ORGANIC LETTERS

XXXX
Vol. xx, No. x

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

Kiyoun Lee, Hyoungsu Kim, and Jiyong Hong*

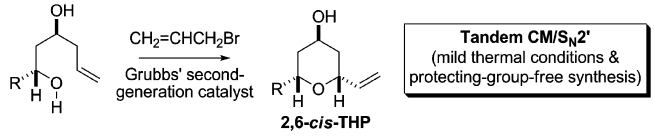
Department of Chemistry, Duke University, Durham, North Carolina 27708

jiyong.hong@duke.edu

Received September 15, 2009

Downloaded by SHANGHAI INST OF ORG CHEM on October 22, 2009 | http://pubs.acs.org
Publication Date (Web): October 13, 2009 | doi: 10.1021/ol902125d

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

(1) For reviews on tandem reaction, see: (a) Bunce, R. A. *Tetrahedron* **1995**, *51*, 13103–13159. (b) Nicolaou, K. C.; Montagnon, T.; Snyder, S. A. *Chem. Commun.* **2003**, 551–564. (c) Padwa, A. *Pure Appl. Chem.* **2004**, *76*, 1933–1952.

(2) Kim, H.; Baker, J. B.; Lee, S.-U.; Park, Y.; Bolduc, K. L.; Park, H.-B.; Dickens, M. G.; Lee, D.-S.; Kim, Y.; Kim, S. H.; Hong, J. *J. Am. Chem. Soc.* **2009**, *131*, 3192–3194.

(3) (a) Westley, J. W. *Annu. Rep. Med. Chem.* **1975**, *10*, 246–256. (b) Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem., Int. Ed.* **1977**, *16*, 585–607. (c) Nicolaou, K. C. *Tetrahedron* **1977**, *33*, 683–710. (d) Back, T. G. *Tetrahedron* **1977**, *33*, 3041–3059. (e) Westley, J. W. *Polyether Antibiotics: Naturally Occurring Acid, Ionophores*; Marcel Dekker: New York, 1983; Vols. I and II. (f) Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569–3624. (g) Westley, J. W. *J. Nat. Prod.* **1986**, *49*, 35–47. (h) Dutton, C. J.; Banks, B. J.; Cooper, C. B. *Nat. Prod. Rep.* **1995**, *12*, 165–181. (i) Faulkner, D. J. *Nat. Prod. Rep.* **1998**, *15*, 113–158. (j) Faul, M. M.; Huff, B. E. *Chem. Rev.* **2000**, *100*, 2407–2474. (k) Yeung, K.-S.; Paterson, I. *Chem. Rev.* **2005**, *105*, 4237–4313. (l) Kang, E. J.; Lee, E. *Chem. Rev.* **2005**, *105*, 4348–4378. (m) Shindo, M. *Top. Heterocycl. Chem.* **2006**, *5*, 179–254.

(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.

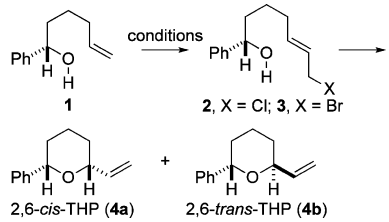
10.1021/ol902125d CCC: $40.75 © XXXX American Chemical Society

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 (±)-diospongin A.

To test the feasibility of the tandem reaction, we prepared hydroxy alkene **1**[6] by the addition of CH_2=$CH(CH_2)_3MgBr$ to PhCHO (84%). Treatment of **1** with CH_2=$CHCH_2Cl$ in the presence of Grubbs' second-generation catalyst (Grubbs II, $(IMesH_2)(PCy_3)(Cl)_2Ru$=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	CH_2=$CHCH_2Cl$, Grubbs II (10 mol %), CH_2Cl_2 (0.1−0.02 M), reflux, 16 h	66	2:1
2	CH_2=$CHCH_2Cl$, Grubbs II (10 mol %), CH_2Cl_2 (0.1 M), reflux, 3 h, then toluene (0.02 M) reflux, 12 h	79	2:1
3	CH_2=$CHCH_2Br$, 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 ^{1}H 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 CH_2=$CHCH_2Cl$ 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 CH_2=$CHCH_2Br$ instead of CH_2=$CHCH_2Cl$ 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

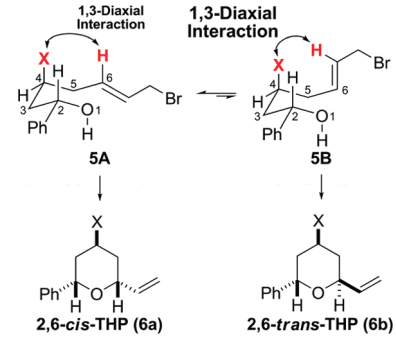


Figure 1. Introduction of 1,3-diaxial interactions to the tandem CM/thermal S_N2' reaction.

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

(5) For recent examples of tetrahydropyran synthesis, see: (a) Minami, T.; Moriyama, A.; Hanaoka, M. *Synlett* **1995**, 663–665. (b) Matsukura, H.; Morimoto, M.; Koshino, H.; Nakata, T. *Tetrahedron Lett.* **1997**, *38*, 5545–5548. (c) Cloninger, M. J.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 1092–1093. (d) Gruttadauria, M.; Lo Meo, P.; Noto, R. *Tetrahedron* **1999**, *55*, 14097–14110. (e) Wong, M.-K.; Chung, N.-W.; He, L.; Yang, D. *J. Am. Chem. Soc.* **2003**, *125*, 158–162. (f) Clark, J. S.; Whitlock, G.; Jiang, S.; Onyia, N. *Chem. Commun.* **2003**, 2578–2579. (g) Hartung, J.; Gottwald, T. *Tetrahedron Lett.* **2004**, *45*, 5619–5621. (h) Lee, E. *Pure Appl. Chem.* **2005**, *77*, 2073–2081. (i) Morris, W. J.; Custar, D. W.; Scheidt, K. A. *Org. Lett.* **2005**, *7*, 1113–1116. (j) Chan, K.-P.; Loh, T.-P. *Org. Lett.* **2005**, *7*, 4491–4494. (k) Alonso, D.; Pérez, M.; Gómez, G.; Covelo, B.; Fall, Y. *Tetrahedron* **2005**, *61*, 2021–2026. (l) Uenishi, J.; Ohmi, M.; Ueda, A. *Tetrahedron: Asymmetry* **2005**, *16*, 1299–1303. (m) Kawai, N.; Lagrange, J. M.; Ohmi, M.; Uenishi, J. *J. Org. Chem.* **2006**, *71*, 4530–4537. (n) Uenishi, J.; Vikhe, Y. S.; Kawai, N. *Chem. Asian J.* **2008**, *3*, 473–484. (o) Smith, A. B., III; Fox, R. J.; Razler, T. M. *Acc. Chem. Res.* **2008**, *41*, 675–687. (p) Bahnck, K. B.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2008**, *130*, 13177–13181. (q) Lu, L.-Q.; Xing, X.-N.; Wang, X.-F.; Ming, Z.-H.; Wang, H.-M.; Xiao, W.-J. *Tetrahedron Lett.* **2008**, *49*, 1631–1635. (r) Hiebel, M.-A.; Pelotier, B.; Goekjian, P.; Piva, O. *Eur. J. Org. Chem.* **2008**, 713–720. (s) Trost, B. M.; Gutierrez, A. C.; Livingston, R. C. *Org. Lett.* **2009**, *11*, 2539–2542.

(6) Ashby, E. C.; DePriest, R. N.; Goel, A. B.; Wenderoth, B.; Pham, T. N. *J. Org. Chem.* **1984**, *49*, 3545–3556.

(7) (a) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956. (b) Chatterjee, A. K.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 1751–1753. (c) Chatterjee, A. K.; Sanders, D. P.; Grubbs, R. H. *Org. Lett.* **2002**, *4*, 1939–1942. (d) Chatterjee, A. K.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 3171–3174. (e) Chatterjee, A. K.; Choi, T. L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370. (f) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900–1923.

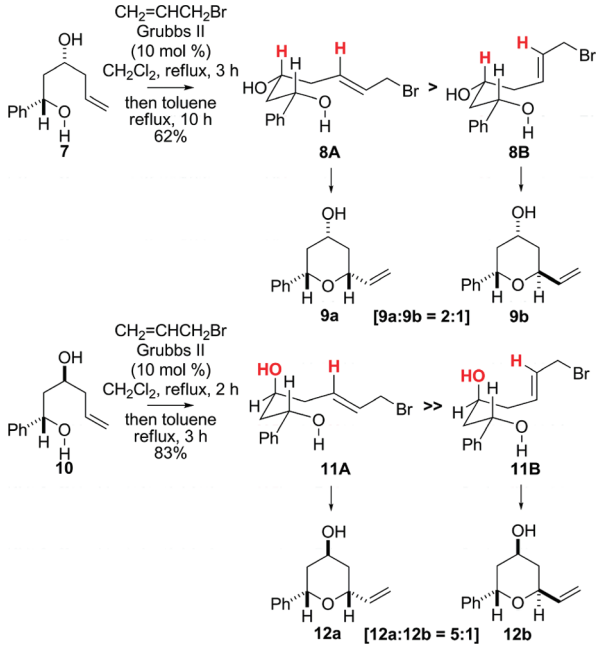
(8) For a review on the intramolecular S_N2' reaction, see: Paquette, L. A.; Stirling, C. J. M. *Tetrahedron* **1992**, *48*, 7383–7423.

(9) For examples of intramolecular S_N2' reaction, see: (a) Kim, D.; Choi, W. J.; Hong, J. Y.; Park, I. Y.; Kim, Y. B. *Tetrahedron Lett.* **1996**, *37*,

Downloaded by SHANGHAI INST OF ORG CHEM on October 22, 2009 | http://pubs.acs.org
Publication Date (Web): October 13, 2009 | doi: 10.1021/ol902125d

conditions (Scheme 1). Treatment of α-hydroxy alkene **7** with CH_2═$CHCH_2Br$ under the tandem reaction conditions

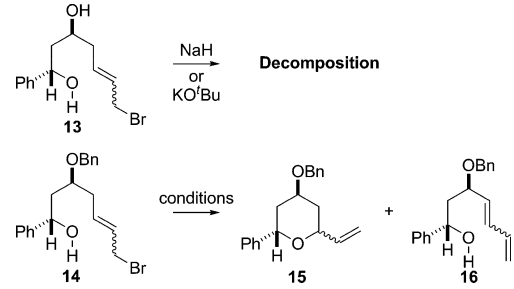
Scheme 1. Synthesis of 4-Hydroxy-2,6-*cis*-tetrahydropyrans



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 S_N2' reaction, **13** and **14** were treated with a base such as NaH or KO^{t}Bu. The S_N2' reaction of **13** under basic conditions (NaH or KO^{t}Bu) completely failed to provide the corresponding tetrahydropyran, but significant decomposition was observed (Table 2). When Bn-protected allylic bromide

Table 2. Intramolecular S_N2' 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 ^{1}H NMR of crude product. [b] Not applicable.

14 was subjected to the basic conditions (NaH or KO^{t}Bu), the S_N2' 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 CH_2═$CHCH_2Br$ 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/S_N2' reaction has never been reported for the stereoselective synthesis of tetrahydropyrans. Indeed, few approaches for the stereoselective synthesis of tetrahydropyrans involve intramolecular S_N2' reactions,[5l−n] perhaps due to the low nucleophilicity of oxygen and a less well-defined transition state.

1433–1434. (b) Li, P.; Wang, T.; Emge, T.; Zhao, K. *J. Am. Chem. Soc.* **1998**, *120*, 7391–7392. (c) Li, P.; Yang, J.; Zhao, K. *J. Org. Chem.* **1999**, *64*, 2259–2263. (d) Lee, J.; Hong, J. *J. Org. Chem.* **2004**, *69*, 6433–6440.

(10) For recent examples of tandem reactions associated with CM, see: (a) Chen, J.-R.; Li, C.-F.; An, X.-L.; Zhang, J.-J.; Zhu, X.-Y.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 2489–2492. (b) Fustero, S.; Jiménez, D.; Sánchez-Roselló, M.; del Pozo, C. *J. Am. Chem. Soc.* **2007**, *129*, 6700–6701.

(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 subjection to refluxing toluene also afforded tetrahydropyran **4a**, demonstrating that the intramolecular S_N2' reaction was a thermal process.

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

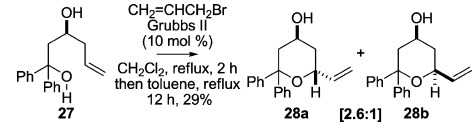
(13) Hoffmann, R.; Brückner, R. *Chem. Ber.* **1992**, *125*, 1471–1484.

(14) Protection of **10** with Bn, Bz, or Piv groups and subjection to the tandem reaction conditions (CH_2═$CHCH_2Br$, 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).

(15) (a) Hoffmann, R. W. *Synthesis* **2006**, 3531–3541. (b) Young, I. S.; Baran, P. S. *Nat. Chem.* **2009**, *1*, 193–205.

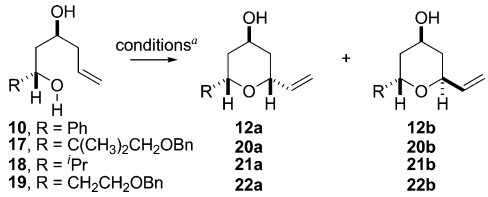
(16) The relative stereochemistries of 1,3-*syn*-diols (**10** and **17**−**19**) were determined by ^{13}C NMR chemical shifts of the corresponding acetonides (see Supporting Information for details).

(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.



Downloaded by SHANGHAI INST OF ORG CHEM on October 22, 2009 | http://pubs.acs.org
Publication Date (Web): October 13, 2009 | doi: 10.1021/ol902125d

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] CH_2=$CHCH_2Br$, 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 ^{1}H NMR of crude product.

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

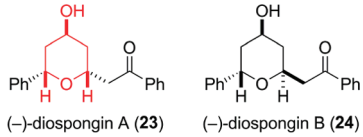
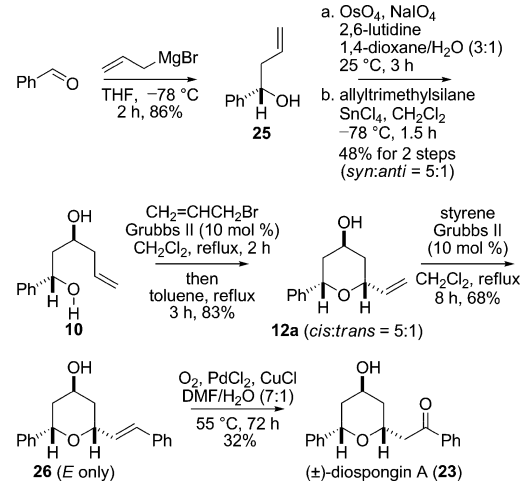


Figure 2. Structure of (−)-diospongins A (**23**) and B (**24**).

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 CH_2=$CHCH_2MgBr$ 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 (±)-Diospongin A (**23**)



tandem reaction of 1,3-*syn*-diol **10** in the presence of CH_2=$CHCH_2Br$ 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** (CH_2=$CHCH_2Br$, 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 (±)-diospongin 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 (±)-diospongin 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 (±)-diospongin 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.

Acknowledgment. This work was supported by Duke University. We acknowledge NCBC Grant #2008-IDG-1010 for funding NMR instrumentation.

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 ^{1}H and ^{13}C NMR spectra; detailed assay procedure. This material is available free of charge via the Internet at http://pubs.acs.org.

OL902125D

(18) Yin, J.; Kouda, K.; Tezuka, Y.; Le Tran, Q.; Miyahara, T.; Chen, Y.; Kadota, S. *Planta Med.* **2004**, *70*, 54–58.

(19) (a) Chandrasekhar, S.; Shyamsunder, T.; Prakash, S. J.; Prabhakar, A.; Jagadeesh, B. *Tetrahedron Lett.* **2006**, *47*, 47–49. (b) Sawant, K. B.; Jennings, M. P. *J. Org. Chem.* **2006**, *71*, 7911–7914. (c) Bressy, C.; Allais, F.; Cossy, J. *Synlett* **2006**, 3455–3456. (d) Bates, R. W.; Song, P. *Tetrahedron* **2007**, *63*, 4497–4499. (e) Hiebel, M.-A.; Pelotier, B.; Piva, O. *Tetrahedron* **2007**, *63*, 7874–7878. (f) Kawai, N.; Mahadeo Hande, S.; Uenishi, J. *Tetrahedron* **2007**, *63*, 9049–9056. (g) Yadav, J. S.; Padmavani, B.; Reddy, B. V. S.; Venugopal, C.; Rao, A. B. *Synlett* **2007**, 2045–2048. (h) Wang, H.; Shuhler, B. J.; Xian, M. *Synlett* **2008**, 2651–2654. (i) Sabitha, G.; Padmaja, P.; Yadav, J. S. *Helv. Chim. Acta* **2008**, *91*, 2235–2239.

(20) (a) Allais, F.; Cossy, J. *Org. Lett.* **2006**, *8*, 3655–3657. (b) Allais, F.; Louvel, M.-C.; Cossy, J. *Synlett* **2007**, 451–452.

Downloaded by SHANGHAI INST OF ORG CHEM on October 22, 2009 | http://pubs.acs.org
Publication Date (Web): October 13, 2009 | doi: 10.1021/ol902125d