Diospongins A (23)



tandem reaction of 1,3-*syn*-diol 10 in the presence of $\text{CH}_2=\text{CHCH}_2\text{Br}$ and Grubbs' second-generation catalyst smoothly proceeded to provide the desired 4-hydroxy-2,6-*cis*-tetrahydropyran 12a (5:1 dr, 83%). A second CM reaction of 12a with styrene gave rise to 26 in 68%. Attempts for one-pot CM/ S_N2' /CM reaction of 10 ($\text{CH}_2=\text{CHCH}_2\text{Br}$, 10 mol % of Grubbs II, CH_2Cl_2 , reflux, 2 h, then toluene, reflux, 3 h; styrene, 10 mol % of Grubbs II, reflux, 10 h) provided 26, but in low yield (16%). Final regioselective introduction of the carbonyl group to complete the synthesis of (±)-diospongins A (23) was accomplished by a Wacker reaction as described previously.^{19f} The efficiency of tandem CM/thermal S_N2' reaction allowed for a synthesis of (±)-diospongins A (23) without the use of protecting groups.

In summary, we explored the tandem CM/thermal S_N2' reactions for the efficient synthesis of 4-hydroxy-2,6-*cis*-tetrahydropyrans, a ubiquitous structural element found in structurally complex natural products with interesting biological activities. The reaction required no base for the S_N2' cyclization step (thermal conditions) and proceeded with modest stereoselectivity (3–5:1 dr). The tandem CM/thermal S_N2' reaction enabled a concise synthesis of (±)-diospongins A (23) with no use of protecting groups. Studies toward the improvement of stereoselectivity of the tandem reaction and its application to the synthesis of natural products are currently in progress.

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Supporting Information Available: General experimental procedures including spectroscopic and analytical data for 1, 4, 7, 9, 10, 12, 15–23, and 26 along with copies of ^1H and ^{13}C NMR spectra; detailed assay procedure. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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